Robust modeling of tracer kinetics in dynamic imaging

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Introduction

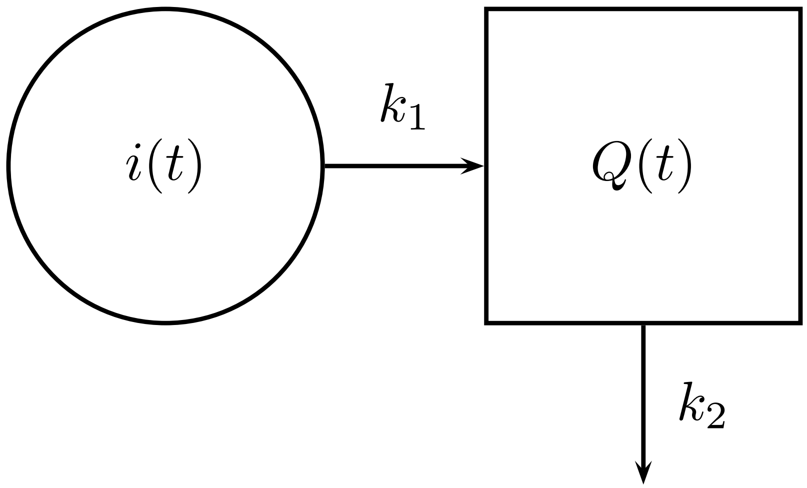
- Many physiological processes are readily described using linear first-order compartment models.
- The output of such models may be represented as the convolution of a forcing function $i(t)$ with an exponential kernel:

$$\phi(t) = i(t) * k_1\, k_2\, \mathrm{e}^{-k_2\, t}.$$

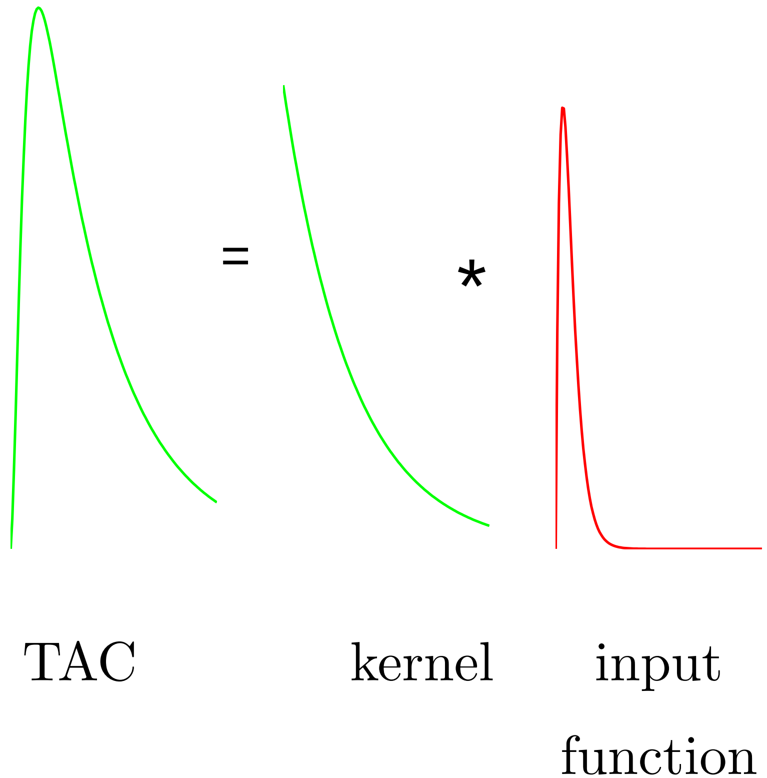
Normalization:

$$\int_0^\infty k_2\, \mathrm{e}^{-k_2\, t} = 1.$$

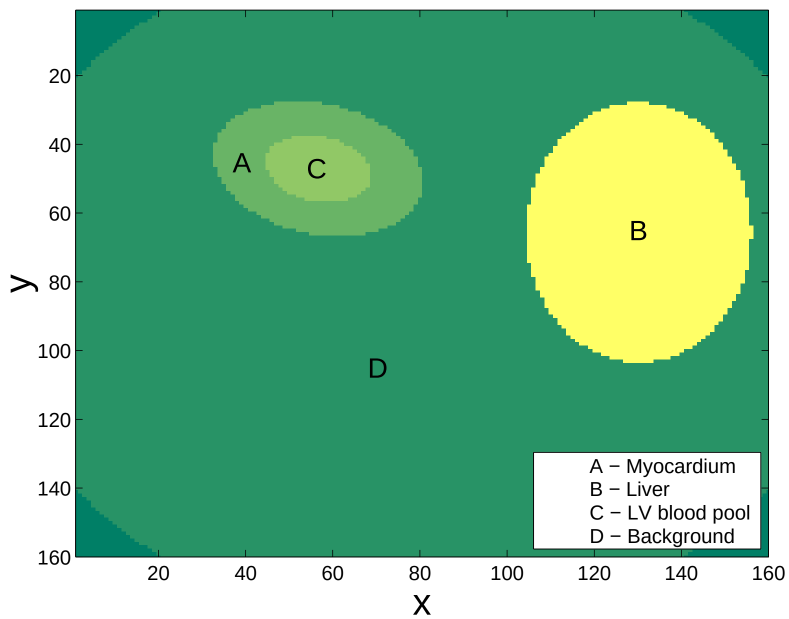
Single compartment model

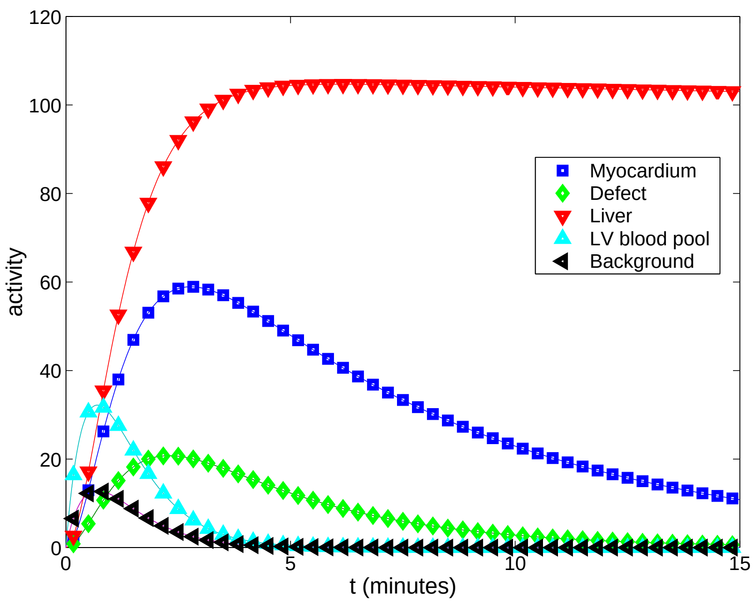


First-order single compartment model



Single compartment model tracer TAC examples





Modeling first-order systems

- Often the observed quantity $\phi(t)$ is comprised of the sum of the responses of several first-order systems:

$$\phi(t) = i(t) * \sum_{\tilde{m}=1}^{\tilde{M}} k_1^{\tilde{m}}\, k_2^{\tilde{m}}\, \mathrm{e}^{\,-k_2^{\tilde{m}}\, t}. \tag{1}$$

- For example, the concentration vs. time curve $\phi(t)$ might represent the superposed responses of several single compartment models describing kinetics of a tracer

Parameter estimation problem:

Fit models of the form (1) to sets of measured data.

Complications

- It is generally not possible to find **unique** sets of parameters.
- Even when uniqueness conditions are met, parameters are generally **extremely sensitive to noise** within the data. "Excessive accuracy" is required even in noise free situations.
- This problem of **parameter redundancy**, is intrinsic to weighted sums of real exponentials.
- The **quality** of the solution is difficult to measure. When multiple solutions exist, the Cramér-Rao lower bound underestimates the true variance of the parameter estimates.

Approach I: Non-linear parameter estimation

- Most direct approach: non-linear estimation of the model parameters:

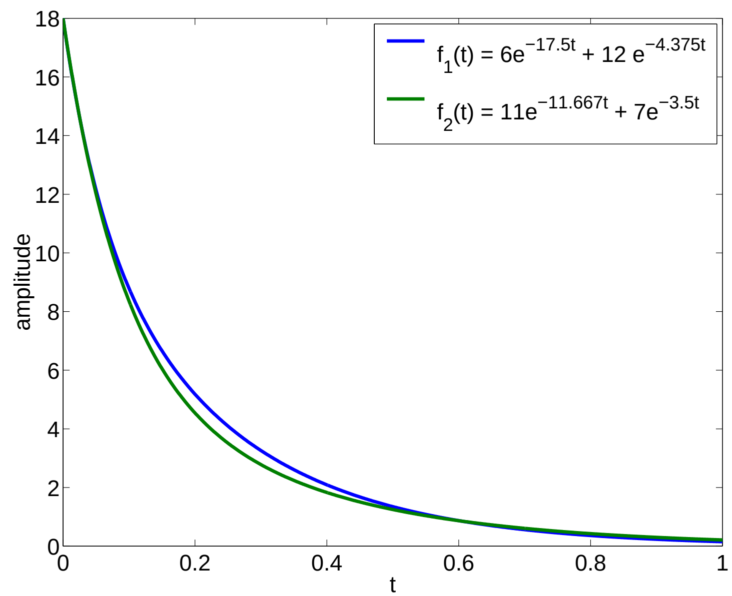
$$\min_{\mathbf{k}_1,\,\mathbf{k}_2} \sum_{l=1}^{L} \Big(\phi'(t_l) - \phi(t_l, \mathbf{k}_1, \mathbf{k}_2)\Big)^2, \quad l = 1, \ldots, L,$$

$\phi'(t_l)$:	measured TAC
$\phi(t_l, \mathbf{k}_1, \mathbf{k}_2)$:	modeled TAC
$\mathbf{k}_1$:	wash-in parameter vector
$\mathbf{k}_2$:	wash-out parameter vector

- Optimization algorithms commonly used: steepest descent, Newton-Raphson method, conjugate descent, Levenberg-Marquardt algorithm.

