Dynamic Contrast Enhanced Magnetic Resonance Imaging for Quantification and Visualization of Perfusion and Tissue Exchange Kinetics

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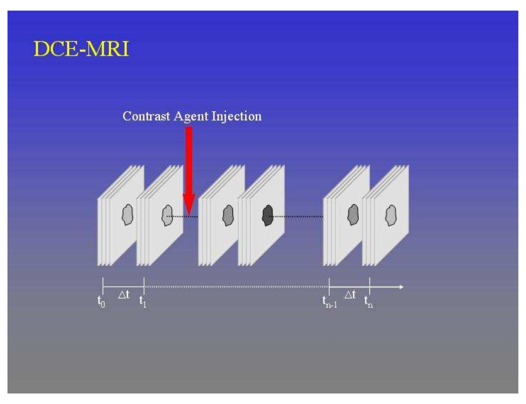
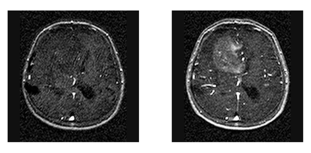
Outline

- Motivation und Definition of the Problem.
- Physiological Model and PDE/Convolution Formulation.
- Previous Methods and Proposed Approach.
- Constrained Splines.
- Constrained Exponential Functions.
- Computational Results.

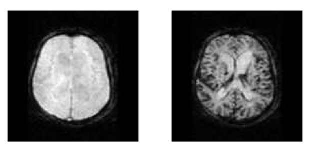
Dynamic Contrast Enhanced MR Imaging



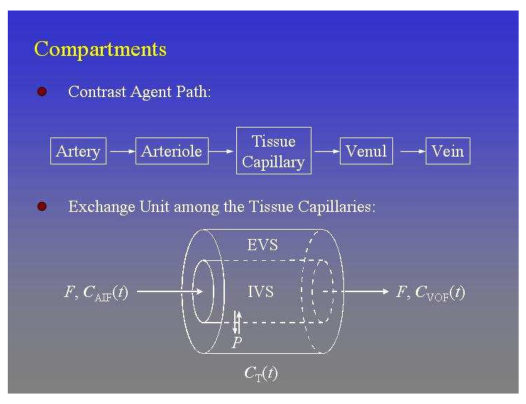
T_1-weighted: intensity elevation improves contrast.



T_2^*-weighted: intensity reduction improves contrast.



Convolution Formulation of the Problem



$$\begin{aligned} C_{\text{AIF}} &= \text{Arterial Input Function (estimated, delay)} \\ C_{\text{T}} &= \text{Tissue Concentration (measured)} \\ C_{\text{VOF}} &= \text{Venous Output Function (not measurable)} \end{aligned}$$

$$\frac{dC_{\text{T}}}{dt} = \frac{F}{V}[C_{\text{AIF}} - C_{\text{VOF}}]$$

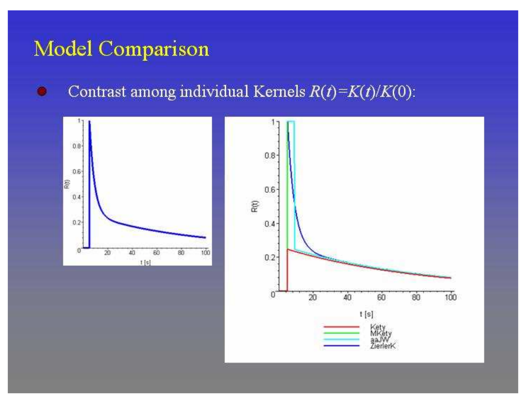
$$C_{\text{VOF}} = h * C_{\text{AIF}} \quad \Rightarrow \quad C_{\text{T}} = K * C_{\text{AIF}}$$

Goals:

- Quantify fluid flow rate (perfusion).
- Quantify blood tissue exchange (membrane permeability).

Can these be determined from K?

Existing Convolution Models

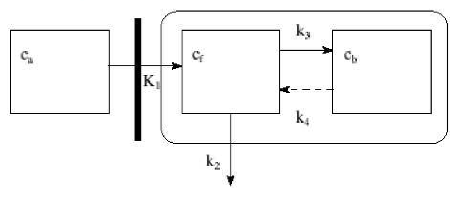


$$C_{\text{T}} = K * C_{\text{AIF}}$$

Perfusion Quantities:

$$\begin{aligned} \text{Flow Rate per unit Volume} &= \mathcal{F}_{\text{T}} = K(0) \\ \text{Volume Fraction} &= \mathcal{V}_{\text{T}} = \textstyle\int_0^\infty K(t)dt \\ \text{Mean Transit Time} &= \mathcal{T}_{\text{T}} = \textstyle\int_0^\infty K(t)/K(0)dt \end{aligned}$$

