Solving Model Discrimination Problems by OED: Applications in Enzyme Stability

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Introduction: Enzyme stability

Enzyme deactivation

Wanted: description of biochemical reaction $S \xrightarrow{r_{\mathrm{E}}} P$

Required: model of deactivation reactions of enzyme E

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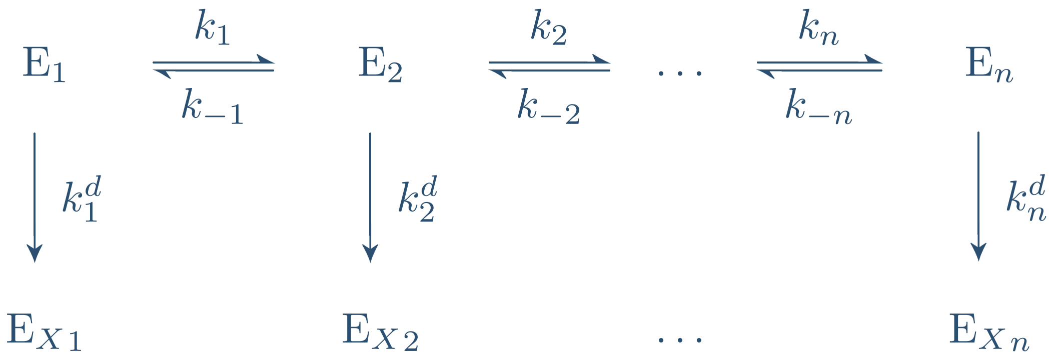
- Many possibilities [Sad91]:



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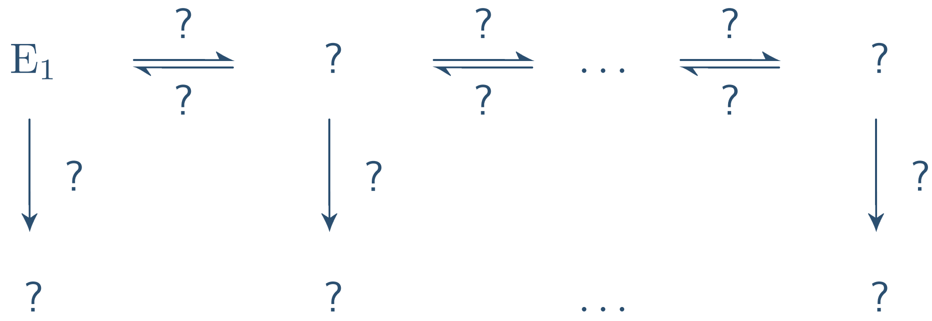

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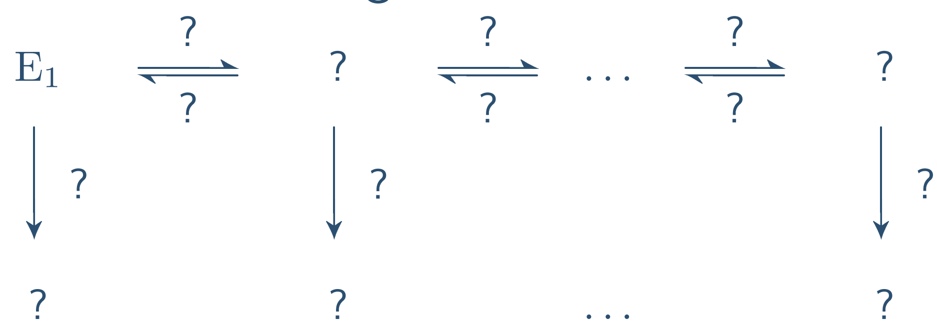
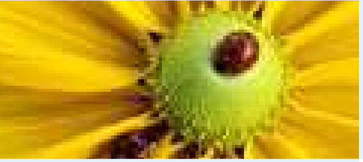


- Limited experimental methods:
  even hard to detect unknown proteins ("?") qualitatively!



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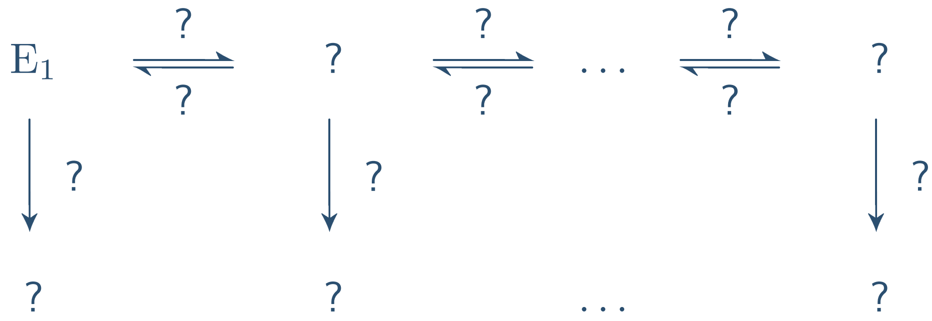

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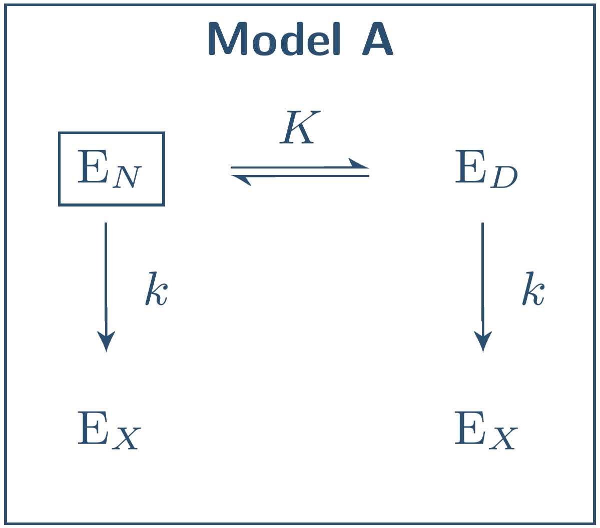
➨ **Formulate several rival model propositions.**
(examples from M.Boy, BASF AG [BDV99])

Proposed rival deactivation models



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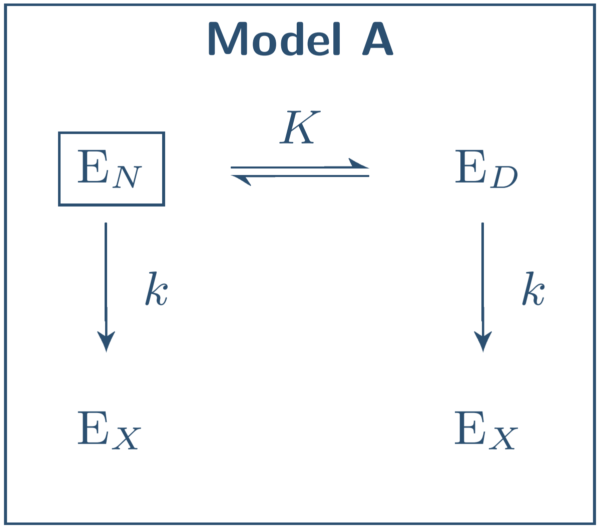

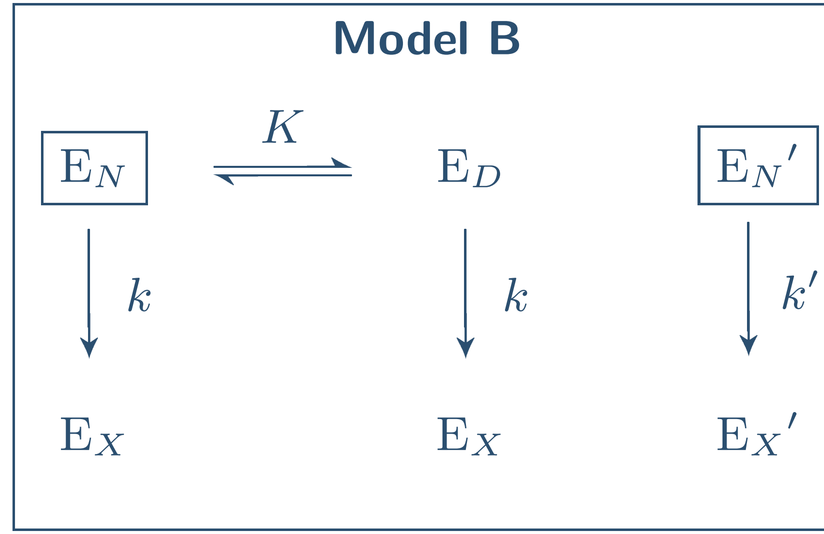

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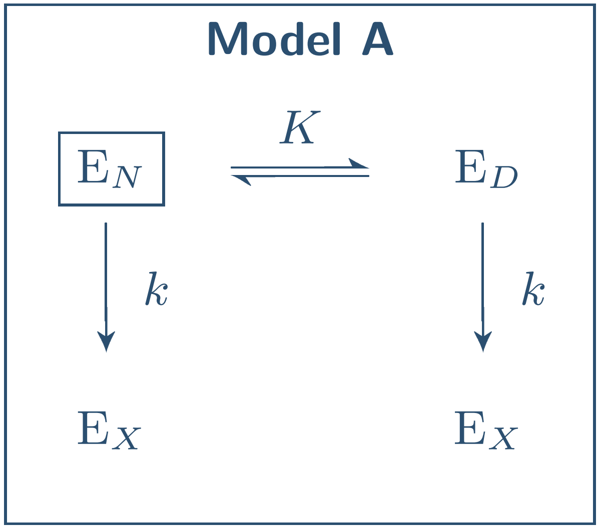

