A Nonlinear Variational Method for Improved Quantification of Myocardial Blood Flow Using $H_2^{15}$O PET

Seminar Wissenschaftliches Rechnen, Kleinwalsertal

Martin Benning
martin.benning@wwu.de

Westfälische Wilhelms-Universität, Münster
Institut für Numerische und Angewandte Mathematik

15.02.09
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Motivation

Every year up to 12 million people die due to cardiovascular diseases. More than 50% of these cases of death could have been prevented by early diagnosis. Cardiovascular diseases are the most common cause of death in industrialized countries.
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![Chart showing major causes of death]
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Motivation

- Many cardiovascular diseases originate in atherosclerosis (especially in the cardiovascular vessels)

- Typical way of diagnosis: **catheterization**.
- Disadvantage: invasive and therefore cumbersome for patients; possible risk of thrombosis, embolism, infections or cardiac arrhythmia
- Furthermore, detected constrictions must not be the result of plaque, but can have different reasons (potential of false diagnosis)
Motivation

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Dynamic $\text{H}_2^{15}\text{O}$ PET

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- In particular, $H_2^{15}O$ as a tracer allows investigation of perfusible tissue
- With the use of simple kinetic models, conclusions on perfusion in myocardium and on blood flow in adjacent vessels can be drawn
Dynamic $\text{H}_2\text{O}^{15}\text{O}$ PET

- Dynamic PET allows noninvasive investigation of physiological processes within the body.
- In particular, $\text{H}_2\text{O}^{15}\text{O}$ as a tracer allows investigation of perfusible tissue.
- With the use of simple kinetic models, conclusions on perfusion in myocardium and on blood flow in adjacent vessels can be drawn.
- Furthermore $\text{H}_2\text{O}^{15}\text{O}$ offers a half-life of about 2 min. and therefore adds a small radiation exposure to the patient.
Dynamic $\text{H}_2^{15}\text{O}$ PET

- Disadvantage: due to the short half-life of $\text{H}_2^{15}\text{O}$ the quality of reconstructed images is very poor
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**Figure:** A 2D $\text{H}_2^{15}\text{O}$ EM reconstruction of a transaxial slice intersecting the cardiovascular region, with added Gaußian smoothing
A couple of low quality reconstructions provide the basis for postprocessing via a kinetic model to obtain physiological parameters that describe e.g. perfusion.
Dynamic $\text{H}_2^{15}\text{O}$ PET

- A couple of low quality reconstructions provide the basis for postprocessing via a kinetic model to obtain physiological parameters that describe e.g. perfusion
- **Main drawback** is that computation of low quality reconstructions and subsequent postprocessing via a kinetic model is done *independently* of each other
Dynamic $\text{H}_2^{15}\text{O}$ PET

- A couple of low quality reconstructions provide the basis for postprocessing via a kinetic model to obtain physiological parameters that describe e.g. perfusion.
- **Main drawback** is that computation of low quality reconstructions and subsequent postprocessing via a kinetic model is done independently of each other.
- **New approach**: integrate the process of kinetic modelling into the reconstruction process to compute more accurate parameters (parameters are computed from the PET data and not from low resolution images).

\[
p(x,t) \xrightarrow{G\text{ nonlinear}} u(x,t) \xrightarrow{B\text{ linear}} f(\sigma, \theta, t)
\]
Basic Mathematics for PET
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- The basic principle of PET

leads to the following inverse problem
The Inverse Problem of PET

The basic inverse problem of PET is to obtain an image $u : \Omega \subset \mathbb{R}^n \rightarrow \mathbb{R}$ from the operator equation

$$\varphi(Bu) = f,$$

where $f : \Sigma \rightarrow \mathbb{R}$ is the measured PET data, $\varphi$ is an operator guaranteeing Poisson statistics and $B$ is the X-ray transform, defined as

$$(Bu)(\theta, x) = \int_{\mathbb{R}} u(x + t\theta) dt,$$

with $\theta \in S^{n-1}$ and $x \in \theta^\perp$. 
The Inverse Problem of PET

The basic inverse problem of PET is to obtain an image \( u : \Omega \subset \mathbb{R}^n \rightarrow \mathbb{R} \) from the operator equation

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(1)

where \( f : \Sigma \rightarrow \mathbb{R} \) is the measured PET data, \( \varphi \) is an operator guaranteeing Poisson statistics and \( B \) is the X-ray transform, defined as

\[
(Bu)(\theta, x) = \int_{\mathbb{R}} u(x + t\theta) dt ,
\]

(2)

with \( \theta \in S^{n-1} \) and \( x \in \theta^\perp \).

