**KATHOLIEKE UNIVERSITEIT LEUVEN**
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Kasteelpark Arenberg 10, B-3001 Leuven (Heverlee)

# BLOOD GLUCOSE CONTROL IN CRITICALLY ILL PATIENTS: DESIGN OF ASSESSMENT PROCEDURES AND A CONTROL SYSTEM

Promotoren:
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Proefschrift voorgedragen tot
het behalen van het doctoraat
in de ingenieurswetenschappen

door

**Tom VAN HERPE**

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# Voorwoord

*Als je iets gevonden hebt wat wezenlijk is,*
*zal het je vragen om verder te zoeken.*

*Stef Bos*

In het najaar van 2000 kreeg ik voor mijn 21ste verjaardag plotsklaps en ongevraagd een vriend voor het leven cadeau, een levensgezel die mijn ogen opende en openhoudt, die me soms verdrietig maakt, maar die me ook leert te relativeren en te genieten van de kleine dingen, steeds weer, die me onbewust ook kansen, een levensdoel en een dankbaar gevoel geeft. *Diabetes* is zijn naam. Daar stonden we dan, hand in hand, een lach en een traan, de toekomst recht in de ogen kijkend...

En nu, wat jaren later, sta ik hier. Vol ongeloof knijp ik mezelf in de arm. Vol dankbaarheid ook. Vooreerst zou ik mijn beide promotoren, Prof. Bart De Moor en Prof. Greet Van den Berghe, van harte willen bedanken. Bart, toen we mekaar voor de eerste keer zagen, vielen je ongelooflijk groot enthousiasme en je gedrevenheid me meteen op. Vol vuur was je aan het vertellen over dat nieuwe project waarin we een systeem gingen ontwikkelen om de bloedglucose bij patiënten op Intensieve Geneeskunde automatisch te regelen. Ondanks het gegeven dat je me helemaal niet kende, gaf je me meteen een warm vertrouwen. “The right man in the right place at the right time”, zou je achteraf gezegd hebben. Ik ben je bijzonder dankbaar voor de kans die je me gegeven hebt om onderzoek te doen in de SCD-onderzoeksgroep en om me steeds te steunen, zeker ook wanneer ik weer eens op internationale missie wilde vertrekken. “Je doctoraatsjaren, dat zijn de mooiste van je hele carrière,” zei je me toen nog. Je zou wel eens gelijk kunnen hebben...

Wat is er stimulerender voor een jonge doctoraatsstudent dan *intensief* samen te mogen werken met dé wereldautoriteit van je onderzoeksdomein?! Greet, ik ben ongelooflijk trots dat ik al bijna vijf jaren deel uitmaak van jouw team. Ondanks je overvolle agenda en je vele verantwoordelijkheden *(het leiden van een afdeling Intensieve Geneeskunde is veelal geen lachertje)* maakte je toch de tijd om je scherpe wetenschappelijke inzichten en je kritische analyses met me te delen en stond je

open voor discussies *over hoe we het gingen aanpakken*. Maar bovenal bewonder ik je enorme doorzettingsvermogen, geduld, gulheid en inspirerende woorden die me telkens weer motiveerden om door te gaan.

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In de eerste plaats wil ik het Intensieve Geneeskunde - team van UZ Gasthuisberg even in de bloemetjes zetten. Pieter, dank je voor je hulp bij het vergaren van de patiëntendata en voor de ontelbare keren dat je me in geuren en kleuren de betekenis verklaarde van al die medische gebruiken. Ook al de artsen, en in het bijzonder Geert, Yves, Dirk, Filip, Björn en Lars, wil ik bedanken voor het mee helpen ontcijferen van de doktersvoorschriften op de verpleegbladen, voor alle snelcursussen geneeskunde, maar vooral ook voor de inspirerende discussies, die me gidsten in het bouwen van de brug tussen de wereld van de clinicus en die van de ingenieur. *De hulp van Frank, onze SCD-arts-ingenieur, was dan ook zeker in de beginfase van het project, bijzonder nuttig.* Tot slot wil ik Lies, Ilse V., Ilse M., Sarah, de overige leden van het labo, het verplegend (in het bijzonder de afdeling C) en administratief (Jenny, An en Myriam) personeel bedanken voor de aangename sfeer en de vlotte samenwerking.

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Een volgende subgroep wordt gevormd door de modellering-experts. Ivan, dank je om me te introduceren in de wondere wereld van de modellen die jij als geen ander kent. *Many thanks go further to Marcelo who carefully and patiently guided me in the design of our patient model in spite of the bunch of "NaNs" and "closed-loops" present in the data. Marcelo, also thank you for your feedback on my thesis! I guess, now, it's really "beer o'clock".*

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*"Mama always said,*
*life is like a box of chocolates,*
*you never know what you're gonna get."*

*Forrest Gump*

"...Maar wat er ook gebeurt, we blijven je altijd steunen!" Make en pake, hoe kan ik jullie ooit bedanken voor al de liefde, de genegenheid, het vertrouwen en de kansen die jullie mij steeds onvoorwaardelijk gegeven hebben? Niets was jullie te veel wanneer het mij wel te veel werd, niets te laat wanneer het al laat was. Bedankt, lieve ouders, voor alles. Samen hebben we al heel wat watertjes doorzwommen. Samen, in een (nog steeds) warm en hecht *nest*, samen met een fantastisch *broerrie* en een geweldig *zussie*. Bart en Hilde, hartelijk dank voor jullie oprechte bekommernissen en dat jullie er steeds voor me zijn, al de volle 28 jaren. Evenzeer heb ik veel dank voor mijn schoonzusje, Els, die steevast vol belangstelling (en met een beetje heimwee?) informeerde naar "hoe het in Leuven ging" en mijn schoonbroertje, Mark, voor de babbelrijke autoritjes Turnhout-Leuven wanneer de trein weer iets te vroeg vertrok op zondagavond. En dan zijn er nog mijn nichtje en neefjes (Natalie, Jonatan, Alexander, Thomas en uiteraard mijn petekindje Tibo) die, zonder het zelf te beseffen, met een zalige knuffel even al de zorgen kunnen doen smelten als sneeuw voor de zon. Dank jullie, *kids*!

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...en weg zijn we...

Tom

Leuven
April 2008

# Abstract

Critically ill patients, typically admitted to the Intensive Care Unit (ICU), show hyperglycemia and insulin resistance associated with adverse outcomes. It has been demonstrated that strict blood glucose control (between 80 and 110 mg/dl) results in an important reduction in mortality and morbidity. Current therapy requires a manual and rigorous administration of insulin and could, therefore, be replaced by a semi- or fully-automatic blood glucose control system. The introduction of this system could potentially lead to tighter glycemic control and to a decrease of hypoglycemic events and workload of the medical staff.

Three objectives are set in this thesis. The **first objective** is the design of a procedure to evaluate the reliability of glucose sensor devices (comprising both time-discrete and near-continuous sensors) with regard to a *gold standard* blood glucose sensor. The quality of blood glucose control depends on the reliability (accuracy) of the measurements. Current methods to assess this reliability level may mislead evaluations and/or lack statistical evidence, however. In this thesis, the GLYCENSIT procedure is developed to assess the performance of a test sensor device with respect to a reference sensor device. We present a method that can be *tuned* according to the clinician's preferences regarding significance level, tolerance level, and glycemic range cut-off values. The potential of this new procedure is shown by analysing hypothetical and real-life clinical (ICU) paired glucose data.

The **second objective** of this dissertation is the design of a procedure to appropriately assess the adequacy of blood glucose control algorithms used in the ICU. Based on clinical expert knowledge, the Glycemic Penalty Index (GPI) is introduced as a measure for the *overall* glycemic control behaviour in ICU patients as current evaluation measures have important weaknesses that may mislead assessments. Further, the importance of keeping the *blood glucose sampling frequency* and the *duration of algorithm application* similar among different patient groups when comparing different insulin titration algorithms, is presented.

The **final objective** of this thesis is the design of a predictive control system that can potentially be used for (semi-)automatically normalizing the blood glucose in the critically ill. This blood glucose control system comprises a *patient model* and a *controller*. Both black-box and grey-box modelling approaches are introduced in this thesis to accurately describe the glucoregulatory system of the critically ill. Only the

grey-box modelling approach, expressed in the ICU - minimal model (ICU-MM) and based on physical insight, is found to be valid for use in a clinical predictive control system. Re-estimating the ICU-MM by following an adaptive modelling strategy, allows to capture inter- and intra-patient variability and gives satisfactory forecasting results. Finally, a Model based Predictive Controller that optimizes the insulin infusion rate based on the ICU-MM, is designed. A simulation study shows that the results of the developed control system are satisfactory both in terms of control behaviour (reference tracking and the suppression of unknown disturbance factors) and clinical acceptability.

# Korte Inhoud

Kritiek zieke patiënten, typisch gelegen op een afdeling Intensieve Geneeskunde, vertonen een verhoogde glucoseconcentratie in het bloed (hyperglycemie) en insulineresistentie. De gunstige effecten (mortaliteits- en morbiditeitsreductie) van een strikte regeling van de bloedglucose (tussen 80 en 110 mg/dl) werden reeds aangetoond. De huidige behandeling bestaat zo uit een *manuele* en nauwgezette toediening van insuline en zou bijgevolg kunnen vervangen worden door een *half-* of *volautomatisch* bloedglucoseregelsysteem. Een dergelijk controlesysteem heeft het potentieel om de bloedglucose nog strikter te regelen en de frequentie van hypoglycemies (te laag glucosegehalte in het bloed) en de werkdruk van het medisch team te verlagen.

In deze dissertatie worden drie objectieven naar voren geschoven. Het **eerste objectief** is de ontwikkeling van een procedure die toelaat de betrouwbaarheid van glucosesensoren te evalueren ten opzichte van een *gouden standaard* bloedglucosesensor. De kwaliteit van de bloedglucoseregeling is immers nauw verbonden met de betrouwbaarheid (nauwkeurigheid) van de glucosemetingen. In de beoordeling van glucosesensoren kan men echter misleid worden door de huidige evaluatiemethoden die bovendien regelmatig een gebrek vertonen aan voldoende statistisch bewijs. In dit proefschrift wordt de GLYCENSIT-procedure ontworpen die de performantie van een *test*-glucosesensor ten opzichte van een *referentie*-glucosesensor evalueert. De ontwikkelde methode kan afgesteld worden volgens de voorkeur van de clinicus betreffende significantie/tolerantie-niveau en de drempelwaarde voor hypo- en hyperglycemie. Het potentieel van deze nieuwe procedure is voorgesteld met behulp van analyses van hypothetische en reële, klinische glycemie-datasets.

Het **tweede objectief** van deze dissertatie is het ontwerp van een procedure voor de evaluatie van insulinetitratie-algoritmen (die gebruikt worden op afdelingen Intensieve Geneeskunde om de bloedglucose te regelen). De Glycemische Kost Index ("Glycemic Penalty Index", GPI) wordt zo voorgesteld als maat om het *totale* glycemieregelgedrag bij kritiek zieke patiënten samen te vatten in één getal. De evaluatiemethoden die momenteel in gebruik zijn, vertonen immers zwakheden die kunnen leiden tot een verkeerde beoordeling van het regelalgoritme. De *glucosebemonsteringsfrequentie* en de *tijdsduur dat het algoritme effectief wordt toegepast* zijn bovendien twee parameters die gelijkaardig moeten zijn onder patiëntengroepen opdat verschillende algoritmen adequaat vergeleken kunnen worden.

Het **derde objectief** van dit proefschrift is het ontwerp van een voorspellend regelsysteem dat het potentieel heeft om (half-)automatisch de bloedglucose bij kritiek zieke patiënten te normaliseren. Dit glucoseregelsysteem bestaat uit een *patiëntmodel* en een *regelaar*. Zowel "black-box" - als "grey-box" - modelleringstechnieken worden toegepast met het oog op het nauwkeurig beschrijven van het *glucoseregulatorisch* systeem van kritiek zieke patiënten. Enkel de "grey-box" - modelleringsmethode, die gefundeerd is op fysische inzichten en die zich uit in het ontworpen *"Intensive Care Unit" - Minimale Model (ICU-MM)*, wordt gevalideerd voor klinisch gebruik in een voorspellend regelsysteem. Het frequent herschatten van het ICU-MM (door gebruik te maken van een adaptieve modelleringsprocedure) laat toe om rekening te houden met de variabiliteit binnen de patiënt en tussen patiënten onderling. Het verloop van het glucosesignaal kan aldus voldoende nauwkeurig voorspeld worden met deze methode. Ten slotte wordt een regelaar ontwikkeld op basis van Modelgebaseerde Predictieve Controle (MPC) technieken zodat het toe te dienen insulinedebiet kan geoptimaliseerd worden op basis van het ontworpen ICU-MM. Een simulatiestudie toont aan dat de resultaten van de MPC voldoen aan de eisen inzake regelgedrag (het volgen van een referentieglycemie en het onderdrukken van ongekende stoorfactoren) en klinische realiseerbaarheid.

# Notation

**Variables used in the Intensive Care Unit - Minimal Model (ICU-MM)**

| | |
|---|---|
| $G$ | Glycemia or Blood Glucose (mg/dl) (1 mmol/l = 18 mg/dl ) |
| $F_I$ | Flow of Insulin (U/hr) |
| $F_G$ | Flow of carbohydrate (Glucose) calories (kcal/hr) |
| $F_F$ | Flow of Fat calories (kcal/hr) |
| $T$ | body Temperature (°C) |
| $F_C$ | Flow of glucoCorticoids (mg/hr) |
| $F_A$ | Flow of Adrenaline ($\gamma$) |
| $F_N$ | Flow of Noradrenaline ($\gamma$) |
| $F_{Dob}$ | Flow of Dobutamine ($\gamma$) |
| $F_{Dop}$ | Flow of Dopamine ($\gamma$) |
| $F_\beta$ | Flow of Beta blockers (mg/hr) |

**Acronyms**

| | |
|---|---|
| ADICOL | ADvanced Insulin infusion using a COntrol Loop |
| AIDA | Automated Insulin Dosage Advisor |
| ANOVA | ANalysis Of VAriance |
| APACHE | Acute Physiology and Chronic Health Evaluation |
| AR | linear AutoRegressive model |
| ARX | linear AutoRegressive model with eXogeneous inputs |
| AST | Alternate Site Testing |
| BIT | Back-In-Time |
| BMI | Body Mass Index |
| D-MM | (type I) Diabetes Minimal Model |
| DETM | Diabetes Error Test Model |
| DIAS | DIabetes Advisory System |
| EKF | Extended Kalman Filter |
| FSIGTT | Frequently Sampled Intravenous Glucose Tolerance Test |
| GLYCENSIT | GLYCemia sENSor Tool *or* GLYCemia sENSe IT |
| GMS | Glucose Monitoring Systems |
| GPI | Glycemic Penalty Index |
| GRIP | Glucose Regulation for Intensive care Patients |
| HGI | HyperGlycemic Index |

| | |
|---|---|
| IBW | Ideal Body Weight |
| ICU | Intensive Care Unit |
| ICU-MM | Intensive Care Unit Minimal Model |
| IQ | InterQuartile |
| ISO | International Organisation for Standardization |
| IVGTT | IntraVenous Glucose Tolerance Test |
| MHE | Moving Horizon Estimator |
| MM | Minimal Model |
| MPC | Model based Predictive Control |
| MPE | Mean Percentage Error |
| MSE | Mean Squared Error |
| MSnE | Mean Squared normalized Error |
| NICE-SUGAR | Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation |
| N-LS | Non-Linear Least Squares |
| OGTT | Oral Glucose Tolerance Test |
| OLS | Ordinary Least Squares |
| PD | Proportional / Differential |
| PDMS | Patient Database Management System |
| PID | Proportional / Integral / Differential |
| RMSnE | Root Mean Squared normalized Error |
| SD | Standard Deviation |
| sMSE | standardized Mean Squared Error |
| SPRINT | SPecialized Relative Insulin and Nutrition Tables |
| SQP | Sequential Quadratic Programming |
| TGC | Tight Glycemic Control |
| VISEP | Volume substitution and Insulin therapy in Severe sEPsis |
| WLS | Weighted Least Squares |

# Contents

# Regelen van glycemie bij kritiek zieke patiënten: ontwerp van evaluatieprocedures en een regelsysteem

## Hoofdstuk 1: Inleiding

Kritiek zieke patiënten, typisch gelegen op een afdeling Intensieve Geneeskunde, vertonen een verhoogde glucoseconcentratie in het bloed (hyperglycemie) en insulineresistentie. De gunstige effecten (mortaliteits- en morbiditeitsreductie) van een strikte regeling van de bloedglucose (tussen 80 en 110 mg/dl) werden initieel aangetoond in 2001 [216]. Zo daalde de mortaliteit van 8.0 tot 4.6% in een **chirurgisch** zieke patiëntenpopulatie die *intensief* met insuline behandeld werd (als alternatief voor de *conventionele* insulinetherapie waarbij de maximum toelaatbare bloedglucose gelijk was aan 220 mg/dl). De toepassing van deze intensieve insulinetherapie bij **medisch** zieke patiënten (die typisch lijden aan chronische ziekten) resulteerde eveneens in een mortaliteitsdaling (van 52.5 tot 43.0%) voor patiënten die minstens drie dagen op de afdeling Intensieve Geneeskunde verbleven [213].

Naast de significante daling van de mortaliteit en de morbiditeit heeft de intensieve insulinetherapie ook een belangrijk financieel voordeel. Figuur 1.2, die gebaseerd is op de resultaten gepubliceerd in [217], toont aan dat de kostendaling per patiënt € 2638 bedraagt (terwijl de extra kost, voornamelijk te wijten aan het regelmatiger bemonsteren van de glycemie en de toediening van meer insuline, per patiënt slechts € 72 is).

Ondanks de gekende klinische en economische voordelen van de intensieve insulinetherapie, kunnen de volgende problemen en uitdagingen geformuleerd worden:

1. Een strikte regeling van de bloedglucose vereist het frequent bemonsteren van de bloedglucose en het vervolgens adequaat aanpassen van het insulinedebiet op basis van het geobserveerde glycemiesignaal en aanwezige stoorfactoren zoals toegediende voeding en medicatie. Het gebruik van het huidige protocol [215], dat geen eenvoudig 'als-dan' protocol is, vereist echter voldoende **ervaring** van de verpleegkundige.

2. Omwille van de niet-triviale toepassing van het huidige protocol, is de **werkdruk** voor het verplegend personeel drastisch toegenomen.

3. Het waargenomen glucosesignaal hangt bovendien af van welke verpleegkundige welke patiënt heeft behandeld (**'subjectieve'** glycemieregeling).

4. Een belangrijk nadeel van de intensieve insulinetherapie is de angst voor **hypoglycemie** (te laag glucosegehalte in het bloed) omwille van het verlaagde doel-bloedglucose-bereik (80-110 mg/dl).

5. Tot slot zou de glycemieregeling vlotter en veiliger kunnen gebeuren indien een betrouwbare **'continue'** glucosesensor beschikbaar zou zijn. Tot op heden echter wordt de arteriële glucosewaarde bij kritiek zieke patiënten slechts elk uur tot elke vier uren gemeten.

De huidige behandeling bestaat uit een *manuele* en nauwgezette toediening van insuline en zou bijgevolg kunnen vervangen worden door een *half-* of *volautomatisch* bloedglucoseregelsysteem. Een dergelijk regelsysteem heeft immers het potentieel om de bloedglucose strikter te regelen en om de frequentie van hypoglycemies en de werkdruk van het medisch team te verlagen. Bovendien kan een dergelijk automatisch systeem leiden tot een 'objectiever' regelgedrag wat de drempel tot toepassing of verbetering van de intensieve insulinetherapie in ziekenhuizen wereldwijd verder kan verlagen. Een andere onderzoeksuitdaging situeert zich in het ontwerp van evaluatieprocedures voor glucosesensoren enerzijds en glycemieregelalgoritmen anderzijds. Bij gebruik van de huidige methoden om een glucosesensor/regelalgoritme te beoordelen, kan men immers misleid worden.

In deze dissertatie worden **drie objectieven** behandeld. Ten eerste wordt een *evaluatieprocedure voor glucosensoren* ontwikkeld die tegemoet komt aan de zwakheden van de huidige beoordelingstechnieken. Ten tweede wordt een *evaluatieprocedure voor regelalgoritmen* die gebruikt worden om de bloedglucose bij kritiek zieke patiënten te normaliseren, ontworpen. Ten derde wordt een *predictief regelsysteem* ontwikkeld dat het potentieel heeft om de glycemie half- of volautomatisch te regelen op Intensieve Geneeskunde - afdelingen. Figuur 0.1 vat de verschillende hoofdstukken in dit proefschrift visueel samen.

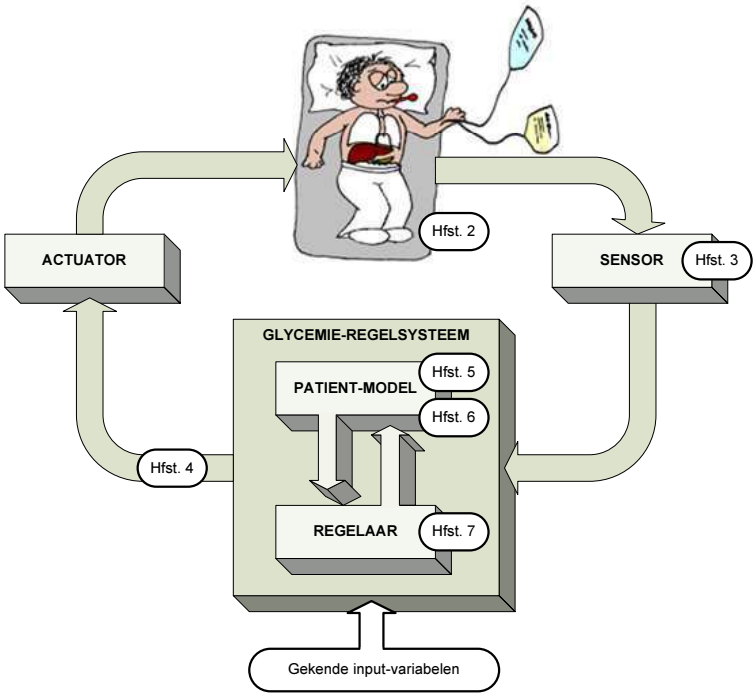


**Figure 0.1:** Vereenvoudigde voorstelling van een *halfautomatisch* bloedglucoseregelsysteem. Hoofdstuk 2 beschrijft de klinische achtergrond en de beschikbare Intensieve Geneeskunde - datasets. Vervolgens worden de nieuwe evaluatieprocedures voor glucosesensoren en regelalgoritmen beschreven in respectievelijk Hoofdstuk 3 en 4. De volgende twee hoofdstukken behandelen de ontwikkeling van een *zwarte-doos*-model (Hoofdstuk 5) en een *grijze-doos*-model (Hoofdstuk 6) die gebruikt worden om het verloop van de glycemie te voorspellen. Tot slot wordt het ontwerp van een modelgebaseerde predictieve regelaar voorgesteld in Hoofdstuk 7.

# I KLINISCHE ACHTERGROND

## Hoofdstuk 2: Intensieve geneeskunde: patiënten en data

In het eerste deel van dit hoofdstuk wordt de klinische achtergrond van dit project geschetst. Het glucoseregulatorisch systeem van een gezonde persoon, een patiënt met (type I) diabetes en een kritiek zieke patiënt wordt eenvoudig voorgesteld in respectievelijk figuur 2.3, figuur 2.4 en figuur 2.5. De verhoogde glucoseconcentratie in het bloed (hyperglycemie) van kritieke zieke patiënten is voornamelijk te wijten aan de verhoogde productie van stresshormonen. Deze hormonen gaan enerzijds de activiteit van insuline tegenwerken en anderzijds de weerstand tegen insuline (insulineresistentie) verhogen. De resulterende hyperglycemie zorgt verder voor een acute toxiciteit in de cellen die glucose kunnen opnemen onafhankelijk van insuline. Het is vermoedelijk die toxiciteit die bepalend is voor de mortaliteit en de morbiditeit bij kritiek zieke patiënten. De normalisatie van de bloedglucose is dan ook een belangrijk aspect bij de behandeling van patiënten die gelegen zijn op een afdeling Intensieve Geneeskunde.

Het tweede deel van dit hoofdstuk beschrijft de data die beschikbaar gemaakt zijn in het kader van deze dissertatie. In het begin van dit project waren geen dynamische data (waarbij parameters bv. elk uur bemonsterd worden) beschikbaar in *electronisch* formaat. Tot enkele maanden geleden werd immers gebruik gemaakt van *papieren* verpleegbladen (zoals afgebeeld in figuur 2.6) waarop de klinische informatie van elke patiënt op werd genoteerd. In eerste instantie was het dan ook van belang om deze *papieren* data accuraat om te zetten naar een *electronisch* formaat. Op basis van beschikbaarheid en klinisch oordeel werd dan ook een lijst van variabelen (waaronder insuline, voedingscalorieën, medicatie, lichaamstemperatuur) opgesteld die mogelijk de bloedglucose kunnen beïnvloeden.

Vier verschillende (electronische) datasets, met elk specifieke kenmerken, werden op die manier geregistreerd:

1. **Dataset 1:** De eerste dataset bestaat uit 41 patiënten waarbij de (arteriële) bloedglucose elke vier uren of frequenter (in geval van complicaties of in de initiële fase) werd gemeten met de ABL700 Radiometer Medical glucosemeter (Radiometer, Denemarken). Het doel-bloedglucose-bereik was 80-110 mg/dl en de data van de volledige verblijfsduur werden geregistreerd. De gemeten glycemies werden vervolgens lineair geïnterpoleerd zodat *één-uur-data* bekomen werden. Tabel 2.1 geeft een overzicht van de eigenschappen van deze dataset.

2. **Dataset 2:** De tweede dataset bestaat uit 15 patiënten waarbij de (arteriële) bloedglucose elk uur (gedurende de eerste 50 uren na opname) gemeten werd met behulp van de ABL700 Radiometer Medical glucosemeter. Het doel-bloedglucose-bereik was 80-110 mg/dl. Tabel 2.2 geeft een overzicht van de kenmerken van deze dataset.

3. **Dataset 3:** De derde dataset bestaat uit 37 patiënten. De (arteriële) glycemie werd hier elk uur (gedurende de eerste 50 uren na opname) gemeten met drie verschillende sensoren: de ABL700 Radiometer Medical glucosemeter, de Accu-Chek Inform meter (Roche Diagnostics, Zwitserland) en de HemoCue B-glucose meter (HemoCue, Engeland). In tegenstelling tot de andere datasets werden hier enkel de glycemie-data geregistreerd (en dus niet de andere geselecteerde variabelen). Tabel 2.3 geeft een overzicht van de eigenschappen van deze dataset.

4. **Dataset 4:** De vierde dataset bestaat uit 20 patiënten waarbij de (arteriële) bloedglucose elk uur gemeten werd met de ABL700 Radiometer Medical glucosemeter. Tevens werd gelijktijdig de *subcutane* glucoseconcentratie gemeten met behulp van het GlucoDay meetsysteem (A. Menarini Diagnostics, Italië). Elke drie minuten werd zo een glucosemeting geëxporteerd zodat voor deze patiënten een benaderend continu glucosesignaal (dat gevalideerd werd met de ABL700 Radiometer Medical *één-uur-bloedglucosedata*) beschikbaar was. De kenmerken van deze dataset worden samengevat in tabel 2.4.

Vanuit ingenieurstechnisch oogpunt kunnen de volgende eigenschappen van de beschikbare datasets onderscheiden worden:

- De bemonsteringsfrequentie van variabelen (zoals de bloedglucose) is *niet steeds gelijk* wat (lineaire) interpolatie noodzakelijk maakt.
- Stoorfactoren (zoals toegediende voeding en medicatie) kunnen *simultaan* gewijzigd worden wat een eenduidige modellering kan bemoeilijken.
- Omwille van het arbeidsintensieve transformatieproces (waarbij de papieren data omgezet werden naar electronische data), is slechts een *beperkte* hoeveelheid data beschikbaar. De variabiliteit van het glucoseregelgedrag voor een patiënt (in functie van de tijd) alsook tussen verschillende patiënten onderling is immers groot.
- Een groot aantal factoren die het glucoseregelgedrag kunnen verstoren, kunnen *niet (rechtstreeks) gemeten* worden (bv. insulineresistentie) of zijn *niet gekend* (bv. mogelijke effect op de glycemie van het wassen van de patiënt).
- Aangezien de verpleegkundigen de bloedglucose van de patiënten zo strikt mogelijk tussen 80 en 110 mg/dl trachten te regelen, kunnen we spreken van *gesloten-lus* data. Deze eigenschap kan de relatie tussen de ingangen (bv. voeding, medicatie) enerzijds en de uitgang (glycemie) anderzijds (gedeeltelijk) verhullen wat het modelleringsproces van het intern glucoseregelgedrag kan bemoeilijken.
- Tot slot moet opgemerkt worden dat een (onbeperkte) experimentele vrijheid ontbreekt omwille van medische en ethische redenen.

# II BEOORDELINGSPROCEDURES

## Hoofdstuk 3: Algemene beoordeling van glucosesensoren

Het regelmatig en accuraat meten van de glycemie is een belangrijke eigenschap van intensieve insulinetherapie bij zowel diabetespatiënten als kritiek zieke patiënten. Zowel **bloedglucosemeters** als **glucosemeetsystemen** worden hiervoor gebruikt. De eerste categorie meet de glucosewaarde in arterieel, veneus of capillair bloed en resulteert typisch in *tijdsdiscrete* metingen (bv. 6 tot 12 metingen per dag). De tweede categorie daarentegen maakt een schatting van de glucosewaarde met behulp van andere technieken zodat het meetinterval verkleind kan worden tot enkele minuten of zelfs seconden. Dit type van glucosesensoren leidt dan ook tot een *continu* glucoseprofiel.

De huidige methoden die gebruikt worden om een glucosesensor te evaluaren vertonen elk bepaalde zwakheden die reeds uitvoerig in de bestaande literatuur werden beschreven. In dit hoofdstuk wordt dan ook een nieuwe methode ontwikkeld (de GLYCENSIT-procedure) die tracht tegemoet te komen aan deze zwakheden. Deze nieuwe methode rust op drie pijlers. Ten eerste dient elke glucosedataset getransformeerd te worden naar een verzameling van gekoppelde metingen. Dit betekent dat voor elke *test*-sensorwaarde ook een *referentie*-waarde gekend moet zijn. Ten tweede wordt verondersteld dat opeenvolgende meetfouten statistisch onafhankelijk zijn en dat ze elk een identieke distributie hebben. Ten derde is de procedure voor een deel gefundeerd op een normalisatiefunctie (zie vergelijking 3.2). Deze functie laat toe om de meetfouten te *normaliseren* op basis van het "International Organisation for Standardization (ISO)" - criterium [75] zodat lage glucosewaarden anders beoordeeld worden dan hoge glucosewaarden.

De ontworpen GLYCENSIT-methode bestaat uit drie complimentaire fasen:

1. **Fase 1:**
   In deze fase wordt de *persistentie* van het meetgedrag in functie van het glycemiegebied statistisch getest met behulp van de Kruskal-Wallis test [175]. Een persistente fout vergemakkelijkt immers de ingebruikname van een nieuwe sensor door verpleegkundigen aangezien in dat geval eenvoudig kan rekening gehouden worden met de (gekende) sensorfout.

2. **Fase 2:**
   De tweede fase wordt gekenmerkt door het testen van de *nauwkeurigheid* van de sensor t.o.v. het ISO-criterium. Er wordt statistisch aangetoond of een test-glucosesensor voldoet aan bepaalde tolerantie-niveaus (bv. een tolerantie-niveau van 4% duidt aan dat de test-glucosensor slechts 4 fouten tegen het ISO-criterium op 100 metingen mag maken).

3. **Fase 3:**
   In de laatste fase worden tolerantie-intervallen berekend om de mogelijke afwijkingen van de test-sensor voor *nieuwe metingen* in kaart te brengen. De waarschijnlijkheid van deze tolerantie-intervallen (die afhankelijk is van het significantieniveau, het aantal gekoppelde metingen en de grootte van de tolerantie-intervallen) wordt tot slot berekend en confronteert de gebuiker met de statistische betrouwbaarheid van de analyse van de specifieke dataset.

Het gebruik van de ontworpen GLYCENSIT-procedure wordt vervolgens aangetoond met behulp van drie hypothetische en drie klinische datasets. In deze laatste categorie wordt achtereenvolgens de betrouwbaarheid van de GlucoDay (A. Menarini Diagnostics, Italië), de Accu-Chek Inform (Roche Diagnostics, Zwitserland) en de HemoCue B-glucose (HemoCue, Engeland) *test*-sensoren geanalyseerd t.o.v. de ABL700 Radiometer Medical glucose (Radiometer, Denemarken) *referentie*-sensor. De bereikte analyses worden verder vergeleken met de resultaten die bekomen werden met de huidige meest gekende evaluatietechnieken (Bland-Altman-analyse [3, 15] en Fouten-Raster-Analyse ("Error Grid Analysis") [44, 52, 54]). Bovendien kan de GLYCENSIT-methode eenvoudig toegepast worden op de bijhorende website: **http://www.esat.kuleuven.be/GLYCENSIT**.

## Hoofdstuk 4: Algemene beoordeling van glycemie - regelsystemen

De normalisatie van de bloedglucose d.m.v. toediening van insuline vormt een standaard onderdeel in de huidige behandeling van kritiek zieke patiënten. Verpleegkundigen passen dan ook op regelmatige tijdstippen de insulinedosis aan met behulp van insulinetitratie-algoritmen. Nieuwe vormen van deze bloedglucoseregel-algoritmen worden sedert enkele jaren ontwikkeld, maar vereisen een gepaste evaluatie alvorens ze aanvaard kunnen worden voor algemeen klinisch gebruik. De huidige beoordelingsmethoden bestaan hoofdzakelijk uit enkelvoudige metingen (bv. de ochtendglycemie), gemiddelden (bv. de gemiddelde glycemie) en de HyperGlycemische Index (HGI). Elk van deze categorieën vertoont echter zwakheden die er voor kunnen zorgen dat men kan misleid worden bij de beoordeling van een regelalgoritme.

In dit hoofdstuk wordt de Glycemische Kost Index ("Glycemic Penalty Index", GPI) ontwikkeld die de zwakheden van de huidige gekende methoden tracht op te heffen. De GPI is een instrument om een glucoseprofiel te beoordelen op basis van klinische expertkennis uit de Intensieve Geneeskunde. Aan elke gemeten glucosewaarde wordt een bepaalde kost toegekend en het gemiddelde van al deze kosten wordt vervolgens uitgedrukt in de GPI (zie vergelijking 4.3) op een schaal van 0 tot 100. Idealiter is de GPI gelijk aan 0 wat inhoudt dat al de gemeten glucosewaarden zich in het 80-110 mg/dl normoglycemisch meetbereik bevinden. In de klinische praktijk kunnen echter onnauwkeurigheden inzake de sensor of de behandeling van het bloedstaal

voorkomen zodat glucoseprofielen die een GPI hebben van 23 of minder toch als klinisch aanvaardbaar kunnen worden beschouwd.

Verder wordt in dit hoofdstuk de performantie van de GPI vergeleken met die van de huidige beoordelingsmethoden (de gemiddelde ochtendglycemie, de gemiddelde glycemie en de HGI). Er wordt aangetoond dat men misleid kan worden bij de beoordeling van een glucoseprofiel wanneer men enkel de huidige evaluatietechnieken toepast (*aanvaardbaar* op basis van de huidige beoordelingsmethoden, maar klinisch *onaanvaardbaar* volgens GPI). Evaluatieverschillen treden voornamelijk op bij de vergelijking tussen de gemiddelde (ochtend)glycemie en de GPI en in mindere mate bij de vergelijking tussen de HGI en de GPI.

Tot slot wordt in dit hoofdstuk onderzocht welke parameters een beoordeling van een insulinetitratie-algoritme kunnen beïnvloeden. Zo wordt het effect van de *tijdsduur dat het algoritme wordt toegepast*, de *gemiddelde glucosebemonsteringsfrequentie*, de *graad van ziekte* en het *type ziekte* op de GPI bestudeerd. Enerzijds blijkt een hogere *gemiddelde glucosebemonsteringsfrequentie* gerelateerd te kunnen worden aan lagere GPI-waarden (strictere glycemiecontrole) indien de *tijdsduur dat het algoritme wordt toegepast* kort en constant is (bv. eerste 48 uren na opname). Anderzijds zal de GPI ook verlagen bij een toenemende *tijdsduur dat het algoritme wordt toegepast*. Immers, hoe langer de patiënt verblijft op Intensieve Geneeskunde (en dus hoe langer het algoritme wordt toegepast en hoe meer data beschouwd worden bij de bepaling van GPI), hoe meer ook de chronische, eerder stabiele fase (die volgt na de initiële, instabiele fase) in rekening wordt gebracht. In deze stabiele fase is de bloedglucose typisch gemakkelijker te regelen binnen het 80-110 mg/dl normoglycemische bereik (resulterend in een lage GPI) zodat de verpleegkundigen de glycemie minder frequent dienen te meten.

# III BLOEDGLUCOSEREGELSYSTEEM

## Hoofdstuk 5: Zwarte-doos-modellering van glycemie

Een predictief regelsysteem dat gebruikt kan worden voor de normalisatie van de glycemie op Intensieve Geneeskunde bestaat enerzijds uit een patiëntmodel dat het glucoseregulatorisch systeem van een kritiek zieke patiënt mathematisch voorstelt en anderzijds uit een regelaar die, gebruikmakend van het model, de meest optimale insulinedosis bepaalt.

In dit hoofdstuk wordt een zwarte-doos ("black-box") - model ontwikkeld om de glycemie van kritiek zieke patiënten te voorspellen. Zwarte-doos-modelleringstechnieken maken gebruik van de beschikbare datasets om zowel de *modelstructuur* te ontwikkelen alsook de *modelparameters* te schatten. Als vertrekbasis wordt een lineair AutoRegressief model met eXterne ingangssignalen (ARX) genomen dat wordt voorgesteld in vergelijking 5.1. Vervolgens wordt op basis van iteratieve $t$-testen bepaald welke ingangsvariabelen (bv. insuline, glucosecalorieën, vetcalorieën, medicatie, e.a.) een significante bijdrage leveren tot de voorspelling van de bloedglucose waarna tevens de modelorde bepaald wordt. De uiteindelijke modelstructuur wordt weergegeven in vergelijking 5.5.

Verder wordt in dit hoofdstuk een adaptieve modelleringsprocedure uitgewerkt. Voor elke patiënt $p$ worden de parameters van het bekomen model (vgl. 5.5) hier namelijk op elke tijdstap $t$ herschat op basis van twee datasets. De eerste dataset bestaat uit de data van de patiënten die gebruikt worden om het initieel model te schatten. De tweede dataset daarentegen bestaat uit de data van patient $p$ tot tijdstip $t-1$ die bovendien nog versterkt worden met een geoptimaliseerde factor. Op die manier wordt elk model aangepast aan de specifieke patiënt en het snel variërende interne dynamische gedrag van de kritiek zieke patiënt in het bijzonder (bv. variërende insulinegevoeligheid).

De voorspelde glycemieprofielen zijn aanvaardbaar vanuit modeltechnisch standpunt. Zoals verwacht verkleint de modelfout bij een predictiehorizon van een uur in vergelijking met een simulatiehorizon van vier uren. Het adaptieve karakter van het model resulteert verder in een hogere modelpredictieperformantie in vergelijking met de performantie van het initiële model. Er dient echter een belangrijke bedenking gemaakt te worden wanneer zwarte-doos-modelleringstechnieken gebruikt worden voor regeldoeleinden in een klinische omgeving. De *gesloten-lus* eigenschap van de beschikbare data leidt immers tot een onderschatting van het belang van de modelcoëfficiënten van de ingangsvariabelen (waaronder insuline in het bijzonder). Gebruik van het ontwikkelde zwarte-doos-model in een predictief regelsysteem kan bijgevolg leiden tot toediening van te grote hoeveelheden insuline wat een potentieel gevaar betekent voor de patiënt. Om die reden kunnen deze modellen niet gebruikt worden voor regeldoeleinden in een klinische omgeving.

## Hoofdstuk 6: Grijze-doos-modellering van glycemie

In dit hoofdstuk wordt een grijze-doos ("grey-box") - model ontwikkeld dat als doel heeft het accuraat voorspellen van het glucosegedrag van kritiek zieke patiënten. In tegenstelling tot zwarte-doos-modelleringstechnieken wordt, naast de beschikbare data, ook gebruik gemaakt van klinische en fysische inzichten. In dit hoofdstuk wordt dan ook het "Intensive Care Unit" - Minimale Model (ICU-MM) ontworpen. Dit model wordt afgeleid van het befaamde Minimale Model dat door Bergman en collega's werd ontwikkeld in de beginjaren '80 [14]. Het gecreëerde ICU-MM bestaat uit vier differentiaalvergelijkingen die voorgesteld worden in vergelijkingsstelsel 6.3. Het model omvat een endogene insulinesectie (eigen werking van de pancreas) en een exogene insulinesectie (extern toegediende insuline). Het ICU-MM heeft verder twee ingangsvariabelen (exogene insuline en toegediende glucosecalorieën) en zeven patiëntspecifieke parameters die dus per patiënt dienen geschat te worden. De modelstructuur wordt in een blokdiagram samengevat in figuur 6.4.

De modeldynamica van het ICU-MM komt kwalitatief en kwantitatief overeen met de dynamica van het echte glucoseregulatorisch syteem zoals wordt aangetoond in een simulatie met 19 (virtuele) kritiek zieke patiënten. Vervolgens wordt een adaptieve modelleringsprocedure toegepast op deze patiëntengroep waarbij de eerste 24-uren data na opname op Intensieve Geneeskunde gebruikt worden om een initieel model te schatten. Dit model wordt dan gevalideerd met de tweede 24-uren data. In dit validatieproces (waarbij het glucoseprofiel telkens een of vier uren verder wordt voorspeld, afhankelijk van de simulatie) wordt in elke tijdstap het model ook herschat op basis van recente data zodat veranderingen in het glucoseregulatorisch systeem (bv. variërende insulinegevoeligheid) mee in rekening kunnen gebracht worden.

Het ICU-MM wordt idealiter elke tijdstap (bv. elk uur of elke vier uren) herschat op basis van de data van de laatste vier à vijf uren. Verder wordt aangetoond dat het elk uur updaten van het model resulteert in kleinere predictiefouten in vergelijking met updates die slechts om de vier uren voorkomen. Algemeen kan echter geconcludeerd worden dat de predictieperformantie van het ICU-MM aanvaardbaar is in beide gevallen vanuit modeltechnisch en klinisch perspectief. Daarenboven wordt met behulp van patientgevalsstudies aangetoond dat het ICU-MM het potentieel heeft om gebruikt te worden in een predictief regelsysteem om de glycemie te regelen van kritiek zieke patiënten.

## Hoofdstuk 7: Regeling van glycemie

Dit hoofdstuk bestaat uit twee bijdragen. Ten eerste wordt een kritisch overzicht gegeven van de algoritmen die de laatste jaren werden voorgesteld om de bloedglucose bij kritiek zieke patiënten te regelen. Het insulinetitratieprotocol [215] dat gebruikt werd bij het normalisatieproces in de twee befaamde Leuven-studies [213, 216] bestaat uit een verzameling van richtlijnen die niet als *absoluut* mogen aanzien worden. De vrije interpretatie van de verpleegkundigen is immers een essentieel

onderdeel van dit protocol. In navolging van dit protocol werden basisprotocols of nomogrammen ontwikkeld die de inbreng van de verpleegkundigen minder of niet meer noodzakelijk maakten. Verder werden eveneens elementaire en meer geavanceerde computerprotocols ontwikkeld.

Ondanks het aantonen van de gunstige effecten (mortaliteits- en morbiditeitsdaling) bij een intensieve insulinetherapie op Intensieve Geneeskunde, is het opmerkelijk dat veel van de voorgestelde protocols een doel-glycemie-bereik hebben dat significant hoger ligt dan het 80-110 mg/dl normoglycemisch doelgebied beschreven in [213,216]. De angst voor hypoglycemie is de hoofdreden van het verhogen van deze doel-bloedglucose. Verder moet opgemerkt worden dat het moeilijk is om de resulaten van al de verschillende algoritmen te vergelijken daar de parameters die een beoordeling van een algoritme kunnen beïnvloeden (*gemiddelde glucosebemonsteringsfrequentie* en de *tijdsduur dat het algoritme wordt toegepast*, zie Hoofdstuk 4) niet gelijk gehouden werden. Het is dan ook opvallend dat verscheidene studies toch een vergelijking maken tussen de regelperformantie van een nieuw algoritme enerzijds en het standaard Leuven-protocol anderzijds; temeer daar dit laatste uit slechts *richtlijnen* bestaat. Verder wordt vastgesteld dat uitzonderlijk in sommige studies zowel insuline als voedingscalorieën als ingangsvariabelen worden beschouwd (en dus niet zoals gebruikelijk enkel insuline). Tot slot is het opmerkelijk dat *capillaire* glucosemetingen uitgevoerd werden bij kritiek zieke patiënten in tal van studies. Het werd immers reeds uitvoerig beschreven dat het bepalen van de glucoseconcentratie in capillair bloed van kritiek zieke patiënten kan leiden tot onbetrouwbare glycemiemetingen [28, 51, 63, 71, 123].

De tweede bijdrage beschreven in dit hoofdstuk is het ontwerp van een Modelgebaseerde Predictieve Controle (MPC) - regelaar. Een dergelijk type regelaar laat toe om het optimale insulinedebiet te bepalen dat moet toegediend worden aan de patiënt. In elke tijdstap wordt dan ook een optimalisatieprobleem opgelost waarbij het glycemieverloop wordt gesimuleerd met behulp van het in Hoofdstuk 6 ontwikkelde ICU-MM. Twee simulatiestudies worden vervolgens beschreven. In een eerste studie wordt de glycemie van 19 (virtuele) kritiek zieke patiënten geregeld waarbij enkel het debiet van glucosecalorieën (dat werkelijk werd toegediend aan de overeenstemmende echte 19 patiënten) als gekende stooringang fungeert. In de simulatie wordt bovendien een meetfout toegevoegd aan het glycemiesignaal en wordt een (voor de MPC ongekende) additieve medicatie-stoorfactor bijgebracht. Een uitgebreide Kalman filter ("Extended Kalman Filter", EKF) wordt hier dan ook gebruikt om deze stoorfactoren te schatten. In een tweede studie worden vervolgens de door de MPC voorgestelde insulinedebieten (zonder extra externe stoorfactoren) kwalitatief vergeleken met de insulinehoeveelheden die in werkelijkheid door de verpleegkundigen werden toegediend. Beide simulatiestudies tonen aan dat de resultaten van de MPC voldoen aan de eisen inzake regelgedrag (het volgen van een referentieglycemie en het onderdrukken van ongekende stoorfactoren) en klinische realiseerbaarheid.

# Hoofdstuk 8: Besluiten en toekomstig onderzoek

In dit proefschrift worden drie objectieven behandeld:

1. een methode om glucosesensoren vanuit statistisch en klinisch perspectief te beoordelen wordt ontworpen: de **GLYCENSIT-procedure**,

2. een methode om insulinetitratieprotocols (algoritmen) die gebruikt worden op afdelingen Intensieve Geneeskunde om de bloedglucose te regelen, te beoordelen wordt ontworpen: de **GPI-methode**,

3. een predictief regelsysteem dat het potentieel heeft om gebruikt te worden om half- of volautomatisch de glycemie van kritiek zieke patiënten te normaliseren wordt ontworpen: het **ICU-MM** dat dienst doet als patiëntmodel in combinatie met een **MPC-regelaar**.

Toekomstig onderzoek situeert zich in vijf verschillende domeinen:

1. **Beoordeling van 'continue' glucosesensoren.** De kwaliteitseisen voor een individuele glucosemeting afkomstig van een 'continue' glucosesensor zijn lager dan die van een individuele intermitterende glucosemeting. Een nieuwe versie van de GLYCENSIT-methode kan ontwikkeld worden specifiek voor de validatie van 'continue' glucosesensoren.

2. **Relatie tussen GPI en klinisch effect.** De relatie tussen een verlaagde GPI en een verlaagde mortaliteit en morbiditeit is te verwachten vanuit klinisch standpunt, maar dient nog aangetoond te worden.

3. **Modellering van glycemie.** Het ontwikkelde ICU-MM kan nog verder verfijnd worden met behulp van experimentele data afkomstig van kritiek zieke konijnen. Het algoritme dat gebruikt wordt om de modelcoëfficiënten aan te passen kan verder geoptimaliseerd worden en de patiëntenclustering kan toegepast worden zodat de initiële coëfficiënten van het model beter bij het dynamisch gedrag van de patiënt aansluiten. Tot slot moet nagegaan worden of de ontwikkelde modellen ook kunnen gebruikt worden om het glycemiepatroon van medisch zieke patiënten (i.p.v. chirurgisch zieke patiënten) te voorspellen.

4. **Regeling van glycemie.** Toestanden en ongekende stoorfactoren kunnen mogelijk efficiënter geschat worden met een toestandsschatter met schuivend tijdsvenster ("Moving Horizon Estimator") als vervanging voor een EKF. De implementatie van de tolerantie-intervallen uit fase 3 van de GLYCENSIT-procedure kan de performantie van het regelsysteem verder verhogen aangezien dan kan rekening gehouden worden met mogelijke afwijkingen van de glucosesensor. Daarenboven is een robuustheidsonderzoek van de regelaar vereist alvorens het regelsysteem klinisch getest kan worden.

5. **Klinische validatie van een glycemieregelsysteem.** Bij de ingebruikname van het regelsysteem in de klinische praktijk dienen een drietal fasen te worden

doorlopen. Ten eerste wordt het regelsysteem getest op kritiek zieke konijnen. Ten tweede wordt nagegaan hoe accuraat de adviserende functie van het half-automatisch regelsysteem werkt bij een groep van kritiek zieke patiënten. Ten derde wordt het volautomatisch systeem getest op een grote groep van kritiek zieke patiënten. De beschikbaarheid van een betrouwbare 'continue' glucosesensor is zeker in deze laatste fase een vereiste.

# Chapter 1

# Introduction

*"The term 'landmark study' is given to Van den Berghe's research [216] because its results have influenced the treatment of hyperglycemia within critical care"*

*– Burns & Grove, 2003 [30] –*

*In this chapter a general introduction on the intensive care unit setting is given together with the clinical, economic, and social context. Next, the problems that form the basis of this study and the corresponding challenges are described leading to the objectives of this dissertation. Finally, the contributions of this work are briefly discussed and a chapter-by-chapter overview is given.*

## 1.1 Motivation

Patients who are *critically ill* are typically admitted to an intensive care unit (ICU). Without the appropriate treatment, either pharmacological or mechanical, these patients die of their (critical) illness. An ICU ward is known for the control and/or the temporary replacement of one or more vital functions of patients. Different reasons for admission to the ICU exist, all potentially life-threatening. This gives the ICU a central role in a hospital. The critical illness of ICU patients necessitates a 24/7-care by experienced medical staff (i.e., a nursing team, medical doctors, technicians, etc.). Bio-medically engineered tools (e.g., artificial kidney, mechanical ventilation equipment, sensors, etc.) are abundantly present in a daily-life ICU environment. Figure 1.1 shows a critically ill patient and some equipment connected to the patient. The concentration of glucose in the blood ('**blood glucose**' or '**glycemia**') is one of the many crucial parameters in the treatment of critically ill patients and is measured with a glucose *meter* (resulting in time-discrete or intermittent measurements) or a glucose *sensor* (resulting in near-continuous measurements). For the scope of this thesis, however, the

term *sensor* is not limited to the strict definition of a 'continuous' glucose sensor in this work but refers also to glucose meters. The work presented in this dissertation is mainly focused on the glucose variable: glucose *measurement*, glycemia *modelling*, and glycemia *control*.

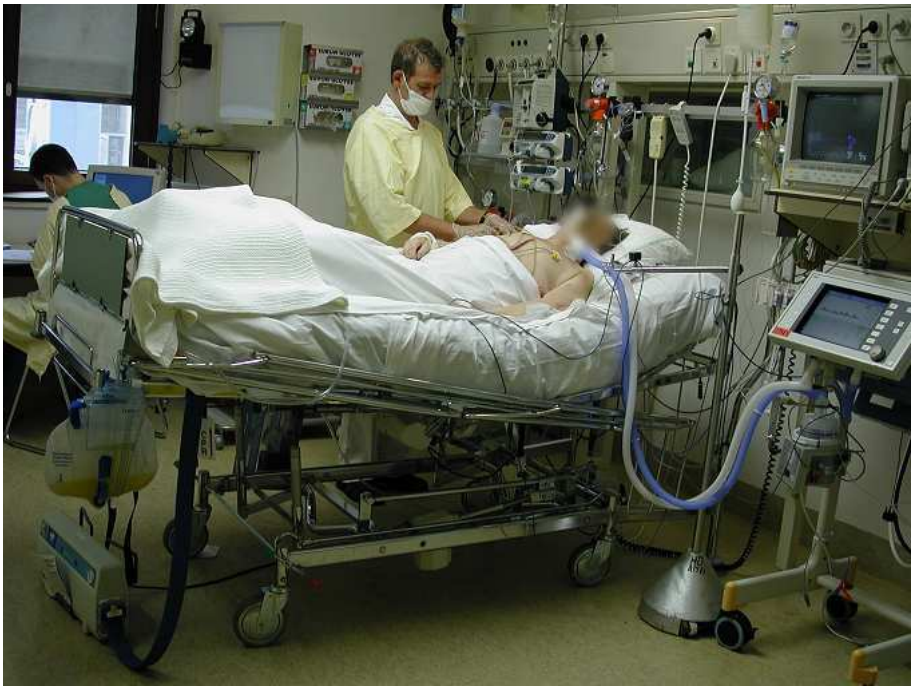

**Figure 1.1:** Critically ill patients are typically admitted to the ICU. The use of medical equipment and the presence of well-trained medical personnel are characteristic of 'intensive' care. This picture is taken from the University Hospital K.U.Leuven (Belgium) with authorization.

In their article [191] entitled "Stress-induced insulin resistance: recent developments", published in *Current Opinion in Clinical Nutrition and Metabolic Care* (2007), the authors indicate the dramatic changes in the treatment of critically ill patients: *Until 5 years ago, when Van den Berghe and colleagues [216] published their large, single-center randomized clinical trial of intensive insulin treatment in the surgical intensive care unit, interest in stress-induced insulin resistance was limited and many textbooks stated that hyperglycemia was a protective response to physiological stress. The Belgian trial, however, convincingly showed that 'diabetes of injury' should be treated aggressively, demonstrating markedly reduced morbidity and mortality in a heterogeneous group of patients requiring mechanical ventilation after undergoing cardiac and other major surgery. This trial inspired a renewed and widespread interest in the risks associated with hyperglycemia in states of acute stress.*

Hyperglycemia (i.e., an increased blood glucose concentration) and insulin resistance (i.e., the resistance of the tissues to insulin) are common in critically ill patients, even those without diabetes mellitus [187, 241, 242]. The development of hyperglycemia during critical illness has long been considered an adaptive and beneficial stress response. Only when glycemia (or blood glucose) was greater than 220 mg/dl, insulin was administered aiming at blood glucose values below this threshold [17]. It was believed that moderate hyperglycemia in critically ill patients could be beneficial for organs like the brain and blood cells. These organs largely rely on glucose for their energy supply but do not require insulin for glucose uptake. An additional reason for favoring moderate hyperglycemia was the fear of occasional hypoglycemia (i.e., a low blood glucose concentration) that could result in brain injury [230].

During the years, however, hyperglycemia and insulin resistance were associated with adverse outcomes in a variety of clinical settings [179, 206]. For example, hyperglycemia predicted a higher risk after stroke and a poor functional recovery in the patients who survived [32]. In patients with myocardial infarction and coronary artery disease, hyperglycemia was associated with an increased risk of death [31]. The real breakthrough in improving intensive care was realized in 2001. A *landmark* prospective, randomized, controlled study on 1548 patients admitted to the **surgical**[1] ICU showed a spectacular reduction in mortality and morbidity in case of tight blood glucose control with insulin [216]. The patients were randomly assigned to receive either *intensive* insulin treatment or *conventional* insulin treatment. In the conventional insulin therapy group a continuous insulin infusion was initiated only when glycemia exceeded 215 mg/dl and then was titrated aiming at blood glucose values between 180 and 200 mg/dl. In the intensive insulin therapy group, however, a continuous insulin infusion was initiated if the blood glucose exceeded 110 mg/dl and was titrated to maintain glycemia between 80 and 110 mg/dl. The insulin dose was adjusted by the clinical nursing staff of the ICU according to whole blood glucose values determined at the bedside and following dosing guidelines which are described in [215]. The mean $\pm$ standard deviation (SD) of blood glucose control in the conventional and the intensive insulin group was $153 \pm 33$ mg/dl and $103 \pm 19$ mg/dl, respectively.

Tight glycemic control (TGC) with insulin resulted in a relative decrease by 43% of intensive care mortality (from 8.0 to 4.6%). This reduction was even higher for patients who required intensive care for more than 5 days: mortality was lowered from 20.2 to 10.6%. Besides saving lives, intensive insulin therapy also prevented several critical illness-associated complications [212, 216]. The occurrence of acute renal failure, critical illness polyneuropathy, transfusion requirements, sepsis[2], and ventilator and intensive care dependency were significantly reduced. Finally, it is important to note that only 13% of the patient population considered in this study were patients with diabetes indicating hyperglycemia appears in critically ill patients independent of the history of diabetes.

[1] An ICU division usually comprises a section for surgically ill patients (surgical ICU) and a section for medically ill patients (medical ICU). This will be clarified in section 1.2.1.

[2] Sepsis is a medical condition, characterized by a whole-body inflammatory state (caused by infection), that frequently appears in patients admitted to the ICU.

Since the previous study was focused on patients admitted to a *surgical* ICU, it remained unclear whether intensive insulin therapy would also improve the prognosis of patients in a **medical** ICU. Patients belonging to this last group are typically more severely ill (compared to patients of the surgical ICU) and have a higher risk of death. Another large (1200 patients), randomized , controlled study showed similar results in a strictly medical ICU patient population [213]. TGC with insulin significantly reduced in-hospital mortality from 52.5 to 43.0% for patients who stayed in the ICU for three or more days. Analogously, morbidity was significantly reduced in the group of patients receiving the intensive insulin therapy. This also led to more positive effects such as reduction in newly acquired kidney injuries, earlier weaning from mechanical ventilation, earlier discharge from the ICU and from the hospital, etc.

The clinical benefits of the intensive insulin therapy compared to the conventional insulin therapy have been largely reproduced by other groups [72, 84, 120]. At present, strict glycemic control is the advised standard of care for the critically ill as declared by the Joint Commission on Accreditation of Healthcare Organization (www.jcaho.org), the Institute for Healthcare Improvement (www.ihi.org), the Volunteer Hospital Organization (www.vha.com), the American Thoracic Society (www.thoracic.org), among others [184]. Recently, a small, randomized, controlled trial has been published showing no benefits of applying the intensive insulin therapy [26]. This study, however, was statistically underpowered to evaluate the reproducibility of the Leuven findings.

## 1.2 Figures and Facts

### 1.2.1 ICU types

A general ICU division consists of two sections: the surgical and the medical ICU. The **surgical** division particularly admits patients with severe cardiac surgery, but also patients with complicated lung or esophageal thoracic surgery[3] and/or respiratory insufficiency, complicated abdominal surgery or peritonitis, complicated vascular surgery, complicated non-cardiac surgery or severe burns, transplantation, neurologic disease, cerebral trauma or complicated brain surgery, etc. Acute illness symptoms are typical of the surgical ICU.

Patients admitted to the **medical** ICU are typically suffering from chronic diseases already before their admission to the ICU. Due to additional physical stress symptoms (e.g., inflammation) patients with a chronic disease (e.g., kidney failure, cancer, diabetes) may need intensive care. The diagnostic categories of patients admitted to the medical ICU can vary from respiratory to cardiovascular, neurologic, renal, metabolic, gastrointestinal, liver, hematologic, oncologic and other sepsis.

The structure of an ICU division can be differently organized for each centre depending on the level of the hospital (university/non-university), the continent (e.g., Europe versus United States), etc. The data used for the purpose of this dissertation originate from the surgical ICU division of the University Hospital (Gasthuisberg) K.U.Leuven.

[3] Esophageal thoracic surgery indicates surgery near the gullet.

### 1.2.2 Clinical context of the intensive insulin therapy

An important limitation of the intensive insulin therapy is the increased workload of the medical staff. There are three different aspects that are responsible for this labour increase. First of all, the **blood sampling frequency** has significantly increased since the introduction of the intensive insulin therapy. Before 2001, arterial blood samples were taken and analysed only four to six times a day to determine the glucose concentration, pH, $pO_2$, $pCO_2$, concentrations of hemoglobin, $HCO_3$, lactate, etc. With the introduction of the intensive insulin therapy, blood is being sampled 8 to 10 times a day. The additional blood samples, however, are only required for the measurement of the blood glucose concentration.

Secondly, the **insulin needs** have drastically increased. During the conventional insulin therapy only 5 patients (on average) out of 16 required insulin whereas this number has increased to 14 with the intensified therapy. Besides the fact that more patients need insulin, the amount of insulin that is administered to these patients has increased as well since the target glycemic range is much lower now. Accordingly, nurses spend more time in preparing and refilling the insulin infusion pumps than before. On average, 30 additional infusion sets per day are required (taking into account at least 3 minutes preparation time per infusion set) for a 16 beds - division.

Thirdly, the medical staff need **more interpretation time** now to determine the insulin rate that should be delivered to the patient. Only titration 'guidelines' are available giving the nurses interpretation freedom in order to define the appropriate insulin needs. The Leuven guidelines are described in detail in Chapter 7 (see 7.3.1). Due to the stricter target blood glucose range (and the corresponding danger for hypoglycemia), the determination of the patient-specific insulin requirements is less straightforward explaining why nurses need more time than before the introduction of the intensive insulin therapy.

In the surgical ICU division of the University Hospital of Leuven, with a total of 56 beds, one nurse is taking care of two patients in general. The increased labour load is an important limitation of the intensive insulin treatment. The introduction of a (semi-)automatic blood glucose control system can potentially reduce the workload without losing the benefit of TGC. Other limitations of the intensive insulin treatment are described below (see 1.3).

### 1.2.3 Economic context of the intensive insulin therapy

Besides the reduction of mortality and morbidity, the use of the intensive insulin therapy is also associated with substantial cost savings compared with the conventional therapy. Hospital costs decrease because of reductions in ICU length of stay (i.e., the number of days that a patient is admitted to the ICU) and several morbid events (e.g., renal failure, sepsis, blood transfusions, and mechanical ventilation dependency) [217]. The cost savings largely compensate for the small additional cost of administering insulin and glucose monitoring.

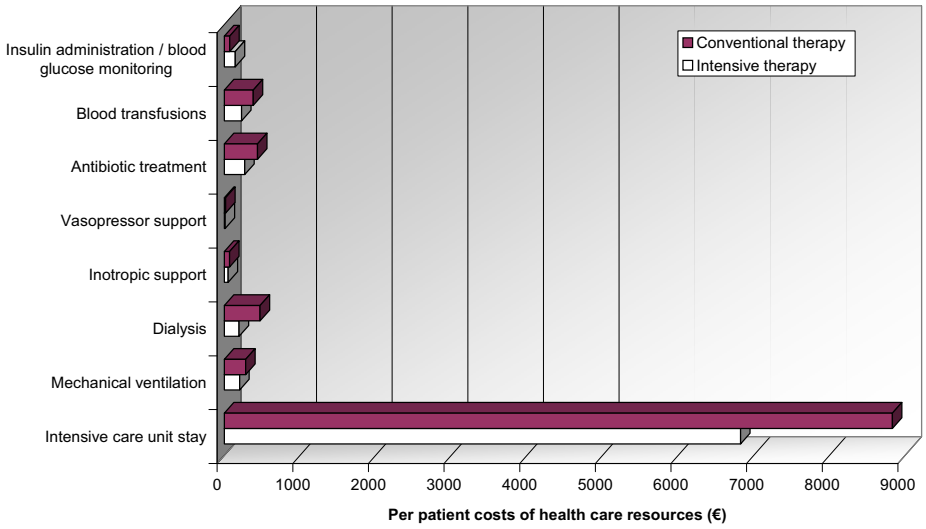


**Figure 1.2:** Per patient costs of health care resources in €. The computed costs and ratios are based on the healthcare resource utilization analysis that was performed on the surgical ICU study (2001) [217].

A healthcare resource utilization analysis [217] was performed based on the data coming from the surgical ICU landmark study [216]. The excess cost of intensive insulin therapy (mainly represented by insulin infusion costs and blood glucose monitoring costs) was found to be € 72 per patient whereas the reduced patient costs of healthcare resources was € 2638 per patient. Figure 1.2 gives an overview of the patient costs of healthcare resources for the intensive and conventional insulin therapy. These costs are split up in different subgroups: intensive care unit stay (i.e., costs related to the number of days in the ICU), duration of mechanical ventilation, days on hemodialysis/hemofiltration, duration of therapy with certain drugs (vasopressors, inotropes, and antiobiotics), blood transfusions, insulin administration, and blood glucose monitoring.

A similar study by Krinsley and Jones [121] confirmed the above mentioned analysis. In a mixed medical-surgical ICU the reduction of costs was found to be 1580 US dollars per patient, which is smaller than the aforementioned cost savings due to the different type of patient group (patients from the medical ICU, who are typically more severely ill compared with surgical ICU patients, are also included here) and the slightly different approach to compute the costs. It is clear, however, that the intensive insulin treatment significantly reduces costs with regard to the conventional insulin treatment. Therefore, the introduction of this more intensified protocol in hospitals world-wide may reduce costs besides the significant lowering of the mortality and morbidity rate.

### 1.2.4 Social context of the intensive insulin therapy

During the last decades, the following social phenomenon has appeared in particularly Western countries. On the one hand, people are ageing but the prevalence of typical 'Western diseases' such as cancer, (type II) diabetes, heart diseases, etc. is increasing as well (mainly due to the Western lifestyle). This increased need for health care is associated with a spectacular growth of the health care *costs*. On the other hand, the number of nurses falls short, which leads to high labour pressure for the existing nursing staff. The introduction of the (manual) intensive insulin therapy in the ICU also increased the workload of the medical staff as already mentioned above. Preservation of the benefits of the intensive insulin therapy (reduction of mortality and morbidity) while reducing the workload of the nursing teams can potentially lower the barrier of implementing the TGC strategy in hospitals world-wide. Therefore, the introduction of a (semi-)automatic system to normalize blood glucose (between 80-110 mg/dl) can potentially fill this gap. In general, the application of engineering techniques in biomedicine plays already a major role in hospitals nowadays and it is expected this role will even increase in the near future. The design of a control system to normalize the blood glucose in critically ill patients is a clear example of the symbiosis between (biomedical) engineering and medicine.

## 1.3 Problems and Challenges

The introduction of the intensive insulin protocol saves lives and reduces morbidity in critically ill patients who are admitted to the surgical and the medical ICU [213, 216]. Nevertheless, a survey study in England and the Netherlands revealed that only approximately 25% of the ICU wards of the hospitals under study effectively set the normoglycemic target range at 80-110 mg/dl [139, 185]. Some aspects may hamper the general application of TGC explaining why TGC is far from standard clinical practice at present:

1. Normalization of glycemia requires a rigorous administration of insulin by means of a very time demanding empirical protocol (which is a set of written guidelines, see also Chapter 7, 7.3.1 [215]) in which expertise from nurses and doctors is a crucial element: "TGC is something you do by heart, not from a sheet of paper" as quoted by some nurses in [58]. The protocol requires blood glucose levels to be measured every four hours (or more frequently, especially in the initial phase or in case of complications). The flow of the continuous insulin infusion is then adjusted based on this schedule which only comprises *recommendations* giving the medical staff the ability to appropriately adapt the proposed insulin rate depending on patient-specific features. Accordingly, this empirical protocol is **no simple 'if-then' protocol** and requires lots of **clinical experience**.

2. Nurses get a certain degree of freedom how to control the blood glucose of the critically ill patients. Since the determination of the most optimal insulin flow is non-trivial, the **workload of the medical staff increases** when intensively treating the patients with insulin. This fact is also described above (see 1.2.2).

3. Next, the rather **'subjective' nurse-driven approach** of the insulin control may lead to **varying levels of TGC** (depending on which nurse is treating which patient). Interviews with nurses (working with the Leuven guidelines [215]) confirmed that no fixed control protocol exists in clinical practice. For example, some nurses take into consideration medication disturbance factors whereas other nurses do not. An 'objective' and approved computerized protocol (that is independent of the experience/skills of the nurse) potentially facilitates the introduction of the intensive insulin treatment word-wide.

4. Furthermore, the threat of administering too much insulin to the patient (leading to **hypoglycemia**) is a barrier to intensive insulin therapy and may lead to a rather 'conservative' (conventional) insulin treatment [144, 183, 211]. The diagnosis of hypoglycemic events in the ICU is more complicated than with patients with diabetes. First of all, sedation can mask (the specific hypoglycemic) symptoms of neuroglycopenia[4]. Secondly, the counter-regulatory responses to hypoglycemic events may be impaired in critically ill patients (see also Chapter 2, 2.1) [210].