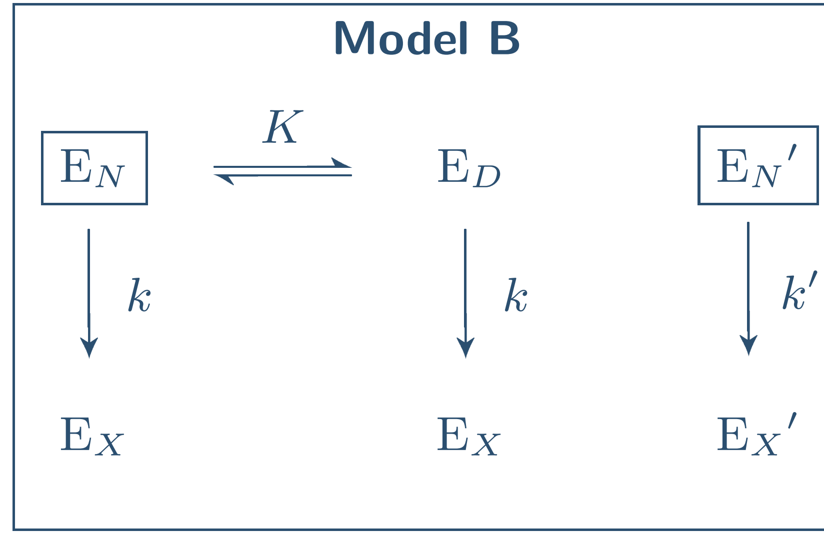

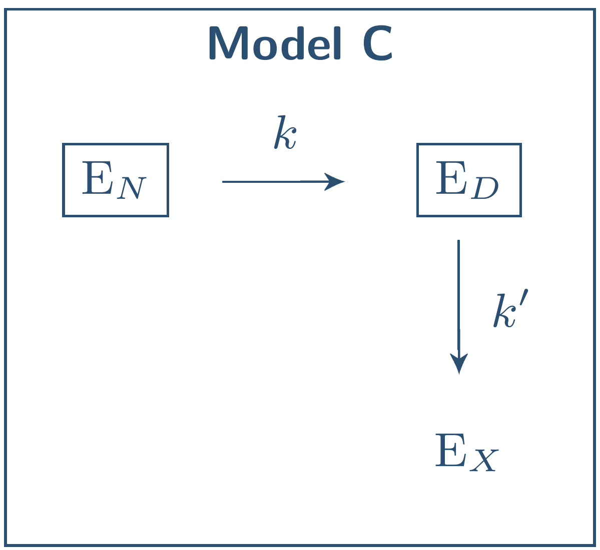

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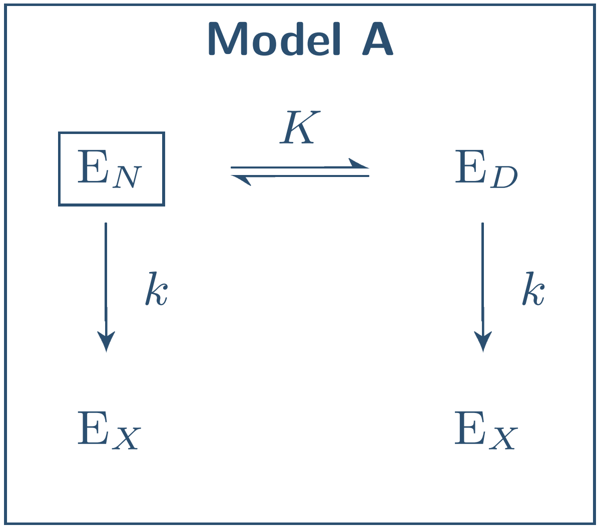
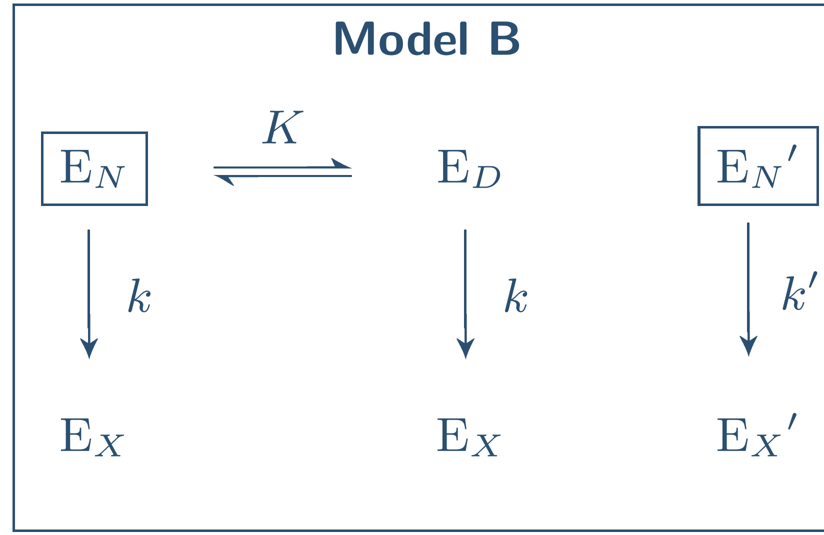
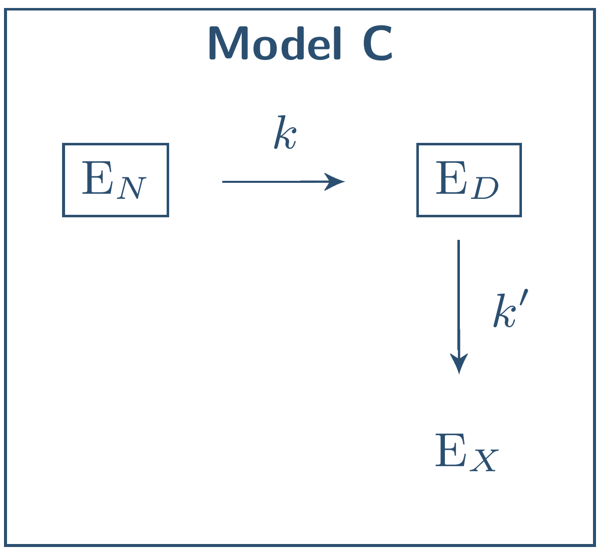






and $\mathrm{S} + \boxed{\mathrm{E}_{(\cdot)}} \xrightarrow{r_{\mathrm{E}}} \mathrm{P} + \boxed{\mathrm{E}_{(\cdot)}}$

Unknown parameters:

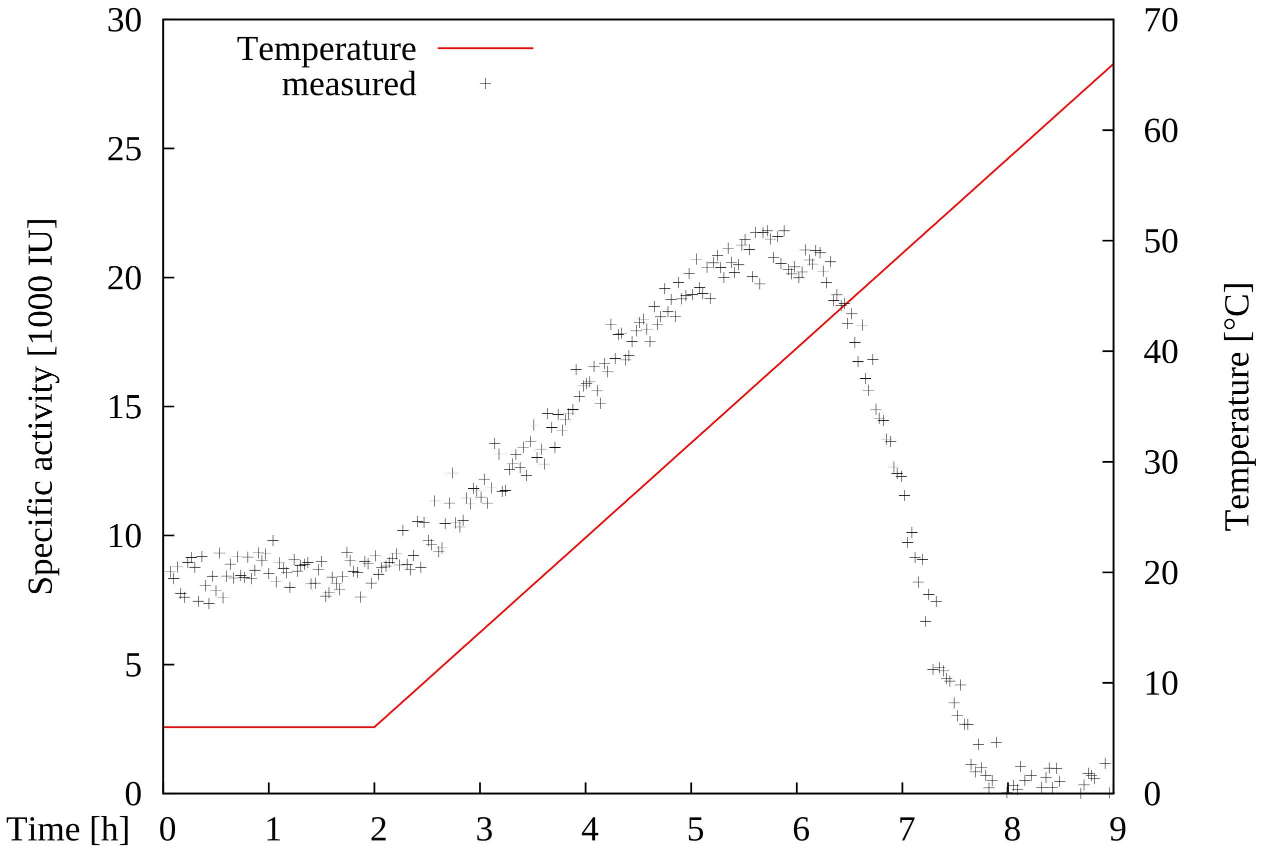
- equilibrium constants
- frequency factors
- activation energies

Only measureable: specific activity

$$a(t) := r_{\mathrm{E}}(t)/m_{\mathrm{E},0}$$

Resulting model discrimination problem

Measurements from experiment 1



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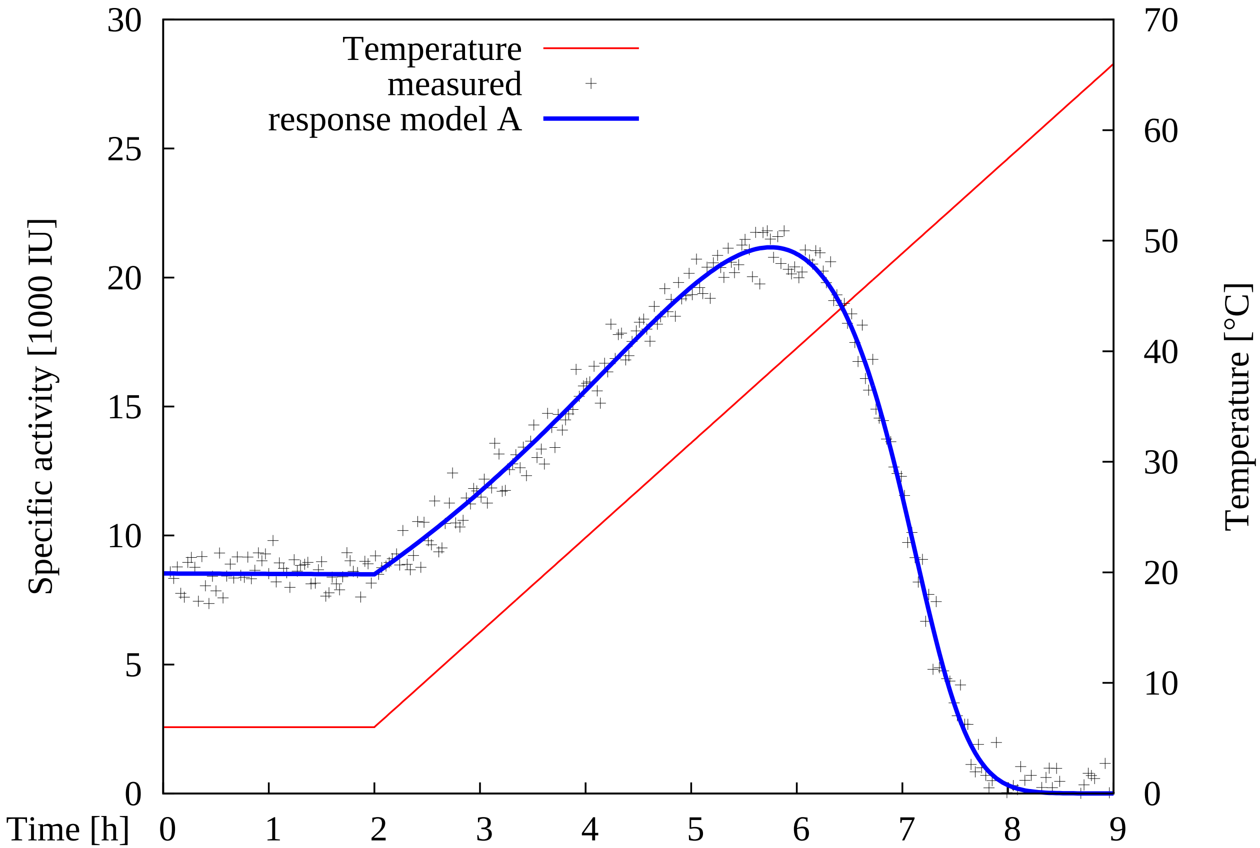