Non-linear parameter estimation: Shortcoming I

Example of parameter redundancy in e-sums.



$$
\begin{aligned}
f_1 &= 6\,\mathrm{e}^{-17.5\,t} + 12\,\mathrm{e}^{-4.375\,t} \\
f_2 &= 11\,\mathrm{e}^{-11.667\,t} + 7\,\mathrm{e}^{-3.5\,t}.
\end{aligned}
$$

16% maximum curve deviation → 50% deviation in rate constants

The result is an extreme tendancy to “fit the noise”.

Non-linear parameter estimation: Shortcoming II

Sensitivity to initial parameter vector example (suboptimal local minima):

Consider again:

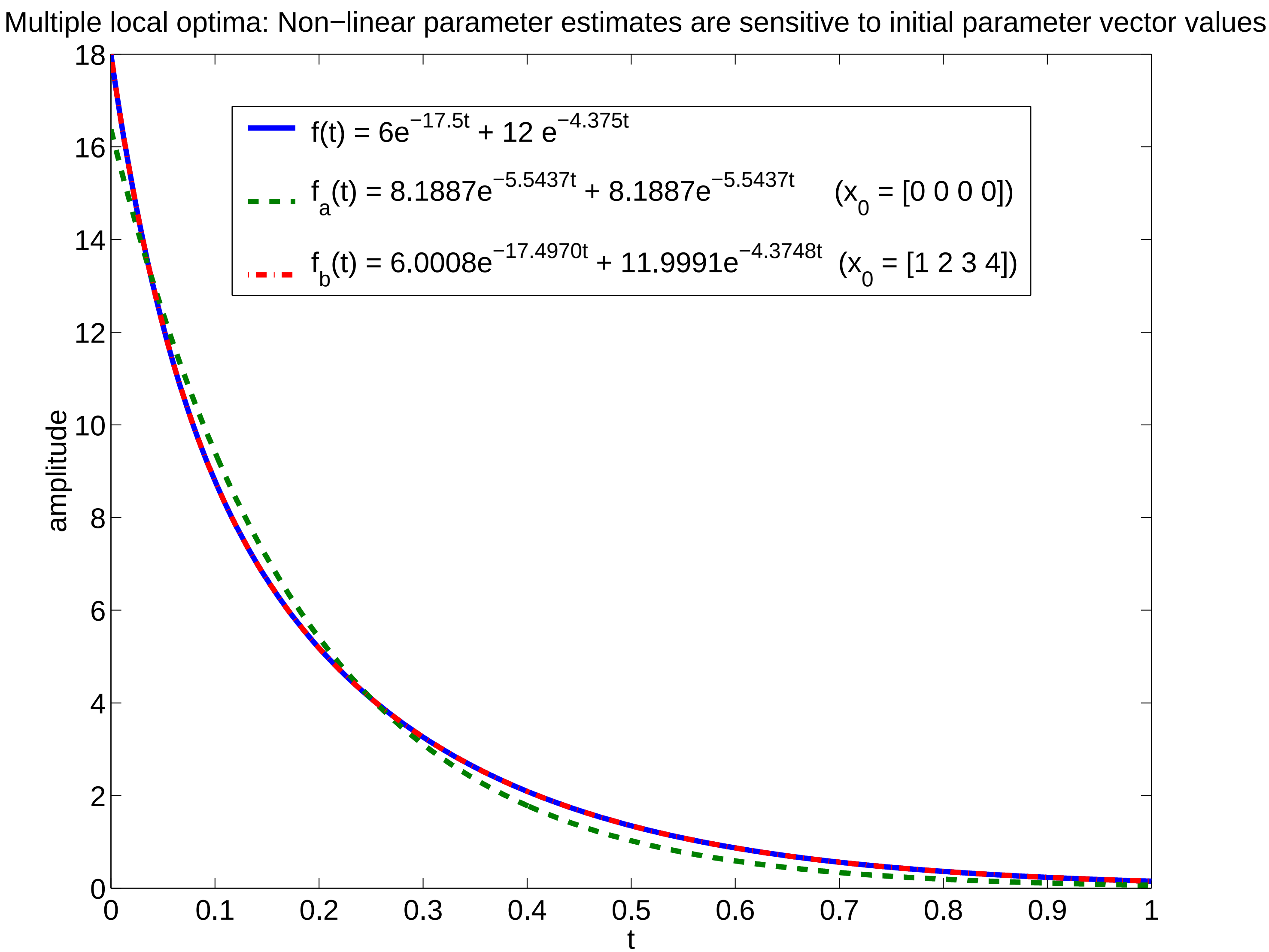
$$f_1 \quad = \quad 6\,\mathrm{e}^{-17.5\,t} + 12\,\mathrm{e}^{-4.375\,t}$$

Performing least squares fit with Levenberg-Marquardt algorithm:

1. Starting at: $x_0 = [k_{10}^1\ k_{10}^2\ k_{20}^1\ k_{20}^2] = [0\ 0\ 0\ 0]$ yields $\hat{x}_a = [8.1887\ 8.1887\ 5.5437\ 5.5437]$. Cost $= 6.17 \times 10^{-1}$
2. Starting at: $x_0 = [1\ 2\ 3\ 4]$ yields $\hat{x}_b = [11.9991\ 6.0008\ 4.3748\ 17.4970]$ Cost $= 8.50 \times 10^{-5}$.

Using multistart optimization to amerliorate this problem is costly.

Non-linear parameter estimation: Shortcoming II



Approach II: Exponential spectral analysis

Instead of solving for the non-linear and linear parameters in:

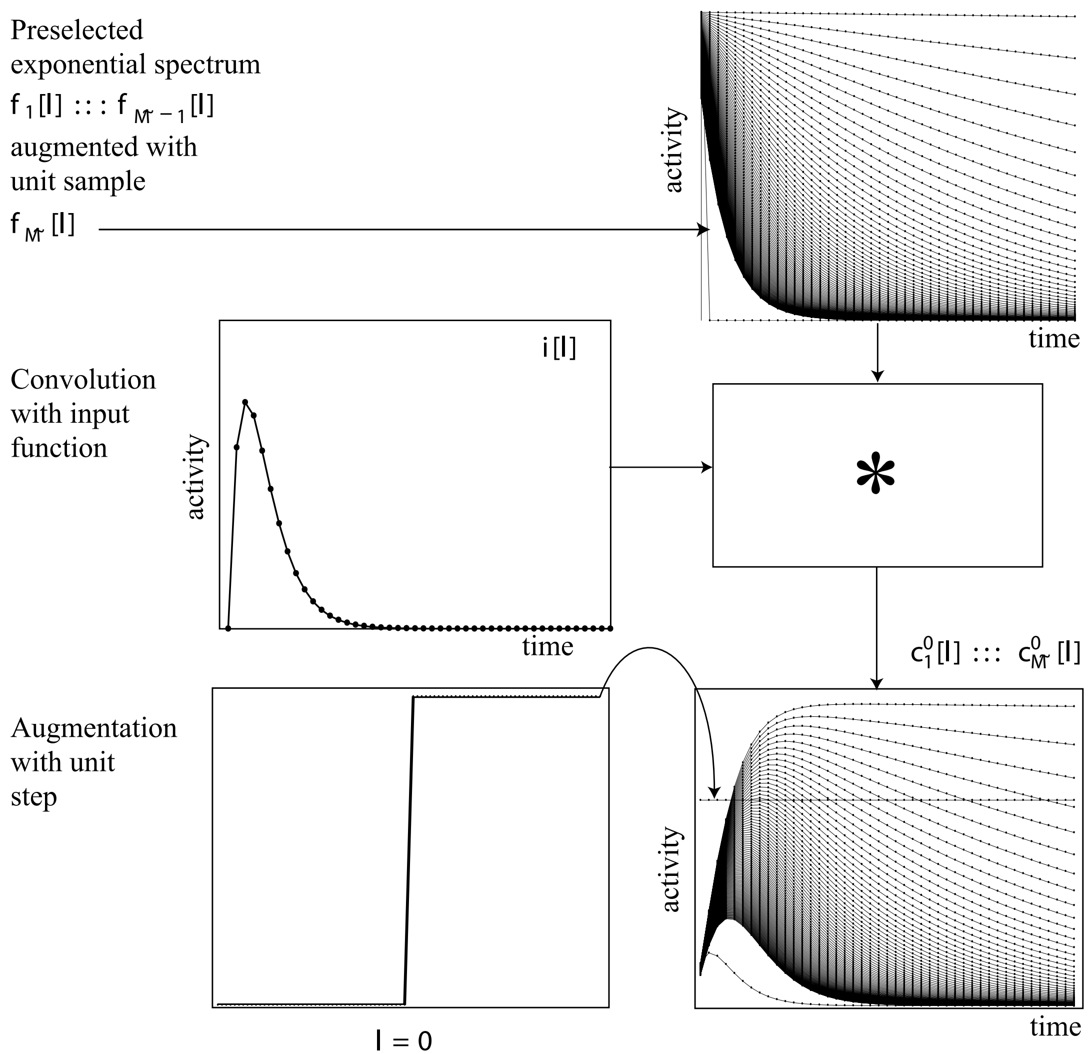
$$\phi(t) = i(t) * \sum_{\tilde{m}=1}^{\tilde{M}} k_1^{\tilde{m}}\, k_2^{\tilde{m}}\, \mathrm{e}^{\,-k_2^{\tilde{m}} t}.$$

Preselect a set of k_2 (maybe 100) and **solve for the linear coefficients** k_1^m:

