Resolution of the spectral technique in kinetic modeling

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ABSTRACT

Physiologic systems can be represented by compartmental models which describe the uptake of radio-labeled tracers from blood to tissue and their subsequent washout. Arterial and venous time-activity curves from isolated heart experiments are analyzed using spectral analysis, in which the impulse response function is represented by a sum of decaying exponentials. Resolution and uniqueness tests are conducted by synthesizing isolated heart data with predefined compartmental models, adding noise, and applying the spectral analysis technique. Venous time-activity curves are generated by convolving a typical arterial input function with the predefined spectrum. The coefficients of a set of decaying exponential basis functions are determined using a non-negative least squares algorithm, and results are compared with the predefined spectrum. The uniqueness of spectral method solutions is investigated by computing model covariance matrices, using error propagation and prior knowledge of noise distributions. Coupling between model parameters is illustrated with correlation matrices.

Keywords:

1. INTRODUCTION

Time-activity curves are modelled by convolving the blood input function with an impulse response function, which characterizes the transport of tracer of interest in living tissue. Compartmental analysis is a useful method of modeling physiology, but requires *a priori* information on the appropriate kinetic model describing the physiologic processes. Without the proper *a priori* assumptions, misguided conclusions may be drawn regarding physiologic structure. Data quality also limits the precision to which the model structure may be retrieved.

As an alternative, we continue to investigate the utility of spectral analysis techniques used to determine the appropriate delineation of physiologic processes in tissues of interest. As outlined by Cunningham and Jones [1], the general approach of spectral analysis is to model the impulse response function as a sum of a large number of decaying exponential terms, the coefficients of which are non-negative. Modeling assumptions are thus minimized by using this large set of model parameters.

The accuracy of the retrieved spectral components will be addressed. The sensitivity of the spectral method can be evaluated by predefining the spectral components of the synthetic impulse response function. Synthetic time-activity curves will be forward-modelled by convolving the synthetic impulse response function with a blood input functional form. Input blood functions can be derived from fits to time-activity curves of reference tracers (which do not leave the vasculature) measured from venous blood of isolated heart experiments.

1.1. Time Activity Curves

The time-activity of perfused tracer in tissue is modelled by convolving in the time domain a blood input function $I(t)$ with an impulse response function $R(t)$. That is,

$$\Omega(t) = \int_0^t I(t-t')R(t')dt'. \tag{1}$$

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The radio-labelled tracer concentration in venous blood flowing from isolated heart experiments is collected over finite time intervals. The acquisition can be expressed as

$$D_i = \frac{1}{t_i - t_{i-1}} \int_{t_{i-1}}^{t_i} \Omega(t)dt \tag{2}$$

where the t_i's are the endpoints of acquisition time intervals, and $i = 1, 2, 3, ...N$ and N is defined by $t_{tot} = \sum_{i=1}^{N} t_i - t_{i-1}$ where t_{tot} is the total acquisition time.

In the forward problem, data from isolated heart reference tracer time-activity is measured for $I(t)$, and the impulse response function is expressed as a sum of decaying exponentials

$$R(t) = \sum_{k=1}^{K} \frac{x_k}{\tau_k} e^{-t/\tau_k}, \tag{3}$$

where the coefficients x_k and τ_k represent, respectively, amount of tracer uptake and rate of tracer washout by channel k. The x_k's are required to be positive values or zero. The lower bound should correspond with the decay of the radio-tracer, and the upper bound for the range of time constant τ_K is chosen in accord with physiologically reasonable values for an input blood function, The τ interval is spaced evenly on a logarithmic scale, where the choice $\tau_k = 1.1^k$ has been made here.

1.2. Synthetic Time Activity Curves

Time activity curves are simulated in order to assess the spectral methodology. Synthetic time activity curves are computed by convolving functional forms of $I(t)$ and $R(t)$ in the time domain.

