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iMinds | Medical Information Technologies Department

The power of low rank MATRIX and TENSOR Approximations in *Smart Diagnostics*

HCM workshop: Low-rank Optimization and Applications
Bonn, Germany
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Prof. Sabine Van Huffel

European Research Council
Established by the European Commission

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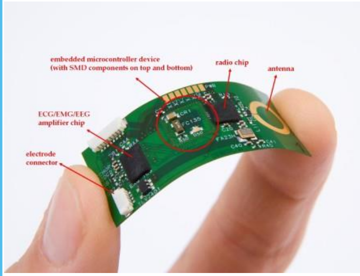
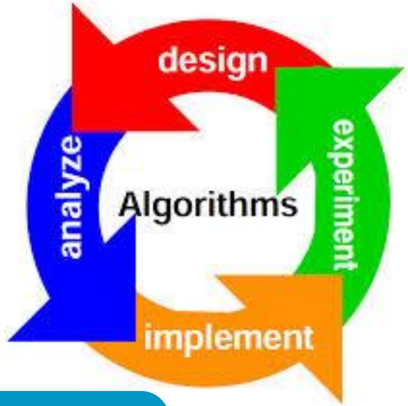
  - Smart Patient Monitoring
  - Blind Source Separation
  - Tensor Decompositions
- Examples in Neonatal Brain Monitoring
- Examples in MR-based Brain Tumor Diagnosis
- Conclusions and new directions





Brain monitoring for neurological

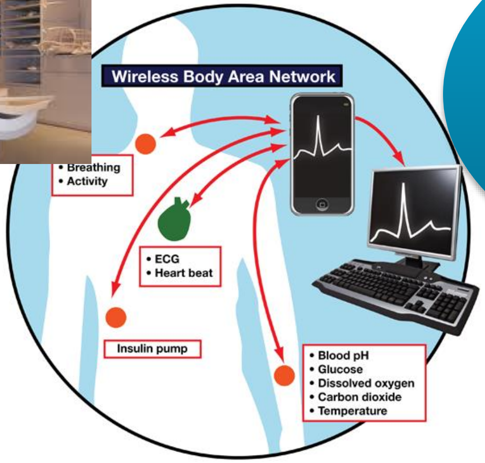
Vital signs monitoring: sleep, stress, cardio risk stratification

Algorithms (Technology)

Sensors (Carriers)

Pathologies (Applications)

Smart Diagnostics



Oncology: cancer diagnosis and prognosis

Chronic disease management & telemonitoring application

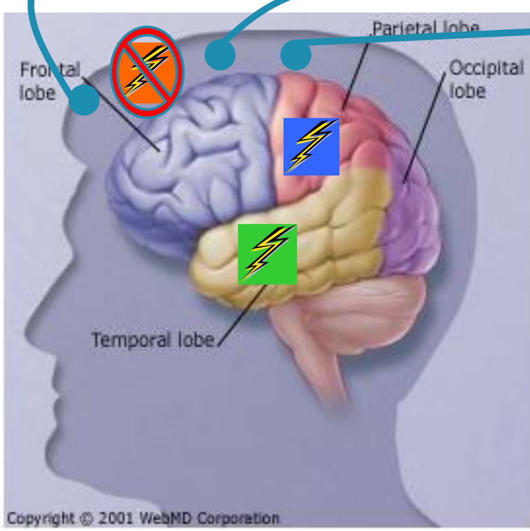
Blind source separation

Signal analysis difficult because of artefacts → REMOVE

Matrix based Blind Source Separation (BSS)

Non-unique → *Constraints are needed!*

- sources orthogonal (PCA),
- sources statistically independent (ICA)
- **sources uncorrelated and of different autocorrelation (CCA)**

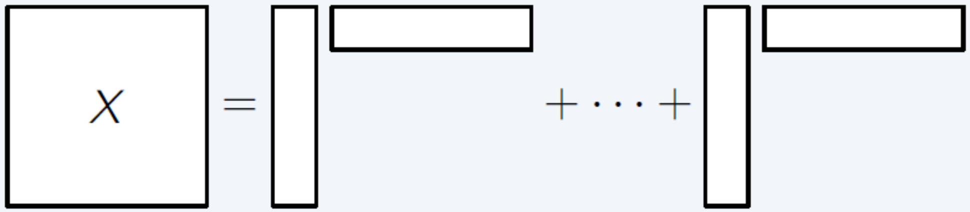


$$EEG_1 = a_{11}\mathbf{s_1} + a_{12}\mathbf{s_2} + a_{13}\mathbf{s_3}$$
$$EEG_2 = a_{21}\mathbf{s_1} + a_{22}\mathbf{s_2} + a_{23}\mathbf{s_3}$$
$$EEG_3 = a_{31}\mathbf{s_1} + a_{32}\mathbf{s_2} + a_{33}\mathbf{s_3}$$

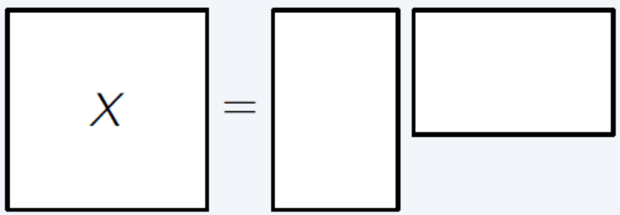
$$EEG = A?\; S^T?$$

From Matrix to Tensor rank

At its core, a matrix decomposition is



or



with some constraints

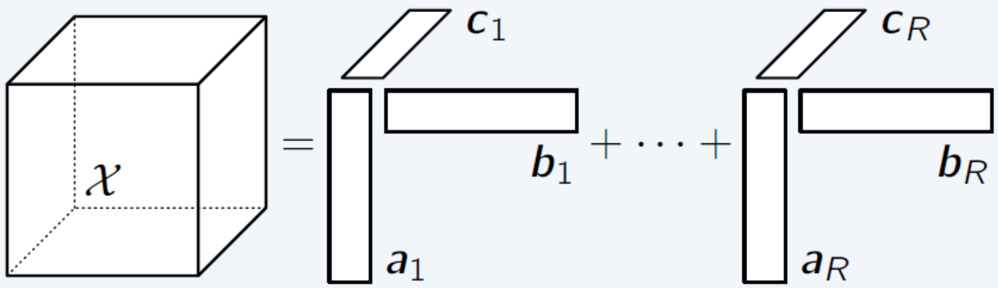
Two equivalent ways to define matrix rank

- Minimal number of rank-one matrices that sum to X
- Dimension of column (or row) space of X

For tensors, these are two different concepts!

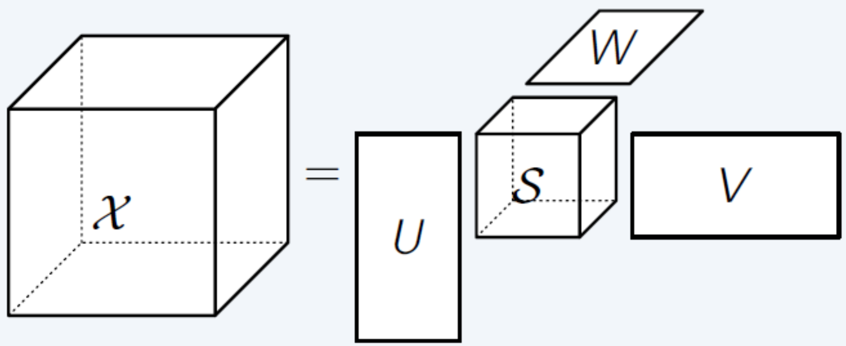
Tensor Decompositions

The canonical polyadic decomposition (CPD) decomposes a tensor into a minimal number of rank-one tensors R



The tensor's rank is defined as R

A low multilinear rank approximation (LMLRA) decomposes a tensor into a core tensor $\mathcal{S}$ and matrices U, V and W



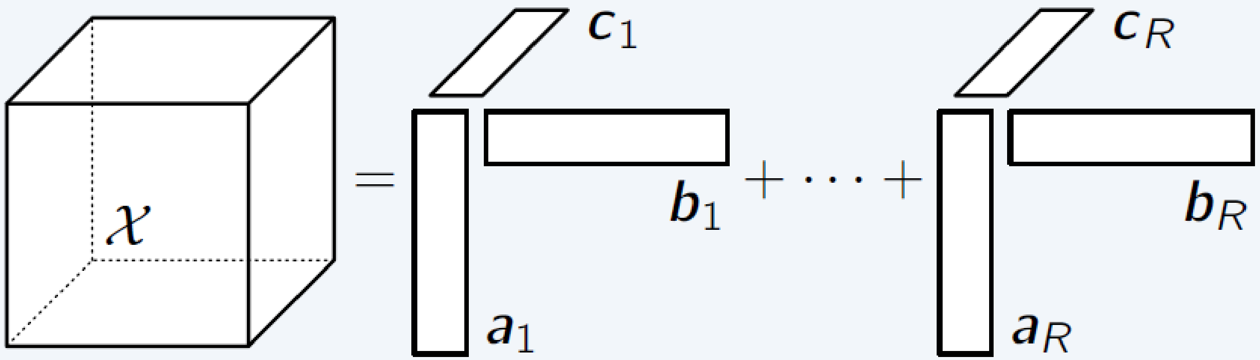
The tensor's multilinear rank is defined as the triplet $(\mathrm{rank}(U), \mathrm{rank}(V), \mathrm{rank}(W))$

Uniqueness means Interpretable

Without constraints, matrix decompositions are not unique

$$X = A \cdot B = (A \cdot M) \cdot (M^{-1} \cdot B) = \hat{A} \cdot \hat{B}$$

Tensor decompositions can be unique under mild conditions!
For example, the vectors $\boldsymbol{a}_r$, $\boldsymbol{b}_r$ and $\boldsymbol{c}_r$ in the CPD



are generically unique when $k_A + k_B + k_C$ >= 2*R+2

$A=[a_1,\ldots,a_R]$
$B=[b_1,\ldots,b_R]$
$C=[c_1,\ldots,c_R]$

Contributors (nonexhaustive list):
L. De Lathauwer, P. Comon, T. Kolda, B. Bader, L-H Lim, C. Van Loan, E. Acar, A. Cichocki, O. Alter, R. Bro, M. Morup, N. Sidiropoulos, I. Domanov, M. Sorensen, L. Sorber, M. Ishteva, L. Albera, M. Haardt, …. and collaborators

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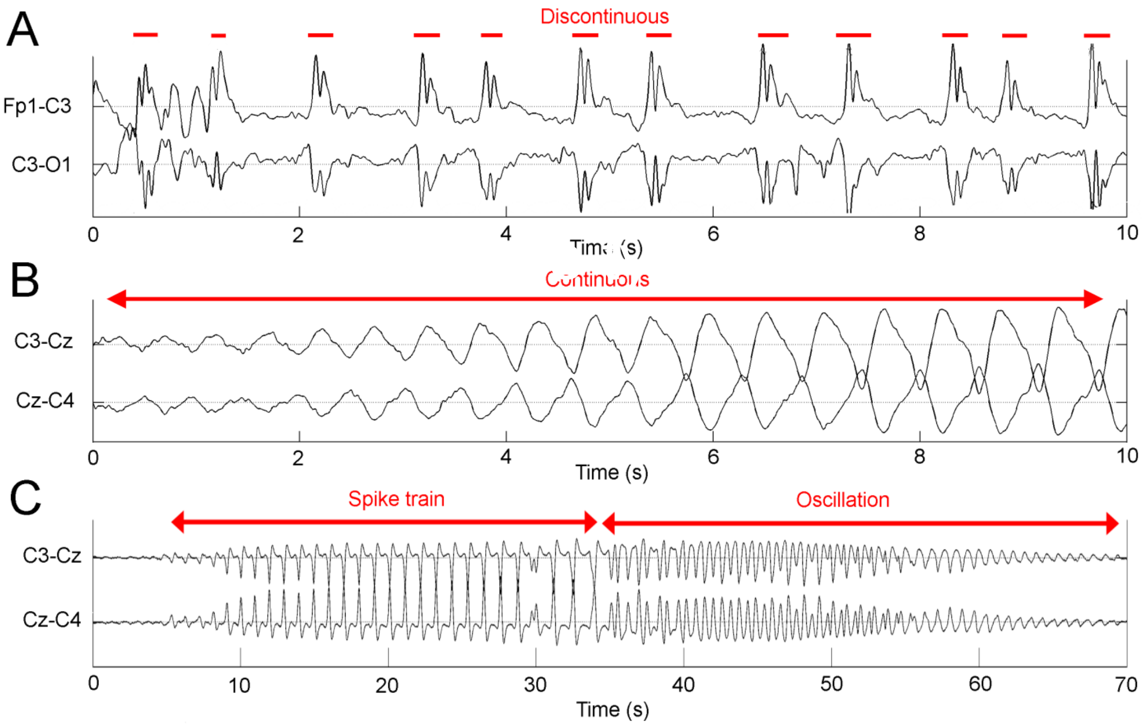
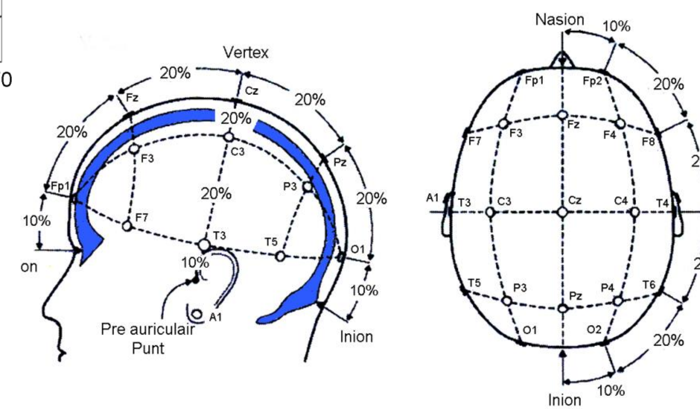
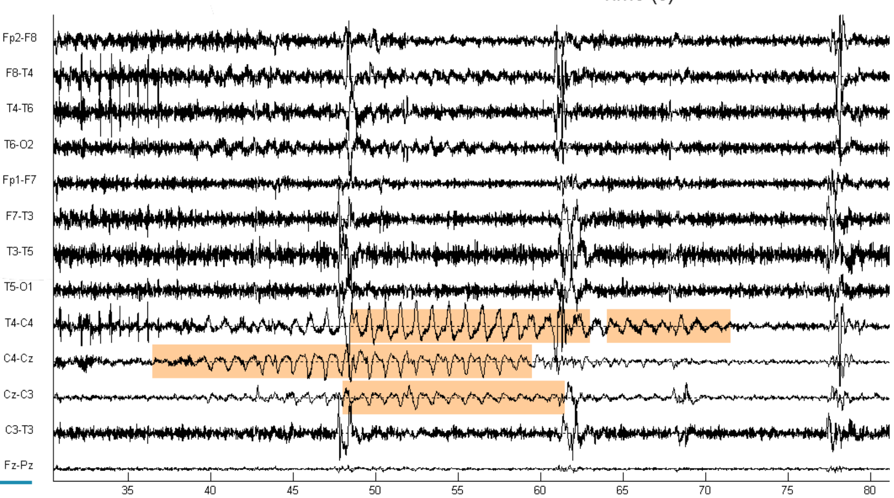
  - Seizure detection
  - Seizure onset localization
  - Background EEG grading
- Examples in MR-based Brain Tumor Diagnosis
- Conclusions and new directions