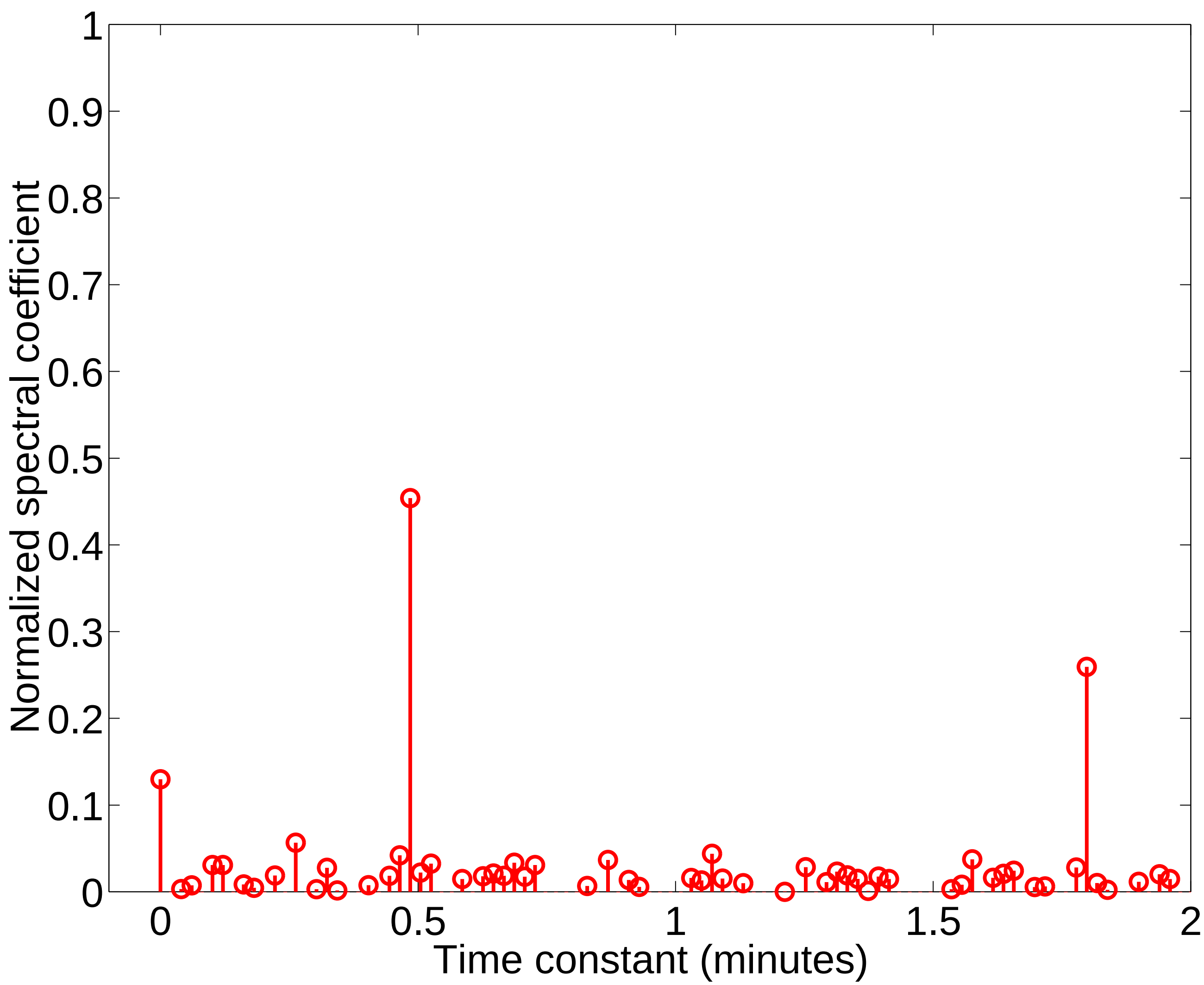
$$\hat{\phi}(t) = \sum_{m=1}^{M} k_1^m \Big[\, i(t) * \big(k_2^m \mathrm{e}^{\,-k_2^m t}\big)\Big],$$

where M is the number of preselected exponentials.
This linear system is easily solved using non-negative least squares (NNLS) algorithms.

Approach II: Exponential spectral analysis



Approach II: Exponential spectral analysis example



Approach II: Exponential spectral analysis: Advantages

1. No need to know *a priori* how many exponential terms to use in the model.
2. No sensitivity with respect to starting estimate.
3. Spectral coefficients may be interpreted as histograms.
4. Comparison of several experiments is facilitated - the same basis is used for each spectrum.

Approach II: Exponential spectral analysis: Shortcoming

$$\begin{bmatrix} \phi(t_1) \\ \phi(t_2) \\ \vdots \\ \phi(t_L) \end{bmatrix} = \begin{bmatrix} k_2^1\,\mathrm{e}^{-k_2^1\,t_1} & k_2^2\,\mathrm{e}^{-k_2^2\,t_1} & \dots & k_2^M\mathrm{e}^{-k_2^M\,t_1} \\ k_2^1\mathrm{e}^{-k_2^1\,t_2} & k_2^2\,\mathrm{e}^{-k_2^2\,t_2} & \dots & k_2^M\,\mathrm{e}^{-k_2^M\,t_2} \\ \dots & \dots & \dots & \dots \\ k_2^1\,\mathrm{e}^{-k_2^1\,t_L} & k_2^2\,\mathrm{e}^{-k_2^2\,t_L} & \dots & k_2^M\,\mathrm{e}^{-k_2^M\,t_L} \end{bmatrix} \begin{bmatrix} \mu_1 \\ \mu_2 \\ \vdots \\ \mu_M \end{bmatrix}$$

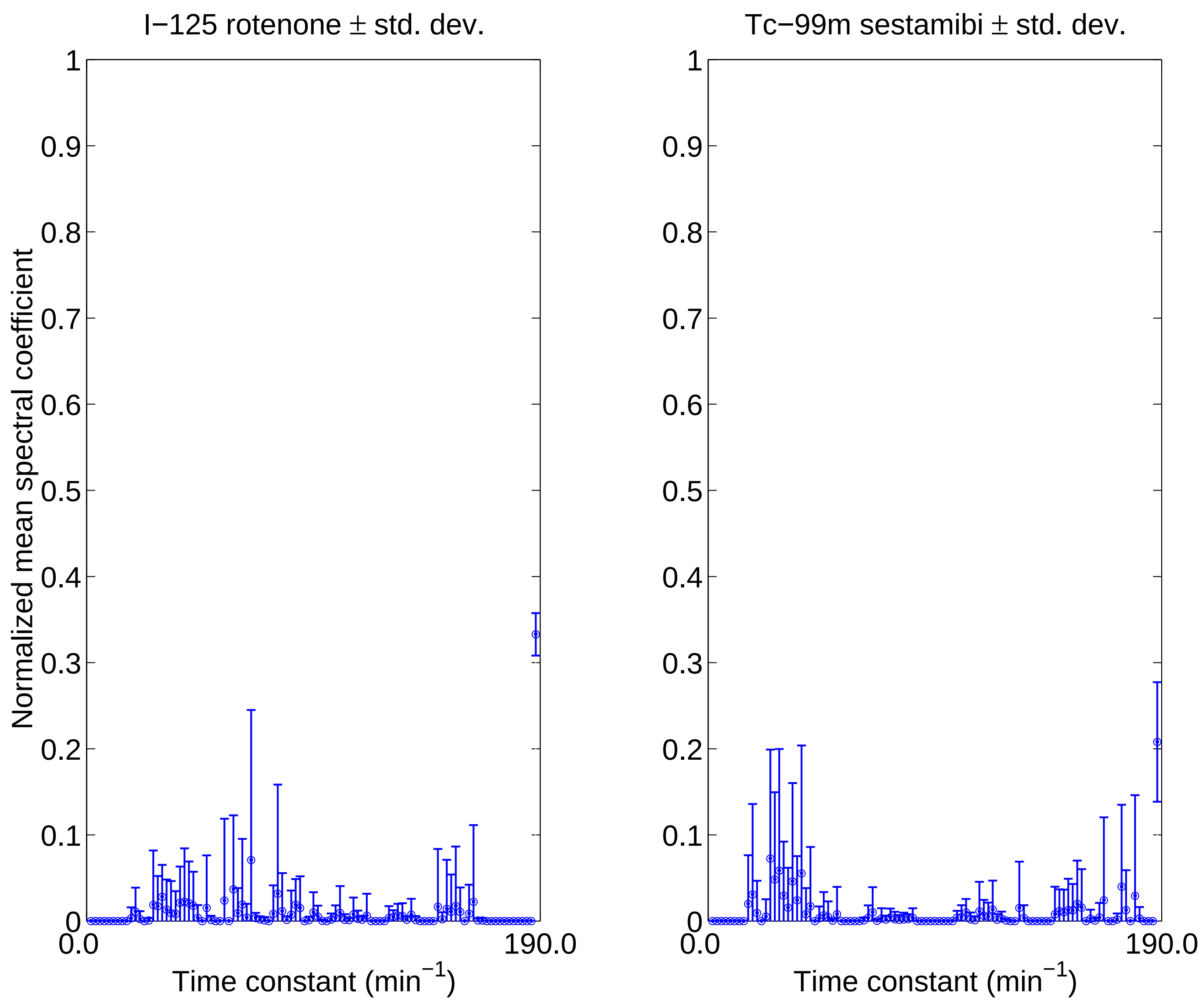
$$\boldsymbol{\phi} = \mathbf{E}\boldsymbol{\mu}$$

E is column rank deficient, even for small M

$\rightarrow$ parameter redundancy is even worse than in the non-linear fitting case.

$\rightarrow$ spectral parameter estimates are unacceptably sensitive to noise, even for small values of M.