5. Finally, these aspects support the need for frequent monitoring of glucose. To safely target normoglycemia in ICU patients, intensivists and ICU nurses anxiously await the availability of **reliable near-continuous glucose sensors**, which are undoubtedly under development [38, 94, 99, 109, 162, 194, 209, 211]. As these sensor devices may export glucose values every second or every minute, the fear of provoking hypoglycemic episodes due to delivering too much insulin would significantly diminish. It must be stressed, however, that no generally accepted procedure to assess the reliability of glucose sensors currently exists.

The general challenges that form the fundamentals of this thesis are twofold:

1. The first challenge considers the **evaluation** of the *reliability of glucose sensors* on the one hand and the *performance of glycemia control systems* on the other hand. It is a first challenge to set up a statistical and adequate assessment procedure for both glucose sensor devices and insulin titration algorithms such that these new assessment methods may be *supplemental to* or *an alternative for* currently existing methods.

2. The second challenge focuses on the development of a **(semi-)automatic glycemia control system**. At present, blood glucose is controlled by the nurses who typically follow the guidelines of a predefined insulin protocol [215].

[4] Neuroglycopenia is a term used to indicate the shortage of glucose in the neurons (cells).

The introduction of a (semi-)automatic glycemia control system to the ICU has the potential to (further) reduce mortality and morbidity. Particularly in hospitals where currently no (manual) intensive insulin protocol is applied (due to staff shortage), the design of a (semi-)automatic glycemia control system can dramatically alter the treatment and outcomes of critically ill patients and can even lower the health care costs (see 1.2.3). Another advantage of a computerized control system is the more 'objective' control approach (compared with the 'subjective' nurse-driven approach) possibly leading to even stricter blood glucose control (as deviations from normoglycemia are still present with the *manual* intensive insulin therapy). Accordingly, a computerized control system can also reduce the incidence of hypoglycemia which can further diminish the fear of applying TGC. Finally, the use of a (semi-)automatic control system does not require any TGC experience of the nurses and, particularly when reliable near-continuous glucose sensors are available, can reduce the labour load of the medical staff.

## 1.4 Objectives

In this work three main objectives are set. First of all, an **assessment procedure for glucose sensor devices** is developed. The quality of blood glucose control depends on the reliability (accuracy) of the observations. Measurement *errors*, however, may have a serious influence on the proposed insulin flow adaptations and can be responsible for administering too low or too high insulin doses. For example, an observed glucose measurement equal to 140 mg/dl, whereas the real blood glucose value is only 100 mg/dl, may lead to an increase of the insulin rate (target glycemic range is 80-110 mg/dl) and may further lead to hypoglycemia. In case the real blood glucose would have been known (by using a *gold standard* glucose sensor device), the insulin rate would not have been increased and hypoglycemic episodes could have been prevented.

Although the glucose monitoring industry has exploded during the last decade, it is surprising to note that no generally accepted validation procedure for glucose sensors exist. The techniques that are currently used for evaluating the performance of glucose sensors show statistical weaknesses or are difficult to interpret from a clinical point of view. Companies or research groups use different methods nowadays for reporting sensor accuracy such that a comparison between sensors becomes non-trivial. The recent development of *near-continuous* glucose sensors, which export a glucose value every second or minute, has the potential to significantly improve the TGC performance in patients with diabetes and critically ill patients. Compared with *discrete-time* blood glucose meters (that are used for measuring glycemia only every few hours), these near-continuous sensor devices return a 'near-continuous' glucose signal giving the opportunity to control glycemia more strictly within the normoglycemic target range. The development of these near-continuous sensors has also recalled the need for the design of a generally accepted tool for appropriately evaluating the performance of glucose sensor devices.

A second main objective is the development of an **evaluation tool for insulin titration algorithms** that are used to normalize blood glucose in the ICU. Since (semi-)automatic glycemia control systems can potentially advise or even replace the nurse in determining the optimal insulin flow, these new algorithms must be appropriately evaluated and compared with the currently standard nurse-driven protocol (guidelines) [215]. Therefore, the overall level of glycemic control must be adequately determined when comparing different (computerized) insulin protocols/algorithms. Classical assessment tools (e.g., computation of average blood glucose) and the study design (e.g., the number of days that the patient is admitted to the ICU, the type of patients, the average blood glucose sampling frequency, etc.) may mislead assessments. Therefore, the second objective in this dissertation is the design of an evaluation tool for insulin titration algorithms and the detection of parameters that can influence an evaluation.

A last main objective in this work is the design of a **(semi-)automatic control system for normalizing blood glucose in ICU patients**. The advantages of (semi-)automated glycemia control have already been discussed above. The general concept of an ICU (semi-)automated control system is summarized in Figure 1.3. Undiluted arterial blood glucose is measured every four hours or more frequently in case of complications by means of a *discrete-time* blood glucose sensor. The availability of a clinically reliable sensor that exports a *near-continuous* glucose signal would allow us to deliver more information as input to the control system, but we currently await these sensor devices. Besides glycemia also other variables (also called *disturbance factors*) are observed as inputs to the control system:

- static upon admission demographics, such as the medical history (e.g., history of diabetes), the Body Mass Index (BMI)[5], and the reason of admission to the ICU,
- dynamic input variables, such as the body temperature and the administered flow of calories/drugs.

The glycemia control system itself comprises a (patient) model and a (predictive) controller. The *model* is in fact a mathematical representation of the glucoregulatory system of a critically ill patient. The use of a model allows to simulate and to predict the blood glucose profile for the next hours. A typical time horizon in this setting is four hours. The *controller* considers the model as the (virtual) patient and computes the most optimal insulin flow that should be delivered to that (patient) model. In this optimization process the controller takes into account the observed blood glucose profile (i.e., the glycemia signal of the last hours), some important (known) dynamic input variables (e.g., input flows present within the predefined time horizon), and the constitution of the patient (e.g., static upon admission demographics, estimated model). It is clear that the model has a central role in this control system. Therefore, the accuracy level of the blood glucose predictions by using the estimated model directly influences the performance of the controller and the full control system in general.

[5] The Body Mass Index is the weight in kilograms divided by the square of the height in meters.

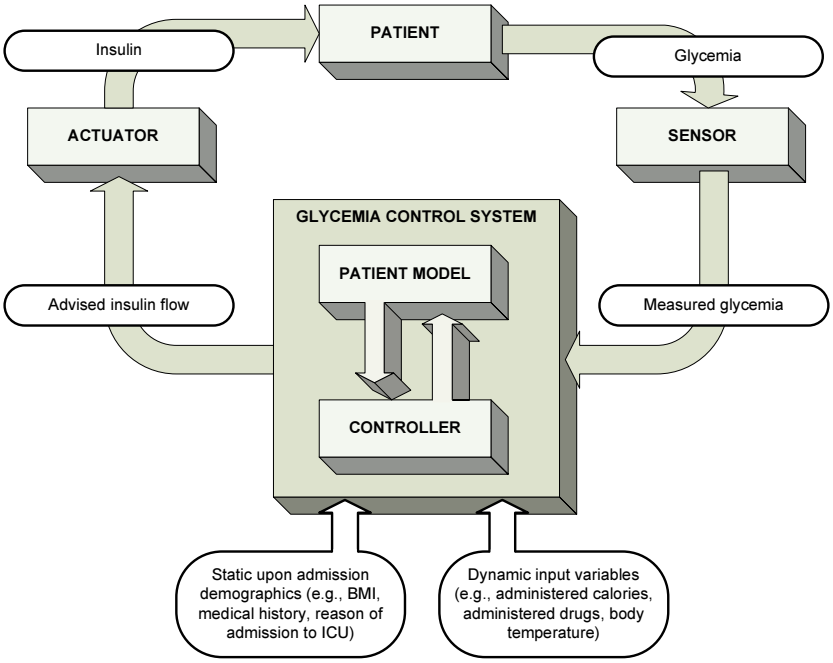


**Figure 1.3:** Presentation of the (semi-)automated control system. Undiluted arterial blood glucose is measured every four hours or more frequently in case of complications. Glycemia values and other (static and/or dynamic) input variables (i.e., the disturbance factors) are denoted as inputs to the control system. At each time step (e.g., every hour), the latter determines the insulin rate that is required to achieve normoglycemia. After confirmation by a nurse, this advised insulin flow is delivered to the patient by means of a pump (actuator).

In a first implementation step, this control system only works semi-automatically. In other words, each insulin flow adaptation that is proposed by the computerized control system must be confirmed by a member of the medical staff (mostly a nurse). Only after approval by the nurse, this insulin flow is delivered to the patient by means of an actuator (i.e., the insulin pump). In the following implementation step, a fully-automated control system is tested. In such a system confirmation by a clinical staff member is not necessary any more. Validation of an *automatic* glycemia control system clears the way for introducing the TGC principle for ICU patients in all hospitals world-wide.

## 1.5 Contributions of this work

### 1.5.1 General assessment of glucose sensors

The first contribution of this work is the development of a statistical assessment tool for testing the significant difference of paired glucose measurements: the GLYCENSIT-procedure. Here, blood glucose is concomitantly measured with a *reference* blood glucose sensor and a *test* glucose sensor. It is our aim to evaluate the performance of the test device based on the measurements that are obtained from the reference (or 'gold standard') sensor.

The developed GLYCENSIT-procedure comprises three phases:

1. **Testing possible persistently deviating measurement behaviour as a function of the glycemic range.** Measurement behaviour that is persistent in the full glycemic range indicates that the measurement error can be assumed to be independent of the glycemic range: hypoglycemic, normoglycemic, or hyperglycemic. Persistent measurement behaviour is preferable from a clinical point of view in comparison with non-persistent behaviour as it allows the interchange between sensors with only one conversion factor. Therefore, a test sensor device with persistent measurement deviations can be implemented in clinical practice more easily than a test sensor whose measurement behaviour is strongly dependent on the glycemic range. The statistical test that is used in this first phase evaluates the persistency of all observed measurement errors.

2. **Testing the number of measurement errors with respect to a standard criterion for binary assessment of glucose sensors.** The statistical test used in this phase states whether the measurement errors do not violate the International Organisation for Standardization (ISO) - criterion too often [75]. This criterion was developed in the past to assess the accuracy of blood glucose meters. The tolerance level is the acceptable rate of errors against this criterion and is determined by the user. In other words, the test in this second phase explores whether the number of errors against the ISO-criterion is tolerable or not.

3. **Computing the tolerance intervals that indicate possible test sensor deviations for new observations.** In the last phase of the GLYCENSIT-procedure some tolerance intervals are calculated. These intervals inform the user about *future* measurement errors. Instead of only retrospectively analyzing the data, this phase informs the user about possible measurement errors corresponding to *new* test sensor readings under the statistical (main) assumption that the new data set is equally distributed as the past data used in the analysis. Based on these intervals, the user gets an idea about how much the test sensor value can deviate from the real blood glucose value that would have been obtained with the reference device. It is the size of these intervals, together with the computed probability that the reference value effectively lies in these intervals, that can help the clinician in making an appropriate decision concerning the validity of the (test) sensor device under study.

The method can be tuned according to the clinician's preferences regarding significance level, tolerance level, and glycemic range cut-off values. The proposed GLYCENSIT-procedure is also implemented as a web-based assessment tool, freely available at http://www.esat.kuleuven.be/GLYCENSIT. The design of the GLYCENSIT-procedure and its application to real-life ICU examples are described in Chapter 3.

*Publications related to this topic: [225, 232].*

### 1.5.2 General assessment of glycemia control systems

The second main contribution that is presented in this dissertation is the new approach for appropriately assessing the adequacy of insulin titration algorithms. This new approach, the glycemic penalty index (GPI), can be used when comparing the *overall* glycemic control behaviour in groups of ICU patients (e.g., the level of glucose control, realized by a new computerized control system, in patient group 1 needs to be compared with the level of glucose control, performed by nurses, in patient group 2).

The development of GPI is based on a penalty function, which is formulated from clinical (ICU) expertise, that assigns a 'penalty' to each observed blood glucose value. The magnitude of this penalty depends on the deviation of the measured blood glucose value from the normoglycemic range (80-110 mg/dl). GPI can be computed for each patient as the average of all these penalties. The designed formula returns a number between 0 and 100 with an 'ideal' level of 0 (indicating that all measured blood glucose values fall within the normoglycemic target range) and a 'clinically acceptable' level of 23.

Two parameters are found to have a significant influence on GPI: the *average blood glucose sampling frequency* and the *duration of algorithm application*. The first parameter is the average number of blood glucose readings (per time unit) that are available and used by the insulin titration algorithm under study. The duration of effectively applying the blood glucose algorithm to the patient aiming at normoglycemia is the second parameter. A high blood glucose sampling frequency and a long algorithm application duration improve the level of TGC (expressed in a lower GPI). Accordingly, these two parameters should be similar among patient groups when assessing or comparing insulin titration algorithms. This new evaluation tool is further described in Chapter 4.

*Publications related to this topic: [218].*

### 1.5.3 Design of a glycemia control system

The third contribution of this work is the design of a control system that can be used to regulate the blood glucose in the critically ill. Both *black-box* and *grey-box* modelling techniques are considered for the design of a model that can predict glycemia. The first modelling type only starts from the observed data to generate a (black-box) structure

for the model whereas the grey-box modelling type is founded on physiological knowledge in the form of a known model structure. Particularly the grey-box modelling method can potentially be considered in a clinical real-life glycemia control system. The grey-box modelling structure that is specifically developed to be used in a glycemia control system in the ICU, is based on the known 'minimal' model structure developed by Bergman and colleagues [14]. Therefore, this new model structure is labeled as the ICU 'minimal' model (ICU-MM) and is presented in Chapter 6. The black-box modelling strategy is studied in Chapter 5.

*Publications related to this topic: [220–222, 226, 227].*

The insulin resistance, which is a crucial factor in the glucoregulatory system of critically ill patients, can vary as a function of time. When entering the ICU, patients typically show a high insulin resistance (or a low sensitivity for insulin). Typically, this resistance decreases as the patient recovers but can suddenly increase again depending on some conditions (e.g., additional inflammation, administration of certain drugs, etc.). For this reason, it is important that the initially estimated ICU-MM is frequently re-estimated. In the 'optimal' re-estimation process the ICU-MM is re-estimated every hour based on the data of the last five hours. Accordingly, changing glucose dynamics of the patient can be incorporated into the glycemia control system by regularly updating the model. The re-estimation strategy is described in detail in Chapter 6.

*Publications related to this topic: [219, 223].*

Finally, a critical review of recently presented blood glucose control algorithms is given and a Model based Predictive Controller (MPC) is developed. An important feature of this last type of controller is the possibility to take into consideration future (known) disturbance factors (e.g., nutritional load) when optimizing the insulin dosage profile. Pure *feedback* controllers only consider the observed output (glycemia) values, and are therefore less robust and less performant compared to *predictive* controllers. A first MPC designed for glycemia control in the ICU and based on the developed ICU-MM (Chapter 6) is presented in Chapter 7.

*Publications related to this topic: [223, 224].*

### 1.5.4 Patent in process

In 2003 our research group applied for a patent to protect the intellectual property of the concept of developing a control system to normalize glycemia in critically ill patients in Europe and the United States. These patents (WO03/080157 for Europe and US2005/0171503 for the United States), entitled *Automatic infusion system based on an adaptive patient model* and written by G. Van Den Berghe, D. Berckmans, J.-M. Aerts, B. De Moor, B. Pluymers, and F. De Smet, are currently still pending. In this pending phase the European and American Examiner are reviewing the patent with regard to novelty and originality.

## 1.6 Chapter-by-chapter overview

This thesis is organized in three parts as shown in Figure 1.4. Part I is related to the clinical setting of this work. A simplified concept of the glucoregulatory system and the available data sets are presented. Part II focuses on the assessment procedures that are developed to evaluate glucose sensor devices and blood glucose control systems (or insulin titration algorithms). Finally, the modelling of the glucoregulatory system and its corresponding control are discussed in Part III.

Here, a more detailed overview of all the chapters of this dissertation is described:

**Chapter 2: Intensive Care: Patients and Data.** This chapter concerns the general clinical setting of this work. A comparison is made between the glucoregulatory systems of healthy persons, patients with diabetes, and critically ill patients, which were *simplified* for the purpose of this thesis. Next, the parameters that may have a significant influence on the blood glucose are presented. Furthermore, the data sets that are made available during this work are discussed. The features of each data set are described and, finally, the data of some patients are shown.

**Chapter 3: General Assessment of Glucose Sensors.** This chapter starts with an introduction to the different techniques used for glucose monitoring. Next, currently existing techniques to assess glucose sensor devices are briefly described and the new method for evaluating glucose sensor devices is extensively explained: the GLYCENSIT-procedure. Next, three hypothetical (theoretical) examples and one real-life clinical example demonstrate the use of the GLYCENSIT-analysis. Further, two *test* blood glucose sensor devices are evaluated against a *reference* blood glucose meter by means of the existing standard evaluation methods and the new GLYCENSIT-procedure. Finally, the developed GLYCENSIT-website, where the user can upload new sets of data, is briefly introduced.

*Publications related to this chapter: [225, 232].*

**Chapter 4: General Assessment of Glycemia Control Systems.** In this chapter the techniques that are used nowadays to assess insulin titration algorithms are discussed. Next, the new method (GPI) for evaluating or comparing insulin titration algorithms is introduced and compared with most known existing techniques. Further, the influence of four selected parameters (the *average blood glucose sampling frequency*, the *duration of algorithm application*, the *severity of disease*, and the *type of illness*) on the performance of an insulin titration algorithm is determined by multiple regression analysis.

*Publications related to this chapter: [218].*

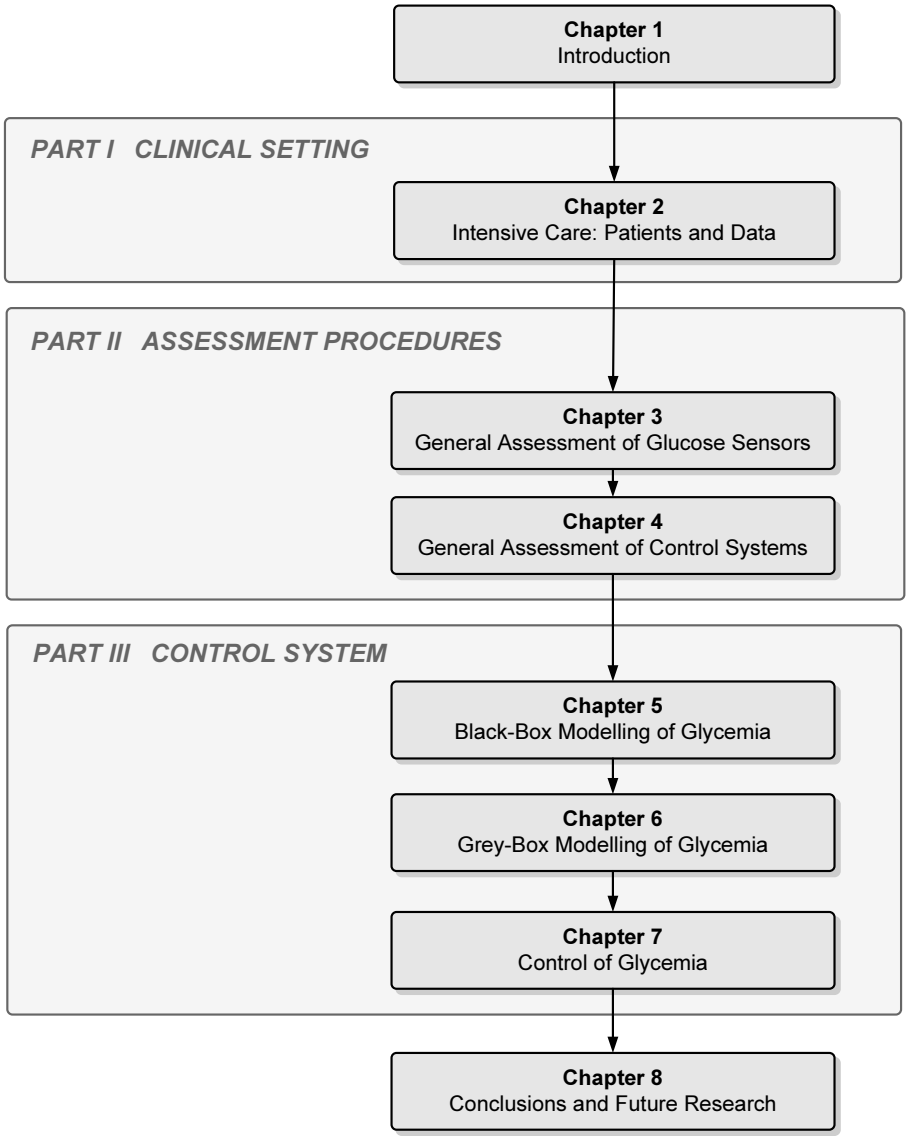


**Figure 1.4:** Thesis outline. Part I of this thesis introduces some medical background that is relevant for this study and describes the data at hand. Part II presents the assessment procedures that are developed to evaluate glucose sensor devices and blood glucose control systems. Part III discusses the design of the models that describe the glucoregulatory system of the critically ill and the developed controller.

**Chapter 5: Black-Box Modelling of Glycemia.** A black-box modelling approach for describing the blood glucose dynamics of critically ill patients is applied in this chapter. Both an initial and an adaptive input-output model are designed and optimized. The results are satisfactory both in terms of forecasting ability and in the clinical interpretation of the estimated coefficients.

*Publications related to this chapter: [220–222].*

**Chapter 6: Grey-Box Modelling of Glycemia.** This chapter presents a grey-box modelling approach to depict the dynamics of the blood glucose of the critically ill. A model structure (ICU-MM), containing typical properties of the ICU, and an adaptive modelling strategy with model re-estimations every hour or every four hours are developed and optimized. The 'optimal' re-estimation strategy gives satisfactory forecasting results explaining its potential use in a predictive control system for critically ill patients admitted to the (surgical) ICU.

*Publications related to this chapter: [219, 223, 226].*

**Chapter 7: Control of Glycemia.** In this chapter a critical overview of the different control strategies known in the area of diabetes and the ICU is given. Next, the design of a controller, that determines the most optimal insulin dose to be delivered to the specific patient aiming at normoglycemia and that takes into account future known disturbance factors, is presented. This 'predictive' controller makes use of the ICU-MM structure developed in Chapter 6. Finally, blood glucose simulations obtained in a (virtual) 'closed-loop' system are evaluated with GPI (that is presented in Chapter 4).

*Publications related to this chapter: [223, 224].*

In Figure 1.5 a simplified concept of the (semi-)automated control system is presented. The relation of the respective chapters of this dissertation with the glycemia control system structure is also illustrated in this figure.

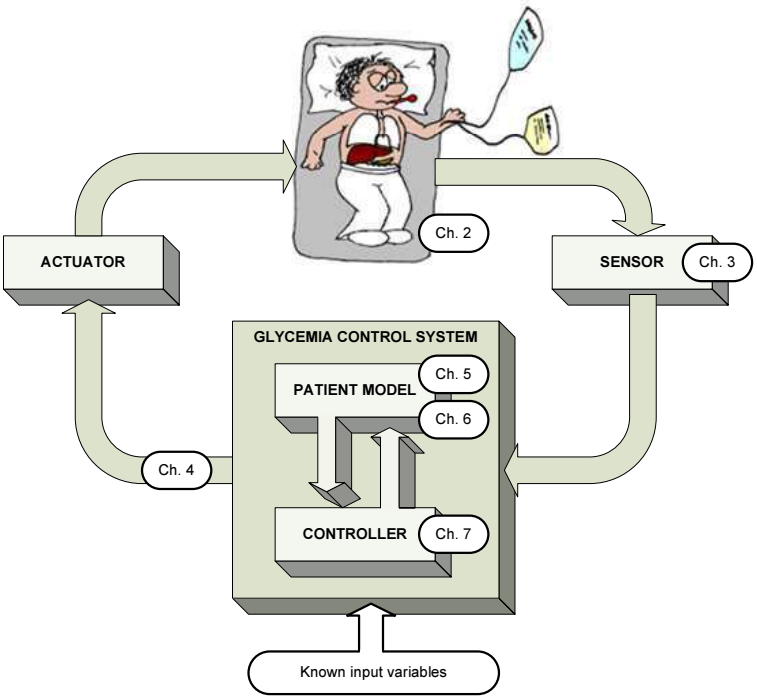


**Figure 1.5:** Simplified presentation of the (semi-)automated control system. Chapter 2 considers the clinical setting and the available ICU data sets. This is followed by Chapters 3 and 4 in which a new assessment procedure for glucose sensors and glycemia control systems, respectively, is presented. Next, a black-box and a grey-box model for predicting the blood glucose profile are discussed in Chapters 5 and 6, respectively. Finally, a first design of a predictive controller is presented in Chapter 7.

# Part I

# CLINICAL SETTING

# Chapter 2

# Intensive Care: Patients and Data

*An introduction to the clinical setting on which this dissertation is founded is given in this chapter. The simplified concept of the glucoregulatory system of healthy persons, patients with diabetes, and critically ill patients is discussed. Next, some parameters that have an important influence on blood glucose are highlighted. Finally, the data that have been made available as part of this work are extensively discussed and shown with examples. In summary, this chapter focuses on the patient as is also visualized in Figure 2.1.*

## 2.1 Glucoregulatory system

The glucoregulatory system is the set of internal functions that regulate the glucose concentration in the blood: glucose homeostasis. In this section both the (simplified) glucoregulatory system of a healthy person and a patient with diabetes are presented.

### 2.1.1 Healthy person

One of the most complex behaviours in a human body is the endocrine (i.e., hormone-producing) system and the blood glucose dynamics. Figure 2.2 gives a simplified model of the glucoregulatory system of a healthy person. The endocrine cells of the pancreas are grouped in the islets of Langerhans. The hormones that are produced in these islets of Langerhans are secreted directly into the blood flow by different types of cells. Most important cells are the *beta* cells and the *alpha* cells. The first type of cells is mainly responsible for the production of **insulin** (which has a lowering effect on glycemia). The second type of cells is particulary aimed to release **glucagon** (i.e., an hormone that raises the blood glucose). The islets of Langerhans (further labeled as the *pancreas* for reasons of simplicity), however, consist of an internal feedback system to avoid that both insulin and glucagon hormones would be released simultaneously. The

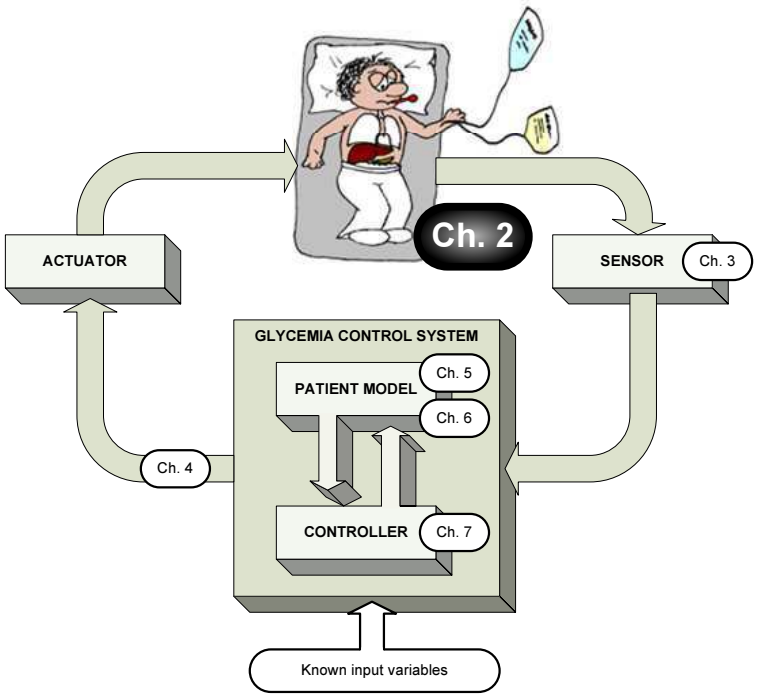


**Figure 2.1:** Simplified presentation of the (semi-)automated control system. The 'patient' is the main focus of Chapter 2. The clinical setting and the available ICU data sets are extensively discussed.

delivery of insulin activates the beta cells and inhibits the alpha cells. Analogously, the release of glucagon activates the alpha cells.

The insulin hormone has a great diversity of functions. For the purpose of this thesis, the working of insulin is oversimplified as only its function regarding circulating glucose in blood is mentioned here. Insulin is released by the pancreas when blood glucose levels are high. For example, these *hyperglycemic* events can appear after a meal or after intake of some medication. The insulin release activates two main events. First of all, the release of glucose in the liver **(gluconeogenesis) is inhibited**. The suppression of the formation of additional glucose further leads to the conversion of glucose to glycogen. Therefore, glycogen functions as storage for glucose, or in other words, as energy store. The second main event that is advanced by releasing insulin is the **stimulated glucose uptake by tissue cells**. All tissue cells (e.g., muscle) require energy to function appropriately. This energy originates from the calories (glucose) that are taken during every meal. However, without insulin these glucose molecules are not able to enter the tissue cells. The function of insulin can be compared to a *key* that can be used by the glucose molecules to open the *gate* of the tissue cells. The availability of insulin (*key*) allows to open the *gates* such that the glucose molecules can be taken up by the tissue cells leading to a decrease of the glucose concentration in

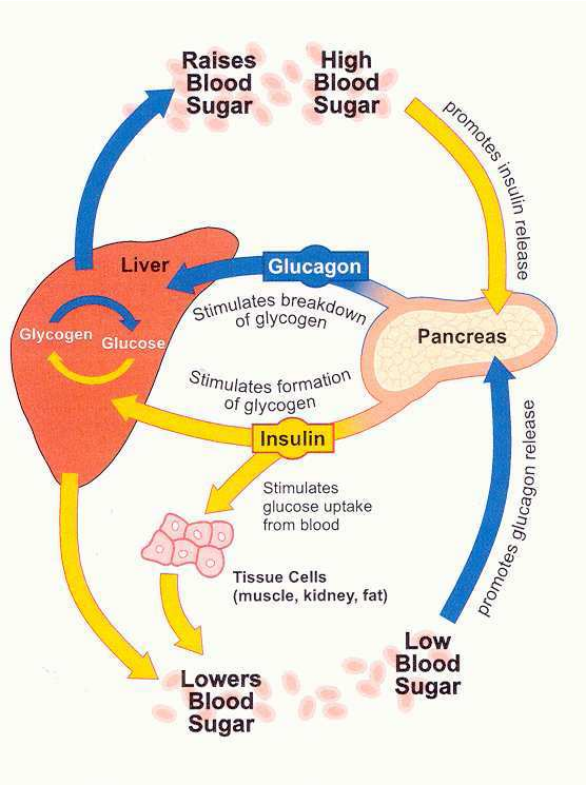


**Figure 2.2:** Glucoregulatory system of a healthy person. Hyperglyemic events (light gray) are responded by the pancreas by releasing insulin. This insulin stimulates the glucose uptake from the blood to some tissue cells. Furthermore, insulin also activates the formation of glycogen. Both events are responsible for glycemia normalization. Alternatively, hypoglycemic events (dark grey) give a release of glucagon in the pancreas. Glucagon further promotes the conversion of glycogen to glucose in the liver again leading to normal blood glucose values. This figure is taken from [8] with authorization of the author.

the blood (glycemia).

Alternatively, the blood glucose concentration can be too low (e.g., due to severe exercise without sufficient energy supply, fasting, etc.) leading to *hypoglycemia*. Here, the pancreas activates the release of the glucagon hormone. The function of this hormone is the opposite to that of insulin. Indeed, glucagon causes the liver to convert stored glycogen into glucose ('hepatic glucose production') and to release it into the bloodstream. The energy store in the liver is depleted. Accordingly, blood glucose levels can raise towards normoglycemia.

From the above it is clear that two manipulated *inputs* (insulin and glucagon) can be

used to 'control' one *output* (blood glucose). The focus of glycemia control strategies, however, has been on the action of insulin to reduce glycemia. This control aspect will further be discussed in Chapter 7. Ultimately, it is important to note that blood glucose is tightly regulated within the narrow range of 60 to 140 mg/dl in normal individuals. Figure 2.3 summarizes the working of the glucoregulatory system (at cell level) in a healthy person.

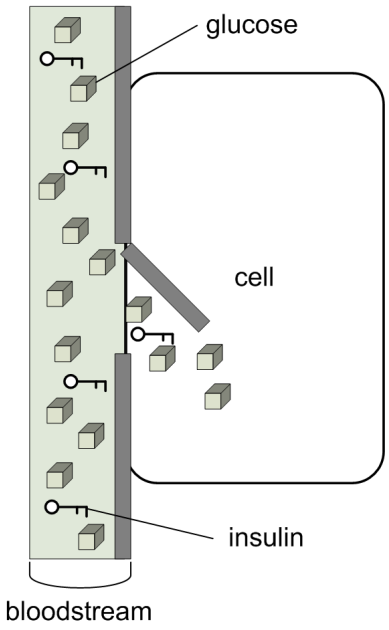


**Figure 2.3:** Simplified overview of the glucoregulatory system (at cell level) of a healthy person. Food intake is transformed to glucose molecules in the digestive system. Next, the available insulin (represented by *keys*) is used to open the *gates* of the tissue cells. As the gates are opened, glucose is able to enter the cells where the glucose is converted to energy. The blood glucose concentration remains 'normal'.

### 2.1.2 Diabetes

According to the World Health Organisation, diabetes mellitus is "a metabolic disorder of multiple aetiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction, and failure of various organs" [155].

There are mainly two types of diabetes: type I and type II. Classic type I diabetes is thought to result from an auto-immunologic destruction of the insulin-producing beta cells [205]. Since the pancreas is no longer able to produce insulin (i.e., the absence of *endogenous* insulin or the absolute insulin deficiency), these patients

require insulin treatment (*exogenous* insulin). Type II diabetes, has a completely different, multifactorial pathophysiology [205]. On the one hand, typical lifestyle factors (obesity, dyslipidemia, hypertension, etc.) and, on the other hand, genetic elements may both lead to cardiovascular diseases, glucose intolerance (i.e., a physical state which is associated with early diabetic symptoms), and insulin resistance. Insulin resistance, as already briefly elucidated above, is present when the biological effects of insulin are less than expected for both glucose disposal in skeletal muscle and suppression of endogenous glucose production in the liver (see also Figure 2.2) [60]. It is the combination of insulin resistance and the insufficient insulin production (due to ageing) that causes type II diabetes. In Figure 2.4 a simplified concept of the glucoregulatory system (at cell level) of a patient with (type I) diabetes is summarized.

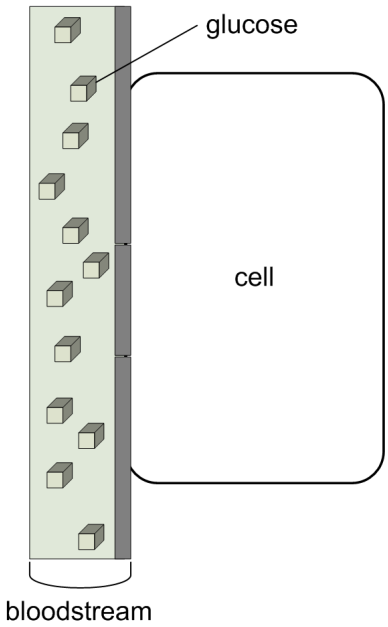


**Figure 2.4:** Simplified overview of the glucoregulatory system (at cell level) of an *untreated* patient with (type I) diabetes. Food intake is again transformed to glucose in the digestive system. Endogenous insulin (*keys*), however, is not available such that the glucose molecules are not able to enter the cells (*gates* are closed). As too few energy is available in the cells, fat is burnt. The resulted energy, however, has a lower quality and the glucose molecules remain in the blood (no conversion to energy) leading to 'hyperglycemia'.

It has been extensively discussed that sustained glycemia control in patients with diabetes prevents the cellular damage that can be inflicted by the presence of hyperglycemia [50]. Therefore, patients with type I diabetes are instructed how to apply intensified insulin therapy (i.e., the administration of insulin) in an optimal

manner. Type II diabetes can be treated by restricting the uptake of calories (diet), favoring physical exercise (increasing the glucose uptake from the blood to the tissue cells, see Figure 2.2), and/or administering oral hypoglycemic agents or even insulin. Although most patients with diabetes realize strict glycemia control is important to avoid long-term complications, the fear of evoking hypoglycemic episodes frequently leads to less strict blood glucose control. However, the TGC-benefit clearly outweighs the risk of hypoglycemia.

Until recently, type I diabetes was particularly associated with children and young adolescents whereas type II diabetes was the diabetes type for elderly patients. The last years, however, type II diabetes is being increasingly diagnosed in obese young and adolescent people [189]. Especially the Western nations are confronted with this new *epidemic*. The typical type I / type II ratio is approximately 10% / 90% of the diagnosed diabetes population. In Belgium, approximately 5% of the full population has a history of diabetes. The real number, however, is supposed to be twice as large (10% of the Belgian population!), but half of them are not yet aware of the disease. In the United States, the number of patients with diabetes keeps on increasing as well: 21 millions of people (7% of the overall population) are diagnosed with diabetes and even 54 millions of people (18%) show symptoms of pre-diabetes.

## 2.2 Blood glucose control in intensive care

Blood glucose levels usually rise during critical illness as already mentioned above. Again, we want to stress this glycemia increase is independent of any history of diabetes. The critical illness disorders the glucose homeostasis of the majority of the patients admitted to the ICU. This phenomenon has been labeled as *stress diabetes* or *diabetes of injury*. Here, the reasons how *diabetes of injury* arises and how the physiological regulation of blood glucose saves lives in the ICU are explained.

### 2.2.1 The origin of 'diabetes of injury'

The complex mechanism that causes elevated blood glucose levels in critically ill patients is not completely unraveled yet. It is known that any type of acute illness or injury leads to a high (physical) stress level that is associated with the development of insulin resistance, glucose intolerance, and hyperglycemia. Although blood glucose levels are high and large amounts of (endogenous) insulin are released (in case of non-diabetic critically ill patients), **hepatic glucose production is up-regulated**. This production of additional glucose in the liver is caused by the elevated levels of several hormones (e.g., cytokines, growth hormone, glucagons, cortisol) and catecholamines [228]. Catecholamines are also released by the adrenal glands in situations of 'stress' such as psychological stress, low blood glucose levels, but also physical stress (e.g., acute injury). Finally, they are also often administered as vasoactive drugs in the ICU [228]. All hormones mentioned above are labeled as *counter-regulatory* hormones because they 'counter' the usual response to insulin and thereby increase blood glucose [198].

Secondly, these counter-regulatory hormones induce **resistance to insulin** further leading to elevated blood glucose levels [198]. Consequently, more glucose becomes available for insulin-independent tissues (e.g., brain and blood cells).

Another reason that favors increased glycemia levels is the **lowered exercise-stimulated glucose uptake** in muscles obviously explained by the immobilization of the critically ill patient [176].

Finally, glucose uptake in the heart, the skeletal muscles, and the adipose tissue is also compromised due to **impaired insulin-stimulated glucose uptake by the glucose transporter 4 (GLUT-4)** [186, 228, 230]. In general, glucose transporters are a family of membrane proteins and play a specific role in the glucose metabolism depending on the pattern of tissue expression, the substrate specificity, and the transport kinetics [200].

Although the exact mechanism that is responsible for the elevation of the blood glucose in critically ill patients may be much more complex, the four reasons mentioned above give a good approximation. Figure 2.5 illustrates a simplified concept of the glucoregulatory system (at cell level) of a critically ill patient. Further, the resulting hyperglycemia provokes toxicity in those cells that can uptake glucose independently of insulin. It is even shown that hyperglycemia is much more acutely toxic in the critically ill than in healthy individuals [230]. Although the time frame of hyperglycemic events in the ICU is much shorter than in patients with diabetes, avoiding even a moderate degree of hyperglycemia leads to a significant reduction of mortality and morbidity [213, 216]. Therefore, the normalization of blood glucose forms an essential element in the daily treatment of critically ill patients and explains the potential of introducing a semi- or fully-automatic blood glucose control system.

### 2.2.2 Physiological regulation of blood glucose

It is not the purpose of this dissertation to describe the biochemical mechanism of intensive insulin therapy in detail. Furthermore, the exact mechanism by which insulin therapy lowers glycemia in the critically ill is not completely understood. It is known that the endothelium, which is located at the interface between the blood and the vessel wall, is protected if normoglycemia is maintained with intensive insulin therapy during critical illness. This protection of the endothelium (among other aspects which are less relevant for this thesis) further contributes to the prevention of organ failure and death [124, 208].

Until recently, it remained unclear whether the beneficial effects of intensive insulin therapy during critical illness were due to maintenance of normal blood glucose values or rather to the effect of insulin itself [147] as it was known that insulin shows anti-inflammatory, vasodilatory, and antiplatelet effects [4, 42, 153, 198].

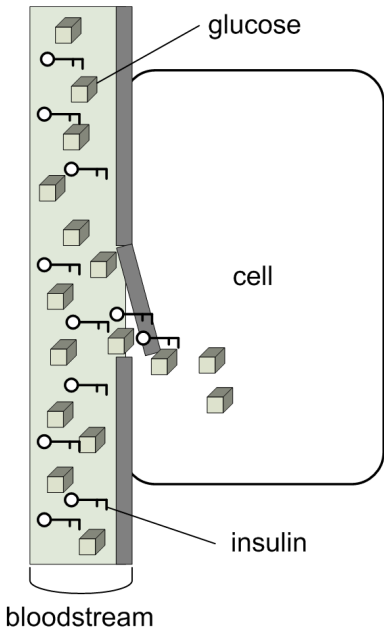


**Figure 2.5:** Simplified overview of the glucoregulatory system (at cell level) of an *untreated* critically ill patient (without any history of diabetes). Glucose calories are directly delivered to the patient. Due to particularly the acute illness and the administration of medication the insulin resistance is high (presented by the narrow *gate* opening). Therefore, the pancreas produces much more insulin (marked by the *keys*) compared with the 'healthy' person. This amount of insulin, however, is still insufficient leading to 'hyperglycemia'.

Therefore, glycemia and plasma insulin levels were independently controlled in burn-injured, fed rabbits to obtain four groups: normoglycemic animals with and without hyperinsulinemia, and hyperglycemic animals with and without hyperinsulinemia [70]. Mortality was found to be significantly lower in the two normoglycemic groups. This result was not affected by the insulin concentrations. Furthermore, normoglycemia prevented organ (liver and kidney) failure and protected the endothelium. This study confirmed that the normalization of blood glucose (and *not* the delivery of insulin) is responsible for the observed mortality and morbidity reduction when applying intensive insulin therapy to critically ill patients.

Since the publication of the first landmark study [216] intensivists and anesthesiologists have been debating what the ideal blood glucose range should be for critically ill patients taking into account hypoglycemic events that are associated with an intensive insulin therapy [72, 143, 151]. *First, do no harm* is the basis of medical ethics [211]. The two Leuven trials [213, 216], the implementation study by Krinsley [119, 120], and the recently published study by Reed *et al.* [172], however, clearly showed that

many lives can be saved with TGC notwithstanding the higher number of hypoglycemic events. Therefore, the target range for blood glucose is set at 80-110 mg/dl. Only for patients with a history of diabetes no survival benefit was found when applying the intensive insulin therapy (probably due to the adaptation to chronic hyperglycemia) [214]. Some insulin titration protocols advise to treat this type of patients to glycemia levels that are similar to the targets from before the admission to the ICU. A more elaborated discussion concerning the target blood glucose range is given in Chapter 7 (see 7.3.5).

## 2.3 Data acquisition

This section focuses on the data that are considered in this work. The origin of the data is described and the different features of the available data sets are discussed.

### 2.3.1 Sources of intensive care data

At the beginning of this study, the medical records of critically ill patients, who were admitted to the ICU division of the University Hospital in Leuven, were only available in paper format. Indeed, until recently the medical staff noted all information concerning the patient and the specific conditions on large 'nurse-papers'. Each nurse-paper represented the information of one patient for one day. Static upon admission demographics (like BMI, reason for intensive care, etc.) as well as dynamic parameters (like blood glucose, flow of insulin, flow of calories, flow of medication, etc.) were noted on these papers. An example of those typical ICU nurse-papers is given in Figure 2.6. Only recently, at the end of the study for this thesis, the implementation of a Patient Database Management System (PDMS) was introduced in our University Hospital. This system allows to automatically record all types of medical information per patient in electronic files.

In view of this work, however, it was necessary to 'record' the *paper* data as *electronic* data. During this data gathering process it was not clear yet which variables would be used in the design process of the semi-automatic glycemia control system. Therefore, all variables that could influence glycemia were selected (see 2.3.2). Next, it is important to indicate that recording the data in electronic files was not straightforward as possible human errors on the *paper* data had to be carefully detected. As a consequence, this process was labour-intensive and, therefore, restricted to four patient groups. Below, an overview of the different electronic data sets that were made available, is given (see 2.4).

### 2.3.2 Variables selected in the framework of this dissertation

A list of parameters was selected based on availability and clinical judgement [215, 238]. Below, a (restricted) inventory of the variables, recorded in the electronic data sheets, is given.

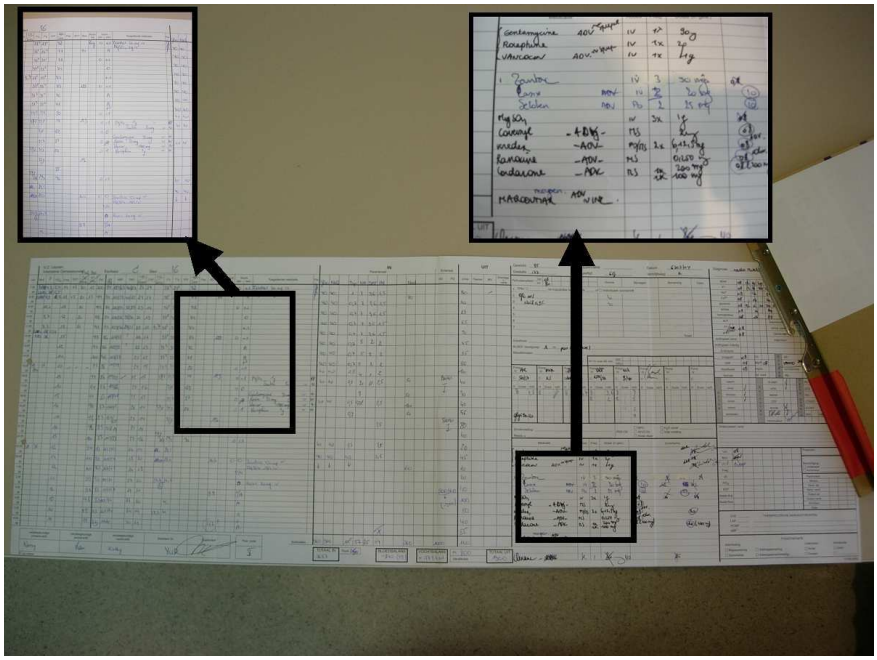

**Figure 2.6:** Example of a nurse-paper. Each paper comprises all medical information (e.g., blood glucose values, insulin doses, flows of calories and medication, body temperature, blood pressure, etc.) of a patient per day.

1. **Blood glucose (glycemia):** $G$ (mg/dl)
   This is the glucose concentration in the blood. Both terms 'blood glucose' and 'glycemia' are alternately used in this work.

2. **Insulin:** $F_I$ (U/hr)
   The protein 'insulin' is a hormone that is released in the islets of Langerhans (pancreas). Typically, the amount of insulin is expressed in units (U): one milligram of insulin corresponds to 24 Units of insulin (or 1 U = 40 $\mu$g insulin). Approximately 40 Units per day are released in a healthy person. The half-life[1] of insulin for disappearing from the blood plasma is five to ten minutes. Insulin is broken down particularly in the liver and the kidneys [146].

3. **Calories:**
   The number of calories (food intake) and the proportion of carbohydrates, proteins and fat represent an important disturbance factor. The daily interruption of caloric intake is a typical feature of the ICU as the feeding lines need to be flushed regularly. Recent developments in the ICU, however, attempt to avoid this flushing process. It must be noted that the type of feeding process is mostly switched from intravenous glucose infusion (at admission) to total parenteral

[1] The half-life of a quantity is the time required for the quantity to decay to half of its initial value.

feeding (particularly during the first days) and finally to enteral feeding (when the patient has sufficiently recovered). Both parenteral and enteral feeding comprise a mixture of carbohydrates, proteins and fat. Parenteral feeding is given intravenously, whereas enteral feeding is administered through a gastric tube. Calories are continuously infused except for some glucose shots (bolus) that are delivered in case of severe hypoglycemic events. All different types of feeding were transformed to two different flows of calories:

(a) Carbohydrate (glucose) calories: $F_G$ (kcal/hr)

(b) Fat calories: $F_F$ (kcal/hr).

4. **Body temperature:** $T$ (°C).
An increased body temperature may be caused by additional inflammations and can lead to extra stress. As we know from above, the presence of physical stress can increase the insulin resistance and can lead to hyperglycemia, accordingly.

5. **Medication:**
A mixture of drugs is administered to critically ill patients. The effect of intake of drugs on glycemia, however, typically depends on the type and the dose of the medication. Possible interactions with other disturbance factors (e.g., other medications) may hamper the modelling (see Chapters 5 and 6) of these effects. Finally, it is important to indicate that these effects are patient-specific in terms of inter- and intra-patient variability.

   Here, the farmaca that potentially influence the blood glucose dynamics are listed. They are administered to the patient as a bolus or by means of a continuous infusion:

   (a) Glucocorticoids: $F_C$ (mg/hr)

      i. Methylprednisolone
      ii. Prednisone / Prednisolone
      iii. Dexamethasone
      iv. Hydrocortisone

   (b) Catecholamines
   The unit $\gamma$ is used in the ICU to symbolize the amount of the considered catecholamine drug ($\mu$g) per kg body weight and per minute.

      i. Adrenaline: $F_A$ ($\gamma$)
      ii. Noradrenaline: $F_N$ ($\gamma$)
      iii. Dobutamine: $F_{Dob}$ ($\gamma$)
      iv. Dopamine: $F_{Dop}$ ($\gamma$)

   (c) Beta-blockers: $F_\beta$ (mg/hr)

6. **Static upon admission demographics:**

   (a) Reason for intensive care
   Eight reasons for admission to the ICU are considered for this work: cardiac surgery (type 1), complicated non-cardiac surgery or severe burns (type 2), neurologic disease, cerebral trauma or complicated brain surgery (type 3), complicated lung or esophageal thoracic surgery, respiratory insufficiency, or both (type 4), complicated abdominal surgery or peritonitis (type 5), transplantation (type 6), complicated vascular surgery (type 7), and others (type 8).

   (b) History of diabetes

   (c) BMI (kg/m$^2$)

   (d) Gender

   (e) Age

   (f) APACHE II score
   The Acute Physiology and Chronic Health Evaluation (APACHE II) score [110] is most known and used in the ICU to objectively score the severity of illness. It is calculated (per day) using parameters of acute physiology and chronic healthcare such as body temperature, arterial pH, breathing frequency, etc.

## 2.4 Data sets

In this section each data set is individually presented and the specific patient features are emphasized. All available data origin from patients who were admitted to the surgical ICU-division of the University Hospital K.U.Leuven.

### 2.4.1 Data set 1

The first data set comprises 41 patients who were retrospectively selected from the data originally described in [216]. They were chosen to cover variable demographics (see Table 2.1) and durations of stay in the ICU. The goal was to retrieve a representative sample for the larger patient group of [216] in terms of duration of intensive care and proportion of diagnostic subgroups. All of them had a specific clinical history and particular evolution during their stay in the ICU. Due to the different nature of the patients, the duration of stay in the ICU varied explaining the generated time series of different lengths in this data set. Nurses were instructed to maintain glycemia between 80-110 mg/dl (target range) using the hospital guidelines for TGC in the ICU [215]. Therefore, whole-blood glucose in undiluted arterial blood was measured every 4 hours or more frequently in the initial phase or in case of complications by means of the ABL700 Radiometer Medical (Denmark) glucose analyser. These measured glycemia values are linearly interpolated to obtain one-hour glycemia data to overcome the feature that the sampling intervals are irregular.

**Table 2.1:** Characteristics of Data set 1.

| Variable | Patient group 1 |
|---|---|
| Number of patients - no | 41 |
| Male sex - no (%) | 27 (65.8) |
| Age - yr (SD) | 59.8 (17.6) |
| BMI - kg/m$^2$ (SD) | 27.0 (5.2) |
| Reason for intensive care - no (%) | |
| Cardiac surgery - Type 1 | 11 (26.8) |
| Non-cardiac indication | 30 (73.2) |
| Multiple trauma or severe burns - Type 2 | 7 (17.1) |
| Neurologic disease, cerebral trauma, or complicated brain surgery - Type 3 | 4 (9.8) |
| Complicated lung or esophageal thoracic surgery, respiratory insufficiency, or both - Type 4 | 7 (17.1) |
| Complicated abdominal surgery or peritonitis - Type 5 | 5 (12.2) |
| Transplantation - Type 6 | 3 (7.3) |
| Complicated vascular surgery - Type 7 | 2 (4.9) |
| Other - Type 8 | 2 (4.9) |
| APACHE II score (first 24 hr) (SD) | 11 (6) |
| History of diabetes - no (%) | 7 (17.1) |
| Type I - diabetes | 2 (4.9) |
| Type II - diabetes | 5 (12.2) |
| Mean blood glucose - mg/dl (SD) | 108 (37) |
| Minimal blood glucose - mg/dl | 37 |
| Maximal blood glucose - mg/dl | 379 |
| Mean duration of stay in ICU - hr (SD) | 174 (154) |
| Min. duration of stay in ICU - hr | 36 |
| Max. duration of stay in ICU - hr | 686 |

Figures 2.7, 2.8, 2.9, and 2.10 show examples of some patient data. Each top panel illustrates the blood glucose signal. However, it is stressed that the stars show the glycemia values that were effectively measured. Indeed, the linear interpolation of the available glucose data may have provoked some inaccuracies but is necessary to impose a (virtually) regular sampling frequency. Figure 2.7 visualizes the data of an 'average' patient (patient no. 10). Some medication flows ($F_C$ and $F_A$) are constant indicating that no glucocorticoids nor adrenaline were prescribed for this patient. As is shown in Figure 2.8 some patients did not get any of the drugs that were selected for the scope of this work. The data of this patient (patient no. 20) also show a strongly fluctuating pattern for the administered calories and insulin. In spite of the varying disturbances, the nurses adequately changed the insulin flow leading to a blood glucose signal that falls within the normoglycemic target range (80-110 mg/dl) to a large extent.

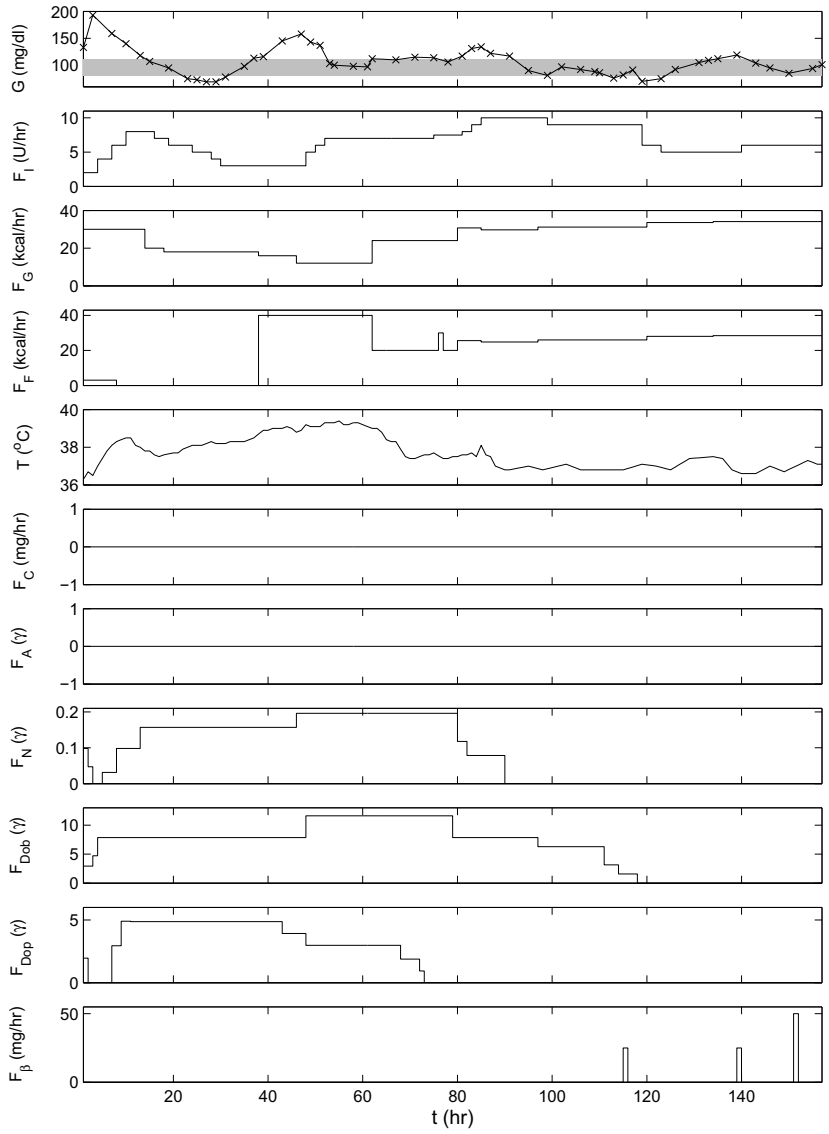


**Figure 2.7:** Data of patient no. 10 from the first patient group. The top (first) panel shows the interpolated blood glucose signal. The stars denote the glycemia values that were measured with the ABL700 Radiometer Medical device. The shaded area represents the normoglycemic target range (80-110 mg/dl). In the following three panels the flows of insulin, carbohydrate calories and fat calories are successively illustrated. The body temperature dynamics are presented in the fifth panel. The other panels successively show the delivered rate of glucocorticoids, adrenaline, noradrenaline, dobutamine, dopamine, and beta-blockers.

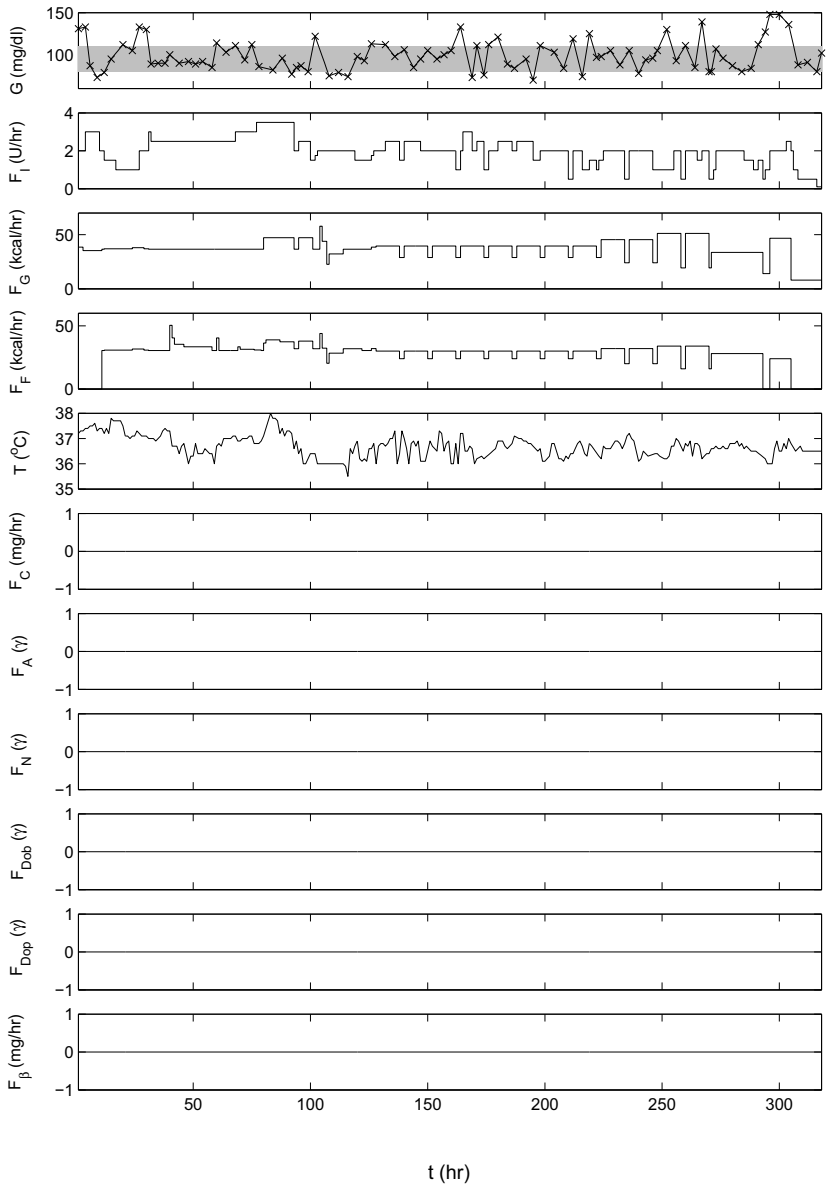


**Figure 2.8:** Data of patient no. 20 from the first patient group. The same notation as presented in Figure 2.7 is used. None of the drugs that were selected for the scope of this work, were effectively administered to this patient explaining the constant medication flows. The administered flows of calories show a fluctuating pattern which is followed by the insulin dosage profile leading to relatively stable blood glucose dynamics (in the normoglycemic target range).

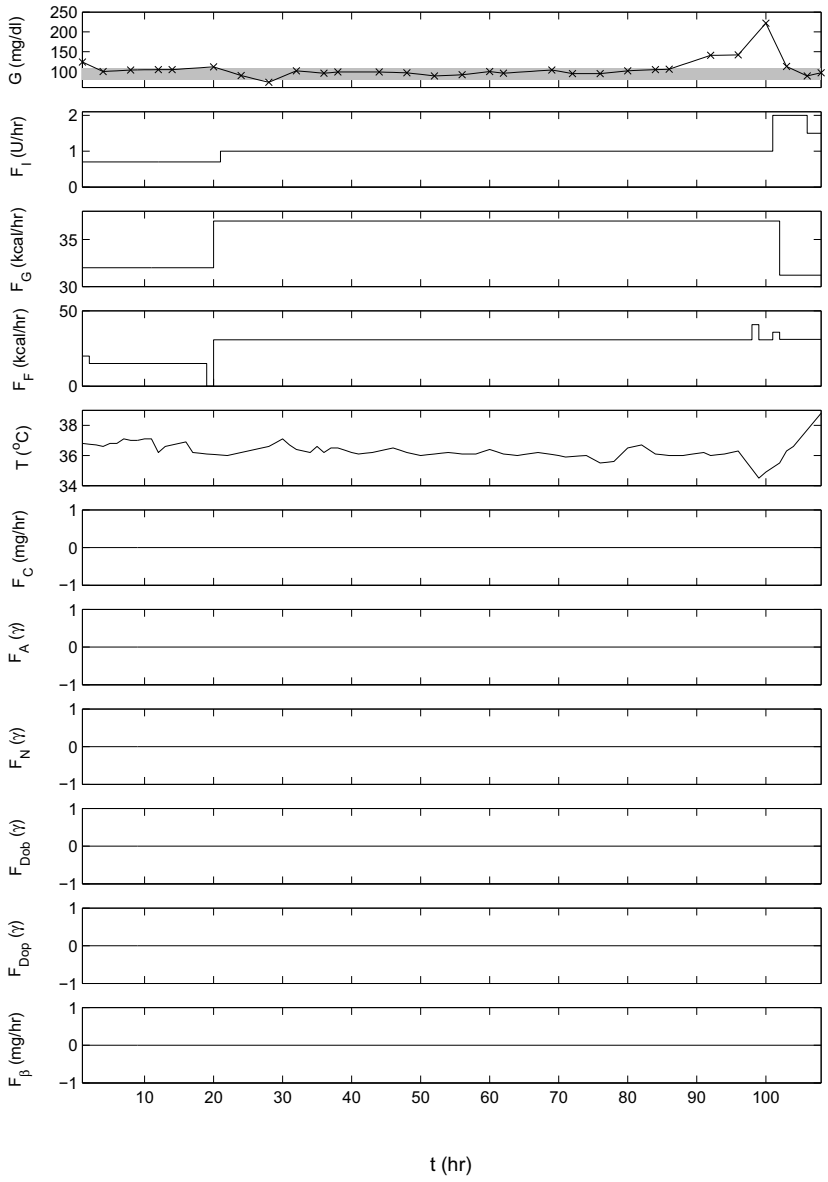


**Figure 2.9:** Data of patient no. 25 from the first patient group. The same notation as presented in Figure 2.7 is used. None of the drugs that were selected for the scope of this work, were effectively administered to this patient and the flows of administered calories were relatively constant. The blood glucose dynamics of this patient were very stable and the nurse did not much adapt the insulin rate, accordingly.

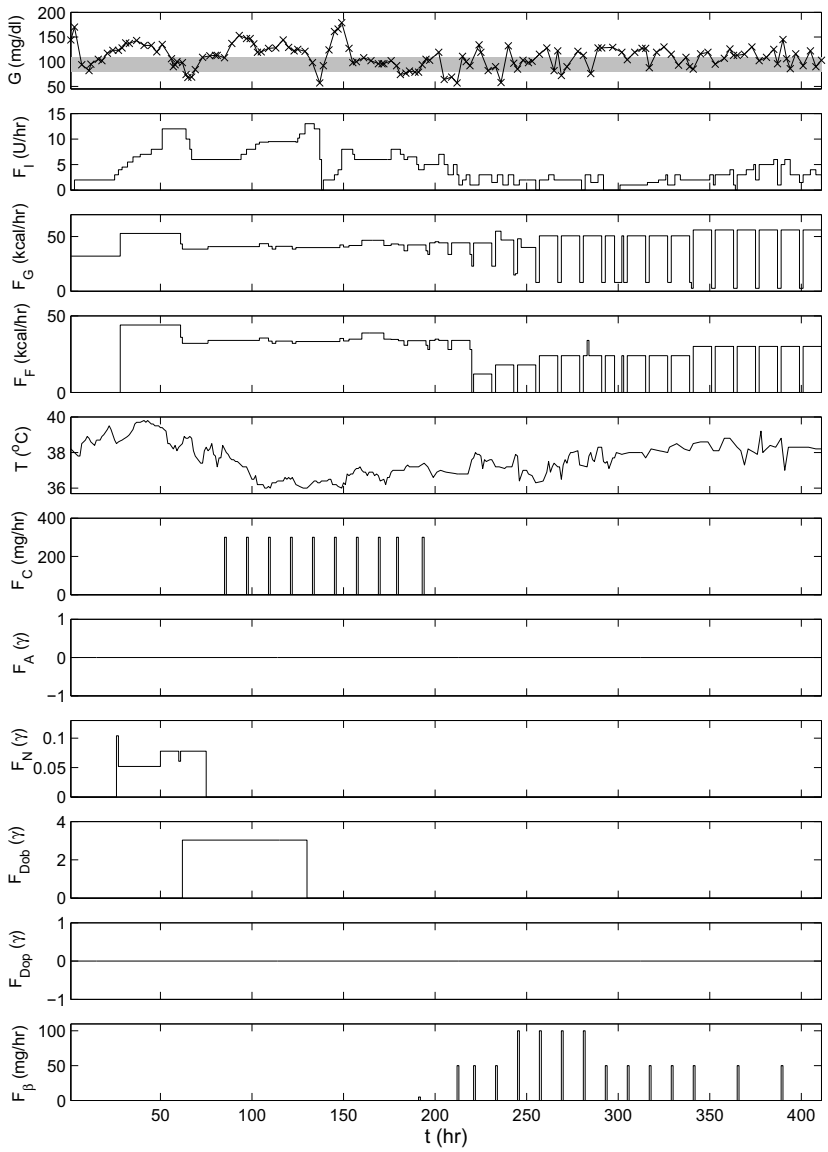


**Figure 2.10:** Data of patient no. 41 from the first patient group. The same notation as presented in Figure 2.7 is used. Both the administered medication and calories show a variable pattern explaining the active contribution of the nurse (who appropriately adapted the insulin flow) leading to relatively stable blood glucose dynamics (particularly shown in the second half of the data).

An example of very stable blood glucose dynamics is shown in Figure 2.9. The insulin and calories flow of this patient (patient no. 25) are also relatively constant and, again, no selected medication was delivered to the patient. Fluctuating disturbance factors are illustrated in Figure 2.10. It is important to note that many (input) flows are simultaneously present. This is an additional complicating factor when modelling (see Chapters 5 en 6) and controlling (see Chapter 7) blood glucose (output) dynamics. Nevertheless, blood glucose is strictly controlled by the adequate nurse-driven changes of the insulin rate.

This first data set will be used in Chapters 4 and 5.

### 2.4.2 Data set 2

The second data set that is made available for this work is analogous to data set 1. It comprises the data of 15 patients who were treated with the intensive insulin therapy (80-110 mg/dl as target blood glucose range). Here, whole-blood glucose in undiluted arterial blood was measured *every hour* using the same glucose analyser (ABL700 Radiometer Medical, Denmark) as used for data set 1. Although the guidelines were identical to the ones used for the first patient group, this study was more intensified in terms of blood glucose sampling during the first two days after ICU admission. After these two intensive sampling days, blood glucose was monitored with the same frequency as in the first group but these additional data were not considered in this data set, for the purpose of this study. Therefore, the length of the data set of each patient was limited to the first 50 hours. Table 2.2 gives an overview of the study population with some important clinical characteristics.