Kinetic Exchange Rates:

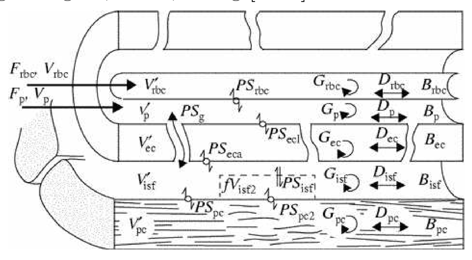


Existing Distributed Parameter Models

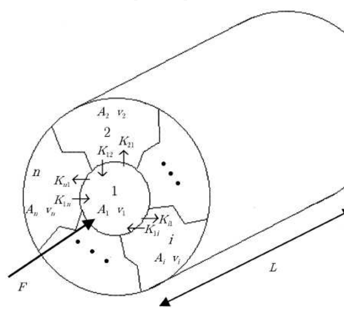
$$\boldsymbol{C}_t + \mathcal{A}\boldsymbol{C}_z = \mathcal{B}\boldsymbol{C}_{zz} + \mathcal{P}\boldsymbol{C}$$

1D convection-diffusion, jump permeation, periodic modules

Bassingthwaighte, Chan, Wang [1992]



Koh, Cheong, Hou, Soh [2003]



Proposed Distributed Parameter Model

$$\partial_t C + \nabla\cdot(F\boldsymbol{v}C) = \nabla\cdot(\mathcal{D}(\boldsymbol{v})\nabla C)$$

$$\mathcal{D}(\boldsymbol{v}) = P\tau[I - \boldsymbol{v}\boldsymbol{v}^{\text{T}}] + D\boldsymbol{v}\boldsymbol{v}^{\text{T}}$$

$$\begin{aligned} F &= \text{mean velocity} \\ \boldsymbol{v} &= \text{bulk flow field}, \ \boldsymbol{v}^{\text{T}}\boldsymbol{v} = 1 \\ D &= \text{streamline oriented diffusivity} \\ P\tau &= \text{streamline orthogonal diffusivity} \\ P &= \text{membrane permeability} \\ \tau &= \text{membrane thickness} \end{aligned}$$

Least Squares Estimation of Coefficients?
Banks, Kareiva [1983].

Toward the Convolution Model:

$$\text{vol}(\Omega)C_{\text{T}}(t) = \int_\Omega C(t)d\boldsymbol{x} = \int_{\boldsymbol{v}^{\text{T}}\boldsymbol{n}<0} F|\boldsymbol{v}^{\text{T}}\boldsymbol{n}|d\boldsymbol{x}\int_0^t C_{\text{AIF}}(s)ds - \int_{\boldsymbol{v}^{\text{T}}\boldsymbol{n}>0} F|\boldsymbol{v}^{\text{T}}\boldsymbol{n}|d\boldsymbol{x}\int_0^t C_{\text{VOF}}(s)ds$$

Diffusive flux at $\partial\Omega$ must vanish. With

$$C_{\text{T}}(t) = K(t) \qquad C_{\text{AIF}}(t) = \delta(t) \qquad C_{\text{VOF}}(t) = h(t)$$

perfusion quantities can be derived:

$$\begin{aligned} \text{Flow Rate per unit Volume} &= \mathcal{F}_{\text{T}} = K(0) \\ \text{Volume Fraction} &= \mathcal{V}_{\text{T}} = \textstyle\int_0^\infty K(t)dt \\ \text{Mean Transit Time} &= \mathcal{T}_{\text{T}} = \textstyle\int_0^\infty K(t)/K(0)dt \end{aligned}$$

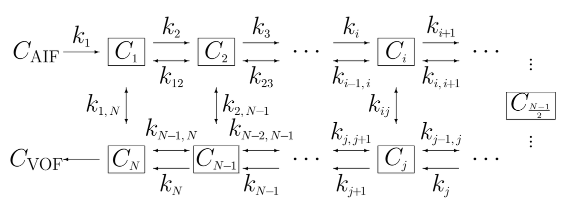
Toward Kinetic Exchange

$$\partial_t C + \nabla\cdot(F\boldsymbol{v}C) = \nabla\cdot(\mathcal{D}(\boldsymbol{v})\nabla C)$$

$$\mathcal{D}(\boldsymbol{v}) = P\tau[I - \boldsymbol{v}\boldsymbol{v}^{\text{T}}] + D\boldsymbol{v}\boldsymbol{v}^{\text{T}}$$