Approach II: Exponential spectral analysis: Shortcoming



Proposed alternative approach to spectral analysis:

1. **Accept the inherent limitations** of first order compartmental model fitting.
2. Define the objective of parameteric modeling as the **ability to compare the results** of several observations. e.g. compare the retention of 2 tracers, or compare studies on several patients.
3. The parameter values should have **physiological significance.**

To realize (1) through (3) we will have to **compromise goodness-of-fit** in order to:

- Achieve lower parameter variance.
- Continue to employ a basis set with meaningful parameters.

Parsimonious exponential spectral analysis (PESA)

Key idea: Find a small set of exponentials that are able to approximate a large set of exponential basis functions:

$$\min_{\mathbf{k_2},\,\boldsymbol{\mu}} \sum_{l=1}^{L} \sum_{\tilde{m}=1}^{\tilde{M}} \left[\tilde{k}_2^{\tilde{m}}\, \mathrm{e}^{-\tilde{k}_2^{\tilde{m}}\, t_l} - \sum_{m=1}^{M} \mu_{\tilde{m}}^{m}\, \mathrm{e}^{-k_2^{m}\, t_l} \right]^2, \quad t_l \in [\,0, T]$$

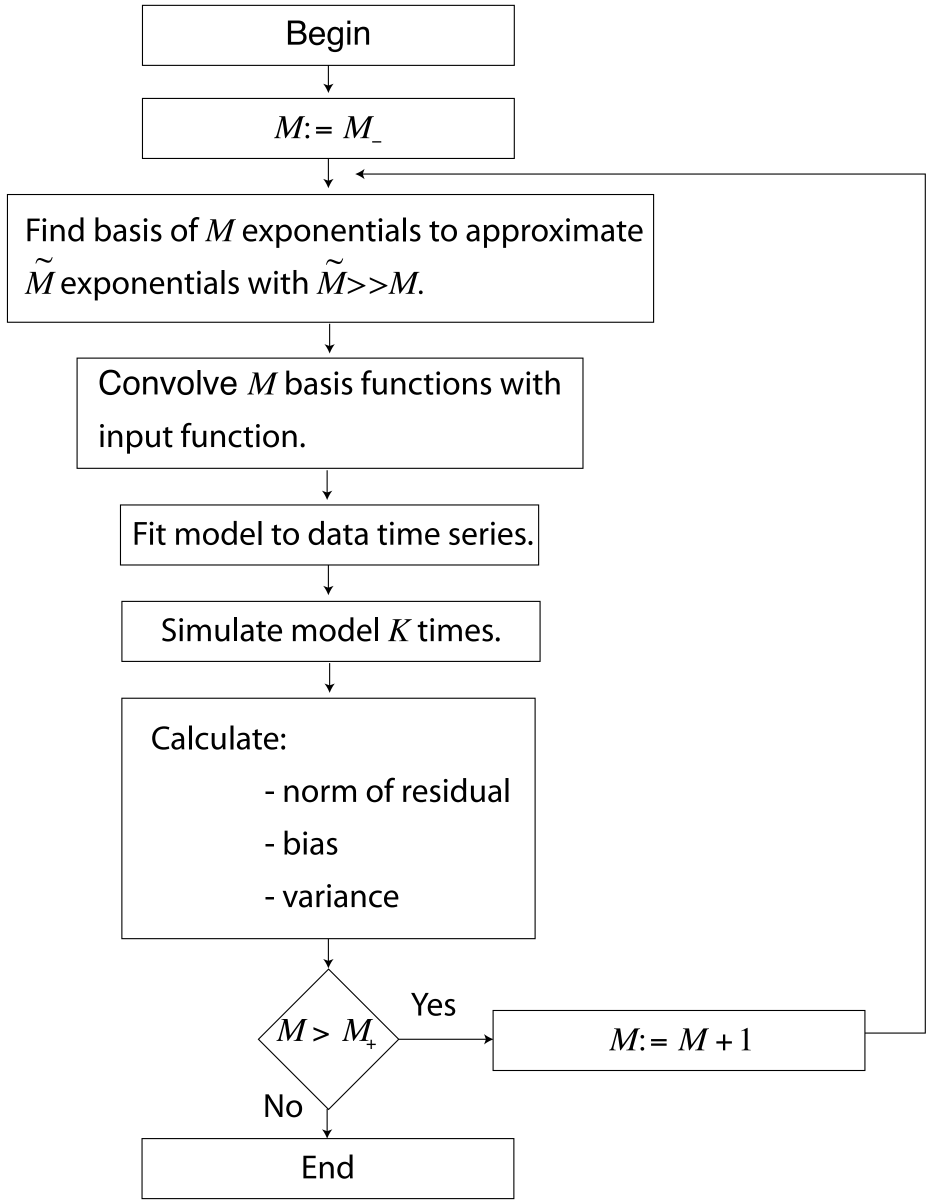
under the constraints $\mu_{\tilde{m}}^{m} \geq 0,\ k_2^{m} \geq 0,\ m = 1, 2, \ldots, M.$

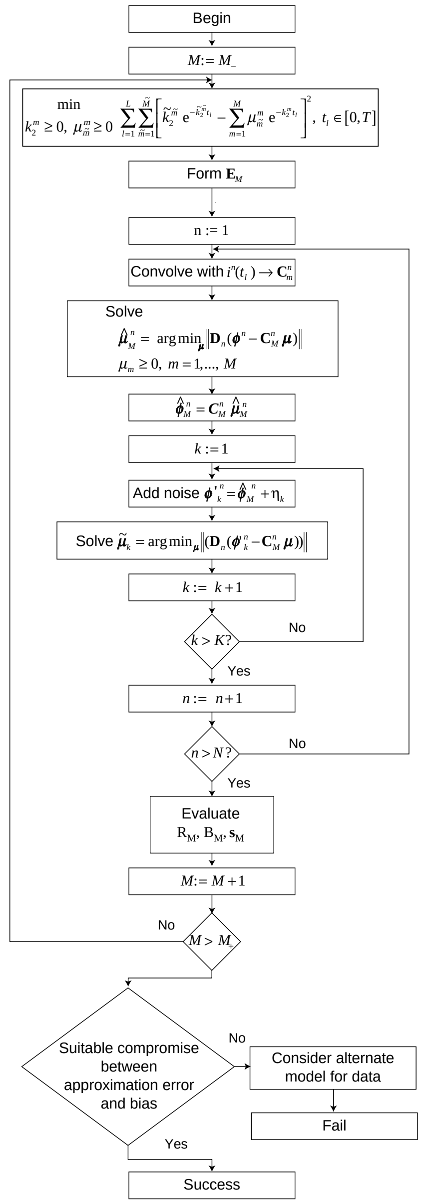
- $\boldsymbol{\mu}$ vector containing the $\mu_{\tilde{m}}^{m}$
- $\mathbf{k_2}$ vector containing the k_2^{m}

We are interested only in the $\mathbf{k_2}$. These constitute the parameters of the parsimonious basis.

How do we choose the number of basis elements M?

$$\min_{\mathbf{k_2},\,\boldsymbol{\mu}} \sum_{l=1}^{L} \sum_{\tilde{m}=1}^{\tilde{M}} \left[\tilde{k}_{\mathbf{2}}^{\tilde{m}}\, \mathrm{e}^{-\tilde{k}_2^{\tilde{m}}\, t_l} - \sum_{m=1}^{\boxed{\mathrm{M}}} \mu_{\tilde{m}}^{m}\, \mathrm{e}^{-k_2^{m}\, t_l} \right]^2, \quad t_l \in [\,0, T]$$


Begin
$M := M_-$
Find basis of M exponentials to approximate $\tilde{M}$ exponentials with $\tilde{M} >> M$.
Convolve M basis functions with input function.
Fit model to data time series.
Simulate model K times.
Calculate:
- norm of residual
- bias
- variance
$M > M_+$
Yes
$M := M + 1$
No
End


Begin
$M := M_-$
$\min_{k_2^m \geq 0,\ \mu_{\tilde{m}}^m \geq 0} \sum_{l=1}^{L} \sum_{\tilde{m}=1}^{\tilde{M}} \left[\tilde{k}_2^{\tilde{m}} e^{-\tilde{k}_2^{\tilde{m}} t_l} - \sum_{m=1}^{M} \mu_{\tilde{m}}^m e^{-k_2^m t_l} \right]^2,\ t_l \in [0,T]$
Form $\mathbf{E}_M$
n := 1
Convolve with $i^n(t_l) \rightarrow \mathbf{C}_m^n$
Solve
$\hat{\boldsymbol{\mu}}_M^n = \arg\min_{\boldsymbol{\mu}} \|\mathbf{D}_n(\boldsymbol{\phi}^n - \mathbf{C}_M^n \boldsymbol{\mu})\|$
$\mu_m \geq 0,\ m = 1,\ldots, M$
$\hat{\boldsymbol{\phi}}_M^n = \mathbf{C}_M^n \hat{\boldsymbol{\mu}}_M^n$
$k := 1$
Add noise $\boldsymbol{\phi}'^n_k = \hat{\boldsymbol{\phi}}_M^n + \eta_k$
Solve $\tilde{\boldsymbol{\mu}}_k = \arg\min_{\boldsymbol{\mu}} \|(\mathbf{D}_n(\boldsymbol{\phi}'^n_k - \mathbf{C}_M^n \boldsymbol{\mu}))\|$
$k := k+1$
$k > K?$
No
Yes
$n := n+1$
$n > N?$
No
Yes
Evaluate
$R_M, B_M, \mathbf{s}_M$
$M := M+1$
No
$M > M_+$
Suitable compromise between approximation error and bias
No
Consider alternate model for data
Fail
Yes
Success

Parsimonious Exponential Spectral Analysis (PESA)