In Figure 2.11 the data of patient no. 11 are illustrated. As glycemia (top panel) is measured every hour, the magnitude of the errors that may be obtained by interpolating the data is restricted. This is again a typical example of strictly controlled glycemia dynamics. The patient enters the ICU with an elevated blood glucose (on-admission glycemia equals 139 mg/dl) and normoglycemia is reached after six hours. Glycemia is kept within the target range during the remaining hours of the first day. Twenty-seven hours after admission, however, the blood glucose signal was suddenly decreasing which was adequately responded by the nurse by gradually decreasing the insulin rate. After some hours a new insulin dose equilibrium was found and glycemia was kept in the target range. It is clear that the higher blood glucose sampling frequency facilitates the control of glycemia.

The second data set will be used in Chapters 4 and 5.

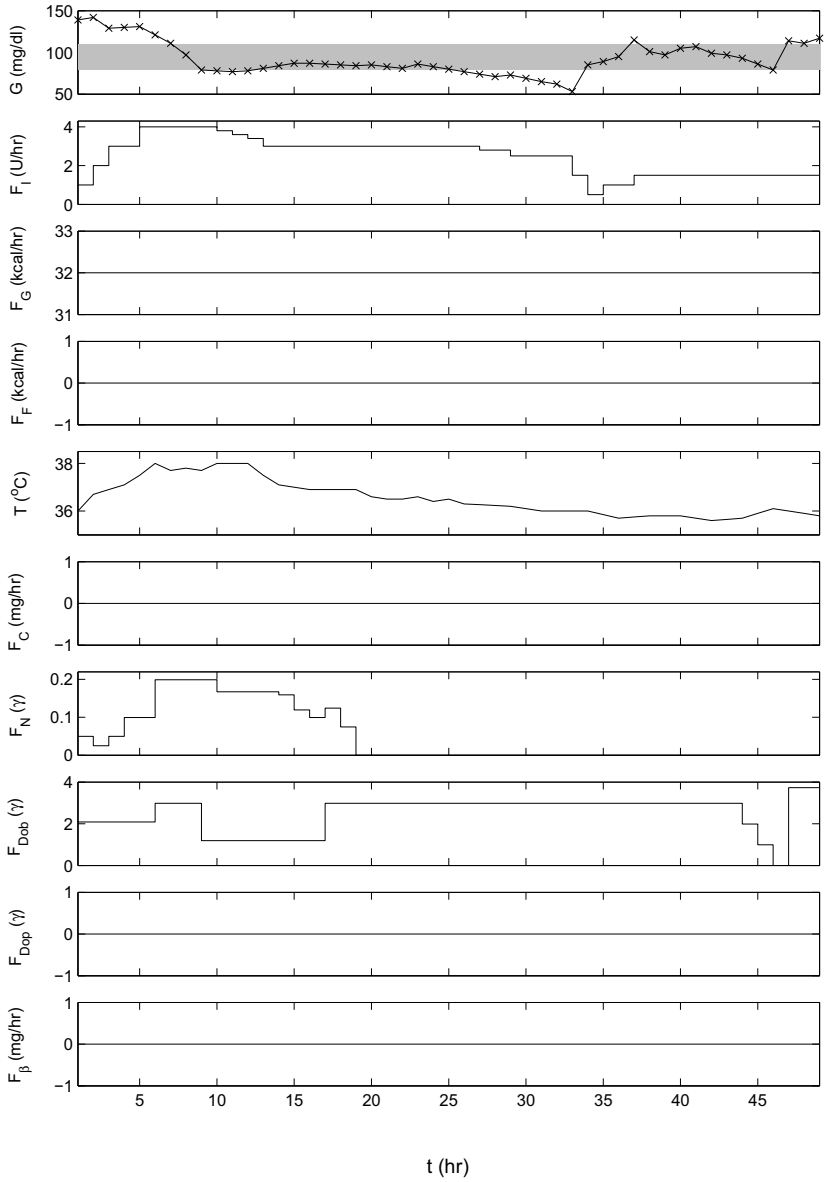


**Figure 2.11:** Data of patient no. 11 from the second patient group. The blood glucose was measured every hour during the initial two days after admission to the ICU. The top (first) panel shows the interpolated blood glucose signal. The stars denote the glycemia values that were measured with the ABL700 Radiometer Medical device. The shaded area represents the normoglycemic target range (80-110 mg/dl). In the following three panels the flows of insulin, carbohydrate calories and fat calories are successively illustrated. The body temperature dynamics are presented in the fifth panel. The other panels successively show the delivered rate of glucocorticoids, noradrenaline, dobutamine, dopamine, and beta-blockers.

**Table 2.2:** Characteristics of Data set 2.

| Variable | Patient group 2 |
|---|---|
| Number of patients - no | 15 |
| Male sex - no (%) | 9 (65.0) |
| Age - yr (SD) | 70.0 (12.6) |
| BMI - kg/m$^2$ (SD) | 25.6 (5.8) |
| Reason for intensive care - no (%) | |
| Cardiac surgery - Type 1 | 10 (66.7) |
| Non-cardiac indication | 5 (33.3) |
| Multiple trauma or severe burns - Type 2 | 0 (0) |
| Neurologic disease, cerebral trauma, or complicated brain surgery - Type 3 | 0 (0) |
| Complicated lung or esophageal thoracic surgery, respiratory insufficiency, or both - Type 4 | 0 (0) |
| Complicated abdominal surgery or peritonitis - Type 5 | 5 (33.3) |
| Transplantation - Type 6 | 0 (0) |
| Complicated vascular surgery - Type 7 | 0 (0) |
| Other - Type 8 | 0 (0) |
| APACHE II score (first 24 hr) (SD) | 18 (4) |
| Mean blood glucose - mg/dl (SD) | 101 (23) |
| Minimal blood glucose - mg/dl | 37 |
| Maximal blood glucose - mg/dl | 214 |
| Mean duration of stay in ICU - hr (SD) | 47 (4) |
| Min. duration of stay in ICU - hr | 36 |
| Max. duration of stay in ICU - hr | 50 |

### 2.4.3 Data set 3

The third data set is similar to the second data set. Thirty-seven adult patients admitted to the ICU of the University Hospital were prospectively enrolled after informed consent was obtained from the next of kin. Nurses followed the intensive insulin therapy guidelines aiming at TGC. During the first 48 hours, an arterial blood sample was withdrawn hourly via an indwelling arterial line and blood glucose was determined on this sample using three different point-of-care sensor devices: the ABL700 Radiometer Medical glucose analyser (Radiometer, Denmark), the Accu-Chek Inform (Roche Diagnostics, Switzerland), and the HemoCue B-glucose analyser (HemoCue, UK). Each sample was immediately analysed with the three different methods. The study was approved by the Institutional Ethical Review Board.

The **ABL 700 series blood gas analyser** determines the glucose concentration in whole blood using the glucose dehydrogenase method with a sensor based on amperometry. The obtained result is further calibrated to a plasma glucose value. This point-of-care blood gas analyser is used as *reference* method or *gold standard* for this study [51].

Maintenance, calibration, and quality control are performed on a daily basis by the central hospital laboratory. The **Accu-Chek Inform** measures blood glucose in whole blood using the glucose dehydrogenase method with a sensor technology based on amperometry. Finally, the **HemoCue B-glucose analyser** measures blood glucose in whole blood after hemolysis of erythrocytes using a glucose dehydrogenase method with a sensor technology based on spectrophotometry. The three devices use the glucose dehydrogenase enzymatic chemical reaction, which prevents the dependency on $P_aO_2$ and thus making it attractive in the ICU setting. To account for a possible interference of pH, $P_aO_2$, or hematocrit each sample was immediately analysed with the three methods and, therefore, we avoided that variations in these critical care variables caused erroneous measurements [75]. Furthermore, as the same arterial sample for the triple simultaneous analysis of blood glucose was used, well-known discrepancies between arterial and capillary blood glucose values could have been avoided [122].

In contrast to the second data set, the different input variables (e.g., insulin, calories, drugs, etc.) were not recorded in the electronic data files. Indeed, only the three different blood glucose signals were electronically stored for the purpose of this study. Table 2.3 gives an overview of the study population with some important clinical characteristics. The third data set will be used in Chapters 3 and 4.

### 2.4.4 Data set 4

The last data set that is made available for the purpose of this dissertation significantly differs from the previous data in terms of glycemia sampling frequency and measurement 'compartment'[2]. Here, the GlucoDay system (A. Menarini Diagnostics, Italy) is validated against the ABL700 Radiometer Medical (Denmark) glucose analyser which functions as *reference* or *gold standard* sensor device. The **GlucoDay system** is a portable instrument provided with a micro-pump and a biosensor coupled to a microdialysis system and serves as *test* sensor device for this work. This amperometric sensor consists of an enzymatic membrane with immobilized glucose oxidase and a platinum electrode used to measure glucose in *subcutaneous* interstitial fluid. As already described above, the **ABL glucose analyser** is an amperometric sensor that measures glucose in whole blood using the glucose dehydrogenase method.

After informed consent from the next of kin, we implanted a microfibre in 20 ventilated adult patients who were admitted to the ICU of the University Hospital (see Table 2.4). After implantation of the fibre in the peri-umbilical subcutaneous tissue, we recorded *near-continuous* subcutaneous glucose levels during the first 48 hours after admission to the ICU. Every 3 minutes the mean value of the last 3 minutes was exported. During the first 24 hours, arterial blood glucose was measured concomitantly every hour using the ABL machine; during the next 24 hours, arterial blood glucose was measured every

[2] A compartment is a quantity of *material* that behaves *homogeneously* meaning that all measures performed on the compartment at a given time instant are equally representative. Here, a compartment is associated with a physical space (e.g., subcutaneous tissue). Chapter 6 further introduces 'compartmental' models.

**Table 2.3:** Characteristics of Data set 3.

| Variable | Patient group 3 |
|---|---|
| Number of patients - no | 37 |
| Male sex - no (%) | 20 (54.1) |
| Age - yr (SD) | 63.3 (17.1) |
| BMI - kg/m$^2$ (SD) | 24.9 (4.3) |
| Reason for intensive care - no (%) | |
| Cardiac surgery - Type 1 | 22 (59.5) |
| Non-cardiac indication | 15 (40.5) |
| Multiple trauma or severe burns - Type 2 | 0 (0) |
| Neurologic disease, cerebral trauma, or complicated brain surgery - Type 3 | 2 (5.4) |
| Complicated lung or esophageal thoracic surgery, respiratory insufficiency, or both - Type 4 | 5 (13.5) |
| Complicated abdominal surgery or peritonitis - Type 5 | 5 (13.5) |
| Transplantation - Type 6 | 2 (5.4) |
| Complicated vascular surgery - Type 7 | 0 (0) |
| Other - Type 8 | 1 (2.7) |
| APACHE II score (first 24 hr) (SD) | 15 (4) |
| ABL700 Radiometer | |
| Mean blood glucose (SD) - mg/dl | 113 (35) |
| Minimal blood glucose - mg/dl | 37 |
| Maximal blood glucose - mg/dl | 282 |
| Accu-Chek Inform | |
| Mean blood glucose (SD) - mg/dl | 119 (43) |
| Minimal blood glucose - mg/dl | 29 |
| Maximal blood glucose - mg/dl | 325 |
| HemoCue B-glucose analyser | |
| Mean blood glucose (SD) - mg/dl | 124 (37) |
| Minimal blood glucose - mg/dl | 37 |
| Maximal blood glucose - mg/dl | 325 |

4 hours. A 2-point (at 12 and 20 hours) retrospective calibration of the test sensor was performed following the supplied software algorithm. Nurses were instructed to maintain the blood glucose between 80-110 mg/dl using the measured glucose data from the ABL glucose analyser in accordance with the TGC guidelines. The study protocol was approved by the Institutional Ethical Review Board.

In Figure 2.12 the data of patient no. 20 are illustrated. The blood glucose dynamics are presented in more detail here as the glycemia sampling interval was decreased to 3 minutes (for GlucoDay). The reference signal (ABL700 Radiometer) is depicted by stars. The (near-continuous) test glucose data of this patient correspond to the concomitantly measured reference signal after retrospectively calibrating the test data

**Table 2.4:** Characteristics of Data set 4.

| Variable | Patient group 4 |
|---|---|
| Number of patients - no | 20 |
| Male sex - no (%) | 14 (70.0) |
| Age - yr (SD) | 61.3 (13.5) |
| BMI - kg/m$^2$ (SD) | 27.4 (5.1) |
| Reason for intensive care - no (%) | |
| Cardiac surgery - Type 1 | 10 (50.0) |
| Non-cardiac indication | 10 (50.0) |
| Multiple trauma or severe burns - Type 2 | 1 (5.0) |
| Neurologic disease, cerebral trauma, or complicated brain surgery - Type 3 | 2 (10.0) |
| Complicated lung or esophageal thoracic surgery, respiratory insufficiency, or both - Type 4 | 3 (15.0) |
| Complicated abdominal surgery or peritonitis - Type 5 | 2 (10.0) |
| Transplantation - Type 6 | 0 (0) |
| Complicated vascular surgery - Type 7 | 1 (5.0) |
| Other - Type 8 | 1 (5.0) |
| APACHE II score (first 24 hr) (SD) | 17 (6) |
| APACHE II score (second 24 hr) (SD) | 17 (6) |
| ABL700 Radiometer | |
| Mean blood glucose (SD) - mg/dl | 111 (23) |
| Minimal blood glucose - mg/dl | 65 |
| Maximal blood glucose - mg/dl | 202 |
| GlucoDay system | |
| Mean glucose (SD) - mg/dl | 112 (25) |
| Minimal glucose - mg/dl | 56 |
| Maximal glucose - mg/dl | 249 |

as mentioned above. Some data originating from other patients, however, show some discrepancies. A detailed analysis of the GlucoDay sensor will be performed in Chapter 3.

Glycemia was strictly controlled in the patient shown in Figure 2.12. The disturbance factors were relatively stable. The on-admission blood glucose value (121 mg/dl) was slightly elevated, but after only one hour normoglycemia was reached by administering insulin. The tendency towards hypoglycemia (at 7 hours after admission to the ICU) necessitated the nurse to decrease the insulin flow (second panel) which, however, led to a slight hyperglycemic episode. Accordingly, the nurses gradually increased the insulin flow aiming at normoglycemia. It is clear that glycemia dynamics may easily fluctuate. The availability of more glucose measurements facilitates the control of glycemia. This last data set will be used in Chapters 3, 6, and 7.

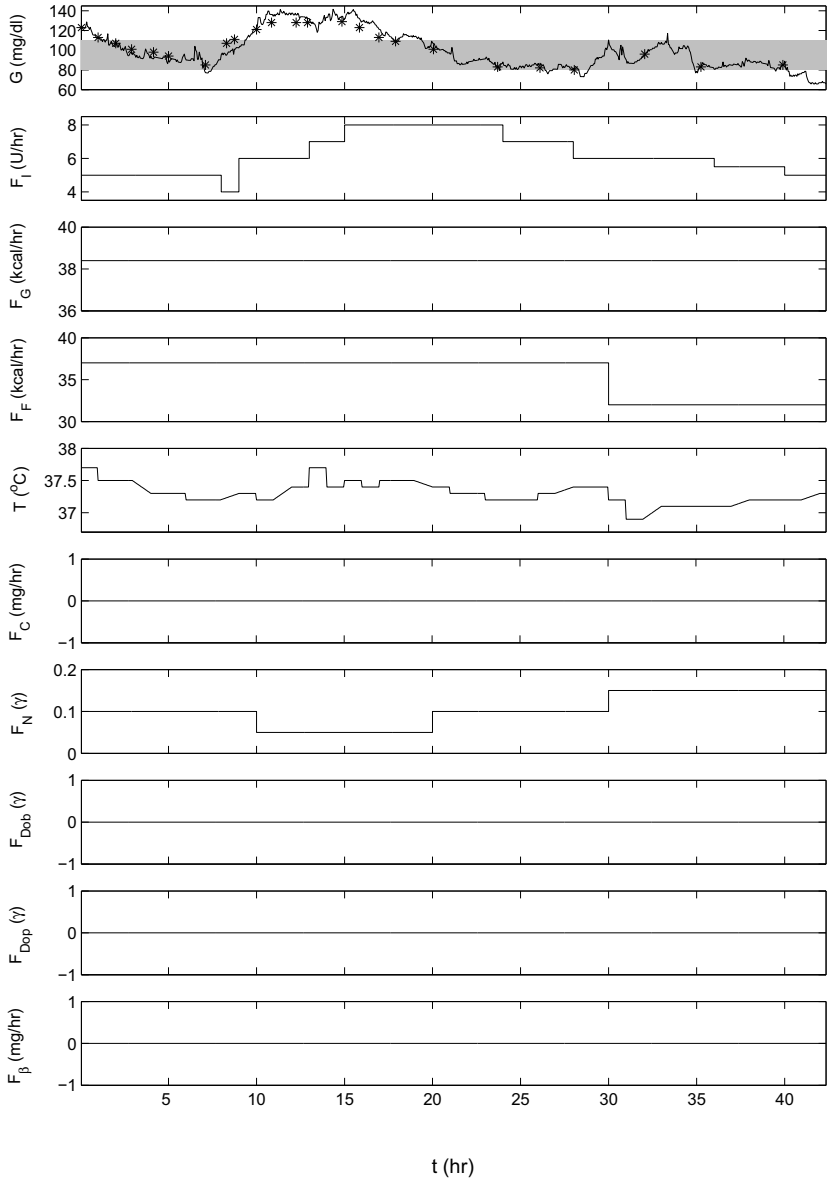


**Figure 2.12:** Data of patient no. 20 from the fourth patient group. The top panel shows the near-continuous glucose signal originating from the GlucoDay sensor device. The stars denote the reference blood glucose values that were measured with the ABL700 Radiometer Medical device. The shaded area represents the normoglycemic target range (80-110 mg/dl). In the following three panels the flows of insulin, carbohydrate calories and fat calories are successively illustrated. The body temperature dynamics are presented in the fifth panel. The other panels successively show the delivered rate of glucocorticoids, noradrenaline, dobutamine, dopamine, and beta-blockers.

## 2.5 Characteristics of current ICU data

The different data sets have specific properties which may complicate the modelling of the glucose dynamics of the critically ill (see also Chapters 5 and 6). Each of them is briefly discussed in this section:

1. **Irregular sampling frequency:**
   All available data origin from real-life ICU patients who were treated by nurses. Due to the high workload and/or the protocols that are present in the ICU, missing values appear in the data. These missing values were estimated or (linearly) interpolated to enforce a regular sampling frequency. For modelling issues this regular sampling frequency is preferred. Particularly the data that come from the first patient group (see 2.4.1) may be influenced due to the interpolation of the glucose signal. In the other data sets, glycemia is measured more frequently (every hour, or even every three minutes for data set 4, see 2.4.4).

2. **Simultaneous change of inputs:**
   As shown in the examples of the patient data, the flow of input variables (e.g., calories, insulin, medication) is adapted simultaneously on a regular basis. When the dynamics of a system or a process (e.g., the glucoregulatory system) are to be modelled, it is preferred that each input variable (or each known disturbance factor) is varied independently. In other words, the influence of changing a certain input variable on the output (i.e., blood glucose) is preferably defined when other disturbance factors behave constantly. However, a nurse treating a critically ill patient obviously does not take into account this modelling issue. Therefore, disturbance factors typically coincide in the ICU. Additionally, delays can further complicate the modelling of the dynamic process as the observed output may be explained by a combination of current and previous disturbance factors. Therefore, the effect of administering, for example, insulin should be described in a dynamic model (and not a static model, see also Chapters 5 and 6).

3. **Few data available:**
   Taking into consideration the high number of patient types and features, more patient data could have been expected from a theoretical perspective. The recording phase of the nurse-paper data in electronic data files, however, was labour-intensive (see 2.3) explaining the limited availability of data. Further, the most important variable for this work (glycemia) could only be regularly measured. The imposed sampling interval for glucose in data sets 2 and 3 was decreased to one hour giving an approach towards a 'continuous' glucose signal. Particularly data set 4 is potentially interesting as near-continuous glucose signals were made available in a test phase. However, it is important to notice that the number of patients in these data sets is limited knowing the ICU is characterized by a large inter- and intra-patient variability. Ideally, accurate and reliable near-continuous sensor devices should be used for measuring glycemia in a high number of patients. However, these sensor devices are unfortunately not yet (commercially) available but are undoubtedly under development [38, 94, 99, 109, 114, 162, 194, 209, 211].

Disturbance factors (e.g., medication) are also strongly patient-specific (not every patient receives the same type of medication nor the same dose). A high variability exists among the disturbance factors for the available amount of data, which may further complicate the modelling process as discussed in Chapters 5 and 6.

4. **Unmeasured and unknown disturbances:**
   It has been shown that blood glucose dynamics behave far from constant due to inter- and intra-patient variability. Although a list has already been provided with all known variables that can influence glycemia of critically ill patients (see 2.3.2), lots of other disturbances are not yet known or cannot be measured. The first category consists of elements whose influence is not known. Let us take a hypothetical example. Each day a patient is being washed by the nurses. It may be possible that this washing process (e.g., a patient is being turned) may influence the blood glucose.
   The second category focuses on disturbances that cannot be directly measured. The insulin resistance (see 2.1.2) is a typical example of this category. The sensitivity of the tissues for insulin (i.e., the inverse of the insulin resistance) typically increases as the patient recovers but can suddenly lower, as well, in case of additional infections or complications. This insulin sensitivity/resistance has a significant impact on the blood glucose profile. Another immeasurable disturbance factor may be the specific treatment of the patient (e.g., the influence of specific surgery, the connection to machines). The availability of accurate and reliable near-continuous glucose sensor devices may clarify these effects in the future.

5. **Closed-loop data:**
   The data that were made available are closed-loop data meaning that the output variable (i.e., blood glucose) is a *controlled* variable and that the next rate of the *control input variable* (i.e., insulin) depends on the previous output signal. Blood glucose is being controlled with insulin by the nurses and the determination of the next insulin rate is largely dependent on the previously monitored glucose signal (see the Leuven guidelines in Chapter 7).
   In most identification issues, however, the system under study behaves as an *open-loop* system: the input variables are modified (without considering the previous output signal) and the result of these adaptations can be observed in the output. A clear relation between input(s) and output may be found, accordingly. In case of *closed-loop* data, this relation may be partly masked. The closed-loop issue is discussed in more detail in Chapters 5 and 6.

6. **No freedom on experiments:**
   The last (and probably most important) property of the data considered in this work is the fact that there exists no freedom on (unconstrained) experiments due to ethical and medical reasons. Only the medical staff (i.e., nurses and doctors) decide which treatment (type of medication/calories, dose, etc.) is appropriate for which patient.

Some (constrained) clinical experiments (such as the comparison study of glucose sensors in data set 3 or the validation study of a new glucose sensor device in data set 4) on patients are only allowed after strict approval by the Institutional Ethical Review Board and when informed consent from the next of kin is obtained. It is obvious that doing any open-loop experiments (e.g., how will the blood glucose profile evolve if the insulin dose is doubled, or if the flow of calories is suddenly stopped, or if a bolus of dopamine is given, etc.) is absolutely forbidden.

Depending on the scope of the respective chapter, only a selection of the available data will be considered.

## 2.6 Conclusions

This section presented some medical background and the data used in this work. The main contribution of this chapter was twofold. First of all, the clinical (simplified) concept of the glucoregulatory system and the most important differences between the glucoregulatory system of a healthy person, a patient with diabetes, and a critically ill patient were introduced. Secondly, the characteristics of the data that were made available for the purpose of this dissertation were described and illustrated with examples. Attention was also given to some typical properties of the used data. The four different data sets, described in this chapter, will be used extensively in the following chapters.

# Part II

# ASSESSMENT PROCEDURES

# Chapter 3

# General Assessment of Glucose Sensors

*Glucose sensors, representing both blood glucose meters and glucose monitoring systems (GMS), are used to monitor the glucose profile. The use of glucose sensors is standard practice to achieve TGC in critically ill patients and in patients with diabetes. However, some of them may lack reliability. In this chapter the development of a statistical assessment tool that can be used for evaluating the performance of a test sensor device with respect to a reference sensor device, the GLYCENSIT procedure (Copyright © 2006), is described. The presented method can be tuned according to the clinician's preferences regarding significance level, tolerance level, and glycemic range cut-off values. Three hypothetical data sets and a real-life clinical (ICU) example are introduced to illustrate the GLYCENSIT analysis. Moreover, two point-of-care sensor devices are validated in a real-life ICU setting. Figure 3.1 further illustrates the focus of this chapter.*

## 3.1 Introduction

### 3.1.1 Glucose sensor devices: Past, present, and future

Frequent and accurate monitoring of glycemia is an important keystone for intensive insulin therapy in critically ill patients and patients with diabetes. Both blood glucose meters and glucose monitoring systems (GMS) are used to achieve this goal.

**Blood glucose meters** measure the glucose value in arterial, venous or capillary *blood* samples by means of a specific enzymatic reaction:

$$\beta\text{- D - glucose} + H_2O + O_2 \xrightarrow{\text{GOx}} \text{gluconic acid} + H_2O_2$$

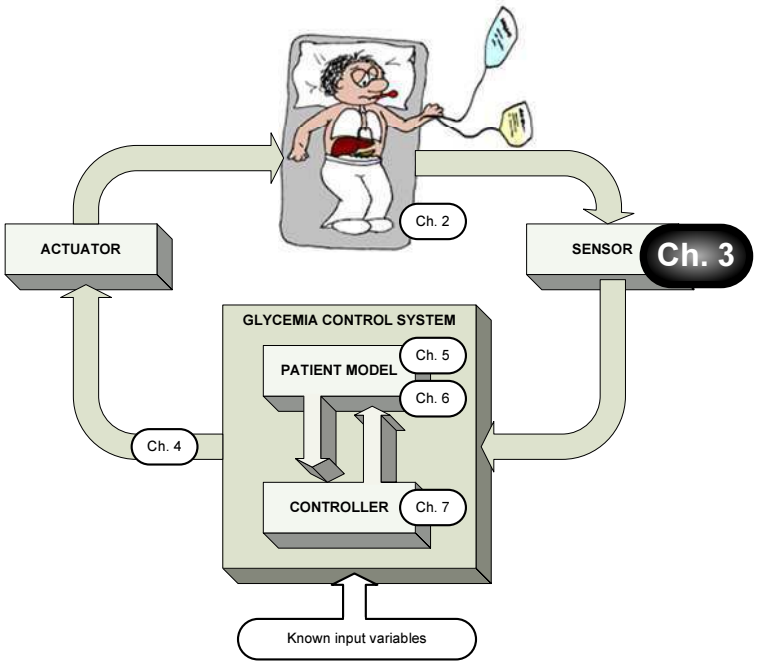


**Figure 3.1:** Simplified presentation of the (semi-)automated control system. The glucose sensor technology and its validation are the fundamentals of Chapter 3. A new assessment tool is presented and applied to hypothetical and real-life ICU data sets.

in which GOx represents the immobilized enzyme 'glucose oxidase'. These enzymatic sensors have been under development since the 1960s. The GOx-enzyme is responsible for the specificity for glucose. This enzyme catalyzes the oxidation of glucose in the presence of oxygen. The concentration of glucose can be determined by monitoring the oxygen consumption (by means of a Clark-type sensor), the production of gluconic acid (by using a pH-sensor), or the production of hydrogen peroxide ($H_2O_2$) (by measuring the current). Typically, the last option is preferred. This amperometrical reaction can be presented as follows:

$$H_2O_2 \rightarrow 2e^- + 2H^+ + O_2$$

where $H_2O_2$ is oxidised. Besides the 'glucose oxidase' technology described above, blood glucose meters can also be based upon the 'glucose dehydrogenase' technology which results in a similar accuracy.

The use of blood glucose meters returns *discrete-time* (meaning *non-continuous*) glycemia measurements [90]. The measurement frequency typically varies from 2 to 6 times per day (in case of patients with diabetes, taking capillary blood samples at the fingertip [50]) and from 6 to 12 times per day (for the intensive insulin treatment of

critically ill patients, taking arterial blood samples [213, 216]).

**GMS** typically *estimate* the glucose level in another compartment[1] than blood (e.g., interstitial fluid present in subcutaneous tissue) by applying different technological methodologies leading to a near-continuous glucose signal (after appropriately calibrating the system) [90]. It is important to note that the term 'continuous' (instead of 'near-continuous') is sometimes used in the available literature. This, however, may be misleading since measurement *intervals* always remain present although they are small (typically varying from 3 minutes to even milliseconds depending on the type of GMS). Of course, it is clear that the number of glucose observations is drastically higher compared with the 'blood glucose' sensor devices of the first group potentially facilitating TGC and avoiding (or at least reducing the number of) hypo- and hyperglycemic events.

The *quest* for an accurate and reliable near-continuous glucose sensor started already many years ago. In 1976, one of the first 'continuous' glucose sensors, as part of a computerized *Biostator Glucose Controlled Insulin Infusion System (GCIIS)*, was presented at a conference in Freiburg (Germany) [46]. So far, however, no commercially available near-continuous glucose sensor device is able to accurately and reliably monitor the glucose signal of patients with diabetes nor critically ill patients. During the last decade, many companies have invested substantially in the development process of near-continuous glucose sensor devices, but currently existing devices do not yet sufficiently meet the clinical requirements [38, 94, 114, 209].

In general, two different types of near-continuous glucose sensor devices are currently under development as is reported by Koschinsky and Heinemann [114]:

1. **Minimal-invasive glucose sensors:**
   This type of sensors is characterized by the measurement of glucose in the interstitial fluid of the skin or in the subcutaneous tissue. As contact with blood is avoided, the name 'minimal-invasive' is given. Most known minimal-invasive techniques are:

   (a) *Transdermal approach:* A device, attached to the skin, removes interstitial intradermal fluid across the skin. The glucose concentration measured in this fluid is related to the blood glucose.

   (b) *Glucose electrodes:* Most of these electrodes immobilize the GOx enzyme on the tip of a needle that is inserted in the skin. The same amperometrical reaction as described above takes place.

   (c) *Microdialysis:* Microdialysis is founded on the slow pumping of a solution (i.e., the dialysate) through a probe that has a semi-permeable membrane. The concentration of the glucose molecules that are transferred to the dialysate is related to the blood glucose.

[1] A compartment is a quantity of *material* that behaves *homogeneously* meaning that all measures performed on the compartment at a given instant are equally representative. Here, a compartment is associated with a physical space (e.g., subcutaneous tissue). The use of 'compartmental' models is introduced in Chapter 6.

(d) *Open-flow microperfusion:* This technique uses a double-lumen catheter with microholes which is inserted in the subcutaneous tissue. A perfusion fluid is pumped through the inner cannula, mixed with the interstitial fluid at the end of the probe, and finally sucked back through the space between the cannulas.

2. **Non-invasive glucose sensors:**
Most non-invasive glucose sensors rely on optical techniques:

(a) *Spectroscopic approach:* A light beam is directed through the skin and the properties of the reflected light are related to the blood glucose.

(b) *Scattering approach:* The induced changes in the physical properties of the skin correspond to the blood glucose level.

A detailed overview and discussion of the considered glucose sensor technologies may be found in [101] and [114]. In [46] and [114] some general requirements for an acceptable (near-continuous) glucose sensor device are described. They can be summarized as follows:

- high specificity for glucose,
- fast response time,
- long-term and short-term stability,
- low drift,
- low noise,
- immediate availability of the measurement,
- high frequency of measurements (though measurement intervals of 5 minutes seem to be sufficiently small),
- easy to operate,
- low cost.

### 3.1.2 Available tools to assess glucose sensors

Some blood glucose meters and GMS show insufficient reliability. Moreover, no generally accepted procedure to test this reliability level exists [90, 137]. In the available literature, analytical and clinical approaches have been described to evaluate the quality of glucose measurements originating from a new sensor device.

The first approach measures the **analytical** accuracy by using classical statistical techniques. Examples of this type are analyses based on regression (or correlation),

mean absolute or relative difference, Bland-Altman[2] [3, 15], and analysis of variance (ANOVA) [175]. Although most of these techniques are frequently used for comparing sensor readings with reference observations, they show some weaknesses that have already been debated. *Regression*, for example, typically measures the strength of a relation between two variables (i.e., any possible correlation that explains the data) but not their numerical agreement (i.e., the bisector correlation) [15, 112]. Wide measurement ranges also give large correlation coefficients in comparison with narrow ranges such that artificial modifications can be easily realized [15]. *Difference measures* are often skewed [111] such that their result can sometimes be misleading. The method proposed by *Bland and Altman*, in its form that is mostly chosen by clinical users, relies on equal severity of measurement errors for the entire blood glucose range (e.g., 20 mg/dl measurement error in hypoglycemic range is as equally severe as 20 mg/dl measurement error in hyperglycemic range) [53]. One also relies on the assumption of a normal distribution of these errors. This assumption, not often fulfilled in clinical practice, is also required when applying classical (parametric) *ANOVA* tests. In general, it is hard to satisfy all imposed statistical conditions (present in these techniques) and to translate statistical results to clinical use.

The second approach evaluates the measurements from a **clinical** point of view. A general weakness, however, is its arbitrary strategy leading to lack of statistical evidence. A typical example of this approach is the *Error Grid Analysis (EGA)*[3] [44,52, 54] and the related *Continuous Glucose - Error Grid Analysis* [117]. Although the last technique is especially developed for testing near-continuous sensors, both techniques are based on a systematic and comprehensive graphical display assessment, which has been debated before [83, 111, 237]. The use of specific regions in the grid pattern gives the opportunity to get different results for only slightly different glucose observations and explains one of the disadvantages of this technique. Parkes *et al.* developed an alternative graphical analysis [164] that shows, however, similar drawbacks as EGA. Recently, the Diabetes Error Test Model (DETM) has been developed [113]. In this novel concept the impact of different factors that may affect postprandial glycemic excursions is simulated giving a clinical evaluation of 'treatment' errors rather than 'measurement' errors. Though the DETM in its current form may be useful in the evaluation of glucose sensors, its simulations are based on assumptions and simplifications and the model is restricted to a specific group of patients with type I diabetes.

[2] Bland and Altman proposed a new method to measure the *agreement* between variables in 1986. This alternative approach is based on graphical techniques and simple calculations, and can be designed depending on the application. In case of evaluating glucose sensors, clinical users typically opt for plotting the difference between the methods against their mean [15].

[3] The EGA, developed by Clarke *et al.* in 1987 [44], is a clinically oriented non-parametric approach to evaluate blood glucose data. This method is founded on a graphical display. The graph is divided into five regions (zones A-B-C-D-E), each associated with a qualitatively different action. The A-zone values are labeled as 'clinically acceptable'. Values from the B-zone are not acceptable but do no put the patient at immediate clinical risk as is the case with zones C-D-E. These last zones are unacceptable, accordingly. Cox *et al.* recommended to label a glucose sensor as 'acceptable' if at least 95% of the observations fall into the A-region and 0% fall in the C-D-E zones [54].

Until now no consensus exists about the technique or combination of techniques that should be applied when assessing glucose sensors since both analytical and clinical approaches show some weaknesses. At present, one (or a selection) of the techniques described above are applied for evaluating the sensor quality [29, 43, 44, 52, 104, 203, 231, 245]. In Kollman *et al.* [111] the use of *bootstrap* is suggested as safe alternative for currently known assessment techniques.

In this chapter the development of the GLYCENSIT analysis (*Glycemia Sensor Tool* or also *Glycemia Sense It*, Copyright © 2006) is presented. This tool offers a statistically sound assessment procedure comprising three complementary phases. The methodology is a first step towards a combined statistically based and clinically supported assessment technique for both blood glucose meters and GMS.

## 3.2 Research design and Methods

In this section the GLYCENSIT procedure is described in detail and an introduction to the real-life clinical ICU examples is given.

### 3.2.1 Pre-processing and Assumptions

The GLYCENSIT analysis statistically compares a set of paired glucose measurements that are gathered form a reference sensor (the so-called *gold standard* sensor) and a test sensor device. The use of a **reference** blood glucose meter (e.g., ABL glucose analyser [216] or laboratory techniques) results in reliable, accurate and discrete-time (i.e., non-continuous) measurements [38]. Typical sampling intervals for this type of sensors (applied in the ICU) vary from one to four hours. **Test** blood glucose meters and **test** GMS need to be adequately evaluated against a **reference** device. In this analysis only concomitantly measured values are considered leading to the necessary transformation of the data to sets of paired glucose measurements.

Although it is not the purpose of this study, the importance of appropriately setting up a clinical study and data pre-processing must be stressed. First of all, a **systematic study approach** to shift blood glucose over the whole clinically relevant range by using glucose clamps[4] [90] can solve the typical problem that few data of the hypo- and hyperglycemic range are available [108]. However, the recommended use of (temporary) glucose clamps is not suitable for specific patient groups (e.g., critically ill patients) for ethical reasons [213, 216]. Secondly, the received data need to be **pre-processed** in advance. In case of GMS, *calibration* is required to convert the received (electric) signal into blood glucose readings (often performed by the supplied software). Further pre-processing is necessary to remove consistent *time shifts* or *physiological lag times* (e.g., time delay between measurements in venous blood and

[4] The glucose clamp is a method to estimate the insulin sensitivity (see also Chapter 5, 5.2). A typical example is the *euglycemic* clamp in which glycemia is kept constant by infusing glucose. Accordingly, different glucose clamps with different blood glucose *targets* (also in the hypo- and hyperglycemic range) allow to generate paired observations in the *full* glycemic range.

interstitial glucose [22, 114, 115, 137], possible additional physiological delays caused by the 'alternate site testing' phenomenon[5] [115]) and *systematic analytical error* [194] by appropriately re-shifting the data. Finally, *noise* can be reduced by introducing filters [169]. However, manufacturers of GMS already frequently use these filters such that this last pre-processing step may be unnecessary.

We assume that the measurement errors are sufficiently statistically independent meaning that no correlation exists between successive errors (i.e., identically and independently distributed errors). Therefore, we advise to concomitantly measure glycemia with a minimum one-hour time interval, which is sufficiently large to meet this assumption. Moreover, the same condition is imposed in other well-known statistical assessment tools like Bland-Altman [15] or ANOVA [175]. However, it must be stressed that the GLYCENSIT procedure described below can be adapted when correlation between successive errors would be present. Still, we choose to adopt the no-correlation assumption for clarity of this exposition. Therefore, the duration of the reference sensor sampling intervals is assumed to be at least one hour.

The developed GLYCENSIT procedure comprises three complimentary phases:

1. **Phase 1:**
   Testing possible persistent measurement behaviour as a function of the glycemic range,

2. **Phase 2:**
   Testing the number of measurement errors with respect to a standard criterion for binary assessment of glycemia sensors,

3. **Phase 3:**
   Computing the tolerance intervals that indicate possible test sensor deviations for *new* observations.

The probability of the tolerance intervals directly reflects the number of samples that are considered in the statistical analysis. Besides the statistically sound assessment procedure, the computed probability level additionally improves on current assessment techniques. The method can be tuned according to the clinician's preferences regarding significance level, tolerance level, and glycemic range cut-off values. The full procedure does not directly answer the question whether a sensor is reliable or not (because of the dependency on the clinicians' preferences), but rather statistically *guides* the clinician in assessing (new) test sensor devices.

[5] The term 'alternate site testing' (AST) origins from the diabetes science. Blood glucose meters have been developed for patients with diabetes allowing the measurement of glucose in capillary blood that is collected at sites other than the fingertips [115]. It is known that capillary blood glucose values correspond to systemic (i.e., arterial) glucose levels in these patients, particularly under steady-state conditions. In critically ill patients, however, capillary blood glucose measurements are unsatisfactory since there is a high degree of imprecision and a high percentage of discordance [71]. Some new sensor devices, mainly developed for patients with diabetes, measure glucose levels **at alternate sites** (i.e., at a place other than the fingertip) and/or **in a compartment other than blood** (e.g., interstitial fluid). During rapid changes in blood glucose levels (e.g., after a meal, during exercise), the measurements with a 'test' sensor device may differ considerably from 'reference' observations [115] leading to the so-called AST phenomenon.

### 3.2.2 Normalization

Given a sample of $n$ paired glucose sensor observations $y_{\text{ref},t}$ and $Y_{\text{test},t}$ (with $t = 1, \ldots, n$), where $y_{\text{ref},t}$ is the gold standard or reference sensor and $Y_{\text{test},t}$ is the test sensor. We frame this problem in a statistical setting by considering the sensor under study as a random variable. This can be formulated as follows:

$$Y_{\text{test},t} = y_{\text{ref},t} + e_t, \tag{3.1}$$

where $e_t$ denotes a stochastic error between test and reference value at time instant $t$. In this step the errors of the set of paired glucose measurements are normalized with regard to the International Organisation for Standardization (ISO) - criterion [75]. This criterion can be summarized as follows:

- for reference values $\leq$75 mg/dl the value resulting from the test sensor is required to fall within $\pm$15 mg/dl limits,
- for reference values $>$75 mg/dl the target variability is defined as $\pm$20%.

The ISO-norm requires that at least 95% of the observations should meet this criterion. Next, the errors are normalized to make the severity of error independent of the actual blood glucose value. The normalization function is formulated as

$$u_t = f(y_{\text{ref},t} - Y_{\text{test},t}) \quad = \frac{1}{15}[y_{\text{ref},t} - Y_{\text{test},t}] \qquad \text{if } y_{\text{ref},t} \leq 75 \text{ mg/dl}, \tag{3.2a}$$

$$u_t = f(y_{\text{ref},t} - Y_{\text{test},t}) \quad = 5[\frac{y_{\text{ref},t} - Y_{\text{test},t}}{y_{\text{ref},t}}] \qquad \text{if } y_{\text{ref},t} > 75 \text{ mg/dl}, \tag{3.2b}$$

such that an error violating the ISO-criterion translates to an absolute normalized error $\geq 1$.
We proceed with normalized errors in phase 2 and 3 of the GLYCENSIT procedure. In the figures, $y_{\text{ref},t}$ and $Y_{\text{test},t}$ are symbolized by $G_R$ and $G_T$, respectively.

Figure 3.2 illustrates the use of the normalization function 3.2. Dependent on the value of the gold standard sensor ($G_R$) the evolution of the normalized error ($u$) as a function of the absolute error ($G_R - G_T$) is presented.

### 3.2.3 GLYCENSIT procedure phase 1: Persistent measurement behaviour

Clinical practice requires a sensor that tends to agree (i.e., persistently deviating measurement behaviour) in the full glycemic range as it allows the interchange between sensors with only one conversion factor. In this first phase the performance of a sensor is assessed by comparing the medians of the errors that belong to the hypo-, normo-, and hyperglycemic range. Therefore, a hypo- and hyperglycemic cut-off-value are chosen a priori and the full set of paired glucose measurements is divided accordingly (with respect to the reference values).

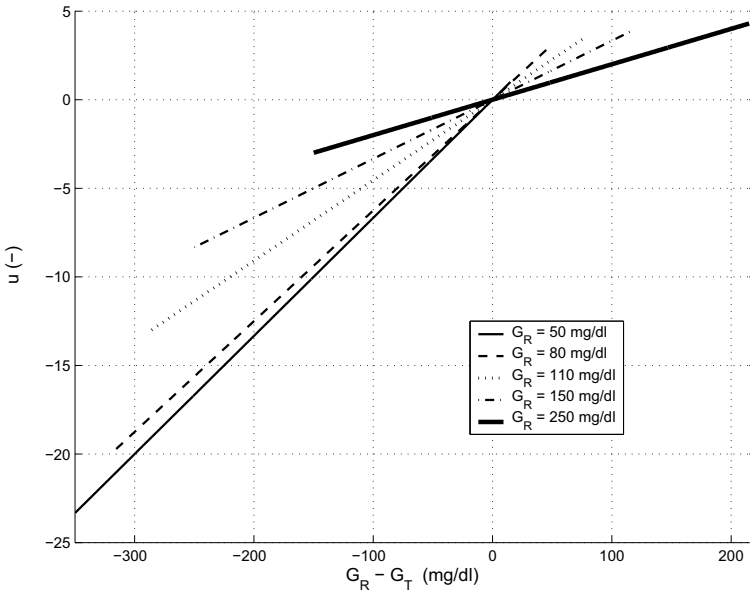


**Figure 3.2:** Illustration of the effect of the ISO normalization function for different values of the gold standard or reference sensor ($G_R$).

Next, the Kruskal-Wallis test [175] performs a non-parametric one-way ANOVA for comparing the medians of two or more groups of data. Since glucose distributions are often skewed, median rather than mean values are used [111]. This test is appropriate when the normality assumption is not met. The null hypothesis $H_0$ that the medians of the errors per glycemic group are equal is tested resulting in a $p$-value [49]. If $p \geq \alpha$ (where $\alpha$ denotes the significance level), we cannot reject $H_0$. If $p < \alpha$, we can reject $H_0$ with a probability of at least $1 - \alpha$.

Furthermore, a box and whisker plot (i.e., a *boxplot*) of the measurement errors per glycemic range is generated to give a first impression of interquartile (IQ) ranges, presence of outliers, and symmetry or skewness of the distribution. Consequently, possible overestimated and/or underestimated measurement behaviour can be easily detected.

### 3.2.4 GLYCENSIT procedure phase 2: Number of measurement errors

The statistical test used in this phase states whether normalized residual values do not violate the ISO-criterion too often. This can be expressed in terms of the number of times that the absolute value of the normalized difference does not exceed 1. The acceptable rate of errors is defined as the tolerance level $q$ (between 0 and 1). For example, a tolerance level $q = 0.04$ indicates that the sensor is allowed to make at most

4 inaccurate (based on the ISO-criterion) measurements out of 100. Mathematically, this hypothesis testing can be represented in terms of a null hypothesis $H_0$ and an alternative hypothesis $H_1$:

$$H_0 : \frac{1}{n}\sum_{t=1}^{n} I(|u_t| > 1) \leq q \text{ versus } H_1 : \frac{1}{n}\sum_{t=1}^{n} I(|u_t| > 1) > q, \tag{3.3}$$

where $I(|u_t| > 1) = 1$ if $|u_t| > 1$ and 0 otherwise.

The estimated parameter is $\hat{\theta} = \frac{1}{n}\sum_{t=1}^{n} I(|u_t| > 1)$. The test statistic is a pivot [175] and is defined as $T_n = \frac{\hat{\theta}-q}{\hat{\sigma}_\theta}$ where $\hat{\theta}$ is an estimate of $\theta$ and $\hat{\sigma}_\theta$ is the standard error of $\hat{\theta}$. The computation of the necessary sample quantities is based on the bootstrap technique. This technique is a method for estimating the distribution of the test statistic by resampling the data with replacement. An excellent introduction to the bootstrap may be found in [66].

Based on the selected significance and tolerance level and the critical $p$-value resulting from the above procedure, the test decides whether the sensor device under study succeeds the second GLYCENSIT phase. If $p \geq \alpha$, we cannot reject $H_0$. If $p < \alpha$, we can reject $H_0$ with a probability of at least $1 - \alpha$. In the last case the test sensor does not suit the stated requirements.

### 3.2.5 GLYCENSIT procedure phase 3: Tolerance intervals

In the last phase, the distribution-free tolerance intervals for reference glucose values are computed considering the test measurements. The tolerance intervals indicate a quantile range (with quantiles $r$ and $s$) in which the value, that would have been obtained with the reference device, lies with a certain probability when a **new** test measurement is presented. Instead of other techniques that only retrospectively apply to a hypothetical situation, this phase informs the user about possible measurement errors corresponding to **new** test sensor readings under *three statistical assumptions*. Firstly, the new data set is equally distributed as the given points (i.e., the data set in the current study). Secondly, the normalized residuals have a similar distribution over the three glycemic ranges. Thirdly, the new test sensor reading is obtained in similar conditions as the current data set was obtained. This phase significantly increases the actual clinical relevance as deviations can be 'predicted'.

Statistically, the computed normalized residual values, which have a common cumulative distribution function $F_u$, are sorted and the order statistics are denoted by $u_{(1)} < \ldots < u_{(n)}$. Let the amount of probability mass in the interval $F_{u_{(s)}} - F_{u_{(r)}}$ be denoted by $Q_{rs}$ with $1 \leq r < s \leq n$, where $r$ and $s$ equal $0.0125n$ and $0.9875n$, respectively, when an $A = 97.5\%$ tolerance interval is considered. For a confidence coefficient $\gamma = 1 - \alpha$ with $0 \leq \alpha \leq 1$, the probability that more than $100\gamma$ % of the probability mass is contained in the range is $P(Q_{rs} > \gamma) = 1 - \beta_\gamma(s - r, n - s + r + 1)$, where $\beta_\gamma(a, b)$ is the incomplete beta-function [56].

The computed tolerance interval can be re-transformed, by means of the inverse normalization function, $f^{-1}(y_{\text{ref},t} - Y_{\text{test},t})$, yielding tolerance intervals depending on glycemia.

This result can be interpreted by considering the *size* of the intervals and its *probability*. The first parameter denotes the clinical interpretability of the sensor under study. Large tolerance intervals indicate that reference observations may significantly deviate from test readings resulting in a clinically unacceptable test sensor performance. The second parameter is the computed probability ($P$) that reference measurements effectively lie in the aforementioned tolerance interval. This probability reflects whether the number of paired glucose measurements is sufficient for drawing statistically strong conclusions. Although this parameter is important, it is not considered in any other glucose sensor assessment technique.

### 3.2.6 Clinical trial procedure

The practical use of the presented procedure is demonstrated with three hypothetical (theoretical) data sets and one real-life clinical example. In the latter the GlucoDay system (A. Menarini Diagnostics **test** sensor, a portable instrument provided with a micro-pump and a biosensor coupled to a microdialysis system) is validated against the ABL700 Radiometer Medical glucose analyser (Radiometer, Denmark), which is labeled as **reference** sensor [51], accordingly. The features of both sensor devices and the corresponding data sets are extensively discussed in Chapter 2 (see data set 4 in 2.4.4).

Blood glucose could not be artificially shifted for ethical reasons. Indeed, the critically ill condition that is specific of this type of patients does not give any freedom to 'experiment' [213, 216]. Due to the retrospective calibration, we restricted the pre-processing phase to the transformation of the near-continuous **test** data and the discrete-time **reference** data into sets of paired glucose measurements.

Both the hypothetical and GlucoDay data sets are only used to illustrate the GLYCEN-SIT procedure. Moreover, a statistical comparison between two sets of glucose measurements always depends on the predefined clinical design parameters ($\alpha$, $q$, and hypo- and hyperglycemic cut-off-value). In this work we cannot reject $H_0$ when $p$-values are larger than $\alpha = 0.05$, $q$ varies from 2% to 10%, and blood glucose values below 80 mg/dl are called *hypoglycemic*, values above 110 mg/dl *hyperglycemic* because of the ICU-origin of the data [213, 216].

### 3.2.7 Clinical examples

Glucose determination in plasma in remote central laboratory facilities of the hospital, often referred to as the *gold standard*, is impractical, inefficient and unsafe to implement TGC. Therefore, the inevitable time delay between sampling and availability of the blood glucose result for the clinical staff necessitates the use of other methods to determine the blood glucose level. Most ICUs typically rely on point-of-

care testing for several laboratory values in the ICU to closely monitor their patients. For example arterial blood gasses, hemoglobin, lactate, glucose and potassium are frequently determined on locally available blood gas analysers and other point-of-care devices. For the measuring of glycemia in our setting, this method has been validated against the gold standard.

A prospective clinical trial in patients admitted to the ICU and in whom TGC was applied, is performed to evaluate two commercially available glucose sensor devices (the Accu-Chek Inform and the HemoCue B-glucose analyser). The ABL700 Radiometer Medical glucose analyser (Radiometer, Denmark) again serves as gold standard glucose sensor [51]. The data that are considered in this analysis are described in detail in Chapter 2 (see data set 3 in 2.4.3). Most popular standard evaluation techniques (EGA and Bland-Altman) as well as the newly developed GLYCENSIT procedure are used to assess the performance of these sensors devices. The same clinical design parameters as defined in 3.2.6 are used.

## 3.3 Results

In this section the GLYCENSIT results of the three hypothetical data sets and the real-life clinical example are firstly described. This analysis is then followed by a full assessment of two point-of-care sensor devices in regard of EGA, Bland-Altman, and GLYCENSIT.

### 3.3.1 Clinical trial procedure

Figures 3.3 to 3.8 show the results when three hypothetical data sets are submitted to the GLYCENSIT, the Bland-Altman and the EGA analysis. The **first (hypothetical) sensor** (Figure 3.3) shows persistently overestimated measurement behaviour ($G_R - G_T < 0$ for most of the errors) compared to the reference signal (phase 1: $p \geq 0.05$). In the second phase the number of measurement errors, with regard to the ISO-criterion, is evaluated as a function of the tolerance level. For all selected tolerance levels, the null hypothesis (that the relative number of measurement errors is smaller than the tolerance level) cannot be rejected ($p \geq 0.05$). The overestimated measurement behaviour returns in the last phase in which the computed tolerance intervals are illustrated. The shaded area informs the user of possible measurement errors for **new** test values. It contains 97.5% of the data ($A = 97.5\%$) and, as expected from phase 2, does hardly cross the ISO-limits. The computed probability ($P$) that 95 **new** measurements out of 100 ($\alpha = 0.05$) lie in the $A = 97.5\%$ observed tolerance interval, however, is only 43.2%. This low percentage indicates that too few paired glucose measurements ($n = 20$) are uploaded. Figure 3.4 illustrates the Bland-Altman and EGA analysis for this (hypothetical) sensor. The limits of agreement (i.e., mean error $\pm 1.96$ SD) are -28.9 mg/dl and 11.3 mg/dl for $G_R - G_T$ with an average bias (i.e., the mean glycemic error) of -8.8 mg/dl. The EGA analysis results in 95.0% of the measurements in the A-zone and 5.0% in the B-zone.

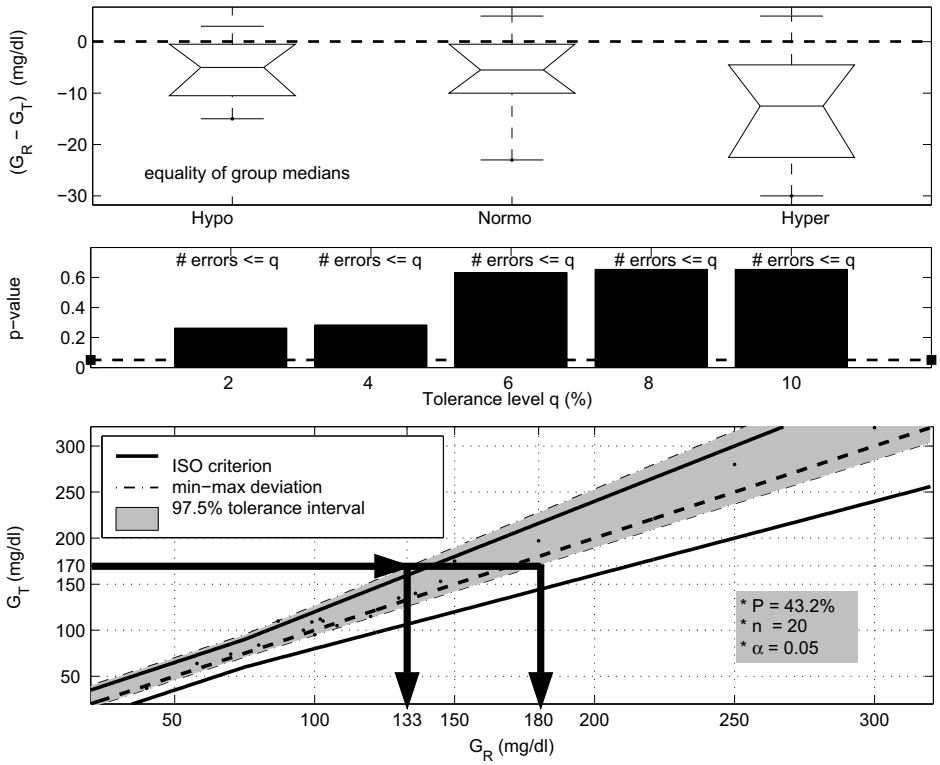


**Figure 3.3:** GLYCENSIT analysis of the first (hypothetical) sensor. The top panel (phase 1) indicates the persistently overestimated measurement behaviour ($p \geq 0.05$): all generated boxplots fall below the $G_R = G_T$ dashed line. The middle panel (phase 2) shows that few errors against the ISO-criterion are observed ($p \geq 0.05$ for all selected tolerance levels indicating the sensor is 'accurate'). The significance level ($\alpha = 0.05$) is represented by the dashed line. The # symbol indicates the "frequency of". Finally, the bottom panel (phase 3) displays the observed 97.5%-tolerance intervals (shaded area) meaning that 95 new measurements obtained from the test sensor out of 100 ($\alpha = 0.05$) lie in this area with a probability of 43.2%. The size of these intervals determines possible future sensor deviations. Let us take an example (illustrated with the arrows). When 170 mg/dl is measured with the test sensor ($G_T$), the real (reference) glycemia value ($G_R$) lies between 133 and 180 mg/dl in 95% of the cases. However, the probability level that the reference observation effectively lies in this area is only 43.2%. This low probability (due to the small number of data ($n = 20$) that are uploaded in this example) indicates the infeasibility to draw any statistically reliable conclusions. The solid and dashed line illustrate the ISO-criterion limits and the $G_T = G_R$ - axis, respectively. The dashed-dotted lines denote the minimum and maximum deviation that are present in the data (given by points).

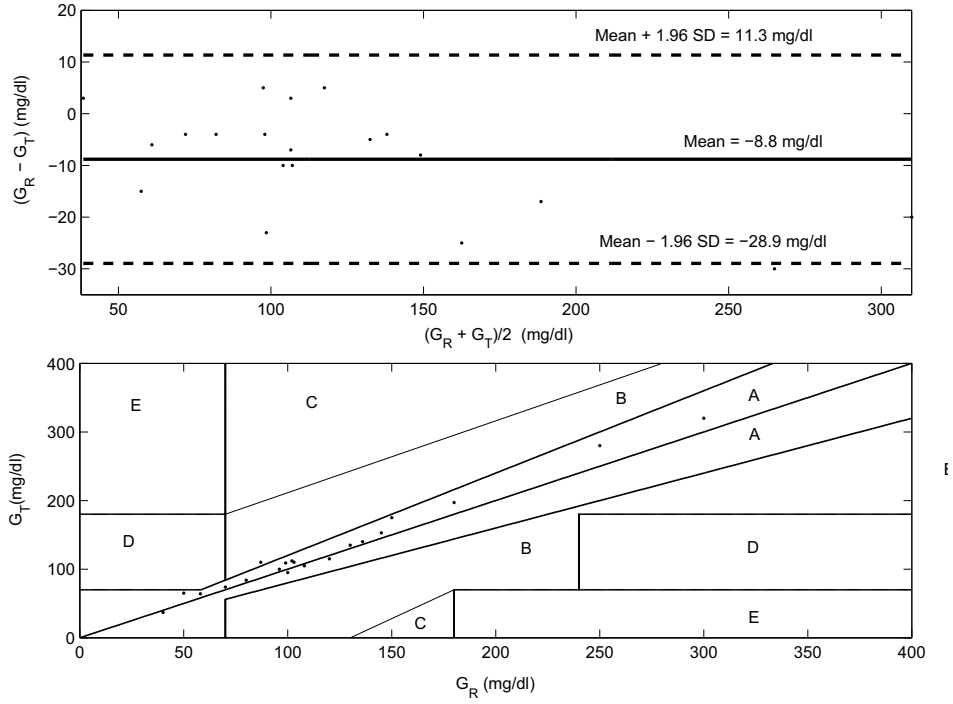


**Figure 3.4:** Bland-Altman (top panel) and EGA (bottom panel) analysis of the first (hypothetical) sensor. The mean difference (SD) between $G_R$ and $G_T$ equals -8.8 mg/dl (10.3 mg/dl) and the relative number of points in the A-region and B-region are 95.0% and 5.0%, respectively. Based on these techniques it can be concluded to accept this (hypothetical) sensor. The number of available data, however, is too small to draw any conclusion about the performance of this (hypothetical) sensor. This is indicated by the computed probability level in phase 3 of the GLYCENSIT analysis (see Figure 3.3).

The **second (hypothetical) sensor** (Figure 3.5) shows a persistent (relative) underestimated measurement behaviour although this is not statistically proven when considering the absolute errors (phase 1: $p < 0.05$). For all selected tolerance levels in phase 2, the null hypothesis can be rejected ($p < 0.05$) with a probability of at least 95% indicating that lots of measurement errors against the ISO-criterion are present. These results are also visualized in the last phase that presents the computed tolerance intervals. The number of available paired glucose data is sufficient to rely on the obtained results: a probability level $P = 98.1\%$ is reached. In Figure 3.6 the Bland-Altman and EGA analysis are presented. The obtained limits of agreement are -9.2 mg/dl and 41.6 mg/dl with 16.2 mg/dl as mean bias. The relative number of points in the A-region is equal to 88.9% whereas the B-region considers 11.1% of the available data.

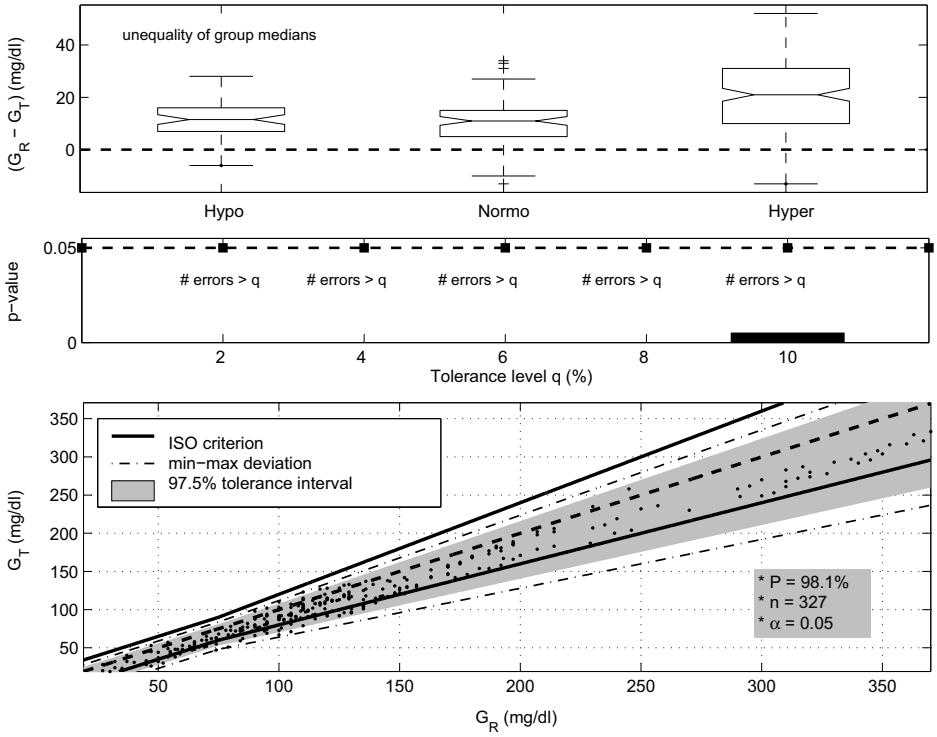


**Figure 3.5:** GLYCENSIT analysis of the second (hypothetical) sensor. The top panel shows underestimated measurement behaviour (all generated boxplots lie above the $G_R = G_T$ dashed line). Since the absolute errors in the hyperglycemic range are larger than in the normo- and hypoglycemic range, no statistical persistency could be shown ($p < 0.05$), however. Although many errors against the ISO-criterion are observed (middle panel, showing the sensor is 'inaccurate'), the performance of this sensor may be 'reliable' and tolerable (due to the relatively small size of the tolerance intervals, bottom panel) when considering a conversion factor to compensate for the underestimated measurement behaviour.

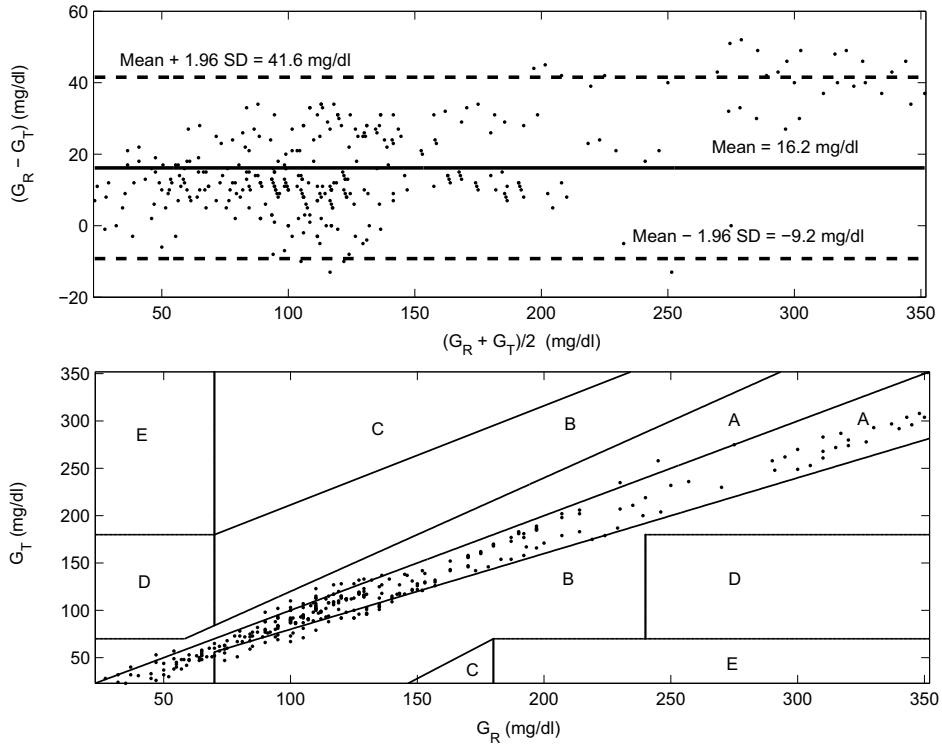


**Figure 3.6:** Bland-Altman (top panel) and EGA (bottom panel) analysis of the second (hypothetical) sensor. The mean difference (SD) between $G_R$ and $G_T$ is equal to 16.2 mg/dl (12.9 mg/dl) and the relative number of points in the A-region and B-region are 88.9% and 11.1%, respectively. The obtained standard deviation and the number of points in the B-region are too large to accept this (hypothetical) sensor. The application of the GLYCENSIT procedure, however, uses a different approach to extract additional information from the data, which may lead to acceptance of the sensor (see also Figure 3.5).

The non-persistent deviations ($p < 0.05$) of the **third (hypothetical) sensor** (Figure 3.7) is observed in the first phase (underestimation in hypoglycemic and overestimation in hyperglycemic range). Few errors against the ISO-criterion are obtained (phase 2: $p \geq 0.05$ for every $q$) leading to tolerance intervals that are fairly comparable with the ISO-limits but that also show that both under- and overestimated behaviour can be expected for new measurements with the test sensor device (phase 3). A high probability level ($P$=97.5%) confirms the reliability of the obtained results. Figure 3.8 depicts the performed Bland-Altman and EGA analysis for this sensor. The limits of agreement are -22.2 mg/dl and 16.6 mg/dl for $G_R - G_T$ with an average bias of -2.8 mg/dl. The EGA analysis results in 97.3% of the measurements in the A-zone and only 2.7% in the B-zone.

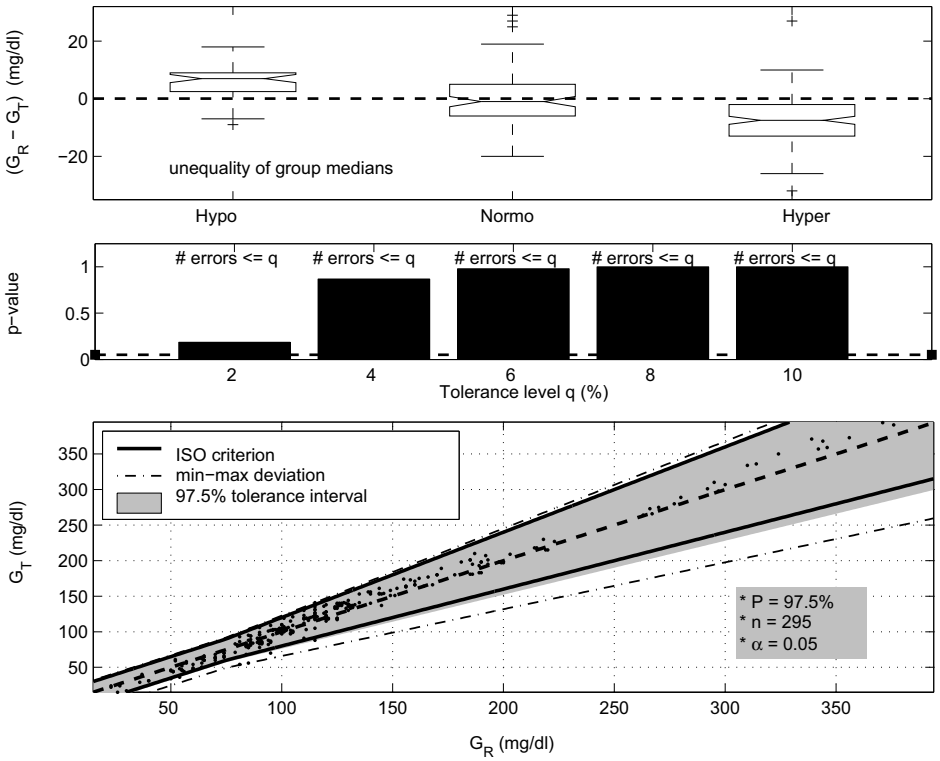


**Figure 3.7:** GLYCENSIT analysis of the third (hypothetical) sensor. The non-persistent measurement behaviour is visualized in the top panel (underestimation in the hypoglycemic range, overestimation in the hyperglycemic range). Consequently, the use of a conversion factor is infeasible in clinical practice. The sensor performs well with regard to the ISO-criterion (middle panel): very few errors are made against this criterion (showing the 'accuracy' of the sensor). The implementation of the sensor depends on the user's clinical assessment of the size of the tolerance intervals (bottom panel).