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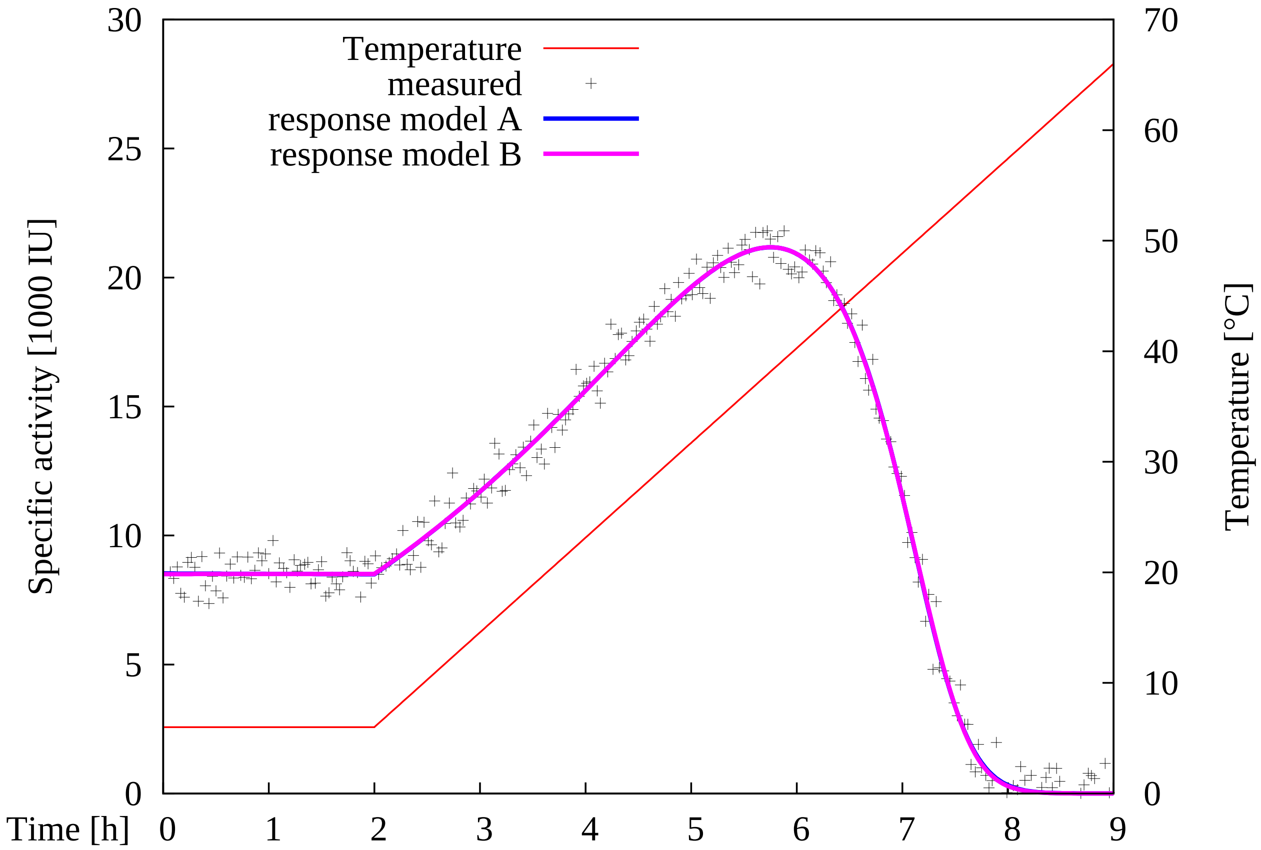

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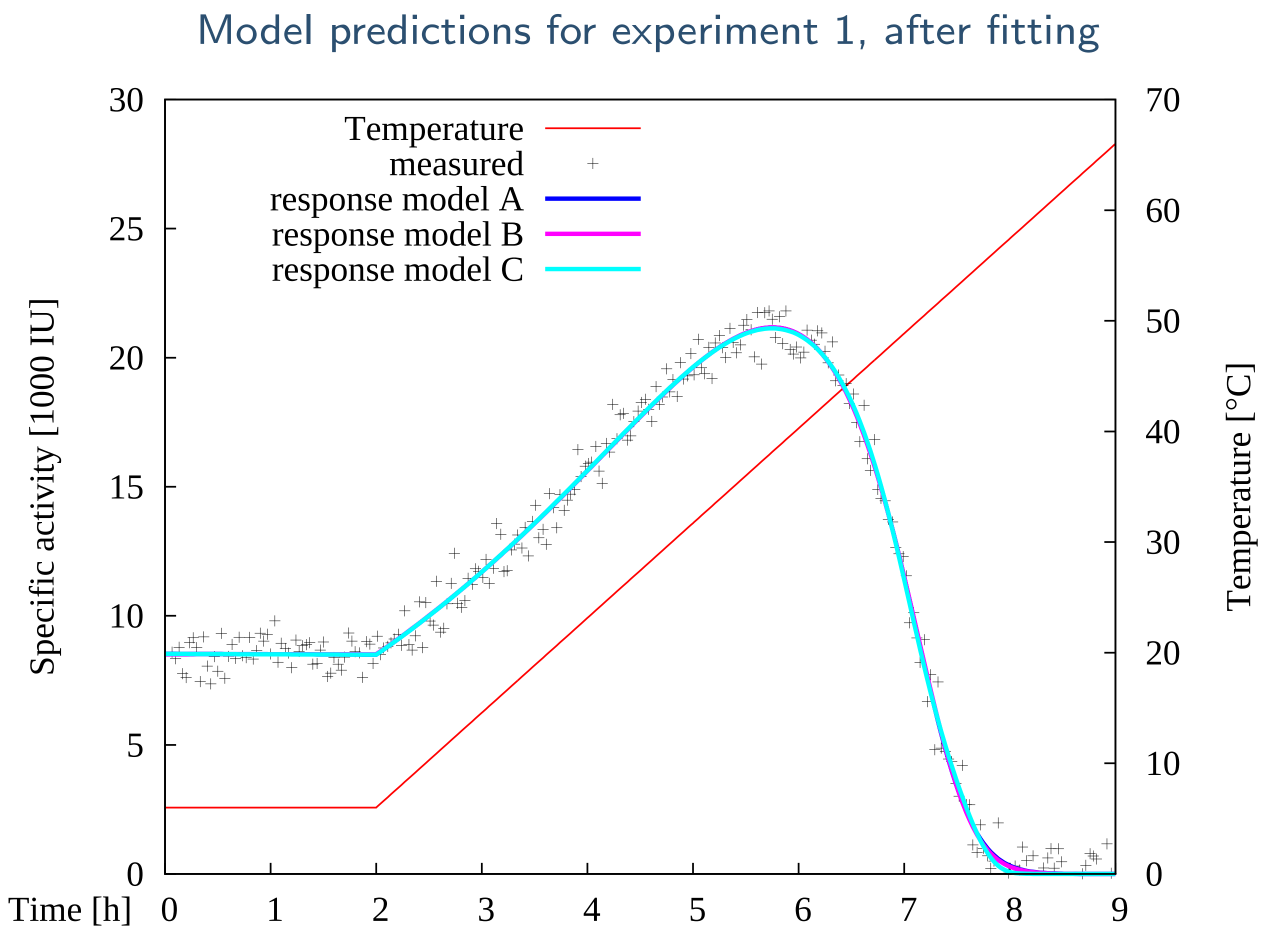

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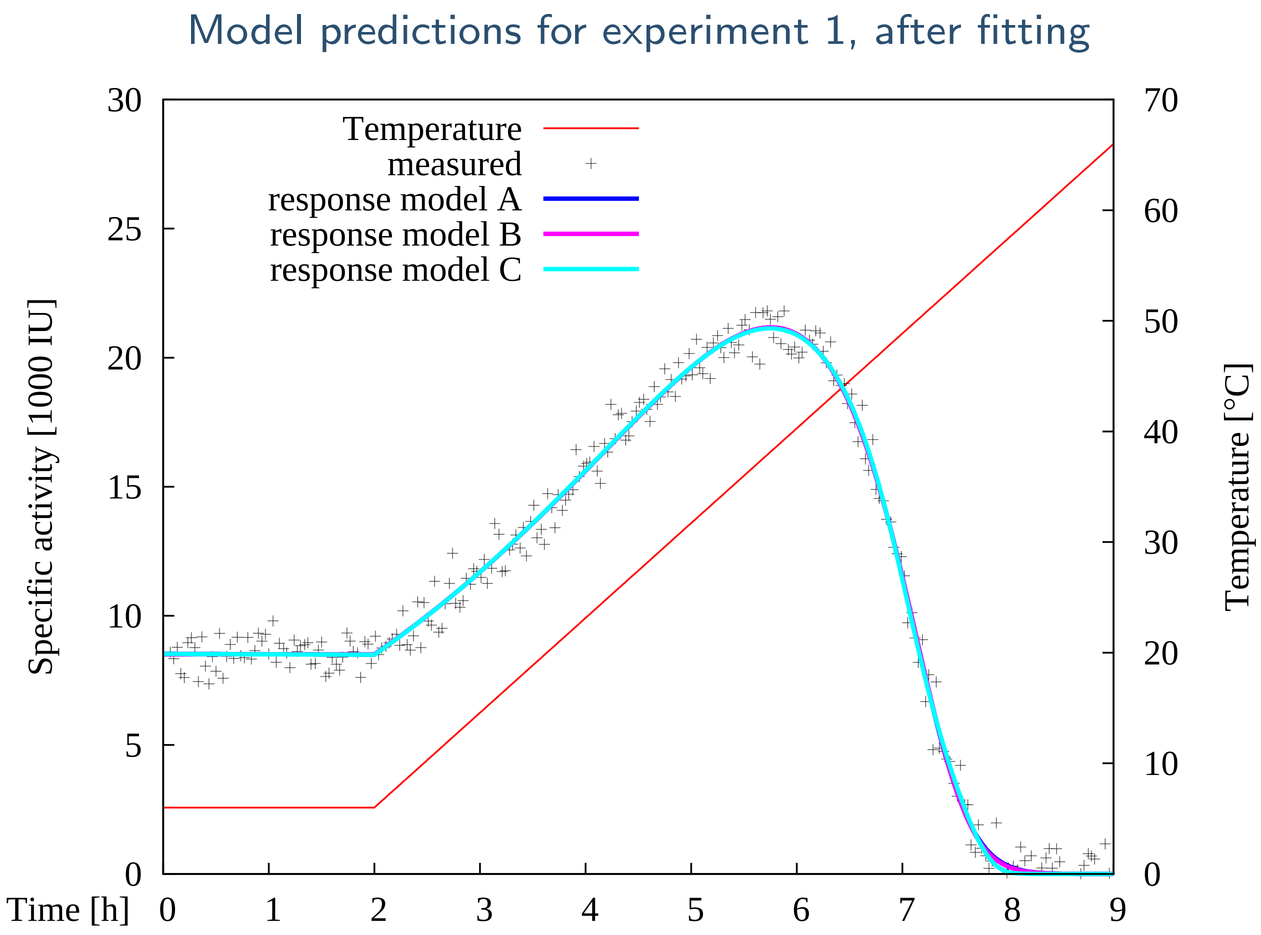
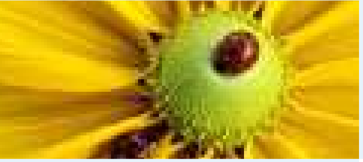


➨ **Models describe data with comparable precision!**

Model discrimination (MD)

One process – several models propositions
Choose which?



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Special challenges in systems biology:

- Little initial knowledge
- Limited experimental methods
- Complex systems, high-dimensional models
- Large number of rival models

Optimal experimental design for model discrimination

When is a model “correct”?