Evaluation using synthetic data

Fit models to:

$$
\begin{aligned}
f_1 &= 6\,\mathrm{e}^{-17.5\,t} + 12\,\mathrm{e}^{-4.375\,t} \\
f_2 &= 11\,\mathrm{e}^{-11.667\,t} + 7\,\mathrm{e}^{-3.5\,t}.
\end{aligned}
$$

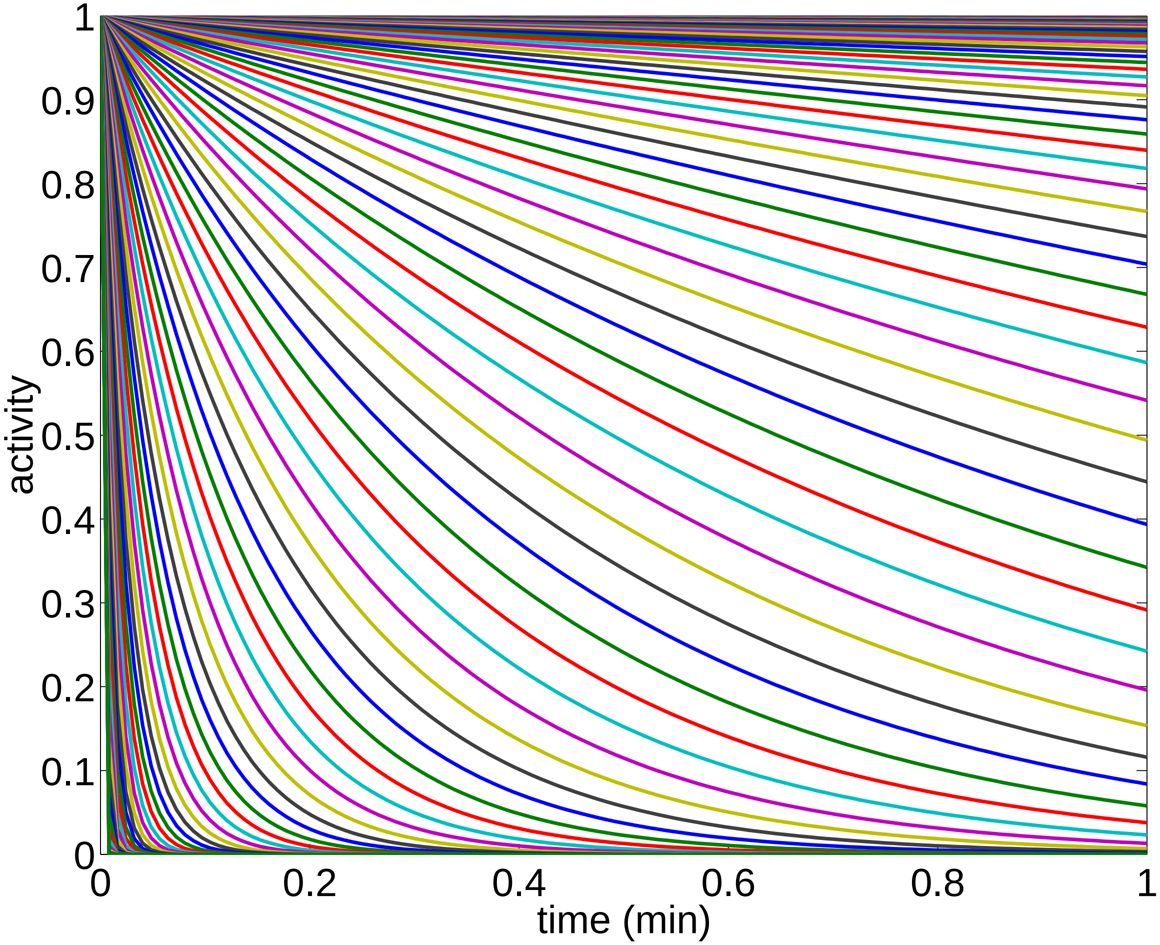
Gaussian noise is added to give SNR of ≈ 400.

Preliminary basis specification

Table 1: Parameters of exponential basis to be approximated using parsimonious basis set

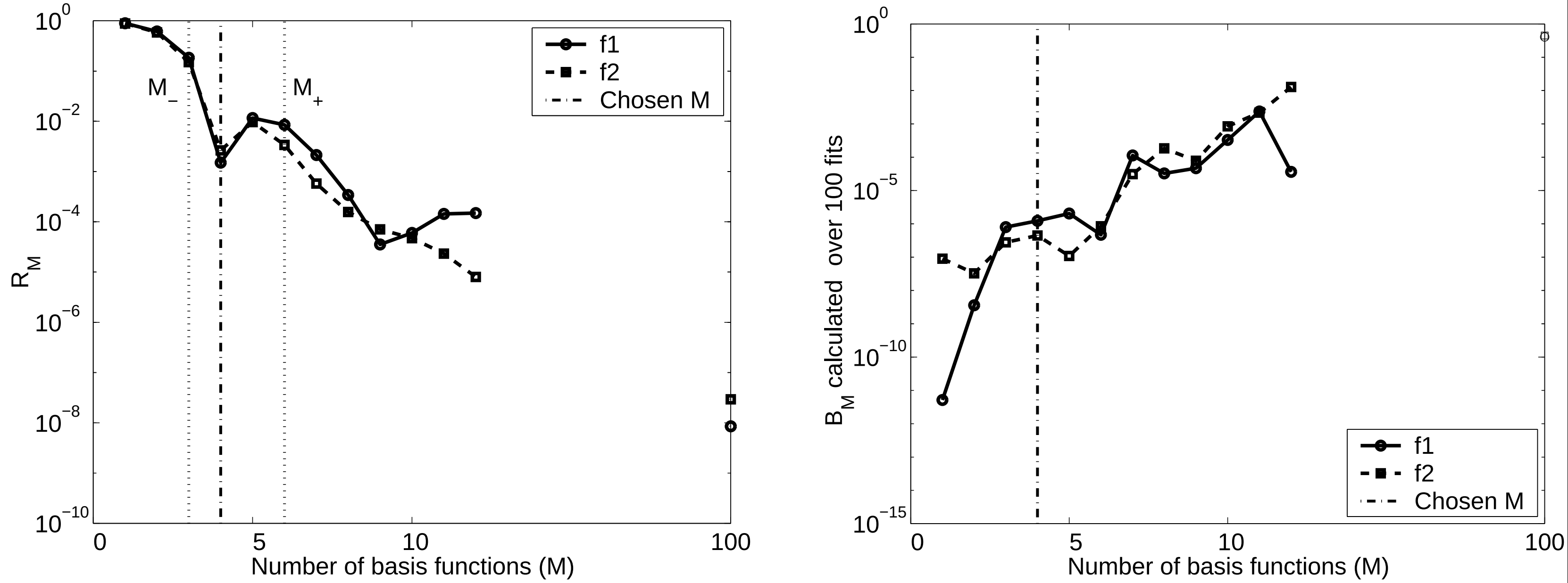
Parameter	Value	Unit
T	1	s
L	125	time samples
$\tilde{M}$	100	unoptimized bases
$\tilde{k}_2^{\tilde{m}}$	0.001-1000 log spaced	s^{-1}
K	100	noise realizations