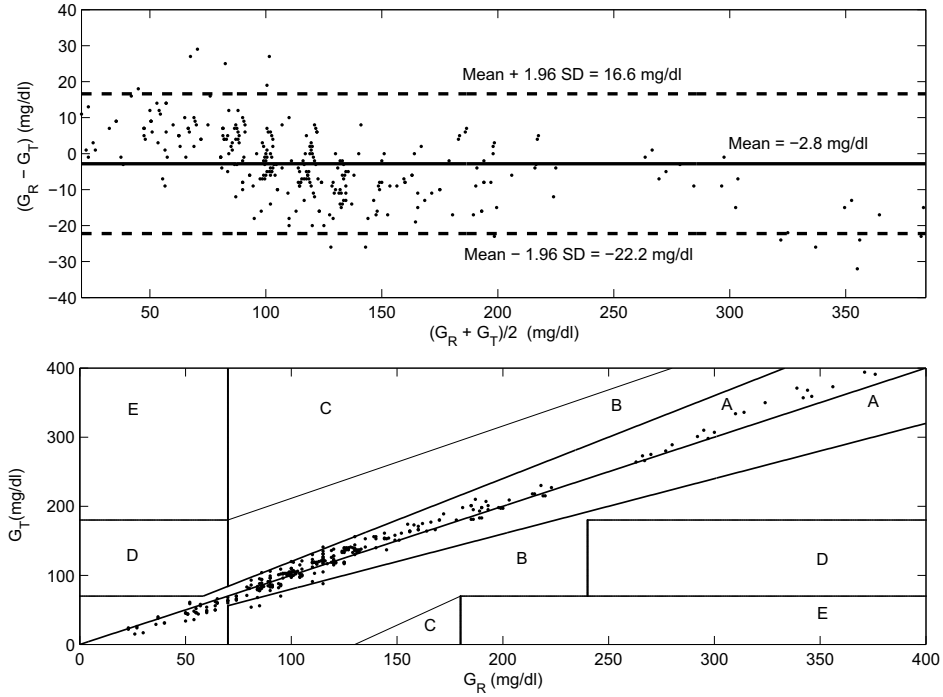


**Figure 3.8:** Bland-Altman (top panel) and EGA (bottom panel) analysis of the third (hypothetical) sensor. The mean difference (SD) between $G_R$ and $G_T$ is equal to -2.8 mg/dl (9.9 mg/dl) and the relative number of points in the A-region and B-region are 97.3% and 2.7%, respectively. The obtained standard deviation and the number of points in the B-region are small enough to accept the (hypothetical) sensor.

Finally, the GLYCENSIT procedure is applied to the **GlucoDay sensor** data (Figure 3.9). The medians of the measurement errors are 0.74, 0.028, and -1.3 mg/dl for the hypo-, normo-, and hyperglycemic range, respectively, leading to persistently deviating measurement behaviour (phase 1: $p \geq 0.05$). A tolerance level of at least 8% is required for not rejecting the null hypothesis in phase 2 ($p = 0.075$ and $p = 0.45$ when $q = 0.08$ and $q = 0.10$, respectively). When smaller tolerance levels are preferred, the null hypothesis can be rejected ($p < 0.05$) with a probability of at least 95% indicating that the test sensor does not suit the predefined performance requirements. The tolerance intervals are much larger than the ISO-criterion and visualize the under- as well as the overestimated measurements (phase 3): the shaded area is larger than the ISO-limits in both directions. The number of available paired glucose data is sufficient to rely on the obtained results: the computed probability level ($P$) equals 98.6%. In Figure 3.10 the Bland-Altman and EGA analysis are illustrated. The obtained limits of agreement are -26.5 mg/dl and 24.5 mg/dl for $G_R - G_T$ with -1.0 mg/dl as mean bias. The relative number of points in the A-zone and B-zone equal 90.9% and 9.1%, respectively.

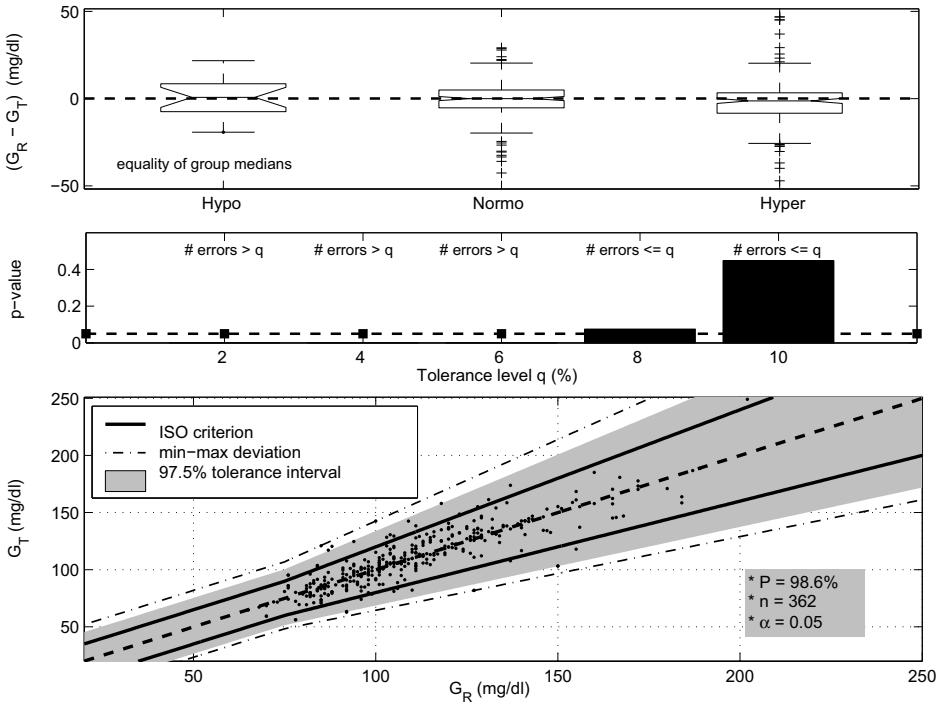


**Figure 3.9:** GLYCENSIT analysis of the GlucoDay sensor. The top panel shows the persistent measurement behaviour as a function of blood glucose (median measurement errors for the hypo-, normo-, and hyperglycemic range are 0.74, 0.028, and -1.3 mg/dl, respectively) although both underestimated and overestimated observations are abundantly present. When less than 8% errors against the ISO-criterion are permitted, the sensor does not perform efficiently (middle panel). The bottom panel illustrates the tolerance intervals that are much larger than the ISO-limits in both under- and overestimation direction. Together with the large min-max deviations this may lead to no acceptance of the sensor for use in the ICU.

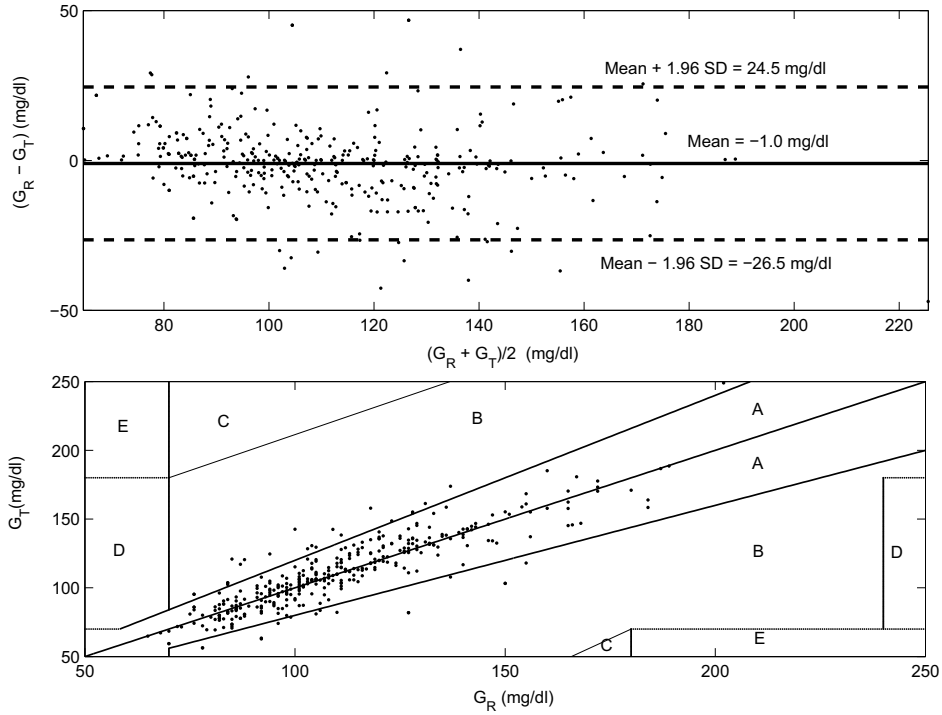


**Figure 3.10:** Bland-Altman (top panel) and EGA (bottom panel) analysis of the GlucoDay sensor device. The mean difference (SD) between the ABL reference sensor ($G_R$) and the GlucoDay test sensor ($G_T$) equals -1.0 mg/dl (13.0 mg/dl) and the relative number of points in the A-region and B-region are 90.9% and 9.1%, respectively. The large limits of agreement and the high number of measurements in the B-zone may lead to disapproval of the GlucoDay sensor for use in the ICU.

### 3.3.2 Clinical examples

The majority of the measurements of Accu-Chek with regard to ABL lie in zone A (97.6%) when applying the EGA analysis. The other 2.4% of the measurements are situated in zone B (see Figure 3.11, top panel). When comparing HemoCue with ABL, 86.9% of the measurements are located in zone A and 13.1% in zone B (see Figure 3.11, bottom panel).

The Bland-Altman analysis clearly illustrates the bias and the corresponding limits of agreement. When comparing the measurements of ABL and Accu-Chek, the bias from the Accu-Chek sensor equals -6.3 mg/dl and the limits of agreement are 14.0 mg/dl and -26.5 mg/dl (see Figure 3.12, top panel). For the analysis of the HemoCue device, the obtained mean glycemic error is -10.9 mg/dl and the computed limits of agreement are 7.6 mg/dl and -29.5 mg/dl (see Figure 3.12, bottom panel).

In the first step of the GLYCENSIT analysis, the null hypothesis is tested by the non-parametric one-way ANOVA test (Kruskal-Wallis). This turned 0 as $p$-value for ABL versus Accu-Chek and 0.002 for ABL versus HemoCue. The null hypothesis that the medians of the errors per glycemic group are equal, is rejected ($p < 0.05$) with a probability of at least 95% in both cases. Indeed, no persistently deviating measurement behaviour is obtained for the sensors under study. (Figures 3.13 and 3.14, top panels). Particularly the use of the Accu-Chek sensor results in both under- and overestimations of the reference blood glucose value. It must be noted that persistently overestimated measurement behaviour is approached (but not statistically proven) for the HemoCue sensor device.

The middle panels of Figures 3.13 and 3.14 illustrate the second phase of the GLYCENSIT analysis. Here, the computed $p$-values as a function of the tolerance level are depicted for both test sensors. In case of Accu-Chek the null-hypothesis, meaning that the two signals are equal with respect to the ISO criterion, cannot be rejected for the selected tolerance levels (for $q$ = 2%, 4%, 6%, 8% or 10%: $p \geq 0.05$, see Figure 3.13). The use of the HemoCue sensor, however, results in $p$-values $< 0.05$ for all the selected tolerance levels (see Figure 3.14) indicating that the null-hypothesis is rejected with a probability of at least 95%. The Accu-Chek sensor clearly outperforms the HemoCue device in terms of 'accuracy' (phase 2).

Finally, in the third phase of the GLYCENSIT analysis some tolerance intervals that indicate possible test sensor deviations for **new** observations are computed. Each shaded area (Figures 3.13 and 3.14, bottom panels) contains 97.5% of the specific data and gives information concerning measurement errors for **new** observations with the respective test sensor device that is under study. The probability that 95 new measurements out of 100 ($\alpha = 0.05$) effectively lie in these shaded areas is 99.4%. This probability is related to the number of measurements and is sufficiently high to rely on the computed tolerance intervals.

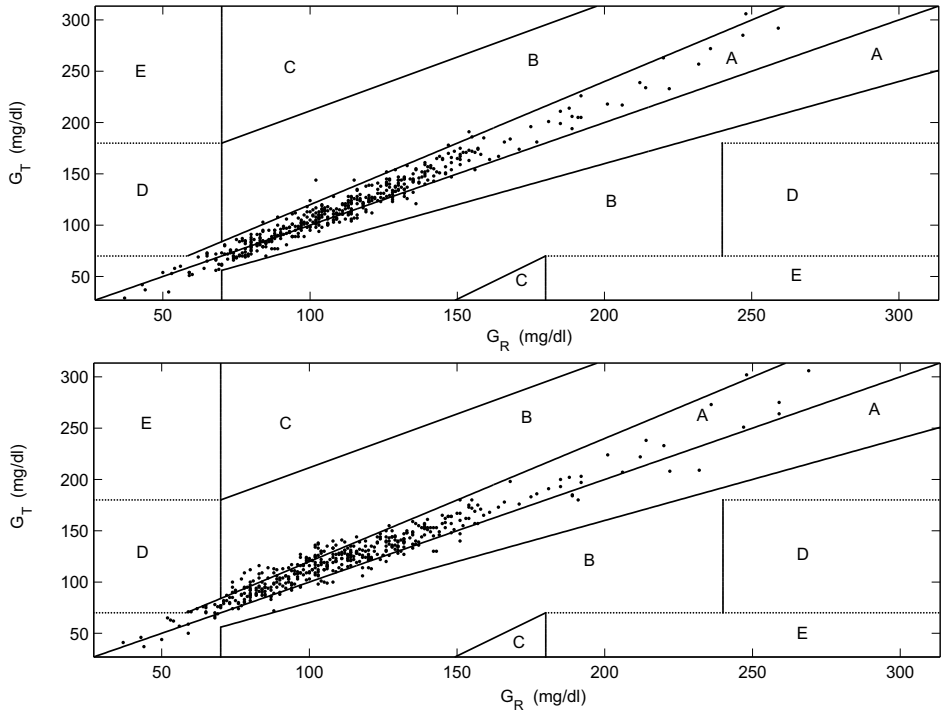


**Figure 3.11:** The EGA analysis for the measurements of the Accu-Chek test sensor ($G_T$) as a function of the ABL reference sensor ($G_R$) is presented in the top panel: 97.6% of the measurements lie in zone A whereas 2.4% lie in zone B. In the bottom panel the observations of the HemoCue test sensor ($G_T$) as a function of the ABL reference sensor ($G_R$) are depicted: 86.9% lie in zone A and 13.1% in zone B.

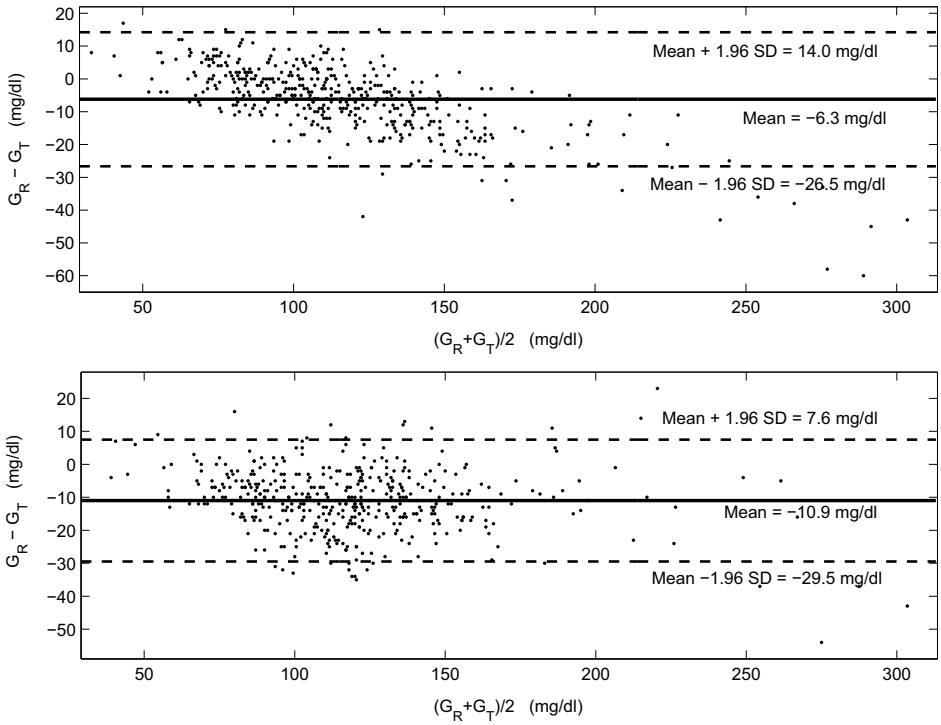


**Figure 3.12:** Bland-Altman analysis for the Accu-Chek (top panel) and the HemoCue (bottom panel) test sensor. The bias (or mean difference) and the limits of agreement are shown for both point-of-care devices in the entire range of measured glycemia. The bias for the Accu-Chek is -6.3 mg/dl and the limits of agreement are 14.0 and -26.5 mg/dl. The bias for the HemoCue is -10.9 mg/dl and the limits of agreement are 7.6 and -29.5 mg/dl. Again, the reference (ABL) and the test sensor devices (Accu-Chek / HemoCue) are marked by $G_R$ and $G_T$, respectively.

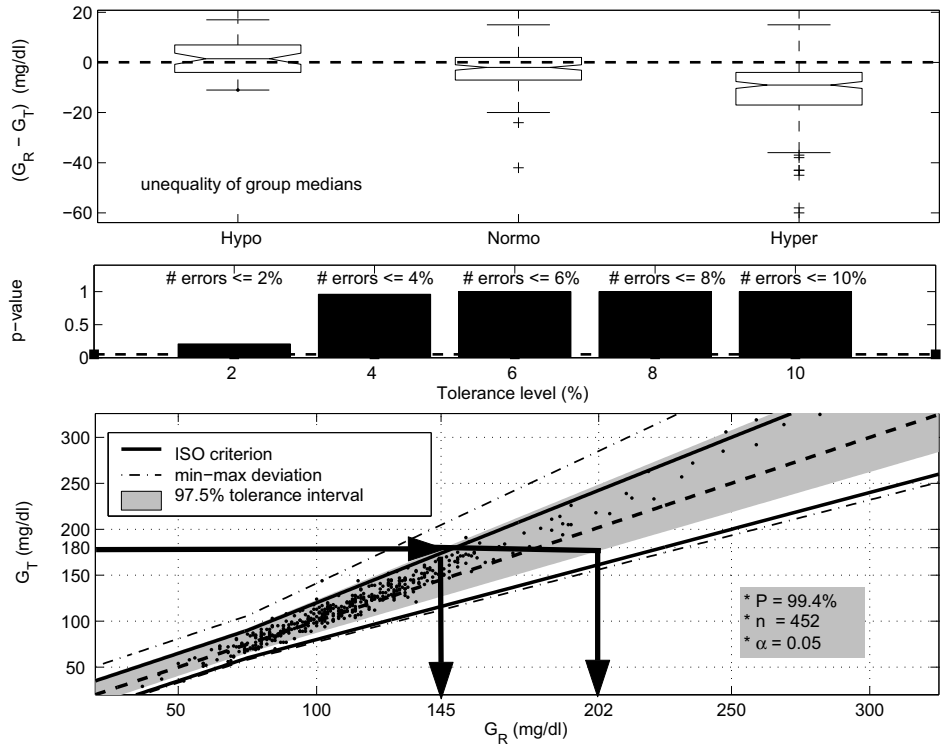


**Figure 3.13:** GLYCENSIT analysis for the Accu-Chek sensor. The top panel (phase 1) indicates the non-persistent measurement behaviour ($p = 0 < 0.05$) shown by the presence of both overestimated and underestimated measurement deviations. The median measurement errors for the hypo-, normo-, and hyperglycemic range are 1.5, -2, and -9 mg/dl, respectively. The middle panel (phase 2) shows that few errors against the ISO-criterion are observed ($p \geq 0.05$ for all selected tolerance levels). The significance level ($\alpha = 0.05$) is represented by the dashed line. Finally, the bottom panel (phase 3) displays the 97.5%-tolerance intervals (shaded area) meaning that 95 new measurements obtained from the test sensor out of 100 ($\alpha = 0.05$) lie in this area with a probability of 99.4%. The size of these intervals determines possible future sensor deviations. Let us take an example (illustrated with the arrows). When 180 mg/dl is measured with the test sensor ($G_T$) (i.e., a new observation), the real (reference) glycemia value ($G_R$) will lie between 145 and 202 mg/dl in 95% of the cases. The probability level ($P$) that the reference observation effectively lies in this area is equal to 99.4%. The solid and dashed line illustrate the ISO-criterion limits and the $G_T = G_R$ - axis, respectively. The dashed-dotted lines denote the minimum and maximum deviation that are present in the data (given by points).

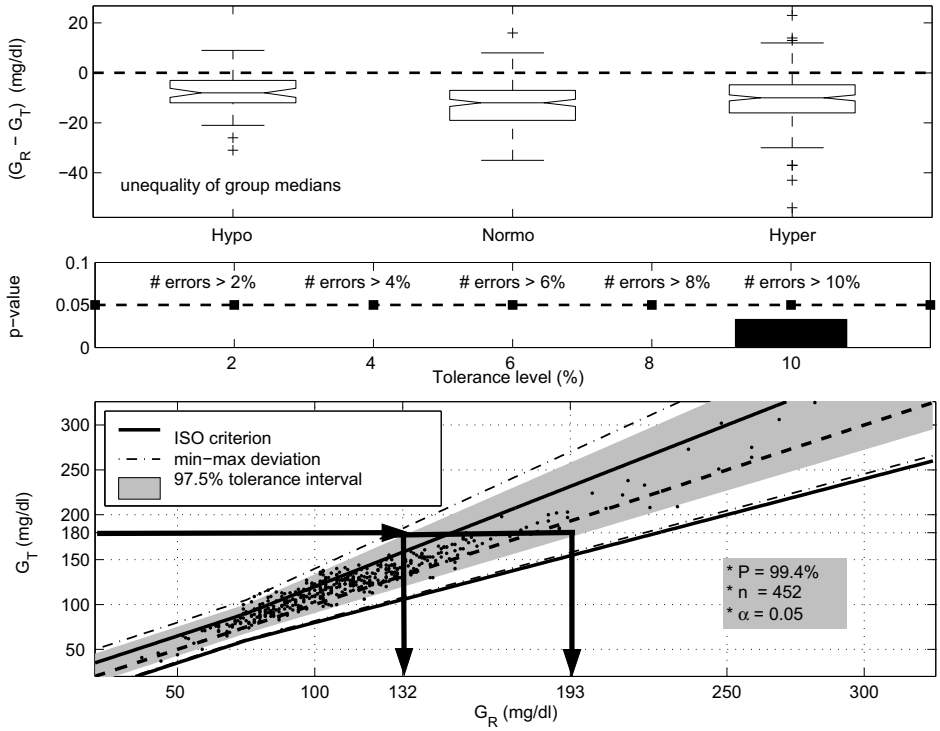


**Figure 3.14:** GLYCENSIT analysis for the HemoCue sensor. Although the used Kruskal-Wallis test indicates non-persistent measurement behaviour ($p = 0.0021 < 0.05$), the top panel (phase 1) shows that this sensor device *approaches* a persistently deviating (overestimated) measurement behaviour. The median measurement errors for the hypo-, normo-, and hyperglycemic range are -8, -12, and -10 mg/dl, respectively. Many errors against the ISO-criterion are observed, as presented in the middle panel (phase 2), since $p < 0.05$ for all selected tolerance levels. The size of the 97.5%-tolerance intervals ($P = 99.4\%$) is comparable to that from the Accu-Chek-sensor (phase 3, bottom panel). When 180 mg/dl is measured with the test sensor ($G_T$), the real (reference) glycemia value ($G_R$) will lie between 132 and 193 mg/dl in 95% of the cases. The (persistently) overestimated measurement behaviour is visualized as well. The use of a general conversion factor to approach 'real' blood glucose may be feasible such that expected measurement errors can be taken into account in the TGC treatment.

## 3.4 Discussion

The results that are obtained in the previous section are extensively discussed here for both the clinical trial procedure (i.e., the three hypothetical data sets and the GlucoDay observations) and the clinical examples (validation of the Accu-Chek and HemoCue sensor device). Further, the interpretation of the statistical reliability is explained. Finally, the presented GLYCENSIT procedure is also implemented as a web-based assessment tool which is briefly introduced.

### 3.4.1 Clinical trial procedure

Existing methods used for the evaluation of (*discrete-time*) blood glucose meters and (*near-continuous*) GMS are based on an analytical or a clinical approach, but often show some weaknesses. Here, we present the GLYCENSIT procedure, which is a new assessment tool for glucose sensors. The procedure consists of three analyses: testing possible persistent measurement behaviour as a function of the glycemic range, testing the number of measurement errors with respect to the ISO-criterion, and finally computing the tolerance intervals for *new* test sensor values. The method can be tuned according to the expert specifications regarding significance level, tolerance level, and glycemic range cut-off values.

Although the **first (hypothetical) sensor** performs well with respect to the ISO-criterion (high accuracy, see phase 2), persistently overestimated measurement behaviour (phase 1) may result in potentially dangerous false negatives (e.g., failure to measure true hypoglycemic events) [196]. Additionally, few uploaded measurements give a low reliability to the computed tolerance intervals (the probability level that new measurements effectively lie in these tolerance intervals is only 43.2%, phase 3) and indicate the necessity for large data sets (ideally spread over the whole clinically relevant range) to draw statistically reliable conclusions. Therefore, no hard conclusions can be made for this first (hypothetical) sensor device. Ignoring this low probability level may lead to acceptance of the sensor which is also suggested by the Bland-Altman and the EGA analysis.

The number of errors against the ISO-criterion is high (inaccurate sensor, phase 2) for the **second (hypothetical) sensor** but this does not necessarily lead to sensor rejection. Indeed, blood glucose is underestimated over the whole range (phase 1, phase 3), which may result in false positives. This can be compensated (using a conversion factor) more safely than overestimated behaviour and may lead to acceptation of the sensor device under study (since the tolerance interval area may be clinically tolerable). This example, *apart from its statistical framework*, shows the merit of the GLYCENSIT procedure in comparison with previously described techniques among Bland-Altman and EGA (see Figure 3.6). The obtained range between the limits of agreement (in the Bland-Altman analysis) is too large to be clinically acceptable (assuming normally distributed errors). Based on the EGA-analysis, the sensor is rejected, too, since the relative number of errors in the B-region is more than 5% [54]. Known (but already debated) techniques may give a restricted view on the results whereas the GLYCENSIT

procedure presents additional information that may lead to different conclusions.

Although only few errors against the ISO-criterion are observed (phase 2), which leads to computed tolerance intervals (phase 3) that are comparable to the ISO-limits, the implementation of the **third (hypothetical) sensor** in clinical practice may be difficult. Indeed, the performance of this (hypothetical) sensor is strongly dependent on the glycemic range (phase 1) and can only be accepted when the computed tolerance intervals (phase 3) are found to be sufficiently small for the user. The current device perfectly meets the 'accuracy' standards (i.e., few errors against the ISO-criterion) but may not be 'reliable' due to the non-persistent measurement behaviour. Since the distance between the limits of agreements is restricted and the mean bias is negligible, this sensor may be accepted when only applying the Bland-Altman analysis. Analogously, since the majority of the points lie in the A-region of the error grid (only 2.7% of the observations is situated in the B-zone) this sensor would also be accepted according to EGA.

The **GlucoDay** data analysis demonstrates the (relative) high number of errors against the ISO-criterion (phase 2). This explains the magnitude of the (reliable, $P = 98.6\%$) tolerance intervals, which are much wider than the ISO-limits for the full glycemic range (phase 3). Although the general measurement deviations are persistent (phase 1), some measurement errors are unacceptably large (phase 1) leading to broad minimum and maximum deviations (phase 3). In view of the preferred design parameters (see above) the GlucoDay sensor may not be efficient for blood glucose control in the ICU. A similar conclusion can be made when considering the Bland-Altman and EGA analysis. The first approach reveals a too large distance between the limits of agreement in spite of the negligible average bias. The second approach illustrates that 9.1% ($> 5\%$) of the measurements fall in the B-zone which is too much to be clinically acceptable [54]. It must be stressed that these results are only related to the performance of the GlucoDay sensor applied to critically ill patients (as possibly different results can be obtained when testing the sensor in patients with diabetes).

From the reasoning above it is clear that all GLYCENSIT phases must be considered next to each other to correctly interpret the results. The GLYCENSIT procedure is a *guideline* for the user who can tune the analysis (depending on the application and type of patients) according to the preferred design parameters (i.e., significance level, tolerance level, and glycemic range cut-off values). The procedure generates a broader view on the data (compared to existing methods) as it approaches the data from three different perspectives. Moreover, the analysis is founded on (non-parametric) statistical techniques that allow the user to draw statistically reliable conclusions. Accordingly, the GLYCENSIT procedure may be an *alternative for* or a *supplemental tool to* existing evaluation techniques to assess the performance of glucose sensors.

### 3.4.2 Clinical examples

The Accu-Chek sensor device can be labeled as 'clinically acceptable' according to the EGA guidelines as more than 95% of the observations fall in the A-region and no measurements are observed in zone C, D, and E. Since the relative number of errors in the B-region is more than 5% for the HemoCue sensor, this sensor device could *not* be approved when following the EGA guidelines (Figure 3.11).

The computed bias and limits of agreement as determined in the Bland-Altman analysis for both sensors under study are fairly wide and therefore questionable for safe clinical use in the ICU. Let us take an example. A blood glucose level of 80 mg/dl obtained by either of these point-of-care methods could in reality be a hypoglycemic event (e.g., 55 mg/dl, see Figure 3.12). Three remarks must be stressed here:

- Firstly, the Bland-Altman analysis is characterized by plotting the difference against the *mean* of the two measurements. It would be expected to plot the difference against the reference value. However, doing so may cause a statistical artefact [15, 79]. In the example mentioned above this 80 mg/dl value is the average of the reference and test sensor. Thus, the computed limits of agreement (i.e., mean error $\pm$ 1.96 SD) are related to the average of the measurements and not to either value separately.

- Secondly, the evaluation of a Bland-Altman analysis particularly relies on the *size* of the limits of agreement in combination with the mean error (bias). The interchange between sensors with only one conversion factor is possible when the limits of agreement are sufficiently narrow. Here, the limits of agreement are found to be too wide to be clinically acceptable for both the Accu-Chek and the HemoCue device.

- Thirdly, the Bland-Altman and EGA analysis only *retrospectively* evaluate the observed data just like all other standard assessment tools do. The newly proposed GLYCENSIT procedure, however, computes tolerance intervals that indicate the range in which the reference value would lie when a **new** test measurement is presented (see 3.2.5).

The overall HemoCue performance is poor (bias = -10.9 mg/dl) and shows a trend to systematically overestimate the blood glucose. Although the bias with Accu-Chek is slightly lower, the limits of agreement are wider (than for HemoCue) with deviations that are glycemia dependent: underestimations appear in the hypoglycemic range, whereas overestimations are observed in the hyperglycemic range (Figure 3.12).

A more detailed and statistically sound evaluation of the two sensor devices under study is found using the GLYCENSIT analysis. Both sensors show non-persistent measurement behaviour as presented in the first phase (Figures 3.13 and 3.14, top panel). These non-persistent deviations are more pronounced with the Accu-Chek sensor: the hyperglycemic range is typically characterized by overestimation behaviour whereas the hypoglycemic range is rather typified by underestimation behaviour.

Although no statistically persistent deviations were found for the HemoCue sensor ($p < 0.05$), it is illustrated in the top panel of Figure 3.14 that persistent overestimation is *approached*. Persistent measurement behaviour is preferred above non-persistent deviations since it allows the interchange between sensors with only one conversion factor. However, it must be noticed that persistent *underestimation* is more safe than persistent *overestimation* as the latter could lead to potentially dangerous false negatives (e.g., failure to measure true hypoglycemic events) [196].

The second phase of the GLYCENSIT procedure reveals an acceptable performance of the Accu-Chek sensor with respect to the number of measurement errors for the selected tolerance levels ($p \geq 0.05$ for each tolerance level, middle panel of Figure 3.13). This is in contrast with the HemoCue sensor, which failed at all tested tolerance levels ($p < 0.05$ for each tolerance level, middle panel of Figure 3.14). The relative number of errors made against the ISO-criterion for this last sensor type is larger than the predefined tolerance levels. In other words, the measurement behaviour of the Hemocue device is more persistent (typically an overestimation of the reference sensor) compared with Accu-Chek, but many errors against the ISO-criterion are observed. The measurement behaviour of the Accu-Chek sensor is much more dependent on the glycemic range, but only few errors against the ISO-criterion are made.

Finally, the last phase of the GLYCENSIT analysis informs the clinician about 'future' measurement deviations. The tolerance intervals for the Accu-Chek and the HemoCue sensor are comparable in terms of size. An important difference, however, is their relation to the ISO-limits as could be expected from the second phase. On the one hand, the Accu-Chek tolerance intervals largely lie within the ISO-limits. The range in which the value, that would have been obtained with the reference device, lies when a **new** test measurement is presented, is illustrated both under and above the dashed line (that represents the $G_T = G_R$ - axis) in the bottom panel (Figure 3.13). This indicates that both under- and overestimations can be expected. On the other hand, the HemoCue tolerance intervals mainly cross the *upper* ISO-limits (with only a slight deviation from the dashed line in the other direction). In other words, the observations of the HemoCue device are more persistently deviating as also shown in the first phase and are predominantly overestimations with regard to the reference sensor whereas the deviations of Accu-Chek are substantially more non-persistent being both over- and underestimations depending on the glycemic range.

Based on these results, none of the tested point-of-care sensors showed good reliability. At first sight, the Accu-Chek sensor seems more accurate but is unpredictable regarding the direction of the measurement error. The HemoCue sensor is somewhat less accurate but the measurement error is more persistent, in particular overestimating the gold standard blood glucose values. While awaiting more reliable point-of-care devices, clinicians should decide what is preferable when choosing such a device: a less accurate sensor but with a more predictable and persistently deviating measurement behaviour or a more accurate sensor with an unpredictable and non-persistent measurement behaviour.

The tolerance intervals that are presented in the bottom panels of Figures 3.13 and 3.14 may further facilitate the interpretation of the GLYCENSIT analysis for the clinician. The arrows illustrate a clinical example: if 180 mg/dl would be measured with the Accu-Chek sensor (i.e., a new observation), the real (reference) blood glucose would lie between 145 and 202 mg/dl (which expresses the $A = 97.5\%$ tolerance interval) in 95% of the cases. Alternatively, the same observed value with the HemoCue device would result in a real (reference) glycemia value between 132 and 193 mg/dl in 95% of the cases. This exercise can be performed for any possible new measurement.

Furthermore, it is important to note that the computed probability level ($P = 99.4\%$) is sufficiently high for relying on these tolerance intervals. This means that the number of paired glucose observations was adequate (with regard to the selected significance level $\alpha = 0.05$) to draw statistically strong conclusions. Although this probability level is only related to the reliability of the tolerance intervals (phase 3 of the GLYCENSIT analysis), it is reasonable to suggest that this probability level is also a good approach for describing the statistical reliability of the first and second phase of the GLYCENSIT analysis. Moreover, the currently standard evaluation tools (e.g., EGA, Bland-Altman, etc.) do not compute any probability level concerning the reliability of the performed test.

### 3.4.3 Statistical reliability

It is clear that the user should have a clear idea about the number of samples that is required for reliably performing any statistical test. Alternatively, the statistical relevance of the performed test is made clear when comparing the number of available data with the number of measurements that would have been necessary for drawing statistically strong conclusions. In case of **parametric** tests (that are only valid for a standard family of distributions), the *power* of the statistical test can be computed. This power is the probability of rejecting the null hypothesis $H_0$ when the alternative hypothesis $H_1$ is true and depends on the significance level, the number of observations, and the 'effect size'[6] [92, 134]. The calculation of the power for robust statistics or non-standard **non-parametric** statistics (which are the fundamentals of the GLYCENSIT procedure) are not addressed at a practical level. The probability level, that is computed in the last phase of the GLYCENSIT analysis and that also depends on the significance level and the number of uploaded observations, however, behaves as an alternative for power calculations. Accordingly, the number of samples that is required for drawing statistically strong conclusions can be determined based on the desired probability level and the selected significance degree.

Figures 3.15 and 3.16 illustrate the probability level as a function of the selected significance level and the number of uploaded paired glucose measurements. It is shown that the probability level increases as the number of paired observations increases and as the significance level increases. However, it is obvious that a large

[6] The effect size is a parameter that reflects the extent to which the null hypothesis $H_0$ is false [92].

significance level (e.g., $\alpha = 0.1$) also corresponds to a weaker 'statistical level' (i.e., more easy to get) explaining the higher probability levels that are obtained in that case. For this reason a significance level $\alpha = 0.05$ is mostly preferred in statistical tests. It is recommended that the probability level is at least 90% (or preferably higher).

The number of uploaded paired glucose observations that is required for adequately performing the GLYCENSIT procedure can be easily determined with Figure 3.16. When a significance level, $\alpha = 0.05$, is selected and a probability level $P = 95\%$ is wished, at least 225 paired observations should be submitted to the GLYCENSIT analysis for drawing statistically reliable conclusions. This number varies as a function of $\alpha$ and $P$ and is only related to phase 3 of the analysis. An important feature is that this computation is independent of the data set under study giving the possibility to compute this required number of samples in advance.

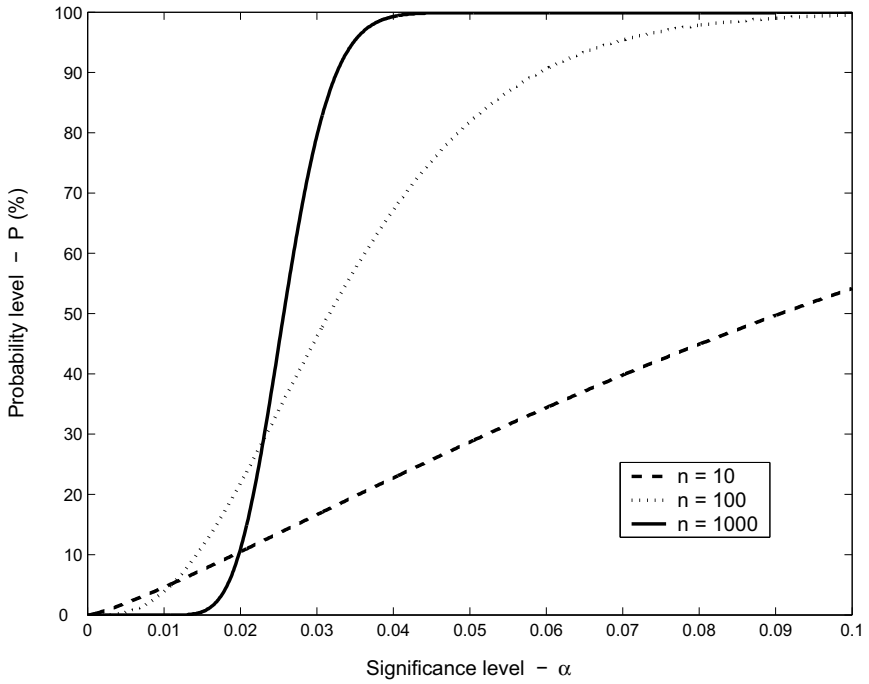


**Figure 3.15:** Visualization of the computed probability levels as a function of the significance level $\alpha$ for a few selected numbers of paired observations $n$.

The higher the number of measurements within a set of paired glucose values, the more powerful the assessment tool will be. It must be noticed that a GLYCENSIT analysis always depends on the design parameters that are defined by the (clinical) user or that are specific of the application (e.g., patients with diabetes, critically ill patients). As for any statistical test, we advise to consider as many paired glucose measurements per

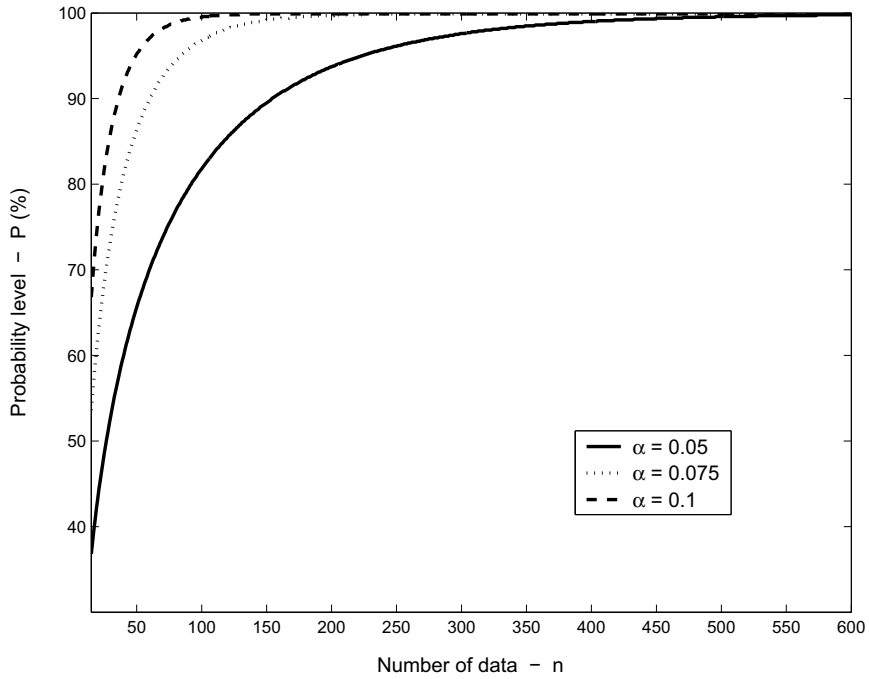


**Figure 3.16:** Visualization of the computed probability levels as a function of the number of paired observations $n$ for a few selected significance levels $\alpha$.

patient as possible (to cover the intra-patient variability), ideally spread over the full glycemic range, and as many patients as possible (to cover the inter-patient variability) although we acknowledge that clinical and financial restrictions are frequently present in a clinical environment.

### 3.4.4 GLYCENSIT website

The proposed GLYCENSIT procedure is implemented as a web-based assessment tool, which is available at **http://www.esat.kuleuven.be/GLYCENSIT** (free of charge). Users can upload sets of paired glucose values and define the preferred significance level and the hypoglycemic, normoglycemic, and hyperglycemic range. Different tolerance levels (varying from 2% to 10%) are automatically selected in phase 2 to give a broad overview of the sensor performance in terms of accuracy. Finally, users are notified by e-mail when the analysis, running on the host server, has finished. The analysis results page (that is only accessible for the specific user) gives an overview of the full GLYCENSIT analysis. It *guides* the clinician for making an appropriate and precise evaluation of the glucose sensor under study.

## 3.5 Conclusions

A statistical assessment tool for evaluating the reliability of blood glucose meters and GMS was developed: the GLYCENSIT procedure. This procedure aimed to statistically guide the clinician in appropriately evaluating glucose sensors. The GLYCENSIT analysis comprised three phases in which the persistency of the measurement behaviour, the number of measurement errors (sensor accuracy), and the magnitude of new measurement errors (tolerance intervals) were successively analysed. Additionally, the procedure provided a probability measure for the tolerance intervals based on the number of available samples and the selected significance level. This probability level was indicative of the statistical evidence for the data under study. It was indicated how the method could be tuned according to the expert specifications regarding significance level, tolerance level, and glycemic range cut-off values. The chapter was concluded with a full evaluation analysis of two point-of-care sensor devices and a presentation of the GLYCENSIT website. The GLYCENSIT procedure may be an alternative or supplemental tool to existing evaluation techniques to assess the performance of glucose sensors. The results obtained in this chapter are further described in [225, 232].

# Chapter 4

# General Assessment of Glycemia Control Systems

*As the normalization of blood glucose is becoming standard practice for critically ill patients, new (semi-automated) 'blood glucose control' algorithms (or 'insulin titration' algorithms) are under development but these algorithms require a stringent validation before they can replace the currently used protocols. In this chapter a new approach, labeled as the 'Glycemic Penalty Index' (GPI), for appropriately assessing the adequacy of different control algorithms is proposed. The performance of this new evaluation tool is compared with the currently standard assessment methods, on an individual as well as a population basis. The impact of four selected parameters (the average blood glucose sampling frequency, the duration of algorithm application, the severity of disease, and the type of illness) on the performance of an insulin titration algorithm is further determined by multiple regression analysis. The GPI is an alternative method for evaluating the performance of blood glucose control algorithms. The blood glucose sampling frequency and the duration of algorithm application should be similar when comparing algorithms. In Figure 4.1 the focus of this chapter is illustrated.*

## 4.1 Introduction

Blood glucose control, aiming at normoglycemia, is now attempted in ICUs worldwide. This is usually performed by nurses or physicians who are guided by 'manual' guidelines or algorithms [25, 81, 120, 197, 215]. These algorithms are developed with the purpose of determining the insulin dose that is required to obtain normoglycemia based on intermittent blood glucose readings. Computer-based protocols (as presented in [35, 38, 40, 41, 89, 94, 97, 138, 148, 166, 224, 234, 243]) have the potential to facilitate and improve glycemic control and to reduce the workload of the medical staff.

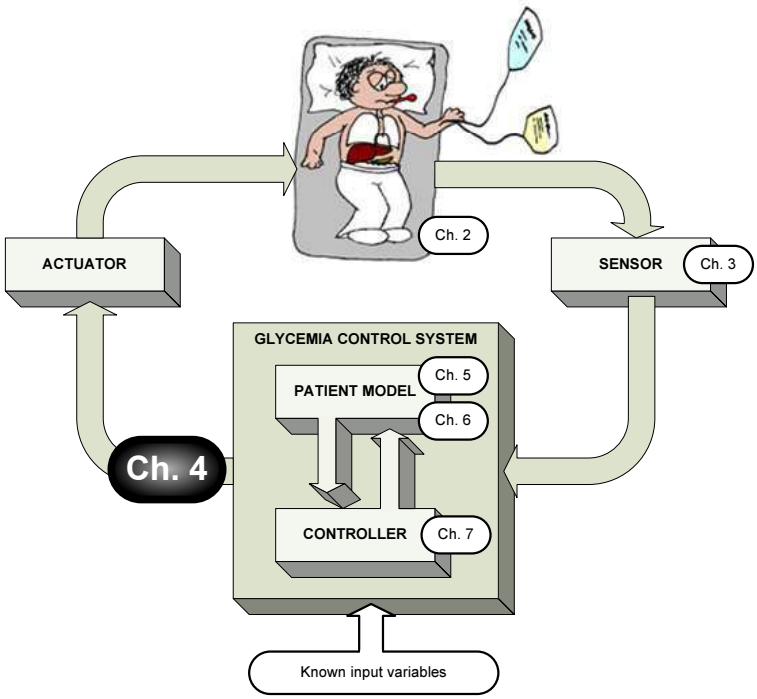


**Figure 4.1:** Simplified presentation of the (semi-)automated control system. This chapter discusses an alternative method (GPI) for evaluating the performance of blood glucose control algorithms and the weight of four selected parameters on GPI.

However, these 'new' protocols require a stringent validation before they can replace the currently existing 'nurse-driven' insulin protocols.

Three types of methods exist for evaluating the adequacy of insulin titration algorithms or glycemia control systems. All of them, however, show weaknesses that may lead to erroneous conclusions. The first method simply computes the **average** of all glycemia readings. In spite of its popularity, it must be stressed that normoglycemia can be falsely assumed even in the presence of severely abnormal blood glucose values. Indeed, hypoglycemic and hyperglycemic events can artificially lower or raise, respectively, the calculated average and can even balance each other, leading to an apparently 'normal' average blood glucose. Consider a theoretical example of a blood glucose profile that follows a sinusoid curve around the target line of 95 mg/dl. Independent of the magnitude of the hypoglycemic and the hyperglycemic events, the average blood glucose equals 95 mg/dl. Although this computed average would suggest a well controlled blood glucose profile, it is clear that the presence of severe hypoglycemic and hyperglycemic episodes indicate that blood glucose was poorly controlled in reality.

A second method comprises **single measurements**; for example the blood glucose reading at a fixed time of day, the minimum/maximum blood glucose values, and the time needed to reach the target blood glucose. Alternative single measurements count the number of hypoglycemic or hyperglycemic events. Although such measurements are useful, they do not capture the blood glucose *dynamics*.

Recently, the **HyperGlycemic Index** (HGI) was presented as a third (more advanced) tool to assess glucose control (in the ICU) with respect to the *hyperglycemic* events [233]. The HGI is defined as the area under the glucose curve above 6.0 mmol/l (108 mg/dl) divided by the length of ICU stay. Two conditions to be satisfied before applying the HGI were proposed [209]. Firstly, the number of blood glucose measurements should be sufficiently high, ideally a near-continuous glucose read-out. Secondly, the considered sampling frequency should be comparable in both patient groups when comparing the adequacy of two insulin titration algorithms. Particularly the first condition is extremely important as the area under the glucose curve is calculated in this method. It is important to note that area-under-the-curve methods (like HGI) currently rely on the assumed (linear) relation between intermittent blood glucose readings since no reliable and accurate near-continuous glucose sensor is presently available [38, 94, 99]. Another critical point of this technique is that outliers can potentially warp the obtained results due to the possible presence of extreme (hyperglycemic) observations that may have an impact on the computed area-under-the-curve. This is an important feature when realizing that sensor accuracy (and reliability) typically decrease as the blood glucose level increases [44, 52, 75]. It is clear that the presence of outliers also affects the computed average blood glucose values (see first method). Finally, HGI only transforms the hyperglycemic (and *not* the hypoglycemic) glucose dynamics into a number. Of course, the design of an alternative *hypoglycemic index* (as already suggested in [140]) would overcome this last aspect.

The aim of the study presented in this chapter is to design a tool for adequately comparing blood glucose control algorithms. In the first part of the study, a grading system that scores normal, hypoglycemic, and hyperglycemic readings is developed: the **Glycemic Penalty Index (GPI)**. In the second part of the study, the performance of GPI is **compared** (on an individual as well as a population basis) with the current standard evaluation methods (average morning blood glucose, mean of all blood glucose readings, and HGI), using data from a selected set of patients. In the third part of the study, the **importance** or the **weight** of four clinically selected parameters (blood glucose sampling frequency, duration of algorithm application, severity of disease, and type of illness) on GPI is investigated.

## 4.2 Research design and Methods

### 4.2.1 Mathematical computation of Glycemic Penalty Index (GPI)

The GPI is defined as a tool that scores blood glucose readings in order to evaluate the *overall* blood glucose dynamics obtained in the considered patient by applying a

specific ICU insulin titration algorithm. The computation of the GPI uses a penalty strategy that is based on clinical 'expert' knowledge. The glycemic target range in the ICU is defined as 80-110 mg/dl [213, 216] (with a penalty value for all blood glucose values lying in this range, therefore set at 0). Hyperglycemic and hypoglycemic events are amplified (in terms of the assigned penalties) in relation to the magnitude of their deviation from the target range. Table 4.1 gives an overview of the glycemic threshold values that are generally accepted for use in the ICU. Each glycemic range is associated with a penalty $\rho$ leading to a *staircase* 'expert' penalty function when considering the full glycemic range (see also Figure 4.2, dashed line).

**Table 4.1:** Threshold values and penalty values for the evaluation of glycemia control in the ICU. The blood glucose value that is measured at time $t$ is represented by $G_t$.

| Range No | Glycemic range (mg/dl) | Clinical description | Penalty ($\rho$) | Reference |
|---|---|---|---|---|
| (1) | $G_t < 40$ | Hypoglycemic alarm | 3 | [210] |
| (2) | $40 \leq G_t < 60$ | Hypoglycemia | 2 | [210] |
| (3) | $60 \leq G_t < 80$ | Slight hypoglycemia | 1 | [210] |
| (4) | $80 \leq G_t \leq 110$ | Normoglycemia | 0 | [213,216] |
| (5) | $110 < G_t \leq 150$ | Slight hyperglycemia | 1 | [214] |
| (6) | $150 < G_t \leq 200$ | Hyperglycemia | 2 | [214] |
| (7) | $200 < G_t$ | Hyperglycemic alarm | 3 | [216] |

The *staircase* function is then smoothed in order to avoid abrupt changes in the penalty function. However, the clinically accepted normoglycemic target range, the hypoglycemic alarm level (i.e., blood glucose values below 40 mg/dl [210]), and the hyperglycemic alarm level (i.e., blood glucose values above 200 mg/dl [216]) are respected in the design of the more *smoothed* function. This gives the advantage that penalties are gradually increasing as a function of the increasing deviation from the target range. Accordingly, blood glucose measurement errors caused by sensor inaccuracies and methodology inaccuracies due to sampling handling only have a limited impact on the overall assessment of a blood glucose algorithm.

The smooth penalty function is subsequently optimized by designing a polynomial function in the blood glucose ranges 20-79 mg/dl and 111-250 mg/dl. The squared differences between the staircase and the more smoothed function are minimized by applying Ordinary Least Squares (OLS) [141]. Given a sample of $N_{\text{Total}}$ glycemia observations $G = (G_1, \ldots, G_{N_{\text{Total}}})$ and a corresponding set of $N_{\text{Total}}$ assigned penalties $\rho = (\rho_1, \ldots, \rho_{N_{\text{Total}}})$. The symbol that represents the number of blood glucose measurements in the full glycemic range (that are available for the considered patient) is $N_{\text{Total}}$. Next, each penalty can be explained as follows:

$$\rho_t = f(G_t) + e_t, \tag{4.1}$$

with $t = 1, \ldots, N_{\text{Total}}$ and where $e_t$ denotes a stochastic error between the 'expert' penalty $\rho_t$ and the smoothed penalty $f(G_t)$ at time instant $t$. The function $f$ can be

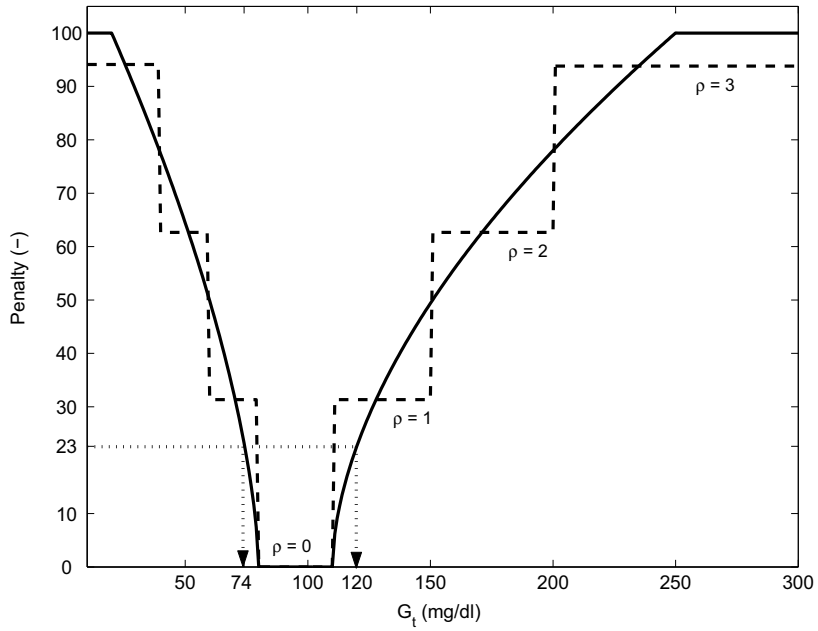


**Figure 4.2:** Each blood glucose observation $G_t$ (measured at time $t$) corresponds to a penalty. The dashed line represents the *staircase* penalty index function (here, the penalty is denoted as $\rho$). For reasons explained in the text, this staircase function is transformed into a more *smoothed* penalty index function, which is illustrated with the solid line. The penalties are symbolized by $\beta$, $\gamma$, and $\delta$ for the low, normal, and high blood glucose measurements, respectively. The 'clinically acceptable' cut-off GPI equals 23 and corresponds to a 'clinically acceptable' blood glucose range of 74-120 mg/dl. The target normoglycemic range, however, remains 80-110 mg/dl with a corresponding penalty value equal to 0.

presented as follows:

$$\begin{aligned} f = \quad & a(80-G)^b \qquad \text{for the blood glucose range 20-79 mg/dl,} \\ f = \quad & a(G-110)^b \qquad \text{for the blood glucose range 111-250 mg/dl.} \end{aligned}$$

The following optimization problem gives the estimated coefficients $\hat{a}$ and $\hat{b}$:

$$(\hat{a} \;\; \hat{b})^T = \min_{a,b\in\mathbb{R}} \quad \sum_{t=1}^{N_{\text{Total}}} (\rho_t - f(a,b,G_t))^2. \tag{4.2}$$

The penalty index corresponding to the normoglycemic range (80-110 mg/dl) is set at 0. Blood glucose values lower than 20 mg/dl and higher than 250 mg/dl are assigned a maximum value to avoid that outliers would distort the obtained GPI (as can be the case with currently used evaluation methods, see above).

### 4.2.2 Comparison of GPI with currently used evaluation methods

The average *morning* blood glucose, the average blood glucose (i.e., the mean of all blood glucose readings), the HGI, and the GPI are computed for each patient in the study set. Though the glycemic target range is 80-110 mg/dl, we define 120 mg/dl as 'clinically acceptable' upper limit taking into account possible sensor inaccuracies and methodology inaccuracies due to sampling handling [84,119,178,228,230]. Therefore, the cut-off values for evaluating the performance of the blood glucose algorithm are arbitrarily set as follows. Average *morning* blood glucose readings below 120 mg/dl, average blood glucose values below 120 mg/dl, and HGIs below 12 mg/dl (i.e., an average hyperglycemic value below 108+12 = 120 mg/dl) are labeled as 'clinically acceptable'. The cut-off GPI that explains whether the insulin titration algorithm is acceptable or not is determined by entering 120 mg/dl, as cut-off blood glucose, to the developed smooth penalty function. Next, the performance of the existing standard evaluation methods and the GPI are compared both on individual and population base.

### 4.2.3 Study procedure and Patient population

Two different data sets, obtained from patients who had been admitted to the surgical ICU-division of the University Hospital K.U.Leuven and who had been treated by the same nursing team but for whom a different blood glucose sampling frequency was used, were assembled. Whole-blood glucose in undiluted arterial blood was measured by means of the same glucose analyser (ABL700 Radiometer Medical, Copenhagen) in both patient groups. The **first** group of patients comprised 41 patients (*patient group 1*) and is further described in detail in Chapter 2 (see data set 1 in 2.4.1). The blood glucose sampling frequency and insulin titration guidelines (as described in [215]) were identical for all patients. The **second** group of patients comprised 52 patients (*patient group 2*) with variable demographics and duration of stay in the ICU, of whom only the first two days were considered, during which the sampling frequency was set at once every hour. The patients of group 2 originate from data sets 2 and 3 that are also depicted in Chapter 2 (see data set 2 in 2.4.2 and data set 3 in 2.4.3). The titration was done by the same nursing staff who followed the same guidelines as used for patient group 1. Except for the different blood glucose sampling frequency and the duration of algorithm application, both patient groups varied for type of illness and the APACHE II score. The average ($\pm$ SD) APACHE II score was higher in group 2 ($11 \pm 6$ for group 1 versus $16 \pm 4$ for group 2). The differences between the patient groups allowed to analyse the influence (weight) of the four selected clinically relevant parameters (see 4.2.4) on GPI in an appropriate way.

### 4.2.4 Definition of parameters

Four different parameters are selected based on their clinically expected influence on GPI. The first parameter is the **average blood glucose sampling frequency** ($f$) which is the average number of blood glucose readings (per time unit) that were available and used by the insulin titration algorithm. The conversion to time dimension is realized by taking the inverse of the frequency (e.g., $f = 0.5\ \text{hr}^{-1}$ corresponds to a time interval

of 2 hours). The second parameter is the **duration of algorithm application** ($D$) which is the time period that the control algorithm was effectively used for a given patient. The next parameter is the **severity of disease** ($A$) scored by the APACHE II score, still the most reported and used in the ICU and, therefore, selected for this study although more recent scoring systems may perform better at grading severity of illness. The APACHE II score of the first 24 hours after admission to the ICU was calculated for each patient using parameters of acute physiology and chronic healthcare. The final parameter under study is the **type of illness**. As an example, eight reasons for admission to the ICU are considered in this analysis: cardiac surgery (type 1), multiple trauma or severe burns (type 2), neurologic disease, cerebral trauma or complicated brain surgery (type 3), complicated lung or esophageal thoracic surgery, respiratory insufficiency, or both (type 4), complicated abdominal surgery or peritonitis (type 5), transplantation (type 6), complicated vascular surgery (type 7), and others (type 8).

### 4.2.5 Statistics

The Kruskal-Wallis test is used for comparing the medians of two or more groups of data. Depending on the distribution of the residuals, general and generalized linear models are built. In the general linear model, the Shapiro-Wilk test is applied for testing the normality of the residuals. The determination of the significance (weight) of the specific parameter on GPI (i.e., 'input selection' for the model) is based on $F$-tests for the general linear model and the likelihood ratio Chi-Square statistics for the generalized linear model. For the last type of model, Wald statistics are used. Pearson's correlation coefficients ($R$) are calculated for quantifying the relation between continuous variables. In all applied tests, $p$ values $< 0.05$ are considered to be significant.

## 4.3 Results

### 4.3.1 Mathematical computation of GPI

The clinically defined *staircase* penalty function is transformed to a more *smoothed* penalty function. The obtained function is mathematically formulated as follows:

For time step $t$ = 1 to $N_{\text{Total}}$,

$$\begin{aligned}
G_t < 20 \text{ mg/dl}: &\quad \beta_i = 100, \\
20 \text{ mg/dl} \leq G_t < 80 \text{ mg/dl}: &\quad \beta_i = 7.4680(80 - G_t)^{0.6337}, \\
80 \text{ mg/dl} \leq G_t \leq 110 \text{ mg/dl}: &\quad \gamma_j = 0, \\
110 \text{ mg/dl} < G_t \leq 250 \text{ mg/dl}: &\quad \delta_k = 6.1767(G_t - 110)^{0.5635}, \\
250 \text{ mg/dl} < G_t: &\quad \delta_k = 100,
\end{aligned}$$

where $\beta_i$ is the penalty index for a glucose reading $G_t$ of the hypoglycemic range (i.e., $G_t < 80$ mg/dl), $\gamma_j$ for the normoglycemic range (i.e., 80 mg/dl $\leq G_t \leq$ 110 mg/dl), and $\delta_k$ for the hyperglycemic range (i.e., $G_t > 110$ mg/dl). The indices $i$, $j$, and $k$

are used to count the number of hypoglycemic, normoglycemic, and hyperglycemic events, respectively. This more smoothed function is illustrated in Figure 4.2 (solid line).

All blood glucose values from a patient correspond to specific penalty values as directly follows from the smoothed function. Next, the GPI is calculated *for each patient*:

$$\text{GPI} = \frac{\sum_{i=1}^{N_{\text{Hypo}}} \beta_i + \sum_{k=1}^{N_{\text{Hyper}}} \delta_k}{N_{\text{Total}}}, \tag{4.3}$$

where $N_{\text{Hypo}}$ is the symbol for the number of blood glucose measurements in the hypoglycemic range, and $N_{\text{Hyper}}$ for the hyperglycemic range. The relative contribution of the hypoglycemic values to GPI (denoted as $C_{\text{Hypo}}$) is determined as follows:

$$C_{\text{Hypo}} = \frac{\sum_{i=1}^{N_{\text{Hypo}}} \beta_i}{\sum_{i=1}^{N_{\text{Hypo}}} \beta_i + \sum_{k=1}^{N_{\text{Hyper}}} \delta_k} 100\%. \tag{4.4}$$

Analogously, the relative contribution of the hyperglycemic values to GPI (denoted as $C_{\text{Hyper}}$) is computed as follows:

$$C_{\text{Hyper}} = \frac{\sum_{k=1}^{N_{\text{Hyper}}} \delta_k}{\sum_{i=1}^{N_{\text{Hypo}}} \beta_i + \sum_{k=1}^{N_{\text{Hyper}}} \delta_k} 100\%. \tag{4.5}$$

### 4.3.2 Comparison of GPI with currently used methods

The 'clinically acceptable' *upper limit* blood glucose (120 mg/dl) is entered in the above developed smoothed penalty function giving 23 as 'clinically acceptable' cut-off GPI. Next, the inverse smoothed penalty function is used to compute the *lower limit* blood glucose that corresponds to GPI = 23 (see also Figure 4.2). The 'clinically acceptable' blood glucose range is found to be 74-120 mg/dl but the glycemic target range remains 80-110 mg/dl. In other words, a computed GPI below 23 allows to conclude that the insulin titration algorithm was able to control blood glucose according to the clinical requirements. Ideally, however, all blood glucose readings should fall within the 80-110 mg/dl zone leading to a GPI equal to 0.

Table 4.2 gives a detailed overview of the results of the evaluation methods (average *morning* blood glucose, average blood glucose, HGI, GPI, and the relative contribution of the low ($C_{\text{Hypo}}$) and high ($C_{\text{Hyper}}$) blood glucose observations to the computed GPI) that are applied to patient group 1. Figures 4.3 and 4.4 further summarize the performance differences between the evaluation methods applied to the individual patients. The correlation coefficients for the already existing measures with respect to GPI are depicted in each respective panel. Finally, Figure 4.5 illustrates the blood glucose profile of patient no. 19 (top panel, no misleading effect of standard assessment methods), whose blood glucose was tightly controlled, and patient no. 23 (bottom panel, assessment misled by average (*morning*) blood glucose) with poor blood glucose control (see also Table 4.2 for exactly computed measures).

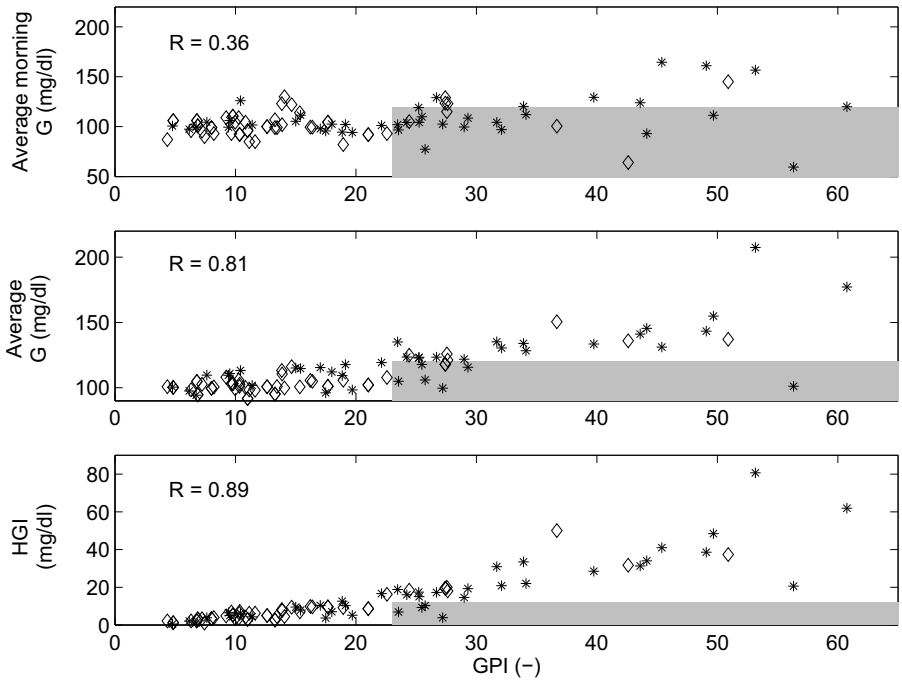


**Figure 4.3:** Standard evaluation techniques versus GPI for patient group 2 and 1 (but considering only the data of the first 48 hours in the latter. The results of the standard evaluation methods are plotted against the results of the new proposed assessment tool (GPI). The top panel shows the average *morning* blood glucose readings as a function of GPI. The middle panel represents the average blood glucose values versus the GPI values. Finally, the bottom panel illustrates the computed HGI values as a function of GPI. The shaded area contains those patients whose blood glucose profile is evaluated differently: 'clinically acceptable' for the standard measures, 'clinically unacceptable' for GPI. The stars denote the patients from group 1 whereas the diamonds represent the patients from group 2. The correlation coefficients ($R$) for the existing measures with respect to GPI are depicted in the respective panels.

In most studies, however, the blood glucose control algorithm is evaluated using the patient population rather than on individual patients [97, 148, 166, 213, 216]. The *population* results for patient group 1 are also mentioned in Table 4.2. The most appropriate way to present the *population* HGI and GPI values is the calculation of the median and 25-75% IQ range as these data are not normally distributed.