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Experiment described by *design quantities* $\boldsymbol{q}$. Provides measurement data:

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Parameterized nonlinear regression models $i = 0, \ldots, \mathrm{N}$:

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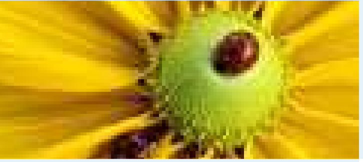
Model i describes the process “correctly”, if

1. the model responses are precise

$$\exists \bar{\boldsymbol{p}}^i : \left\| \bar{\boldsymbol{\eta}}_{\boldsymbol{q}} - \boldsymbol{h}^i \left[\boldsymbol{q}, \bar{\boldsymbol{p}}^i\right] \right\| \leq \delta, \; \forall \boldsymbol{q} \in \mathcal{Q}$$



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2. *and* the error model is adequate ($\delta = 0$ for convenience)

(DC) $$\mathbb{E} \left\|\boldsymbol{r}\right\|_2^2 := \mathbb{E} \left\| \boldsymbol{\eta_q} - \boldsymbol{h}^i \left[\boldsymbol{q}, \bar{\boldsymbol{p}}^i\right] \right\|_2^2 = \boldsymbol{s}, \; \forall \boldsymbol{q} \in \mathcal{Q}$$

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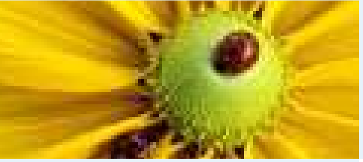
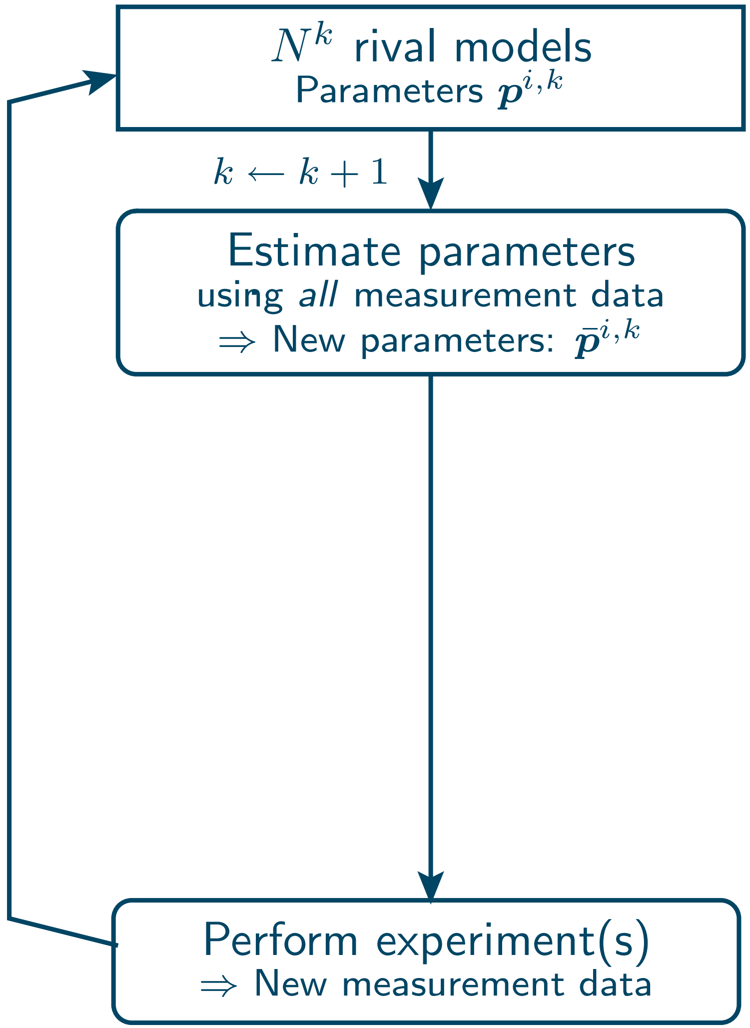
Discrimination criterion (DC) can be used to **falsify** models:
Take samples, perform adequate statistical tests (F-tests and relatives)



Sequential discrimination procedure



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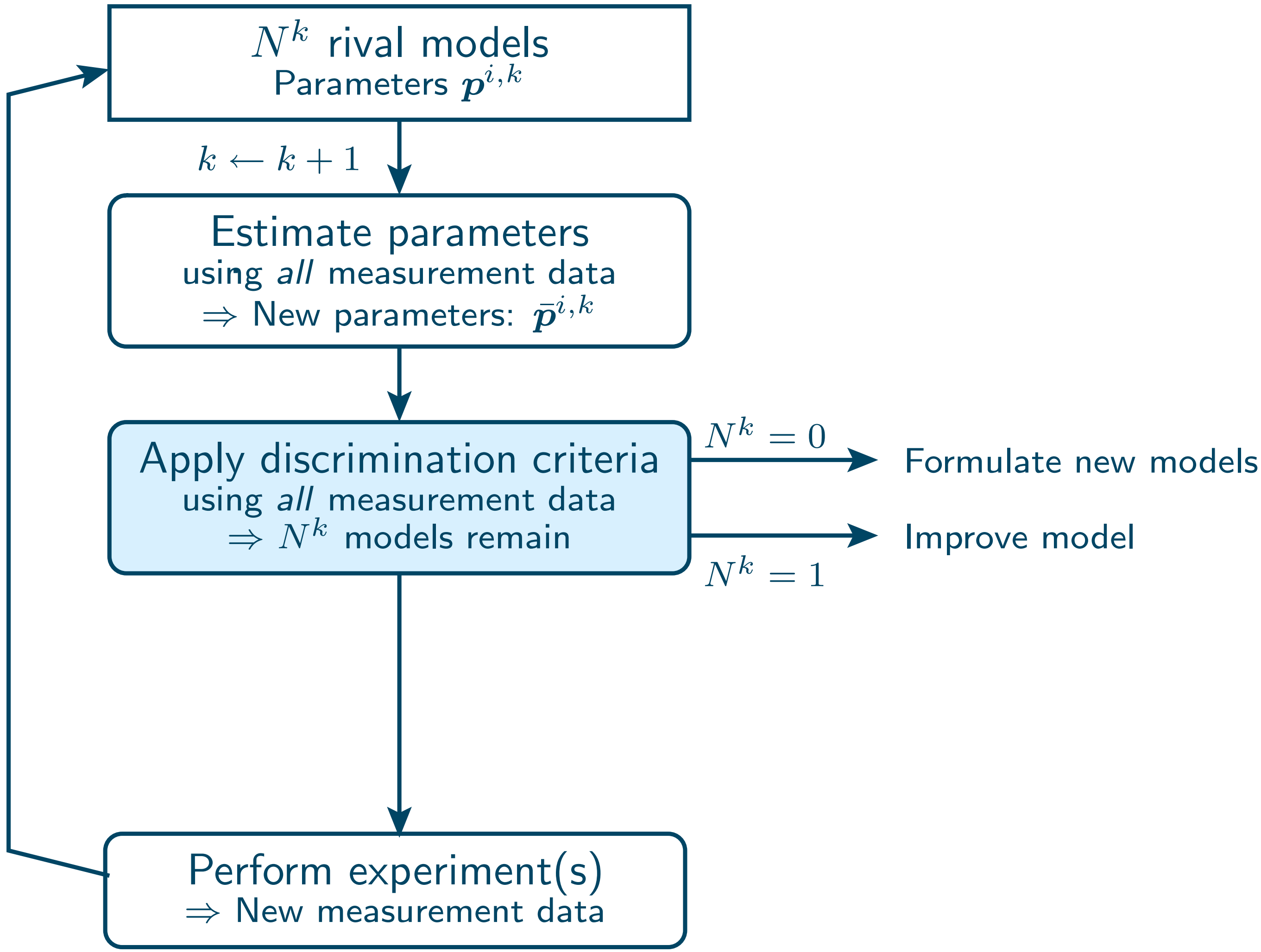

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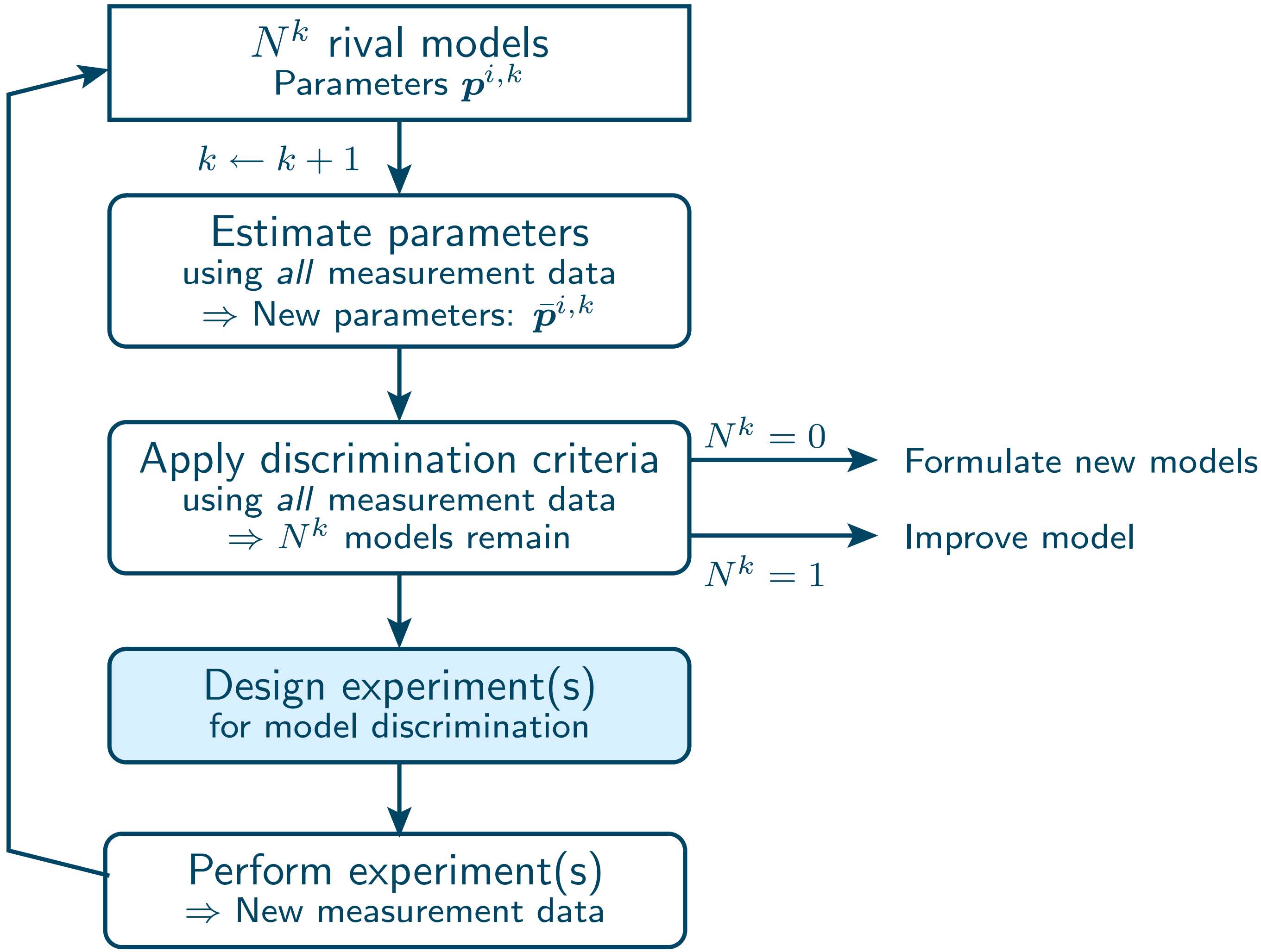


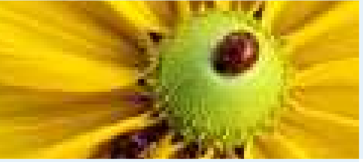
Design criterion

,,Perform the experiment which will most strain the incorrect model to explain the data." [HR65]

For a single model i:
perform the experiment described by a design solving

$$\max_{\boldsymbol{q}} \left\| \boldsymbol{\Sigma}^{-1}(\bar{\boldsymbol{\eta}}_{\boldsymbol{q}} - \boldsymbol{h}^i[\boldsymbol{q}, \boldsymbol{p}^i]) \right\|_2^2, \ \boldsymbol{q} \in \mathcal{Q}$$

T-Optimal experimental design
"Optimal design with respect to a certain statistical **T***est"*



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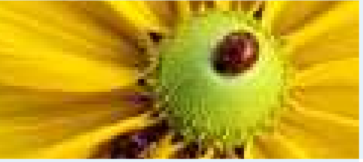

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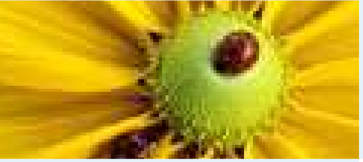

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➡ T-optimal design: theoretical "upper limit"!