Neonatal Brain Monitoring:

Seizure detection







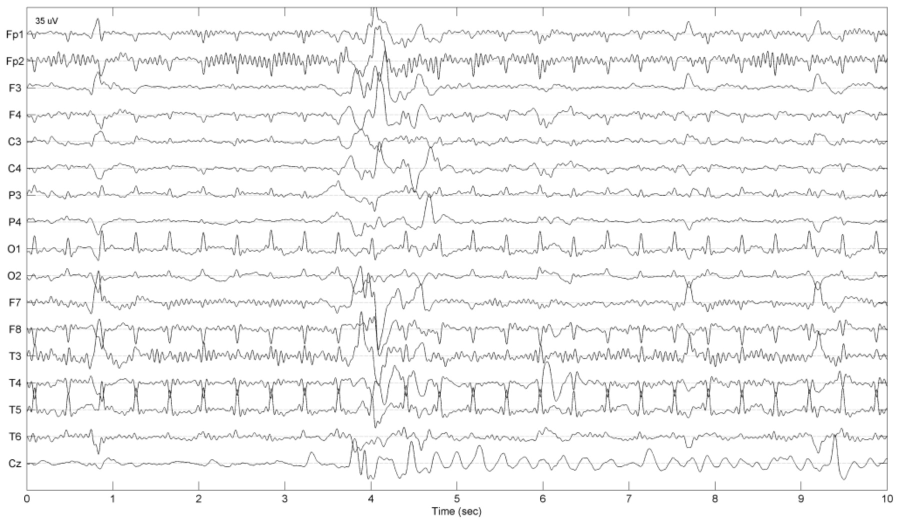
Deburchgraeve, PhD thesis, 2011; P.J. Cherian 2011; W. Deburchgraeve et al, Clin. Neurophys. 2008 & 2009
Alternatives using classification: See pubs of Temko, G. Boylan, etc.

Artefact removal: ECG, respiration, pulsation

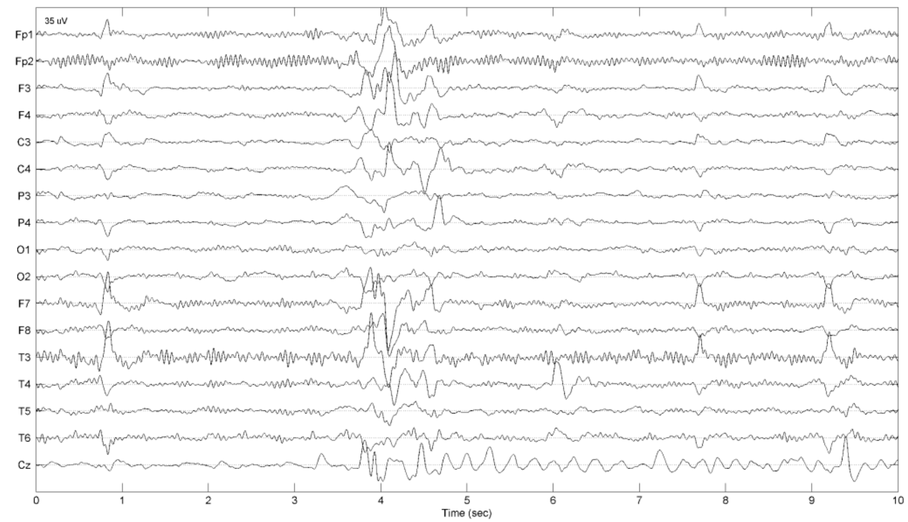
BSS based algorithm removes these 3 artifacts **before** seizure detection starts

ECG artefact removal: *with RobustICA* (spiky)
Respiration & Pulsation removal: *with SOBI* (oscillatory, autocorrelated)
Number of sources: *estimated with PCA and variance threshold*
IC source recognition: *correlation with reference after transformation*

ECG spike artefact



Cleaned EEG



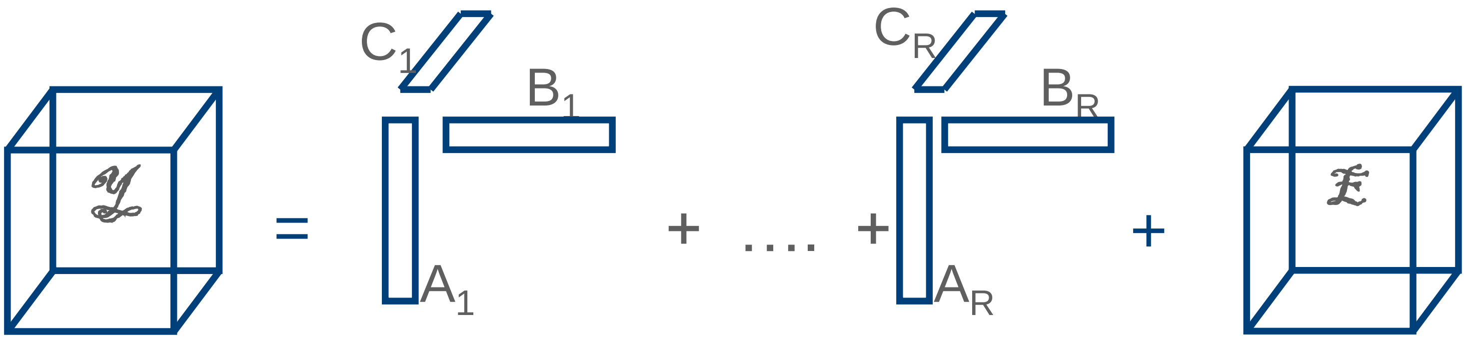
VALIDATION study artefact-removal: *M. De Vos et al., Clinical Neurophys., Dec. 2011*

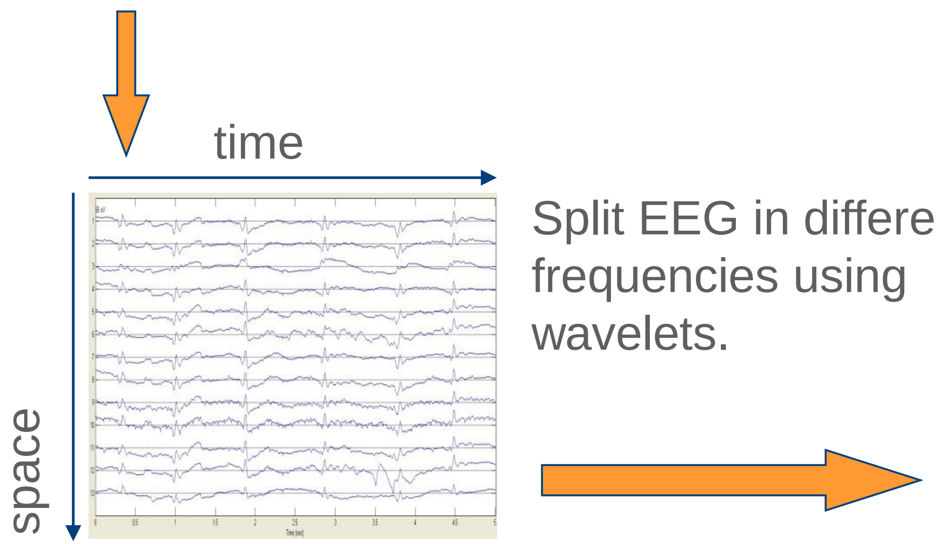
•13 patients: asphyxia (9 with artefacts, 4 artefact-free), 8h EEG per patient

	Fp/h	Seizure detection Rate (%)
No-AR:	0.38 (0-5)	87.1 (20-100)
With-AR:	0.00 (0-0.875)	100 (20-100)

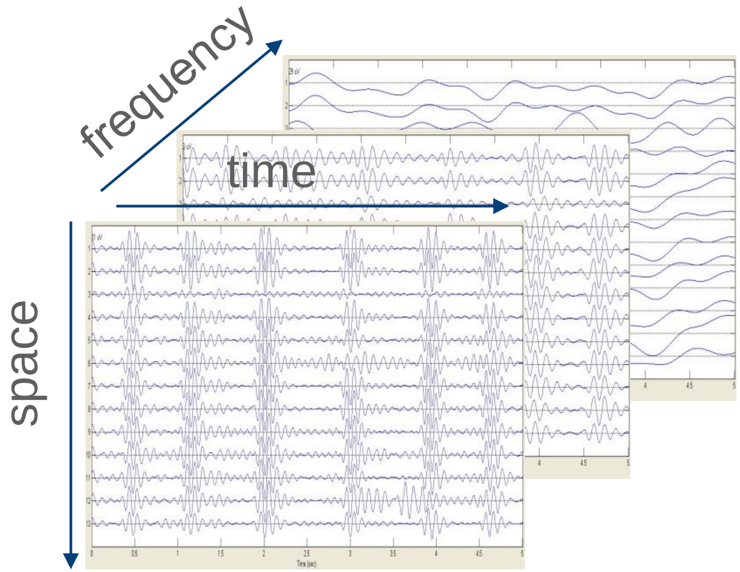
Seizure onset localization:

CPD





Split EEG in different frequencies using wavelets.



=> Analysis in 3 dimensions instead of just 2

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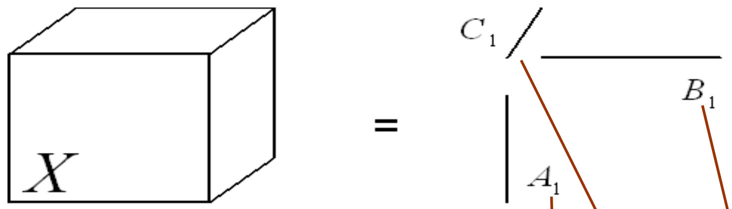
Interpretation of a trilinear component