**Table 4.2:** Evaluation of blood glucose control by computing the average *morning* blood glucose, the average blood glucose, the HGI, and the GPI for patient group 1.

| Patient No. | Average *morning* blood glucose (mg/dl) | Average blood glucose (mg/dl) | HGI (mg/dl) | GPI ($C_{\text{Hypo}}$ (%)-$C_{\text{Hyper}}$ (%)) | |
|---|---|---|---|---|---|
| 1 | 161 | 143 | 39 | 49 | (16.2 - 83.8) |
| 2 | 129 | 123 | 17 | 27 | (4.0 - 96.0) |
| 3 | 124 | 141 | 28 | 42 | (9.6 - 90.4) |
| 4 | 165 | 131 | 41 | 45 | (23.0 - 77.0) |
| 5 | 97 | 101 | 6 | 20 | (34.7 - 65.3) |
| 6 | 77 | 105 | 9 | 22 | (36.6 - 63.4) |
| 7 | 104 | 115 | 9 | 18 | (4.2 - 95.8) |
| 8 | 129 | 127 | 27 | 35 | (18.4 - 81.6) |
| 9 | 93 | 132 | 26 | 37 | (29.5 - 70.5) |
| 10 | 109 | 106 | 8 | 16 | (23.5 - 76.5) |
| 11 | 103 | 100 | 4 | 27 | (49.8 - 50.2) |
| 12 | 97 | 117 | 15 | 29 | (21.4 - 78.6) |
| 13 | 100 | 101 | 4 | 10 | (31.2 - 68.8) |
| 14 | 103 | 113 | 9 | 18 | (11.5 - 88.5) |
| 15 | 98 | 98 | 4 | 13 | (47.5 - 52.5) |
| 16 | 111 | 114 | 18 | 28 | (27.5 - 72.5) |
| 17 | 101 | 101 | 6 | 15 | (40.0 - 60.0) |
| 18 | 104 | 105 | 4 | 7 | (1.7 - 98.3) |
| 19 | 97 | 99 | 1 | 5 | (39.0 - 61.0) |
| 20 | 102 | 99 | 3 | 9 | (25.7 - 74.3) |
| 21 | 102 | 107 | 4 | 12 | (16.2 - 83.8) |
| 22 | 126 | 115 | 10 | 17 | (11.9 - 88.1) |
| 23 | 60 | 101 | 21 | 56 | (59.7 - 40.3) |
| 24 | 102 | 135 | 19 | 23 | (0 - 100) |
| 25 | 101 | 107 | 7 | 9 | (10.3 - 89.7) |
| 26 | 100 | 106 | 8 | 19 | (29.7 - 70.3) |
| 27 | 112 | 107 | 6 | 14 | (27.8 - 72.2) |
| 28 | 104 | 111 | 10 | 15 | (1.3 - 98.7) |
| 29 | 105 | 110 | 7 | 10 | (0 - 100) |
| 30 | 120 | 177 | 62 | 61 | (5.2 - 94.8) |
| 31 | 110 | 96 | 6 | 23 | (57.1 - 42.9) |
| 32 | 99 | 102 | 5 | 11 | (18.3 - 81.7) |
| 33 | 120 | 119 | 14 | 21 | (12.1 - 87.9) |
| 34 | 96 | 96 | 2 | 9 | (51.2 - 48.8) |
| 35 | 94 | 97 | 3 | 12 | (48.0 - 52.0) |
| 36 | 157 | 194 | 74 | 55 | (19.5 - 80.5) |
| 37 | 94 | 97 | 4 | 13 | (49.1 - 50.9) |
| 38 | 106 | 102 | 2 | 4 | (10.6 - 89.4) |
| 39 | 104 | 104 | 7 | 13 | (24.2 - 75.8) |
| 40 | 112 | 115 | 8 | 15 | (6.9 - 93.1) |
| 41 | 119 | 109 | 9 | 18 | (18.0 - 82.0) |
| **mean (SD)** | 108 (20) | 114 (21) | 14 (16) | 22 (14) | |
| **median** | 104 [98 - 112] | 107 [101 - 116] | 8 [4 - 17] | 18 [12 - 27] | |
| **[25-75% IQ range]** | | | | $C_{\text{Hypo}}$ : 21.4 [10.3-34.7] | |
| | | | | $C_{\text{Hyper}}$ : 78.6 [63.4-89.4] | |

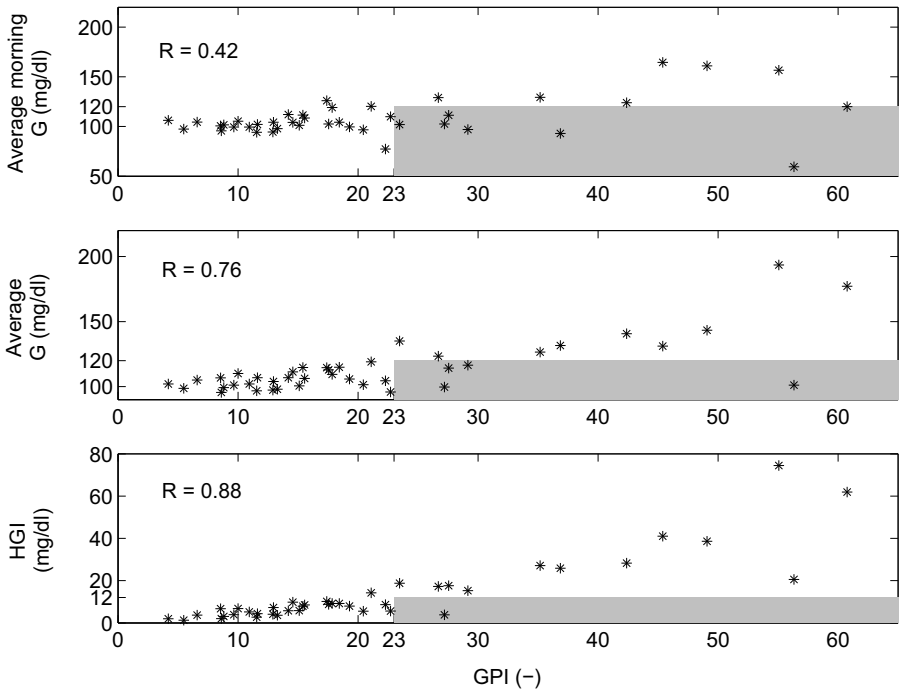


**Figure 4.4:** Standard evaluation techniques versus GPI for patient group 1 (considering the full dataset). The blood glucose profiles of the patients of group 1 are evaluated by applying the same standard techniques as mentioned in Figure 4.3 and are again presented as a function of GPI. The patients that belong to the shaded area got a different algorithm evaluation dependent on the method that was used (respective 'standard' method versus GPI). The shaded area contains those patients whose blood glucose profile is evaluated differently: 'clinically acceptable' for the standard measures, 'clinically unacceptable' for GPI.

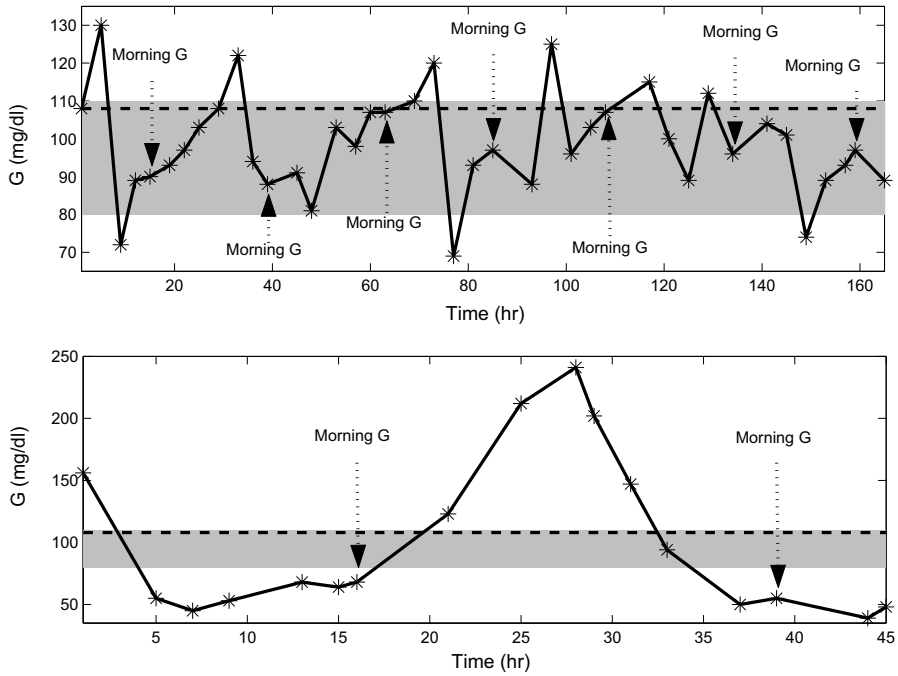


**Figure 4.5:** The measured blood glucose readings (ABL700 Radiometer Medical) of patient no. 19 (top panel) and 23 (bottom panel) from group 1 are represented by stars. These blood glucose profile examples denote TGC for patient no. 19 but rather poor glycemic control for patient no. 23. It is important to note that different time scales are used as patient no. 23 stayed in the ICU for only a short time period. Further, the obtained blood glucose measurements are linearly interpolated. The normal blood glucose range (target range) is indicated by the shaded area (80-110 mg/dl). The HGI is the area under the glucose curve above 6 mmol/l (108 mg/dl, as illustrated with the dashed line [233]). The *morning* blood glucose values are indicated by the dotted arrows. Table 4.2 shows all computed measures in detail. Only the advanced methods (HGI and GPI) indicate the poorly controlled blood glucose profile for patient no. 23).

### 4.3.3 Weight determination for the selected parameters

The impact of the variables under study on GPI for the patients belonging to patient group 2 and 1 (but considering only the data of the first 48 hours in the latter) is illustrated in Figure 4.6. As the *duration of algorithm application* was set at 48 hours, this variable is not included in this analysis. The $p$-values of the null hypothesis that the GPI medians per group are equal are noted in each respective panel (only significant inequality for the *average blood glucose sampling frequency* is observed). Multiple regression analysis on these data reveals that the *average sampling frequency* is the only parameter that significantly ($p = 0.0051$) impacts the assessment of insulin titration algorithms: an inversely proportional effect is observed.

Figure 4.7 illustrates the independent impact of all four variables under study on GPI for patient group 1 (considering all the available data of this group). The obtained $p$-values of the null hypothesis that the GPI medians per group are equal are again noted in the respective panels (significant inequality for the *average blood glucose sampling frequency* and *duration of algorithm application*). Multiple regression analysis returns that both *duration of algorithm application* ($p = 0.032$) and the product of *duration of algorithm application* and *average blood glucose sampling frequency* ($p = 0.025$) significantly influence GPI. The first parameter is directly proportional to GPI whereas the product is inversely proportional to GPI. Moreover, a negative correlation ($R = -0.42$, $p = 0.0069$ for the 'no-correlation' null hypothesis) between the variables *duration of algorithm application* and *average blood glucose sampling frequency* is found.

The impact of the duration of algorithm application on GPI is further clarified in Figure 4.8 for the patients (from group 1) who stayed for at least 100 hours in the ICU. Every 24 hours, the GPI is computed based on all previous blood glucose observations of each particular patient. Each line of Figure 4.8 represents the GPI evolution of this specific patient as a function of the number of data (i.e., the time spent in the ICU) that are considered in the calculation process of GPI. For the majority of the patients, a decreasing GPI trend is observed as more data (longer duration of the applied algorithm) are taken into consideration.

## 4.4 Discussion

In this study the GPI is developed as tool to assess the dynamics of glycemic control in ICU patients. The designed formula returns a number between 0 and 100 with an 'ideal' level of 0 (indicating that all measured blood glucose values fall within the normoglycemic target range) and a 'clinically acceptable' level of 23. Next, it is shown that GPI summarized the monitored glucose profile into one number more precisely than the traditional evaluation tools based on currently available clinical expertise. Finally, the *average blood glucose sampling frequency* and the *duration of algorithm application* are found to be parameters that should be similar for patient groups when comparing the performance of insulin titration algorithms.

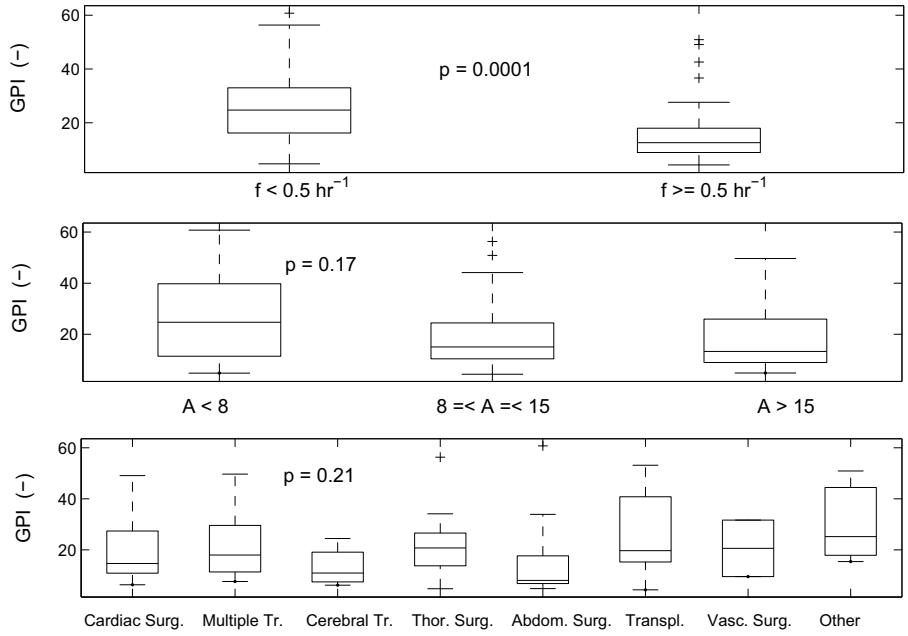


**Figure 4.6:** Univariate relation (expressed in boxplots) between average blood glucose sampling frequency ($f$) and GPI (top panel), APACHE II score ($A$) and GPI (middle panel), and type of illness and GPI (bottom panel) for patient group 2 and 1 (but considering only the data of the first 48 hours in the latter). The $p$-values of the null hypothesis that the GPI medians per group are equal are mentioned in each panel. A significant difference is found for the *average blood glucose sampling frequency*: the blood glucose profiles with $f \geq 0.5$ hr$^{-1}$ (i.e., time intervals less than 2 hours) are related to stricter glycemic control (lower GPI).

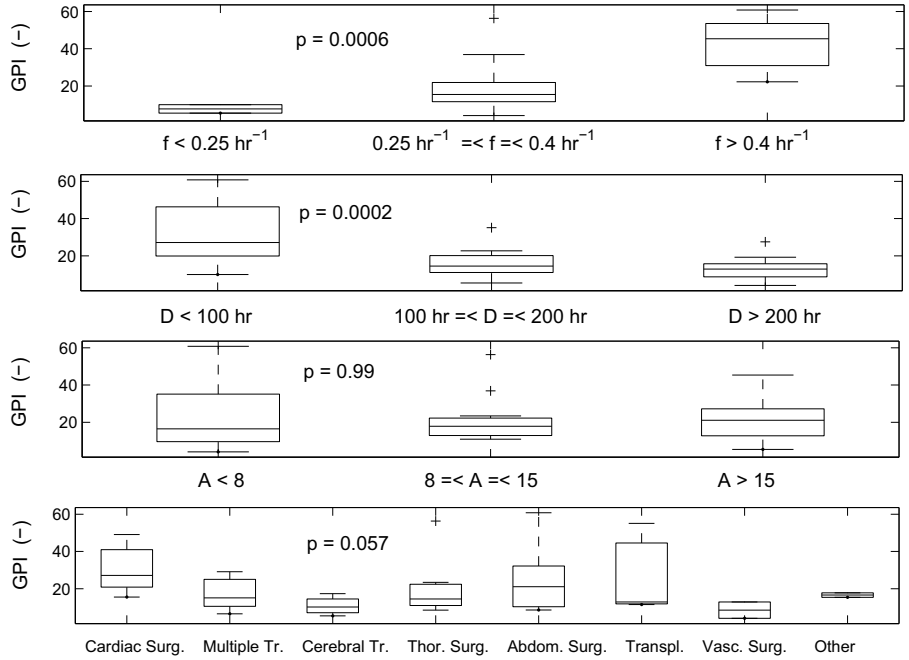


**Figure 4.7:** Univariate relation (expressed in boxplots) between average blood glucose sampling frequency ($f$) and GPI (top panel), duration of algorithm application ($D$) and GPI (second panel), APACHE II score ($A$) and GPI (third panel), and type of illness and GPI (bottom panel) based on patient group 1. The $p$-values of the null hypothesis that the GPI medians per group are equal are mentioned in each panel. A significant difference is found for the *average blood glucose sampling frequency* and the *duration of algorithm application*. The longer the algorithm is applied to the patient and the longer the time intervals between successive measurements, the tighter the glycemic control (lower GPI). The apparently contradictory impact of the blood glucose sampling frequency on GPI (compared to top panel of Figure 4.6) can be explained by the negative correlation between the variables *duration of algorithm application* and *average blood glucose sampling frequency* (see also text).

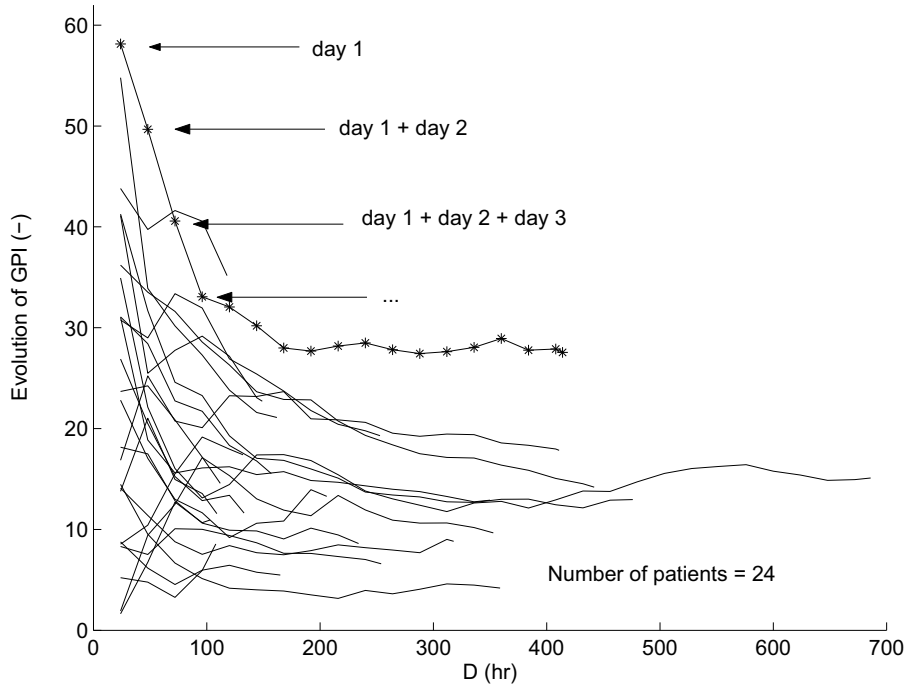


**Figure 4.8:** The evolution of the GPI values as a function of duration of algorithm application ($D$) for the patients of group 1 who stayed for at least 100 hours in the ICU. Each line represents a patient. Let us take the example of a patient that is illustrated with stars. The first star represents the GPI value that is calculated based on the blood glucose observations of the first 24 hours of that specific patient. The second star gives the GPI value based on the measured blood glucose signal of the first 48 hours; the third GPI value is computed based on the data of the first 72 hours; etc. For the majority of the patients, a decreasing GPI trend is observed.

### 4.4.1 Mathematical computation of GPI

The developed GPI tool summarizes the level of TGC into a single number based on a grading system that scores low and high blood glucose readings depending on their deviation from the target range. There are many advantages of GPI over the currently standard methods. Firstly, since both low and high blood glucose readings are taken into account, GPI measures the ***overall* blood glucose dynamics**. Since the assigned penalties are always absolute (positive), it is not possible that hypoglycemic and hyperglycemic penalties balance each other as can be the case when computing the average (morning) blood glucose.

Secondly, only the blood glucose readings that were effectively monitored are used in the GPI evaluation tool. Accordingly, unlike for area-under-the-curve methods, the **GPI does not rely on any assumed (linear) relation between measurements**. While awaiting the creation of reliable near-continuous sensor devices for blood glucose monitoring in an ICU setting, this is an important aspect as these assumed (linear) relations between observations do not necessarily approach the real (non-linear) blood glucose dynamics.

Thirdly, a **smooth** penalty function (see Figure 4.2) forms the basis of GPI leading to a gradual increase of the assigned penalties as the deviations from normoglycemia are enlarging. Measurement errors caused by sensor inaccuracies and methodology inaccuracies due to sampling handling have only a small level of influence on the assignment of the penalty, accordingly.

A fourth important feature of GPI is the **independency of outlier measurements**. Due to the imposed limits in the penalty function (if $G < 20$ mg/dl or $G > 250$ mg/dl, then $\beta = \delta = 100$), extreme blood glucose measurements (that may be related to sensor/methodology inaccuracies) cannot mislead the general algorithm assessment. Moreover, blood glucose values lower or higher than these imposed limits would not lead to a clinically different treatment. This concept formed the basis of the specific region strategy in the EGA analysis (see Chapter 3, 3.1.2) for the evaluation of glucose sensors, as reported previously [44, 52, 53].

Finally, the computation of the relative contribution of the hypo- and hyperglycemic events to GPI allows us to further **interpret** the obtained GPI value. Consider the blood glucose profile of patient no. 1 (from patient group 1) as an example (see Table 4.2). Based on the high GPI that is obtained (GPI $= 49 > 23$), it could be concluded that blood glucose was poorly controlled in this patient. The relative contributions (expressed in terms of percentage) of the hypo- and hyperglycemic events ($C_{\text{Hypo}}$ and $C_{\text{Hyper}}$, respectively) to GPI inform the clinician whether this non-optimal control behaviour was caused by particularly low glucose events (if $C_{\text{Hypo}} > 75\%$), high glucose events (if $C_{\text{Hyper}} > 75\%$), or both (if $C_{\text{Hypo}} \approx C_{\text{Hyper}}$). The non-optimal performance of the algorithm for this patient example is mainly caused by the hyperglycemic events due to the large value for $C_{\text{Hyper}}$ (see Table 4.2).

### 4.4.2 Comparison of GPI with currently used methods

The computed GPI can be used to appropriately evaluate the level of TGC in a **single** patient based on clinical expertise. Existing methods may mislead an assessment as is shown for patient no. 23 in Figure 4.5 (bottom panel). The average *morning* blood glucose (60 mg/dl $\leq$ 120 mg/dl) and the average blood glucose (101 mg/dl $\leq$ 120 mg/dl) both suggest strict glycemic control whereas only HGI (21 mg/dl $>$ 12 mg/dl) and GPI ($56 > 23$) denote the poorly controlled blood glucose signal. Both hypoglycemic and hyperglycemic events can be observed in the blood glucose profile which is further confirmed by the similarity between $C_{\text{Hypo}}$ and $C_{\text{Hyper}}$ for this patient.

Figures 4.3 and 4.4 summarize the assessment of the individual blood glucose profiles by applying the existing methods and GPI. The shaded area is defined by the GPI 'clinical *unacceptability*' cut-off (GPI $>$ 23) and the 'clinical *acceptability*' limits of the known techniques (average (*morning*) blood glucose $\leq$ 120 mg/dl, HGI $\leq$ 12 mg/dl). In other words, the evaluation of the blood glucose profiles of the patients belonging to this area may be misled by the existing methods (particularly the average *morning* blood glucose and the average blood glucose, due to their high number of patients in the shaded areas and, to a lesser degree, the HGI). In fact, only few blood glucose profiles are evaluated differently with HGI indicating that this method most approaches the clinical 'expert' GPI function. This also occurs in the high correlation coefficients for HGI and GPI.

The assessment of the performance of the blood glucose algorithm on a **population** base also depends on the selected technique. The average *morning* blood glucose ($108 \pm 20$ mg/dl) and the average blood glucose ($114 \pm 21$ mg/dl) are below 120 mg/dl suggesting that the algorithm under study is adequate. The computed IQ ranges for the average (*morning*) blood glucose, both below 120 mg/dl, confirm this hypothesis. The computed IQ ranges of HGI and GPI, however, indicate that the applied algorithm does not result in clinically acceptable blood glucose control for at least 25% of the patients. Indeed, a quarter of the HGI values are above 17 mg/dl ($>$ 12 mg/dl) and a quarter of the GPI values are above 27 ($>$ 23).

This study shows that the two most traditional measures (average *morning* blood glucose and average blood glucose) used for summarizing the overall glycemic control behaviour, can mislead assessments of blood glucose algorithms. This confirms the results described in [67]. Techniques that take into account the *duration* of hyperglycemia/hypoglycemia, like HGI or the recently proposed 'notional duration of hyperglycemia/hypoglycemia' (i.e., the time since the observation of an abnormal blood glucose till it returns to the accepted range [67]) may better indicate TGC. The GPI technique proposed in this manuscript, however, is explicitly founded on ICU expertise and may therefore be an *alternative* (or at least a *supplemental*) tool for adequately evaluating insulin titration algorithms in the ICU. The blood glucose profiles of most individual patients were equally assessed using GPI and HGI, except for some patients as was illustrated in Figures 4.3 and 4.4 (shaded areas of the bottom panels).

A first weakness of GPI is the non-consideration of the *duration* of hypoglycemic and hyperglycemic episodes since no (linear) relation between discrete-time blood glucose observations is assumed. Accordingly, the algorithm assessment may be misled as the number of intermittent blood glucose measurements (and the number of assigned penalties) can typically be higher with unstable blood glucose behavior (i.e., blood glucose observations outside the normoglycemic target range). Only area-under-the-curve measures (like HGI) can potentially take into consideration the duration of these glycemic deviations under the assumption that the imposed (linear) relation between the measurements approaches the real blood glucose dynamics. Moreover, the duration

of deviating episodes can only be precisely taken into account with a reliable and accurate near-continuous glucose sensor. The use of such a device for the evaluation of a blood glucose algorithm even allows to label the GPI measure as area-under-the-curve method (that incorporates the duration of glycemic deviations) since then a penalty is 'continuously' assigned to each blood glucose (measured at each time instant, e.g., every minute) and since hypoglycemic and hyperglycemic deviations cannot balance each other. While awaiting these reliable near-continuous glucose sensors [38, 94, 99], it is advised to sample blood glucose at fixed time intervals (e.g., every hour or every two hours for the duration of the study) to minimize the effect of the current weakness.

A second weakness of GPI is the ignorance of the *severity* of extreme (but exceptional) blood glucose measurements due to hypo- and hyperglycemic cut-off values (e.g., $\delta_{300\text{ mg/dl}} = \delta_{450\text{ mg/dl}} = 100$). Though the reasons for using these cut-off values are well founded (see above), we advise counting the number of alarm glycemia observations (i.e., $G < 40$ mg/dl [210] and $G > 200$ mg/dl [216]) to better interpret the obtained GPI.

Previous studies have already indicated the relation between improved clinical outcome on the one hand and reduced average morning blood glucose [213, 216] and reduced HGI [233] on the other hand. It is important to note that the relation between GPI and clinical outcome has not been shown yet. The design of GPI is purely founded on currently available clinical expertise. Future studies are necessary to verify whether low GPIs effectively correspond to reduced mortality and morbidity, which is however expected from a clinical 'expert' point of view and from the high correlation between GPI and HGI.

### 4.4.3 Weight determination for the selected parameters

The blood glucose sampling frequency in the insulin titration guidelines used in patient group 1, varied as a function of the level of glycemic control. When the blood glucose was more difficult to control (unstable glucose dynamics), more frequent sampling occurred. The full patient data of group 1 comprised the initial (unstable) and more chronic (stable) phase of each patient's stay in the ICU. An increasing *duration of algorithm application* (which implicitly indicates a longer stay in the ICU, typically associated with more stable glucose dynamics) artificially improved the average overall blood glucose control behavior leading to lower GPIs (see second panel of Figure 4.7). Figure 4.8 additionally clarifies the relation between GPI and *duration of algorithm application*. The GPI decreases when more data (i.e., longer time/duration in the ICU) are considered in its computation process.

Further, this increasing *duration of algorithm application* lowered the *average blood glucose sampling frequency* (expressed in the negative correlation between *duration of algorithm application* and *average blood glucose sampling frequency*) since less glycemia observations were required in the chronic 'stable' period (due to the nature of the used protocol). Therefore, the first panel of Figure 4.7 that illustrates the relation between TGC (low GPI) and a low average blood glucose sampling frequency

is explained by the long time that the algorithm was applied to the patients of group 1. In case the *duration of algorithm application* was kept constant and limited (only the first 48 hours after admission), an increase of the glycemia sampling frequency resulted in more strict blood glucose control (lower GPI) as depicted in the top panel of Figure 4.6. It can be concluded that both *duration of algorithm application* and *average blood glucose sampling frequency* are two important parameters that should be taken into consideration when assessing or comparing different blood glucose control algorithms.

### 4.4.4 Practical use

For the design of future studies that compare the performance of different insulin titration algorithms applied to critically ill patients, it is encouraged to rely on the 'similarity' condition: the *duration of algorithm application* and the *blood glucose sampling frequency* should be similar in patient groups. It is further encouraged to consider GPI as supplemental tool to other advanced measures (e.g., HGI, 'notional duration of hyperglycemia/hypoglycemia') besides more traditional measures (e.g., average *morning* blood glucose, average blood glucose) for adequately assessing the overall level of blood glucose control.

## 4.5 Conclusions

The use of nurse-driven blood glucose control algorithms is becoming standard practice in ICUs. New (semi-automated) insulin titration algorithms are currently under development but require an appropriate evaluation before accepting them as state-of-the-art. In this chapter, the computation of the GPI as a tool to compare different blood glucose control algorithms was presented. This index encompassed the *overall* blood glucose dynamic behavior per patient in a single number based on clinical expertise. The method was affected by the *blood glucose sampling frequency* and the *duration of algorithm application* which should be similar for adequately comparing insulin titration algorithms. The results obtained in this chapter are further described in [218].

# Part III

# GLYCEMIA CONTROL SYSTEM

# Chapter 5

# Black-Box Modelling of Glycemia

*This chapter focuses on the design of a 'black-box' model (i.e., a data-driven approach for model selection and estimation) to describe the blood glucose dynamics of critically ill patients (see Figure 5.1). The objective is to determine whether the data contain enough information to build a model for simulation and control purposes. An initial input-output model is firstly estimated after which an adaptive modelling strategy, in which the model is re-estimated every hour, is presented. The optimized adaptive modelling technique outperforms the general initial model. The results are satisfactory both in terms of forecasting ability and in the clinical interpretation of the estimated coefficients.*

## 5.1 Introduction

Identification methods are applied for the purpose of designing a model that can be used to predict the (dynamic) behaviour of a system. They can be classified as follows [190]:

- **White-box models:** These models are perfectly known as they are entirely constructed from prior knowledge and physical insight.
- **Grey-box models:** Physical insight is available and used to develop these models, but some parameters still need to be determined from the observed data.
- **Black-box models:** No physical insight is used in the design process of these models. Based on 'input-output' data a linear or a non-linear model structure is constructed and the model parameters are estimated.

In this chapter the **black-box modelling approach** is considered for the development of a linear black-box model that describes the glucoregulatory system of critically ill patients. The known input data (e.g., administration rate of insulin, calories,

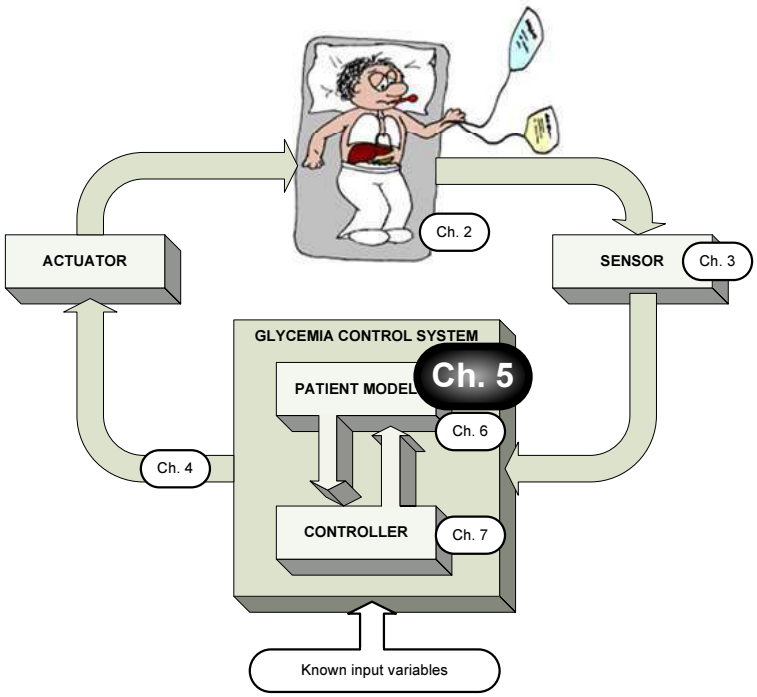


**Figure 5.1:** Simplified presentation of the (semi-)automated control system. In this chapter the results that are obtained when applying the black-box modelling approach are described.

medication) and the observed output signal (glycemia) are used to develop a *model structure*. Next, the model is *estimated* or, in other words, *fitted* (expressed in the model coefficients) within this given structure. In general, the design of a model structure (i.e., selection of the relevant variables in the model, the interactions between them, and the dynamic effect) is the key problem when identifying a system or a process [190].

Most black-box modelling techniques assume that the inputs of the system under study are independent of the past outputs, or in other words, that the system can be labeled as 'open-loop'. In case of 'closed-loop' systems this assumption is not valid any more due to the relation between the previous output signal with the future input signal. This relation is typically expressed in a controller that regulates the output by adapting the control input variable. This closed-loop aspect prevents a clear distinction between cause and effect and explains that the standard algorithms used in black-box modelling techniques can generate false results. Figure 5.2 further clarifies the differences between open-loop and closed-loop systems.

Due to the fact that the nurses determined the required insulin dose (i.e., the control input variable) partly based on the patient's blood glucose level (i.e., the output signal),

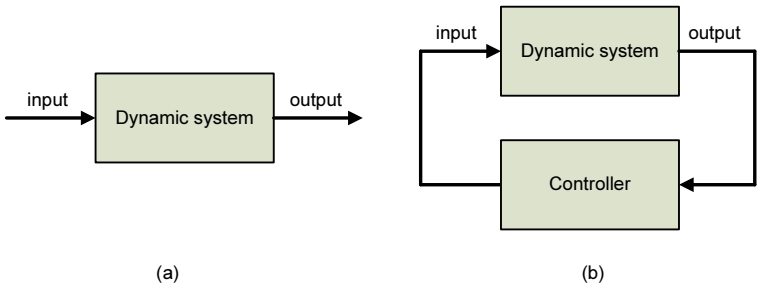


**Figure 5.2:** Schematic depiction of an open-loop (a) and closed-loop (b) dynamic system.

they are performing as the equivalent of a *controller* that introduces the notion of feedback in the data explaining the closed-loop feature in the data at hand (see Chapter 2, 2.5).

In the available literature, some (black-box) identification methods to cope with closed-loop data are distinguished. Most important techniques are the *Direct Approach*, the *Indirect Approach*, and the *Joint Input-Output Approach* [82, 136]. The first approach considers the output and the inputs of the glucoregulatory process in the same way as for open-loop operation, ignoring any possible feedback or closed-loop feature. In the Indirect Approach, the relationship between the output and the reference signal is modelled by making use of the known regulator or controller. The third approach considers the output and the inputs of the system when this system is driven by the reference signal and noise. Some general features, advantages, and disadvantages of closed-loop identification techniques are further described by Ljung, Goodwin *et al.*, among others [82, 136].

Particularly the Indirect and the Joint Input-Output approach assume perfect knowledge of the controller, or constant (i.e., fidelity of the controller), or even linear control behaviour. The nurses controlled the blood glucose of the patients, based on 'experience', by using a set of *guidelines*, as presented in Van den Berghe *et al.* [215]. Accordingly, the controller (i.e., the control behaviour of the nurses) applied to the patients was not identical in time (i.e., different nurses successively treated a patient) and could not be exactly defined. Therefore, the Indirect and the Joint Input-Output approach could not be used for the scope of this work. In this chapter, the Direct Identification approach is used as this technique forms a natural approach to closed-loop data: the complexity of the regulator does not influence the modelling performance and knowledge about the controller is not required [136].

In the following chapter (Chapter 6), the **grey-box modelling approach** is applied. In this approach, the *model structure* is founded on physical knowledge. The data are only used for *estimation* purposes. Accordingly, the closed-loop issue that is typical of the data at hand influences the modelling of the glucoregulatory system to a lesser

degree. As perfect knowledge of the physiology of the glucoregulatory system of the critically ill is not available (see Chapter 2, 2.2.1), the **white-box modelling approach** is not considered in this thesis.

## 5.2 Design of the model structure

### 5.2.1 Introduction

The major processes controlled by insulin in a healthy person are the stimulation of glucose uptake (mainly by muscles and adipose tissue) and the inhibition of the hepatic glucose production as addressed above (see Chapter 2, 2.1). The glucose utilizing tissues offer resistance to insulin, however, which results in an increase of the blood glucose level [187,241,242]. Therefore, this insulin resistance (which is the inverse of the insulin sensitivity) is an important aspect that should be incorporated in the model. The insulin sensitivity is typically *estimated* as it cannot be directly measured. Its determination can be defined as the assignment of a value to the change of glucose disappearance from blood (following a glucose load) for a unit change of insulin. Most common methods to estimate the insulin sensitivity can be summarized as follows [12, 157]:

- **Glucose clamp:** The glucose clamp has evolved in two classical paradigms: the *euglycemic (i.e., normoglycemic) hyperinsulinemic* and the *hyperglycemic* clamp. In the first clamp test, glycemia is kept constant by infusing glucose under an increased insulin concentration condition. The second clamp test is characterized by a glucose bolus at the start of the test aiming at hyperglycemia which stimulates insulin secretion in the pancreas. This hyperglycemic target value is maintained by infusing additional glucose. In both clamp tests glycemia is frequently monitored. The infused glucose and insulin flows and the monitored glycemia signal are used to assign a value to the insulin sensitivity.

- **Intravenous glucose tolerance test (IVGTT):** During the first minute of this test, a bolus injection of glucose is intravenously delivered to the subject. Next, blood glucose, insulin concentrations, and possibly C-peptide[1] concentrations after the glucose bolus injection are frequently monitored for the coming three to four hours. The observed data can be analysed with the 'minimal model' [14], which is extensively discussed in Chapter 6 (see 6.2.2). When glycemia is sampled with a high sampling frequency, this test is also called the 'frequently sampled intravenous glucose tolerance test' (FSIGTT).

- **Oral glucose tolerance test (OGTT):** This test is similar to IVGTT except for the method of delivering the glucose bolus. Here, the subject ingests 75 g glucose and glycemia, insulin, and C-peptide concentrations are measured for the next three hours.

[1] A C-peptide is a peptide (i.e., a short polymer) which is made when proinsulin (i.e., the prohormone precursor to insulin made in the beta cell of the islets of Langerhans) is split into insulin and C-peptide. Since one C-peptide corresponds to one insulin molecule ('equimolarity'), the monitoring of C-peptide allows to measure the insulin production capacity of the pancreas [156].

Many people who suffer from increased insulin resistance, produce large amounts of insulin to maintain normoglycemia. The tests described above make it possible to quantify the extent of insulin resistance and, accordingly, the risk to develop diabetes. There are two main reasons why it is advised that these tests should not be used to determine the insulin resistance in the critically ill:

- First of all, it would be unethical to perform such tests in critically ill patients. Since patient conditions in the ICU are typically life-threatening, additional disturbance factors (i.e., additional 'tests' that are not necessary for the treatment of the patient) should be avoided. Furthermore, these tests necessitate the monitoring of glycemia, insulin, and C-peptide concentrations on a very regular base (e.g., every 5 minutes) during three to four hours. The workload of the medical staff is already very high, which explains that it would be difficult to implement this frequent monitoring process in clinical practice as no near-continuous glucose monitoring device is yet available.
- Secondly, the estimation of the insulin sensitivity based on the tests described above would only result in a value that is valid at that particular moment in time. As already discussed above, the insulin sensitivity in critically ill patients is characterized by a high inter- and intra-patient variability. The recovery process of the patient is usually related to an increase of the insulin sensitivity but additional inflammations, administration of drugs (e.g., glucocorticoids), etc. may be responsible for sudden decreases of the insulin sensitivity. Accordingly, it would be necessary to frequently re-estimate the insulin sensitivity (e.g., every 5 hours) which would be unreasonable from a clinical point of view. It is also not possible to take all the parameters that may influence the insulin resistance, into account individually as the size and the accuracy of the data set at hand is insufficient for doing this.

In this chapter, it is assumed that the insulin resistance is directly related to internal body temperature. It can be expected that body temperatures surpassing 37.5°C (which indicate early fever conditions) are related to an increase of the critical illness (e.g., additional inflammations) and an increase of the insulin resistance. This study considers data set 1, which is depicted in Chapter 2 (see 2.4.1), to design a 'black-box' model structure. The used sampling interval equals one hour after linear interpolation. An alternative method to estimate time-varying insulin sensitivity in the critically ill is recently reported by Hann *et al.* [87].

### 5.2.2 Modelling methodology

The overall modelling methodology is presented in this section. Firstly, a specific model structure is selected after which a modelling method that is independent of the particular set of patients used for estimating or testing, is described.

#### 5.2.2.1 Model structure

A linear ARX (AutoRegressive model with eXogenous input variables) model structure is postulated because of the small available data sample size. In this way the complexity

of the model can be restricted [136, 190]. The aim is to predict the blood glucose behaviour from a set of clinical inputs, using a model of the following form:

$$G_{t+1} = \sum_{i=1}^{n_a} a_i G_{t-i+1} + b_1 F_{I,t} + b_2 F_{I,t} D_{\text{Fever},t} + b_3 F_{G,t} + b_4 F_{F,t} + b_5 T_t + b_6 F_{C,t} + b_7 F_{A,t} + b_8 F_{N,t} + b_9 F_{Dob,t} + b_{10} F_{Dop,t} + b_{11} F_{\beta,t} + b_{12} + e_t, \quad (5.1)$$

where $a_i \in \mathbb{R}, b_j \in \mathbb{R}$, $i = 1, \ldots, n_a$, $j = 1, \ldots, 12$ are the model coefficients to be estimated; $G_t$ is the glycemia level at time $t$; $F_{I,t}$ is the insulin flow at $t$; $D_{\text{Fever},t}$ is a dummy variable that takes 1 if the body temperature at time $t$ is above 37.5°C and zero otherwise; $F_{G,t}$ the flow of carbohydrate calories; $F_{F,t}$ the flow of fat calories; $T_t$ the body temperature; $F_{C,t}$ the glucocorticoids level; $F_{A,t}$ the adrenaline level; $F_{N,t}$ the noradrenaline level; $F_{Dob,t}$ the dobutamine level; $F_{Dop,t}$ the dopamine level; and $F_{\beta,t}$ the level of beta-blockers. Table 5.1 gives an overview of the input variables and their units. The residuals $e_t$ are assumed to have zero mean and constant (and finite) standard deviation.

**Table 5.1:** Overview of the input variables that were used in the modelling process.

| Variables | Symbol | Units |
|---|---|---|
| Insulin | $F_{I,t}$ | U/hr |
| Insulin*Dummy fever | $F_{I,t} D_{\text{Fever},t}$ | U/hr |
| Total carbohydrate calories | $F_{G,t}$ | kcal/hr |
| Total fat calories | $F_{F,t}$ | kcal/hr |
| Body temperature | $T_t$ | °C |
| Glucocorticoids | $F_{C,t}$ | mg/hr |
| Adrenaline | $F_{A,t}$ | $\gamma$ (1) |
| Noradrenaline | $F_{N,t}$ | $\gamma$ (1) |
| Dobutamine | $F_{Dob,t}$ | $\gamma$ (1) |
| Dopamine | $F_{Dop,t}$ | $\gamma$ (1) |
| Beta-blockers | $F_{\beta,t}$ | mg/hr |

(1) The unit $\gamma$ is used in a medical environment to symbolize the amount of the considered catecholamine drug ($\mu$gr) per kg body weight and per minute.

Since insulin resistance significantly influences the effect of insulin on glycemia, we parameterize the insulin effect as a combination of a base effect and as a possible additional effect due to fever in the model described above. This is further explained in Table 5.2. When the body temperature of the patient is below or equal to 37.5°C (no fever, $D_{\text{Fever},t} = 0$) the effect of insulin is captured by $b_1$, which is expected to be negative since insulin is a protein that decreases the blood glucose. In case of fever ($D_{\text{Fever},t} = 1$) the insulin activity is captured by the total contribution of ($b_1$ + $b_2$), which is assumed to be negative as well. However, the (positive) coefficient $b_2$ is expected to cause a reduction of the insulin activity. Similarly, the model coefficient values for administered calories are expected to be positive. Although the glycemia reactions on administered drugs are patient specific, a positive value for catecholamines, beta-blockers, and glucocorticoids can also be expected (see Chapter 2).

**Table 5.2:** Effect of insulin (to predict blood glucose at $t$+1) in case of fever or no fever.

| | Effect of insulin | Clinical expectation |
|---|---|---|
| No fever | $b_1$ | $b_1 < 0$ |
| $T_t \leq 37.5°C$ | | |
| $D_{\text{Fever},t} = 0$ | | |
| Fever | $b_1 + b_2$ | $b_2 > 0$ |
| $T_t > 37.5°C$ | | $(b_1 + b_2) < 0$ |
| $D_{\text{Fever},t} = 1$ | | |

#### 5.2.2.2 Order selection

The data set under study (data set 1, see Chapter 2, 2.4.1) comprises 41 patients. In order to select the model order $n_a$ in equation (5.1), we look at the prediction performance of a model evaluated on data that have not been used for model estimation. Thus, we define an *estimation* ($S_E$) and a *test* ($S_T$) set. By selecting different partitions between estimation and test sets, we look for the order that maximizes the average performance over different random data partitions. In this way, and for a given order $n_a$, we define a set of 30 patients for model estimation and a remaining set of 11 patients for testing. The model performance is measured on the test set for a particular data partition by computing the standardized mean squared error (sMSE), given by

$$\text{sMSE} = \sum_{t \in S_T}^{N} \frac{(G_t^s - \hat{G}_t^s)^2}{N}\,, \tag{5.2}$$

where $G_t^s$ is the actual and $\hat{G}_t^s$ the predicted standardized glycemia value, computed by

$$G_t^s = \frac{G_t - \overline{G}}{\text{SD}(G)}, \tag{5.3a}$$

$$\hat{G}_t^s = \frac{\hat{G}_t - \overline{G}}{\text{SD}(G)}, \tag{5.3b}$$

with $G_t$ the actual and $\hat{G}_t$ the predicted glycemia value at time instant $t$, $\overline{G}$ the obtained average of the observed glycemia signal $G$. Finally, $N$ represents the number of evaluation points. Each time, the estimation/test partitions are randomized 500 times to avoid data selection bias. Figure 5.3 gives an overview of this randomization process. The value of 500 was taken as a sample large enough such that the performance assessment based on the average sMSE over the different test sets is representative of an asymptotic behaviour. Finally, we select the order $n_a \in [1, 10]$ which gives the lowest sMSE averaged over these 500 random partitions.

#### 5.2.2.3 Model estimation and input selection

Each model is estimated in the following way. Given the order $n_a$ and the estimation data, a first model $M_{\text{all}}(n_a)$ of the form of equation 5.1 is estimated by applying

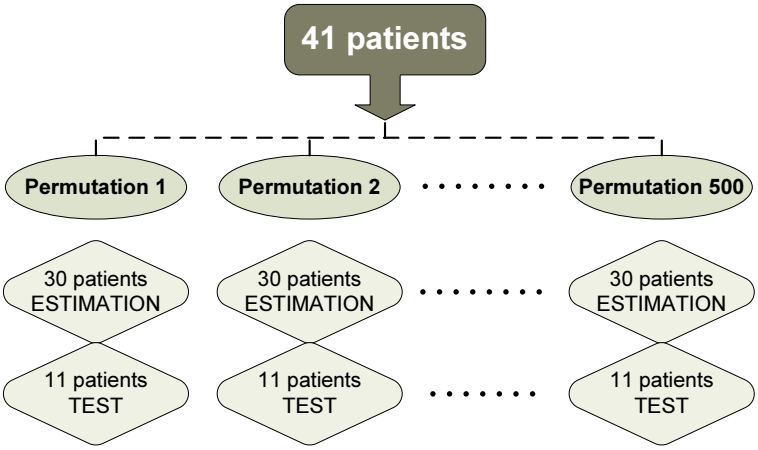


**Figure 5.3:** The patients of the first data set (see Chapter 2, 2.4.1) are considered for the design of the model structure. Different sets of patients were used for estimating and testing the developed models. This randomized process is repeated 500 times to avoid data selection bias.

OLS [141] using *all* regressors such that the squared error (i.e., the squared difference between the predicted and the observed glycemia value) is minimized. This can be presented by

$$\min_{\beta,e} \quad e^T e, \qquad \text{s.t.} \quad Y = X\beta + e, \tag{5.4}$$

where the $n \times 1$-vector $Y$ denotes the output variable (blood glucose), the $n \times m$-matrix $X$ the $m$ input variables, and the $n \times 1$-vector $e$ the error. The model coefficients to be estimated are represented by the $m \times 1$-vector $\beta$. This set of model coefficients is estimated for each permutation. Based on the $t$-statistics [175] of the estimated coefficients from $M_{\text{all}}(n_a)$, we *select* only those inputs which are statistically significantly different from zero. This is an iterative process, where one variable is removed at a time, and the model is re-estimated until all variables are found to be statistically significant (at a 95% level). This final model is denoted as $M_{\text{sel}}(n_a)$. The model $M_{\text{sel}}(n_a)$ is the one used for evaluation with the test set when selecting the order $n_a$. Once the optimal order $n_a^*$ is selected, a new model $M_{\text{all}}(n_a^*)$ with optimal order $n_a^*$ is estimated using all data from all patients, and its reduced model $M_{\text{sel}}(n_a^*)$ is the final model to be considered. The outline of the modelling procedure is presented in Figure 5.4. The overall methodology can be summarized as follows:

1. For order $n_a$ = 1 to 10,
   (a) Repeat $k$ = 1 to 500,
      i. Define a set of 30 patients for estimating ($S_E^k$) and 11 for testing ($S_T^k$) on each repetition $k$,
      ii. Estimate model $M_{\text{all}}(n_a)$ with $S_E^k$,

iii. Based on iterative $t$-tests of significance at 95% level, find model $M_{\text{sel}}(n_a)$ in which all variables are significant,

iv. Evaluate $M_{\text{sel}}(n_a)$ on the test data $S_T^k$ to predict glycemia $\hat{G}_{S_T^k}$,

v. Compute the standardized mean squared error $\text{sMSE}_k(n_a)$ between $\hat{G}^s_{S_T^k}$ and $G^s_{S_T^k}$ (which represent the standardized predicted and actual glycemia, respectively),

(b) Compute the average standardized mean squared error $\text{sMSE}(n_a) = \frac{1}{500}\sum_{k=1}^{500} \text{sMSE}_k(n_a)$,

2. Find optimal $n_a^*$ that minimizes the average $\text{sMSE}(n_a)$,

3. Estimate a model $M_{\text{all}}(n_a^*)$ with optimal order $n_a^*$ using all data from all patients,

4. Use the iterative $t$-tests until the final model $M_{\text{sel}}(n_a^*)$ is obtained.

### 5.2.3 Modelling results and clinical assessment

After applying the modelling strategy described above the results are shown in this part. Furthermore the final model is clinically assessed.

#### 5.2.3.1 Modelling results

Figure 5.5 presents the average sMSE as a function of the model order. The optimal model order is $n_a^* = 2$. The average sMSE (over 500 randomizations) is 0.0557. Having selected $n_a^* = 2$, now we estimate a unique model $M_{\text{all}}(n_a^*)$ using all data from all patients, the results of which are shown on Table 5.3. The corresponding final model $M_{\text{sel}}(n_a^*)$, for which all variables are statistically significant, is reported on Table 5.4.

The predictor of the glycemia value $\hat{G}_{t+1}$ can now be written as

$$\hat{G}_{t+1} = \hat{a}_1 G_t + \hat{a}_2 G_{t-1} + \hat{b}_1 F_{I,t} + \hat{b}_2 F_{I,t} D_{\text{Fever},t} + \hat{b}_3 F_{G,t} + \hat{b}_{10} F_{Dop,t}, \quad (5.5)$$

which results in a sMSE of 0.0514 computed in-sample[2] for the model $M_{\text{sel}}(n_a^*)$. This is not very different from the average sMSE (0.0557) that was obtained for the same order using 500 random test partitions, which indicates that the methodology based on input selection using $t$-tests is able to produce a model which does not overfit (or overtrain) the in-sample data.

[2] The data used for parameter estimation are commonly known as *in-sample* data in statistical literature.

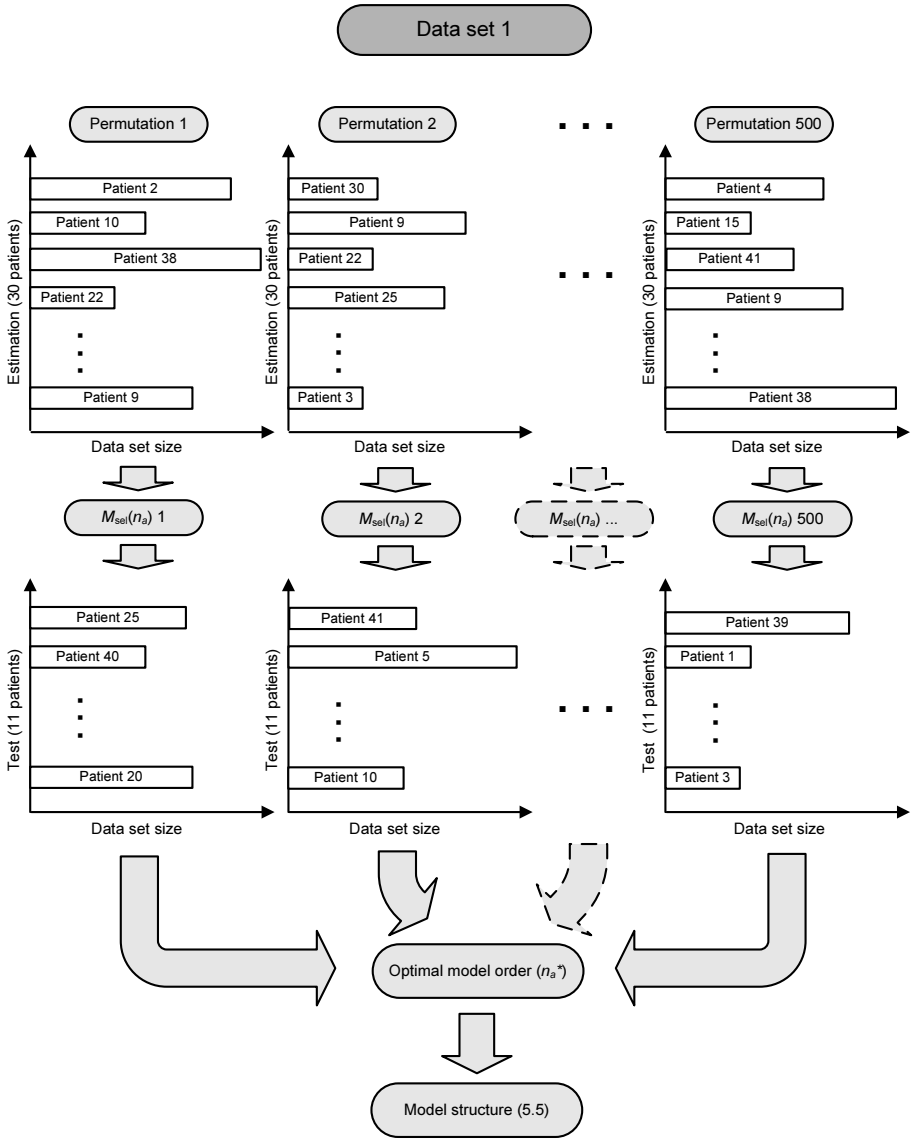


**Figure 5.4:** Outline of the procedure to determine the model structure. The estimation/test partitions are randomized 500 times to avoid data selection bias. Based on iterative $t$-tests, the data of the estimation set are used to determine the variables that are statistically significant leading to $M_{\text{sel}}(n_a)$ for each permutation and for the (varying) model order $n_a$. Next, the found $M_{\text{sel}}(n_a)$ is evaluated on the test set of each permutation aiming to find the optimal model order $n_a^*$. The final model $M_{\text{sel}}(n_a^*)$, using all data from all patients, is presented in equation 5.5.

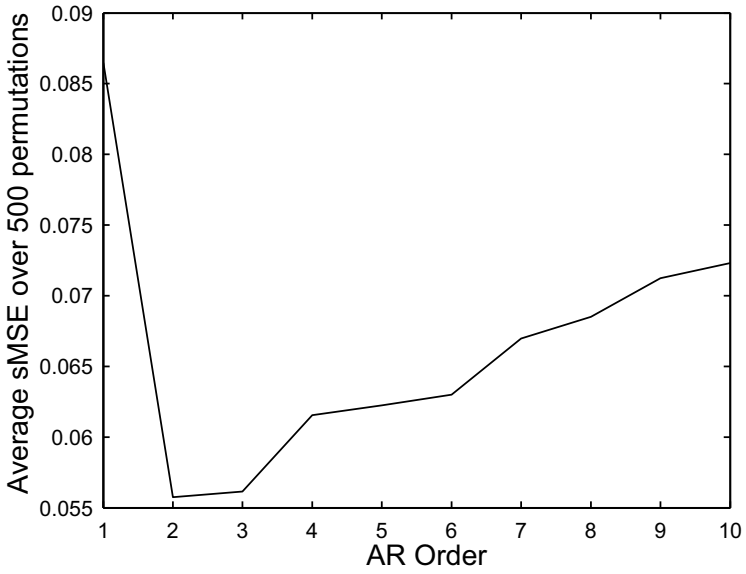


**Figure 5.5:** The average sMSE as a function of the model order. The use of model order 2 resulted in the smallest average sMSE (0.0557).

**Table 5.3:** Results for Model $M_{\text{all}}(n_a^*)$ with $n_a^* = 2$ after first iteration.

| Variables | Estimation | SD | $t$-stat |
|---|---|---|---|
| Output variables | | | |
| Glycemia at $t$ | 1.4959 | 0.0094 | 159.2171 |
| Glycemia at $t$-1 | -0.5692 | 0.0094 | -60.7940 |
| Input variables at $t$ | | | |
| Insulin | -0.2145 | 0.0276 | -7.7782 |
| Insulin*Dummy fever | 0.0783 | 0.0347 | 2.2541 |
| Total carbohydrate calories | 0.0257 | 0.0072 | 3.5634 |
| Total fat calories | -0.0070 | 0.0057 | -1.2248 |
| Body temperature | 0.1971 | 0.0881 | 2.2365 |
| Glucocorticoids | -0.0019 | 0.0037 | -0.5043 |
| Adrenaline | -1.3072 | 1.3534 | -0.9659 |
| Noradrenaline | 0.8073 | 0.9440 | 0.8551 |
| Dobutamine | 0.0153 | 0.0421 | 0.3627 |
| Dopamine | 0.1754 | 0.0745 | 2.3545 |
| Beta-blockers | -0.0051 | 0.0149 | -0.3418 |
| Constant | -6.8497 | 3.2746 | -2.0917 |

**Table 5.4:** Final Model $M_{\text{sel}}(n_a^*)$ containing only statistically significant variables.

| Variables | Estimation | SD | $t$-stat |
|---|---|---|---|
| Glycemia at $t$ | 1.4960 | 0.0094 | 159.5903 |
| Glycemia at $t$-1 | -0.5690 | 0.0093 | -60.9982 |
| Insulin | -0.2131 | 0.0267 | -7.9857 |
| Insulin*Dummy fever | 0.1044 | 0.0308 | 3.3859 |
| Total carbohydrate calories | 0.0336 | 0.0030 | 11.1282 |
| Dopamine | 0.2362 | 0.0697 | 3.3907 |

The Durbin-Watson (dw) statistic is a test statistic used to detect the presence of autocorrelation in the residuals from a regression analysis. A value of 2 indicates that no correlation is found [64, 65]. Here, dw = 1.9775. The parameter $R^2$ evaluates the regression: $R^2 = 0.9486$, which is close to 1 indicating a good performance. Finally, the in-sample sMSE = 0.0514.

#### 5.2.3.2 Clinical assessment

In this part the model coefficients are clinically interpreted and the clinical features are considered with respect to the generated model errors. First of all, $\hat{b}_1 < 0$ and $(\hat{b}_1 + \hat{b}_2) < 0$ (with $\hat{b}_1 = -0.2131$ and $\hat{b}_2 = 0.1044$, see Table 5.4) as was clinically expected. The increasing insulin resistance in case of fever is captured by $\hat{b}_2 > 0$. The latter causes a smaller reduction of blood glucose when insulin is administered to a patient with fever than without fever. The positive value of $\hat{b}_3$ (with $\hat{b}_3 = 0.0336$) indicates the glycemia raising effect with the intake of carbohydrate calories. Moreover, the positive value of $\hat{b}_{10}$ (with $\hat{b}_{10} = 0.2362$) was also clinically expected, due to the features of the catecholamine type of drugs.

Secondly, in order to relate the model errors with the clinical features of each patient individually, the standardized mean squared error per patient $p$ (sMSE$_p$) is calculated in-sample as follows:

$$\text{sMSE}_p = \sum_{t=1}^{N_p} \frac{(G_{t,p}^s - \hat{G}_{t,p}^s)^2}{N_p} , \tag{5.6}$$

where $N_p$ equals the number of observations per patient $p$ used in the estimation, and $G_{t,p}^s$ and $\hat{G}_{t,p}^s$ are the standardized actual and predicted glycemia, respectively, at time instant $t$. The different nature of patients influences the duration of stay in the ICU. Therefore, the sMSE$_p$-values versus the duration of stay are plotted for all patients in Figure 5.6. It is striking that four of the six patients whose sMSE$_p$ is above 0.1 belong to the *cardiac* surgery group. Patients from this group are typically characterized by shorter time periods in the ICU than patient groups with other pathologies.

In general, it is easily seen that the model performs better for patients whose length of stay is more than five days (smaller sMSE$_p$ values). This can be explained as follows. Firstly, the data set sizes of short-staying patients are smaller than the other data sets giving a smaller contribution to the estimation process of the in-sample model $M_{\text{sel}}(n_a^*)$. Indeed, the model is particularly estimated with the data of long-staying

patients. Secondly, the first days after admission to the ICU are characterized by rather unstable blood glucose dynamics as explained above. This means that accurately predicting glycemia is more difficult in the first 'acute' days compared with the rather 'chronic' phase. For patients who stay for a long time in the ICU, the model prediction performance is averaged and possible less accurate glycemia predictions, typical of the first days after admission, are masked.

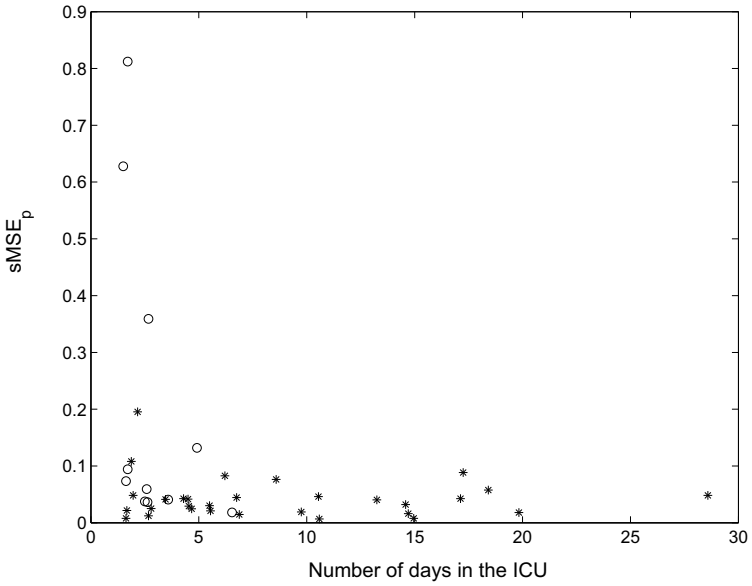


**Figure 5.6:** The $\text{sMSE}_p$ as a function of the individual length of stay in the ICU. Cardiac patients (marked by circles) typically stay for a shorter time period in the ICU than the other patients (marked by stars) which results in larger $\text{sMSE}_p$s than the other patient groups.

## 5.3 Initial and adaptive input-output modelling approach

In this section an *initial* and *adaptive* modelling strategy that are based on the previously developed model (equation 5.5), are presented. In the first strategy, a model is estimated using data of a set of patients and validated with other patients. In the second strategy, this initially estimated model is adapted with the data of each individual validation patient. Both initial and adaptive modelling techniques are evaluated by applying a one-hour-ahead prediction and a four-hours-ahead simulation process. Again, the models are estimated using different randomizations of the available data to avoid data selection bias.

### 5.3.1 Modelling strategy

We apply an initial and an adaptive modelling strategy on a new surgical ICU data set in which a glycemia sampling interval of 1 hour was imposed for this purpose: data set 2 (see Chapter 2, 2.4.2). The main advantage of this data set (compared with data set 1) is the higher glycemia sampling frequency potentially leading to a better identification of the system under consideration. The other features of the data set have already been described in Chapter 2.

#### 5.3.1.1 Patient selection procedure

In order to enforce independence of the patient selection, the available data set (15 patients) is divided into an estimation, a test, and a validation set in a random way during 500 successive times leading to 500 randomized estimation-test-validation partitions or permutations. Each permutation consists of an estimation set (8 patients), a test set (another 4 patients), and a validation set (the remaining 3 patients):

- For all permutations, the *estimation* set is used to estimate the initial model giving 500 initial model coefficients (see 5.3.1.2),
- Next, the optimal weighting factor is detected by applying the adaptive modelling strategy on the selected *test* sets for different weighting factors (see 5.3.1.3),
- Finally, the implementation of the found optimal weighting factor in the adaptive modelling strategy is validated on the remaining *validation* set for each particular data partition and compared with the model performance (by computing the MSE) when no adaptive modelling strategy is applied (see 5.3.1.3).

In Figure 5.7 the followed patient selection procedure is visualized.

#### 5.3.1.2 Initial model

For each permutation an initial model is estimated based on the data of the patients in the estimation set by applying OLS such that the squared error (i.e., the squared difference between the predicted and the observed value) is minimized (see equation 5.4). The model coefficients to be estimated are represented by the $m \times 1$-vector $\beta$, as $\beta = \begin{pmatrix} a_1 & a_2 & b_1 & b_2 & b_3 & b_{10} \end{pmatrix}$ from equation 5.5. This set of (initial) model coefficients is estimated for each permutation. In the validation process this estimated set has two different functions. In case the adaptive modelling methodology (see 5.3.1.3) is applied, this set will only be equal to the initial set of coefficients. At each time step the model coefficients will be adapted based on the recent data originating from the specific validation patient. In case there is no adaptive modelling strategy to be applied, this initial set will be kept constant during the full validation process.

#### 5.3.1.3 Adaptive model

Due to the large inter- and intra-patient variability that exists in the ICU (e.g., patient specific initial and dynamic known input variables, reaction on medical treatment,

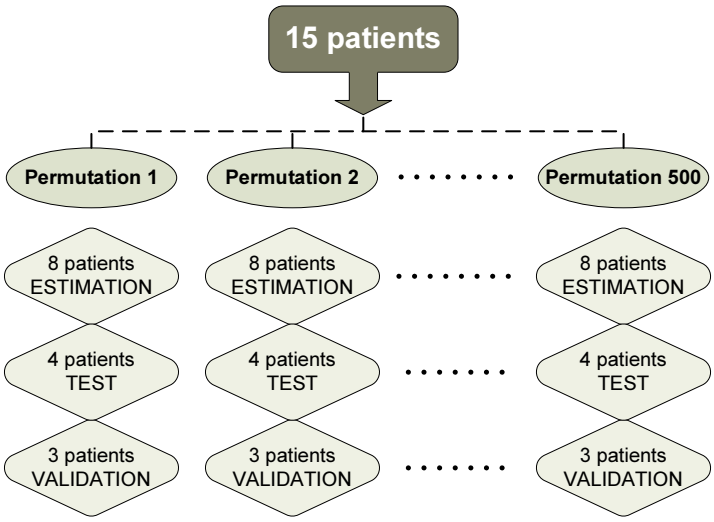


**Figure 5.7:** The patients of the second data set (see Chapter 2, 2.4.2) are considered for the evaluation of the initial and adaptive input-output model. Different sets of patients were used for estimating, testing, and validating the developed models. This randomized process is repeated 500 times to avoid data selection bias.

insulin resistance, etc.), the use of the initial model (i.e., a model valid for all patients) for accurately predicting glycemia may be insufficient. Therefore, the implementation of an **adaptive** modelling technique is proposed. In the presented procedure the model coefficients belonging to each test and each validation patient (both are called the *considered* patient) are re-estimated at each time step $t$ by combining two different data files:

- The **first** data file is fixed and comprises the data from the *estimation* set (i.e., the data used to define the initial model),
- The **second** part denotes the data from the *considered* patient up to time $t$-1 and grows as a function of time, consequently.