• In two dimensions, the X-ray transform is equivalent to the Radon transform
Since positrons are Poisson distributed, the standard approach to solve (1) is to compute the unique and global minimizer

Minimization of Kullback-Leibler functional

\[ u \in \arg\min_{u \in \mathcal{U}} KL(f, Bu), \quad (3) \]

with

\[ KL(f, Bu) = \int_{\Sigma} f \log \left( \frac{f}{Bu} \right) + Bu - f \, dx, \quad (4) \]

in an appropriate function space \( \mathcal{U} \) (e.g. \( \mathcal{U} = L_2(\Omega) \)).
The minimum of (3) can be computed via

Optimality condition

\[ B^*1 - B^* \left( \frac{f}{Ru} \right) = 0. \]
The minimum of (3) can be computed via

**Optimality condition**

\[ B^*1 - B^* \left( \frac{f}{Ru} \right) = 0. \]  \hspace{1cm} (5)

In discrete terms equation (5) can be computed via the standard EM algorithm

**Standard EM algorithm**

\[ u_{k+1} = \frac{u_k}{B^*1} B^* \left( \frac{f}{Bu_k} \right), \]  \hspace{1cm} (6)

with 1 being the constant 1-function and an initial value \( u_0 > 0 \).
State-of-the-art MBF Quantification

To obtain physiological parameters, a sequence of images (frames) has to be computed via (6)
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State-of-the-art MBF Quantification

- To obtain physiological parameters, a sequence of images (frames) has to be computed via (6) \( \Rightarrow u(x, t), \text{ for } t \in [0, T] \)
- Sequence \( u(x, t) \) provides the basis for computation of physiological values, as e.g. MBF, via a kinetic model.

Subsequent parameter computation via nonlinear fitting.
To apply a kinetic model, segmentation of the cardiovascular region is needed, e.g. via factor images.
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The cardiovascular region has to be segmented into myocardial tissue, left and right ventricle to extract information on the radioactive distribution in the chambers and to apply a kinetic model to the myocardial tissue region.

In this talk we do not want to address the problem of segmentation but the challenge of computing parameters with given segmentation from the data instead of the images.
Since we use a rough segmentation in image space we want to introduce some basic notations to differ between the different spatial regions.
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**Notation**

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<thead>
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<tbody>
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**Notation**

- Ω denotes the whole image
- ℰ denotes the region of myocardial tissue
- ℬ represents the left ventricular region
- ℰ stands for the right ventricular region
Since we use a rough segmentation in image space we want to introduce some basic notations to differ between the different spatial regions

**Notation**

- $\Omega$ denotes the whole image
- $\mathcal{T}$ denotes the region of myocardial tissue
- $\mathcal{A}$ represents the left ventricular region
- $\mathcal{V}$ stands for the right ventricular region
- $\mathcal{H}$ with $\mathcal{H} = \mathcal{T} \cup \mathcal{A} \cup \mathcal{V}$ represents the whole cardiovascular region

With given segmentation a physiological model has to be applied to the myocardial region
Physiological Models for MBF-Quantification

The standard model for MBF quantification is the one-tissue-compartmental model:

\[
\frac{\partial C_T(x,t)}{\partial t} = F(x)(C_A(t) - C_T(x,t))\lambda,
\]

respectively its associated integral equation:

\[
C_T(x,t) = F(x)\int_0^t C_A(\tau)e^{-F(x)\lambda(t-\tau)}d\tau,
\]

where \(F\) denotes the MBF, \(C_A\) represents the left ventricular blood over time and \(\lambda\) is a fixed partition coefficient (e.g. \(\lambda = 0.96\)).
Physiological Models for MBF-Quantification