Discretization:

$$C_i' + k_i(C_i - C_{i-1}) = \sum_{j\neq i} k_{ij}(C_j - C_i).$$



A_D and A_P with Neumann boundary conditions:

$$\boldsymbol{C}' = A\boldsymbol{C} + \boldsymbol{b}C_{\text{AIF}}, \qquad A = A_F + A_D + A_P$$

$$\boldsymbol{C}(t) = e^{At}\boldsymbol{C}(0) + \int_0^t e^{A(t-s)}\boldsymbol{b}C_{\text{AIF}}(s)ds$$

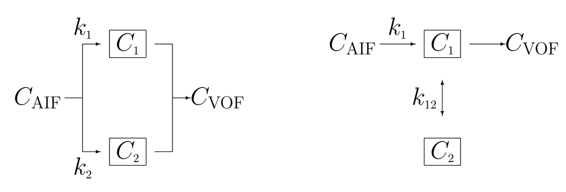
$$\boldsymbol{V}^{\text{T}}e^{At}\boldsymbol{b}/\text{vol}(\Omega) \longrightarrow K(t)$$

Representative solutions:

$$\begin{aligned} A = A_F, &\quad K(t) = \text{(Erlang) step for plug flow} \\ A = A_D, &\quad K(t) = \text{sum of exponentials} \\ A = A_P, &\quad K(t) = \text{recirculation} \end{aligned}$$

Nonidentifiability

Identical Kernels:



Convective — Diffusive

Purely Convective Coefficient Matrix:

$$A = \begin{bmatrix} A_1 & & & \\ & A_2 & & \\ & & \ddots & \\ & & & A_M \end{bmatrix} \qquad A_m = \begin{bmatrix} -\lambda_1 & & & \\ \lambda_2 & -\lambda_2 & & \\ & \ddots & \ddots & \\ & & \lambda_N & -\lambda_N \end{bmatrix}$$

Purely Convective Kernel:

$$K_{\text{conv}}(t) = \boldsymbol{V}^{\text{T}}e^{At}\boldsymbol{b}/\text{vol}(\Omega), \qquad \boldsymbol{V} \geq 0, \quad \boldsymbol{b} \geq 0$$

Theorem For a given $p \in [1,\infty)$, any non-negative, non-increasing $K(t) \in \mathcal{L}^p[0,\infty)$ can be approximated arbitrarily well in $\mathcal{L}^p[0,\infty)$ by a purely convective kernel.

Conclusion: Kinetic exchange parameters cannot in general be identified from the convolution model.

Ill-posedness with Typical Data

Impulsive injection, bolus travels through n compartments:

$$C_{\text{AIF}}(t) = \delta(t) * [\nu e^{-\nu t}]_1 * \cdots * [\nu e^{-\nu t}]_n = \nu\frac{(\nu t)^n}{n!}e^{-\nu t}.$$

Assume exact: $C_{\text{T}} = K_{\text{e}} * C_{\text{AIF}}$.

Discontinuous dependence upon data C_{T}:

$$C_{\text{T}}(t) + \underbrace{N_\varepsilon(t)}_{\text{noise}\to 0} = \int_0^t C_{\text{AIF}}(t-s)[K_{\text{e}}(s) + \underbrace{E_\varepsilon(s)}_{\text{error}\to\infty}]ds$$

with noise:

$$N_\varepsilon(t) = \varepsilon\Re\left[\nu^{n+1}\sum_{m=0}^n \binom{n}{m}(-1)^m\frac{e^{\text{i}mt/\varepsilon} - e^{-\nu t}}{\varepsilon\nu + \text{i}m}\right] = \mathcal{O}(\varepsilon)$$

and kernel estimation error:

$$E_\varepsilon(t) = \varepsilon^{-n}\Re\left[\sum_{m=0}^n \binom{n}{m}(-1)^m(\varepsilon\nu + \text{i}m)^n e^{\text{i}mt/\varepsilon}\right] = \mathcal{O}(\varepsilon^{-n})$$

Conclusion: The more compartments through which the bolus must travel, the smoother is C_{AIF}, and the more sensitive is the solution to noise.