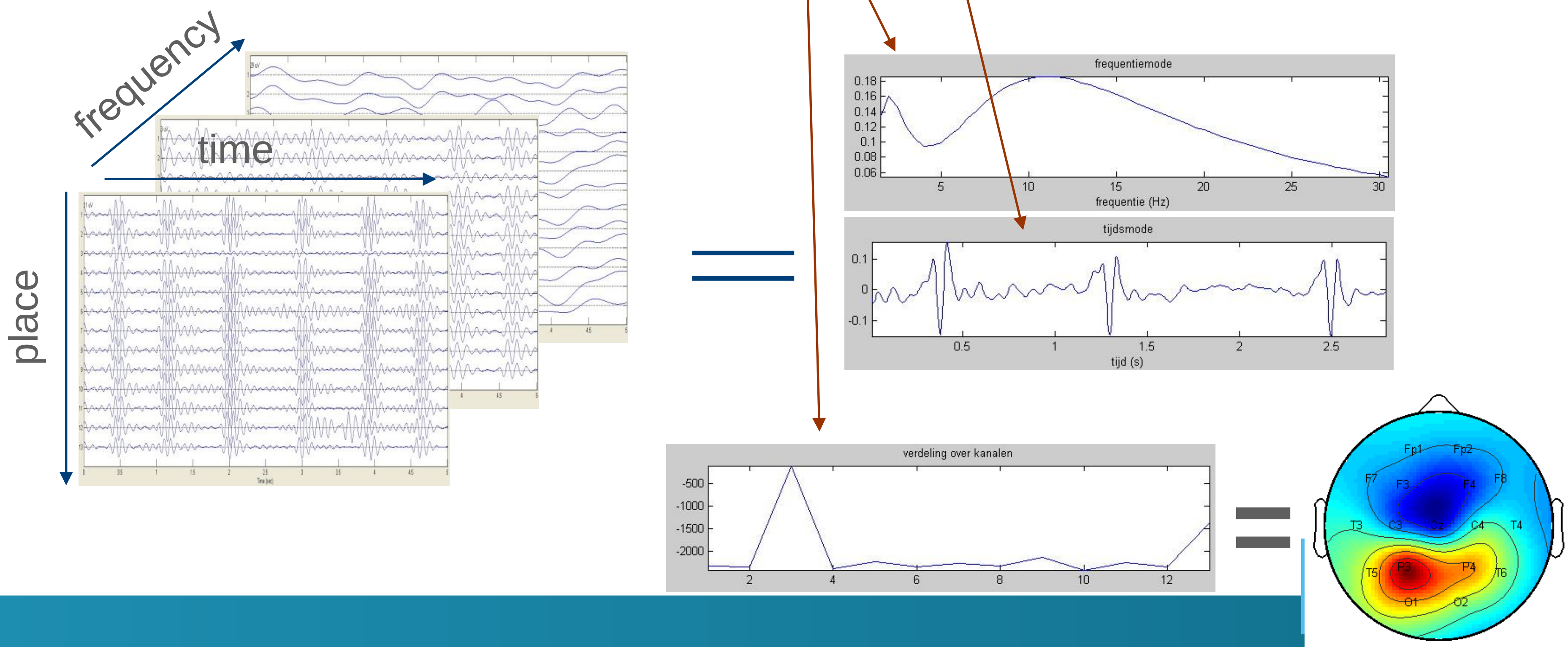
CPD: Example extracting 1 component



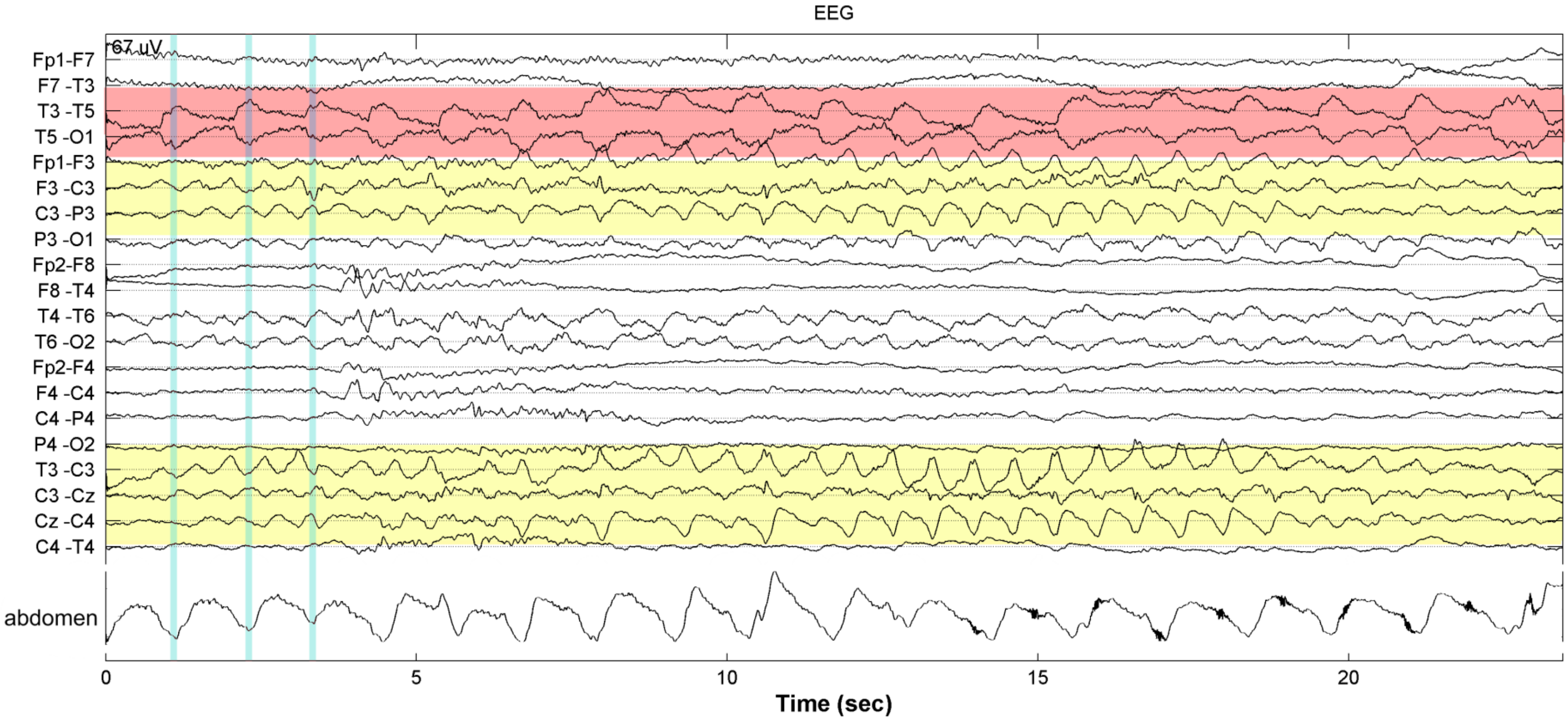
B_1: time course

A_1: distribution over channels

C_1: frequency content (distribution across scales).



separation seizure from background activity



⇒ Extract spatial distribution of the seizure without distortion of the artifact

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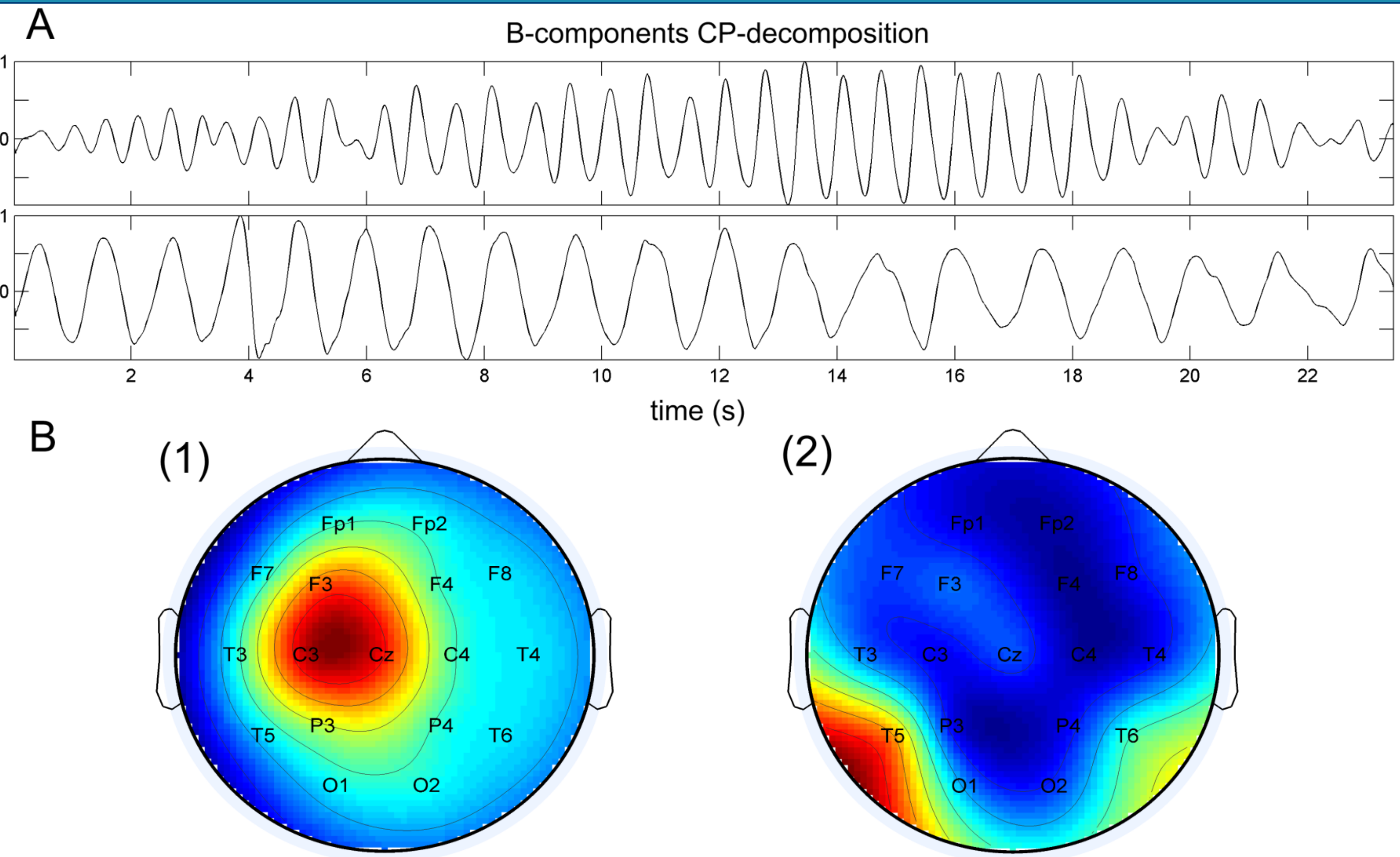
CPD: spatial source components

(1) Seizure:

(2) Artefact:



VALIDATION Study: *W. Deburchgraeve et al., Clinical Neurophys., 2009*

good qualitative correspondence between visual analysis by expert and algorithm.
Together with seizure detector useful for bedside brain monitoring

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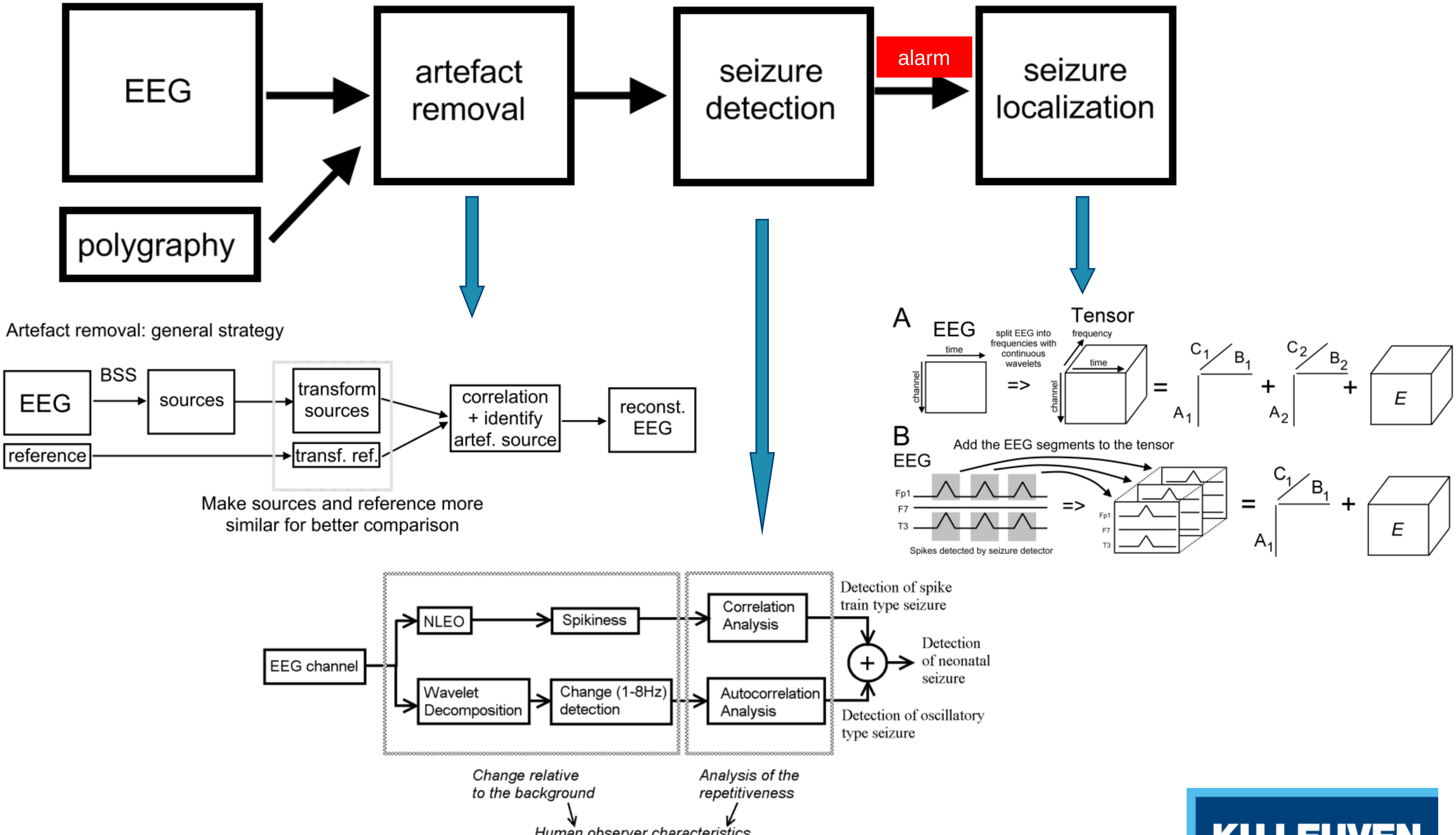
Automated seizure monitoring



NeoGuard : decision support

Brain injury estimate

- Detection of neonatal epileptic seizures
- **Seizure onset localization**
- Inter-burst intervals

Clinician's expertise

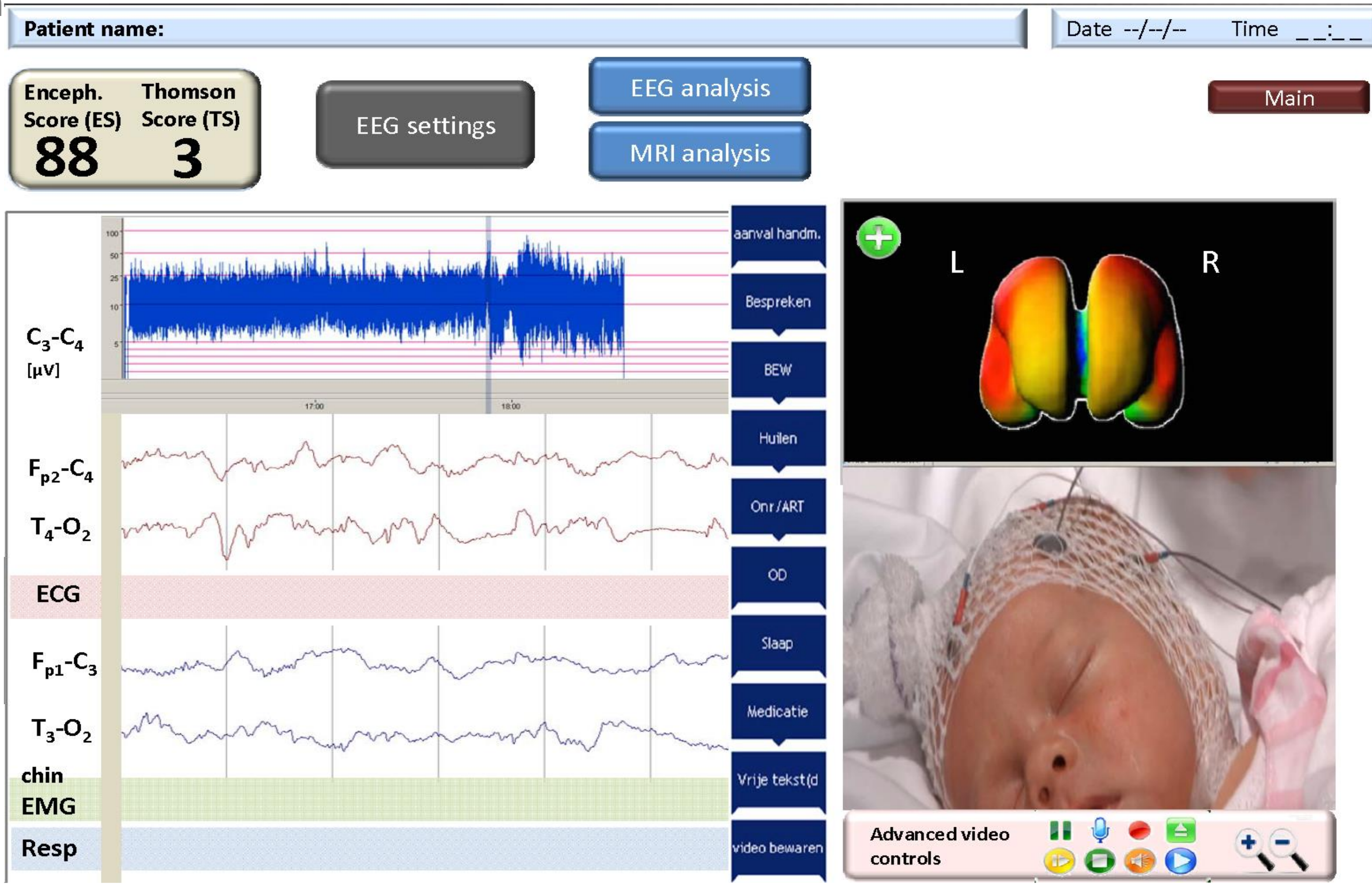
- Neurophysiological knowledge included in algorithms