Unoptimized set of basis functions

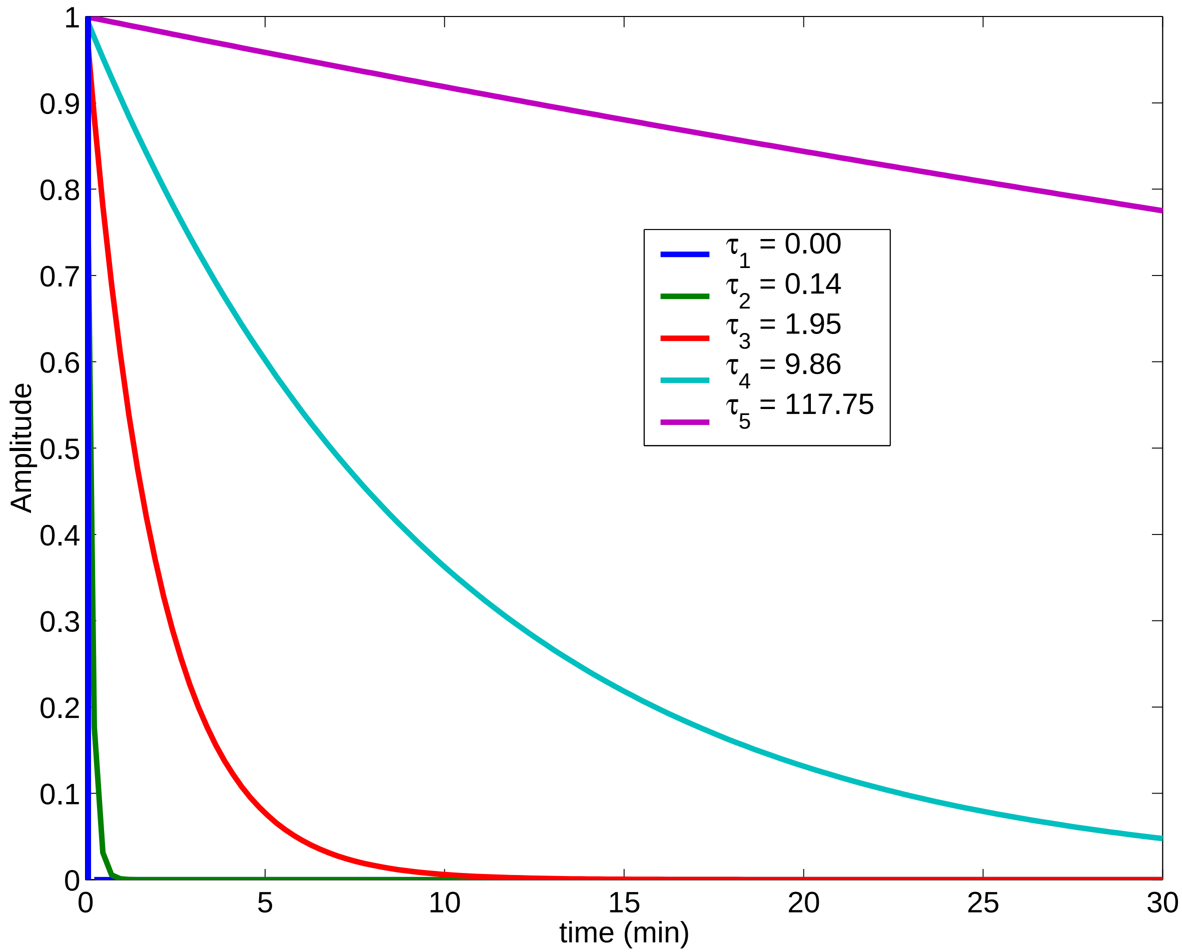


E matrix: Columns = 100, Rank = 30

Choosing M: compromise between goodness-of-fit and parameter bias metric

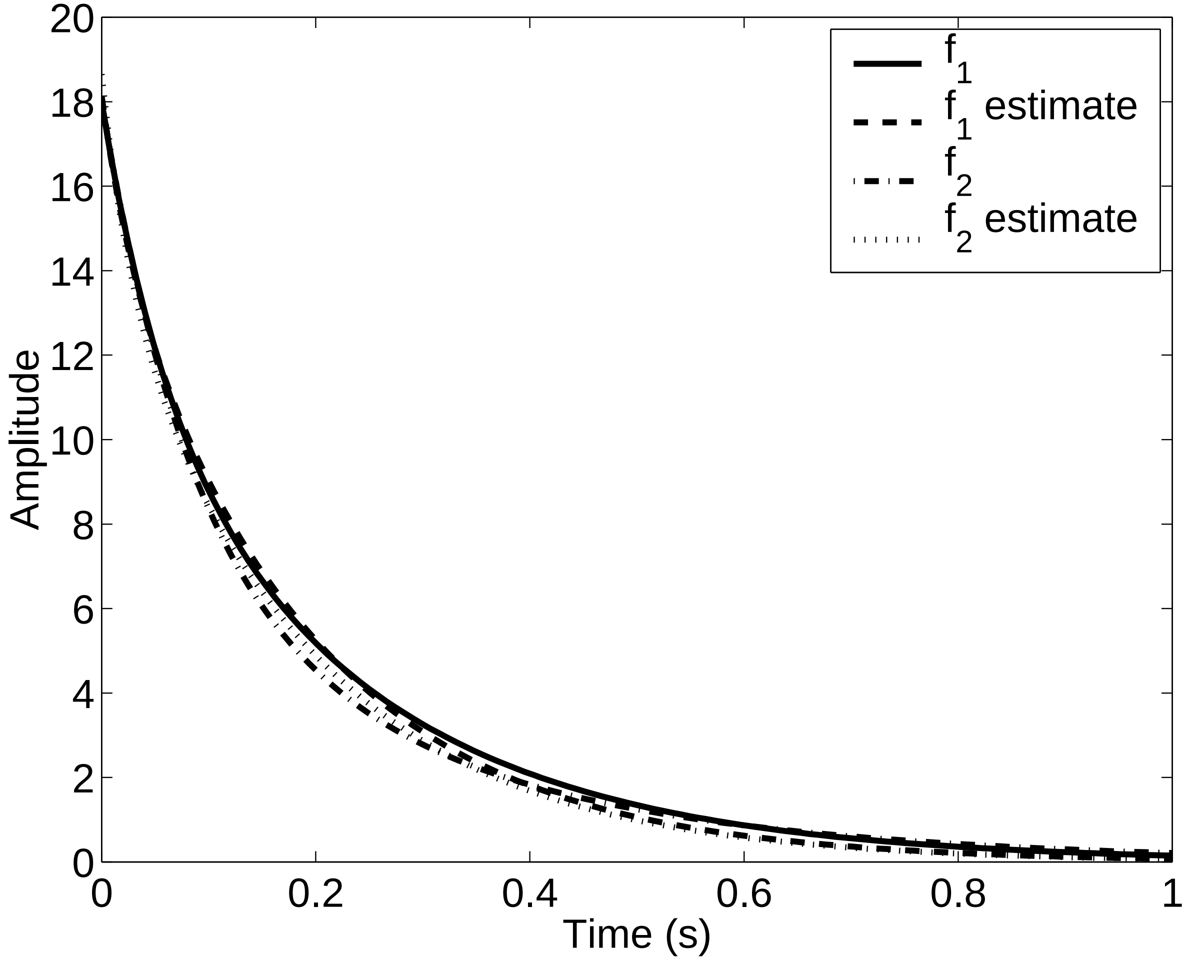


Optimized set of basis functions

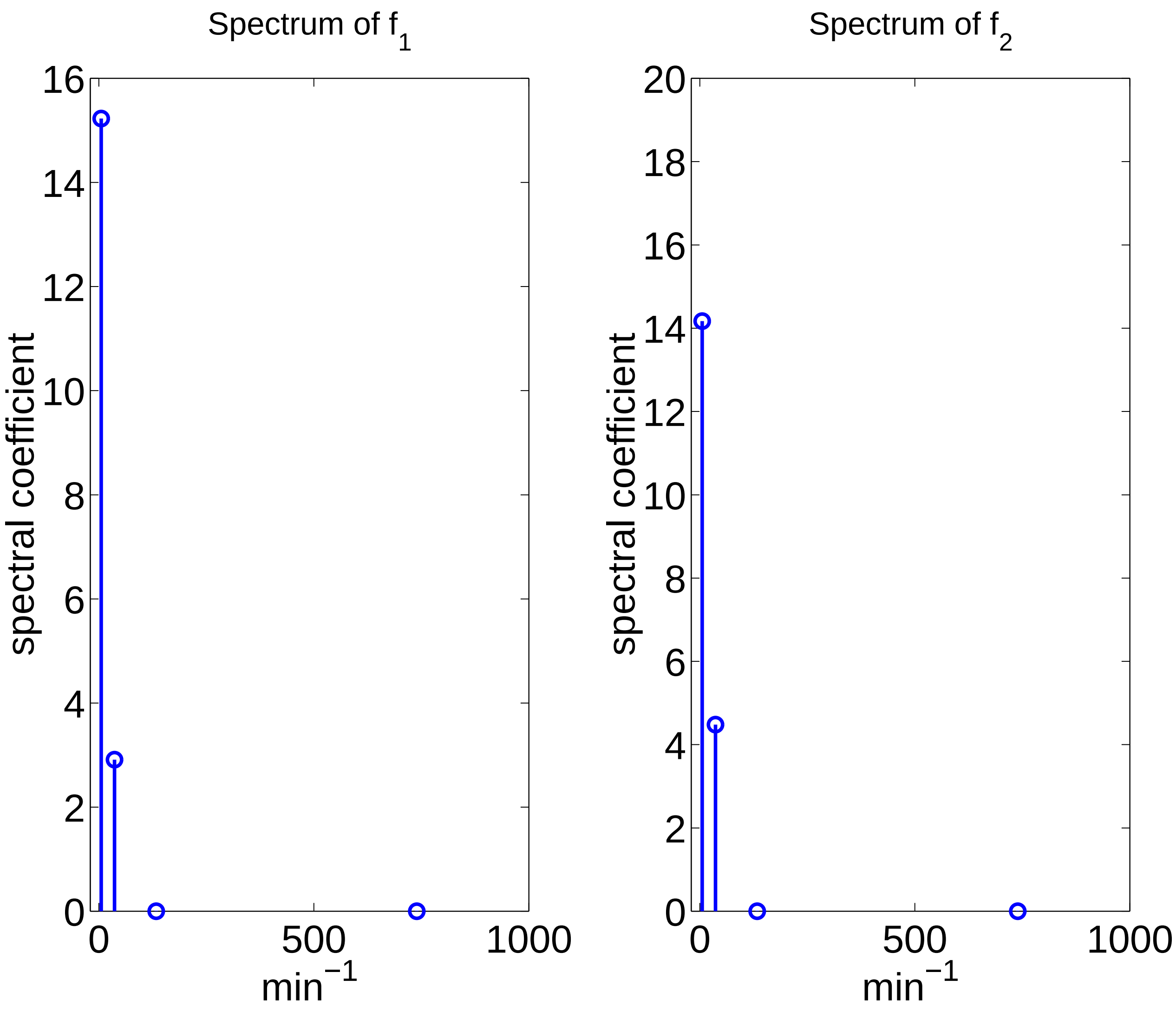


E matrix: Columns = 4, Rank = 4

PESA fits at $M = 4$



PESA spectra at $M = 4$



Quality of the solution

$$W_M \triangleq \frac{\sqrt{\mathrm{CRLB}\{\hat{\boldsymbol{\mu}}_M\}}}{\hat{\boldsymbol{\mu}}_M} \times 100,$$

		PESA $M = 4$	ESA $M = 100$
Maximum element of W_M:	f_1	15.4%	328%
	f_2	10.0%	784%

Application to real experimental data

Objective: Compare the kinetics of a new myocardial flow tracer (^{125}I-iodorotenone) with those of the well characterized tracer (^{99m}Tc-sestamibi).

Data: Consist of TACs obtained from 25 artificially perfused isolated rabbit hearts. Activity is measured in the venous outflow by a well counter.

Input function: A reference tracer that is not preferentially retained in the myocardial compartment (^{131}I-albumin) provides the blood input function for each experiment.