Popularized Regularization Techniques

- Discrete Fourier Transform with Wiener Filtering. [Østergaard et al, 1996]
$$K = \text{DFT}^{-1}\{W\cdot\text{DFT}\{C_{\text{T}}\}/\text{DFT}\{C_{\text{AIF}}\}\}$$
- Singular Value Decomposition. [Østergaard et al, 1996]
$$C_{\text{AIF}} * K = C_{\text{T}} \quad\longrightarrow\quad M\boldsymbol{k} = \boldsymbol{c}$$
$$\boldsymbol{k} = \{K(t_i)\}, \quad M = U\Sigma V^{\text{T}}$$
$$\boldsymbol{k}^\star = V\tilde\Sigma^{-1}U^{\text{T}}\boldsymbol{c}, \quad \tilde\Sigma^{-1} = \text{diag}\{(\sigma_i > \mu\sigma_{\max})/\sigma_i\}$$
- Tikhonov Regularization. [Calamante et al, 2003]
$$\boldsymbol{k}^\star = \text{argmin}\{\|M\boldsymbol{k} - \boldsymbol{c}\|^2 + \mu^2\|D\boldsymbol{k}\|^2\}, \quad D\boldsymbol{k} \approx K'$$
- Penalized Monotonicity. [Østergaard et al, 1996]
$$\boldsymbol{k}^\star = \text{argmin}\{\|M\boldsymbol{k} - \boldsymbol{c}\|^2 + \mu^2\|D_\varepsilon\boldsymbol{k}\|^2\}$$
$$D_\varepsilon\boldsymbol{k} = \{[k_i - k_{i-1}]\cdot[k_i < (1+\varepsilon^2)k_{i+1}]\}$$
- Constrained Monotonicity. [Griebel et al, 2001]
$$\boldsymbol{k}^\star = \text{argmin}\{\|M\boldsymbol{k} - \boldsymbol{c}\|^2 : k_{i+1} \leq k_i\}$$

Proposed Solution Framework

Data $\{a_k = C_{\text{AIF}}(t_k)\}$ und $\{c_l = C_{\text{V}}(t_l)\}$ represented by hat functions:

$$C_{\text{AIF}}(t) = \sum_{k=1}^K a_k s_k^{(1)}(t) \qquad C_{\text{V}}(t) = \sum_{l=1}^L c_l s_l^{(1)}(t)$$

Kernel computed by constrained minimization:

$$\min_{K\in B}\|C_{\text{T}} - K * C_{\text{AIF}}\|_{\mathcal{L}^2[0,T]} \qquad \text{subject to:} \quad K' \leq 0, \quad K \geq 0$$

over a suitable basis B.

Theorem. For piecewise linear, continuous data which vanish initially with positive slope, the solution K to the necessary optimality conditions is bounded in terms of the data values and hence has bounded variation.

Conclusion: Expect a staircasing effect.

Choose a basis B with:

- approximation properties for increasing dimension,
- realistic representation for small (regularizing) dimension,
- easy implementation of constraints.

Deconvolution with a Spline Basis

Given degree m, nodes $\{x_j\}_{j=0}^{M-1}$, knots $\{y_l\}$,

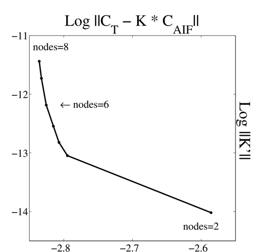
$$K(t) = \sum_{l=1}^L k_l s_l^{(m)}(t)$$

Theoretical properties, Schumaker [1981]:

- Approximation properties: Even $\{s_l^{(0)}\}$ total in $\mathcal{L}^p[0,\infty)$.
- Sufficient monotonicity conditions:
$$k_l \geq k_{l+1} \geq 0, \qquad l = 1,\ldots,L-1$$

From experimentation:

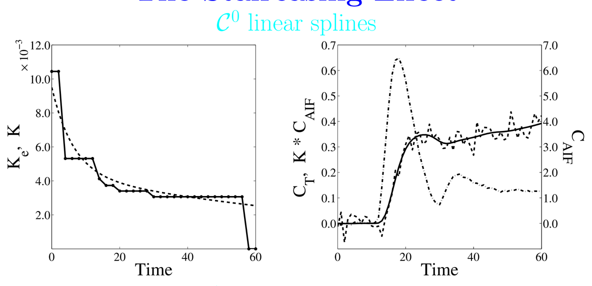
- Nodes $\{x_j\}_{j=0}^{M-1}$ uniform among data points $\{t_i\}_{i=0}^{N-1}$.
- Multiplicities of knots $\{y_l\}$ selected for desired smoothness.
- Number of nodes M determined from L-curve criterion:



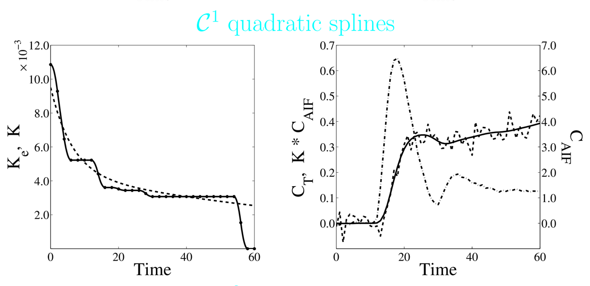
- K computed by linearly constrained least squares.