Brain Monitoring

- **Recovery after damage**
- Maturation in preterms

Outcome prediction

- Good
- Poor



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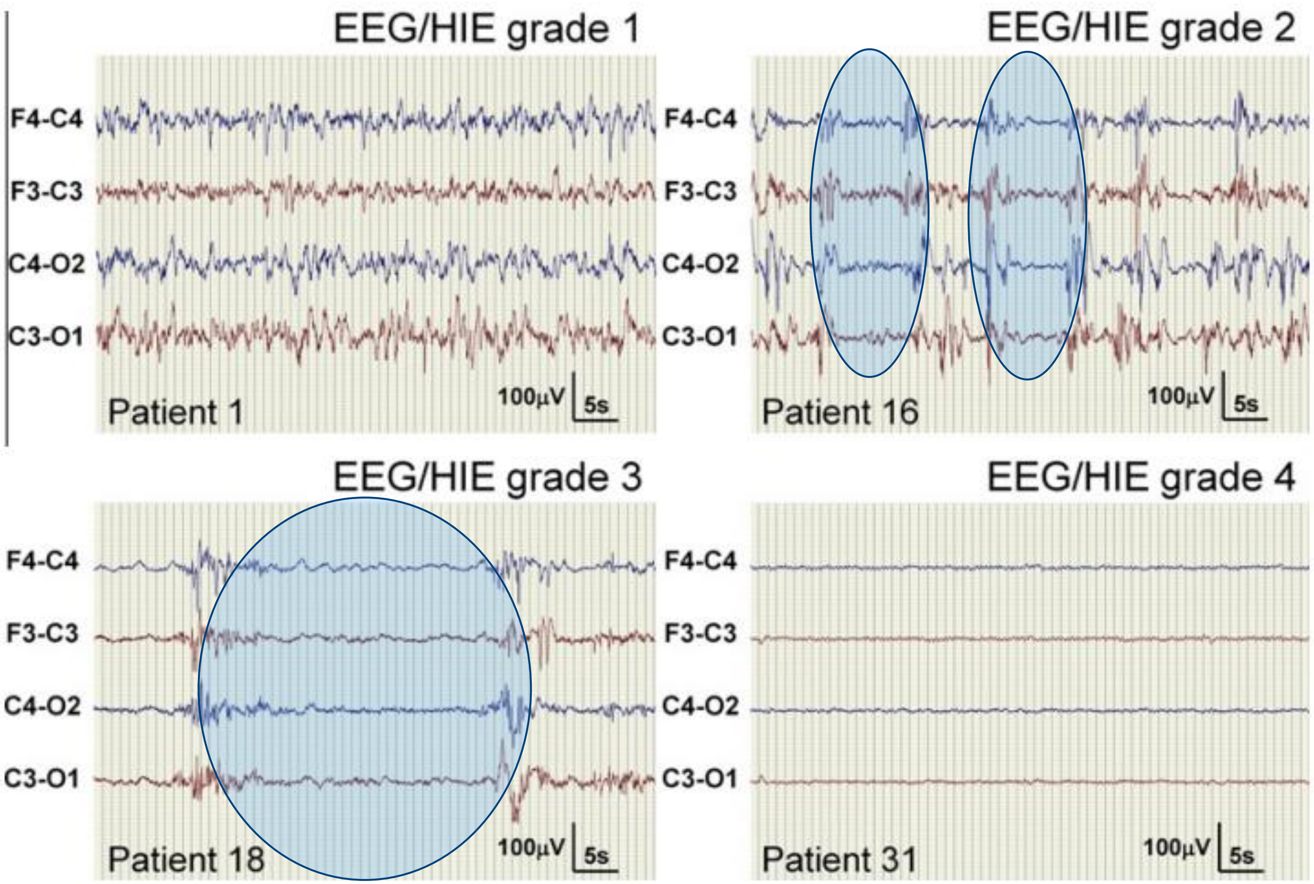
How Assessing Brain Recovery?
→ monitor abnormality of Background EEG

mildly abnormal

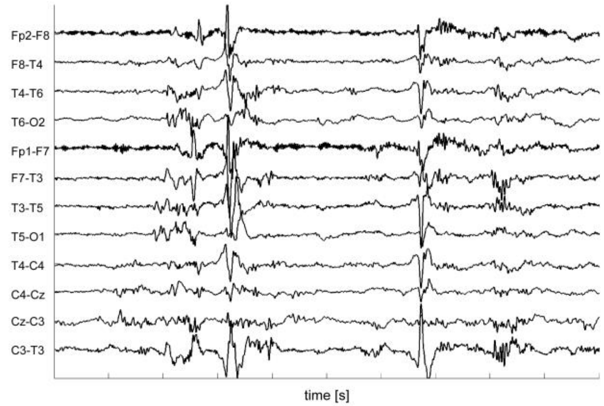
moderately abnormal

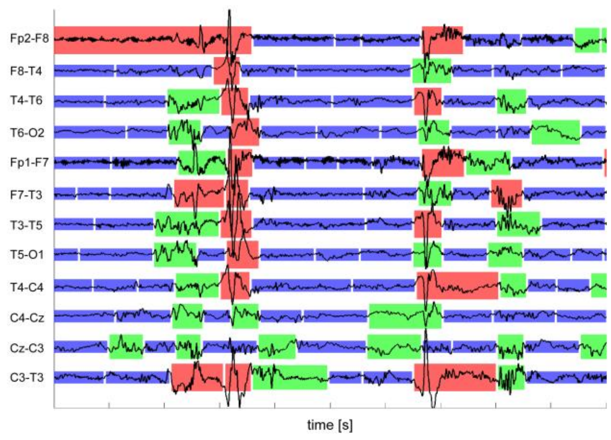


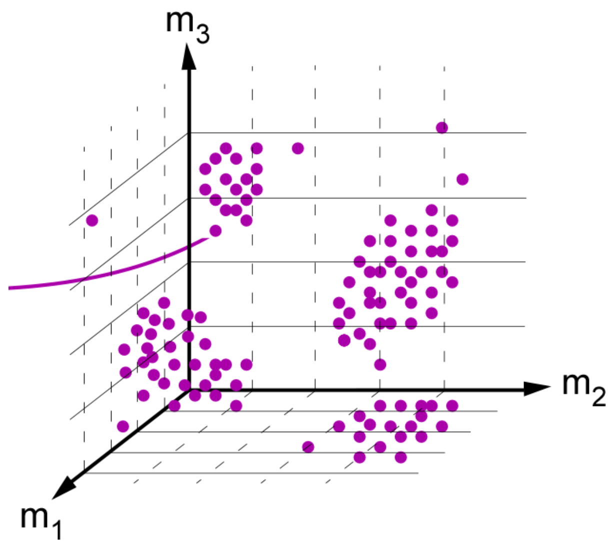
severely abnormal

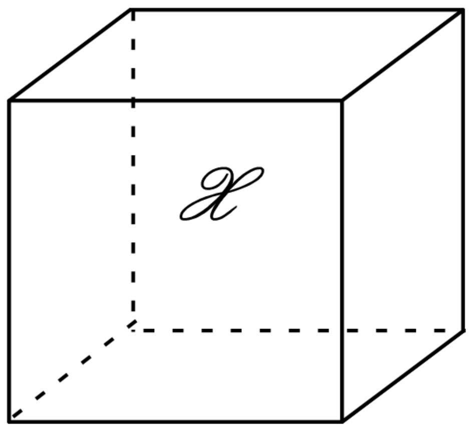
Ideal examples, taken from [Korotchikova et al., 2011]

Monitoring neonatal background EEG:
The power of structuring data









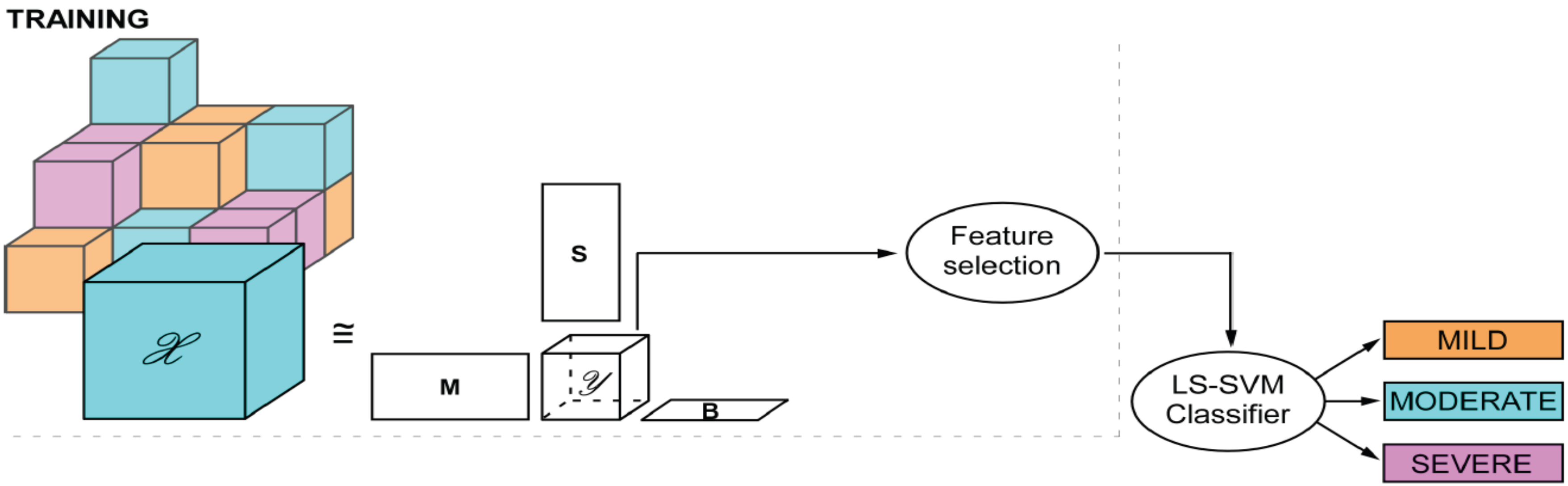
V. Matic et al., J. Neural Engineering, Oct. 2014

Higher Order Discriminant Analysis

-> compute simultaneous LMLRA

-> factors M, S, B common and orthogonal

-> maximizing the Fisher ratio between core tensors



Phan A and Cichocki A, Nonlinear Theory Appl., IEICE, 2010
Phan A, 2011, Matlab Software Toolbox
(www.bsp.brain.riken.jp/˜phan/nfea/nfea.html)