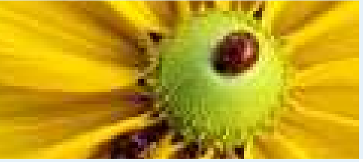
Practical solution approach

Use what you have: several model responses

For two models A, B:
Perform the experiment described by the design q solving

$$\max_{\boldsymbol{q}} \left\| \boldsymbol{\Sigma}^{-1} \left(\boldsymbol{h}^{A}[\boldsymbol{q}, \boldsymbol{p}^{A}] - \boldsymbol{h}^{B}[\boldsymbol{q}, \boldsymbol{p}^{B}] \right) \right\|, \boldsymbol{q} \in \mathcal{Q} \tag{1}$$

"Perform the experiments where model predictions differ most."



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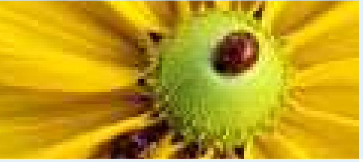
- In sequential discrimination procedure:
  Converges to T-optimal design almost surely. [Fed75, AD92]



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  - Use (1) with the two best-fitting models ("ranking" [AF75])
  - Apply (1) pairwise to all models, weight by model reliability

$$\max_{\boldsymbol{q}} \sum_{\substack{i,j=1 \\ i \leq j}}^{\mathrm{N}} \boldsymbol{w}_{ij} \left\| \boldsymbol{h}^i - \boldsymbol{h}^j \right\|$$

OED for model discrimination: a complex optimal control problem [Hof05]

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- the *model dynamics*,
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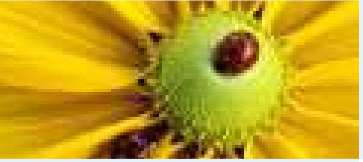
$$\begin{aligned} \bar{\boldsymbol{\eta}}_{\boldsymbol{q}} &\approx \boldsymbol{h}^i[\boldsymbol{q}, \boldsymbol{x}^i, \boldsymbol{p}^i] \\ 0 &= \boldsymbol{f}^i\left(\dot{\boldsymbol{x}}^i(t), \boldsymbol{x}^i(t), \boldsymbol{p}^i, \boldsymbol{q}\right) \end{aligned}$$



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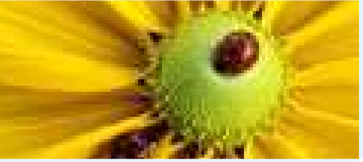
- *experimental constraints*:
  initial conditions, security regulations, measurement limits, ...
  formulated in terms of the relevant model

$$0 \leq \boldsymbol{b}^i\left(\boldsymbol{x}^i(t_0), \ldots, \boldsymbol{x}^i(t_{\mathrm{B}}), \boldsymbol{p}^i, \boldsymbol{q}\right)$$
$$0 \leq \boldsymbol{c}^i\left(\boldsymbol{x}^i, \boldsymbol{p}^i, \boldsymbol{q}\right)$$

Optimal control problem of MD

Resulting OED problem for $i = 1, \ldots, \mathrm{N}$ models:



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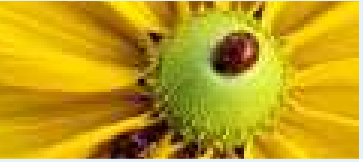

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s.t. contraints from model dynamics:

$$0 = \boldsymbol{F} := \begin{cases} \boldsymbol{f}^1\left(\dot{\boldsymbol{x}}^1, \boldsymbol{x}^1, \boldsymbol{p}^1, \boldsymbol{q}\right) \\ \qquad \vdots \\ \boldsymbol{f}^\mathrm{N}\left(\dot{\boldsymbol{x}}^\mathrm{N}, \boldsymbol{x}^\mathrm{N}, \boldsymbol{p}^\mathrm{N}, \boldsymbol{q}\right) \end{cases}$$

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s.t. experimental constraints:

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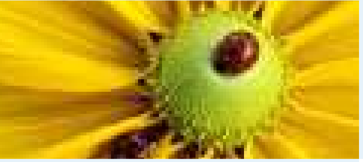

Optimal control problem of MD

Resulting OED problem for $i = 1, \ldots, \mathrm{N}$ models:

$$\max_{\boldsymbol{x}^1, \ldots, \boldsymbol{x}^{\mathrm{N}}, \boldsymbol{q}} \Phi\left(\boldsymbol{h}^1, \ldots, \boldsymbol{h}^{\mathrm{N}}\right), \quad \text{with } \boldsymbol{h}^j = \left[\boldsymbol{q}, \boldsymbol{x}^j, \boldsymbol{p}^j\right]$$

s.t. contraints from model dynamics:

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➨ High-dimensional, nonlinear, constrained optimal control problem

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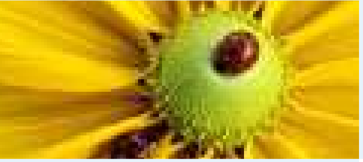

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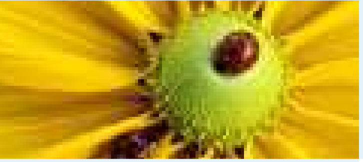
Required: gradient of Φ, Jacobians of $\boldsymbol{\zeta}$, $\boldsymbol{\xi}$
Derivative computation is expensive:
involves solution of complex initial value problems

Structure exploitation

Problem contains N mutually independent models:

$$\frac{d\boldsymbol{f}^i}{d\boldsymbol{x}^j} = \frac{d\boldsymbol{b}^i}{d\boldsymbol{x}^j} = \frac{d\boldsymbol{c}^i}{d\boldsymbol{x}^j} = 0, \ \forall i \neq j$$

Only coupled via objective function $\Phi\left(\boldsymbol{h}^1, \dots, \boldsymbol{h}^{\mathrm{N}}\right)$



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$$\frac{d\boldsymbol{F}}{d\boldsymbol{x}} = \begin{pmatrix} \boldsymbol{J}_1 & & & \\ & \boldsymbol{J}_2 & & \\ & & \ddots & \\ & & & \boldsymbol{J}_{\mathrm{N}} \end{pmatrix}, \text{ with } \boldsymbol{J}_i := \frac{d\boldsymbol{f}^i}{d\boldsymbol{x}^i}$$

➨ **Efficient derivative generation**: effort $\propto \mathrm{N}$, instead of $\propto \mathrm{N}^2$!

Implementation: MUSCOD-II, prototype phase

Numerical results: Enzyme deactivation

Test procedure

Aim: proof of concept

I need to *know* which model describes process correctly!

- Define: model X is ,,nature".
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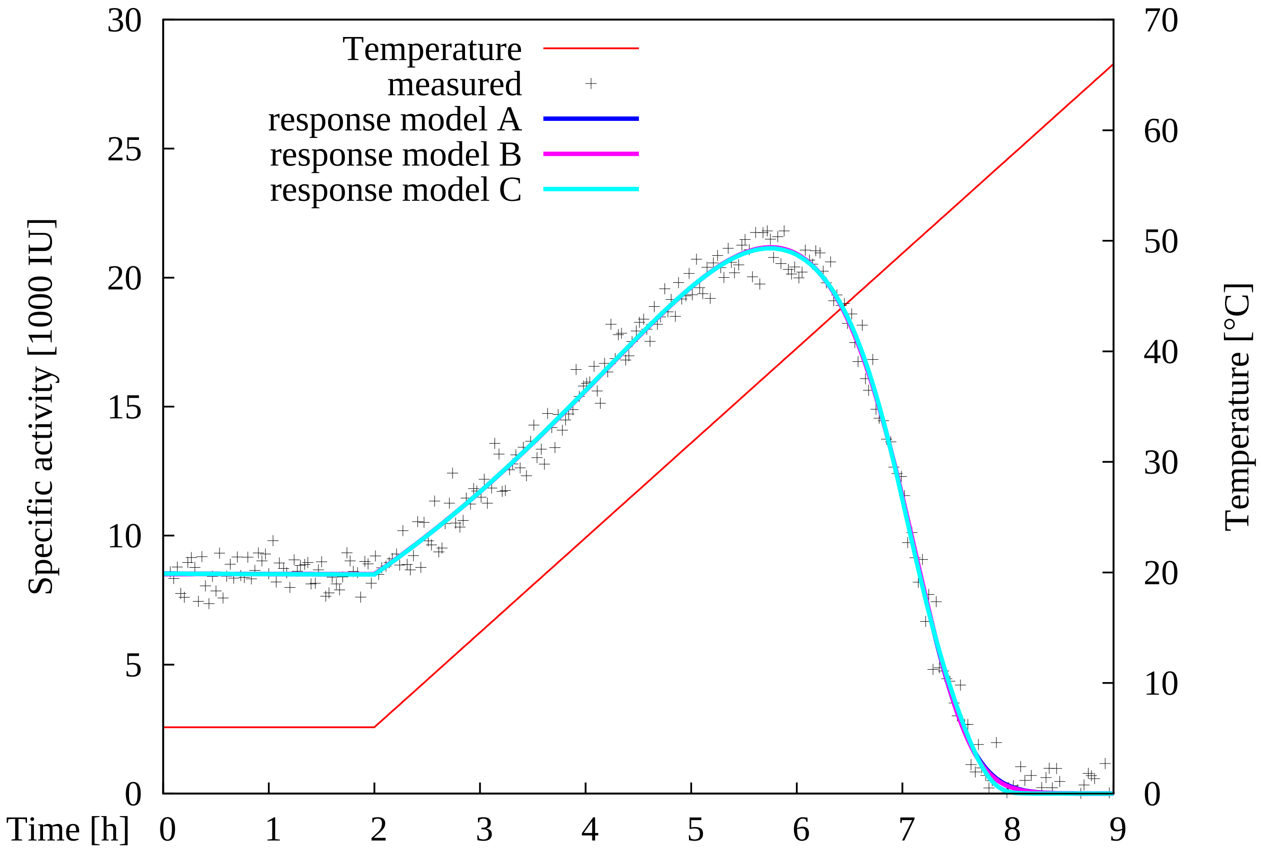
Results:

- 12 test series, various conditions
- designed >30 experiments

➨ All unsuitable models correctly identified, no false positive.