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\frac{\partial C_T(x, t)}{\partial t} = F(x) \left( C_A(t) - \frac{C_T(x, t)}{\lambda} \right), \tag{7}
\]

respectively its associated integral equation

\[
C_T(x, t) = F(x) \int_0^t C_A(\tau) e^{-\frac{F(x)}{\lambda}(t-\tau)} d\tau, \tag{8}
\]

where \(F\) denotes the MBF, \(C_A\) represents the left ventricular blood over time and \(\lambda\) is a fixed partition coefficient (e.g. \(\lambda = 0.96\)).
Interesting properties of $C_T$
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- The operator $\mathbf{C}_T$ represented by (8) offers the following interesting properties

Properties of $\mathbf{C}_T$

- $\mathbf{C}_T : \mathcal{D}_p(\mathbf{C}_T) \to L_p(\Omega \times [0, T])$ is non-negative,
Interesting properties of \( C_T \)

- Equation (8) represents a nonlinear operator \( C_T(F, C_A) \) with solution \( C_T \)
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**Properties of \( C_T \)**

- \( C_T : D_p(C_T) \to L_p(\Omega \times [0, T]) \) is non-negative,
- \( C_T : D_p(C_T) \to L_p(\Omega \times [0, T]) \) is well-defined and \( L_p \)-continuous on \( D_p(C_T) \),
Interesting properties of $C_T$

- Equation (8) represents a nonlinear operator $C_T(F, C_A)$ with solution $C_T$.
- The operator $C_T$ represented by (8) offers the following interesting properties:

**Properties of $C_T$**

- $C_T : \mathcal{D}_p(C_T) \rightarrow L_p(\Omega \times [0, T])$ is non-negative,
- $C_T : \mathcal{D}_p(C_T) \rightarrow L_p(\Omega \times [0, T])$ is well-defined and $L_p$-continuous on $\mathcal{D}_p(C_T)$,
- $C_T : \mathcal{D}_p(C_T) \cap (L_{2p}(\Omega) \times L_{2p}([0, T])) \rightarrow L_p(\Omega \times [0, T])$ is Fréchet differentiable, with

$$\mathcal{D}_p(C_T) := \{F \in L_p(\Omega), C_A \in L_p([0, T]) \mid F \geq 0, C_A \geq 0\} \quad (9)$$

and for $p \geq 1$.
Recall the basic principle of novel MBF quantification as a Nonlinear Inverse Problem.

Based on (8) we introduce a new operator $G$ that produces an image sequence $u$ from physiological parameters $p$, i.e. $G(p) = u$, e.g.

$G(F, C_A, C_V) = C_T | T + C_A | A + C_V | V (10)$
Recall the basic principle of novel MBF quantification

\[ p(x, t) \xrightarrow{G} u(x, t) \xrightarrow{B} f(\sigma, \theta, t) \]

Inversion of nonlinear operator \( G \)
Quantification as a Nonlinear Inverse Problem

- Recall the basic principle of novel MBF quantification

\[
p(x, t) \xrightarrow{G} u(x, t) \xrightarrow{B} f(\sigma, \theta, t)
\]

\[
G(p) = u, \text{ e.g.}
\]

Exemplary Operator \( G \)

\[
G(F, C_A, C_V) = C_T |_T + C_A |_A + C_V |_V
\]
Since we are interested in the parameters $p$ we now need to consider the inverse problem

**Modified Minimization Problem**

$$p \in \arg \min_{p \in \mathcal{P}} \{ KL_T(f, BG(p)) + \mathcal{R}(p) \},$$  \hspace{1cm} (11)

$$KL_T(f, Bu) = \int_0^T \int_\Sigma \sum f \log \left( \frac{f}{Bu} \right) + Bu - f \, dx \, dt,$$  \hspace{1cm} (12)

with $\mathcal{P}$ denoting the domain of parameters and $\mathcal{R}$ guaranteeing regularization to the parameters $p$. 
This minimization problem can be rewritten to the constrained problem

\[
KL_T(f, Bu) + R(p) \rightarrow \min_{p \in \mathcal{P}} \quad \text{subject to } u = G(p)|_\mathcal{H},
\]
This minimization problem can be rewritten to the constrained problem

**Constrained problem**

\[
KL_T(f, Bu) + \mathcal{R}(p) \rightarrow \min_{p \in P} \quad \text{subject to } u = G(p)|_\mathcal{H},
\]

Rewritten in terms of a Lagrange multiplier with \( L_2 \) dual product we obtain