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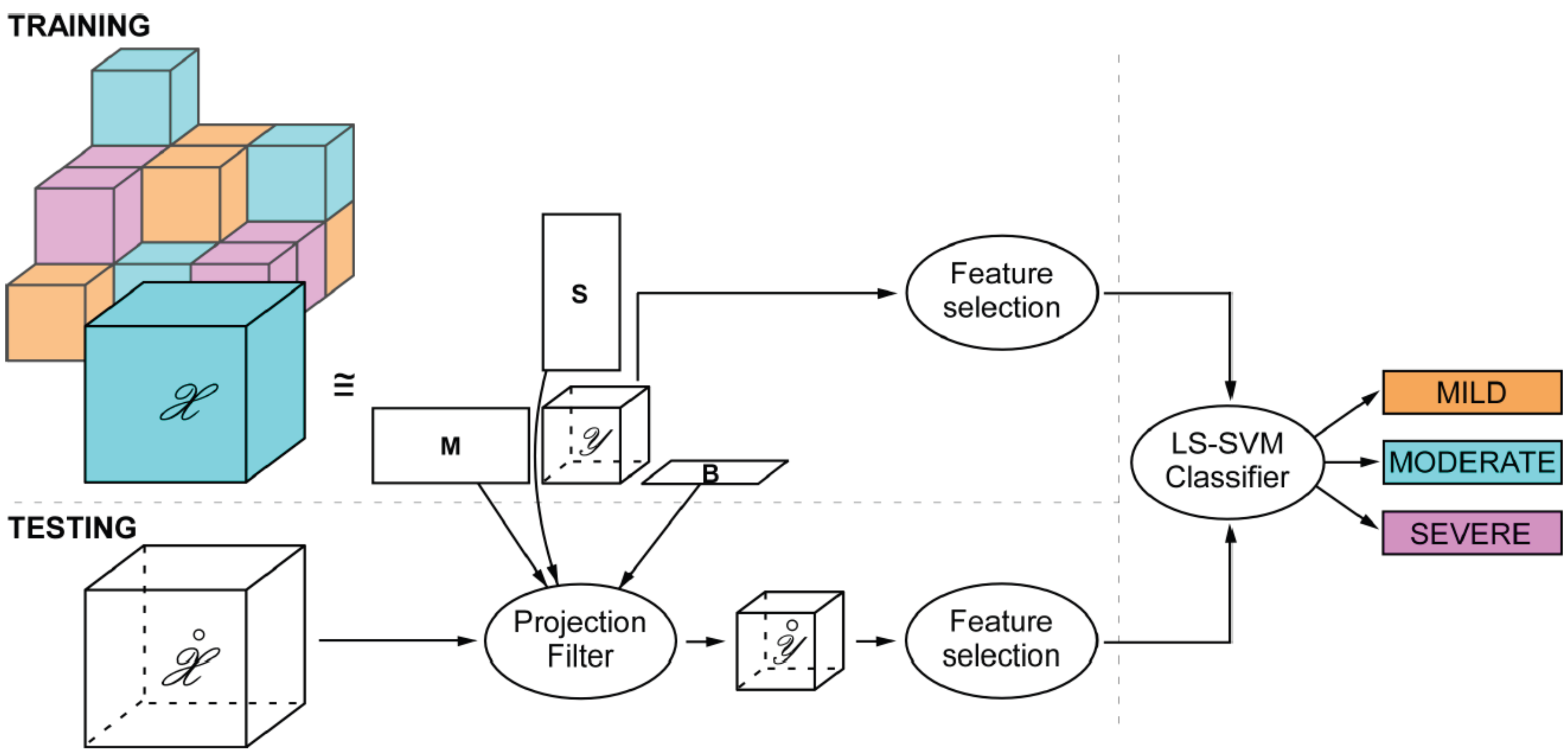
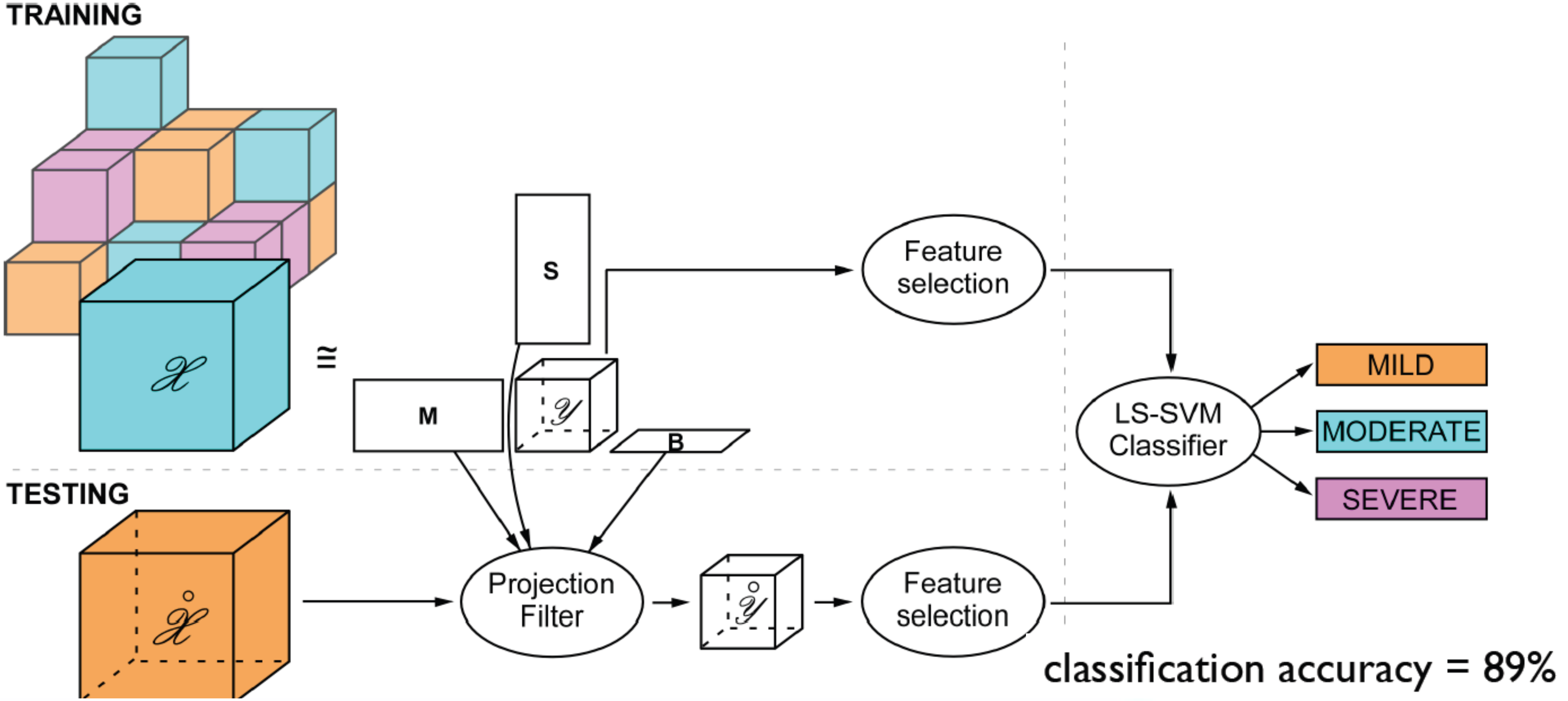
Higher Order Discriminant Analysis



Higher Order Discriminant Analysis



classification accuracy = 89%

Automated \ Expert EEG reader	MILD	MODERATE	SEVERE
MILD	73 (91%)	6	1
MODERATE	7	44 (76%)	7
SEVERE	0	8	126 (94%)
Achieved accuracy	91%	76%	(94%)

(V. Matic et al, J. Neural Eng. 11, 2014)

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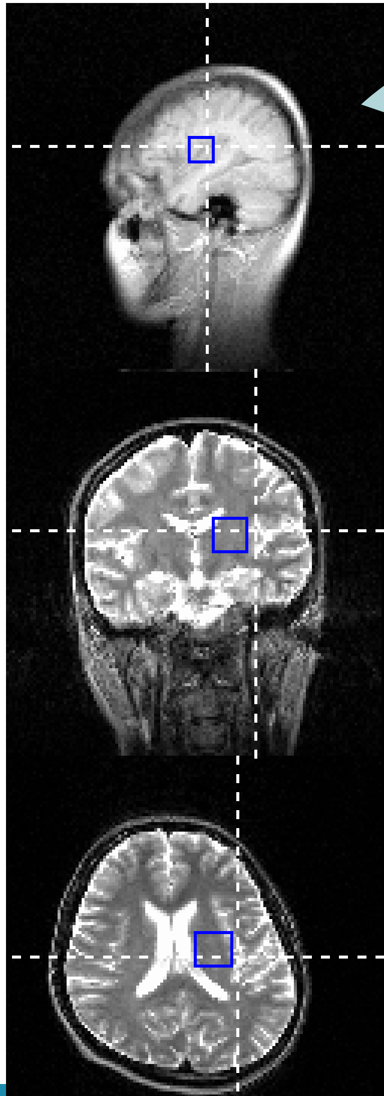
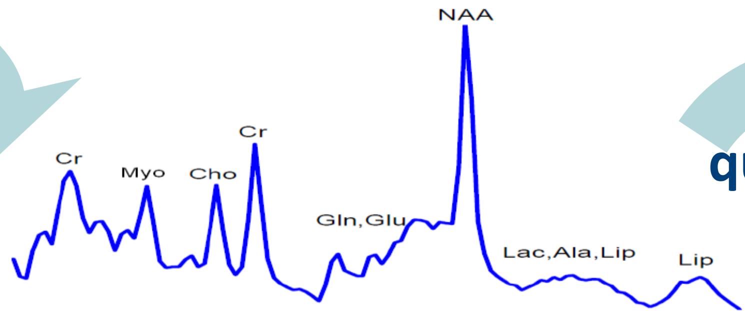
- Examples in Neonatal brain monitoring
- Examples in MR-based Brain tumor diagnosis
  - NMF
  - Hierarchical(h) NMF
  - Multimodal hNMF
  - Non-negative Tensor Factorization
- Conclusions and new directions

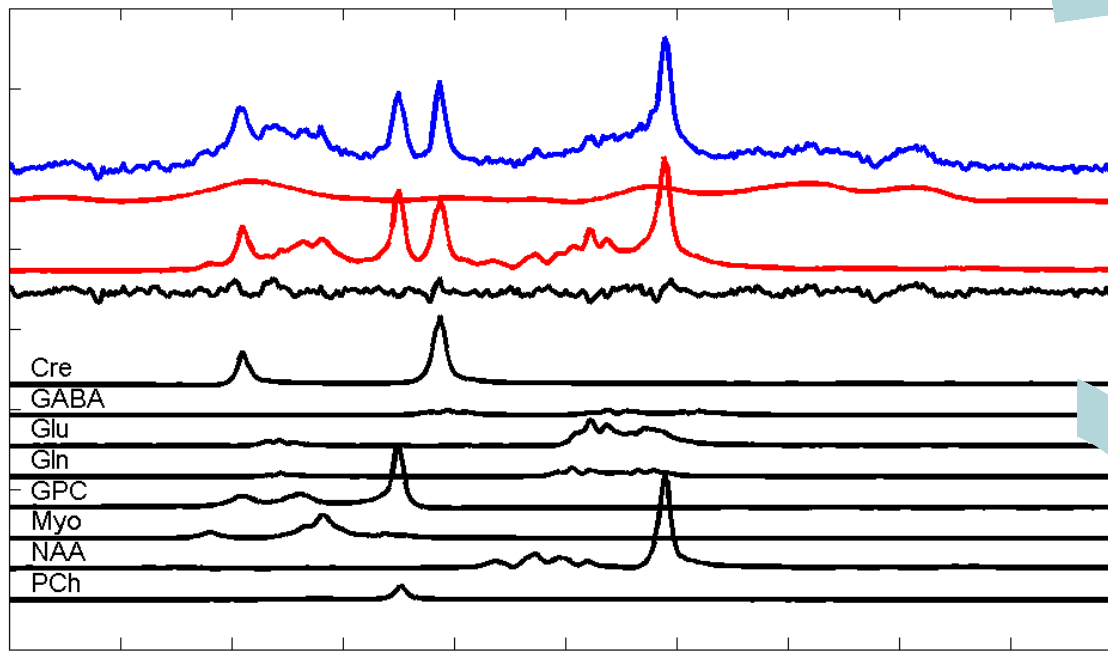
Metabolite quantification for MR Spectroscopy (MRS)



Single-voxel MRS

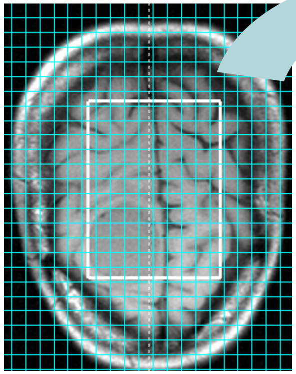


MRS quantification

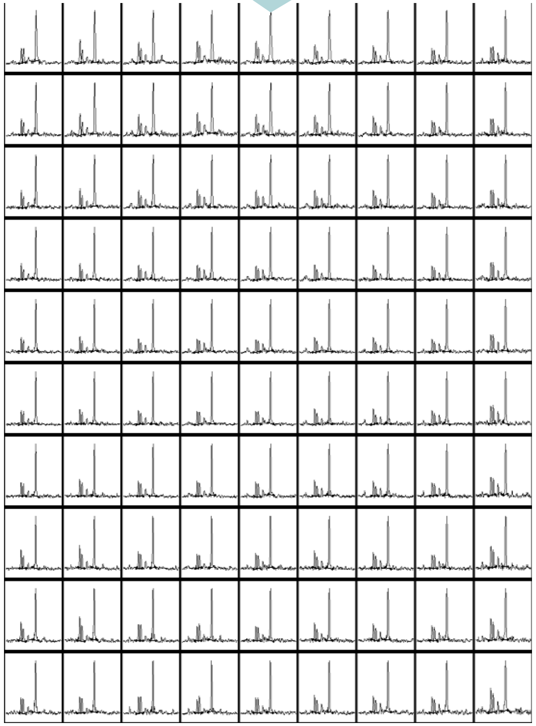


Metabolite conce

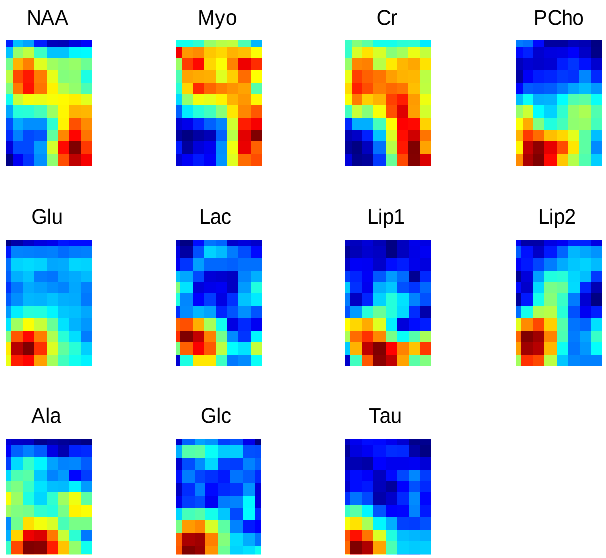
Metabolite quantification for MRS Imaging (MRSI)



Multi-voxel MRS



MRS quantification using spatial information



Metabolite maps

Metabolite concentrations = biomarkers of disease

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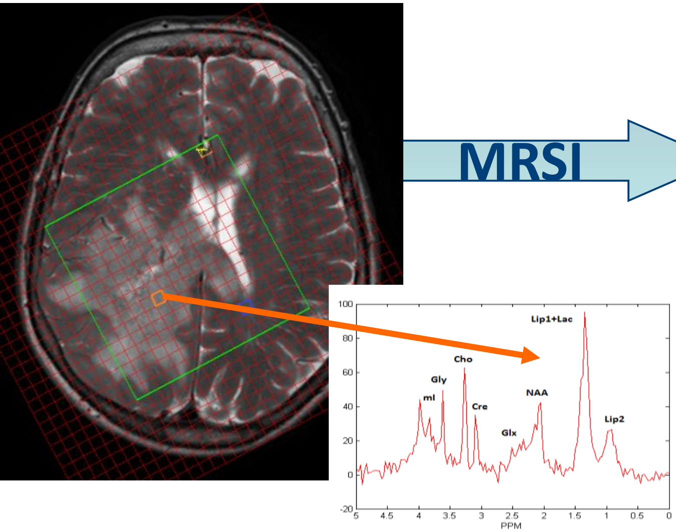
Unsupervised Brain Tumor Diagnosis using NMF