Weighted Least Squares (WLS, [141]) is applied in the estimation process. In this implementation the weighting factor is used to increase the influence of the squared errors of the second data set such that the model is more influenced by the data of the new patient. Accordingly, some time varying factors that may cause changes in the glucoregulatory behaviour (e.g., insulin sensitivity) are preferably included in the model. The minimization process can be summarized as follows,

$$\min_{\beta,e} \quad e^T \Phi e, \qquad \text{s.t.} \quad Y = X\beta + e, \tag{5.7}$$

where the diagonal $n \times n$-matrix $\Phi$ consists of elements equal to 1 (in case of errors related to the estimation set of patients) and equal to the hyperparameter $\phi$ (in case of

errors related to the data from the considered patient).

The hyperparameter $\phi$ is varied from 1 to 30 for optimization purposes. The total MSE is calculated considering all 500 permutations per weighting factor. The applied methodology to optimize $\phi$ is summarized as follows:

1. For weighting factor $\phi$ = 1 to 30,
   (a) Repeat k = 1 to 500,
      i. Define a set of 8 patients (called $S_E^k$) for estimating the initial model,
      ii. Define a set of 4 patients (called $S_T^k$) for testing the adaptive model,
      iii. For test patients $p$ = 1 to 4,
         A. Estimate a new model $M_t$ (of which the structure is defined in equation 5.5) at each time step $t$ by using WLS based on the fixed estimation set $S_E^k$ and on the data of the test patient $p$ (who is part of $S_T^k$) up to time $t$-1. The squared errors related to the second data file, are amplified by $\phi$,
         B. Predict glycemia $\hat{G}_{S_{T,t+1}^k}$ with the designed model $M_t$,
         C. Compute the error at $t+1$ (i.e., the difference between the predicted ($\hat{G}_{S_{T,t+1}^k}$) and the observed ($G_{S_{T,t+1}^k}$) glycemia value at time step $t+1$),
      iv. Store all errors that are generated for $S_T^k$,
   (b) Compute the total MSE of all stored errors corresponding to the respective $\phi$,
2. The weighting factor that is used to generate the smallest total MSE is the *optimal* weighting factor, $\phi_{\text{opt}}$, that will be used in the adaptive model simulations for each validation set $S_V^k$ (see 5.3.2).

### 5.3.2 Validation strategy

After selecting $\phi_{\text{opt}}$, the initial and the adaptive modelling algorithms are used for every randomly selected validation set (3 patients per permutation). The MSE is computed for every permutation. To compare the MSE-sets from the initial and the adaptive model, the Wilcoxon signed rank test is used. Figure 5.8 summarizes the adaptive modelling procedure. The overall methodology is further explained below:

1. Repeat k = 1 to 500,
   (a) Define a set of 8 patients (called $S_E^k$) for estimating the initial model,
   (b) Define a set of 4 patients (called $S_T^k$) for testing the adaptive model in order to optimize $\phi$ (full procedure described in section 5.3.1.3),
   (c) Define a set of the remaining 3 patients (called $S_V^k$) for validating the initial and the adaptive model,

(d) For validation patients $p$ = 1 to 3,

i. Predict the blood glucose signal during the considered time horizon (which is one hour (section 5.3.2.1) or four hours (section 5.3.2.2)) by implementing the initial and the adaptive model (using $\phi_{\text{opt}}$) at every time step. The input variables are assumed to be known in the considered time horizon,

ii. Compute the difference between the predicted and the observed glycemia value (i.e., the error),

(e) Compute the MSE belonging to $S_V^k$,

2. Compare the 500 MSEs from the initial model with those from the adaptive model.

#### 5.3.2.1 One-hour-ahead predictions

To validate the developed initial and adaptive models a one-hour-ahead prediction is performed using the data of each validation set. Equation 5.5 is applied in every time step with the estimated coefficients obtained from algorithm 5.4 and 5.7. The model performance is measured by computing the MSE, given by $\sum \frac{(\hat{G}_{t+1}-G_{t+1})^2}{N}$, where $G_t$ is the actual and $\hat{G}_t$ the predicted glycemia value, and $N$ the number of evaluation points in $S_V^k$.

#### 5.3.2.2 Four-hours-ahead simulations

Since a model operating in a real-life ICU should also be able to predict glycemia for a longer time horizon and since the current manual control strategy imposes a glycemia sample period of four hours [215], the developed models are also validated with a four-hours time horizon. In the simulation process the input variables are assumed to be known during this time horizon which is a clinically reasonable assumption. The simulation process can be presented as follows:

$$\begin{aligned}
\hat{G}_{t+1} &= \hat{a}_1 G_t + \hat{a}_2 G_{t-1} + \hat{b}_1 F_{I,t} + \hat{b}_2 F_{I,t} D_{\text{Fever},t} + \hat{b}_3 F_{G,t} + \hat{b}_{10} F_{Dop,t},\\
\hat{G}_{t+2} &= \hat{a}_1 \hat{G}_{t+1} + \hat{a}_2 G_t + \hat{b}_1 F_{I,t+1} + \hat{b}_2 F_{I,t+1} D_{\text{Fever},t+1} + \hat{b}_3 F_{G,t+1} + \hat{b}_{10} F_{Dop,t+1},\\
\hat{G}_{t+3} &= \hat{a}_1 \hat{G}_{t+2} + \hat{a}_2 \hat{G}_{t+1} + \hat{b}_1 F_{I,t+2} + \hat{b}_2 F_{I,t+2} D_{\text{Fever},t+2} + \hat{b}_3 F_{G,t+2} + \hat{b}_{10} F_{Dop,t+2},\\
\hat{G}_{t+4} &= \hat{a}_1 \hat{G}_{t+3} + \hat{a}_2 \hat{G}_{t+2} + \hat{b}_1 F_{I,t+3} + \hat{b}_2 F_{I,t+3} D_{\text{Fever},t+3} + \hat{b}_3 F_{G,t+3} + \hat{b}_{10} F_{Dop,t+3},
\end{aligned} \tag{5.8}$$

where $G_t$ and $\hat{G}_t$ denote the observed and predicted glycemia value. The model performance (measured by MSE) is now computed as $\sum \frac{(\hat{G}_{t+4}-G_{t+4})^2}{N}$.

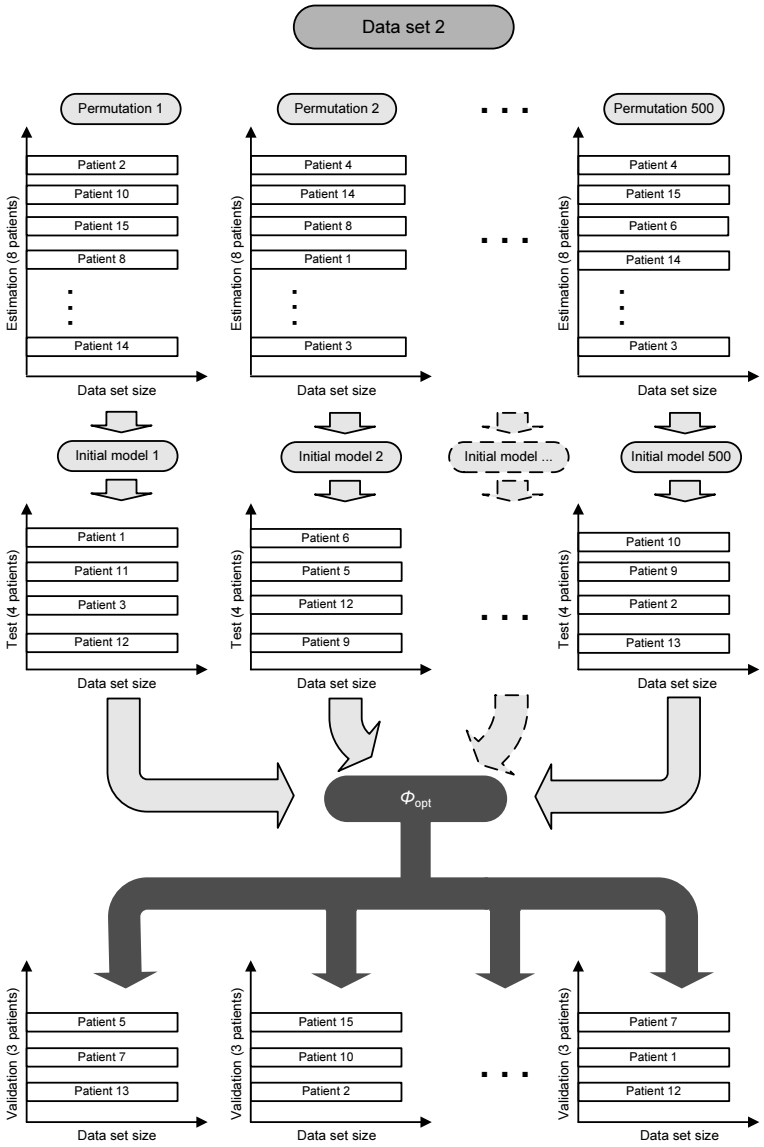


**Figure 5.8:** Outline of the adaptive black-box modelling approach. The estimation/test partitions are randomized 500 times to avoid data selection bias. An initial model is estimated for each permutation using the data of the estimation data and the found model structure 5.5 (see also Figure 5.4). Next, the adaptive modelling approach, using the data of the respective estimation set and a growing part of the data of each test patient (that is made more important by means of the (varying) weighting factor $\phi$), is evaluated on each specific test patient for each permutation. The most optimal weighting factor $\phi_{opt}$ is used in the final validation of the adaptive black-box modelling approach for each individual patient and for each permutation. Comparisons between one-hour-ahead predictions and four-hours-ahead simulations are made for both the initial and the adaptive modelling strategy.

### 5.3.3 Results

In this section the results of the initial model are presented, followed by the consideration of the optimal weighting factor used in the adaptive modelling procedure. Finally, the results of the comparison study of the initial and the adaptive modelling strategy in a one-hour-ahead prediction scenario and a four-hours-ahead simulation scenario are also shown.

#### 5.3.3.1 Initial model

Since 500 different permutations to randomize the selected estimation, test, and validation set of patients were considered, also 500 initial models were developed. Table 5.5 shows the mean of the estimated coefficient values and the corresponding standard deviations. The clinically expected signs of the estimated model coefficients are obtained again, similar to the developed model based on data set 1 (see 5.2.3.2).

**Table 5.5:** Results for the initial model considering all 500 permutations for data set 2 (see Chapter 2, 2.4.2).

| Variables | Corresponding model coefficient | Estimation | SD |
|---|---|---|---|
| Output variables | | | |
| Glycemia at $t$ | $\hat{a}_1$ | 0.9648 | 0.1043 |
| Glycemia at $t$-1 | $\hat{a}_2$ | -0.0278 | 0.1085 |
| Input variables at $t$ | | | |
| Insulin | $\hat{b}_1$ | -2.1375 | 0.5517 |
| Insulin*Dummy fever | $\hat{b}_2$ | 0.1472 | 0.5172 |
| Total carbohydrate calories | $\hat{b}_3$ | 0.3193 | 0.1353 |
| Dopamine | $\hat{b}_{10}$ | 6.6625 | 2.9161 |

#### 5.3.3.2 Optimal adaptive model

The process to optimize the weighting factor $\phi$ is applied to all *test* sets as explained in Section 5.3.1.3. In Figure 5.9 the MSEs as a function of $\phi$ are shown. The weighting factor that generates the smallest MSE over all permutations, $\phi_{\text{opt}}$, is 5. Consequently, this value is introduced in the adaptive modelling process used for the *validation* sets (see 5.3.2).

#### 5.3.3.3 Validation simulations

The validation of the developed model is performed with the data of the *validation* set during every permutation. A one-hour-ahead prediction scenario and a four-hours-ahead simulation scenario are both considered.

First of all, the models are validated by using a time horizon of one hour: the patient's glycemic value at time step $t$ is predicted by means of the last two blood glucose values

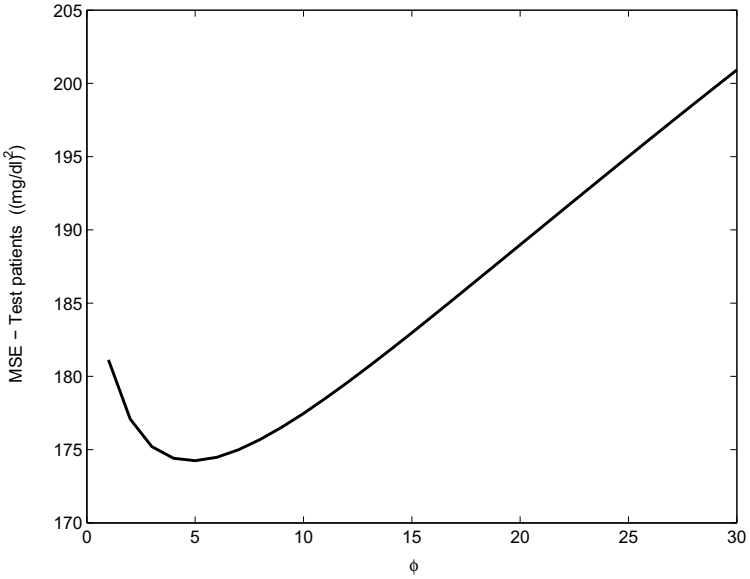


**Figure 5.9:** The MSE from the errors obtained for all permutations and for all test patients is computed as a function of the weighting factor $\phi$. The optimal weighting factor ($\phi_{\text{opt}}$) is found to be 5.

(at $t$-1 and $t$-2) and the considered input variables at $t$-1. The MSE of every validation set is computed as a function of the model type (initial or adaptive) and the permutation. The spread of the MSEs is visualized by means of a box and whisker plot in Figure 5.10. There is a significant difference ($p < 0.001$) between the MSEs belonging to the initial model and those belonging to the adaptive model. The average $\pm$ SD of the MSE for the initial model is $188 \pm 84$ (mg/dl)$^2$ and $171 \pm 90$ (mg/dl)$^2$ for the proposed adaptive modelling technique (with $\phi_{\text{opt}}$).

The use of a four-hours time horizon results in a larger difference in performance between the initial and the adaptive modelling strategy. The use of the former strategy results in $761 \pm 400$ (mg/dl)$^2$ as average $\pm$ SD of the MSE and $582 \pm 224$ (mg/dl)$^2$ for the (optimal) adaptive modelling strategy. Again, a significant difference ($p < 0.001$) exists between those two groups. The spread of the MSEs is visualized by means of a box and whisker plot in Figure 5.11.

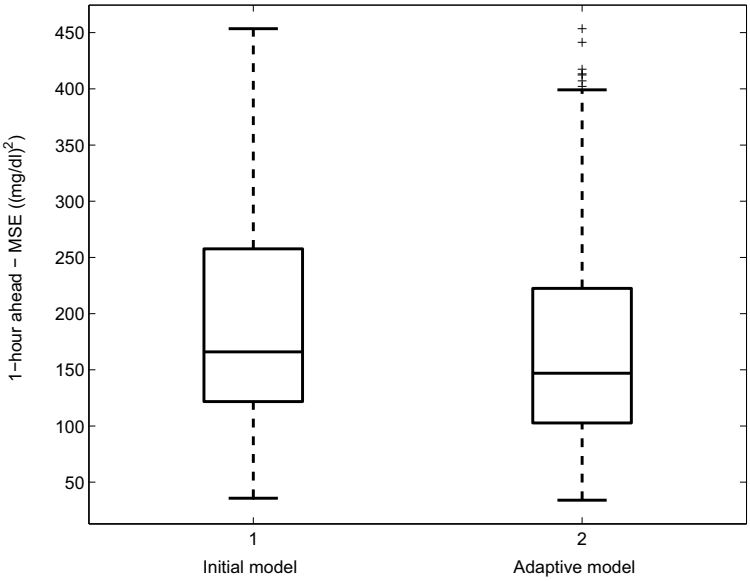


**Figure 5.10:** Boxplot of the MSEs obtained for all validation sets in a one-hour-ahead prediction scenario and after 500 permutations. The optimal weighting factor ($\phi_{\text{opt}} = 5$) is used in the adaptive modelling strategy.

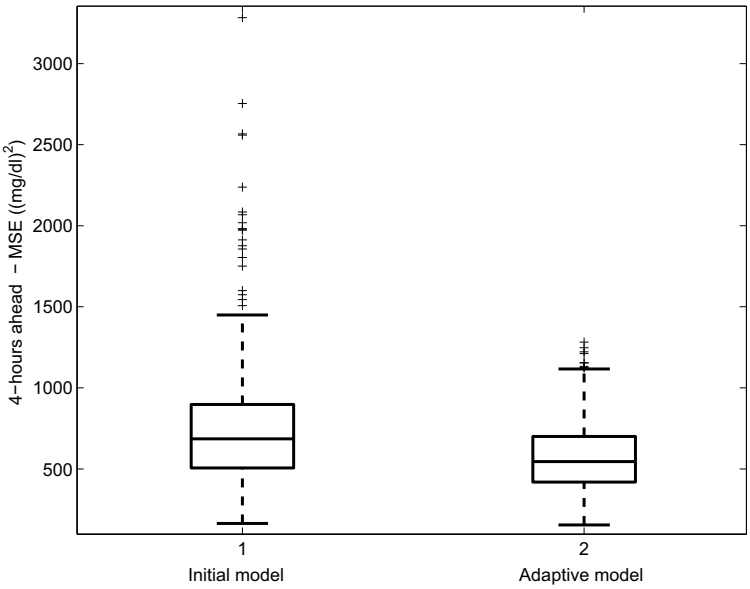


**Figure 5.11:** Boxplot of the MSEs obtained for all validation sets in a four-hours-ahead simulation scenario and after 500 permutations. The optimal weighting factor ($\phi_{\text{opt}} = 5$) is used in the adaptive modelling strategy.

## 5.4 Discussion

The signs of the estimated initial model coefficients (Table 5.5) correspond to their clinical expectations. This result is important since this initial set of coefficients may serve as *initial guess* in the adaptive modelling procedure applied to new ICU patients. In case of a one-hour time horizon, a root average MSE of 13.7 mg/dl for the initial and 13.1 mg/dl for the adaptive modelling strategy are obtained. The difference between the initial and adaptive modelling methodology becomes more clear by considering the four-hours time horizon: 27.6 mg/dl as root average MSE for the initial and 24.1 mg/dl for the adaptive model.

As is shown in Figures 5.10 and 5.11 the proposed adaptive modelling strategy results in significantly smaller MSEs than the initial model methodology for 500 particular definitions of the validation data. This is an important result since it proves the usefulness of considering individual patient features in the modelling process. The initial model is too 'general' to cover the glucose - insulin dynamics of each patient admitted to the ICU. In the proposed adaptive modelling procedure, a new model is estimated at each sample instant $t$ (i.e., every hour) based on both the fixed estimation data and the data from the specific validation patient up to time $t$-1, giving more importance to the latter.

The adaptive modelling strategy has the advantage that it can follow closely the evolution of the patient. This effect might be more visible if data with a larger time span would be available (the current time span of the data at hand only corresponds to the first 48 hours after admission to the ICU; see features of the data set in Chapter 2, 2.4.2). The longer the time span, the more patient-specific data are considered in the re-estimation process and the better the evolving dynamics are captured in the model.

Although the estimated coefficients of the models show clinical relevance for the behaviour of glycemia with regard to insulin, insulin resistance, intake of carbohydrate calories, etc. and although the obtained MSEs are relatively small, some **reservations** must be made when using this black-box modelling approach for **control purposes in clinical real-life**. Consider the following illustrative example. We assume no carbohydrate calories nor dopamine drugs are administered to the patient whose body temperature is below 37.5°C, giving

$$\hat{G}_{t+1} = 0.9648G_t - 0.0278G_{t-1} - 2.1375F_{I,t},$$

to predict the glycemia value of the next hour (see Table 5.5). We further assume that $G_t$ and $G_{t-1}$ equal 150 mg/dl and 180 mg/dl, respectively. A simple controller would be able to compute the insulin flow that would be required to reach normoglycemia within one hour ($G_{t+1}$ = 95 mg/dl): $F_{I,t} = 21$ U/hr. However, the administration of this amount of insulin in clinical real-life conditions is rather exceptional (though not infeasible). The average $\pm$ SD insulin flow (of the available data, see Chapter 2) is only 3.7 $\pm$ 3.5 U/hr. The following *artificial* example for the model,

$$\hat{G}_{t+1} = 1.5G_t - 0.5G_{t-1} - 10F_{I,t},$$

would return more realistic insulin flows. Under the assumption that $G_t$ and $G_{t-1}$ equal 150 mg/dl and 180 mg/dl, a simple controller would advise now to infuse 4 U/hr which is a similar flow as observed in the data at hand. In other words, the quantitative analysis of the coefficients presented in Table 5.5 returns that the estimated models may not be efficient (due to underestimation of the importance of the input variables) for use in a predictive control system as too high insulin dosages would be determined by the controller.

It is important to note that the black-box modelling procedure is purely data-driven. The performed $t$-tests indicate the importance of the selected input variables (based on the data at hand) leading to the generated model structure depicted in equation 5.5. Irrelevant input variables are not selected in this model. Further, the coefficients are estimated with these observed data. There are two reasons why the importance of the model coefficients of the *input* variables is underestimated. First of all, the model is based on an AutoRegressive (AR) structure meaning that some of the explanatory power is given to past values of the output (glycemia). In other words, particularly the past values of glycemia can explain the future glucose profile. Secondly, the data is generated under closed-loop conditions, because the patients were always under the supervision of the nurses and the medical staff, who act as a 'controller' (see also Chapter 2, 2.5). Despite the intention of the nurses to regulate the blood glucose very strictly (between 80-110 mg/dl), deviations from normoglycemia are observed due to remaining partly uncompensated disturbances. The resulting varying (non-constant) glucose profile allows to find non-zero model coefficients (for the input variables) in the estimation process.

The following thought experiment may further clarify this closed-loop aspect. Let us suppose the existence of an absolutely perfect control system, which is able to 'control' the blood glucose towards a target blood glucose range of 80-110 mg/dl. This (virtual) control system is perfect such that it manages to supply the right insulin dose (quantity, frequency, etc.) leading to blood glucose signals that are almost constant around 95 mg/dl (although the patient is critically ill). In other words, the insulin infusion sequence, which is determined by the control system, has a fluctuating pattern (input of the system) whereas glycemia is almost constant (output of the system). If black-box system identification techniques would be applied to these observed data, trying to develop a model explaining the constant signal (glycemia) based on the fluctuating input series (insulin), the model coefficient for insulin would be 0 as glycemia *seems* not to react to any change of insulin. This example tries to illustrate the effect of the closed-loop nature of the data on input-output modelling techniques.

A final remark concerning the followed black-box modelling method is that the approach of relating the insulin resistance to the body temperature may not always be correct. In this chapter, we parameterized the insulin resistance by approaching the insulin effect as a combination of a base effect and as a possible additional effect in case of body temperatures surpassing 37.5°C as mentioned above. However, this approach may not be ideal since high body temperatures may be masked in some patients by the administration of certain drugs. Although the insulin resistance might have raised

(due to for example additional inflammations and possibly leading to hyperglycemic episodes), the body temperature remains 'normal' (due to the administration of the appropriate medication) giving misleading information to the model.

In summary, the developed input-output models show an acceptable model prediction performance. Particularly, the adaptive modelling technique is promising in terms of considering patient-specific parameters. The qualitative analysis indicates that the signs of the estimated model coefficients behave as expected. However, because these are closed-loop data, the estimated models cannot be used on a clinical controller for the purpose of normalizing blood glucose in the critically ill.

## 5.5 Conclusions

In this chapter an initial input-output model to predict glycemia of critically ill patients was presented. Different dynamic input variables and a combined approach to the insulin resistance (by considering the body temperature) were implemented, in order to give the model a clinical interpretation. Secondly, an adaptive modelling strategy that was based on giving more importance to the individual patient data by applying WLS, was further described. By using a methodology based on random partitions of the data between estimation, test, and validation sets, the independence of the selected data could be enforced.

The estimated coefficients of the initial model showed clinical relevance with respect to the behaviour of blood glucose in relation to insulin, insulin resistance, intake of carbohydrate calories, etc. The application of an adaptive modelling strategy on the data of the validation sets of patients resulted in a significantly better performance (measured by computing the MSE) than that of the initial model. A one-hour-ahead prediction scenario and a four-hours-ahead simulation scenario were both considered. The performance difference between the initial and the adaptive model was found to be larger when a four-hours time horizon was introduced. However, because these are closed-loop data, the estimated models cannot be used on a clinical controller for the purpose of normalizing blood glucose in the critically ill. The results discussed in this chapter are further depicted in [220–222].

# Chapter 6

# Grey-Box Modelling of Glycemia

*This chapter presents a grey-box modelling approach to depict the dynamics of the blood glucose of the critically ill (see Figure 6.1). A new model structure, founded on physiological knowledge, is developed containing typical features of the ICU. To incorporate the time-varying behaviour of the glucoregulatory system, the model is estimated every hour or every four hours. This adaptive modelling approach is further optimized. The 'optimal' re-estimation strategy gives satisfactory forecasting results explaining its potential use in a predictive control system for critically ill patients admitted to the (surgical) ICU.*

## 6.1 Introduction

In system identification literature, a 'grey-box' model is typically founded on physical insight and contains some parameters that are fitted to observed data [190]. In the context of glycemia modelling, this type of *physical* or *physiological* models mostly comprises different compartments that are connected leading to the more popular term *compartmental* models. Each compartment is a quantity of material that behaves homogeneously meaning that all measures performed on the compartment at a given instant are equally representative. The interconnections express the fluxes of material between the different compartments. Compartmental models can be used for modelling complex systems that can be approximated by a number of subsystems that interact by exchanging these materials [5, 23].

In some cases the compartments can be associated with a physical space (e.g., blood). Then, the variable (or the material) could be really measured in this physical space. In other cases, however, there is no such precise correspondence. Compartmental models have become very popular in biomedicine, particulary in the fields of pharmacokinetics, metabolism, and endocrinology as will become clear in this chapter.

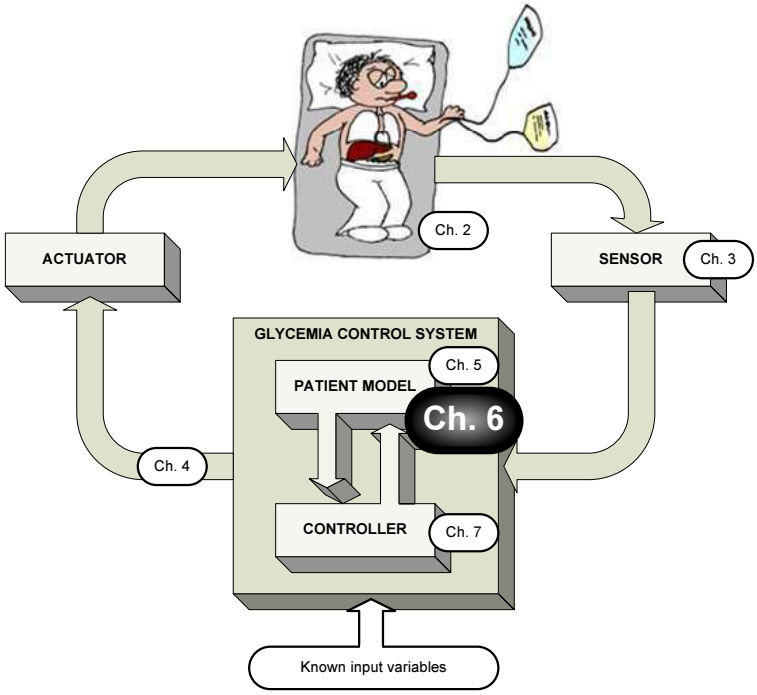


**Figure 6.1:** Simplified presentation of the (semi-)automated control system. In this chapter a grey-box modelling approach (i.e., the design of a physical model) is considered for predicting glycemia in critically ill patients.

Although physical insight forms the basis of the design of physiological models, parameters still need to be estimated from the observed data. The closed-loop feature of the data at hand has already been discussed in Chapters 2 and 5. Since the model structure (i.e., selection of the relevant variables in the model, the interactions between them, and the dynamic effect) is known in advance thanks to the physical insight of the system under study, the data at hand (and the closed-loop issue in particular) only affect the model in the determination process of the model coefficients. Accordingly, the impact of the closed-loop feature of the data on the model is limited compared to that of the black-box modelling approach.

Missing data form the major problem in identifying the glucoregulatory system of healthy persons, patients with diabetes, and critically ill patients since the blood glucose concentration (which behaves as the most important variable in this system) is measured only a few times per day (see Chapter 2, 2.4) [23]. Patients and clinicians anxiously await the commercial availability of accurate and reliable near-continuous glucose sensors. Our research group had the opportunity to test a recently developed glucose sensor (the GlucoDay system from A. Menarini Diagnostics, Italy) for use in a real-life ICU setting. We used this near-continuous sensor device to monitor

the subcutaneous glucose concentration in 20 patients during the first 48 hours after admission to the ICU. The considered data set is described in detail in Chapter 2 (data set 4, see 2.4.4). One patient of this patient group was allowed to leave the ICU already after 24 hours. Therefore, only 19 patients were considered in the study presented in this chapter. The glycemia sampling interval was 3 minutes but these glucose data were linearly interpolated to obtain one-minute glucose sampling intervals.

The performance of the near-continuous sensor device used in this study has already been discussed in Chapter 3 (see 3.4.1). There, it was found that the GlucoDay sensor device may not be efficient for blood glucose control in the ICU regarding the selected values for significance level, tolerance level, and glycemic range cut-off values. Although the monitored GlucoDay signal may not exactly represent the real ('reference') blood glucose signal, it can be used for data modelling purposes. The abundant presence of glucose observations allows to model the glucoregulatory system more precisely than with discrete-time glycemia data. Glucose dynamics (presented by the *near-continuous* signal), rather than the exact (*discrete-time*) blood glucose values, are more relevant for designing a dynamic model.

## 6.2 Physiological modelling of the glucoregulatory system

This section presents a general overview of the physical models that have been developed for describing the glucoregulatory system of healthy persons. This is followed by an introduction to the 'minimal model' which forms the base of the model that is generated for use in the ICU.

### 6.2.1 General overview

Most mathematical models that describe the glucoregulatory system originate from an IVGTT, FSIGTT, or OGTT (see Chapter 5, 5.2). Although Bolie was probably one of the pioneers in estimating the glucose disappearance and the insulin-glucose dynamics in general [16], the first breakthrough was realized by Bergman and his colleagues. In the early eighties, this team developed the famous 'minimal model' [14] which will be discussed below (see 6.2.2). Surprisingly, this study was virtually uncited for the first five years after publication. Since then, approximately 50 major studies that are founded on this model have been published every year [11]. To indicate the importance of the minimal model and his research related to diabetes, Bergman received the *Banting medal for Scientific Achievement* which is awarded by the American Diabetes Association. The work that is presented in this chapter is mainly based on this model structure as will become clear in the next section (see 6.3).

Instead of choosing for a rather simple model structure, Guyton *et al.* developed a more complex, comprehensive model [85] that approached the glucoregulatory system from an organ-by-organ perspective but which was not suitable for parameterization in individual subjects [158]. Further, Sorensen *et al.* [192] extended Guyton's model

and Lehmann and Deutsch [130] combined Guyton's model with the pharmacokinetic model for insulin action that was designed by Berger and Rodbard [9]. The model of Lehmann and Deutsch [130] aimed to serve as an educational tool about type I diabetes for both patients and health-care providers: the AIDA (Automated Insulin Dosage Advisor) tool [126–129, 131]. Although AIDA was not suited for therapeutic use, this computer simulation tool helps the user to understand the glucoregulatory system in patients with type I diabetes and the decision making concept concerning insulin dosages that these patients are confronted with.

Another popular model was designed by Parker *et al.* [159–161, 163]. He extended Sorensen's model by implementing the carbohydrate meal dynamics that were presented in the AIDA model. Moreover, Cobelli *et al.* developed an alternative comprehensive model that comprised glucose, insulin, and glucagon dynamics [48]. A last important model for describing the glucoregulatory system of patients with type I diabetes was developed by Hovorka *et al.* [95, 98]. This model represented the relation between subcutaneous insulin infusion and the blood glucose signal and comprised a glucose subsystem, an insulin subsystem, and an insulin action subsystem. It must be noted that also other models have been developed during the last years (e.g., the model defined by Hipszer *et al.* [93], Derouich and Boutayeb [59], among others) but these models have not yet the impact of previously mentioned models. Although more recent models are not included, a more detailed overview of the history of glucoregulatory models is given by Parker [160] and Palerm [158].

In general, *simple models* have the advantage of using only a small number of parameters but can be inadequate in terms of prediction accuracy if they are 'too' simple. *Comprehensive models* typically try to represent the full (biological/clinical) system by taking into account all interactions which makes them complex using a large number of parameters. The description of the overall performance, after putting together the individual compartmental descriptions, may be weak due to the merging of the confidence intervals [132]. While observing this trade-off, four criteria should be met for designing a physiological model [20]:

1. the model should be physiologically based,
2. the estimation of the model parameters should be sufficiently precise,
3. the values of parameters should be physiologically interpreted,
4. the system dynamics should be reliably simulated with the smallest number of identifiable parameters.

In spite of the large variety of models to describe the glucoregulatory system in healthy persons, none of them has been implemented in an artificial pancreas for use by patients with diabetes so far [132, 193]. Parameter estimates are associated with a high level of **uncertainty** that mainly arises from the large number of (un)known and/or (im)measurable factors (e.g., exercise, stress, glucose counter-regulatory effect[1], etc.) that may affect blood glucose, and the missing data issue (i.e., glycemia is measured

[1] The glucose counter-regulatory effect is caused by the *counter-regulatory* hormones that 'counter' the usual response to insulin and thereby increase the blood glucose; see Chapter 2, 2.2.1.

only a few times a day). Furthermore, it is known that the glucoregulatory behaviour is **not consistent** or regular as a function of time, even though external conditions seem to be equal (e.g., fixed meal times, standard meals, similar activities, etc.) [133]. Finally, it is important to note that the endocrine processes of a healthy person are **not yet fully understood**; let alone the endocrine behaviour of a patient who is critically ill. Accordingly, currently existing models are interesting simulation tools but have not yet been applied in routine clinical practice for the treatment of patients with diabetes due to the low reliability of the glycemia predictions. Moreover, it is surprising to see that comparisons of *monitored* versus *predicted* blood glucose signals are only rarely demonstrated in modelling studies [132].

Strict blood glucose control in the ICU has only become popular since the publication of the two landmark studies of Van den Berghe *et al.* in 2001 [216] and 2006 [213]. So far, no model that is able to accurately describe the glucose dynamics of the critically ill has been validated for use in a predictive control system (see Chapter 7, 7.4.1). It must also be noticed that the modelling conditions in the ICU significantly differ from the conditions present when modelling the glucose dynamics of patients with diabetes:

- On the one hand, the ICU is a strictly controlled environment: the amount/type of calories, insulin, and drugs that are delivered to the patient are carefully recorded, many system variables are frequently monitored (e.g., glycemia, body temperature), etc. In case of modelling the 'healthy' glucoregulatory system, the test conditions imposed on patients with diabetes or healthy volunteers are typically less controlled explaining the inaccuracy of the obtained models. Therefore, artificial conditions (e.g., fixed meal contents, limited exercise) are sometimes introduced in order to create a set of controlled conditions, but this has the disadvantage that the obtained models lie far away from reality.
- On the other hand, a high number of different (unknown) disturbance factors causes a high variability of glucose dynamics of critically ill patients (compared to patients with diabetes) which complicates the modelling process. As an example, the list of medications that directly or indirectly (via the influence on the insulin resistance) may affect the blood glucose is long (see for example the list in Chapter 2, 2.3.2). Moreover, the insulin resistance itself typically decreases when the patient recovers, but can increase again within a short time period in case of acute illness or stress.

### 6.2.2 Minimal Model (MM)

While developing their model, Bergman and his colleagues imposed two objectives. Firstly, the model had to be *complex* enough to account for the dynamics of glucose and insulin in the plasma. Secondly, the model had to be *simple* enough to estimate the parameters from a simple clinical test.

The original MM [14] comprises two sections: one for the glucose dynamics and one for the insulin dynamics. The **glucose** dynamics [13] are described by two compartments. The first compartment depicts glucose in the tissues (represented by

equation 6.1a) whereas the second compartment denotes the effect of insulin in these tissues (represented by equation 6.1b). The second section [202] presents the dynamics of **insulin** in the plasma which are summarized in a mono-compartmental structure (represented by equation 6.1c).

Plasma insulin is assumed to act through a so-called remote compartment to influence net glucose uptake [74]. The MM reliably describes the plasma glucose disappearance and the insulin kinetics during an IVGTT in a healthy person. In this test 300 mg glucose per kg bodyweight is intravenously administered to a person after which the plasma glucose and insulin concentration are measured with a high sampling frequency.

The MM is described by

$$\frac{dG(t)}{dt} = (P_1 - X(t))G(t) - P_1 G_b, \tag{6.1a}$$

$$\frac{dX(t)}{dt} = P_2 X(t) + P_3(I(t) - I_b), \tag{6.1b}$$

$$\frac{dI(t)}{dt} = \max(0, \gamma(G(t) - h)t) - n(I(t) - I_b), \tag{6.1c}$$

where $G(t)$ and $I(t)$ are the glucose and the insulin concentration in the blood plasma, respectively. The variable $X(t)$ describes the effect of insulin on net glucose disappearance and is proportional to insulin in the remote compartment. In other words, the variable $X(t)$ represents the substantial delay between the appearance of insulin in the plasma and the expression of the effect of insulin to promote the disappearance of glucose [10]. This is a clear example of a 'virtual' compartment meaning there is no precise correspondence between the compartment and a physical space (see 6.1). In fact, this delay can be physiologically explained by the transport of insulin across the capillary endothelium from plasma to the interstitial space, the binding to and the activation of the insulin receptor, the translocation and activation of glucose transporters to the plasma membrane, and the transport and intracellular phosphorylation of glucose as described by Bergman *et al.* [10].

$G_b$ and $I_b$ are the basal value[2] of plasma glucose and plasma insulin, respectively. The parameter $P_1$ represents the *glucose effectiveness*[3] or the fractional clearance of glucose when insulin remains at the basal level; $P_2$ and $P_3$ are the fractional rates of net remote insulin disappearance and insulin dependent increase, respectively. The ratio $P_3/P_2$ is referred to as the *insulin sensitivity*[4] index. The MM is a very popular technique to assess the insulin sensitivity in vivo. Accordingly, the use of this model prevents the performance of glucose clamps.

[2] The basal value corresponds to the value just before the administration of the glucose load during an IVGTT.

[3] Definition of **glucose effectiveness** by Bergman *et al.* [10, 13]: This is "the efficiency by which glucose can restore its own concentration independent of any dynamic insulin response".

[4] Definition of **insulin sensitivity** by Bergman *et al.* [10, 12, 13]: This is "the augmentation by insulin of the ability of glucose to normalize its own plasma concentration".

The endogenous insulin release during an IVGTT is composed of two different phases. First-phase insulin release is represented as a bolus of insulin (proportional to the glycemia rise) that enters the plasma compartment when glucose is injected. The first-phase insulin concentration in the plasma is symbolized by $I_0$. This insulin concentration cannot be estimated directly. Second-phase insulin release (which is modelled in equation (6.1c)), however, is represented as the insulin flow that is released in proportion (by $\gamma$) to the degree by which glycemia exceeds a glucose threshold level $h$. The time constant for insulin disappearance is denoted as $n$. In case glycemia does not surpass the glucose threshold level $h$, the first part of this equation (that represents the endogenous insulin production) equals 0. The time that has passed since the administered glucose shot is denoted as $t$.

In this model six parameters need to be estimated based on the input-output data during an IVGTT: $P_1$, $P_2$, $P_3$, $\gamma$, $h$, and $n$. The glucose threshold ($h$) turned out to be the basal blood glucose for the majority of the cases [156]. In [14], the above model was applied to a group of 18 human subjects who were classified in four groups (I: lean with good glucose tolerance[5], II: lean with poor glucose tolerance, III: obese with good glucose tolerance, and IV: obese with poor glucose tolerance).

In order to describe the glucose dynamics and the insulin kinetics of a patient with type I diabetes, the original MM has been extended to a *type I diabetes minimal model* (D-MM) in [74, 78]. Type I diabetes is characterized by insulin deficiency caused by an auto-immune destruction of the $\beta$-cells of the pancreas as is described in detail in Chapter 2 (see 2.1.2). Consequently, the endogenous insulin section (represented in equation (6.1c)) is replaced by an exogenous insulin flow (symbolized by $F_I$ in equation (6.2c)) and the basal insulin flow ($I_b$) is set at 0. In addition, a meal glucose disturbance variable $F_G$ is added to denote the flow of glucose calories that enters the glucose compartment. The full D-MM is described by

$$\frac{dG(t)}{dt} = (P_1 - X(t))G(t) - P_1 G_b + \frac{F_G}{V_G}, \tag{6.2a}$$

$$\frac{dX(t)}{dt} = P_2 X(t) + P_3 I(t), \tag{6.2b}$$

$$\frac{dI(t)}{dt} = \frac{F_I}{V_I} - nI(t), \tag{6.2c}$$

where $V_G$ and $V_I$ are the glucose distribution space and the insulin distribution volume, respectively.

[5] The **glucose tolerance** is the tolerance to oral or injected glucose. In other words, this tolerance level determines how much the blood glucose level has increased since a certain glucose load was administered to the subject. The glucose tolerance depends on both the *insulin sensitivity* and the *glucose effectiveness*. It is determined by factors like the insulin secretion capacity, the insulin clearance, the counter-regulatory hormones, etc.

## 6.3 Intensive Care Unit - Minimal Model (ICU-MM)

In this section an extended minimal model for use in an ICU setting is presented. Next, the features of this new model structure are studied and an adaptive estimation procedure is proposed.

### 6.3.1 Model structure

The physiological model used in this study is founded on the original (simple) MM (see 6.2.2) aiming to restrict the number of parameters to be estimated. There are two main reasons why an extension of previously presented models (MM and D-MM) may be necessary. First of all, the ICU-MM contains an **endogenous and an exogenous insulin section**, whereas the exogenous part is not included in the original Bergman model. Because the majority of critically ill patients are non-diabetic, the endogenous insulin section is still active. Due to the increased insulin resistance and the insufficient activity of the pancreas, some exogenously administered insulin flow is required for most of the patients (see Chapter 2, 2.2.1). Therefore, both the endogenous and the exogenous insulin sections that are represented in 6.1c and 6.2c, respectively, are included in the ICU-MM.

Secondly, the endogenous insulin section in the original Bergman model is transformed mathematically into a set of two equations with the goal of the model to **not be an explicit function of time**. The original MM is considered to describe the glucose and insulin dynamics only during a single IVGTT which has a typical duration of approximately three hours (taken into account the time $t$ related to the start of the glucose shot). In the MM, the endogenous insulin equation 6.1c is a direct function of time. The ICU-MM, however, is developed for use in a predictive control system (see Chapter 7) with a continuous flow (i.e., a series of single shots) of delivered carbohydrates (and other input variables). Considering the possible use of the original MM in a predictive control system, even a one-minute reset approach (in which $t$ is reset at 0 at each administered glucose shot in order to approximate the continuous flow) would significantly increase the complexity level. Therefore, we transformed the plasma insulin equation (i.e., equation (6.1c) for MM and equation (6.2c) for D-MM) into a set of two equations which are not explicit functions of time, but still lead to similar glycemia responses to an IVGTT.

The ICU-MM is presented as

$$\frac{dG(t)}{dt} = (P_1 - X(t))G(t) - P_1 G_b + \frac{F_G}{V_G}, \tag{6.3a}$$

$$\frac{dX(t)}{dt} = P_2 X(t) + P_3(I_1(t) - I_b), \tag{6.3b}$$

$$\frac{dI_1(t)}{dt} = \alpha \ \max(0, I_2) - n(I_1(t) - I_b) + \frac{F_I}{V_I}, \tag{6.3c}$$

$$\frac{dI_2(t)}{dt} = \beta \, \gamma \, (G(t) - h) - n I_2(t), \tag{6.3d}$$

where $G$ and $I_1$ are the glucose and the insulin concentrations in the blood plasma. The variable $X$ describes the effect of insulin on net glucose disappearance and is proportional to insulin in the remote compartment. The variable $I_2$ is introduced in order to describe the endogenous insulin section without any time-dependence while maintaining the second order behaviour of $I_1$ after glucose administration. It is a purely mathematical manipulation such that $I_2$ does not have a strictly defined clinical interpretation. However, this mathematical variable can be approached by the fraction of insulin concentration derived from the endogenous insulin secretion. It should be remarked that the ICU-MM structure also incorporates the closed-loop feature as the blood glucose ($G$) is directly influenced by the effect of insulin ($X$) which is determined by $I_2$ via $I_1$. The variable $I_2$, however, is also affected by $G$ (expressed in the endogenous insulin secretion part in equation 6.3d) illustrating that the loop is *closed*. This feature is important when realizing the data at hand are labeled as *closed-loop data* as discussed in Chapters 2 and 5.

The parameters $G_b$ and $I_b$ in the ICU-MM denote the basal value of plasma glucose and plasma insulin, respectively. It is, however, not possible to determine the plasma glucose/insulin values *before* the administration of the bolus glucose load (like for an IVGTT) as patients are entering the ICU when the acute stress level (corresponding to a *virtual* continuous glucose load) is *already* present. Therefore, these basal values are determined based on the patient-specific body weight (body mass) with regard to the patient's ideal body weight (IBW). Linear models are estimated with the patient data that are described in [14] using OLS:

$$G_b = 83 + 0.12\ \mathrm{IBW_R}, \tag{6.4a}$$

$$I_b = -13 + 0.22\ \mathrm{IBW_R}, \tag{6.4b}$$

where $\mathrm{IBW_R}$ denotes the body weight relative to IBW (expressed in %). The IBW values can be found in the Metropolitan Life Insurance tables [100]. The top panel of Figure 6.2 illustrates the relation between $G_b$ and $\mathrm{IBW_R}$ whereas the bottom panel depicts the relation between $I_b$ and $\mathrm{IBW_R}$.

The developed ICU-MM has two input variables: the exogenous insulin flow ($F_I$) and the carbohydrate (glucose) calories flow ($F_G$), both administered intravenously. The glucose distribution space and the insulin distribution volume are denoted as $V_G$ and $V_I$, respectively. The parameters $P_1$, $P_2$, $P_3$, $\gamma$, $h$, and $n$ have equal meanings as presented with the MM (see 6.2.2). Two extra parameters ($\alpha$ and $\beta$), both without any physiological significance, are included in the ICU-MM in order to keep the correct units. The coefficient $\beta$ equals 1 min. The coefficient $\alpha$ is optimized (by applying OLS) for the set of patients whose data are described in [14] such that every single IVGTT simulation, for insulin kinetics, should give a similar representation as that of the MM.

In [14], four different 'healthy' patient groups were described segregated on the bases of body weight and glucose tolerance. Considering the high insulin resistance that is present in most of critically ill patients, ICU glucose and insulin dynamics are mostly

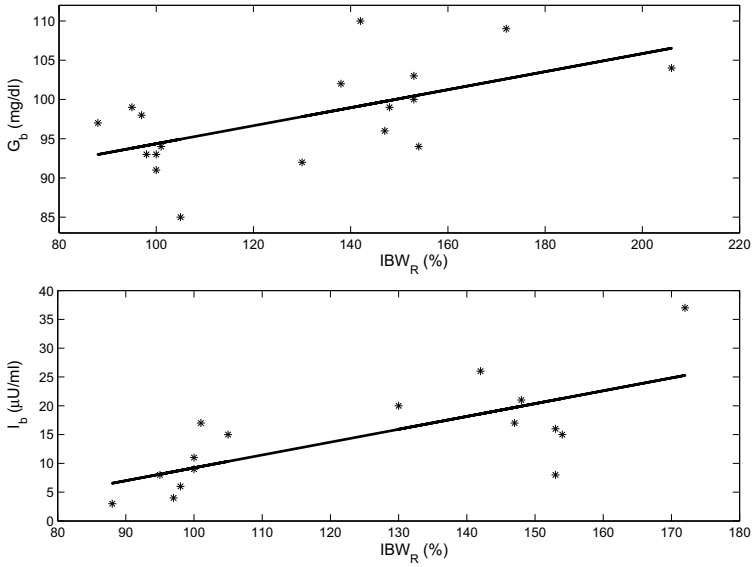


**Figure 6.2:** The top panel illustrates the basal glycemia ($G_b$) as a function of $\text{IBW}_\text{R}$. The bottom panel depicts the relation between the basal insulin concentration ($I_b$) and $\text{IBW}_\text{R}$ based on the patient data described in [14].

comparable to those patients who are classified into the obese and low glucose tolerance patient group [14]. The importance of avoiding the explicit time-dependence is further clarified in Figure 6.3 in which several successive IVGTTs are introduced to patient 16 who belongs to this obese - low glucose tolerance patient group [14]. The successive IVGTTs are meant to *approach* the continuous delivery of glucose (carbohydrate) loads that is typical of the ICU. Glucose dynamics and insulin kinetics are simulated by using both the MM and the ICU-MM. The sequence of IVGTTs is illustrated in the second panel of Figure 6.3. If the general condition of the patient does not change during this sequence, it is intuitive to expect a similar glycemia (top panel) and insulin (panel 3, 4, and 5) pattern for each new IVGTT.

The original model (MM), however, does not show similar behaviour. The plasma insulin concentration ($I_1$) and the effect of insulin on net glucose disappearance ($X$) that are described by the MM, increase with every IVGTT due to the explicit dependence on time in equation (6.1c). Time $t$ cannot be reset at 0 with every new IVGTT as this example approaches the ICU setting (in which the resetting is infeasible due to the *continuous* calories flow). The new model structure (ICU-MM), however, generates an insulin trajectory that follows the expected behaviour. Table 6.1 gives an overview of the variables, patient features, and coefficients used in the ICU-MM. Figure 6.4 illustrates the ICU-MM structure.

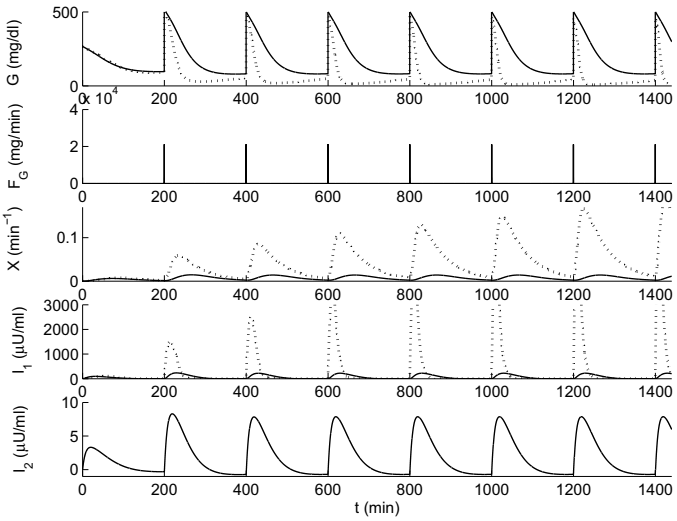


**Figure 6.3:** Presentation of the glucose and insulin dynamics during several successive IVGTTs ($F_G$, shown in the second panel) for patient 16 (whose data are described in [14]). The solid and dotted line represent the simulated trajectories by using the ICU-MM and the MM, respectively. Although the glycemia ($G$) behaviour shows a similar progress after every IVGTT (top panel), the insulin variables (both $X$ and $I_1$) show exploded trajectories (see the third and fourth panel) after simulating with MM. This phenomenon is clinically infeasible. In contrast, the use of the ICU-MM (which has an additional insulin variable $I_2$) results in an identical behaviour for insulin and glycemia after every IVGTT.

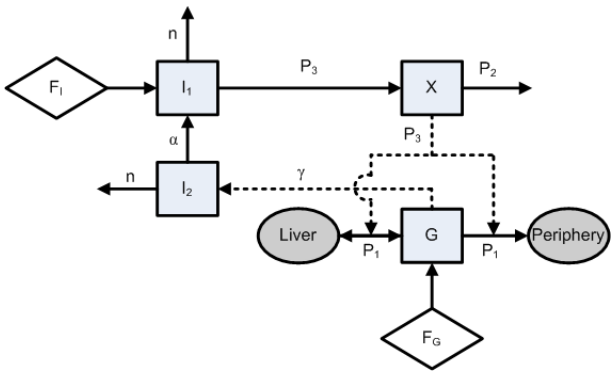


**Figure 6.4:** Representation of the ICU-MM. The state variables of the model ($G$, $X$, $I_1$, and $I_2$) and the body segments (liver and periphery) are denoted as squares and ellipses, respectively. The exogenous input variables ($F_I$ and $F_G$, administered intravenously to the patient) are illustrated as diamonds. The model parameters are related to the respective state variables: a direct physical relation is represented by a solid arrow, whereas a rather mathematical relationship is denoted as a dashed arrow.

**Table 6.1:** Variables, patient features, and coefficient values applicable in the ICU-MM.

| Variable | Unit | Variable | Unit |
|---|---|---|---|
| $G$ | mg/dl | $I_2$ | $\mu$U/ml |
| $X$ | 1/min | $F_I$ | $\mu$U/min |
| $I_1$ | $\mu$U/ml | $F_G$ | mg/min |

| Patient feature | Unit | Value |
|---|---|---|
| $BM$ | kg | Body mass (Body weight) |
| $V_G$ | dl | 1.6 $BM$ [95] |
| $V_I$ | ml | 120 $BM$ [95] |
| $G_b$ | mg/dl | Basal glycemia |
| $I_b$ | $\mu$U/ml | Basal insulin |

| Coefficient | Unit | Value $^{(1)}$ |
|---|---|---|
| $P_1$ | 1/min | -1.31 $10^{-2}$ $^{(1)}$ |
| $P_2$ | 1/min | -1.35 $10^{-2}$ $^{(1)}$ |
| $P_3$ | ml/(min$^2\mu$U) | 2.90 $10^{-6}$ $^{(1)}$ |
| $h$ | mg/dl | 136 $^{(1)}$ |
| $n$ | 1/min | 0.13 $^{(1)}$ |
| $\alpha$ | 1/min | 3.11 |
| $\beta$ | min | 1 |
| $\gamma$ | $\frac{\frac{\mu U}{ml}\frac{dl}{mg}}{min^2}$ | 5.36 $10^{-3}$ $^{(1)}$ |

$^{(1)}$ As initial value for the model estimation process (see 6.3.3), mean model coefficient values for the obese - low glucose tolerance patient group, described in Bergman et al. [14] are used.

### 6.3.2 Analysis of the ICU-MM

The ICU-MM is used as a general template, which is estimated for each individual patient such that the model parameters $P_1$, $P_2$, $P_3$, $h$, $n$, $\alpha$, and $\gamma$ are patient-specific. This is done by minimizing the (squared) errors between the simulated and observed blood glucose trajectories, by using non-linear least squares (N-LS) in Matlab®. The simulated glucose signal is obtained directly from the integration of the ICU-MM over the corresponding time span. In this way, an optimization problem is formulated in such a way that the optimal model parameters are found to be those that give the best possible simulation for the patient. For this optimization process, the starting values for the parameters within the optimization are taken from the obese - low glucose tolerance patient group coming from [14] (see Table 6.1).

Nineteen patients (data set 4, see section 2.4.4) are involved in the clinical analysis of the ICU-MM. Each set of the *in-sample* estimated coefficients is used in a simulation where successively a 3.6 U insulin bolus (at $t = 500$ min) and a 10 g glucose calories bolus (at $t = 1000$ min) are administered. These amounts are typical 'real-life' doses except that in the ICU these doses are continuously delivered during an hour. Figure 6.5 shows the effect of the two boluses on the model dynamics for the 19 patients. The glucose load (at $t = 1000$ min) results in an increase of the blood glucose ($G$) which activates the endogenous insulin production ($I_2$) leading to a *gradual* increase of the plasma insulin concentration ($I_1$) aiming at normalizing blood glucose. When administering exogenous insulin (at $t = 500$ min), a *direct* increase of the plasma insulin concentration ($I_1$) is observed.

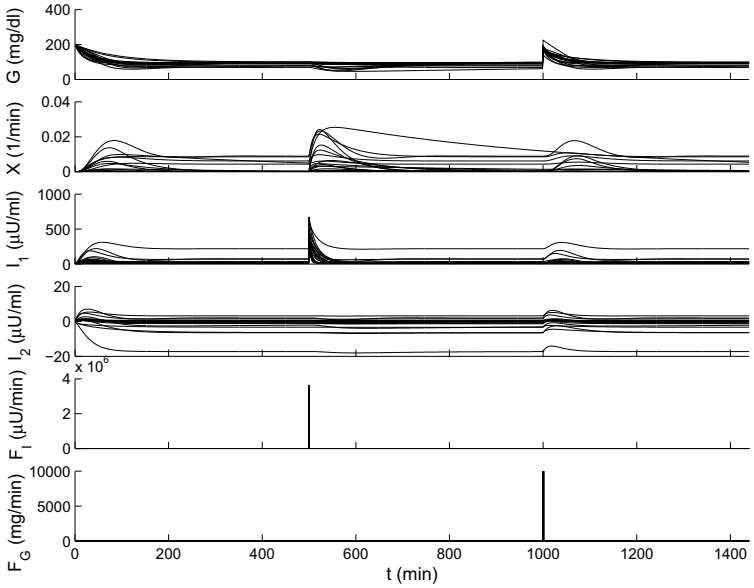


**Figure 6.5:** Simulation of the model dynamics when a glucose and insulin bolus are administered to 19 (virtual) critically ill patients. At $t = 500$ min an insulin shot ($F_I$) of 3.6 U is delivered which is followed by a glucose calories shot ($F_G$) of 10 g at $t = 1000$ min.

Figure 6.6 depicts the effect of the administered bolus of insulin and glucose calories in more detail. Although the estimated set of model parameters is patient-specific, it is observed that the half-life, defined by $t_{1/2}$, for insulin in the blood plasma is on average 8 minutes. This obtained half-life is comparable to the clinically expected half-life (see Chapter 2, 2.3.2). Recall that the *effect* of insulin on net glucose disappearance (marked by $X$) has a certain delay. This is clearly illustrated in the second panel of Figure 6.5. Alternatively, the half-life for intravenously delivered glucose calories is approximately 20 minutes which is clinically reasonable, as well. It can be concluded that the estimated ICU-MM shows clinically realistic dynamics.

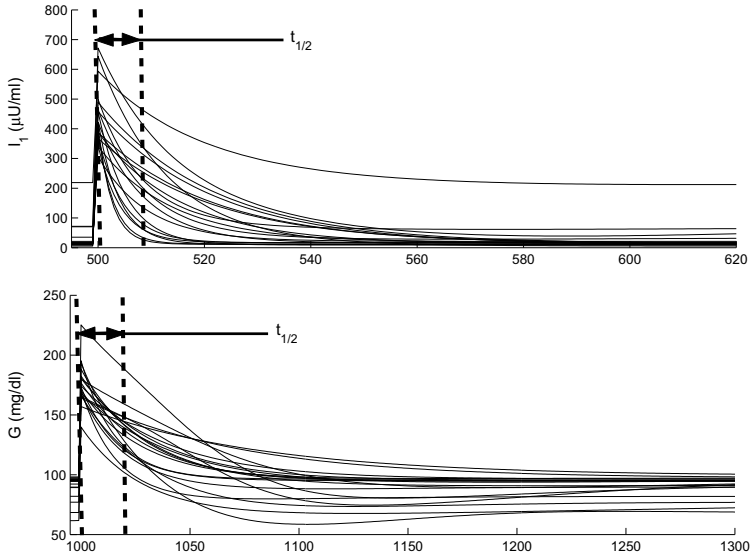


**Figure 6.6:** Detail of Figure 6.5. The top panel illustrates the simulation of the plasma insulin ($I_1$) dynamics after an insulin bolus at $t = 500$ min. The obtained half-life ($t_{1/2}$) for plasma insulin is approximately 8 minutes. The bottom panel shows the glycemia ($G$) dynamics after a glucose calories bolus at $t = 1000$ min. The obtained half-life ($t_{1/2}$) for glucose calories is approximately 20 minutes.

Finally, it must be stressed that the discrete-time version of the ICU-MM is considered in this work instead of the continuous model. Integration of the continuous model returns exactly simulated trajectories but with a corresponding higher computation time. The discretisation of the ICU-MM (using the forward Euler method) significantly reduces the computation time and still results in relatively exact simulations if the sampling time $T_s$ is sufficiently small. In this work the sampling time is set at 1 minute. Figure 6.7 illustrates the model dynamics of patient 1 of the data at hand. It is observed that only a slight difference between the simulated trajectories exists explaining the use of the discrete-time ICU-MM for the further course of this work.

In [55], the *stability* and the *sensitivity* of the ICU-MM were preliminary analysed giving promising results. These model properties will, however, be explicitly and more elaborately studied in future research.

### 6.3.3 Adaptive modelling approach: Study design

In this study the model structure described earlier (ICU-MM) is estimated and validated using the same data (19 critically ill patients, see data set 4 in section 2.4.4). Because of the large inter- and intra-patient variability that exists in the ICU (e.g., patient-specific

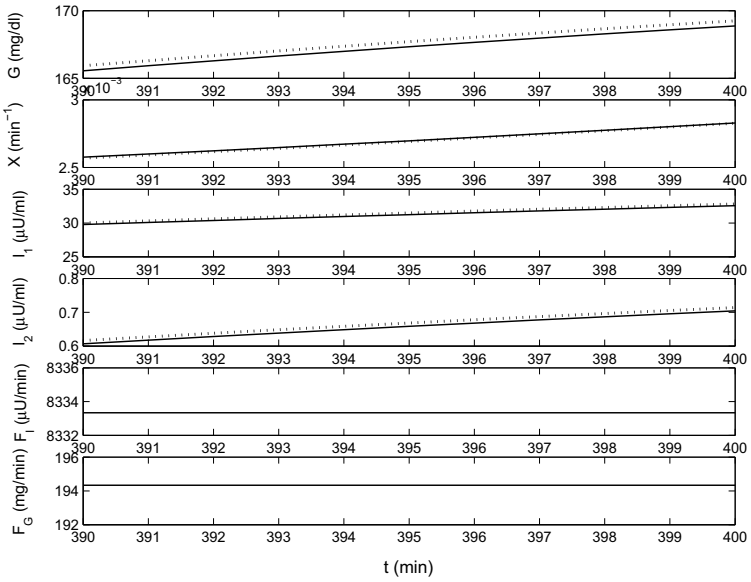


**Figure 6.7:** Detail of simulations with the continuous ICU-MM (by integrating the model, solid line) and the discrete-time ICU-MM (with forward Euler, $T_s = 1$ min, dotted line) for patient 1. Due to the slight difference between the simulated trajectories, the discrete-time version is further used to restrict computation efforts in simulations.

initial and dynamic known input variables, reaction on medical treatment, time-varying insulin resistance), it is required to re-estimate the ICU-MM at frequent time intervals to capture dynamic features as much as possible [220]. Here, a re-estimation strategy is presented. The adaptive modelling approach can be described as follows.

First of all, the ICU-MM, with model parameters $P_1$, $P_2$, $P_3$, $h$, $n$, $\alpha$, and $\gamma$ is used as a general template, which is estimated for each individual patient based on data belonging to the first 24 hours of each patient's data set. This first estimation leads to the 'initial' model for that patient. The parameter estimation is again solved as a N-LS program in Matlab® (see also 6.3.2). The least-squares objective function arrives from penalizing deviations between simulated and observed glycemia trajectories using the non-linear ICU-MM. Two different penalizing strategies or cost functions are considered:

1. **Minimize MSE:** The squared difference between the predicted and the observed glycemia trajectories is minimized. Although this method is mostly known in the field of system identification, the severity of error is dependent on glycemia. Indeed, prediction errors in the hyperglycemic range have a larger contribution to the minimization issue than errors in the hypoglycemic range. Accordingly, the minimization of the absolute errors potentially leads to an underestimation of hypoglycemic errors.

2. **Minimize mean squared normalized error (MSnE):** The difference between the predicted and the observed glycemia value is firstly *normalized* by using the normalization function that was developed in Chapter 3 (equation 3.2) in order to make the severity of error independent of the glycemic level. Secondly, the squared *normalized* errors are minimized.

For the reason of (future) on-line use in a control scheme the N-LS program is solved by means of local optimization. In particular, Nelder-Mead's method is used [152]. The initial state variables are chosen as follows: $\hat{G}(0) = G(0)$, $\hat{X}(0) = 0$, $\hat{I}_1(0) = 0$, and $\hat{I}_2(0) = 0$. The optimal model parameters are found to be those that give the best possible representation for true patient behaviour during the first 24 hours (i.e., 1440 minutes) given glycemia measurements, input observations (i.e., the insulin rate $F_I$ and the flow of carbohydrate calories $F_G$), and the ICU-MM structure. To solve this problem, the starting parameters are taken from the obese - low glucose tolerance patient group coming from Bergman and co-workers [14] (see Table 6.1) whose patient characteristics are most comparable to ICU patients.

Secondly, the model is re-estimated at certain time periods $P$ for the rest of each patient's data set, which is denoted as $S_V$. Two different settings are proposed: re-estimations every hour and every four hours. The number of recent data considered in each re-estimation process is called the back-in-time (BIT) number and may influence the performance of the model. Therefore, BIT is varied in each setting. In the re-estimation procedure the same non-linear estimation technique as described earlier is applied. The starting parameters in each optimization process are the end values of the previous period $P$. The model performance for each patient $p$ is measured by computing the MSE, the mean percentage error (MPE), and the MSnE as follows:

$$\text{MSE}_p = \sum_{t \in S_V}^{N} \frac{(G_{t,p} - \hat{G}_{t,p})^2}{N}, \tag{6.5a}$$

$$\text{MPE}_p = \sum_{t \in S_V}^{N} \frac{\frac{|G_{t,p} - \hat{G}_{t,p}|}{G_{t,p}}}{N} 100\%, \tag{6.5b}$$

$$\text{MSnE}_p = \sum_{t \in S_V}^{N} \frac{(u_{t,p})^2}{N}, \tag{6.5c}$$

where $G_{t,p}$ is the actual and $\hat{G}_{t,p}$ the predicted glycemia value of patient $p$ at time $t$. Further, $N$ represents the number of evaluation points and $u_{t,p}$ refers to the *normalized* glycemia error (see Chapter 3, 3.2.2) of patient $p$ at time $t$. The overall methodology for optimizing the re-estimation process is explained next:

1. Estimate the 'initial' model (ICU-MM) based on the first data set (first 24 hours, see earlier discussion),

2. For a re-estimation period $P = 1$ hour and $P = 4$ hours,

   (a) For BIT = 20-18-16-14-12-10-8-6-5-4-3-2-1-0.5 hours,

      i. Re-estimate the ICU-MM based on every last section (i.e., BIT) of the (moving) data set, with the starting set of coefficients the values corresponding to the last period $P$ (or the set of coefficients from the 'initial' model for the first re-estimation),

      ii. Predict the glycemic course for the next period $P$ (which is the *validation* set of the re-estimated model in this case),

      iii. Compute the MSE, MPE, and MSnE for all validation sets per patient,

   (b) Compare the MSEs / MPEs / MSnEs that are generated for the different BITs. The BIT that belongs to the smallest (average) MSEs / MPEs / MSnEs is called 'optimal' and is ideally used in the re-estimation process,

3. Compare the optimal BIT and the computed MSEs, MPEs, and MSnEs for the $P = 1$ hour and $P = 4$ hours setting.

The Wilcoxon signed rank test is used to test significant differences (significance level 5%). An overview of this adaptive modelling approach is illustrated in Figure 6.8.

## 6.4 Results

Table 6.2 gives an overview of the BIT values that generated the smallest prediction errors for the 19 patients as a function of the time period $P$, the penalizing strategy (i.e., the cost function: MSE or MSnE), and the evaluation method (MSE, MPE, or MSnE). The data that correspond to the last four (BIT $= 4$) or five (BIT $= 5$) hours need to be considered in each re-estimation process in order to minimize the prediction error. Figure 6.9 illustrates the distributions of the MSnEs for the validation parts of all 19 patients as a function of BIT for an estimation procedure based on the minimization of MSnE. In case of re-estimations that take place every four hours, the optimal BIT is found to be four hours. When the model is re-estimated every hour, BIT equals five hours. Significant differences ($p < 0.05$) with regard to other selected BITs are marked with asterisks. The other figures presenting the prediction performance distributions as a function of BIT, the time period, and the penalizing strategy are given in Appendix A.