**Lagrange multiplier**

\[
\mathcal{L}(u, p; q) = KL_T(f, Bu) + \mathcal{R}(p) + \langle G(p) - u, q \rangle_{L_2([0, T] \times \mathcal{H})}
\]
The optimality conditions of (14) are

\begin{align*}
q &= B^* 1 - B^* \left( \frac{f}{Bu} \right), \\
(G')(p) q &= -\mathcal{R}'(p),
\end{align*}

\begin{align*}
u &= G(p).
\end{align*}
The optimality conditions of (14) are

\[ q = B^*1 - B^* \left( \frac{f}{Bu} \right), \quad (15) \]

\[ (G')^*(p) \ q = -R'(p), \quad (16) \]

\[ u = G(p). \quad (17) \]

If we multiply (15) with \( u \) this yields

\[ 0 = uB^*1 - uB^* \left( \frac{f}{Bu} \right) - uq. \quad (18) \]
Reminder

\[ 0 = u_B^* - u_B^* (f_{Bu}) - u_q = B^* \begin{bmatrix} u - u_B^* (f_{Bu}) \\ \end{bmatrix} - u_q \]

Adding * to * and setting this equation to zero satisfies the optimality condition of the Kullback-Leibler functional (5) for each timestep.

Idea: Replace * with the discrete solution of (5) and solve equation (18) with the iterative scheme.
Reminder

\[ 0 = uB^*1 - uB^* \left( \frac{f}{Bu} \right) - uq \]

\[ = B^*1 \left( u - \frac{u}{B^*1} \left( \frac{f}{Bu} \right) \right) - uq \]
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- Adding \( u \) to \( * \) and setting this equation to zero satisfies the optimality condition of the Kullback-Leibler functional (5) for each timestep \( t \)
- **Idea:** Replace \( * \) with the discrete solution of (5) and solve equation (18) with the iterative scheme
Semidiscrete equation for Lagrange multiplier

\[ u_k q = B^* 1 \left( u_{k+1} - u_{k+\frac{1}{2}} \right) \] (19)

\[ \Leftrightarrow u_{k+1} = u_{k+\frac{1}{2}} + \frac{u_k q}{B^* 1} , \] (20)

to \( u_{k+1} \), with \( u_{k+\frac{1}{2}} \) being the EM update (6) of \( u_k \).
Semidiscrte equation for Lagrange multiplier

\[ u_k q = B^* 1 \left( u_{k+1} - u_{k+\frac{1}{2}} \right) \]  
\[ \iff u_{k+1} = u_{k+\frac{1}{2}} + \frac{u_k q}{B^* 1}, \]  

\[ \text{to } u_{k+1}, \text{ with } u_{k+\frac{1}{2}} \text{ being the EM update (6) of } u_k. \]

- We set \( \kappa(x, t) := \frac{B^* 1}{u_k} \)
• Solving (20) to $u_{k+1}$ can be seen as solving the minimization problem

\begin{equation}
\begin{aligned}
\text{Semidiscrete Minimization Problem 1} \\

u_{k+1} &\in \arg\min_{u\in L_2([0, T] \times \Omega)} \left\{ \frac{1}{2} \int_0^T \int_{\Omega} \left( u - u_{k+\frac{1}{2}} \right)^2 \kappa \, dx \, dt \\
&\quad - \left\langle u, q \right\rangle_{L_2([0, T] \times \Omega)} \right\}. \\
\end{aligned}
\end{equation}
Applying (17) results in

\begin{equation}
\begin{aligned}
\text{Semidiscrete Minimization Problem 2} \\
p \in \arg \min_{p \in \mathcal{P}} \left\{ \frac{1}{2} \int_0^T \int_{\mathcal{H}} \left( G(p) - u_{k+\frac{1}{2}} \right)^2 \kappa \, dx \, dt \\
- \langle G(p), q \rangle_{L^2([0,T] \times \mathcal{H})} \right\},
\end{aligned}
\end{equation}

subject to \( u_{k+1} = G(p)|_{\mathcal{H}} \).
It is easy to see that the Fréchet derivative of $\langle G(p), q \rangle$ in $p$ simply equals $G'(p)^*q$. 
• It is easy to see that the Fréchet derivative of $\langle G(p), q \rangle$ in $p$ simply equals $G'(p)^* q$