Isolated artificially perfused rabbit heart configuration

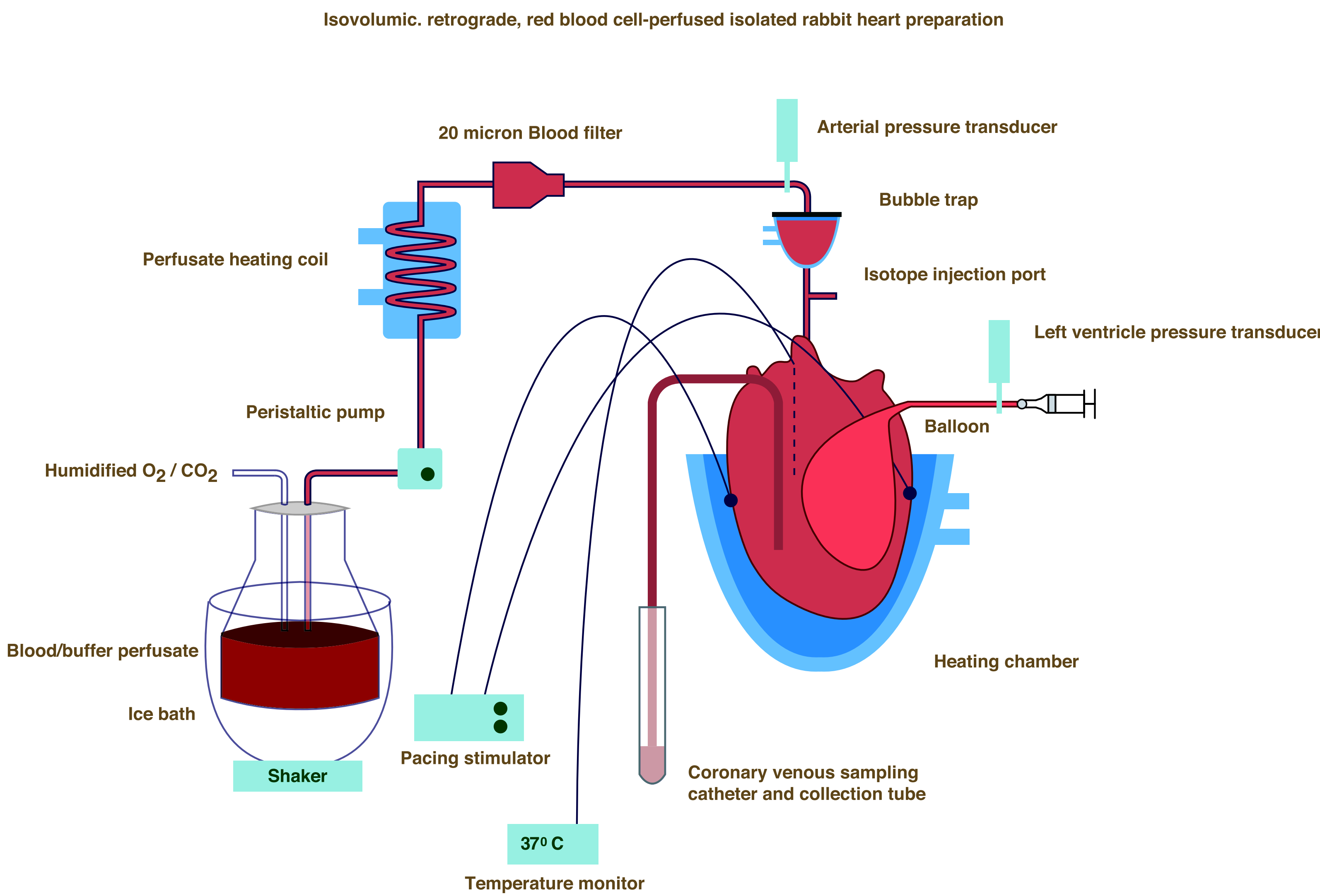
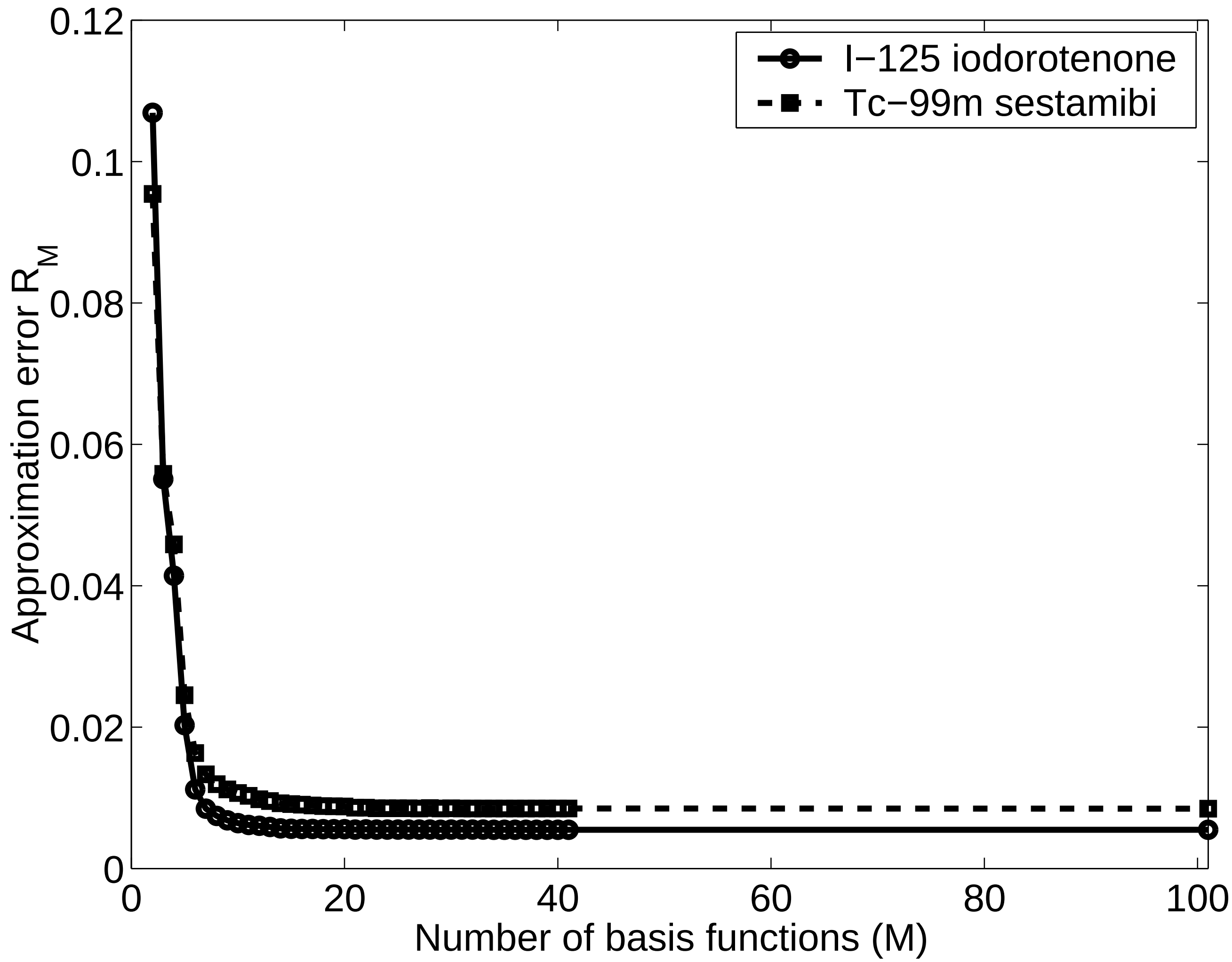


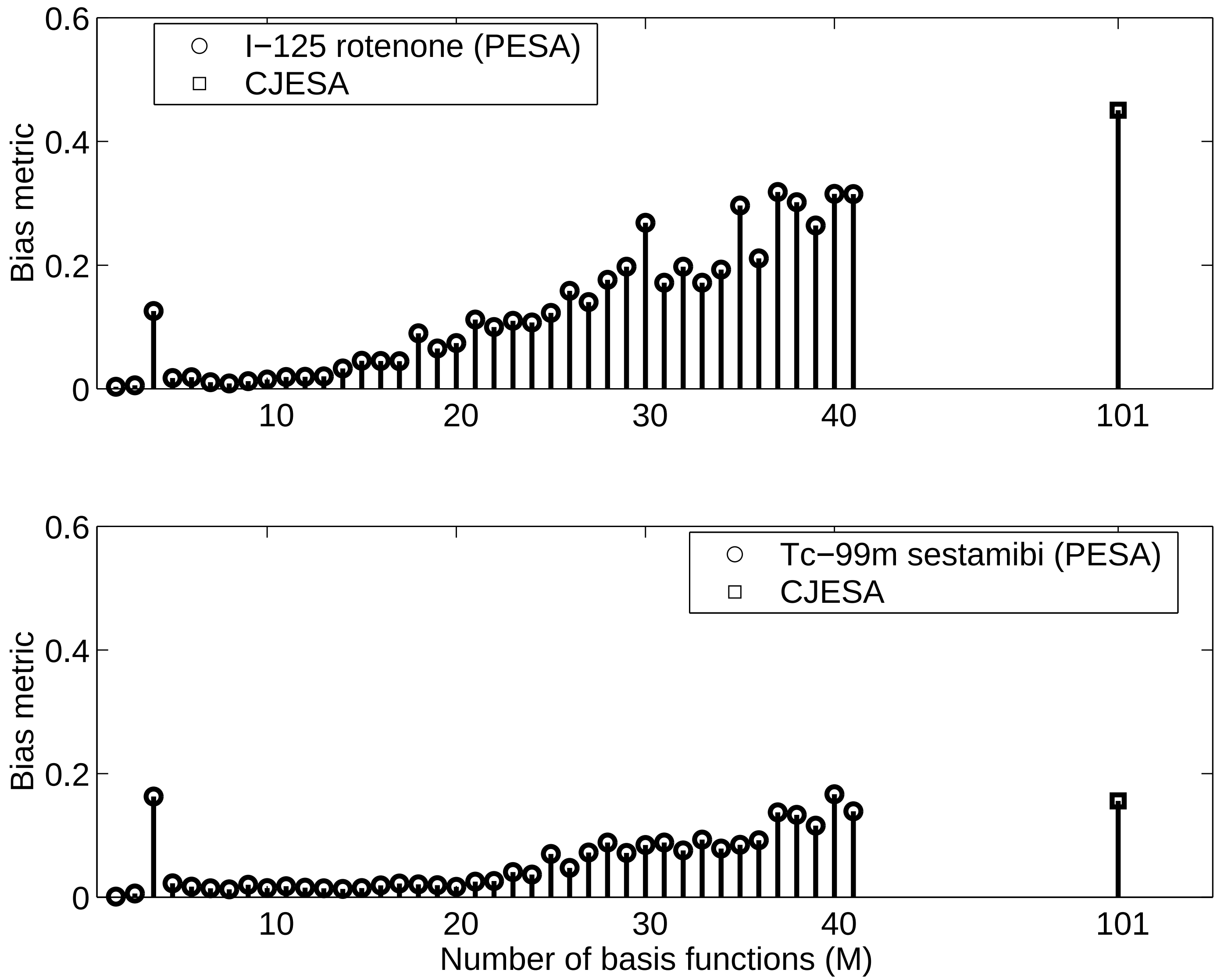
Table 2: Parameters of exponential basis to be approximated using parsimonious basis set for the isolated rabbit heart application