The Staircasing Effect

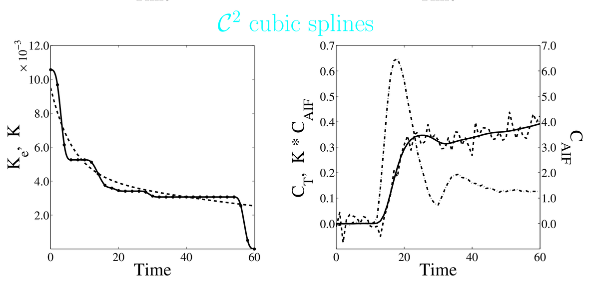
$\mathcal{C}^0$ linear splines



$\mathcal{C}^1$ quadratic splines

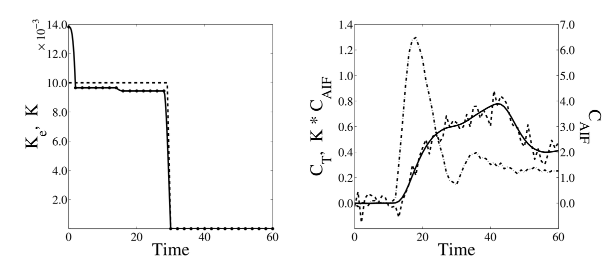


$\mathcal{C}^2$ cubic splines

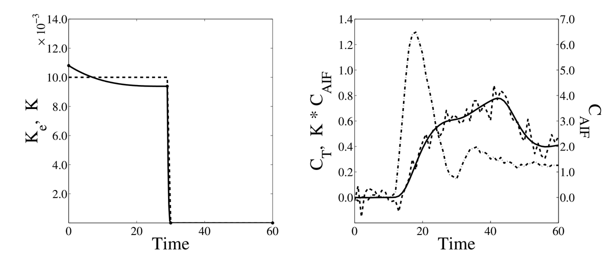


Reconstruction of *Blocky Data*

Nodes situated at every other data point:



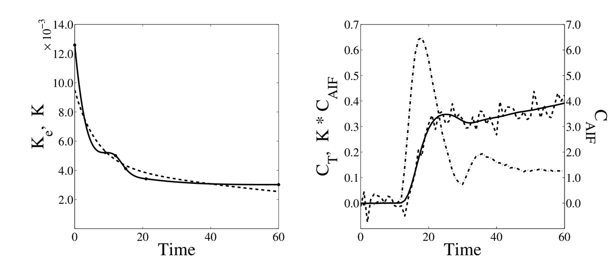
Constrained residual minimized wrt 4 nodes:



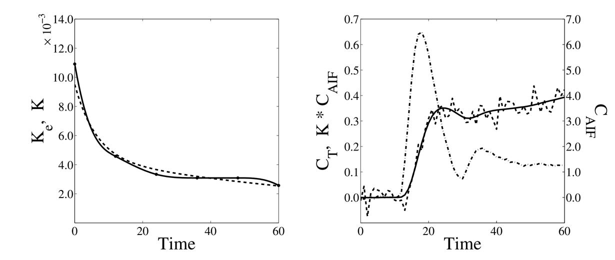
Node Optimization? No...

Uniform Nodes are Regularizing

Constrained residual minimized wrt 6 nodes:

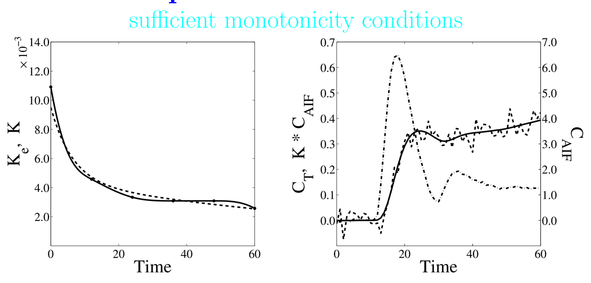


Uniformly placed 6 nodes (L-curve determined):