• Together with (16) we obtain the reduced problem

Semidiscrēte Minimization Problem 3

$$p \in \arg \min_{p \in \mathcal{P}} \left\{ \frac{1}{2} \int_0^T \int_{\mathcal{H}} \left( G(p) - u_{k+\frac{1}{2}} \right)^2 \kappa \, dx \, dt + R(p) \right\} . \quad (23)$$
A solution of (23) can be obtained by computing the optimality conditions of the Lagrange multiplier

Parameter Identification Problem

\[
\mathcal{L}_k(u, p; \mu) = \frac{1}{2} \int_0^T \int_\Omega \kappa \left( u - u_{k+\frac{1}{2}} \right)^2 \, dxdt + \mathcal{R}(p)
\]

\[
+ \int_0^T \int_\mathcal{H} (G(p) - u) \mu \, dxdt
\]
A solution of (23) can be obtained by computing the optimality conditions of the Lagrange multiplier.

Parameter Identification Problem

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\]

\[
+ \int_0^T \int_{\mathcal{H}} (G(p) - u) \mu dx dt
\]

(24)

The optimality conditions \(\partial_u \mathcal{L}_k(u, p; \mu) = 0\) and \(\partial_\mu \mathcal{L}_k(u, p; \mu) = 0\) can be computed analytically.
The optimality conditions for $p$ can be computed iteratively, e.g. via a Landweber iteration of the gradient descent of $\partial_p \mathcal{L}_k$

**Computational Parameter Identification**

Given a set of $n$ parameters $p = (p^i)_{i=1,...,n}$, each parameter can be computed via

$$p^i_{j+1} = p^i_j - \tau \partial_{p^i} \mathcal{L}_k(u, p^j; \mu), \quad (25)$$

with $\tau > 0$ being small, such that $\partial_u \mathcal{L}_k(u, p^j; \mu) = 0$ and $\partial_\mu \mathcal{L}_k(u, p^j; \mu) = 0$. 
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$$p_{j+1}^i = p_j^i - \tau \partial_{p^i} L_k(u, p; \mu),$$  \hspace{1cm} (25)

with $\tau > 0$ being small, such that $\partial_u L_k(u, p; \mu) = 0$ and $\partial_\mu L_k(u, p; \mu) = 0$.

• Iteration is stopped after $m$ iterations (e.g. if $\|p_m - p_{m-1}\| < \varepsilon$, $\varepsilon$ small)
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### Computational Parameter Identification

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with \( \tau > 0 \) being small, such that \( \partial_u \mathcal{L}_k(u, p_j; \mu) = 0 \) and \( \partial_{\mu} \mathcal{L}_k(u, p_j; \mu) = 0 \).

Iteration is stopped after \( m \) iterations (e.g. if \( \|p_m - p_{m-1}\| < \varepsilon, \varepsilon \) small) \( \Rightarrow u_{k+1} = G(p_m) \)
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**Computational Parameter Identification**

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with $\tau > 0$ being small, such that $\partial_u \mathcal{L}_k(u, p_j^j; \mu) = 0$ and $\partial_\mu \mathcal{L}_k(u, p_j^j; \mu) = 0$.

Iteration is stopped after $m$ iterations (e.g. if $\|p_m - p_{m-1}\| < \varepsilon$, $\varepsilon$ small) $\Rightarrow u_{k+1} = G(p_m)$.
Ill-posedness and Regularization

As most inverse problems, the inverse problem of MBF quantification is ill-posed. Hence, appropriate regularization is needed:

Tikhonov Regularization:

$$R_T(p_i) = \alpha^2 \int \Psi_i(p_i(s) - p_i^*)(s)^2 \, ds$$  \hspace{1cm} (26)

With given a-priori knowledge $p_i^*$, Tikhonov regularization secures that computed parameters $p_i$ are bounded (e.g. $p_i^*$ can be a typical average value for the parameter $p_i$).
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with \( \alpha > 0 \)
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(26)

with \( \alpha > 0 \)

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Disadvantage of Tikhonov regularization: reconstructed parameters are bounded but can still contain oscillating patterns
Disadvantage of Tikhonov regularization: reconstructed parameters are bounded but can still contain oscillating patterns.