MRSI

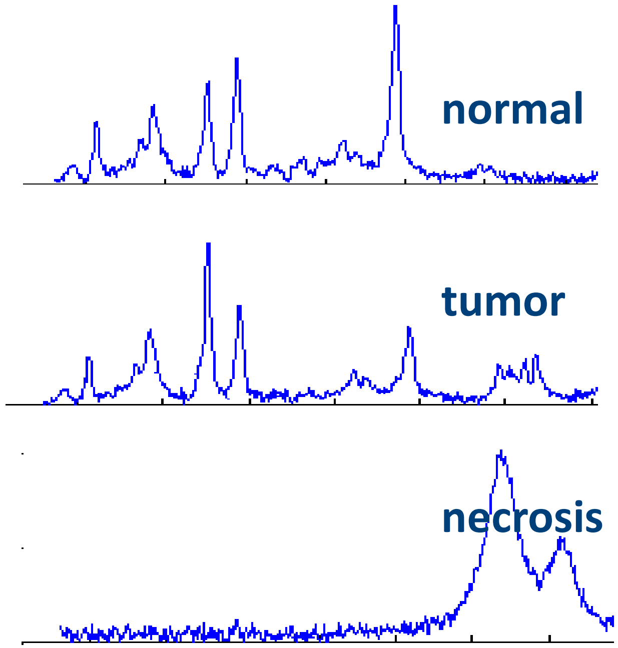
$\boldsymbol{Y}$ = matrix of spectra, $\boldsymbol{Y} \approx \boldsymbol{W}\,\boldsymbol{H}$

min || $\boldsymbol{Y}$ - $\boldsymbol{W}\,\boldsymbol{H}$ ||

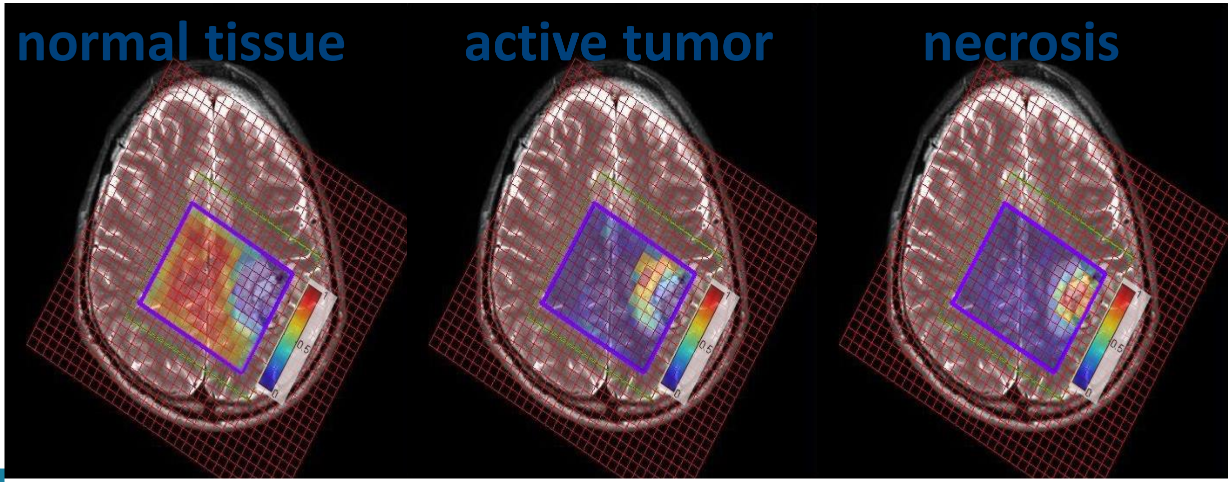
such that $\boldsymbol{W} \geq \boldsymbol{0}$, $\boldsymbol{H} \geq \boldsymbol{0}$

non-negative matrix factorization

W = tissue-specific spectral patterns:

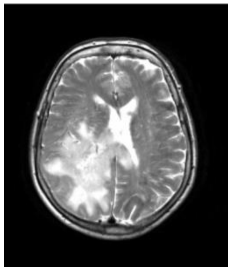


H = spatial distribution of tissue types:

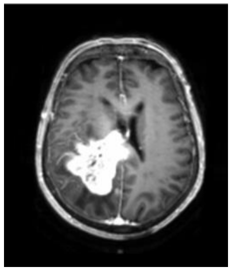


glioblastoma multiforme patient

Multi-Parametric (MP) NMF

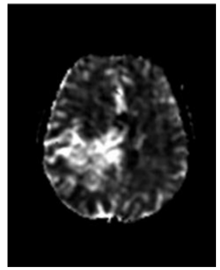


T2



T1

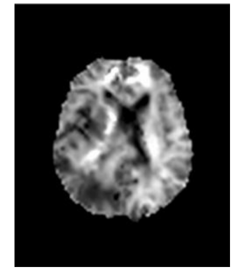
Anatomical MRI



CBV
Cerebral Blood Volume

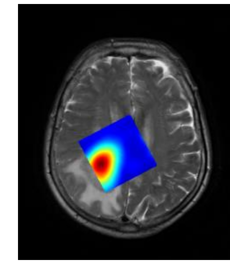
Perfusion MRI

MD
Mean Diffusion



MK
Mean Kurtosis

Diffusion MRI



NAA, Cre, tCho, Lip1,...

Spectroscopic MRI

<u>Research study:</u>

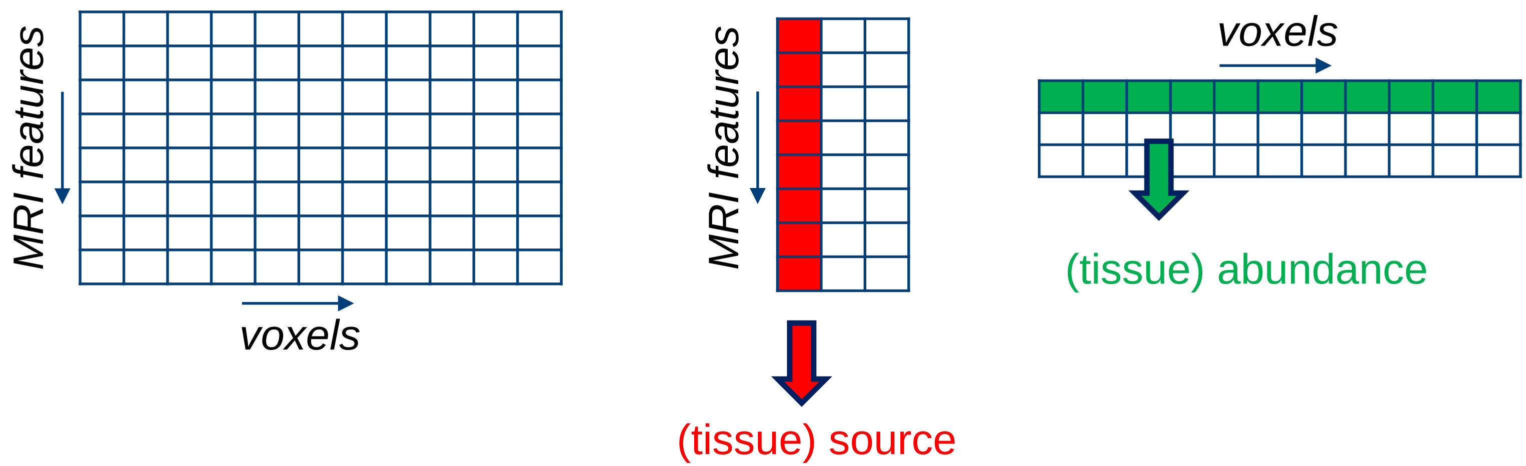
- 14 high-grade glioma (HGG) patients with complete MP-MRI dataset (3 grade III, 11 grade IV, UZ Leuven) and 10 low-grade gliomas

Research questions:

- *Do we get valid tissue differentiation with NMF on MP-MRI?*
- *What is added value of individual MRI modalities?*
- *How to improve NMF→ hierarchical NMF ? Tensor Factorisation?*

Non-negative matrix factorization (NMF)

$$\boldsymbol{Y} \approx \boldsymbol{W} \times \boldsymbol{H}$$

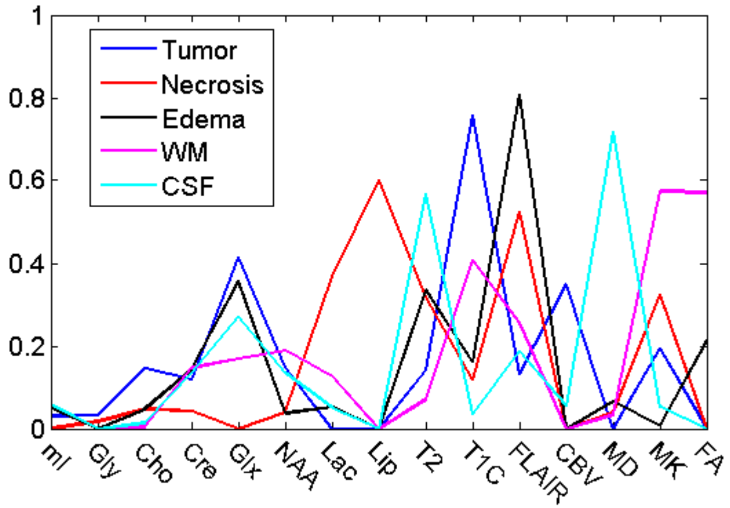


- Non-negativity constraint: $Y_{i,j}, W_{i,j}, H_{i,j} \geq 0, \forall i,j$
- Unsupervised: → applicable patient-by-patient,
  → tissue classes not a priori known
- MP-NMF:
  1. integrate ALL features of each modality into one vector
  2. use NMF

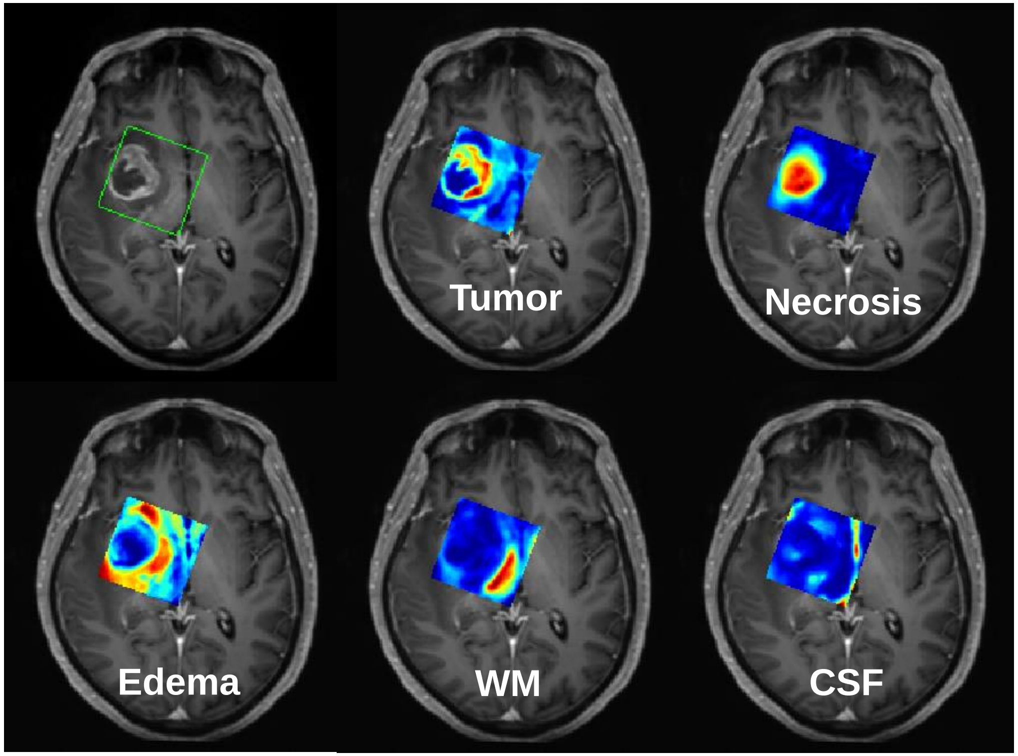
Case study: single stage NMF

5 tissue types within region of interest: active tumor, necrosis, edema, white matter, CSF

Tissue sources (W)



Tissue abundances (H)



Is this good/bad result?