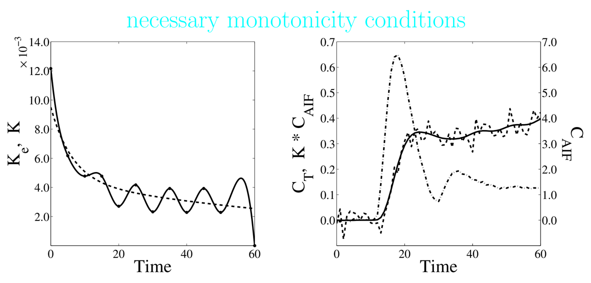


Comparison of Constraints

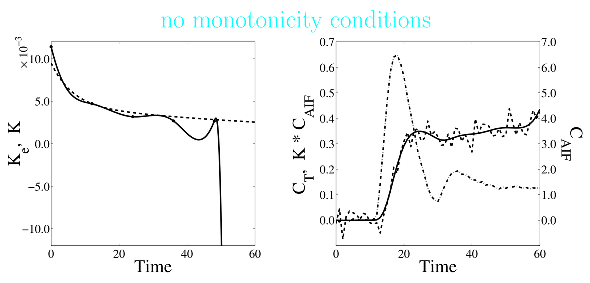
sufficient monotonicity conditions



necessary monotonicity conditions

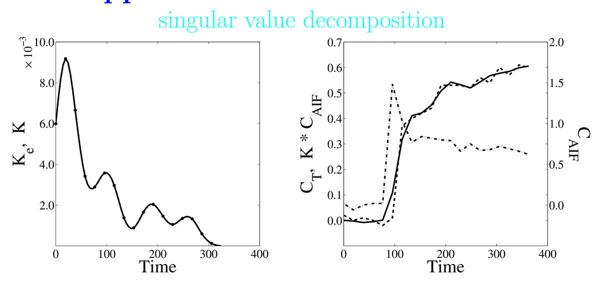


no monotonicity conditions

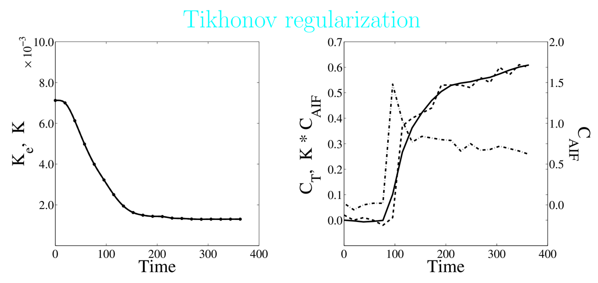


Application to Measured Data

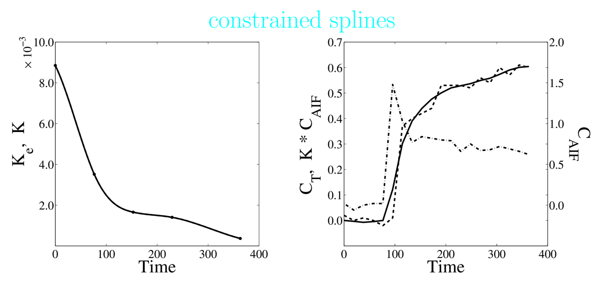
singular value decomposition



Tikhonov regularization



constrained splines



Deconvolution with an Exponential Basis

Given positive time scales $\{\lambda_m^{-1}\}_{m=1}^M$,

$$K(t) = \sum_{m=1}^M k_m e^{-\lambda_m t}$$

Approximation properties: [Müntz] Suppose

$$\lim_{m\to\infty}\lambda_m = +\infty.$$

Then the span of $\{e^{-\lambda_m t}\}$ is dense in $\mathcal{L}^p[0,\infty)$ for $1 \leq p < \infty$ if and only if

$$\sum_{m=1}^\infty \lambda_m^{-1} = +\infty.$$

Monotonicity Conditions.

Consider Laplace Transform of signed measure:

$$K(t) = \int_0^\infty e^{-xt}d\mu(x), \quad \text{e.g.,} \quad \mu'(x) = \sum_{m=1}^M k_m\delta(x - \lambda_m)$$

If μ is non-decreasing:

$$-K'(t) = \int_0^\infty xe^{-xt}\underbrace{d\mu(x)}_{\geq 0} \geq 0, \quad \text{e.g.,} \quad k_m \geq 0$$

then K is *completely monotone*:

$$(-1)^n K^{(n)}(t) = \int_0^\infty x^n e^{-xt}d\mu(x) \geq 0$$

Alternatively,

$$-K'(t) = \int_0^\infty dx_n t^n\exp(-x_n t)\times \underbrace{\int_0^{x_n}dx_{n-1}\int_0^{x_{n-1}}dx_{n-2}\cdots\int_0^{x_1}d\mu(x_0)x_0}_{\geq 0} \geq 0$$

Discretization:

$$-K'(t) = \sum_{m=1}^M k_m\lambda_m e^{-\lambda_m t} = \boldsymbol{k}^{\text{T}}\Lambda\exp(-\boldsymbol{\lambda}t)$$

$$= \boldsymbol{k}^{\text{T}}[\Lambda D_1^{-1}\cdots D_{M-1}^{-1}][D_{M-1}\cdots D_1]\exp(-\boldsymbol{\lambda}t)$$

where for $\Delta_i^j = (\lambda_i - \lambda_j)^{-1}$,

$$D_m = \text{tridiag}\left\{\begin{bmatrix} -\Delta_{m+1}^1 & -\Delta_{m+2}^2 & \cdots & -\Delta_M^{M-m} & 0 & \cdots & 0 & - \\ \Delta_{m+1}^1 & \Delta_{m+2}^2 & \cdots & \Delta_M^{M-m} & 1 & \cdots & 1 & 1 \\ - & 0 & \cdots & & 0 & 0 & \cdots & 0 \end{bmatrix}^{\text{T}}\right\}$$

and with $e_t(\lambda) = e^{-\lambda t}$,

$$D_{M-1}\cdots D_1\exp(-\boldsymbol{\lambda}t) = \{(-1)^{M-m}e_t[\lambda_m,\ldots,\lambda_M]\}_{m=1}^M$$