In order to synthesize the blood input function, the time-activity curve from isolated heart reference tracer data (albumin data) [2] is fit to

$$I(t) = \alpha t^n e^{\beta t}. \tag{4}$$

The synthetic impulse response function $R_s(t)$ then was modelled in two forms:

- as a sum of decaying exponentials

  $$R^s(t) = \sum_{k=1}^{n_s} \frac{x_k^s}{\tau_k^s} e^{-t/\tau_k^s} \tag{5}$$

  where $n_s \ll K$, and
- an integration over a number of neighboring exponentials in the spectrum of λ's. The x_k^s's included in the range of integration are set to equal value ($x_k = 1$), forming a spectral boxcar function:

  $$R^s(t) = \int_{\tau_1}^{\tau_2} \frac{e^{-t/\tau}}{\tau} d\tau \tag{6}$$

We define an acquisition time schedule for concentration of the tracer of interest (Equation (2)) in accordance with typical isolated heart studies.

Normally distributed random noise is then added to each time point D_i^s. By specifying variances for each measurement D_i^s, the errors can be propagated so that it will be possible to define uncertainties for model parameters x_k and τ_k.

1.3. Model estimation

Adopting the spectral approach, the "data" can be estimated by

$$\mathbf{b} = \mathbf{A}\mathbf{x} \tag{7}$$

where $\mathbf{b}$ is a vector of time activity, $\mathbf{x}$ is the vector of tracer amounts defined in Equation (3), and $\mathbf{A}$ is the data kernel matrix. The elements of $\mathbf{A}$ are

$$A_{ik} = \int_{t_{i-1}}^{t_i} I(t) \frac{e^{t/\tau_k}}{\tau_k} dt \tag{8}$$

where $i = 1, 2, \ldots, N$ and $k = 1, \ldots, K$. $I(t)$ is piecewise constant over the time interval $t = [t_{i-1}, t_i]$. Then, given a synthetic time series of D_i^s's, the minimum of

$$\begin{aligned} E &= (\mathbf{D}^s - \mathbf{b})^T \mathbf{W}^{-1} (\mathbf{D}^s - \mathbf{b}) \\ &= (\mathbf{D}^s - \mathbf{A}\mathbf{x})^T \mathbf{W}^{-1} (\mathbf{D}^s - \mathbf{A}\mathbf{x}) \end{aligned} \tag{9}$$

is sought, subject to the constraint that $\mathbf{x} \geq 0$. $\mathbf{W}$ is a weighting matrix consisting of data covariance estimates. $\mathbf{W}$ is diagonal as the activity measurements at each time point are independent of each other. We use a non-negative weighted least-squares algorithm [3] to estimate the spectral values $\mathbf{x}$. Estimates for which $x_k > 0$ are often interpretted to correspond with identification of metabolic rates τ_k's.

The covariance of model parameters $\mathbf{x}$ can then be calculated from

$$[\mathbf{cov\ x}] = (\mathbf{A}^T \mathbf{W}^{-1} \mathbf{A})^{-1} \mathbf{A}^T \mathbf{W}^{-1} [\mathbf{cov\ D}^s] \mathbf{W}^{-1} \mathbf{A} (\mathbf{A}^T \mathbf{W}^{-1} \mathbf{A}), \tag{10}$$

where $[\mathbf{cov\ D}^s]$ is the covariance matrix of data vector $\mathbf{D}^s$.

2. RESULTS

2.1. Individual spectra

Impulse response functions modelled by single exponentials were recovered well in amplitude and spectral value, for spectral values λ_k^s belonging in the basis (Fig. 1). In all the cases described below, a positive amplitude is returned from the inversion for a fast decay constant corresponding to $1/\lambda \simeq 2.5 (log_{10} 1/\lambda \simeq 0.4)$. This decay constant is not predefined in the synthetic, but its presence in the solution indicates an erroneous peak, although apparently necessary to the fit. The presence of this exponential could in part be due to the approximation of the input blood function as piecewise constant when computing the forward model, in which higher 'frequency' decay constants are averaged out in the piecewise constant approximation of the input blood function.

When 10% noise was added to the output response function, a peak spread and amplitude decrease was present in the solution spectrum (Fig. 2). Shifting the model impulse response λ_k value to fall between two basis spectral values resulted in two adjacent spectral peaks to be returned in the solution, straddling the input value (Fig. 3). The sum of the returned amplitudes (x_k's) matched the input single peak amplitude.