Presented results: Model B is ,,nature"

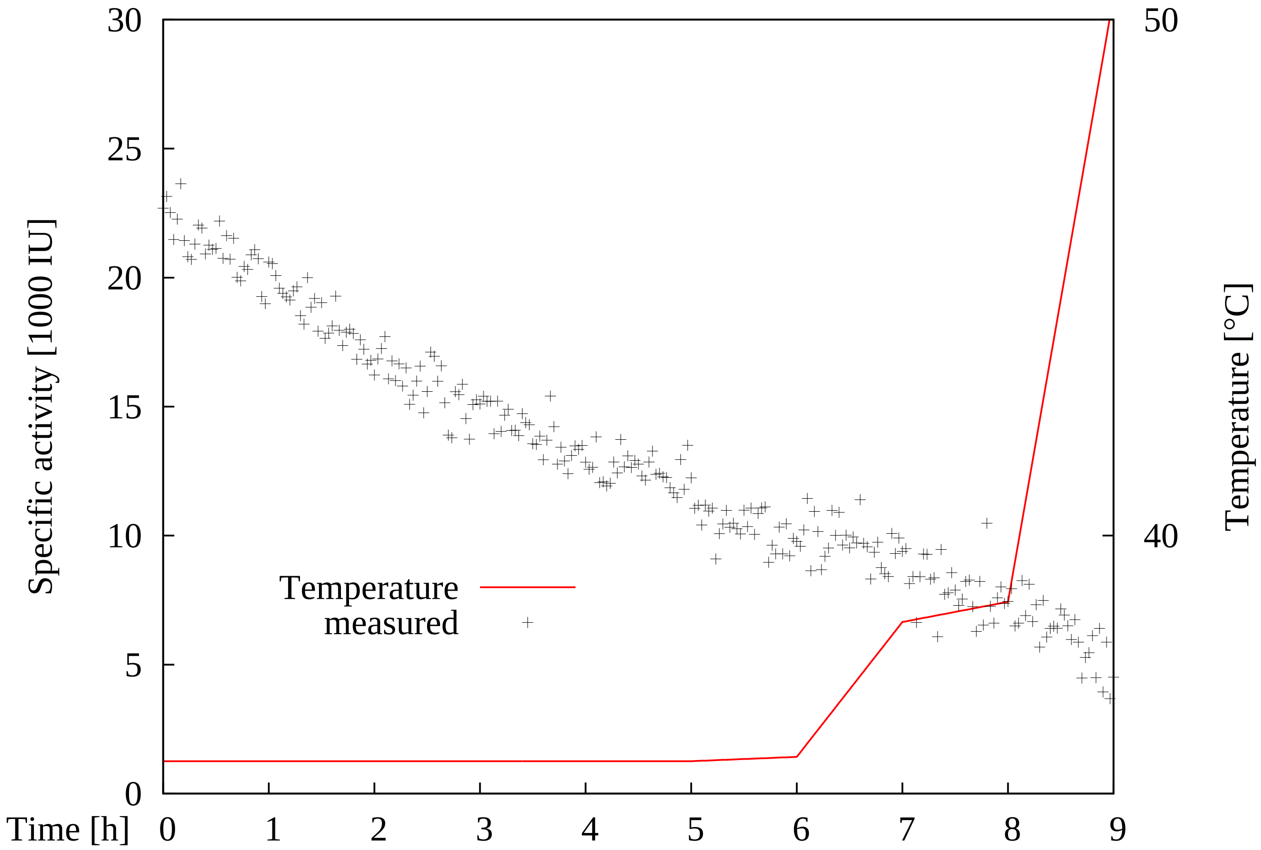
Model predictions for experiment 1, after fitting to experiment 1