Theorem. Under the condition,

$$\boldsymbol{k}^{\text{T}}[\Lambda D_1^{-1}\cdots D_{M-1}^{-1}] \geq 0$$

$K(t) = \boldsymbol{k}^{\text{T}}\exp(-\boldsymbol{\lambda}t)$ is non-negative and non-increasing.

Deconvolution with an Exponential Basis

Given positive time scales $\{\lambda_m^{-1}\}_{m=1}^M$,

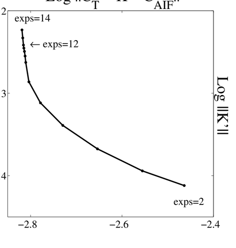
$$K(t) = \sum_{m=1}^M k_m e^{-\lambda_m t}$$

Theoretical properties:

- Approximation properties [Müntz]: Dense in $\mathcal{L}^p[0,\infty)$ when
$$\lim_{m\to\infty}\lambda_m = +\infty \qquad \sum_{m=1}^\infty\lambda_m^{-1} = +\infty$$
- Sufficient monotonicity condition:
$$\boldsymbol{k}^{\text{T}}[\Lambda D_1^{-1}\cdots D_{M-1}^{-1}] \geq 0$$

From experimentation:

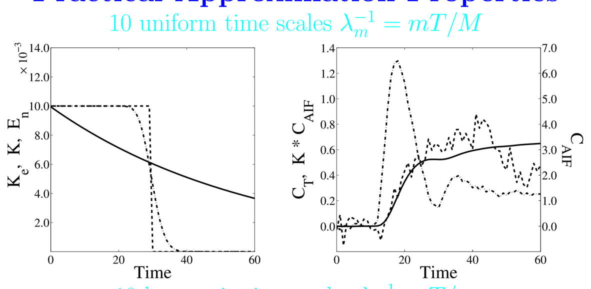
- Time scales harmonically distributed $\lambda_m^{-1} = T/m$.
- Number of times scales determined from L-curve criterion:



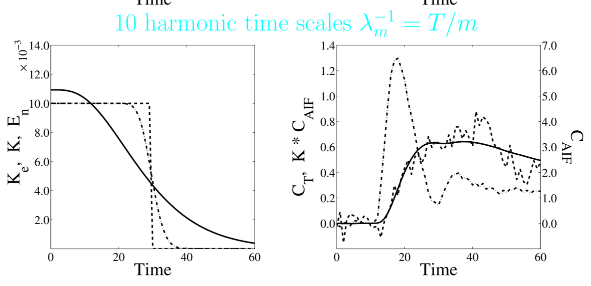
- K computed by linearly constrained least squares.

Practical Approximation Properties

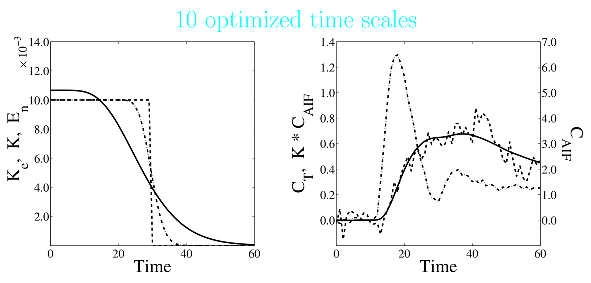
10 uniform time scales $\lambda_m^{-1} = mT/M$



10 harmonic time scales $\lambda_m^{-1} = T/m$



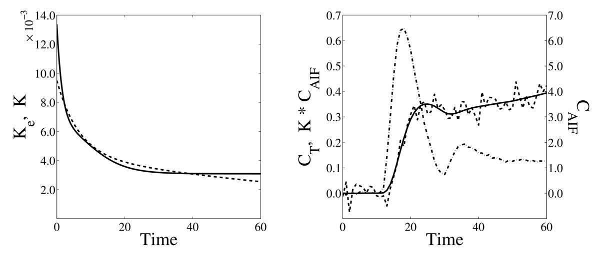
10 optimized time scales



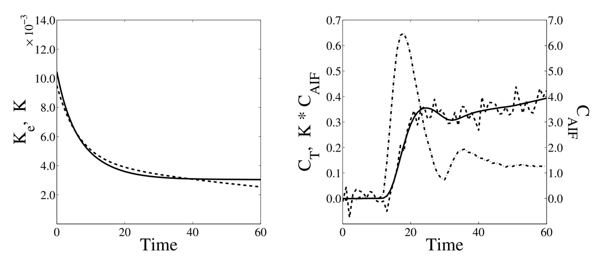
Remarks:

- Exponentials resist staircasing, steps approximated poorly.
- Uniform time scales give poor approximation.
- Harmonic time scales satisfy Müntz Theorem.
- Optimized time scales give marginal improvement.
- Evidence for time scale optimization? No...