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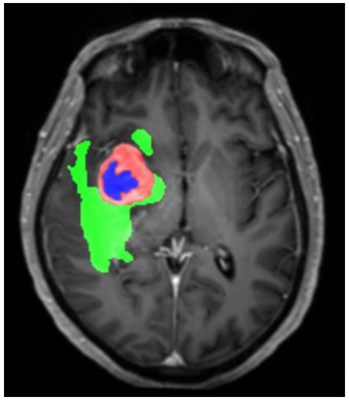
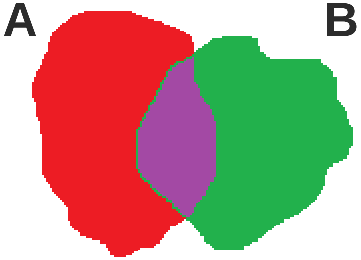
Validation



Based on manual segmentation by radiologist (only pathological tissue types)

1) **Dice-scores** (based on H)

$$Dice = 2x \frac{area(A \cap B)}{area(A) \cup area(B)}$$



2) **Correlation coefficients** (based on W)

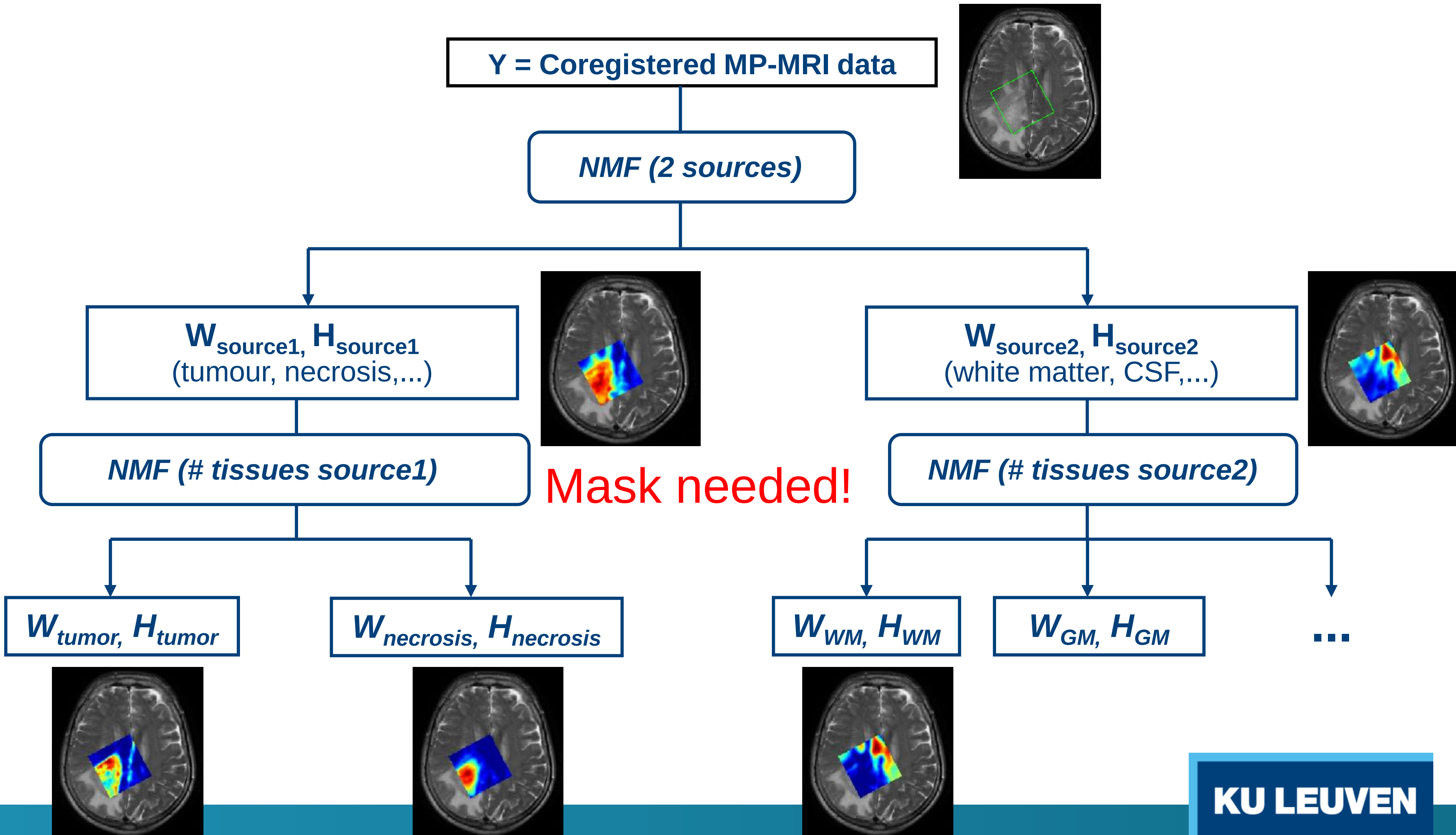
$$Corr = \frac{\vec{a}.\vec{b}}{\|\vec{a}\|.\|\vec{b}\|}$$

$\vec{a}$: tissue source vector

$\vec{b}$: average feature vector over corresponding tissue region

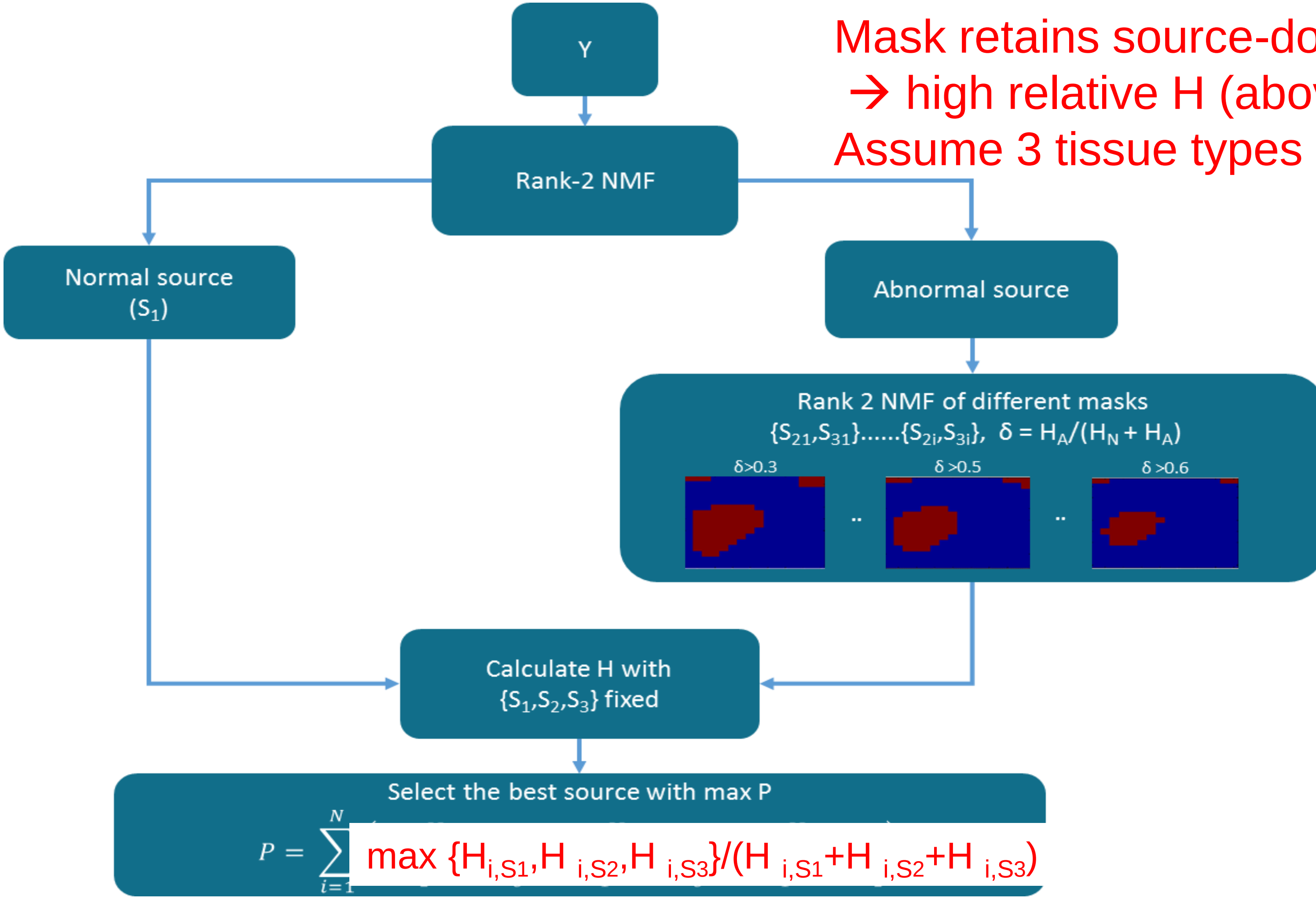
Hierarchical NMF (hNMF)

- Improved results on MRSI data only (Li et al., NMR in BioMed. 2013)



Hierarchical NMF: Select best Mask

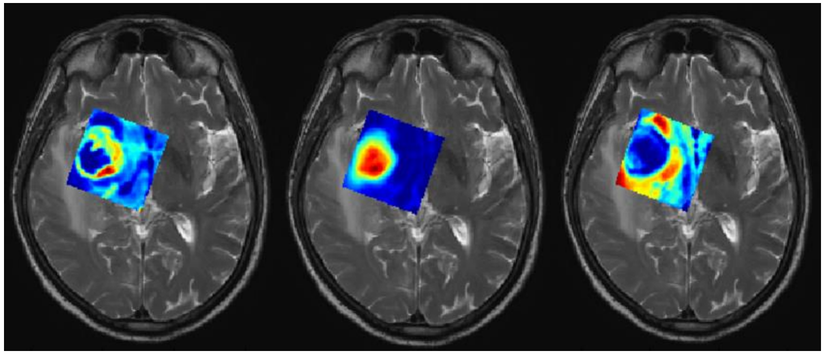
Mask retains source-dominant voxels:
→ high relative H (above threshold δ)
Assume 3 tissue types for simplicity



Sauwen N, Sima D, Van Cauter S, Veraart J, Leemans A, Maes F., Himmelreich U, Van Huffel S. Hierarchical non-negative matrix factorization to characterize brain tumor heterogeneity using multi-parametric MRI. NMR in BioMedicine, 2015, paper in review

Case study: single stage NMF vs hNMF

Single stage NMF



$Dice_{tumor}$ = 71%

$Dice_{tumor+necrosis}$ = 83%

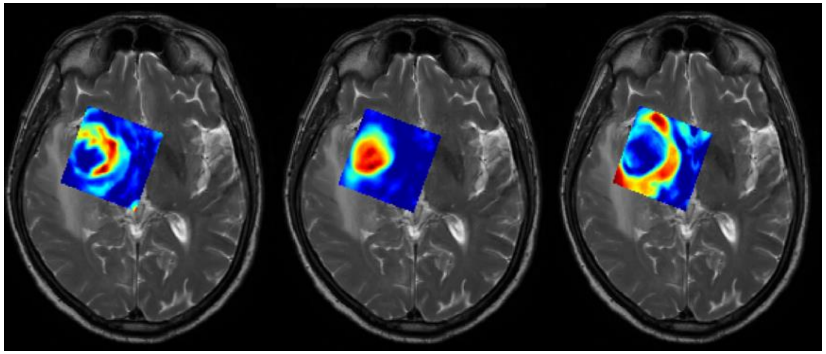
$Dice_{complete\ tumor}$ = 75%

$Corr_{tumor}$ = 0.60

$Corr_{necrosis}$ = 0.97

$Corr_{edema}$ = 0.93

hNMF



$Dice_{tumor}$ = 81%

$Dice_{tumor+necrosis}$ = 92%

$Dice_{complete\ tumor}$ = 83%

$Corr_{tumor}$ = 0.78

$Corr_{necrosis}$ = 0.98

$Corr_{edema}$ = 0.97

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Full study results: Dice-scores

HGG	Dice-score active tumor [%]						Dice-score tumor core [%] (active tumor + necrosis)						Dice-score complete tumor [%] (active tumor + necrosis + edema)					
	Full MP-MRI	no-cMRI	no-PWI	no-MRSI	no-DKI	cMRI only	**Full MP-MRI**	no-cMRI	no-PWI	no-MRSI	no-DKI	cMRI only	**Full MP-MRI**	no-cMRI	no-PWI	no-MRSI	no-DKI	cMRI only
Average	**78**	65	76	71	76	69	**85**	77	81	79	79	71	**83**	75	79	76	77	68
Std dev	**10**	14	19	16	12	18	**11**	14	18	17	14	17	**14**	15	17	18	14	18
p-value	-	0.001*	0.54	0.03*	0.18	0.004*	-	0.003*	0.28	0.01*	0.002*	0.001*	-	0.002*	0.03*	0.001*	0.003*	0.001*

** Statistical significance of lower Dice-scores compared to full MP-MRI based on one-tailed Wilcoxon signed rank test, $p<0.05$*

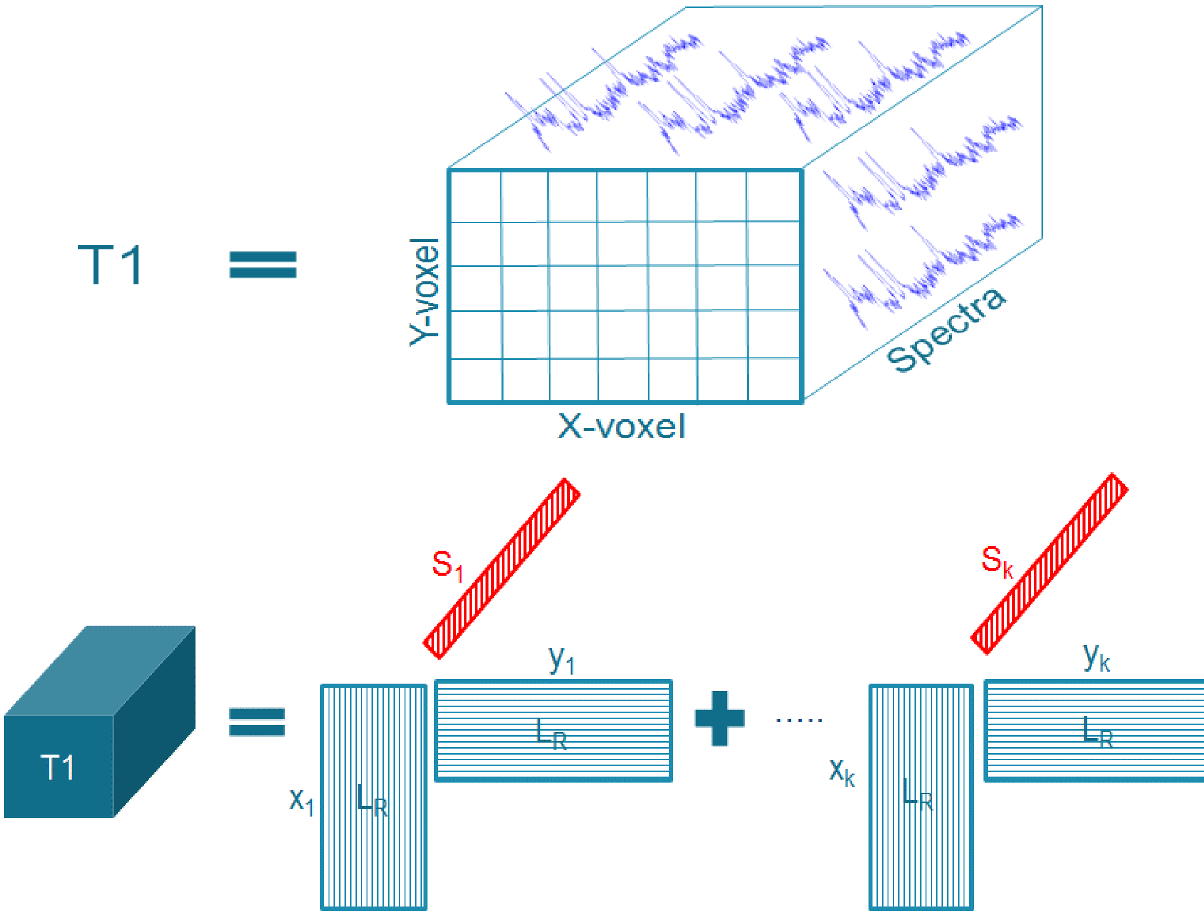
Combining 4 MRI modalities
improves brain tissue differentiation