Test results: A, B, C suitable

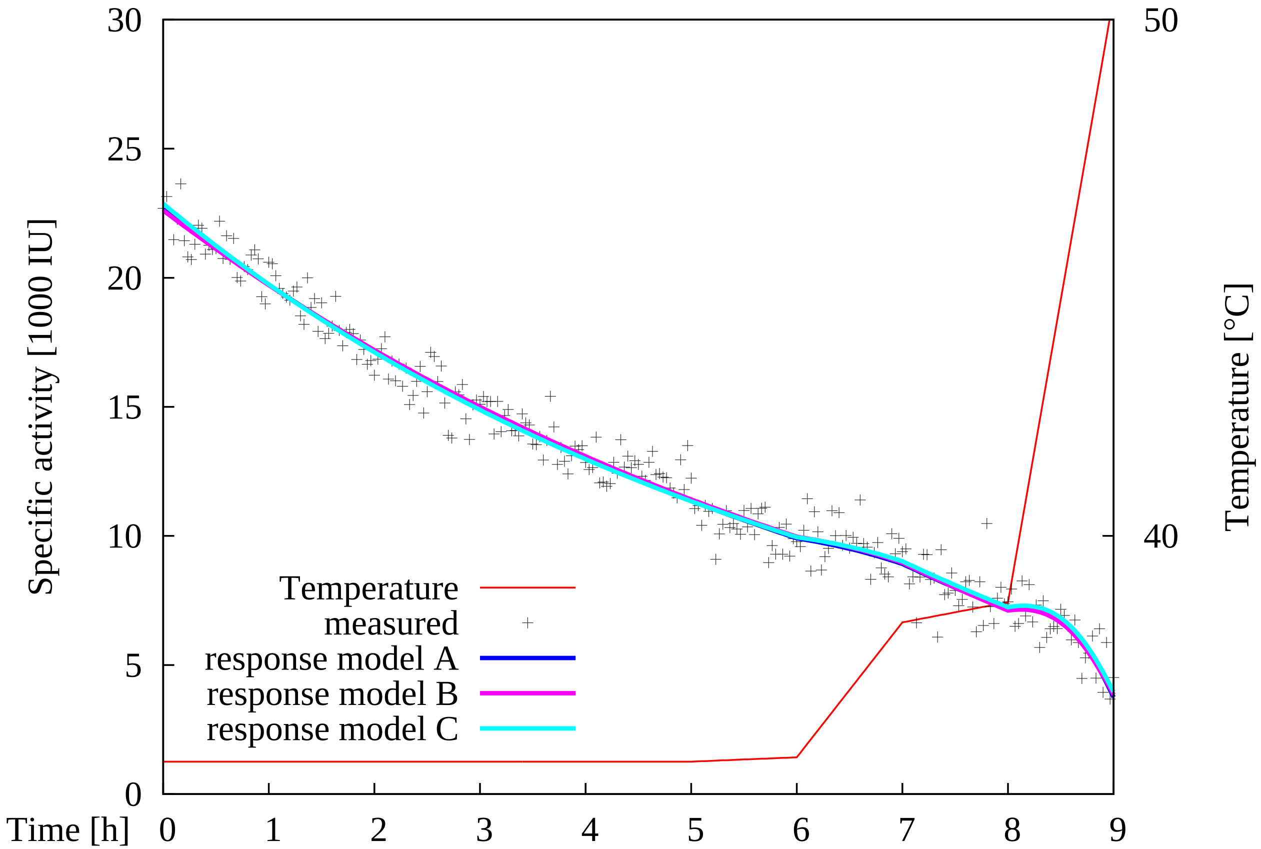
Results

Measurement data from experiment 2



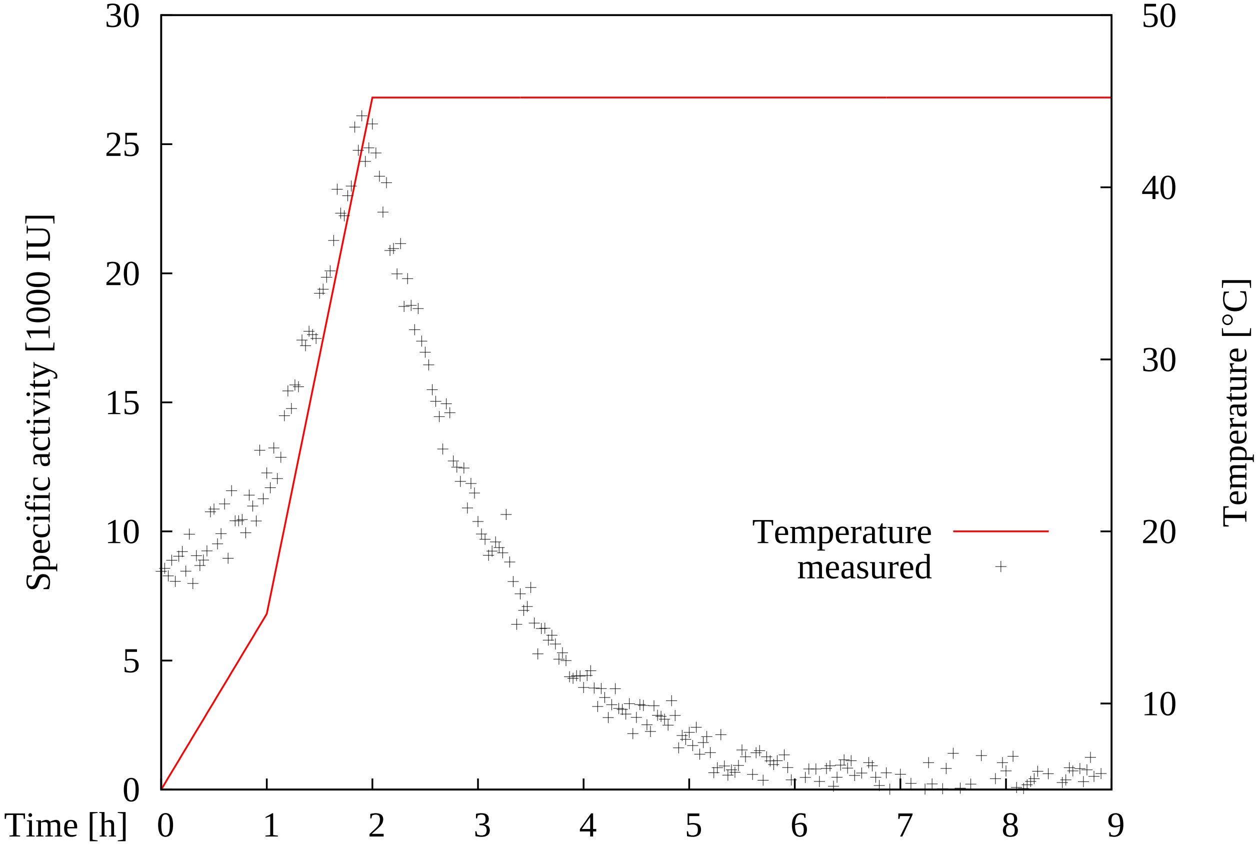
Results

Model predictions for experiment 2, after fitting to experiments 1-2

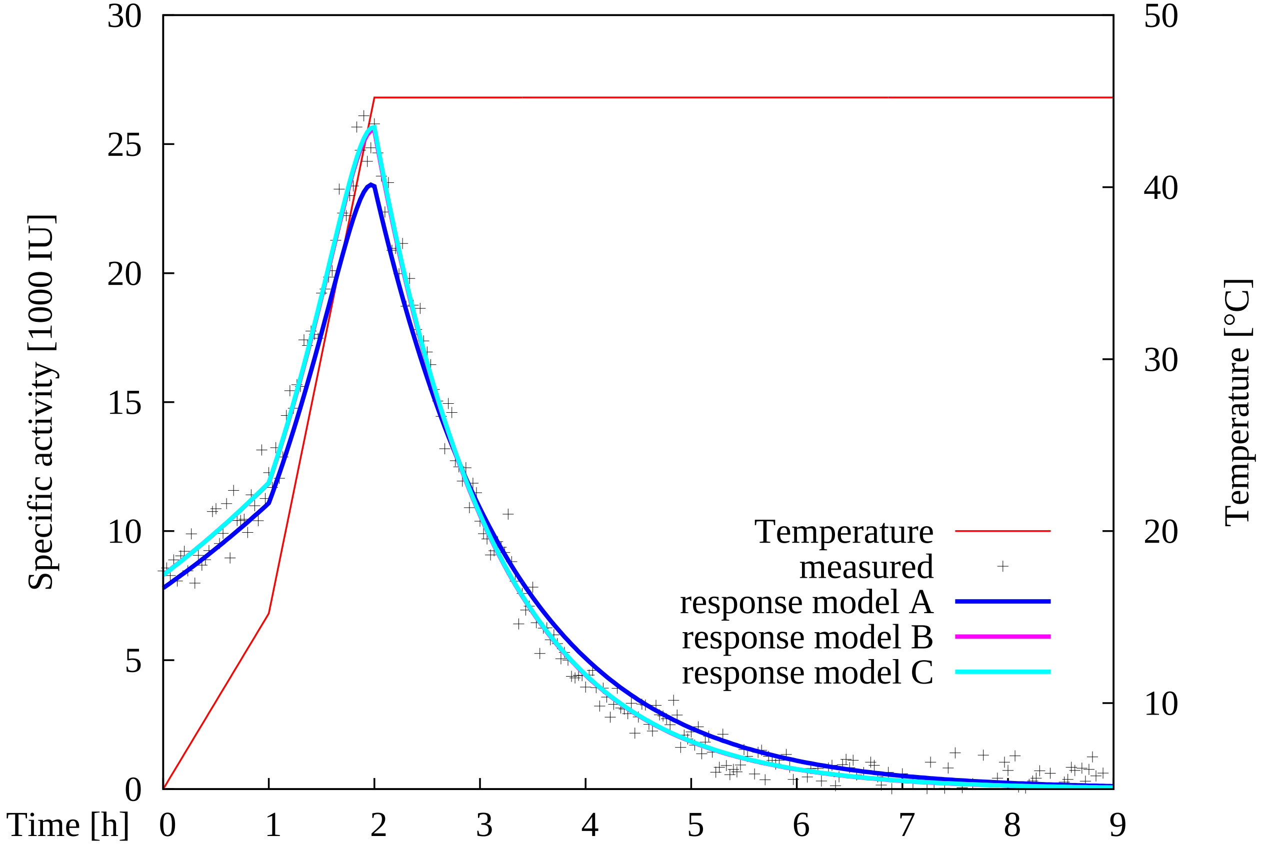


Test results: A, B, C suitable

Measurement data from experiment 3



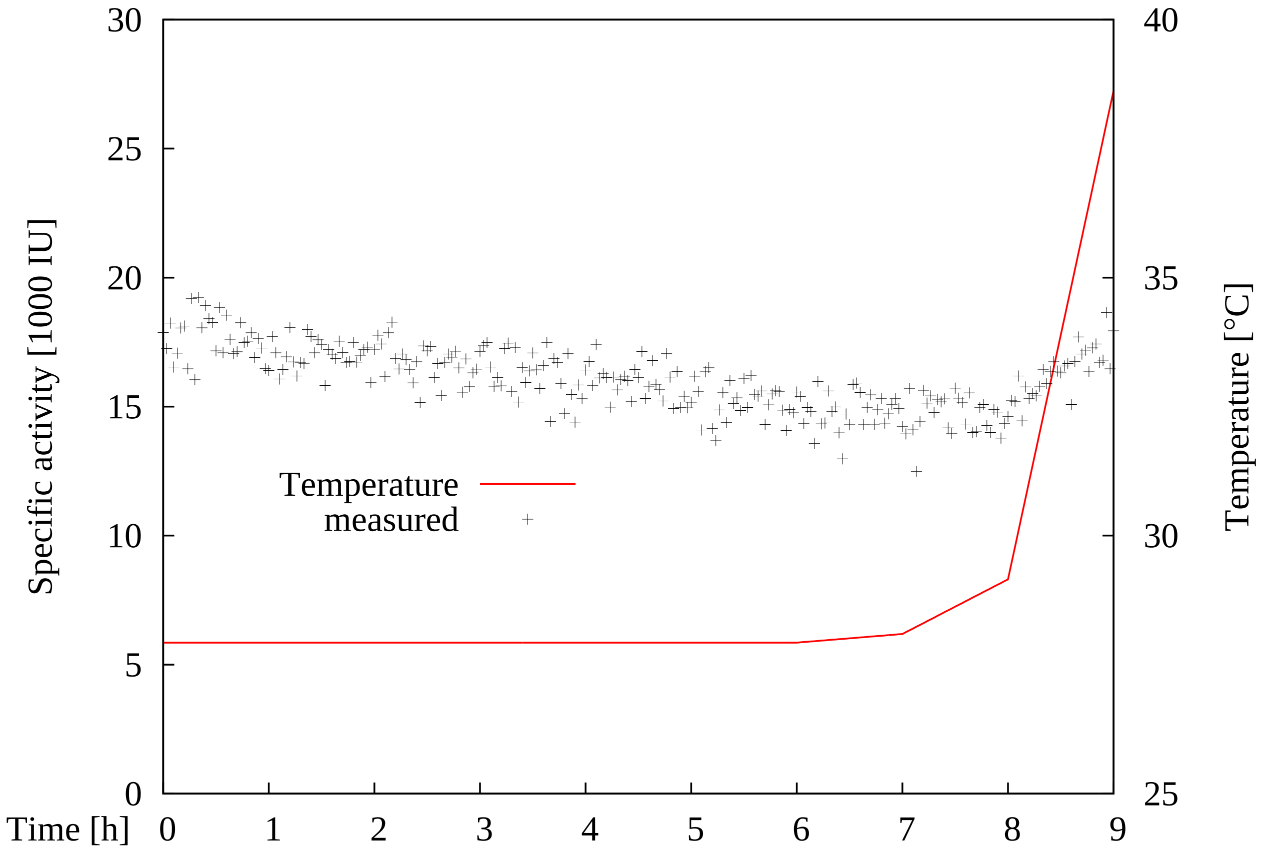
Model predictions for experiment 3, after fitting to experiments 1-3