Constrained residual minimized wrt 12 time scales:

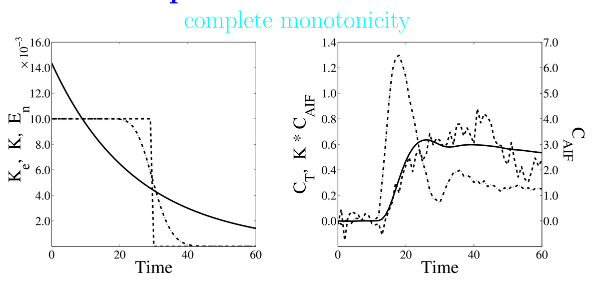


Harmonically distributed 12 time scales (L-curve determined):

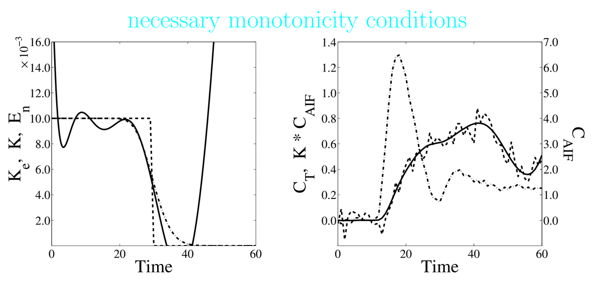


Comparison of Constraints

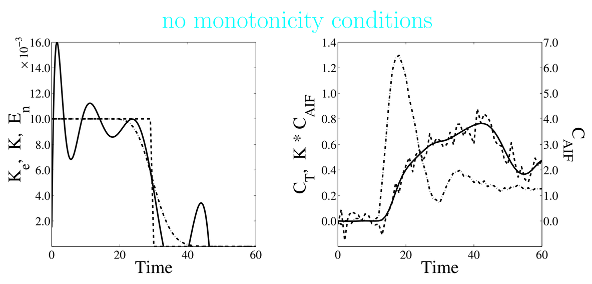
complete monotonicity



necessary monotonicity conditions

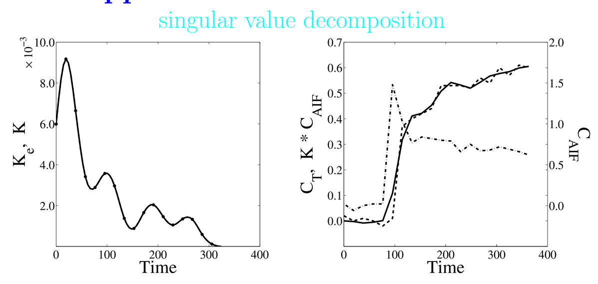


no monotonicity conditions

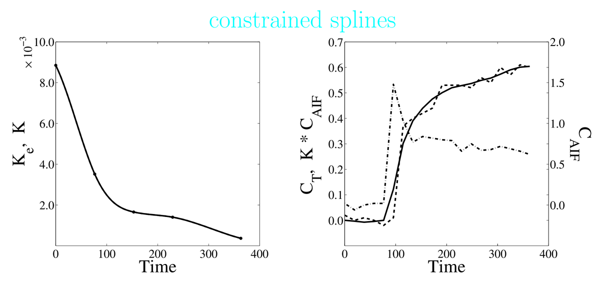


Application to Measured Data

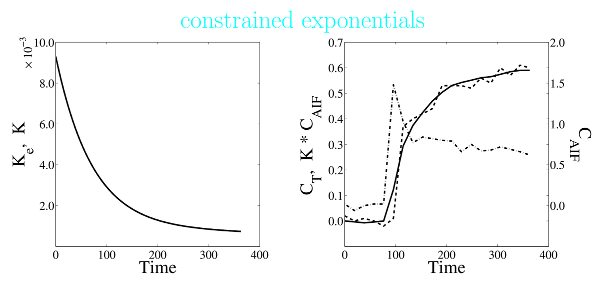
singular value decomposition



constrained splines



constrained exponentials



Pixelwise Application to Measured Data Comparison between EXP and SVD