To obtain smooth, non-oscillating parameter reconstructions, the $H^1$-norm can be applied as a regularizer:

### $H^1$-Regularization

\[
\mathcal{R}_{H_1}(p^i) = \| p^i - p^i_* \|_{H_1}^2 = \mathcal{R}_T(p^i) + \frac{\alpha}{2} \sum_{j=1}^{n} \int_{\psi_i} \left( \frac{\partial}{\partial s_j} p^i(s) \right)^2 ds
\]

(27)

with $\alpha > 0$
Disadvantage of Tikhonov regularization: reconstructed parameters are bounded but can still contain oscillating patterns.

To obtain smooth, non-oscillating parameter reconstructions, the $H^1$-norm can be applied as a regularizer:

$$
\mathcal{R}_{H_1}(p^i) = \| p^i - p^i_* \|_{H_1}^2 = \mathcal{R}_T(p^i) + \frac{\alpha}{2} \sum_{j=1}^{n} \int_{\psi_i} \left( \frac{\partial}{\partial s_j} p^i(s) \right)^2 ds
$$

with $\alpha > 0$

Discontinuities are not preserved; this might not be a disadvantage for this type of application, due to cardiac motion.
With added $H^1$-Regularization we are able to prove existence of a solution and continuous dependency on the input data.
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Uniqueness would be desirable, to obtain a completely well-posed problem.
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Unfortunately, $C_T$ is not a (strictly) convex operator.
With added $H^1$-Regularization we are able to prove existence of a solution and continuous dependency on the input data.

Uniqueness would be desirable, to obtain a completely well-posed problem.

Unfortunately, $C_T$ is not a (strictly) convex operator $\Rightarrow$ No guarantee of global minima.
We generated a very simple synthetic dataset with the following simple segmentation:

- **A**
- **V**
- **T**

Figure: Simple Segmentation
Synthetic Data

- We generated a very simple synthetic dataset with the following simple segmentation:

**Segmentation**

(a) $A$

(b) $V$

(c) $T$

*Figure: Simple Segmentation*
We generated a synthetic dataset with the following parameters.
We generated a synthetic dataset with the following parameters

**Parameters**

- (a) MBF $F$ in ml/min/mg
- (b) $C_A$ and $C_V$ in kBq/ml over time

**Figure:** Exact parameters
We generated a synthetic dataset with the following parameters:

(a) MBF $F$ in ml/min/mg

(b) $C_A$ and $C_V$ in kBq/ml over time

**Figure:** Exact parameters

- Partition coefficient $\lambda = 0.96$ has been set to a fixed value
We set $u(x, t) = G(F, C_A, C_V)|_{\mathcal{H}} + 0|_{\Omega \setminus \mathcal{H}}$.
We set \( u(x, t) = G(F, C_A, C_V)|_H + 0|_{\Omega \setminus H} \)

We generate \( \varphi(Bu) = f \) via a simple Monte-Carlo algorithm with a maximum number of counts of 61415
We set $u(x, t) = G(F, C_A, C_V)|_H + 0|_{\Omega \setminus H}$

We generate $\varphi(Bu) = f$ via a simple Monte-Carlo algorithm with a maximum number of counts of 61415

The following image shows the 9-th frame of a standard EM-reconstruction (without any regularization) of the synthetic PET data

![Image of a standard EM-reconstruction](image-url)
Reconstructions
Reconstructions

Comparison: Exact vs Reconstruction

(a) Exact MBF

(b) Reconstructed MBF

Figure: Reconstructions
Reconstructions

Comparison: Complete Image Sequences

Synthetic Data

Video animated with the help of Jahn 😊
To conclude this talk we want to present some computational results for real $\text{H}_2^{15}\text{O}$ PET data. The data is obtained from a two-dimensional transaxial slice containing the cardiovascular region. The (rough) segmentation has been done manually with the help of EM-TV reconstructions.
To conclude this talk we want to present some computational results for real \( \text{H}_2^{15}\text{O} \) PET data.
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The data is obtained from a two-dimensional transaxial slice containing the cardiovascular region.

The (rough) segmentation has been done manually with the help of EM-TV reconstructions.
Segmentation

Figure: Simple Segmentation obtained from EM-TV Reconstructions
Reconstructions

(a) MBF $F$

(b) Arterial Input $C_A$ & Venous Input $C_V$

Figure: Reconstructions obtained from real $H_2^{15}O$ PET data
Reconstructions

Reconstruction of Complete Image Sequence

Real Data

- Again, the video was animated with the help of Jahn 😊
Thank you for your attention!