Parameter	Value	Unit
T	variable	s
L	variable	time samples
$\tilde{M}$	100	unoptimized bases
$\tilde{k}_2^{\tilde{m}}$	1/60-190 log spaced	min^{-1}

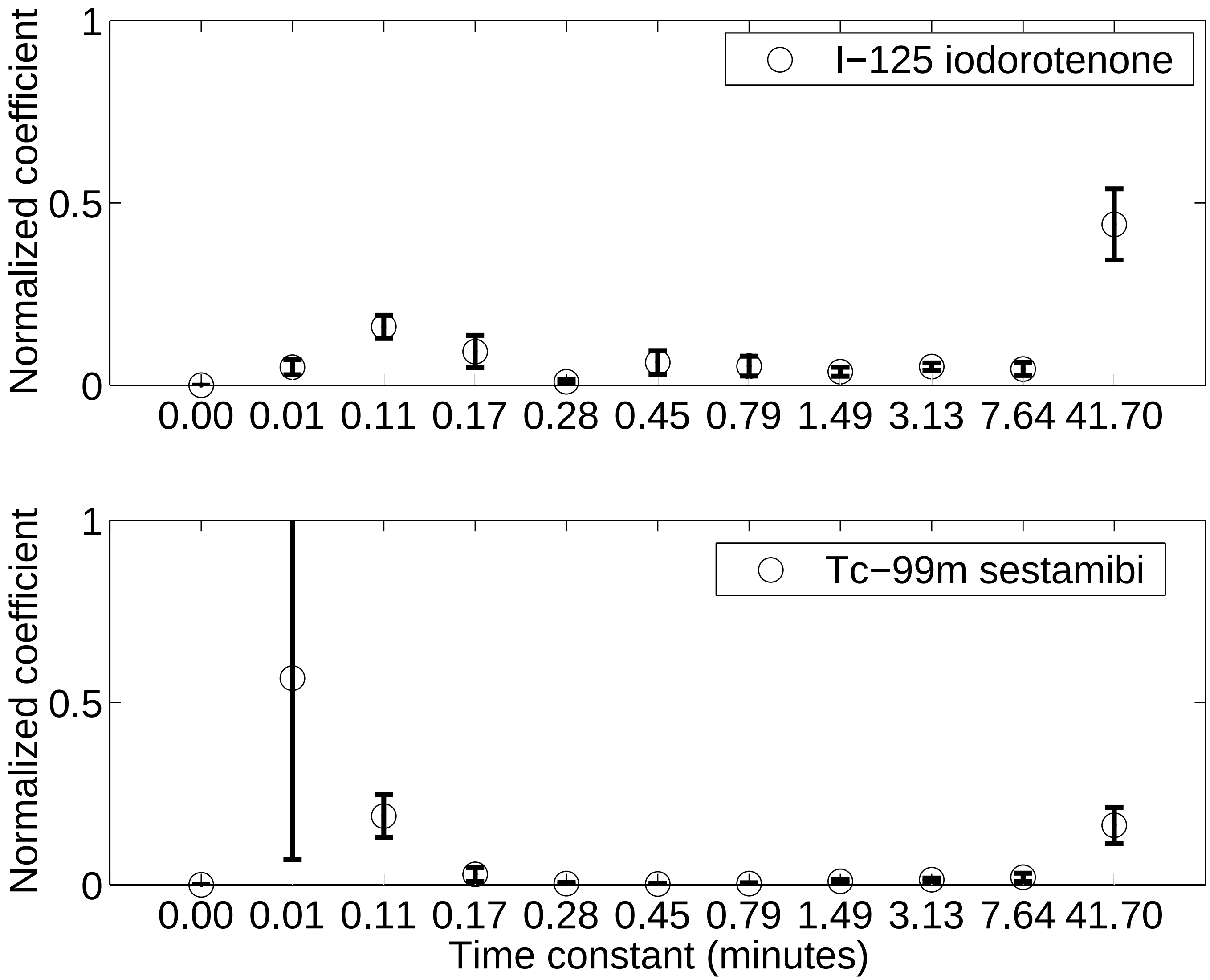
Approximation error metric vs. M



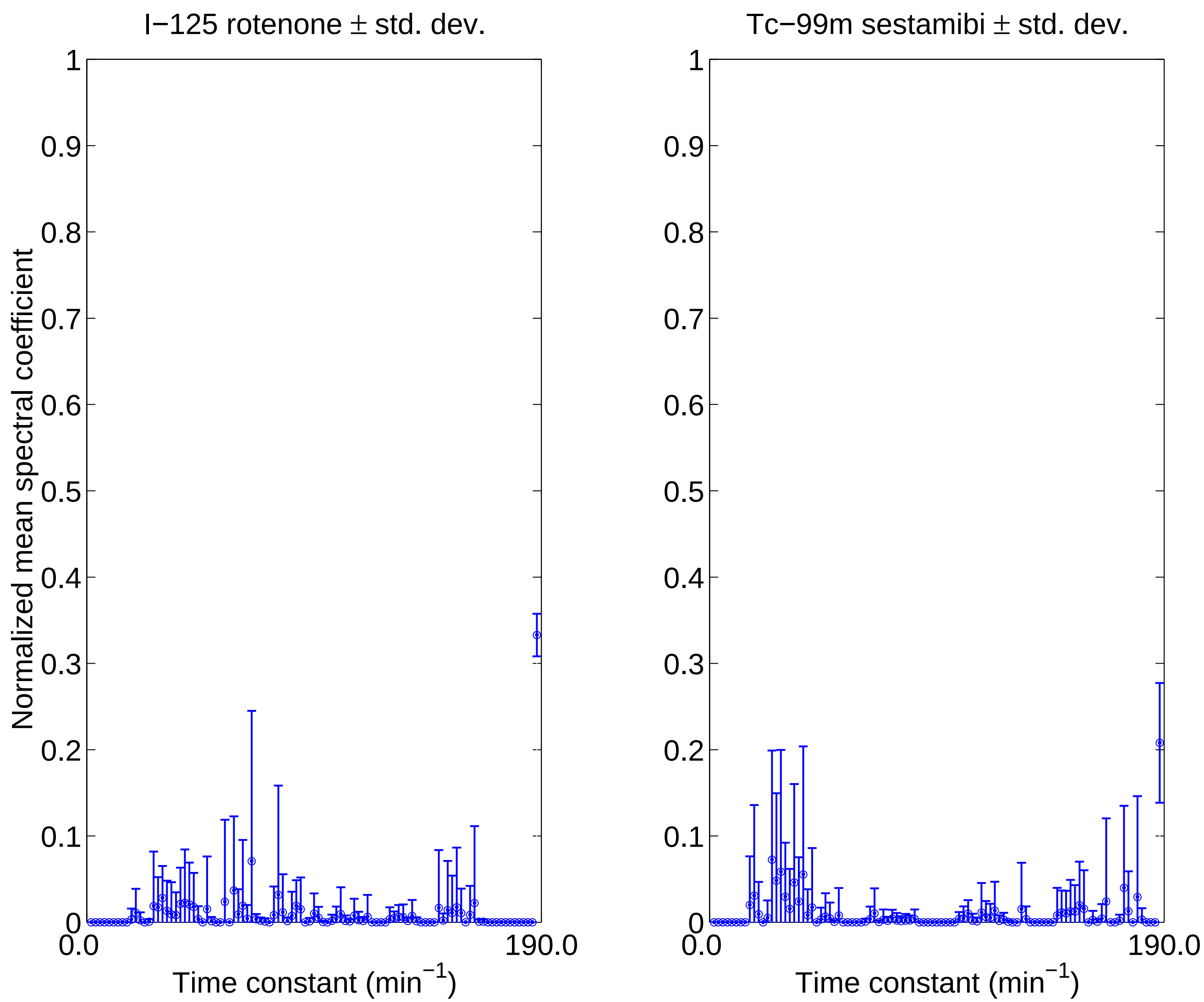
Bias metric vs. M



PESA Spectra at chosen $M = 11$



ESA spectra at $M = 101$:



Conclusion

1. PESA appears to be very useful for analysis of comparative tracer kinetic studies.
2. ESA as proposed by Cunningham and Jones (1993) should not be expected to yield robust results.

Limitations:

- PESA requires an input function estimate.
- An estimate of the data SNR is required for the simulation stage of the algorithm.

Reference

JS Maltz, Parsimonious Exponential Spectral Analysis *Physics in Medicine and Biology*, 47(13):2341-65, 2002.

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