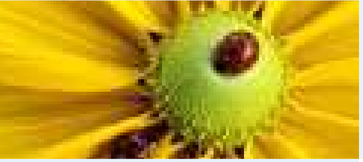


Test results: A unsuitable, B, C suitable

Results

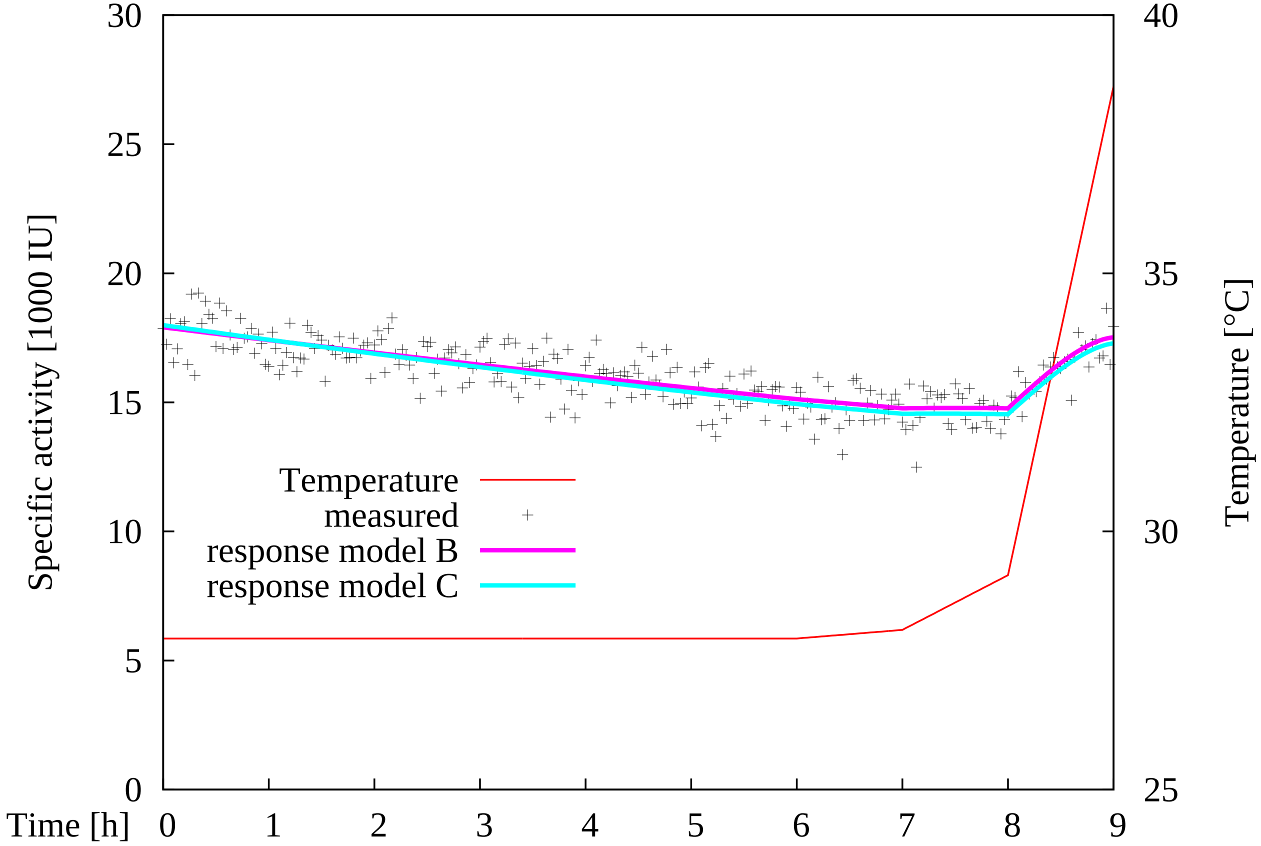
Measurement data from experiment 4





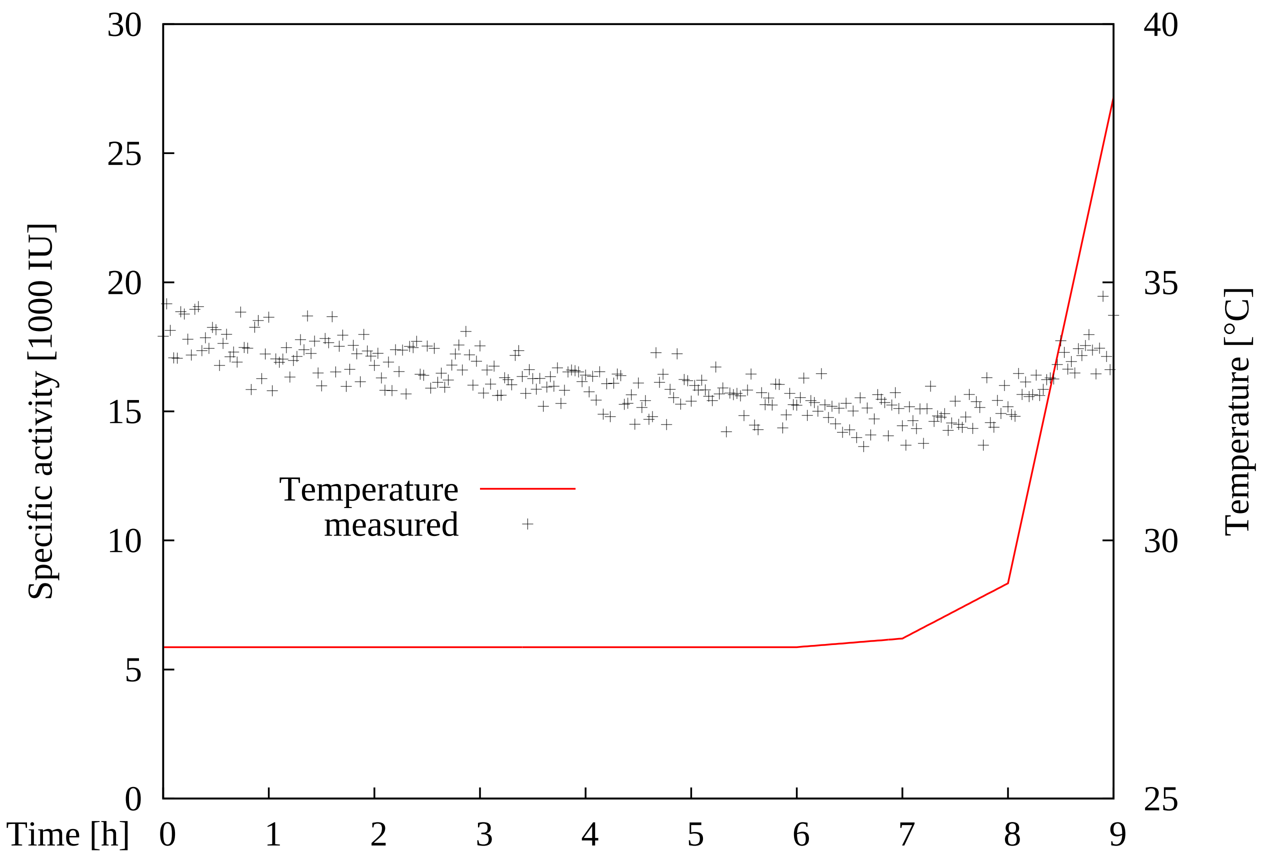
Results

Model predictions for experiment 4, after fitting to experiments 1-4

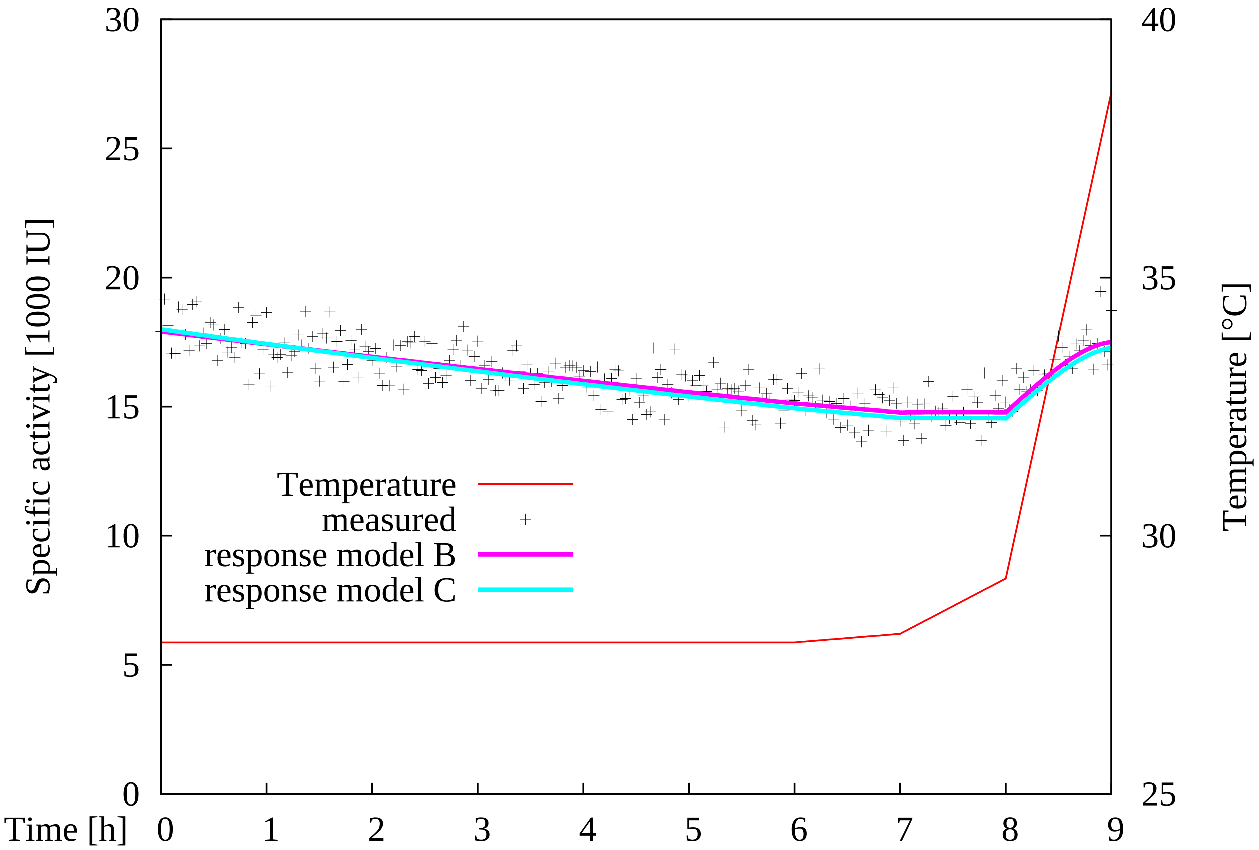


Test results: B, C suitable

Measurement data from experiment 5



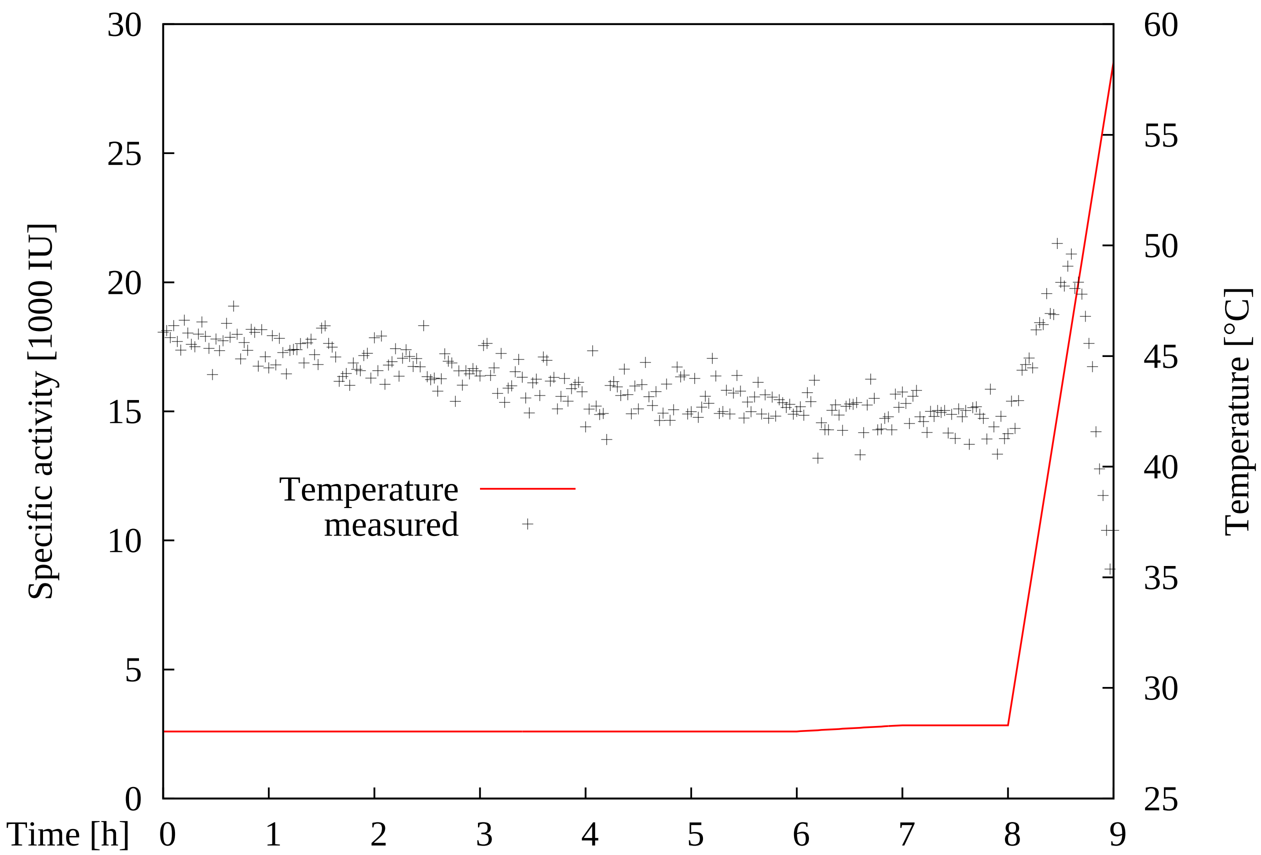
Model predictions for experiment 5, after fitting to experiments 1-5



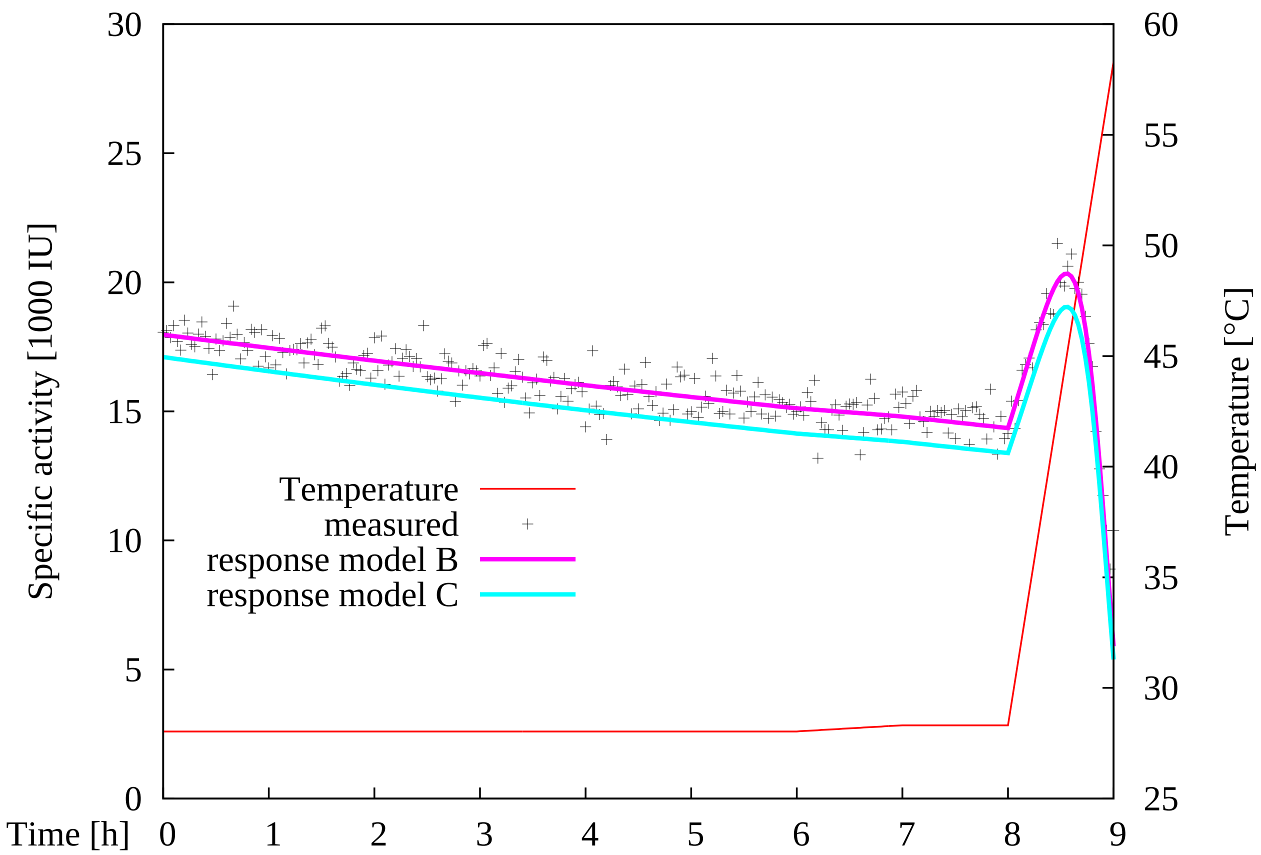
Test results: B, C suitable

Results

Measurement data from experiment 6



Model predictions for experiment 6, after fitting to experiments 1-6



Test results: C unsuitable

➨ **correct model B remains**

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- They can be solved efficiently using targeted experimental design.
- The design tasks leads to high-dimensional OC problems.
  Their specific structure allows efficient solution even for many models.

Thank you very much for your attention!

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