Similar conclusions when comparing correlation coefficients

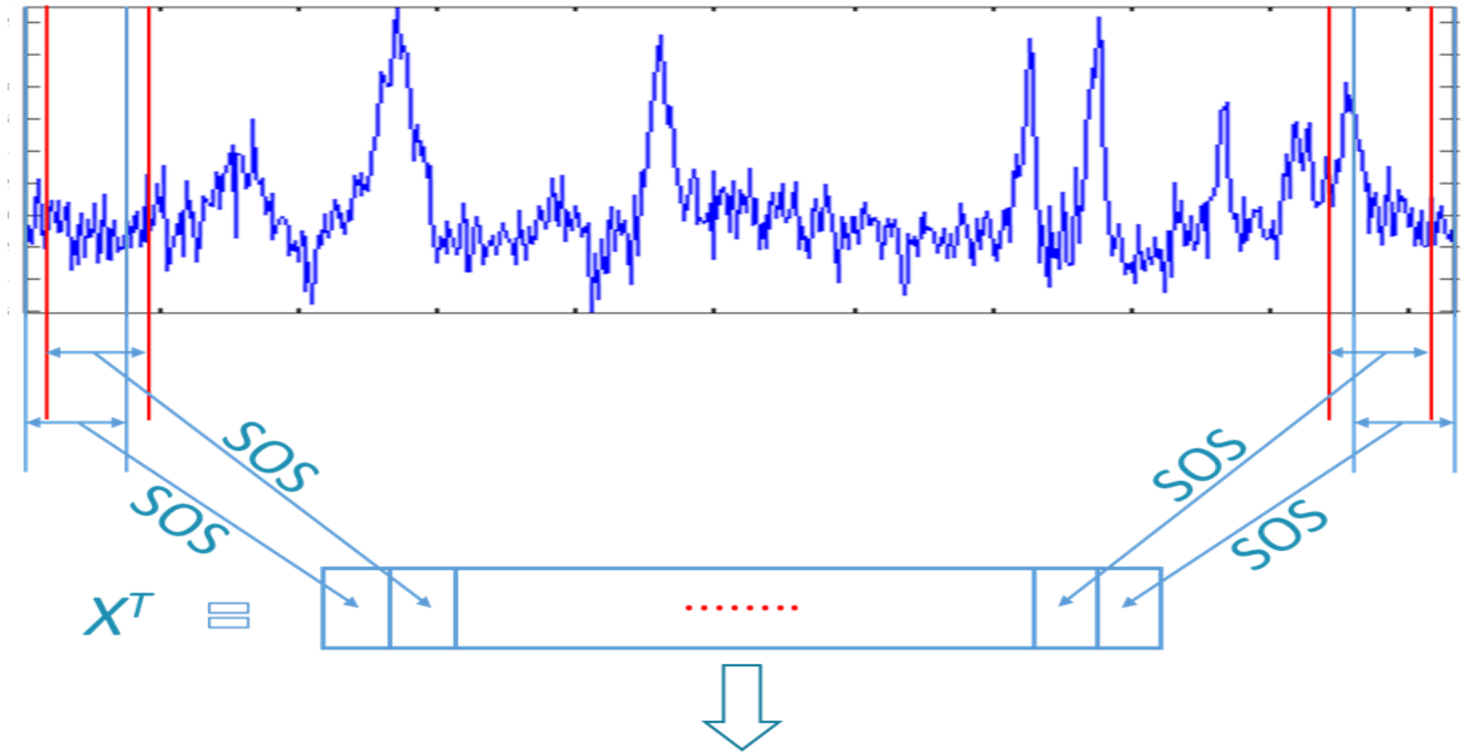
Spatial Tensor Representation (MRSI only)

- Frontal slices (XY^T) representing the spatial distribution of a tissue type does not have low rank structure.

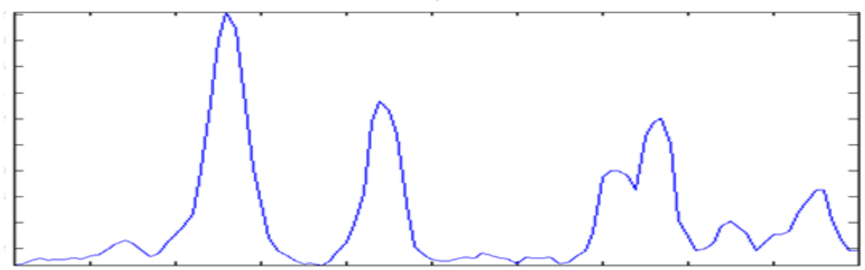
- Difficult to find the rank L_R for a particular tissue type distribution.



XX^T based Tensor Representation (MRSI only)



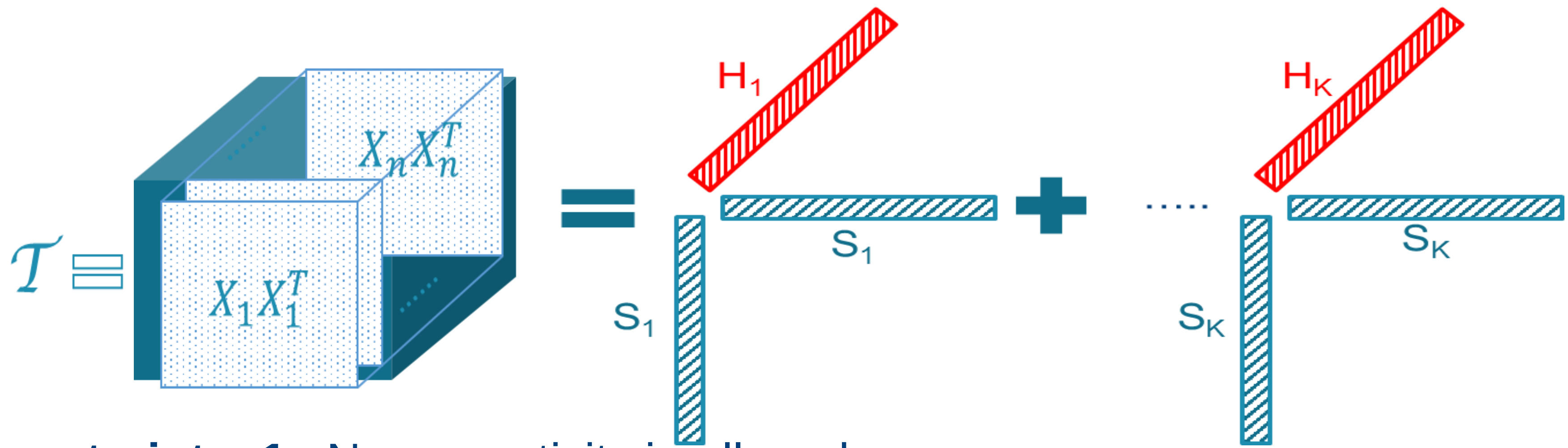
$$X(i) = \sum_{j=1}^{L} S_{ij}^2$$



- Spectra reduced in length and denoised without losing vital information,
- Peaks get higher weights,
- Peaks coupled because of XX^T in the frontal slices

HN Bharath et al, Proc. IEEE-EMB Symposium, Milan, Italy, Aug 2015, to appear

Non-negative CPD for Tumor Differentiation



- **Constraints: 1.** Non-negativity in all modes

  2. Symmetry in frontal slices

  3. Sparsity in H-factor

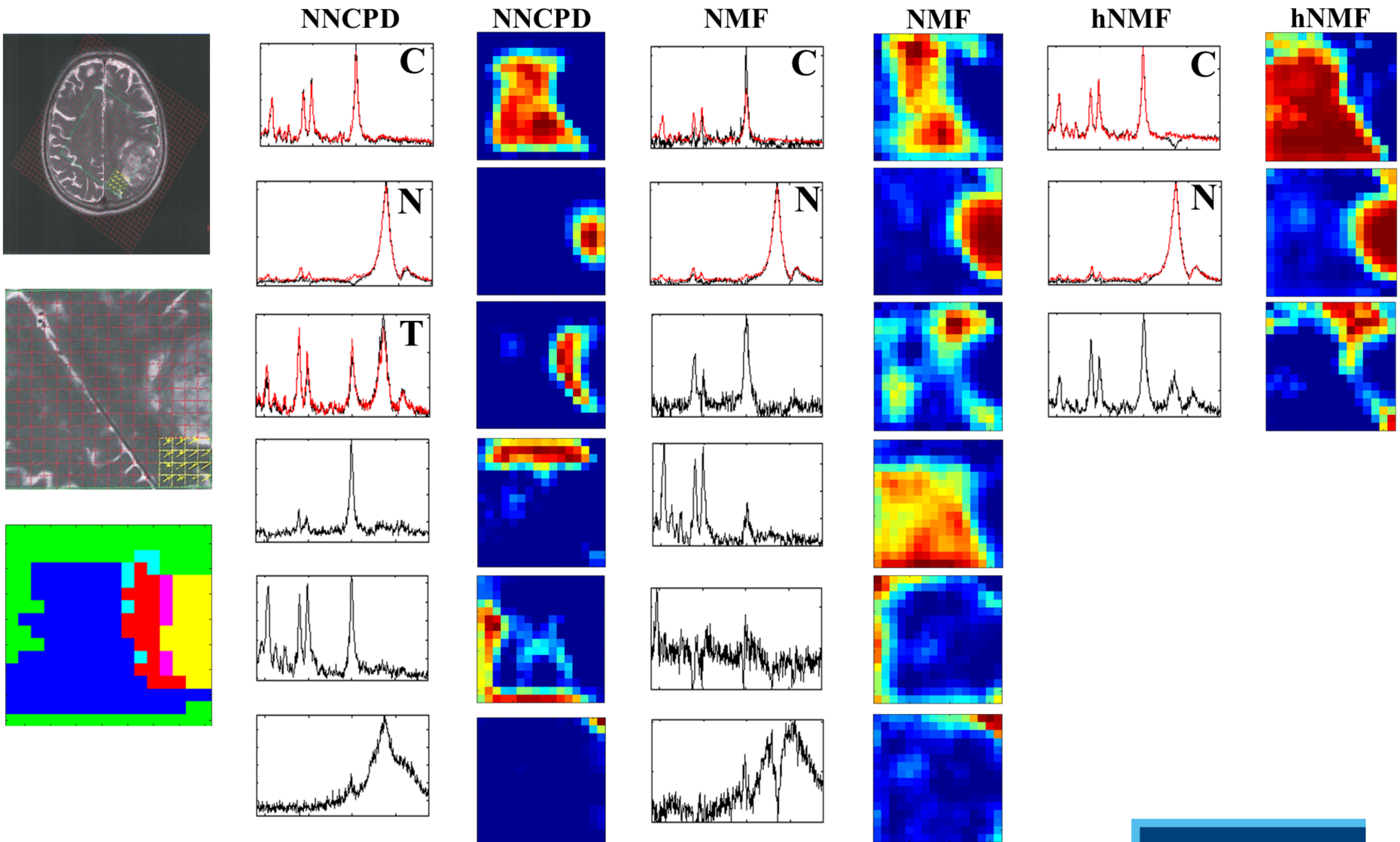
→ apply Non-negative CPD with L_1 regularization using Tensorlab[1]

$$[S^*, H^*] = \min_{S\geq 0, H\geq 0} \left\| T - \sum_{r=1}^{K} S(:,r) \circ S(:,r) \circ H(:,r), \right\|_2^2 + \lambda |Vec(H)|_1$$

- Using H*, recover tissue-specific spectra W from Y via LS
- Using W, recover tissue-type spatial distributions H from Y via NN-LS

[1] *Laurent Sorber, Marc Van Barel and Lieven De Lathauwer. Tensorlab v2.0, Available online, January 2014. URL: http://www.tensorlab.net/.*

Result: Patient-2



Source Correlation: Algorithm vs Expert labeling (MRSI only)

W		NCPD	Single stage NMF	hNMF	Grade
PATIENT-2	T	**0.99**	X	X	High
PATIENT-2	N	**0.9975**	0.9971	0.9972	High
Median/MAD	T	**0.98** /0.0112	0.67 /0.0514	0.87 /0.0093	High
Median/MAD	N	**0.9969**/0.0013	0.9945/0.0028	0.9967/0.0005	

Abundance map Correlation: Algorithm vs Expert labeling

H		NCPD	Single stage NMF	hNMF	Grade
PATIENT-2	T	**0.80**	X	X	High
PATIENT-2	N	**0.9552**	0.8949	0.8967	High
Median/MAD	T	**0.79** /0.0380	0.69 /0.0849	0.69 /0.0731	High
Median/MAD	N	**0.87**42/0.0276	0.7876/0.0662	0.8009/0.0716	

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Contents Overview

- Introduction
- Examples in Neonatal brain monitoring
- Examples in MR-based Brain tumor diagnosis
- Conclusions and new directions

Conclusions and new directions

- Many BSS problems in Smart Diagnostics are low rank
  → solve via matrix or tensor factorization plus constraints

- Successful examples shown, e.g., in neonatal brain monitoring, brain tissue typing

- Extensions to biomedical data fusion emerge, e.g. EEG-fMRI
  → solve via coupled matrix /tensor decompositions

- Other BSS applications: *bioinformatics (O. Alter, E. Acar), BCI (Cichocki, Mørup, Martinez-Montes), mobile EEG, multichannel ECG*

New directions?

- *Adaptive tensor decompositions, rank & structure estimation*
- *Applications increasing in BCI, (single-trial) ERP, ECG, MRSI*

→ *exploit full potential of Tensor toolbox*

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Thank you!

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Local Organisers: Sabine Van Huffel and Lieven De Lathauwer

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