In general, it is observed that the prediction performance of the model is higher (i.e., smaller MSEs / MPEs / MSnEs) when the model is re-estimated every hour ($P = 1$ hour) in comparison with model re-estimations every 4 hours ($p < 0.001$). The use of MSnE as cost function is preferred from a clinical perspective since the severity of error is made independent of glycemia and hypoglycemic and hyperglycemic deviations are equally penalized then. The average $\pm$ SD of the MSE, average $\pm$ SD of the MPE, and average $\pm$ SD of the MSnE obtained when applying an *optimal*

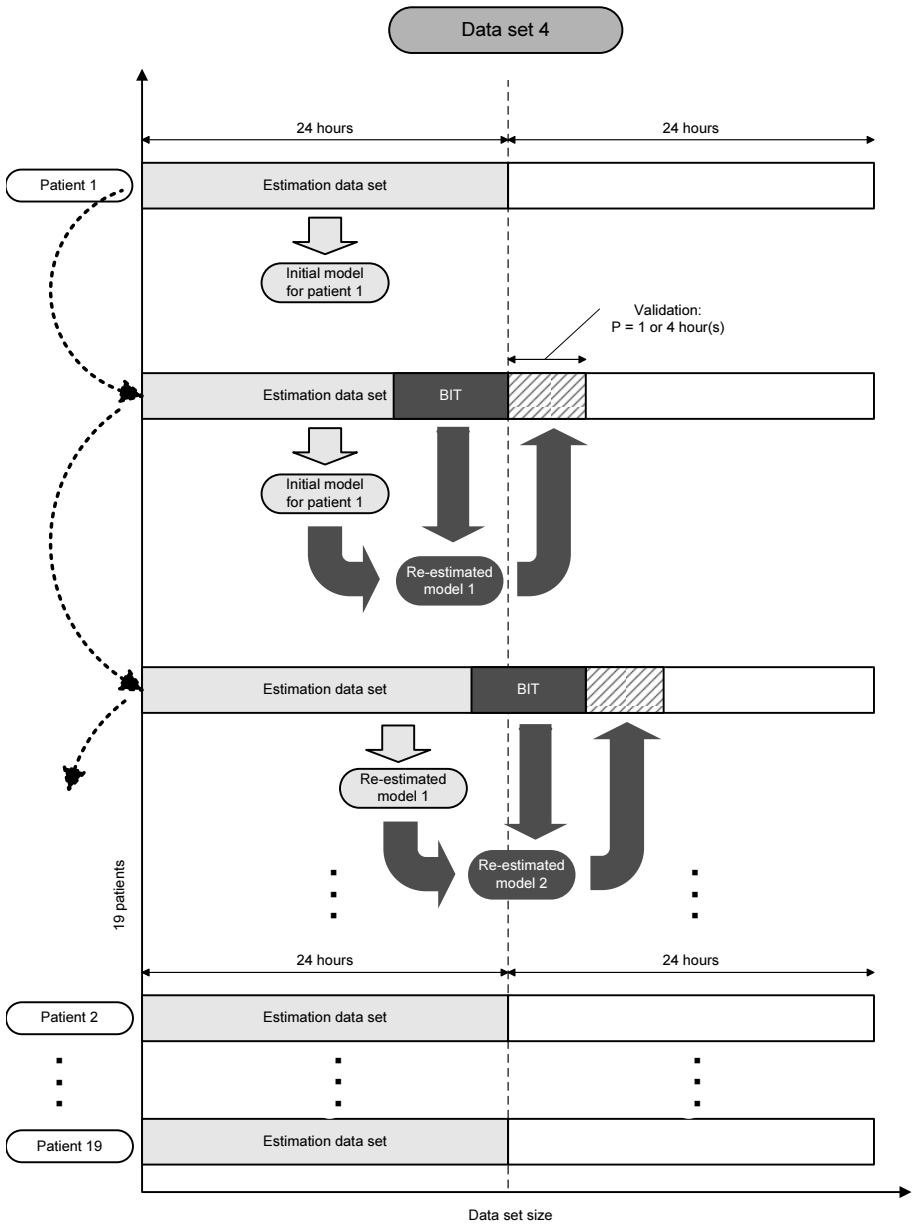


**Figure 6.8:** Outline of the adaptive grey-box modelling approach. The data corresponding to the first 24 hours after admission to the ICU are used to estimate the initial model for each individual patient. The second 24 hours are considered as validation data for the adaptive modelling approach. Based on the most recent data (represented by the (varying) BIT) and the previously estimated model coefficients (or the initial model for the first re-estimation) that serve as starting set of coefficients, the model is updated to incorporate the changing glucose dynamics of the patient. Then, each re-estimated model is evaluated on the next 1-hour or 4-hours data after which the BIT block is moved ahead (with one or four hour(s)) and the full procedure is repeated.

**Table 6.2:** Overview of the 'optimal' BIT values (expressed in number of hours) depending on time period, the penalizing strategy (cost function), and the evaluation method. The graphs that further illustrate these prediction performances are depicted in Appendix A.

| | **Time period** | | | |
|---|---|---|---|---|
| | $P = 4$ hours | | $P = 1$ hour | |
| | **Cost function** | | **Cost function** | |
| **Evaluation** | MSE | MSnE | MSE | MSnE |
| MSE | 5 | 4 | 5 | 5 |
| MPE | 5 | 4 | 5 | 4 |
| MSnE | 5 | 4 | 5 | 5 |

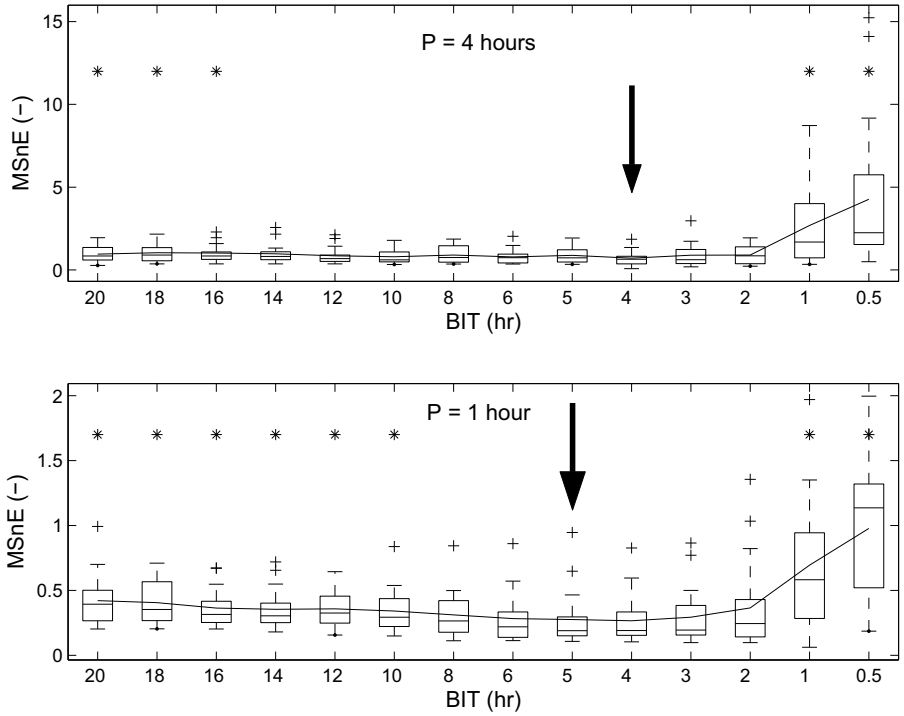


**Figure 6.9:** Distribution of the MSnEs (that are computed to evaluate the model prediction performance for each patient) as a function of BIT with re-estimations every 4 hours (top) or every hour (bottom). The followed penalizing strategy is founded on the minimization of MSnE. The line connects the averages of the MSnEs. Re-estimations based on the last 4-hours data set (for $P = 4$ hours) or the last 5-hours data set (for $P = 1$ hour) result in the smallest prediction errors. Significant differences with respect to this 'optimal' BIT setting are marked by asterisks.

one-hour re-estimation strategy ($P = 1$ hour, BIT $= 5$ hours) to present data are $122 \pm 85$ (mg/dl)$^2$, $7.3 \pm 2.6$ %, and $0.27 \pm 0.22$, respectively. When model re-estimations every 4 hours are preferred ($P = 4$ hours, BIT $= 4$ hours), the average $\pm$ SD of the MSE, average $\pm$ SD of the MPE, and average $\pm$ SD of the MSnE are equal to $407 \pm 566$ (mg/dl)$^2$, $12.5 \pm 4.0$ %, and $0.71 \pm 0.45$, respectively.

Figures 6.10 and 6.11 illustrate the performance of the ICU-MM for predicting glycemia of patients 3 and 10, respectively. The glycemic evolution is shown in the top panels ($P = 4$ hours: BIT $= 4$ hours; $P = 1$ hour: BIT $= 5$ hours). The dotted line represents glycemia measured by the GlucoDay system. Data of the first 24 hours are used to estimate the initial model. Glycemia predictions using this initial model on the first part of the data set (in-sample data) is indicated by the dashed line. The re-estimation strategy is applied on the second 24 hours and the resulting simulated glycemia signal is depicted by the solid line. The vertical lines in these figures indicate the time-instants when the model is re-estimated by considering data of the previous four hours when $P = 4$ hours (top panel), and data of the previous five hours when $P = 1$ hour (second panel). Finally, the input variables included in the ICU-MM are shown in the third (administered insulin) and the last (administered carbohydrate calories) panels in Figures 6.10 and 6.11. Figures 6.12 and 6.13 present the model dynamics for patients 3 and 10, respectively, when the ICU-MM is re-estimated every hour by means of the data corresponding to the last five hours.

## 6.5 Discussion

This chapter presents a new model structure (ICU-MM) and an optimized adaptive 'minimal' modelling approach that can potentially be used in the design of a predictive control system to normalize glycemia in the critically ill. The methodology proposed here is based on the near-continuous monitoring of glucose which will be a standard technique in the near future [38, 99, 209]. In that scenario, the data of the first 24 hours after admission to the ICU will be used to estimate the initial patient-specific ICU-MM. During this first period, the blood glucose will be controlled by medical staff using a (manual) standard nurse-driven protocol [215]. From the second day onward, the predictive control system (see Chapter 7) will (semi-)automatically regulate glycemia. The frequent re-estimation of the ICU-MM will be able to incorporate dynamic changes within the critically ill patient (e.g., varying insulin resistance). The feasibility of the re-estimation modelling approach is shown in this study.

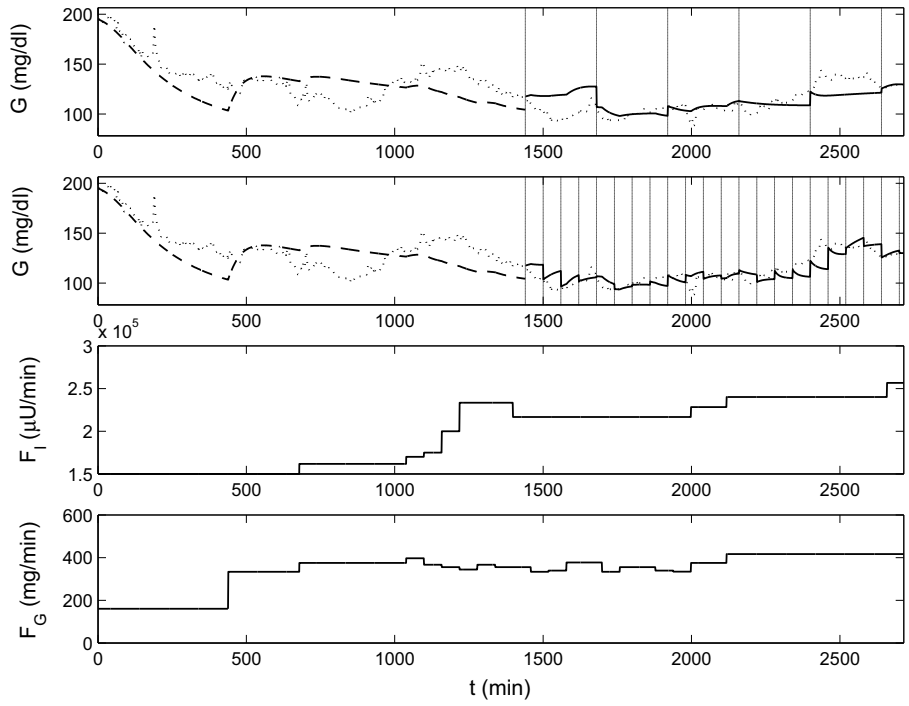


**Figure 6.10:** Example of the re-estimation strategy (with the use of MSnE as cost function) applied to the ICU-MM. The evolution of glycemia of patient no. 3, measured with the GlucoDay system, is presented in the first and second panel (dotted line). Data of the first 24 hours are used to estimate the initial ICU-MM. The *in-sample* prediction is represented by the dashed line. Glycemia simulations present in the second 24 hours of the data (i.e., the *validation* part) are illustrated with the solid line for both the 4-hours (top panel) and the 1-hour (second panel) re-estimation process. Re-estimation time instants are illustrated with vertical lines. The flows of insulin and carbohydrate calories are shown in the third and fourth panel, respectively.

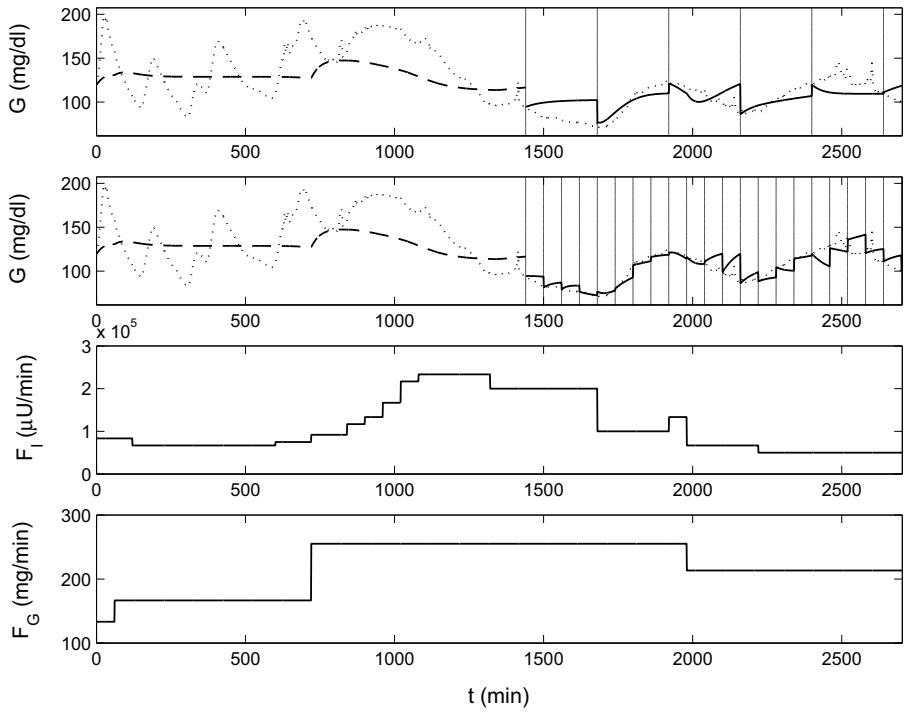


**Figure 6.11:** Another example of the re-estimation strategy applied to the ICU-MM on patient no. 10. The different line types in this figure have similar meanings as in Figure 6.10.

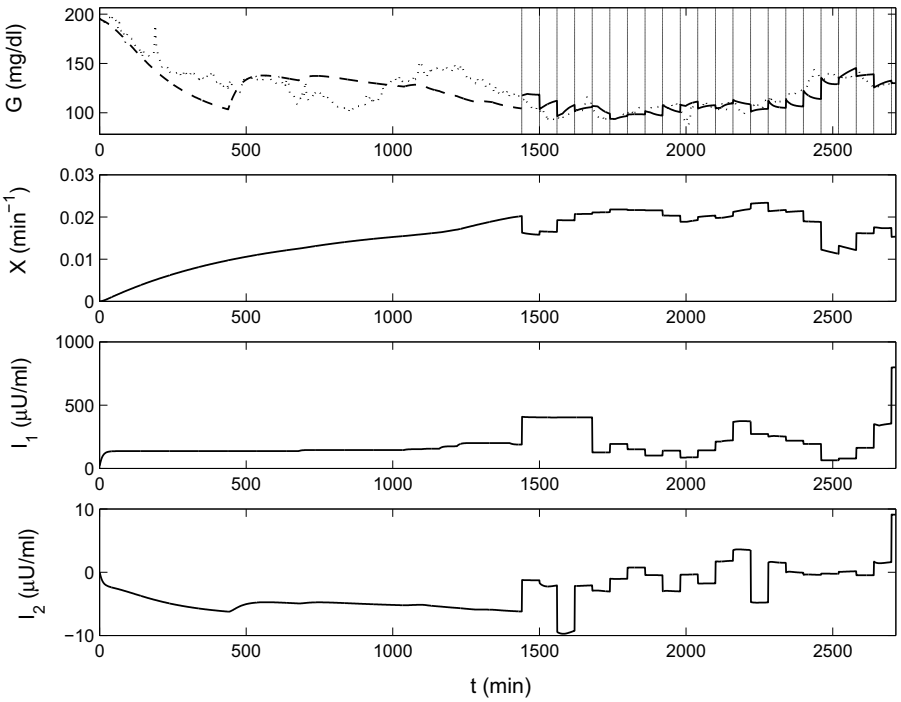


**Figure 6.12:** Illustration of the ICU-MM dynamics when applying the 'optimal' $P = 1$ hour re-estimation strategy to patient no. 3. The top panel presents the glycemia signal measured by the GlucoDay sensor device (dotted line). The *in-sample* prediction during the first 24 hours is illustrated with the dashed line; the glycemia simulations (during the rest of the data set or the *validation* part) are represented by the solid line. The second panel depicts the effect of insulin on net glucose disappearance, the third panel the insulin concentration in the blood plasma, and finally the bottom panel the evolution of the mathematical insulin variable.

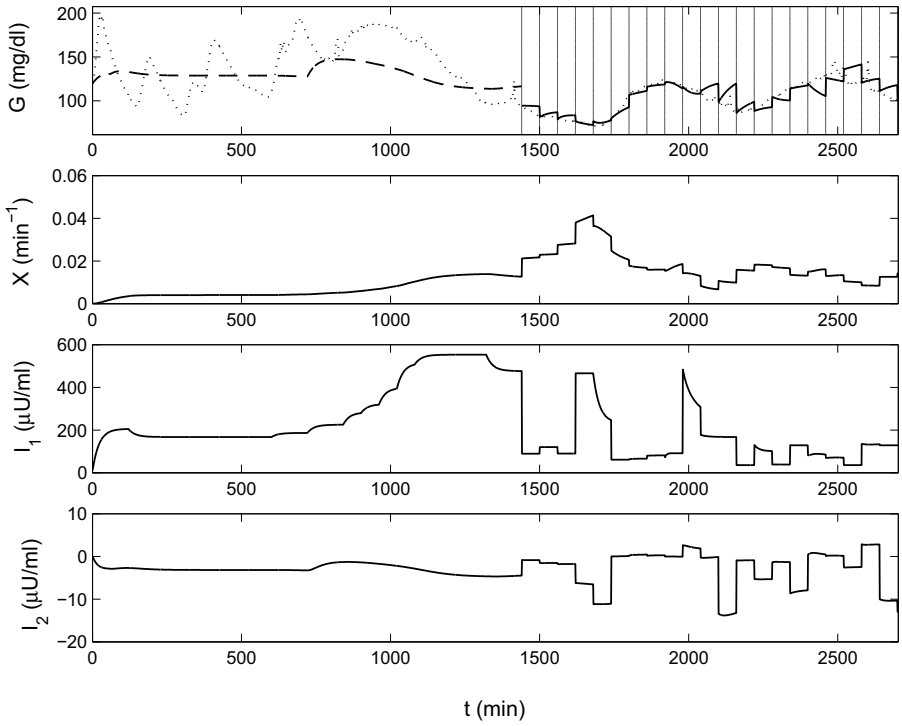


**Figure 6.13:** Illustration of the ICU-MM dynamics when applying the 'optimal' $P = 1$ hour re-estimation strategy to patient no. 10. The different line types in this figure have similar meanings as in Figure 6.12.

### 6.5.1 Choice of cost function

Two penalizing functions are used in the estimation process of the ICU-MM: the minimization of MSE and the minimization of MSnE. Although the use of the minimization of MSE as cost function is mostly known in system identification theory, we here prefer to focus on the minimization of MSnE as cost function. As already described earlier, it is important that prediction errors are penalized independent of the glycemic range (i.e., hypoglycemic, normoglycemic, or hyperglycemic range) that they belong to. When using the MSE cost function, particularly the (squared) *hyperglycemic* errors are penalized as the (squared) *hypoglycemic* errors are much smaller. In case of minimizing the squared *normalized* errors (with MSnE) the model prediction errors are equally penalized with regard to the clinically defined ISO-criterion which is a standard norm for the binary assessment of the accuracy of glucose sensors (see Chapter 3, 3.2.2) [75]. The accuracy requirements of a test *sensor* device, which is assessed by considering its signal toward the concomitantly measured reference (or gold standard) values, are in fact comparable to the prediction performance requirements of a *model*. Both sensor and model are crucial elements in (future) predictive control systems in terms of determining the optimal insulin flow to be administered to the patient. Though the selection of the cost function does not much influence the determination of the 'optimal' BIT number (as is depicted in Table 6.2), it is recommended to consider the MSnE as penalizing function in the estimation process of the ICU-MM because of its clinical interpretability.

### 6.5.2 Choice of evaluation measure

The use of the MSnE to evaluate the prediction performance of the model is preferred above the MSE for the same reasons as described in the previous section. An alternative technique to assess the performance of a model is the computation of the MPE. On the one hand, the MPE has the advantage that the model prediction performance can be easily clinically interpreted as an error in terms of percentage whereas the MSnE returns a squared *normalized* value which is typically less easy to interpret. Extracting the root of the MSnE (leading to the Root Mean Squared normalized Error or RMSnE) clarifies the clinical interpretation, however. When the obtained RMSnE is higher than 1, the ISO-criterion is violated meaning that the 'average' model prediction capacity is inaccurate (see Chapter 3, 3.2.2). On the other hand, the MSnE has the advantage that the model is evaluated based on a clinically well-defined criterion [75] whereas the MPE may be too simple as assessment tool.

### 6.5.3 Choice of re-estimation time period

Re-estimating the model every hour results in smaller prediction errors than re-estimations that take place every four hours. This result is expected, as frequent updates of the model lead to smaller prediction horizons and, as a usual result, smaller (absolute and relative) prediction errors. As described previously, it is our aim to implement the developed ICU-MM in a (semi-)automatic predictive control system. The controller (see Chapter 7) is assumed to optimize the insulin dose that should be

delivered to the patient by simulating glycemia trajectories with the model (e.g., the ICU-MM). In a first phase, this predictive control system will only act as an **advisory system** (semi-automatic). This means that confirmation (by a nurse) of the insulin rate adaptations will be mandatory before administering the insulin flow (that is proposed by the controller) to the patient. Consequently, the workload of the medical staff is expected to increase significantly. For this reason the insulin adaptation frequency will be limited to once per hour. This immediately explains why updating the model more frequently than once per hour would be futile. Hence, $P$ was only set at 1 and 4 hour(s) in this study. Of course, after a thorough clinical validation of this semi-automatic system, the insulin adaptation frequency may be increased further (e.g., $P = 15$ min) for use in a **fully-automatic control system** (i.e., confirmation by a nurse is not required any more), which may lead to even smaller prediction errors than obtained when $P = 1$ hour.

### 6.5.4 Choice of BIT

The 'optimal' size of the data set to be considered in each re-estimation process of the ICU-MM is found to be 4 hours when $P = 4$ hours, and 5 hours when $P = 1$ hour (although no statistically significant difference exists between the 'optimal' BIT data set size and its neighbouring data set sizes). This means that only relatively recent data need to be taken into account in each re-estimation process for accurately predicting the glycemia signal (or at least the glycemia trends). Figure 6.9 clearly illustrates the trade-off between model overfitting, when BIT is small, on the one hand and the restricted modelling capacity of fast-changing dynamics, when BIT is large, on the other hand (see also the figures in Appendix A). Re-estimations based on large amounts of previous data (e.g., BIT $= 18$ hours) do not efficiently capture the varying patient dynamics typical of critically ill patients and lead to large prediction errors. However, only considering the most recent data of the specific patient (e.g., BIT $= 1$ hour) leads to model overfitting and, similar to large BITs, explains the poor prediction performance in that case.

### 6.5.5 Evaluation of the 'optimal' re-estimation strategy

Figure 6.14 illustrates the distribution of the 19 computed RMSnEs for the 'optimal' re-estimation strategy. In case model re-estimations every hour ($P = 1$ hour) are allowed, all RMSnEs are found to be smaller than 1. This result indicates the clinical feasibility of this 'optimal' re-estimation strategy as the ISO-criterion is not violated *on average* (i.e., computing the *average* model prediction performance per patient). When model re-estimations only every four hours are permitted, it is clear that the model prediction performance decreases (larger RMSnEs) though the majority of the calculated RMSnEs remains below 1.

Furthermore, the number of normalized errors that are larger than 1 can be determined for all observations (i.e., packing all individual simulated glycemia data of all 19 patients). Then, this relative number of normalized errors can be related to the tolerance levels that were introduced in Chapter 3 (see 3.2.4) such that the *overall*

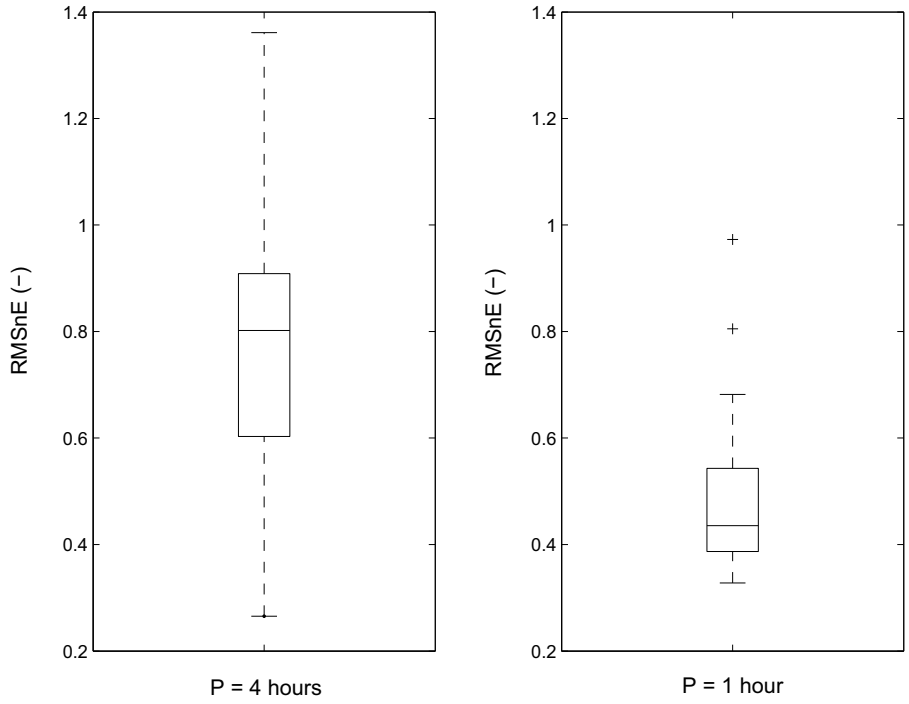


**Figure 6.14:** Distribution of RMSnE for $P = 4$ hours (left) and $P = 1$ hour (right) when the 'optimal' re-estimation strategy is applied to the data (cost function = MSnE; $P = 4$ hours: BIT $= 4$ hours, $P = 1$ hour: BIT $= 5$ hours).

model prediction performance is expressed instead of the *average* model prediction performance that is obtained by computing the RMSnE per patient. The relative number of errors that do not violate the ISO-criterion is 93.0% when $P$ equals 1 hour, and 90.3% when $P$ is equal to 4 hours. In other words, the one-hour re-estimation strategy of the ICU-MM satisfies ('clinically acceptable') the ISO-criterion on a 7% tolerance level. The four-hours re-estimation strategy only satisfies the ISO-criterion on a 10% tolerance level. Although this last simulation horizon is four times longer compared with the one-hour re-estimation strategy, the model performance is still tolerable.

The obtained average MPE values (7.3% and 12.5% for the *optimal* one-hour and four-hours re-estimation strategy, respectively) further confirm these results. The relative prediction errors obtained when re-estimating the ICU-MM every hour and every four hours are smaller than the 20% target variability that is allowed in the ISO-criterion for reference (sensor) values $> 75$ mg/dl (see Chapter 3, 3.2.2 [75]. This confirms the clinical acceptance for both adaptive modelling approaches (assuming the availability of an accurate and reliable near-continuous glucose sensor device).

### 6.5.6 Patient case studies

Figures 6.10 and 6.11 show the predicted glycemia signal of patients 3 and 10. The individual MPEs and RMSnEs for these 'average' patients are equal to 5.6% and 0.37, respectively, for patient 3, and 6.4% and 0.45 for patient 10, respectively, when $P = 1$ hour. Analogously, the individual MPEs and RMSnEs when $P = 4$ hours are found to be 8.5% and 0.56, respectively, for patient 3, and 12.1% and 0.78 for patient 10. The ICU-MM approaches the real glucose dynamics of critically ill patients. Although only two input variables (i.e., the flow of carbohydrate calories and insulin) are effectively taken into consideration, the ICU-MM generally succeeds in predicting glycemia trends for both $P = 1$ hour and $P = 4$ hours. The rather flat predicted glycemia (*output*) dynamics that appear in some segments in Figures 6.10 and 6.11 are caused directly by the corresponding flat *input* behaviour (e.g., Figure 6.10 top panel; starting at $t = 2120$ min the fluctuating glycemia signal is not predicted accurately by the ICU-MM, as its input variables, which play a significant role in predicting the glycemia behaviour, have a constant flow). Observed glycemia fluctuations, that are not predicted by the ICU-MM, hence result from unmodelled disturbance factors. Updating the model on a regular base (every hour) is advised to compensate for these unavoidable missing glycemia dynamics.

The model dynamics of patients 3 and 10 are further illustrated in Figures 6.12 and 6.13 for the one-hour re-estimation scenario. The second panel ($X$) depicts the typical delay effect of the administered insulin flow on the glycemia signal. The flows of the insulin variables ($I_1$ and $I_2$) show some abrupt changes caused by adaptations of the input rates ($F_G$ and $F_I$) and the one-hour model re-estimations. The variable $X$, which is the only state variable that directly influences the blood glucose (see equation 6.3a), tempers this sometimes abruptly changing insulin pattern leading to realistic glycemia evolutions. Moreover, Figures 6.12 and 6.13 illustrate the advantage of estimating the initial ICU-MM based on the data of the first 24 hours. The $X$, $I_1$, and $I_2$ state variables are initially set at 0 as these states are not (cannot[6] be) measured in the patient. The in-sample estimation of the initial ICU-MM allows to make a reliable guess of the $X$, $I_1$, and $I_2$ state variables at $t = 1441$ min. Accordingly, glycemia can be predicted more accurately starting from the second day onward.

A final feature of the proposed model re-estimation strategy is the limited computation time. The current study was (off-line) implemented in Matlab® on a standard computer (Intel Pentium-M, 1400-MHz processor). The N-LS program required only approximately 1 minute to be solved (discrete-time model using Forward Euler, $T_s = 1$ min). Accordingly, the on-line application of this technique is no issue in terms of computation time.

[6] It would be clinically feasible to measure the insulin concentration in the plasma ($I_1$) regularly although this would additionally increase the workload of the nursing team. In that case both $G$ and $I_1$ would be known which would improve model prediction accuracy. However, only the state variable $G$ was measured in the data at hand. Finally, the state variables $X$ and $I_2$ do not correspond to a physical compartment and cannot be 'measured'.

## 6.6 Conclusions

In this chapter a brief overview of existing physiological models that describe the glucoregulatory system of healthy subjects or patients with diabetes was given. A new model structure (ICU-MM) was developed for potential use in a predictive control system to normalize the blood glucose of critically ill patients. Typical features of the ICU were therefore included in this ICU-MM. Since the model structure was developed based on physiological insight, the closed-loop data were only used for parameter estimation. Two different penalizing functions and three different model evaluation tools were discussed. It was found that the MSnE was ideally used as cost function and evaluation tool due to its clinically interpretable fundamentals.

Next, an adaptive modelling strategy that takes into account the time-varying character of the glucose behaviour of the critically ill was proposed. The implementation of the ICU-MM that was re-estimated every four hours or (preferably) every hour gave promising results in terms of prediction performance. As expected, the prediction performance of the model with re-estimations every hour was higher than with re-estimations only every four hours. The first scenario satisfied the ISO-criterion on a 7% tolerance level and the second strategy on a 10% tolerance level. Finally, its potential use in a predictive control system for critically ill patients admitted to the (surgical) ICU was illustrated with patient case studies. The results presented in this chapter are further discussed in [219, 223, 226].

# Chapter 7

# Control of Glycemia

*The contribution of this chapter, which is focused on the control aspect as illustrated in Figure 7.1, is twofold. First of all, an overview of already presented control algorithms in the area of diabetes and the ICU to be used for normalizing blood glucose is given and critically discussed. The second contribution of this chapter is the development of a predictive controller to be applied for normalizing glycemia in critically ill patients. States and unknown disturbance factors are estimated with an Extended Kalman Filter in a simulation study. The results of the developed control system are satisfactory both in terms of control behaviour (reference tracking and the suppression of unknown disturbance factors) and clinical acceptability.*

## 7.1 Introduction

A (predictive) control system typically comprises a predictive patient model and an optimizing controller. The design of the patient model was described in Chapters 5 and 6. In this chapter an overview of the different control strategies that have already been applied in the development of an 'artificial pancreas' is presented. Moreover, a predictive controller for use in the ICU has been designed.

Before elucidating the features of glycemia controllers, it is important to indicate what is **not** meant with the term 'artificial pancreas' in the context of this dissertation. Already in 1968, the use of microencapsulated islets as artificial beta cells was presented [33]. With the introduction of a semipermeable membrane on the top of the microcapsules, a system could be developed to protect the transplanted islets against rejection from the immune system [170]. Accordingly, the requirement of immunosuppressive drugs could be eliminated further lowering the step towards a '*bio*-artificial pancreas'. Moreover, the use of animal islets or insulin-producing cells engineered from stem cells can potentially compensate for the shortage of donors [107]. Though the recent developments in stem cell research are hopeful for the future

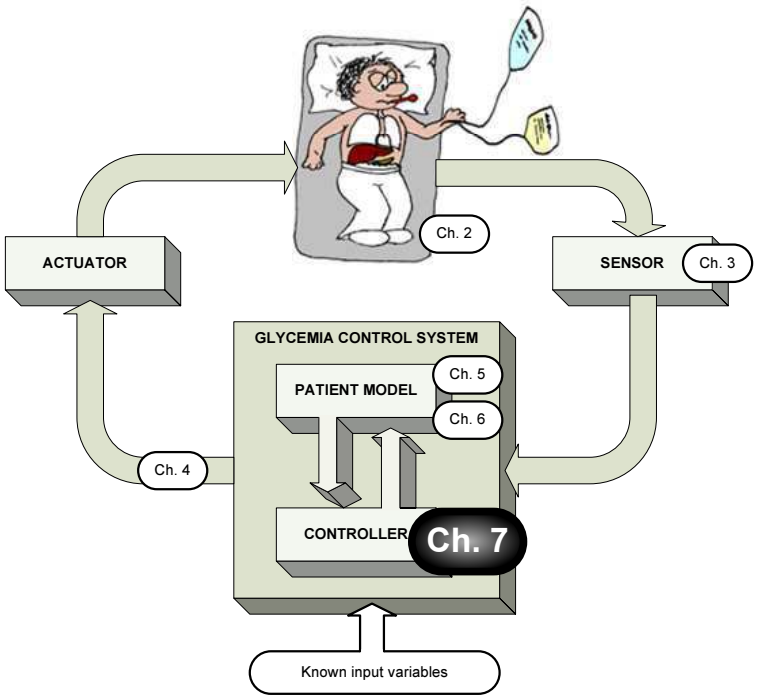


**Figure 7.1:** Simplified presentation of the (semi-)automated control system. This chapter (Chapter 7) discusses the different control strategies already described in diabetes and ICU literature. Next, the design of a predictive controller for use in an ICU setting is shown and applied in a simulation study. The developed control system can potentially be used to normalize blood glucose in the critically ill.

treatment of diabetes as well as other diseases (e.g., cancer, Parkinson's disease, etc.), it is not further studied in this work.

For the scope of this dissertation the term 'artificial pancreas' indicates a computerized system that determines the insulin needs aiming at normoglycemia. In the ideal scenario the artificial pancreas should operate in a fully-closed-loop setting meaning that the input of the nurse (or the patient with diabetes) in computing the required insulin dosage is reduced to a minimum. Further, this 'ideal' control system should achieve perfectly normal blood glucose levels [99]. This ideal world differs from reality for both patients with diabetes and critically ill patients as is explained in this chapter.

In general, a fully functional and 'ideal' artificial pancreas comprises a reliable near-continuous glucose sensor, the control computer (i.e., the control system), and an insulin pump (actuator). This is further illustrated in Figure 7.1. It has already been extensively described before that a reliable near-continuous glucose sensor is the major missing element of these three components [38, 94, 99, 101, 109, 162, 194, 209].

However, it must be pointed out that the design of a 'computerized' controller (or the control system, in general) to be used in patients with diabetes or in patients admitted to the ICU to normalize glycemia is not yet a *solved* research issue. This chapter firstly gives an overview of the control developments in the diabetes area. Next, an overview of currently existing controllers developed for use in the ICU is presented. Finally, the design of a first predictive controller based on the developed ICU-MM (see Chapter 6, 6.3) is explained and the results of this simulation study are discussed.

## 7.2 Blood glucose control in patients with diabetes

Patients with diabetes are instructed how to apply intensified insulin therapy in an optimal manner. In 1993, the known Diabetes Control and Complications Trial study demonstrated that intensive insulin treatment in patients with diabetes significantly reduced the risk of diabetes complications [50]. This study confirmed the interest in developing an artificial pancreas. The artificial pancreas is aimed to replace the malfunctioning beta cells with the goal of achieving normoglycemia.

Therefore, understanding how these beta cells 'control' the blood glucose in healthy persons is a first step in the design of an artificial pancreas. In Chapter 6 the typical biphasic insulin response to a glucose load has already been described [14,69,106,194]. The first phase typically comprises an early peak plasma insulin concentration in order to avoid a hyperglycemic 'peak event'. This insulin rise can be directly related to the glycemia rise (typically observed after administering a load of glucose calories). The first phase is immediately followed by the second phase in which the plasma insulin concentration behaviour follows the pattern described by the MM (see Chapter 6, 6.2.2). The rate of rise of second-phase insulin concentration is found to be proportional to the blood glucose.

Besides the typical biphasic insulin pattern, it is known that the beta cells also adjust the insulin secretion based on antecedent hyperglycemic events and the current plasma insulin concentration. Further, the insulin release is dependent on the amount of free-fatty-acids and it can be stimulated by neural signals and gut hormones. Finally, a tendency towards oscillating behaviour or the release by means of discrete pulses can both be observed. These beta cell features, summarized in [194], illustrate that the replacement of the 'active' pancreas by an artificial device may not be straightforward.

It is important to note that all existing prototypes of an artificial pancreas to be used in patients with diabetes only work by *lowering* glycemia [99]. Only the action of the insulin hormone is incorporated in current control strategies. In other words, 'hyperglycemic' episodes can be compensated by increasing the insulin rate whereas 'hypoglycemic' episodes can only be treated by diminishing the insulin flow (eventually till 0 U/hr). Since the insulin action is not instantaneously faded away when reducing the insulin rate till 0 U/hr (see the insulin dynamics described in Chapter 6, 6.3.2), however, it is clear glycemia will be elevated only after a (serious) time delay. Obviously, this rather conservative control strategy has some limitations. When too

much insulin is delivered to a patient (e.g., when the expected glycemia increase after a meal was overestimated), the resulting hypoglycemic drip (that appears when the meal is consumed) cannot be adequately treated. From a (theoretical) control perspective, at least two **manipulation variables**[1] would be expected. The first manipulation variable would be the *insulin hormone* (to lower blood glucose) and the second manipulation variable would be *glucose calories* or the *glucagon hormone* which both have a glycemia raising effect [8, 99].

Though some studies show the interest of controlling blood glucose in critically ill patients using both insulin and glucose calories [38, 243, 244] and in diabetic swines using both insulin and glucagon [68], clinical experts are not yet convinced of this counteracting approach because of two reasons. First of all, at present only very few is known about the features and the dynamics of the glucagon hormone (in contrast to the insulin hormone). Secondly, it is questioned whether such an additional device (that delivers glucose or glucagon) and the related increased complexity is justified as it will be used only a few (but critical) times of severe hypoglycemia [99]. A trade-off arises between the glycemia normalization performance on the one hand and the social/ethical issue for the patient with diabetes (who has to carry the apparatus) on the other hand.

An overview, presenting most important trends in the development of an artificial pancreas for patients with diabetes, is given below. *Elementary* and rather *advanced* control strategies can be distinguished. Finally, some prototypes that most approach clinical reality are briefly discussed.

### 7.2.1 Elementary control strategies

The very first approach to closed-loop glycemia control was realized by Kadish in 1964 [102]. Glycemia was 'continuously' monitored and both insulin and glucose/glucagon were intravenously delivered to a patient with diabetes. The controller was a relatively simple *on/off system*. Insulin was infused if glycemia was above 150 mg/dl and glucose/glucagon was administered if blood glucose was below 50 mg/dl.

In 1974, an artificial pancreas based on a first controller algorithm was independently set up by Albisser *et al.* [1, 2] and Pfeiffer *et al.* [165] eventually leading to the design of a commercial device: the Biostator [45–47]. This device comprised a dual infusion system: insulin and glucose. The proportional-derivative (PD)[2] structure of the applied (feedback) control algorithm was based on a five-point moving average of the glucose measurements [162]. Accordingly, glucose noise effects could be minimized. The

[1] A **manipulated** variable (e.g., insulin) is the variable that is used to regulate the **controlled** variable (e.g., blood glucose).

[2] A proportional-integrative-derivative (PID) controller is a typical example of a pure *feedback* controller. The insulin infusion rate is adjusted based on the deviation from the target blood glucose (proportional component), the area-under-the-curve between ambient and target glycemia (integral component) and the change in ambient glycemia (derivative component) [94]. Here, only a subset of these three components is consisered: PD.

size of the device, however, was too bulky (due to the dual-reservoir system) to use the system in real-life situations. Moreover, venous blood had to be 'continuously' withdrawn for glycemia monitoring and constant supervision was suggested.

Further, Botz [19], Marliss *et al.* [142], and Kreagen *et al.* [118] modified the control algorithm. A similar glucose control algorithm was finally developed by Fischer *et al.* [73]. Excellent review papers concerning these rather elementary control strategies may be found in [8, 24, 94, 162]. It was concluded that none of these first glycemia controllers were adequate to normalize blood glucose in patients with diabetes.

### 7.2.2 Advanced control strategies

Since the nineties, more advanced control strategies have been considered in the design of an artificial pancreas for patients with diabetes. Most important studies are the *neural network controller* developed by Trajanoski and Wach [204], the *H-infinity controller* by Kienitz and Yoneyama [105], by Parker *et al.* [163] and by Ruiz-Velzquez *et al.* [180] and the *model based predictive controller (MPC)* concept by Parker *et al.* [159–162] and by Hovorka *et al.* [95, 181].

Particularly the use of MPC has found increasing interest to be applied to an artificial pancreas [7, 8, 162]. The estimation of the *future* glycemia behaviour in response to insulin and food inputs is a key benefit compared with classical pure *feedback* control algorithms. The use of MPC enables the artificial pancreas to pro-actively (i.e., *before* a known event actually occurs) adapt the insulin infusion rate whereas pure feedback controllers change the insulin flow only *after* the effect of the (known) disturbance. Accordingly, predicted hypo- or hyperglycemic events can be avoided with an MPC. An essential feature of an MPC, however, is the required availability of a model that accurately describes the patient dynamics. The possibility to update the model parameters in order to increase the patient-specificity and the possibility to impose some constraints on the inputs are further advantages of MPC. The characteristics of MPC are further discussed in detail below (see 7.4.1).

### 7.2.3 Prototype systems

In this section a summary of the most known prototypes of the *artificial pancreas* for patients with diabetes is given. A more detailed review of these prototypes may be found in [7, 94].

#### 7.2.3.1 Diabetes Advisory System (DIAS)

DIAS aimed to propose the optimal insulin rate based on the previous blood glucose measurements, a quantification of the meal intakes (in terms of carbohydrates), and the past insulin injections [91]. The used model had two unknown parameters (the insulin sensitivity and the peak time of the specific insulin type) which were estimated based on a Bayesian approach [7]. A double-blind study in a limited number of patients showed a more strict glycemic control in the patient group who was daily advised by DIAS [91].

#### 7.2.3.2 Automated Insulin Dosage Advisor (AIDA)

This computer simulation tool assessed the insulin scheme of a patient with diabetes (number of insulin injections, type of insulin, insulin rates) [126–129, 131]. The assessment was based on the 'average' day of the patient and solutions were suggested, accordingly (e.g., regular hypoglycemic events at lunch time could be avoided by reducing the morning insulin dosage, changing the type of insulin, etc.) [7]. Though glycemia predictions were rather inaccurate, this simulation tool found its merit in helping to understand the glucoregulatory system of patients with type I diabetes and the corresponding treatment.

#### 7.2.3.3 Advanced Insulin infusion using a Control Loop (ADICOL) project

The ADICOL project was a European project, initiated in 2000, with academic, clinical as well as industrial partners. The aim was to design an artificial pancreas that would near-continuously monitor and control the glucose concentration in patients with type I diabetes [96]. Loss of sensitivity of the developed subcutaneous (near-continuous) glucose sensor explained why eventually (delayed) intravenous (discrete-time) glucose measurements were used in the clinical evaluation of the controller [94, 182]. The major contributions of the ADICOL project were the simulation and initial clinical closed-loop studies using the intravenous sensor with a 15 min sampling time and subcutaneous delivery of insulin. The selected MPC strategy [95] was based on a compartmental model developed by Hovorka *et al.* [98]. In order to individualize this glucoregulatory model and to overcome the inter- and intrapatient variability, Bayesian parameter estimation techniques were used. Although the ADICOL project showed the potential and feasibility of using MPC in a closed-loop setting, it must be pointed out that the clinical studies were performed only on a limited number of patients and the test conditions were far from 'real-life' (e.g., fasting conditions, fixed meal times, standard meals, etc.). Moreover, the proposed strategy was founded on the reliable near-continuous monitoring of the glucose concentration since the high intravenous sampling frequency (as imposed in the study) would not be feasible in long-term clinical practice. However, such reliable near-continuous sensor device is currently not available as already mentioned above. Still, this approach can be considered as the first and, to the best of the author's knowledge, *most close to reality* closed-loop artificial pancreas prototype.

#### 7.2.3.4 Others

Other closed-loop projects were executed by, among others, the company Medtronic Minimed (that used an individualized PID controller) [195], the company Roche Diagnostics (that converted an empirical algorithm into an MPC approach) [201], Renard *et al.* (who followed a PD controller approach) [173, 174], and the group of Freckmann (showing an MPC approach) [77]. Currently existing prototypes have similar drawbacks as discussed for the ADICOL project.

## 7.3 Blood glucose control in critically ill patients

The landmark study of Van den Berghe *et al.* [216] demonstrated the numerous advantages of TGC in the (surgical) ICU. Normalization of blood glucose between 80 and 110 mg/dl was achieved by following a list of *guidelines*. Since then, different alternative algorithms and control systems have been proposed. In this section an overview of most known protocols and algorithms is given. It must be stressed, however, that a detailed *qualitative* comparison of these protocols is not straightforward as not all algorithms were described in detail. Moreover, as already discussed in Chapter 4, a *quantitative* comparison (in terms of the obtained results) between algorithms is rather difficult since an assessment depends on the selected measure (e.g., average blood glucose) and the design of the study (e.g., duration of stay in the ICU and blood glucose sampling frequency). Therefore, the *results* that are obtained with these protocols are not the main focus of this overview.

### 7.3.1 Leuven guidelines

The two TGC landmark studies [213,216], performed in the Leuven University hospital were based on a set of *guidelines* used by the nursing teams. These guidelines, however, do not behave as a simple 'if-then' protocol. Further, it is important to note that insulin requirements have a wide *inter* and *intra* patient variability. The need for insulin depends on insulin production reserves, insulin sensitivity before and during critical illness, caloric intake, and the severity and nature of the underlying disease [205]. Finally, the presence of (additional) infections and the administration of medications (e.g., glucocorticoids) may severely affect the insulin resistance and the need for exogenous insulin, consequently.

In [215] the insulin requirements of the patients from the 2001 study were studied. Only 36% of the variance of the insulin requirements could be explained by some patient- and disease-related factors (BMI, history of diabetes, reason for ICU admission, at-admission hyperglycemia), the mean daily amount of calories per kilogram of body weight, the time in the ICU, and medication (e.g., glucocorticoids). Accordingly, 64% of the variation of the insulin doses were not predictable by the variables mentioned above, but were based on the frequent monitoring of glycemia (i.e., every four hours or more frequently in the initial phase or in case of complications), the time course of the previous changes in blood glucose, an eventual rise in body temperature, and the presence of additional infections. Moreover, these last variables are considered in a set of guidelines, as already mentioned above, which can be summarized as follows [207, 215]:

**INITIATION OF INSULIN INFUSION**

- If blood glucose level exceeds 110 mg/dl then start insulin at 2 U/hr,
- If blood glucose level exceeds 220 mg/dl then start insulin at 4 U/hr.

**INITIAL STABILIZATION OF BLOOD GLUCOSE LEVEL**

During first 12-24 hours after admission, until targeted level is reached, measurement of blood glucose is advised every 1-2 hours:

- If blood glucose is $> 140$ mg/dl, then increase insulin dose by 2 U/hr,
- If blood glucose is between 110-140 mg/dl, then increase insulin dose by 1 U/hr,
- If blood glucose approaches target range of 80-110 mg/dl, then increase insulin dose by 0.1-0.5 U/hr,
- If blood glucose lies within target range of 80-110 mg/dl, then maintain insulin dose.

**DOSE ADJUSTMENT AFTER INITIAL STABILIZATION**

Check blood glucose at least every 4 hours. More frequent blood glucose measurements are appropriate in case of steep changes of hypoglycemic events. Dose adjustments should be proportionate to the observed change in blood glucose:

- If blood glucose decreased by 50%, then reduce dose by half and check blood glucose again in 1 hour,
- If blood glucose is between 60-80 mg/dl, then reduce insulin depending on previous measurement and check again within 1 hour,
- If blood glucose is between 40-60 mg/dl, then stop insulin infusion and ensure adequate baseline glucose intake; check blood glucose within 1 hour,
- If blood glucose $< 40$ mg/dl, then stop insulin infusion and ensure adequate baseline glucose intake. Administer glucose via 10 g intravenous boluses and check blood glucose within 1 hour,
- If blood glucose starts to decrease within normal range, assume recovery of insulin sensitivity and reduce insulin infusion by 20%.

Additional blood glucose controls are advised when body temperature is increasing (typically associated with infection).

**INSULIN ADMINISTRATION AND OTHER GUIDELINES**

- Administer insulin by continuous intravenous infusion through a central venous catheter. Use a standard concentration of 50 U of Actrapid HM in 50 ml of 0.9% NaCl,
- Intravenous glucose-containing solutions should always be administered by an infusion pump,
- At times of planned interruptions of feeding, adjust insulin dose proportionately (mostly 0 U/hr, or 0.5 U/hr in case of patients with a history of diabetes),

- When high doses of glucocorticoids are given ($> 90$ mg/day hydrocortisone or its equivalent), increase insulin dose to overcome associated insulin resistance. Total daily dose of glucocorticoids is administered as a continuous infusion to avoid fluctuating insulin requirements,
- When substitution (glucose) liquids need to be administered to overcome possible renal insufficiency, neutralize the (glucose) liquids by adding insulin: 16 U/liter for glucose 5% liquid, 12 U/liter for glucose 3.3% liquid, or 10 U/liter for glucose 2.5% liquid.

It is obvious this set of guidelines is *not* a strict protocol. Lots of *nursing-experience* is necessary for adequately controlling blood glucose in this type of patients. For this reason alternative protocols and algorithms that aim to reduce the workload of the nurses have been proposed.

### 7.3.2 Basic protocols or nomograms

The first type of alternative insulin protocols is the 'basic' protocol or the nomogram. This is a detailed plan providing the nurse specific instructions concerning the treatment of patients. Nomograms have the advantage that implementation in the currently existing treatment therapy is rather simple and does hardly need any training of the personnel. The efficiency of these basic protocols, however, may be insufficient for two reasons. First of all, the protocol is aimed to be used for a large group of patients leading to a rather *general* protocol without any patient-specific influence on the treatment. Secondly, the nurses follow the respective protocol avoiding any *active* contribution (i.e., deviation from the protocol).

This group of protocols can be further subdivided in 'sliding scale protocols' and 'dynamic scale protocols' [145, 240]. The first subgroup is characterized by the delivery of a predetermined insulin flow defined by the glycemic range in which the actual blood glucose lies. Let us give an example. When the patient's blood glucose is between 110 mg/dl and 140 mg/dl, 1 U/hr of insulin is administered; when the blood glucose is between 141 mg/dl and 170 mg/dl, 2 U/hr of insulin are delivered; etc. The second subgroup comprises basic protocols that are founded on a dynamic scale. In that case, the next insulin rate is determined based on the previous insulin flow and the actual blood glucose. Even glycemia trend information can be incorporated here. For example, if the patient's glycemia is between 110 mg/dl and 140 mg/dl, the previous insulin rate is increased by 1 U/hr.

Some known basic protocols are listed below:

#### 7.3.2.1 Balkin *et al.* [6]

In this work the authors presented different tables for determining the amount of insulin. Depending on the previous insulin flow and the current and previous blood glucose the amount by which the insulin flow was changed could be easily found. This protocol was a typical example of the dynamic scale category and could be labeled

as a pure 'feedback' protocol as no future disturbances were taken into account. The default glycemia sampling interval was two hours and the goal glycemic range was 100-120 mg/dl although the protocol was only commenced at glycemia levels above 150 mg/dl. In total, the protocol was applied to 188 patients (with a minimum duration of protocol application of 12 hours) divided over three different hospitals. The best obtained average blood glucose was $134 \pm 44$ mg/dl.

#### 7.3.2.2 Chee *et al.* [39,40]

A closed-loop system, based on a sliding scale algorithm, was tested on five critically ill patients. The insulin dose was computed using a formula that consisted of three parameters: the basic dose (the basic sliding scale), the offset (that was related to the glycemia trend), and a shutting-off parameter for insulin in case of hypoglycemic events. The target glycemic range was 108-180 mg/dl, which was significantly higher than that of the Leuven guidelines (80-110 mg/dl), and the insulin infusion rate was adjusted every hour. The computed mean blood glucose for these 5 patients (trial during 24 hours) was $189 \pm 43$ mg/dl.

#### 7.3.2.3 Taylor *et al.* [197]

Two nurse-driven insulin infusion protocols were compared with a conservative physician-initiated protocol (i.e., no target blood glucose). The nurse-driven protocols were similar to each other but differed in thresholds for initiating and discontinuing insulin. The target glycemic range was 120-150 mg/dl for the first protocol and 80-110 mg/dl for the second. There were 71 patients who received a physician-initiated insulin infusion, 95 patients who were involved in the study for the first nurse-driven protocol, and 119 patients for the second nurse-driven protocol, respectively. Further, this dynamic scale protocol was only based on the actual blood glucose and the glycemia trend. The glycemia sampling interval varied from one to four hours depending on the glycemic stability. The average blood glucose in the group with the second nurse-driven protocol (132 mg/dl) was lower than that of the group with the first nurse-driven protocol (163 mg/dl) and that of the group with the physician-initiated protocol (190 mg/dl). One of the drawbacks of this protocol, as already mentioned by the authors, was the high complexity level (33 potential interventions) explaining why the protocol may not have been strictly followed by the nurses.

#### 7.3.2.4 Goldberg *et al.* [80,81]

The protocol defined in this study was another typical dynamic scale protocol that determined the next insulin rate based on the actual and previous (trend information) blood glucose and the previous insulin flow. The glycemia sampling period was set at 1 hour and the target blood glucose range was 100-139 mg/dl. The protocol was applied to 52 medical ICU patients and 118 cardiothoracic ICU patients. The first patient group obtained a mean blood glucose of $125 \pm 12$ mg/dl for patients with a history of diabetes and $121 \pm 18$ mg/dl for patients without any history of diabetes. The duration of protocol application was variable ($D \geq 72$ hours in 48% of the cases). Mean blood

glucose levels for the second group were $122 \pm 17$ mg/dl and $119 \pm 14$ mg/dl depending on the hospital.

#### 7.3.2.5 Chant *et al.* [34]

The dynamic scale nomogram presented in this work was founded on the actual blood glucose value, the glycemia trend, and the previous insulin flow. The target blood glucose range equalled 90-144 mg/dl and the glycemia sampling interval mostly varied from 1 to 2 hours. The protocol was applied to 44 patients (admitted to a medical/surgical ICU) resulting in an average morning blood glucose of $128 \pm 32$ mg/dl. These results were compared to the glycemic behaviour of 42 patients receiving a non-standardized insulin sliding scale (i.e., patient-specific alterations by the medical staff were permitted). In this last group an average morning blood glucose of $176 \pm 50$ mg/dl was obtained.

#### 7.3.2.6 Kanji *et al.* [103]

Similar to the previous protocols, the next insulin rate was determined based on the actual and previous blood glucose and the previous insulin dosage. The sampling interval of this dynamic scale protocol varied from 30 minutes to 2 hours. The target blood glucose range was the same as used in the landmark studies: 80-110 mg/dl. The protocol was applied to 50 critically ill patients admitted to a mixed medical/surgical ICU. The results were compared to another patient group (50 patients) receiving a conservative physician-initiated treatment. Target glycemia was achieved more rapidly and fewer patients experienced severe hypoglycemia when using the proposed protocol. Nearly half of the glucose measurements (47%) fell in the target blood glucose range supporting the concept of standardizing intensive insulin therapy.

#### 7.3.2.7 Lonergan *et al.* [35, 138]

The Specialized Relative Insulin and Nutrition Tables (SPRINT) approach was an alternative dynamic scale protocol aiming to provide an easy-to-use 'paper' protocol (compared with the computerized protocols, see below). The SPRINT protocol comprised an insulin and a feed *wheel*. This protocol was progressive due to the presence of two manipulated variables: both the insulin input as well as the nutritional input could be modulated. Accordingly, the actual and the previous glycemia value, the previous insulin dosage, and the previous nutrition feed rate were used to determine the insulin and nutrition intervention for the next interval. The patient's age, body frame size, and gender could further influence the nutrition manipulation variable. The target glucose range was 72-110 mg/dl and glycemia was measured every 1-2 hours. The SPRINT protocol was applied to 11 critically ill patients (with a varying duration of algorithm application) resulting in an average blood glucose of $104 \pm 16$ mg/dl with 64% of the measurements in the target glucose range.

### 7.3.3 Elementary computerized protocols

This category mainly consists of standard insulin infusion protocols that are computerized aiming to facilitate glycemia control in the ICU. Ideally, these protocols are integrated in a computerized decision support program. The obtained results seriously differ depending on the considered protocol and may not give a clear view on the general effect of computerizing protocols [188]. Important computerized but rather elementary protocols are presented in the following overview:

#### 7.3.3.1 Rood *et al.* [177]

In this study a blood glucose regulation guideline was implemented in paper and computerized form. The actual and previous blood glucose combined with the previous insulin infusion rate determined the next insulin flow. The recommended time interval between two glycemia measurements could range from 15 minutes to 3 hours and the target glycemia range was set at 72-126 mg/dl. The computer protocol was tested on 66 patients and compared to the paper protocol that was applied to 54 patients. The duration of algorithm application did not remain constant. The time that was spent in the target range was 54% for the computerized and 53% for the paper protocol explaining that this difference was too small to be clinically significant (due to the crossover effect when randomizing the patients). Compared to the results obtained with the paper protocol before (44% in target range) and after (42% in target range) this test phase, a clinically relevant improvement was found showing that integrated computerized guidelines are useful.

#### 7.3.3.2 Davidson *et al.* [57]

The 'Glucommander' algorithm that was presented in this study was founded on the formula $F_I = (G - 60)m$, where $m$ symbolized a variable multiplier with starting value usually set at 0.01 or 0.02. Depending on the glycemia trend and the actual glycemia value, this multiplier was adapted leading to alteration of the insulin flow. The suggested time interval for the next sampling varied from 20 to 120 minutes with a target blood glucose range of 100-140 mg/dl. Data ($> 120000$ glucose measurements), *not* limited to critically ill patients (most of the patients were admitted to general medical and surgical wards with a variable duration of algorithm application), were analysed giving mean glucose levels $< 150$ mg/dl achieved in 3 hours. The authors claimed the proposed algorithm could be used in all units of any hospital, would be easy to use by nurses (no responsibility for determining the required insulin doses), and could lead to a lower prevalence of hypoglycemia (compared with the Leuven protocol). A derivative of this algorithm, with a target blood glucose range lowered to 80-110 mg/dl, was recently proposed by Boord *et al.* [18]. The computer-based insulin protocol outperformed the manual nurse-driven protocol in terms of time spent in the target range.

#### 7.3.3.3 Thomas *et al.* [199]

An electronic insulin dose calculator was developed based on the Leuven protocol but with a higher glycemic target range: 97-128 mg/dl. The suggested insulin rate was determined based on the actual and previous glucose measurement and the previous insulin dose. The time interval between glucose measurements varied from 30 minutes to 4 hours. The study population comprised 288 patients (before introduction of protocol), 502 patients (after its introduction), and 101 patients (after introducing a modified protocol) and led to a decrease of the mean blood glucose ($131 \pm 32$ mg/dl vs. $119 \pm 29$ mg/dl vs. $112 \pm 23$ mg/dl, respectively). The duration of algorithm application was not kept constant. The mortality rate remained constant during the study in spite of the tighter glycemic control (possibly due to the higher target blood glucose compared to the Leuven trials) but the study was also not designed for showing potential survival improvements with TGC.

#### 7.3.3.4 Meynaar *et al.* [148]

The computerized protocol presented in this study was based on a set of 'if-then' rules that considered the actual and previous blood glucose, the previous insulin flow and the amount of feeding (either $\leq 25$ ml/hr or $> 25$ ml/hr) as inputs to the system. The target blood glucose range was 81-135 mg/dl and mean blood glucose decreased from 166 mg/dl (without protocol) to 138 mg/dl (with protocol, 179 patients and with a variable duration of algorithm application). The time to the next glucose measurement could vary from 30 minutes to 4 hours.

#### 7.3.3.5 Shulman *et al.* [188]

An insulin protocol was implemented into a bedside clinical information system aiming at blood glucose levels between 80-110 mg/dl. A relative adaptation of the insulin flow was suggested based on the actual and the previous measured glucose. Blood glucose was sampled every 15 minutes, every one or two hours or even every 4 hours depending on the observed glucose profile. The protocol was applied to 50 critically ill patients (with a variable duration of algorithm application) leading to a median 23% of the time spent in the target range (nearly half of the time the measured glycemia values fell in the range 111-144 mg/dl). The rather low percentage in the target range explained why the authors concluded that the used protocol (independent of the paper or computerized format) was not efficient for TGC.

#### 7.3.3.6 Vogelzang *et al.* [234]

This work presented a computer program, GRIP (Glucose Regulation for Intensive care Patients), that recommended insulin infusion adaptations mainly based on the mean insulin flow over the last 4 hours, the deviation from the actual blood glucose to the target glycemia (that was set at 117 mg/dl), the glycemia trend over the last 4 hours, and changes in the administration of enteral or intravenous glucose calories. The advised sampling interval could vary from 30 minutes to 12 hours. The GRIP system was tested on 179 patients (with a variable duration of algorithm application and a median

4.9 glucose measurements per day). The target blood glucose range (72-135 mg/dl) was achieved for 78% of the time favoring the use of computer-driven protocols over nurse-driven protocols.

### 7.3.4 Advanced computerized protocols

The most promising category of protocols is founded on more advanced engineered 'controllers'. Here, both pure *feedback* as well as *predictive* control systems are presented. This last type of control system has the feature that future known disturbance factors can be taken into account in the determination of the most optimal insulin infusion dose. The following list of advanced computerized protocols gives an overview:

#### 7.3.4.1 Doran *et al.* [61]

A two-compartmental glucose system model was used in combination with a *heavy* derivative PD controller to determine the intravenous insulin flow. The derivative gains of this pure feedback controller were higher than the proportional gains as it was the aim to control the shape of the blood glucose profile rather than its magnitude. Glucose was sampled every 15 minutes in 4 proof-of-concept clinical trials. The first day of each trial started by giving the patient a 75 g OGTT glucose dose. The data of this first day were used to estimate the 4 parameters of the two-compartmental glucose system model such that the fundamental (glucose) dynamics could be approximated by the model output. The second day, every 15 minutes a new insulin rate was computed by the PD controller and delivered to the patient. The second-day control in these 4 patients showed the potential of automated insulin administration. However, this control approach relied on an OGTT test during the first day leading to poor blood glucose control in this period. Due to the critical illness of this type of patients, this strategy may not be ethically approved for standard clinical use. Moreover, this approach also relied on a high glycemia sampling frequency which will only be feasible in real-life ICU if reliable near-continuous glucose sensor devices are available.

#### 7.3.4.2 Chase *et al.* [36,37,86,243,244]

A control algorithm modulating intravenous insulin infusion and bolus with an enteral feed rate was developed in this work. Therefore, a two-compartmental model was used to determine nutritional flow variations. Further, the insulin sensitivity was initially estimated with the glucose data of the first hour (sampling interval equalled 15 minutes) and adapted as a function of previously computed insulin sensitivities. The target blood glucose range was 72-108 mg/dl though the target glycemia *reduction* in the control algorithm was set at only 10-15% per hour in case of blood glucose values larger than the target range. Every hour, the insulin bolus size, insulin infusion rate and nutritional feed could be iteratively determined based on the estimated insulin sensitivity, the used model, and the glucose values (sampled every 30 minutes) with the aim to achieve the target glycemia at the end of the next hour. The system was applied to 8 proof-of-concept clinical trials of whom the duration of algorithm application was 10 hours

for seven patients and 24 hours for one patient showing acceptable stepwise glycemia reduction.

#### 7.3.4.3 Hovorka *et al.* [97,166]

These studies presented the clinical feasibility of using a *predictive* control system (expressed in a MPC format, see 7.4.1), instead of previously described rather classical pure *feedback* control approaches, for normalizing blood glucose in the critically ill. A MPC control strategy is explicitly founded on a model that describes the dynamic glucoregulatory system of a patient. Here, the model was based on former studies in patients with type I diabetes [95, 96]. Incoming glucose measurements were used to update the model parameters. The blood glucose profile, the previous insulin flow, and the carbohydrate calories determined the next insulin infusion dosage. The target blood glucose range was set at 80-110 mg/dl and the sampling frequency was variable (depending on the estimated prediction accuracy). It must be stressed that the initial study [166] considered a one hour glycemia sampling interval, which was found to be too short for use in clinical practice [135, 167]. The updated MPC version was applied to 30 critically ill patients and compared to a standard glucose management algorithm (also 30 patients). The duration of algorithm application was set at 24 hours and the average sampling interval was $1.5 \pm 0.3$ hours (compared to $2.1 \pm 0.2$ hours for the standard protocol). The obtained average blood glucose values were $112 \pm 20$ mg/dl for the MPC approach and $130 \pm 20$ mg/dl for the standard approach. The percentage of the measurements in the target range was found to be 60% for the MPC approach and 27% for the standard approach. Though the comparisons between the two approaches may be partly falsified (due to the different average blood glucose sampling frequencies in both groups), this study clearly shows the potential of using MPC to normalize blood glucose in critically ill patients.

#### 7.3.4.4 Van Herpe *et al.* [224]

This work introduced the design of another MPC approach that, however, incorporated the developed ICU-MM (presented in Chapter 6, 6.3) as model, which was especially designed for describing the glucoregulatory system of critically ill patients. This predictive controller was tested in simulation with the first 48 hours-after-admission data of 19 critically ill patients. The ICU-MM was initially estimated with the near-continuously monitored data of the first 24 hours and the glucose profiles were simulated (using the insulin flows determined by the MPC) for the next 24 hours and compared with the real data of the second 24 hours. Accordingly, the duration of algorithm application was set at 24 hours. The controller was able to adapt the insulin infusion rate every hour or every four hours based on the measured glucose signal, the recent insulin dosage profile, and the (future) flow of carbohydrate calories. A detailed analysis of this study is presented below (see 7.4.2).

### 7.3.5 Discussion

The previous overview presents the evolution of the Leuven TGC guidelines to some basic insulin infusion protocols to elementary computerized protocols and to more sophisticated blood glucose controllers. Particularly the use of the last group of controllers can potentially lead to fully-automated glycemia control reducing the workload of the nursing team. A few remarks should be stressed, however.

First of all, it is surprising to see that the **blood glucose target values were raised** in many of the studies presented above although the two landmark Leuven studies [213, 216] clearly showed a significant reduction of mortality and morbidity in case of TGC between the narrow limits 80-110 mg/dl. The most important reason for this is the fear of hypoglycemia when the lower glycemia threshold is set too low. In general, hypoglycemia is defined as blood glucose values lower than 50 mg/dl with neuroglycopenic symptoms or blood glucose values lower than 40 mg/dl in the absence of these symptoms [211]. Infusing insulin (aiming at normoglycemia) bears the risk of inducing life-threatening hypoglycemic events, particularly in sedated patients [97, 211] and explains why this strict target range was elevated in many protocols: hypoglycemia is often considered more dangerous than hyperglycemia.

Though the incidence of hypoglycemia was comparable to the Leuven landmark studies (11%), two trials were prematurely stopped due to the apparently unacceptable high number of hypoglycemic events. The German VISEP (Volume Substitution and Insulin Therapy in Severe Sepsis) trial [26, 27], which was stopped after the inclusion of 488 patients, reported 12% for incidence of hypoglycemia in the intensive treatment group without any significant reduction of mortality. The European GLUCONTROL study [168], that was stopped after the inclusion of 1109 patients, notified 10% as relative number of patients who have experienced at least one hypoglycemic episode. The median blood glucose was found to be 118 mg/dl (IQ range: 109 - 131 mg/dl). It is obvious that the applied insulin infusion protocol in these two studies was not adequate to achieve TGC as patients were exposed to increased hypoglycemic risks (incidence of hypoglycemia was comparable to the intensive insulin patient group of the Leuven trials) without bringing the benefit of TGC (reaching normoglycemia leading to a reduction of mortality and morbidity).

Nevertheless, some authors advise to set higher blood glucose targets (e.g., target glycemia $<$ 140-150 mg/dl in [168] to avoid these apparently hypoglycemic risks. However, as often unstressed in articles, the Leuven landmark studies compared the intensive insulin treatment (aiming at blood glucose levels between 80-110 mg/dl) with the conventional treatment (administration of insulin only if the blood glucose level exceeded 215 mg/dl and then maintenance of glucose at a level between 180-200 mg/dl). In the conventional treatment, however, blood glucose was not *forced* to lie in this 180-200 mg/dl target range [213, 216]. In other words, when glycemia was below 180 mg/dl the insulin flow was *not* adapted aiming at blood glucose values between 180-200 mg/dl. Accordingly, the obtained average morning blood glucose of the conventional patient group in the first landmark study [216] was

153 $\pm$ 33 mg/dl. Surprisingly, this average is similar to the recommended target blood glucose mentioned in some studies described above. The landmark studies clearly showed the relation between mortality/morbidity reduction and TGC (80-110 mg/dl) suggesting the conventional treatment may be harmful to the patients. The studies from above, however, illustrate that some newly proposed insulin titration algorithms still use 'more conventional' target blood glucose ranges which are not related to the mortality/morbidity reduction.

Application of the intensive insulin therapy in the critically ill is expected to reduce absolute mortality by 3 to 4% and even to 8% when the therapy is continued for at least three days [213,216,229]. Confirmation of this 3 to 4% absolute mortality reduction in similar studies would require a sample size of at least 5000 to 6000 patients [229]. The Australian NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) multicenter trial [154], which is currently still ongoing, may have sufficient statistical power to confirm the mortality reduction when applying TGC in a mixed medical/surgical patient population.

While awaiting the results of the NICE-SUGAR study it is recommended to consider 80-110 mg/dl as target blood glucose range in the critically ill as many studies have already shown that many lives were saved with the intensive insulin therapy [120, 172, 213, 216]. Indeed, hyperglycemia is more deleterious than hypoglycemia in this type of patients. Moreover, incidental, brief episodes of hypoglycemia may not cause serious harm when appropriately and rapidly treated [140, 185, 236] confirming the recommended compromise between perceived safety concerns (avoiding hypoglycemia) and published evidence (avoiding hyperglycemia). Finally, it is important to stress that no association between hypoglycemia and early or late mortality was found in a recent study [236].

Secondly, it is **hard to compare the results** of different studies due to the non-uniform evaluation strategy and the different study design. In most studies a new (computerized) insulin infusion algorithm is compared to a more conservative (nurse-driven) protocol. However, the selected measure (e.g., mean morning blood glucose, mean blood glucose, time spent in target range, HGI, number of hypoglycemic events, etc.) or the combination of measures differ over the mentioned studies. Moreover, definitions of the target glycemic range, hypoglycemia, and others are dependent on the study. The use of GPI, as presented in Chapter 4 (see 4.3.1), can potentially lead to a uniform evaluation strategy in future studies. Next, the study design can falsify the obtained results as has also been addressed in Chapter 4 (see 4.3.3). At least the variables *duration of algorithm application* and *blood glucose sampling frequency* can mislead evaluations when they are not similar among patient groups. Accordingly, performance comparisons of algorithms published in different studies (e.g., computer protocol 1 presented in study 1 versus computer protocol 2 presented in study 2) or even within a study (e.g., computer protocol versus nurse-driven protocol) can be falsified.

Thirdly, it is remarkable that some studies tend to **compare** the results obtained with a newly proposed algorithm to the **results of the Leuven landmark studies** without taking into account the influence of external factors. For example, the reduction of the number of hypoglycemic events or the improvement of the level of TGC (compared with the Leuven trials) are often mentioned without considering the increase of the blood glucose sampling frequency, the shorter duration of algorithm application, the different type of patients, etc. (see for example [38, 57, 166]). Furthermore, it is important to note that the Leuven nursing team only applied some titration *guidelines* instead of a real *protocol*. However, in simulation studies these Leuven guidelines are typically transformed to an 'if-then' protocol, which is obviously not identical to the real set of guidelines (that allow interpretation by the nurses) generating misleading conclusions (see for example [35]).

Next, most of the present insulin infusion algorithms have only one manipulation variable (i.e., insulin). Few exceptions are the studies described by Chase and co-workers [35, 138, 243, 244] in which **both insulin and the nutritional calories** are determined by the control algorithm. From a control perspective, the incorporation of this additional manipulation variable may give more freedom to the algorithm to improve the performance of the control system. However, wide-spread use of a system with two manipulation variables does not seem to be accepted yet for clinical standard practice as the rate of nutritional calories is typically based on a set of measured patient-specific parameters and is certainly not only dependent on the blood glucose profile. Moreover, it was shown that intensive insulin treatment works irrespective of the load of parenteral glucose calories [214] explaining there is no urgent need to have the flow of nutritional calories determined by the control algorithm. An alternative approach to potentially increase the performance of a control system could be the inclusion of a glucose/glucagon manipulation variable that is only aimed to pick up rapidly measured hypoglycemic episodes. Accordingly, the fear of hypoglycemia due to the intensive treatment with insulin could diminish. Nonetheless, it is likely that this extra feature may only be incorporated in the first commercial (fully-)automated blood glucose control systems when reliable near-continuous glucose sensor devices are available.

Finally, it is remarkable that some studies presented in the list above were based on **capillary glucose measurements** (i.e., the 'fingerstick' which is typically used for glucose monitoring by patients with diabetes) [6, 34, 57, 103, 138, 148, 178, 197, 243, 244]. Capillary samples should be avoided to be used with ICU patients as they can lead to unreliable glucose measurements as previously shown [28,51,63,71,123]. Only arterial and venous blood samples should be used to determine the blood glucose in the critically ill.

In conclusion, the interest to design a computerized algorithm (control system) for semi- or fully-automated blood glucose control in the ICU is increasing [235]. During the last years different control strategies were presented generating promising results. Though the usability of a *fully*-closed-loop system may depend on the availability of a reliable near-continuous sensor device, it is expected that *semi*-closed-loop systems (that require confirmation of the proposed insulin dosage by the nurse) may be soon

commercially available on the condition that the blood glucose sampling frequency could be lowered (aiming at sampling intervals between 1 and 4 hours). Further, different control systems should be appropriately validated by taking into account the similarity conditions (with regard to, at least, the *blood glucose sampling frequency* and the *duration of algorithm application*) and the efficiency of the measure (e.g., HGI, GPI) as already mentioned in Chapter 4. Finally, it is important to note that the introduction of (advanced) computerized algorithms can potentially further reduce mortality and morbidity. None of the studies mentioned above, however, have sufficient statistical power to show this feature as the number of patients enrolled in these studies was too limited.

## 7.4 Design of a Model based Predictive Controller

In this section the features of MPC are explained and the advantages of this control strategy over rather classical pure feedback control approaches are discussed. Next, the design of a first predictive controller based on the earlier developed ICU-MM is presented and the results of this simulation study are discussed.

### 7.4.1 Features of MPC

As it is generally understood in the field, MPC is a control paradigm that, based on a dynamic model of the system to be controlled, solves a mathematical optimization problem in order to find the optimal sequence of input signals within a finite future time window of length $N$ after which only the first input signal is applied to the system. At the next sampling time, the procedure is repeated based on new measurements of the state of the system. This process goes on indefinitely [116, 150].

In summary, it can be stated that any MPC control system should be constituted of at least the following elements:

- a dynamic mathematical model describing the system to be controlled,
- explicit on-line mathematical optimization,
- the notion of a finite future time horizon of length $N$ within which an optimal input sequence is computed by aforementioned optimization problem.

Other important explicit features of any MPC are:

- the possibility to impose constraints in the optimization problem (e.g., no negative insulin flow, maximum insulin rate),
- the possible use of an adaptive model to capture varying dynamics of the patient (e.g., changing insulin resistance),
- the tracking of a reference trajectory in a fully-closed-loop.

The application of the MPC in this setting is as follows: the system to be controlled is the patient (or more precisely: the glucoregulatory dynamics of the critically ill patient) and the input signal is the insulin dosage profile. The control paradigm is based on the dynamic model of the patient (system), and solves a mathematical optimization problem in order to find the optimal sequence of the insulin dosage profile (input signal). Typically, for patients in intensive care units, after a time period of about four hours (corresponding to the finite future time window of length $N$) only the first insulin dosage (input signal) is applied to the patient (system). At the next sampling time, the procedure is repeated based on new blood glucose measurements (i.e., information on the state of the system). The MPC optimization process is repeated at each time instant by moving the time-window for which the optimal insulin dosage is computed. This principle is depicted in Figure 7.2.

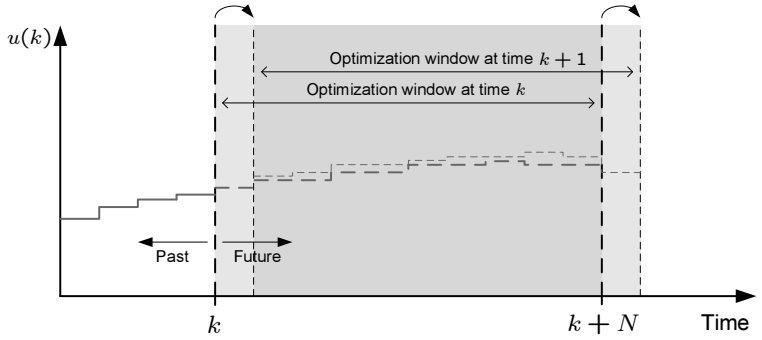


**Figure 7.2:** MPC optimization process at arbitrary time instant $k$. In this setting $u(k)$ represents the insulin flow at time instant $k$. The future time window $N$ is set at 4 hours. This time horizon is typical of blood glucose control in the ICU (see also Chapters 5 and 6). The MPC optimization process is repeated at each time instant $k$ by moving the horizon leading to 'receding horizon control'. At every time instant $k$ an optimal control problem of length $N$ is solved after which only the first insulin dosage is delivered to the patient.

MPC is a practical method for the real-time application of optimal control theory that introduces the notion of feedback by using incoming measurements, while avoiding the need for excessive storage space for storing *off-line* computed optimal input signals. The use of MPC in this particular field is distinguishing from other control strategies by its flexibility with regards to adaptive models. Since an optimization problem is imposed at each time instant, the adaptations made to the dynamic mathematical model (model updates), as discussed in Chapter 6, can be easily implemented and directly influence the control behaviour. Moreover, classical algorithms only use feedback control to maintain normoglycemia meaning that they *respond* to monitored hypo- or hyperglycemic episodes. Predictive control algorithms, however, take into account future known disturbances aiming to *prevent* deviations from normoglycemia. The use of *dynamic* models further allows to achieve the target effect (e.g., normoglycemia) in a shorter time compared with control strategies that are based on a *static* model or

no model at all. This shorter settling time is of the utmost importance when treating critically ill patients.

## 7.4.2 Simulation study

Consider the following *future* semi- or fully-closed-loop automated blood glucose control approach. When a new patient enters the ICU, the dynamic model that is used in that predictive control system is an *initial model* based on the patient profile (determined by BMI, history of diabetes, etc.) and some on-admission parameters (e.g., reason for ICU admission, blood glucose on admission, etc.). Distinct classes, each associated with their own parameter settings for the initial model, are classified in advance. The closed-loop measurements are used to adapt these initial model parameters such that it more closely approximates the real dynamic behaviour of the considered patient. As the patients, admitted to the ICU, are characterized by highly varying patient dynamics (e.g., the insulin resistance is related to the severity of illness of the patient, which evolves as a function of time), the use of an *adaptive model strategy* is necessary to capture these inter- and intra-patient variability. This adaptive modelling strategy was discussed in Chapter 6. In this section the design of a MPC using an Extended Kalman Filter (EKF) is presented and its potential is demonstrated with simulations.

### 7.4.2.1 Mathematical formulation of a MPC with EKF for use in the ICU

The use of MPC to normalize glycemia in the ICU gives the advantage to consider the effect of current and future control moves (i.e., the insulin rates) on the future outputs (i.e, glycemia). It consists of solving a fixed-size optimal control problem at each time instant after which only the first control move (i.e., the insulin rate for the next time instant) of the optimal input sequence is applied to the system (i.e., the patient). In this setting, only the flow of delivered carbohydrate calories $F_G$ is a known **disturbance** input variable of the system. We assume this rate is known for the particular prediction horizon ($N = 4$ hours), which is a clinically feasible condition. As a result, this knowledge can be incorporated into the optimization problem leading to pro-active behaviour.

The MPC methodology explicitly takes imposed constraints into account, which classical control algorithms [21, 62, 76] typically cannot. For medical reasons the maximum insulin infusion rate (i.e., the control input) is set at 50 U/hr. In addition, the administered insulin flow is obviously constrained to be positive. The cost function that needs to be minimized in each optimization problem is described as follows:

$$\min_{\mathbf{x},\mathbf{u}} \mathscr{J}_k(\mathbf{x},\mathbf{u}) = \sum_{i=1}^{N} (x_{k+i} - x_{k+i}^{\text{ref}})^T Q (x_{k+i} - x_{k+i}^{\text{ref}}) + \sum_{i=0}^{N-1} u_{k+i}^T R u_{k+i}, \quad (7.1)$$

where $\mathbf{x}$ and $\mathbf{u}$ denote vector sequences containing all states respectively inputs within the horizon. Every state vector $x_k$ represents the four states of the ICU-MM (as presented in Chapter 6, 6.3): $G$, $X$, $I_1$, and $I_2$ at time $k$ of which $G$ is the **controlled**

variable. The input vector $u_k$ represents the **manipulated** variable $F_I$ at time $k$. The design parameters of the MPC are the weighting matrices $Q$ and $R$ (of which the ratio $Q/R$ was found to be $10^7$ based on the available patient data), and the prediction horizon $N$. The cost function comprises a trade-off between inputs and deviations from the desired glycemia level (reference trajectory = 95 mg/dl). The discrete-time model used in the MPC is obtained implicitly via integration of its continuous time counterpart over piecewise constant inputs with a sampling time of $T_s = 1$ min. For reasons of computational complexity time steps of 10 minutes are considered in the optimization problem. The integrating method is a standard Matlab® ODE (Ordinary Differential Equation) solver.

Numerically the optimization problem is solved in an SQP (Sequential Quadratic Program) fashion by means of local linearizations of the ICU-MM [149]. The gradients and the Hessians are computed by applying the forward Euler discretisation method. However, in the simulations the non-linear format of the ICU-MM is used. The initial value for insulin in each optimization problem is defined as the rate that is administered at the last time instant before the new optimization. A safety procedure is introduced to restrict hypoglycemic episodes by halving this initial value if a threshold glycemia value of 85 mg/dl is reached.

#### 7.4.2.2 Assessment method

The considered first 48 hours-after-admission data set, of which one patient was allowed to leave the ICU already after 24 hours, is described in detail in Chapter 2, 2.4.4. Therefore, the data of 19 patients are used in the simulation study that is presented here. The monitored glucose signals (sampling interval 3 minutes) are linearly interpolated to one-minute glucose sampling data. The ICU-MM is initially estimated with the near-continuously monitored data of the first 24 hours (following the procedures explained in Chapter 6) and the glucose profiles are simulated (using the insulin flows determined by the MPC) for the next 24 hours. The assessment of the developed control system consists of a quantitative and a qualitative analysis:

1. **Assessment 1: Quantitative analysis**

   In this part the performance of the MPC is evaluated by computing the GPI (see Chapter 4, 4.3.1) for each patient in **two sets of simulations**. In each set of simulations the prediction horizon is equal to 4 hours whereas the insulin flow adaptation frequency depends on the considered set of simulations.

   - The **first** set of simulations is characterized by an adaptation frequency of once per hour. This is further called the 'one-hour-period' simulations meaning that the most optimal insulin dosage profile for the next 4 hours (i.e., the prediction horizon) is determined every hour, but that only the first insulin rate (that corresponds to the flow of the next hour) is effectively imposed to the ICU-MM. A new optimization problem is defined at the next time instant (i.e., one hour later) leading to an updated insulin infusion scheme for the following 4 hours. Again, only the first insulin flow is delivered to the ICU-MM.

- In the **second** set of simulations the insulin infusion rate can only be adapted every 4 hours leading to solving the optimization problem only every 4 hours. This set of simulations is further defined as the 'four-hours-period' simulations. The ICU-MM used in the simulations, however, remains to be updated every hour to incorporate the changing physical conditions of the patient.

The patient specific series of model coefficients (with BIT $=$ 5 hours for the one-hour-period simulations and BIT $=$ 4 hours for the four-hours-period simulations) that were gathered in the estimation process (see also Chapter 6, 6.4) are considered in the simulations. The MPC simulations start after the first 24 hours (which were used to estimate the initial set of coefficients) and continue until the end of each patient's data set (with a maximum simulation run of 24 hours). Some additional and non-modelled disturbance factors are added in this set of simulations in order to test the robustness of the developed MPC:

- **Measurement error**: The *in-vitro* error, for glucose sampling, varies around 4% depending on the measurement device [171]. However, this percentage is lifted to 15% (gaussian noise) as a worst-case scenario for the *in-vivo* measurement error [239].
- **Medication**: The administration of medication $F_M$ (e.g., glucocorticoids) can disturb blood glucose levels. Although this disturbance factor is not included in the ICU-MM (see model 6.3 in Chapter 6), it is also introduced as an additional disturbance factor (unknown to the MPC) in the simulations. After a first simulation period of 6 hours, a (fictitious) continuous drug flow (leading to a glycemia increase of 2 mg/dl/min) is administered to the patient for 5 hours, followed by a continuous drug flow (that results in a blood glucose increase of 1 mg/dl/min) for another 5 hours.

MPC is a practical method for the real-time application of optimal control theory that introduces the notion of feedback by using incoming measurements (i.e., the simulated glucose signal in which 15% gaussian noise is added). In the MPC framework it is assumed that full state information is available. In our case only noisy measurements of glycemia are available and states need to be estimated. A non-linear state estimator - in casu an EKF - is employed for this purpose [125, 162]. The tuning of the state estimator is based on the auto-covariance of the additive measurement noise. As discussed, to make the case more realistic an unknown input disturbance $\hat{d}_k$ is added to the ICU-MM. This disturbance could represent plant-model mismatch or could originate from administered medication or other unknown/unmeasurable disturbance factors. To account for these disturbances the EKF equations are augmented. In the MPC it is assumed that the currently estimated disturbances are constant over the future window: $\hat{d}_{k+i} = \hat{d}_k, i = 0 \ldots N-1$. This approach proved to be effective for dealing with slowly varying input disturbances as encountered in this application.

2. **Assessment 2: Qualitative analysis**

   In the second assessment the performance of the MPC is compared with the performance of the nursing team assuming the ICU-MM (that is estimated for each patient individually and re-estimated every hour to capture the patient's changing conditions) completely represents the particular patient (i.e., without any to the model unknown disturbance factors).

   Since we do not know the exact blood glucose profile if a certain insulin infusion rate, other than the rate determined by the nurse, would have been administered to the patient, this analysis is purely qualitative. The near-continuous glucose values, that were measured by the GlucoDay system (see Chapter 2, 2.4.4), are submitted to the MPC and the optimization problem is defined every hour by using the one-hour model re-estimation sets (with BIT $= 5$ hours). The adaptation frequency of the insulin rate is set at once per hour and the prediction horizon equals 4 hours. The flow of carbohydrate calories that was effectively administered to the patient serves as (known) disturbance input variable of the system.

#### 7.4.2.3 Results and Discussion

In this section the performance of the MPC is firstly discussed for both the 'one-hour-period' and the 'four-hours-period' simulations. In the next phase the performance of the MPC is qualitatively compared with the control behaviour of the nursing team.

1. **Assessment 1: Quantitative analysis**
   Table 7.1 presents the results of the simulation study, expressed in GPI, for the one-hour-period and four-hours-period simulations. The relative contributions of the hypo- and hyperglycemic values to GPI (symbolized by $C_{\text{Hypo}}$ and $C_{\text{Hyper}}$, respectively) are also depicted. The median and 25-75% IQ range are found to be lower than the 'clinically acceptable' cut-off GPI $= 23$ (as discussed in Chapter 4) for both approaches. This indicates that blood glucose is tightly controlled in these simulations in spite of the inclusion of a large (medication) disturbance factor (that is unknown to the MPC) and a high measurement error (15%). Moreover, Table 7.2 shows the relative times spent in each glycemic range when considering all simulated glucose data (all patients). It can be observed that the relative time spent in the normoglycemic range is almost 60% in spite of the imposed disturbance factors and the short simulation period (in the initial phase after admission to the ICU, that is typically related to unstable glucose behaviour as presented in the re-estimated models), which was restricted to 24 hours due to the nature of the available data set. Further, the relative number of severe hypo- and hyperglycemic episodes is also negligible (see ranges 1 and 7 of Table 7.2). It can be concluded that the developed MPC strategy, independent of the one-hour-period or the four-hours-period approach, allows to tightly control glycemia in this simulation study with 19 (virtual) critically ill patients.

**Table 7.1:** GPI-evaluation of the simulation study

| | | Median | 25% - 75% IQ range |
|---|---|---|---|
| **One-hour-period** | GPI | 9 | 6 - 15 |
| | $C_{\text{Hypo}}$ | 35.6% | 8.3% - 41.5% |
| | $C_{\text{Hyper}}$ | 64.4% | 54.5% - 89.4% |
| **Four-hours-period** | GPI | 12 | 8 - 15 |
| | $C_{\text{Hypo}}$ | 46.7% | 17.0% - 67.1% |
| | $C_{\text{Hyper}}$ | 53.3% | 31.2% - 82.1% |

However, it is clear that an insulin flow adaptation frequency of once per hour generates better results than the scenario in which the controller is allowed to alter the insulin rate only every 4 hours. Indeed, the obtained GPI values are lower for the one-hour-period simulations than the computed GPI values for the four-hours-period simulations (see Table 7.1). This result could be expected since the first approach allows to update the model (used in the MPC) more frequently than the second (leading to a more adequate representation of the real patient behaviour) and further allows to appropriately adapt the insulin infusion dosage more frequently (leading to a better *prevention of* or *response to* deviations from normoglycemia). An even larger difference between both cases can be expected when applying more high-frequent disturbances. Further, the contribution of the hypoglycemic events (that are the main reason why clinicians may be afraid of applying TGC) to the computed GPI is lowered for the one-hour-period simulations compared with that of the four-hours-simulation (from 46.7% to 35.6% for the median values). In other words, the (simulated) blood glucose profile is stricter controlled (lower GPI than in the four-hours-period simulations) and, in addition to this better control, the contribution of the hypoglycemic deviations to this (lowered) GPI is also lowered. This means that fewer deviations from normoglycemia are observed in the one-hour-period simulations and that the majority of the remaining deviations originate from hyperglycemic episodes (which appear to be more acceptable than severe hypoglycemic events for most clinicians).

It must be remarked, however, that the relative time spent in the hyperglycemic range is slightly more in the one-hour-period approach. This may be explained by the introduced safety procedure to prevent hypoglycemic episodes, which is more frequently activated in case of the one-hour-period simulations. This safety procedure halves the initial value for insulin in the optimization problem if a threshold glycemia value of 85 mg/dl is reached. Accordingly, a decrease of the insulin flow is proposed by the MPC which may lead to more (slight) hyperglycemic episodes (if the decrease of the insulin flow appears to be too much). Thus, the computed GPI values are lower for the one-hour-period simulations indicating that the level of *overall* glycemic control is tighter than for the four-hours-period simulations based on current clinical 'expert' knowledge. This lower GPI value can be explained by the lower number of hypoglycemic

**Table 7.2:** Relative time spent per glycemic range for the 'one-hour-period' and the 'four-hours-period' simulations when all patients are considered.

| Range No | Clinical description | Glycemic range (mg/dl) | One-hour-period (%) | Four-hours-period (%) |
|---|---|---|---|---|
| (1) | Hypoglycemic alarm | $G < 40$ | 0.1 | 0.2 |
| (2) | Hypoglycemia | $40 \leq G < 60$ | 0.7 | 2.2 |
| (3) | Slight hypoglycemia | $60 \leq G < 80$ | 9.7 | 15.9 |
| (4) | Normoglycemia | $80 \leq G \leq 110$ | 58.6 | 55.8 |
| (5) | Slight hyperglycemia | $110 < G \leq 150$ | 26.6 | 23.2 |
| (6) | Hyperglycemia | $150 < G \leq 200$ | 4.2 | 2.6 |
| (7) | Hyperglycemic alarm | $200 < G$ | 0.1 | 0.1 |

events and the higher number of normoglycemic events (see Table 7.2). The (slightly) higher number of hyperglycemic episodes (i.e., more time is spent in the hyperglycemic range for the one-hour-period approach) does not have sufficient weight to increase GPI suggesting that these events are particularly *slightly* hyperglycemic.

Figure 7.3 illustrates the simulated glucose profile of patient no. 11 (as example) that is generated with the one-hour-period and four-hours-period simulations and the delivered known and unknown input flows. The individually computed measures for this patient are 4 for GPI, 35.6% for $C_{\text{Hypo}}$, and 64.4% for $C_{\text{Hyper}}$ in case of one-hour-period simulations and 14 for GPI, 68.8% for $C_{\text{Hypo}}$, and 31.2% for $C_{\text{Hyper}}$ in case of four-hours-period simulations. Although the MPC is able to suppress the unknown medication disturbance factor in both approaches, the insulin flow is increased faster (at $t = 420$ min) when a once-per-hour insulin adaptation frequency is applied so that glycemia relatively fast re-enters the normoglycemic range in spite of the existing unknown disturbance factor. This proof of robustness is an important feature of the controller for possible use in a real-life ICU setting. It indicates its skill to take into consideration unknown disturbance factors that are abundantly present in the ICU by exploiting the EKF.

Due to the ability to frequently adapt the insulin infusion rate with the one-hour-period MPC, blood glucose profiles that are evolving to hypoglycemia can be prevented. This is visualized in Figure 7.3 when the unknown medication disturbance factor is halved (at $t = 660$ min) and dropped (at $t = 960$ min). The simulated blood glucose - in case of an adaptation frequency of once per hour - stays only for a limited amount of time in the slight hypoglycemic range. The observed (simulated) glycemia values, the future known disturbance factor (i.e., the administered carbohydrate calories) and the use of the EKF (to estimate unknown disturbances) provide the appropriate information to the MPC for optimizing the insulin infusion sequence.

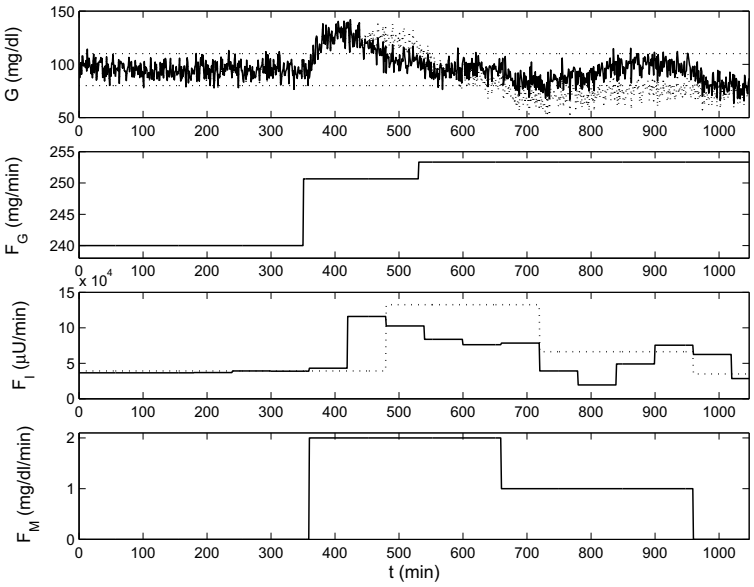


**Figure 7.3:** The evolution of the simulated blood glucose $G$ (top panel) for the one-hour-period (solid line) and the four-hours-period (dotted line) simulations of patient no. 11. The flow of the carbohydrate calories $F_G$ (second panel) is the disturbance factor that is known to the MPC whereas the insulin rate $F_I$ (third panel) is the insulin sequence that is proposed by the one-hour-period MPC (solid line) and the four-hours-period MPC (dotted line). A fictitious medication disturbance factor $F_M$ (that is unknown to the MPC) is visualized in the bottom panel.

It is important to note that the (to the MPC unknown) disturbance factor is introduced at $t = 360$ min whereas the one-hour-period MPC and the four-hours-period MPC are only able to change the insulin rate after observing the disturbed glucose signal (i.e., at $t = 420$ min and $t = 480$ min, respectively). If, however, the unknown disturbance factor would have been introduced earlier (e.g., $t = 240$ min), then the one-hour-period MPC would have changed the insulin flow again one hour later ($t = 300$ min), but the four-hour-period MPC would still have to keep the current insulin flow constant till $t = 480$ min since the insulin flow adaptation frequency is limited to once per four hours. This indicates that the controller performance difference between the one- and four-hours-period MPC would further increase. In general, we can conclude that the performance of a controller will increase if the insulin infusion adaptation frequency is higher. Possible disturbed glucose profiles can be captured more quickly so that, by properly modifying the insulin infusion rate, the reference glycemia value can still be tracked.

2. **Assessment 2: Qualitative analysis**
   Figure 7.4 represents the real-life glucose signal, measured with the GlucoDay system (A. Menarini Diagnostics), of patient no. 4. These real glucose values are delivered to the MPC in order to introduce the notion of feedback. However, we want to stress the infeasibility to compare quantitatively the insulin infusion rates proposed by the MPC with the flows that were delivered to the patient in real-life. The evolution of the real blood glucose when an insulin rate (determined by the MPC) other than the nurse-driven insulin flow would have been administrated, cannot be known. Therefore, this second set of simulations is restricted to a qualitative analysis. It must also be noted that the nurses made use of the blood glucose values that were measured with the ABL machine (for determining the insulin flows) and *not* the GlucoDay system since *retrospective* calibrations of the near-continuous GlucoDay glucose data with the ABL machine were necessary (see also Chapter 2, 2.4.4).

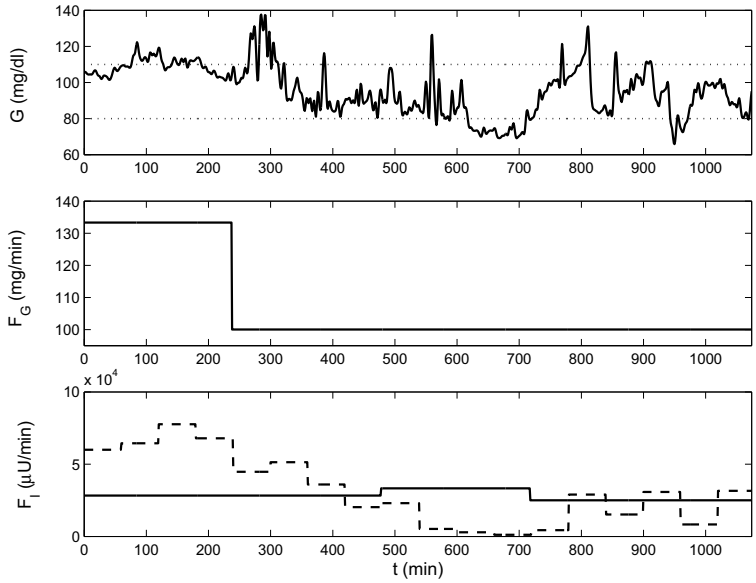


**Figure 7.4:** The evolution of the real glycemia $G$ (top panel), measured with the GlucoDay system (A. Menarini Diagnostics), of patient no. 4 after administration of carbohydrate calories $F_G$ (middle panel) and insulin $F_I$ (bottom panel, solid line). The insulin infusion flow that is proposed by the MPC is presented in the bottom panel (dashed line) and can be qualitatively explained (see text).

During the first three hours, the MPC proposes to infuse a larger insulin rate than was administered in real-life. This increasing rate can be explained by the slight hyperglycemic episode (top panel) and the fact that this insulin rise *seems* to be not sufficient to evolve glycemia to the reference signal (95 mg/dl). It can, however, be assumed that glycemia would have been evolved to the

reference signal if the initial higher insulin flow would have been delivered to the patient instead of the nurse-driven insulin flow. The decrease in administered carbohydrate calories at time $t = 240$ min is known by the MPC in advance such that the proposed insulin flow is pro-actively decreased at that time instant. In reality, however, the nurse did not take into account this decreased calories flow. Because of the slight hyperglycemic event in the initial phase and the decreased nutritional rate (while maintaining a constant insulin flow) glycemia evolved to the normoglycemic range. At time $t = 480$ min the nurse increased the insulin flow leading to a slight hypoglycemic event two hours later. Since the cut-off glycemia value (85 mg/dl) is reached, the initial insulin value is halved (in the MPC optimization problem) leading to a significant reduction of the proposed insulin flow that can be observed at time $t = 540$ min. Next, the nurse decreased the insulin rate (at time $t = 720$ min) leading to increased glycemia values. It is clearly illustrated that the MPC proposes to gradually increase the insulin flow in response to this glucose raising effect. The fluctuating blood glucose profile visualized in the last phase and the designed safety procedure are responsible for the fluctuating insulin infusion sequence that corresponds to these last hours.

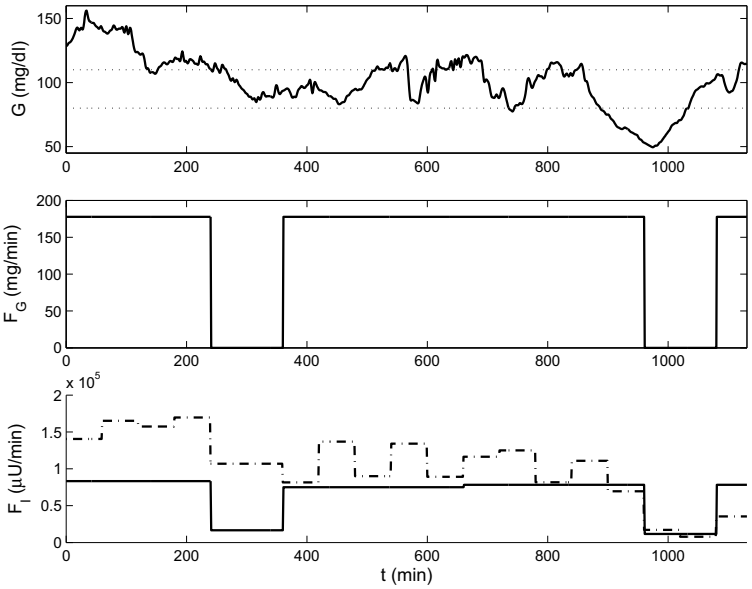


**Figure 7.5:** The evolution of the real glycemia $G$ (top panel), measured with the GlucoDay system (A. Menarini Diagnostics), of patient no. 12 after administration of carbohydrate calories $F_G$ (middle panel) and insulin $F_I$ (bottom panel, solid line). The insulin infusion flow that is proposed by the MPC is presented in the bottom panel (dashed line) and can be qualitatively explained (see text).

Another patient example is illustrated in Figure 7.5 that represents the real-life glucose course of patient no. 12, measured with the GlucoDay system.

During the first three hours the MPC proposes to infuse a larger insulin rate than was administered in real-life. This proposed flow could have led to normoglycemia instead of the hyperglycemic episode that was obtained after administering the (lower) nurse-driven insulin infusion rate. At time $t = 240$ min the flow of carbohydrate calories is decreased to 0 mg/min for 2 hours (because of medical reasons). Since this input is known to the MPC, the proposed insulin infusion is significantly decreased as well. The safety procedure that is introduced to restrict hypoglycemic events is clearly shown in the next phase. Each time that the smoothed glycemia signal reaches the threshold glycemia value (85 mg/dl), the initial value in the optimization process is halved (e.g., at time $t = 480, 600,$ and $780$ min). Since the real glucose signal evolves to the hyperglycemic range in the time period that follows, the insulin rate is again increased each time. At time $t = 900$ and $960$ min the insulin flow is decreased again which can be explained by the active safety procedure (threshold level) and by the compensation for the known decrease of the flow of administered carbohydrate calories.

## 7.5 Conclusions

The first main part of this chapter presented a critical overview of the different control strategies known in the area of diabetes ranging from elementary to more advanced control approaches. The Leuven guidelines are generally accepted as 'gold standard' algorithm for blood glucose control in the ICU but require interpretation of the nurse. Therefore, novel algorithms have been presented in the available literature for automating this insulin infusion process. These algorithms range from basic protocols (or nomograms), elementary computerized protocols to rather more advanced computerized protocols and were briefly presented and discussed in this chapter. Particularly the advanced computerized algorithms can potentially automate the normalization of blood glucose in the critically ill (with reduced input of the nursing team) though the availability of a reliable near-continuous glucose sensor device seems to be an essential element.

The second main part of this chapter introduced the design of a MPC to be used for controlling blood glucose in critically ill patients based on the earlier developed ICU-MM. Simulated glycemia and insulin profiles were quantitatively and qualitatively analysed. The robustness of the MPC approach was shown by estimating states and unknown disturbance factors with an EKF. In general, the MPC performance increased if the insulin infusion rate could be adapted by the control system every hour instead of every four hours. From a qualitative point of view, the developed MPC proposed clinically feasible insulin infusion sequences. When comparing the MPC insulin schemes to the nurse-driven insulin rates that were effectively administered to the patient, some hyperglycemic and hypoglycemic episodes (that were present in the current nurse-driven data sets) might have been avoided. These results are further described in [223, 224].

# Chapter 8

# Conclusions and Future Research

## 8.1 Conclusions

Critically ill patients show hyperglycemia and insulin resistance associated with adverse outcomes. It has been shown that strict blood glucose control (between 80 and 110 mg/dl) results in an important reduction of mortality and morbidity. Preservation of these benefits demonstrated with the *manual* intensive insulin therapy while reducing the prevalence of hypoglycemia and the workload of the nursing teams can lower the barrier of implementing this TGC strategy in hospitals world-wide. The introduction of a blood glucose control system that *semi-* or *fully-automatically* determines and administers the optimal insulin dose to the patient can potentially fill this gap. Further, automated blood glucose control can potentially reduce the patient costs of healthcare resources and the mortality/morbidity rate in ICUs that currently apply the manual intensive insulin therapy.

In this thesis, three different objectives are set:

1. the design of an assessment procedure for glucose sensor devices,
2. the design of an evaluation tool for blood glucose control algorithms used in the ICU,
3. the design of a (semi-)automatic control system for normalizing the blood glucose in the critically ill.

Each of these objectives are successively discussed with respect to the achieved results in this final chapter.

## Conclusions for Objective 1

Chapter 3 of this thesis addresses the problem of evaluating the performance of blood glucose meters and GMS. Existing methods, that approach the data with analytical techniques on the one hand or with clinical techniques on the other hand, show some important weaknesses. The developed GLYCENSIT procedure, founded on statistical analytical tools which are clinically interpretable, comprises three phases. The persistency of the measurement behaviour as a function of the glycemic range is tested in the **first** phase. Persistent measurement behaviour allows the interchange between sensors with only one conversion factor which makes it easy to replace a *gold standard* sensor by a new (cheaper, more user-friendly) sensor device in clinical practice. The **second** phase tests the number of measurement errors with respect to the ISO-criterion. Based on the preferred tolerance level, the sensor device is found to be accurate or not. In the **third** phase, the tolerance intervals (that indicate possible measurement deviations for *new* observations) are computed. These intervals (whose probability level is also calculated) allow to clinically interpret future (predicted) deviations (e.g., are these possible measurement errors acceptable or not).

The GLYCENSIT procedure is a statistical *guideline* for the clinician rather than an overly simple 'yes/no'-analysis. The advantages of the presented procedure can be summarized as follows:

- the procedure is founded on sound statistical theorems such that conclusions (written in clinical reports) may be statistically more reliable,
- a broader view on the data at hand may be obtained due to an analysis from three different perspectives (three phases),
- possible measurement deviations for *new* observations with the sensor device under study are illustrated in the third phase (under the statistical assumptions described in Chapter 3, 3.2.5), indicating this approach is an alternative to the *retrospective* analyses present in existing methods,
- the probability level that is computed in the third phase confronts the user with the number of uploaded paired measurements: a low number of available data corresponds to a low probability of the computed tolerance intervals, but is also an indication that no statistically reliable conclusions can be formulated with the data set at hand,
- the user can express the procedure depending on the application (e.g., what are the features of the target patient group) and the clinical requirements/preferences in terms of the design parameters (i.e., significance level, tolerance level, and hypo- and hyperglycemic cut-off values),
- the proposed GLYCENSIT procedure is implemented as a web-based assessment tool, which is available at http://www.esat.kuleuven.be/GLYCENSIT.

The current version of the GLYCENSIT analysis is based on the assumption that measurement errors are sufficiently statistically independent meaning that no correlation exists between successive errors. When 'test' and 'reference' sensor values are

concomitantly measured with a minimum one-hour time interval, this assumption can be met. In case of near-continuous 'test' sensors, the temporal dynamics inherent to a frequently sampled time series are not considered in the analysis as no *gold standard* trend information is available at present [38, 94, 99, 109, 162, 194, 209, 211]. Three hypothetical data sets and a real-life clinical (ICU) example are introduced to illustrate the GLYCENSIT analysis. Furthermore, two point-of-care sensor devices are validated in a real-life ICU setting by using the EGA, the Bland-Altman, and the GLYCENSIT approach. The GLYCENSIT procedure is proposed to be an *alternative for* or a *supplemental tool to* existing evaluation techniques.

## Conclusions for Objective 2

Chapter 4 of this thesis addresses the problem of measuring the *overall* glycemic control behaviour. The GPI as a tool to compare different blood glucose control algorithms is presented. This proposed measure is the average of the penalties that are assigned to all monitored glucose values. The method is founded on a staircase penalty function showing the 'expert' clinical (ICU) knowledge. The designed formula returns a number between 0 and 100 with an 'ideal' level of 0 (indicating that all measured blood glucose values fall within the normoglycemic target range) and a 'clinically acceptable' cut-off level of 23. The advantages of the proposed method can be summarized as follows:

- the GPI expresses the *overall* blood glucose dynamics in an absolute (positive) value such that hypoglycemic and hyperglycemic episodes cannot balance each other,
- only the glucose readings that were effectively monitored are used in the GPI evaluation tool (no assumed, e.g., linear, relation between measurements),
- measurement errors caused by sensor inaccuracies and methodology inaccuracies due to sampling handling have only little influence on GPI as the 'expert' function is smoothed and a maximum penalty value is assigned to outlier measurements,
- the relative contributions of the hypo- and hyperglycemic events to GPI clarify whether particularly low blood glucose episodes, high blood glucose episodes, or both are responsible for the obtained GPI.

Assessments of blood glucose profiles using GPI, founded on clinical expertise, can be different from traditional evaluation methods like the average *morning* blood glucose and the average blood glucose. The use of (accurate and reliable) near-continuous glucose sensors allows to take into account the duration of hyperglycemic and hypoglycemic episodes in the computation of GPI (since a penalty is assigned to each monitored glucose value). Thus, the performance of GPI will further improve when these devices are made available. Finally, the *average blood glucose sampling frequency* and the *duration of algorithm application* are parameters that should be similar among patient groups when comparing the performance of different insulin titration algorithms. The GPI is proposed to be a supplemental tool to other advanced

measures (like HGI) besides more traditional measures (like the average *morning* blood glucose and the average blood glucose) for adequately assessing the overall level of blood glucose control.

## Conclusions for Objective 3

The design of a glycemia control system is addressed in Chapters 5-7. Firstly, a black-box modelling approach, that relates the varying insulin resistance to the measured body temperature, is applied in Chapter 5. The forecasting ability of the optimized adaptive modelling method allows to accurately predict the blood glucose profile from one to four hours ahead. It is recommended to frequently (every hour) re-estimate the model using the data of the patient under treatment (leading to a patient-specific adaptive model) instead of only estimating an initial model based on a previously recorded data set (originating from other patients). Although the forecasting ability of this modelling approach is satisfactory, some important reservations need to be made concerning the validity of the modelling approach for use in a predictive control system in clinical real-life. The closed-loop feature of the data at hand has an impact on both the design of the model structure and the estimation of the parameters leading to underestimation of the importance of the input (insulin) variable. Eventual use of the considered black-box modelling approach in a clinical real-life predictive control system would lead to the administration of clinically unrealistically high insulin flows and should be avoided, accordingly.

Since the black-box modelling approach is found not to be appropriate for use in a predictive control system, the glucoregulatory system of critically ill patients is further described by following the grey-box modelling approach (Chapter 6). This modelling concept has the advantage that the developed model structure (the ICU-MM) is founded on physical insight of the system under study, which explains why the closed-loop feature of the data only has impact on the parameter estimation. The ICU-MM is estimated using the data of the first day (after admission to the ICU) of the patient under treatment and its clinical interpretability is shown. Next, an adaptive modelling procedure (with re-estimations every four hours or preferably every hour using the data corresponding to the last five hours, BIT $= 5$ hours, of each specific patient) is presented to incorporate inter- and intra-patient variability. This procedure gives satisfactory forecasting results and indicates the potential use of the presented model structure in a (semi-)automatic control system to normalize blood glucose in the (surgical) ICU.

Chapter 7 of this thesis addresses the design of an MPC controller based on the earlier developed ICU-MM. A simulation study shows the robustness of the MPC by estimating states and unknown disturbance factors with an EKF. The ability to frequently (every four hours or preferably every hour) adapt the insulin rate allows to strictly (GPI was lower than the 'clinically acceptable' cut-off GPI of 23) regulate blood glucose towards the normoglycemic target range (80-110 mg/dl) in spite of the presence of disturbance factors (measurement errors and administration of medication) which are unknown to the MPC. Further, a qualitative analysis of the insulin infusion rates

(proposed by the MPC) that correspond to the observed glucose profiles (controlled by the nurses) illustrate that some hyperglycemic and hypoglycemic episodes might have been avoided.

## 8.2 Future research

The commercial availability of accurate and reliable near-continuous glucose sensor devices can dramatically change the treatment of patients with diabetes and critically ill patients in the (near) future. These devices may behave as the *key* for fully-automated blood glucose control, more than the control systems themselves. Further, the implementation of a PDMS system in an ICU-setting (as was recently introduced in the University Hospital K.U.Leuven) allows to automatically record all types of medical information per patient in electronic files. Accordingly, a mass of dynamic data of the critically ill can be made available creating opportunities for analyses.

Several potentially interesting future research topics can be identified in five different areas. Each of them are briefly discussed.

### Assessment of near-continuous glucose sensors

Accurate and reliable near-continuous glucose sensor devices are currently not available, but are undoubtedly under development [38, 94, 99, 109, 162, 194, 209, 211]. The presented GLYCENSIT analysis (Chapter 3) is developed to assess the reliability of both 'discrete-time' and 'near-continuous' glucose sensor devices with regard to a *gold standard* blood glucose sensor. It must be pointed out that trend information, which is available in near-continuous glucose signals, is not used in the current assessment procedure since the data are transformed to sets of paired glucose measurements. The quality requirements for the individual measurement value obtained with a near-continuous glucose sensor, however, probably can be lower than that for a discrete glucose meter. Unfortunately, *gold standard* trend information is currently missing. Therefore, it is more suitable to consider only the paired glucose measurements in the current version of the GLYCENSIT procedure (even in case of near-continuous test devices), assuming that the pre-processing phase (see Chapter 3, 3.2.1) is properly performed, instead of using trend information that is generated from the (possibly unreliable) *test* sensor device itself. While awaiting the availability of accurate and reliable near-continuous *reference* glucose sensors, future research can already be focused on the implementation of the **temporal dynamics** (which are inherent to a frequently sampled time series) in a new version of the GLYCENSIT procedure.

### Relation between GPI and clinical outcome

Although the design of GPI is founded on currently available clinical expertise, the relation between GPI and **clinical outcome** has not been shown yet. At present, particularly the relation between improved clinical outcome on the one hand and reduced average *morning* blood glucose [213, 216] and reduced HGI [233] on the other

hand have been depicted. From a clinical 'expert' point of view and from the found high correlation between GPI and HGI (see Chapter 4, 4.4.2), it is expected that low GPIs can be related to reduced mortality and morbidity as well, but future studies are necessary to verify this. The (future) availability of a mass of dynamic glucose data allows to find associations between GPI and clinical outcome with sufficient statistical evidence.

## Modelling of glycemia

Thirdly, more efficient models that describe the glucoregulatory system of critically ill patients can be developed. Four topics can be investigated here:

- The **dynamic behaviour** of the blood glucose can be recorded more accurately by using (future) reliable near-continuous glucose sensors. These sensor devices can even be implanted in burn-injured, fed *rabbits* for the purpose of performing *open-loop* tests. Accordingly, the effect of administered calories, medication, and other disturbance factors on the glucose profile can be better defined and possible time delays can be detected. This information can be considered as prior knowledge when extrapolating this 'critically-ill-rabbits-information' to models describing the glucose dynamics of critically ill 'patients' possibly leading to inclusion of additional disturbance factors (e.g., medication) in the ICU-MM.

- The use of accurate and reliable near-continuous glucose signals further allows to develop an improved algorithm for updating (**adapting**) the model coefficients or a selection of these coefficients. Statistical tests (e.g., $t$-tests) can be used to guarantee an improvement of the prediction performance of the model compared to the previous model.

- Next, the introduction of the PDMS system allows to **classify** the patients in distinct 'clusters' or 'classes' depending on the patient profile (which can comprise one or more of the following static upon admission demographics: BMI, prior history of diabetes, reason for ICU admission, etc.) and some on-admission dynamic parameters (like on-admission glycemia, on-admission caloric intake, on-admission concomitant medication, on-admission APACHE II score, etc.). Then, each cluster can be associated with its own parameter settings for the initial model such that a new patient entering the ICU can be classified in one of the clusters. Accordingly, the glycemia control system can be able to normalize the blood glucose (based on the selected initial model) immediately after admission (and not after 24 hours as presented in this dissertation) and this initial model can be updated using the incoming closed-loop measurements.

- Finally, the forecasting ability of the presented models in this work is only shown with the data of surgical ICU patients. It is required to investigate whether the same (adaptive) modelling approach is sufficiently efficient for predicting the blood glucose profile of **medical** ICU patients.

## Control of glycemia

A fourth research area can be found in improving the design of the proposed MPC:

- The controller (MPC) described in this dissertation makes use of an EKF to estimate states and unknown disturbance factors. The use of a **Moving Horizon Estimator (MHE)**, however, allows to estimate states and parameters using a moving and fixed-size window of data. When a new measurement becomes available, the oldest measurement is discarded and the new measurement is added. The philosophy is to penalize deviations between measurement data and predicted outputs. Two important characteristics distinguish MHE from other estimation strategies, such as the EKF. First of all, prior information in the form of constraints on the states, disturbances and parameters can be included. Secondly, since MHE is optimization based it is able to handle explicitly non-linear system dynamics through the use of approximative non-linear optimization algorithms. In [88], it was shown that MHE possesses superior estimation properties compared to the EKF. The potential of the MHE approach in this ICU application has recently been presented in [89].

- **Recognition of glucose sensor failings** can further improve the performance of the glycemia controller. Therefore, the introduction of the tolerance intervals (that indicate possible measurement deviations for *new* observations with a sensor device), presented in phase 3 of the GLYCENSIT analysis (see Chapter 3, 3.2.5), can be used to establish more adequate insulin infusion dosages.

- In view of a future clinical validation phase, it is recommended to investigate the **robustness** of the developed control system. A trade-off between model prediction performance on the one hand and model complexity on the other hand should always be considered. The controller can be tested in simulations where the MPC uses the ICU-MM for predicting the glucose profile and where the real patient behaviour is represented by a more complex 'critically ill patient model' (e.g., the model used in the MPC strategy presented in [97]). Unfortunately, to the best of the author's knowledge, no 'critically ill patient models', other than the ICU-MM, that can be used in a predictive control setting have been described in the available literature so far.

## Clinical validation of a glycemia control system

A last research area is the clinical validation of the developed control system. This validation issue can comprise three phases:

- In a first phase, the semi- or fully-closed-loop control system can be tested on a group of critically ill **rabbits**. The MPC approach used in this phase should consider an appropriate 'critically ill *rabbit* model'. Therefore, the ICU-MM could be adapted based on the open-loop measurements that are described above.

- The second phase is necessary to test a **semi-closed-loop** control system on a group of critically ill patients. Here, the computerized control system only

gives *advice* concerning the insulin infusion rate that should be administered to the patient. Only after confirmation by the nurse (as a safety procedure), the proposed insulin dose should be delivered to the patient.

- In a last phase, the **fully-closed-loop** control system should be tested on a *larger* critically ill patient group. The availability of an accurate and reliable sensor to near-continuously measure the glucose profile is a prerequisite for performing these tests, however. Clinical validation of such a fully-closed-loop glycemia control system, in combination with a reliable near-continuous glucose sensor, may open the door for the commercial exploitation of this medical device.

# Appendix

# Appendix A

# Overview of the prediction performance of the ICU-MM

## A.1 Introduction

This appendix summarizes the main results of the re-estimation process of the ICU-MM that is applied to 19 patients admitted to the surgical ICU (see data set described in Chapter 2, 2.4.4). Re-estimations take place every four hours ($P = 4$ hours) or every hour ($P = 1$ hour). The number of recent data considered in each re-estimation process (BIT) is varied from 0.5 hours to 20 hours. Next, two different penalizing strategies are used in the cost function: the minimization of MSE and the minimization of MSnE. Finally, the prediction performance of the modelling strategy under study is evaluated by computing the MSE, the MPE, and the MSnE. The full study approach is described in detail in Chapter 6 (see 6.3.3).

## A.2 Evaluation by MSE

In this section the results that are obtained with the MSE as *evaluation method* are presented. When the minimization of MSE is used as *cost function*, the smallest distribution of MSEs is obtained when the re-estimations are based on the last five hours (BIT $= 5$ hours), independent of the re-estimation frequency ($P = 4$ hours or $P = 1$ hour). Significant differences (Wilcoxon signed rank test, $p < 0.05$) with regard to other selected BITs are marked with asterisks in Figure A.1. When MSnE is considered in the *cost function*, the 'optimal' BIT is found to be four hours (for $P = 4$ hours) and five hours (for $P = 1$ hour) as illustrated in Figure A.2.

## A.3 Evaluation by MPE

This section presents the results when the model performance is *evaluated* by computing the MPE. The most optimal distribution of the MPEs is again obtained

with re-estimations based on the last 5-hours data set (BIT $= 5$ hours), independent of the re-estimation frequency, for MSE as *cost function*. In case of selecting MSnE to be minimized in the *cost function*, the re-estimations are preferably based on the data that correspond to the last four hours (BIT $= 4$ hours, independent of the re-estimation frequency). The distributions of the MPEs are illustrated in Figure A.3 for the first cost function and in Figure A.4 for the latter.

## A.4 Evaluation by MSnE

The use of MSnE as *evaluation tool* has the advantage that model prediction errors are made independent of glycemia. Accordingly, hypoglycemic, normoglycemic, and hyperglycemic deviations are equally penalized with regard to the clinically defined ISO-criterion [75]. The smallest MSnEs (for the minimization of MSE in the *cost function*) are obtained when the re-estimations are based on the data that correspond to the last five hours (BIT $= 5$ hours, independent of the re-estimation frequency) (see Figure A.5). Alternatively, when the MSnE is minimized in the *cost function*, the 'optimal' BIT is found to be four hours (for $P = 4$ hours) or five hours (for $P = 1$ hour) (see Figure A.6).

## A.5 Conclusion

Table 6.2 (see Chapter 6) presented a summary of the 'optimal' BIT values depending on the re-estimation frequency, the penalizing strategy, and the evaluation method based on the figures illustrated above. In general, the model prediction performance was satisfactory if the data that corresponded to the last four to five hours were taken into account in each re-estimation process. It was clinically reasonable to associate this time period with the time span in which glucose dynamics vary (e.g., due to changing insulin resistance). As the use of the MSnE was based on clinical expertise (i.e., the ISO-criterion [75]), it was preferred to consider the minimization of MSnE in the cost function of the estimation processes. For the same reason it was recommended to use MSnE as evaluation tool although the use of MPE was advantageous in terms of simply interpreting the results. This is further described in detail in Chapter 6.

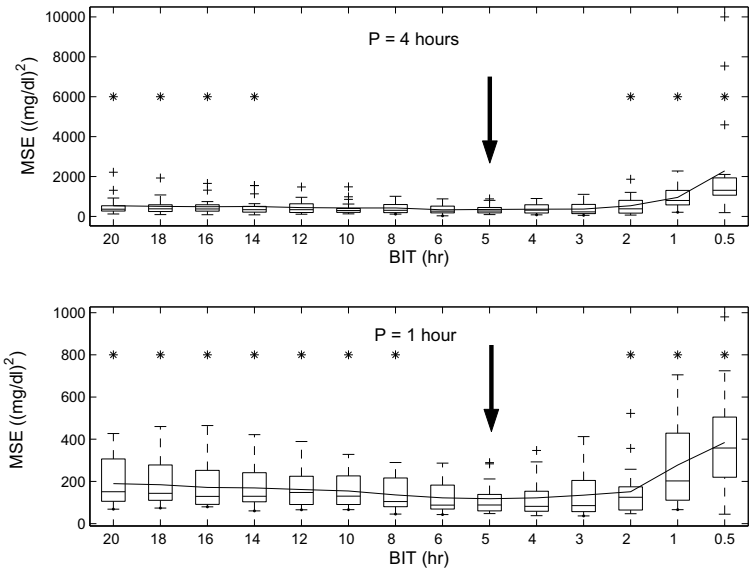


**Figure A.1:** Distribution of the MSEs (generated for each patient) as a function of BIT with re-estimations every 4 hours (top) or every hour (bottom). The *minimization of MSE* is the selected penalizing strategy. The line connects the averages of the MSEs. Re-estimations based on the last 5-hours data set (BIT $= 5$ hours) result in the smallest prediction errors. Significant differences ($p < 0.05$) with respect to the 'optimal' (here: BIT $= 5$ hours) setting are marked by asterisks.

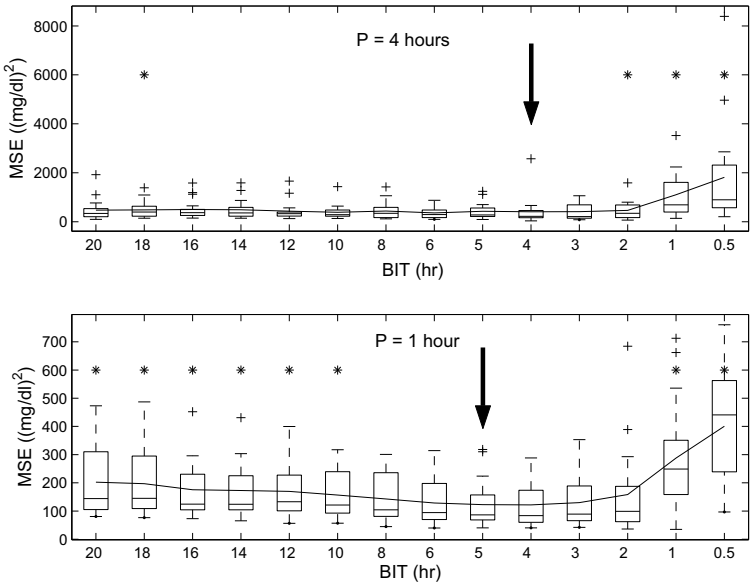


**Figure A.2:** Distribution of the MSEs as a function of BIT with re-estimations every 4 hours (top) or every hour (bottom). The *minimization of MSnE* is the selected penalizing strategy. The line connects the averages of the MSEs. Re-estimations based on the last 4-hours data set (for $P = 4$ hours) or the last 5-hours data set (for $P = 1$ hour) result in the smallest prediction errors. Significant differences ($p < 0.05$) with respect to the 'optimal' BIT setting are marked by asterisks.

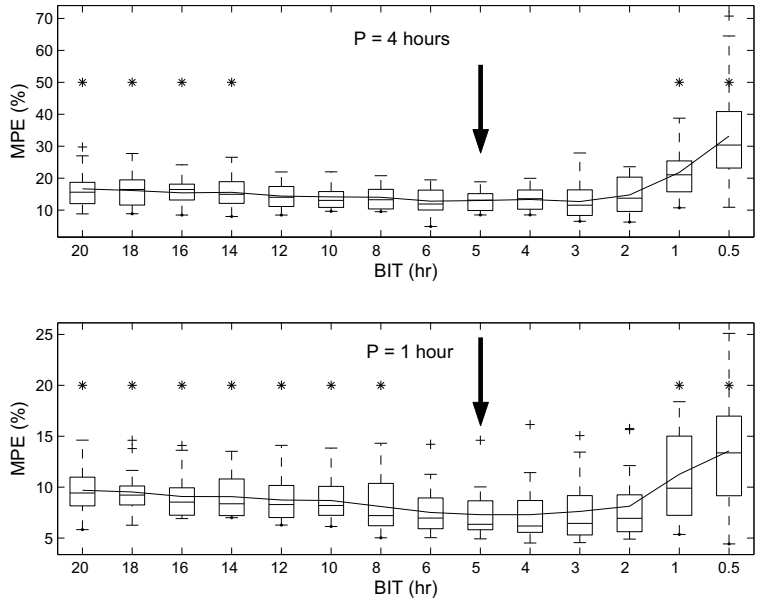


**Figure A.3:** Distribution of the MPEs as a function of BIT with re-estimations every 4 hours (top) or every hour (bottom). The *minimization of MSE* is the selected penalizing strategy. The line connects the averages of the MPEs. Re-estimations based on the last 5-hours data set (BIT $= 5$ hours) result in the smallest prediction errors. Significant differences ($p < 0.05$) with respect to the BIT $= 5$ hours setting are marked by asterisks.

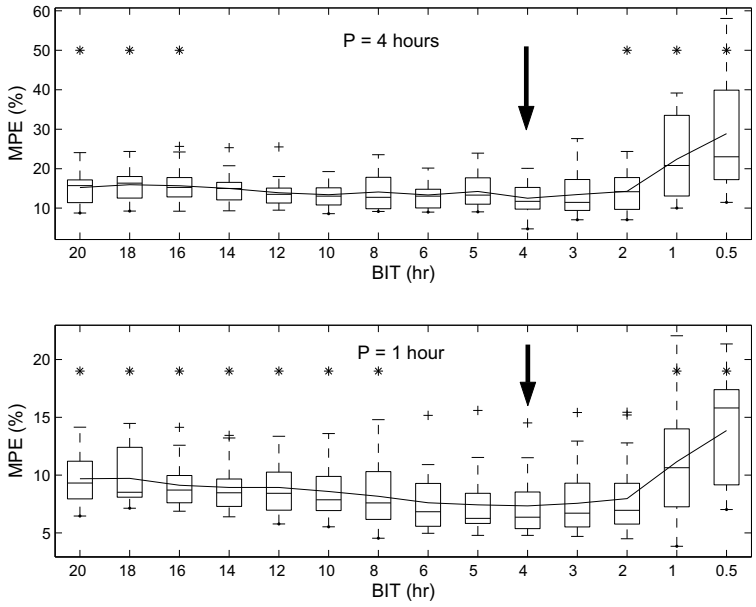


**Figure A.4:** Distribution of the MPEs as a function of BIT with re-estimations every 4 hours (top) or every hour (bottom). The *minimization of MSnE* is the selected penalizing strategy. The line connects the averages of the MPEs. Re-estimations based on the last 4-hours data set (BIT $= 4$ hours) result in the smallest prediction errors. Significant differences ($p < 0.05$) with respect to the BIT $= 4$ hours setting are marked by asterisks.

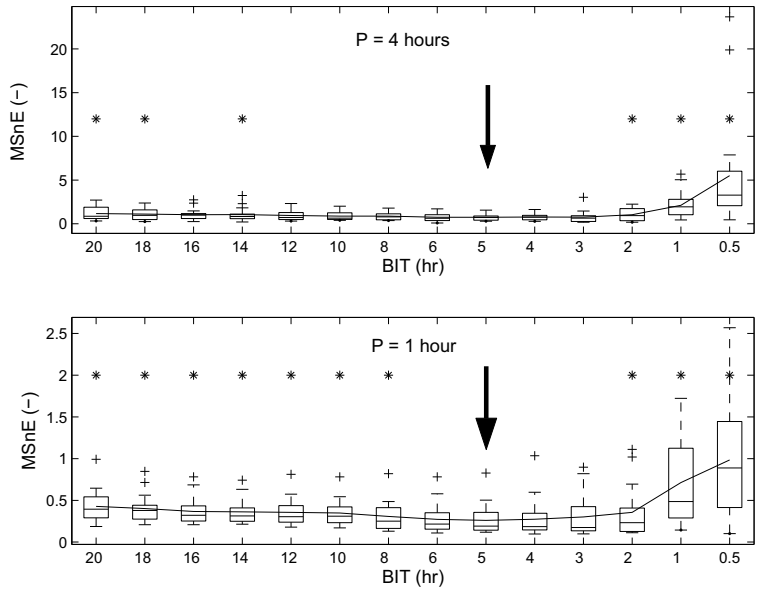


**Figure A.5:** Distribution of the MSnEs as a function of BIT with re-estimations every 4 hours (top) or every hour (bottom). The *minimization of MSE* is the selected penalizing strategy. The line connects the averages of the MSnEs. Re-estimations based on the last 5-hours data set (BIT $= 5$ hours) result in the smallest prediction errors. Significant differences ($p < 0.05$) with respect to the BIT $= 5$ hours setting are marked by asterisks.

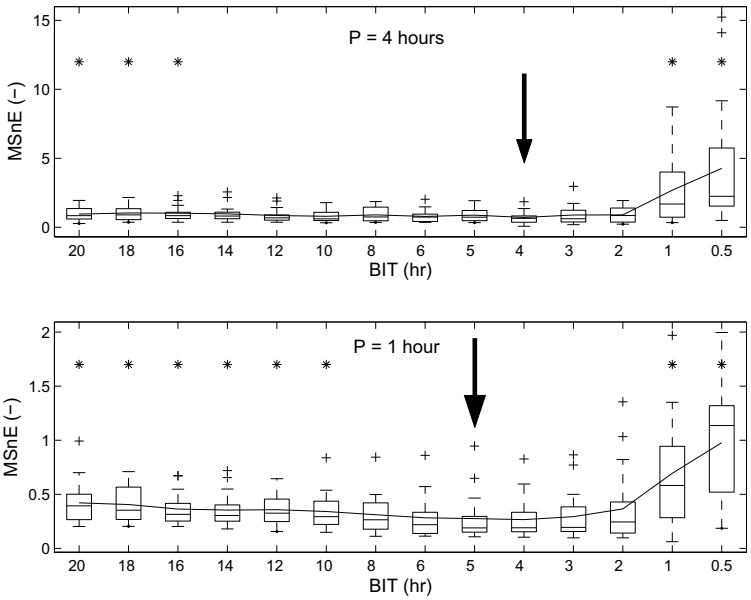


**Figure A.6:** Distribution of the MSnEs as a function of BIT with re-estimations every 4 hours (top) or every hour (bottom). The *minimization of MSnE* is the selected penalizing strategy. The line connects the averages of the MSnEs. Re-estimations based on the last 4-hours data set (for $P = 4$ hours) or the last 5-hours data set (for $P = 1$ hour) result in the smallest prediction errors. Significant differences ($p < 0.05$) with respect to the 'optimal' BIT setting are marked by asterisks.

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# Curriculum Vitae

Tom Van Herpe was born in Turnhout, Belgium, on November 30, 1979. He graduated from the Sint-Jozefcollege (Turnhout), with majors in science and mathematics, in June of 1997. Next, he graduated with a M.Sc. in Chemical Engineering (Process Technology) at the Hogeschool voor Wetenschap en Kunst - De Nayer, St-Katelijne Waver, Belgium, in July 2001. The subject of his master's thesis was "Onderzoek naar gebruik van metalen filtermaterialen in Nutsche filters" ("Research to the use of metal filter material in Nutsche filters") which he realized in Janssen Pharmaceutica (Johnson & Johnson). Next, he graduated with a master's degree in Industrial Management from the Katholieke Universiteit Leuven, Belgium, in July 2002. His master's thesis was entitled "The organisation of working with third parties" (in cooperation with IMEC). He finally graduated with a master's degree in Biomedical Engineering Techniques at the same university in July 2003. The subject of that master's thesis was "Invloed van ademhaling op cardiovasculaire variabiliteit" ("Influence of respiration on cardiovascular variability").
In October 2003 he started a Ph.D. at the SCD-SISTA research group at the Electrical Engineering Department of the Katholieke Universiteit Leuven; in close cooperation with the Intensive Care Unit of the same university, under the supervision of Prof. Bart De Moor and Prof. Greet Van den Berghe. In 2005, he won the Diabetes Technology Peterson Student Research Bronze Prize during the Fifth Annual Diabetes Technology Meeting in San Francisco.

# Publications by the author

## International Journal papers

- **T. Van Herpe**, M. Espinoza, B. Pluymers, I. Goethals, P. Wouters, G. Van den Berghe, and B. De Moor. An adaptive input-output modeling approach for predicting the glycemia of critically ill patients. *Physiol. Meas.*, 27(11):1057–1069, 2006.

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