The inversion did not perform as well when a second exponential was added to the synthetic impulse response function. The main peak values were returned with decreased amplitude, and were broadened at the base (Fig. 4).

The sensitivity of the inversion to spectral peak isolation was tested with the sum of three exponentials comprising the synthetic impulse response function ($R^s(t) = \sum_{k=1}^{3} x_k^s \lambda_k^s e^{-\lambda_k^s t}$. In one case, the impulse response function composed of three neighboring basis functions(eg., k,k+1,k+2) returned one peak centered on the middle model peak (Fig. 5). Identification of individual peaks were more resolvable with increased separation between input peaks. A peak separation of one (eg., k,k+2,k+4) was sufficient to retrieve two spectral peaks in the solution (Fig. 6). Although the peak separation distance threshold which returned three correct peaks was not investigated at this time, input peak separation distances of 2 and 3 (k,k+3,k+6 and k,k+4,k+8) were not sufficient in returning three separated peaks, but 2 peaks with broadening (Fig. 7). Separation distances over 6 (k,k+7,...) returned the solution peaks aligned with the input model peaks, although broadened and at times offset (Fig. 8). These tests were performed without noise.

2.2. Boxcar Model

Spectral analysis of tracer kinetic data has in general retrieved a small (< 5) number of exponential components (Cunningham and Jones, 1993; Turkheimer et al., 1998). The robustness of the spectral technique is investigated with impulse response functions which are defined as an integral over a continuous range of exponential functions of equal amplitude. The spectrum of such an impulse response function is a boxcar function in exponential decay constant space.

Impulse response functions expressed as integrals of boxcar functions were used in convolutions with blood input functions, to model time activity curves. The spectral decomposition method was applied, using n-basis exponential functions (where $n = 100$).

Rather than returning a large number of neighboring peaks continuously distributed over the boxcar range, the inversion returned a small number (< 5) of isolated and discrete spectral peaks distributed over the boxcar range (Figs 9-12). The erroneous fast decay exponential is also present in the solutions. Inversions using boxcar functions defined with longer decay (Fig.12) ranges ($1/\lambda > 100$) returned smaller amplitudes of this exponent than shorter decay ranged ($1/\lambda > 10$) boxcar functions (Fig. 10).

2.3. Time Sampling of Functions

In the previous computational experiments, the blood input function and impulse response function were convolved using the routine CONV in Matlab. CONV convolves two vectors which are arguments to the routine, which, in the case of the computational experiments, would be the blood input function and impulse response function sampled at discrete time points. Specifically, a 1 second time sampling was implemented for the above experiments. We wish to address the effect that sampling has on the retrieved spectral model parameters.

As an alternative to using Matlab routines which convolve discretely sampled blood input and impulse response functions, we implemented the symbolic tools of Mathematica to calculate directly the simulated acquired data (eq. 2) from the output response function, $\Omega(t)$, using the convolution (eq. 1) of functional forms of I(t) (eq. 4) and R(t) (eq. 6), for $\lambda_1 = 0.005$ and $\lambda_2 = 0.01$.

The spectral decomposition of this symbolic method returned the same spectral peaks as the discretely sampled $I(t)$ and $R(t)$.

3. DISCUSSION

We have observed that the precision spectral analysis technique of determining the number of compartments and washout parameter values from synthetic time activity curves, without *a priori* assignment of a compartmental model, is limited by the coarseness of basis function separation in decay constant space.

Spectral decomposition in general refers to systems for which the bases which span the system space are orthogonal functions. In the case of the basis set comprised of 100 decaying exponentials, which is utilized for this kinetic spectral analysis, there is a redundancy in the expression of the feasible solution space. If the spectral peaks in the forward computation of the synthetic impulse response function are well isolated in decay constant space, then the non-negative least squares inversion is capable of returning the correct spectral values (corresponding to the decay constants), but with decreased amplitudes (corresponding to washout flow parameters). Closely spaced spectral peaks which are included in the synthetic impulse response function are not retrieved individually by the inversion, but returned with a smaller number of widely spaced peaks.

Model covariance matrices can be constructed to investigate the trade-offs between model parameters set up by the modeling theory in the noise-free synthetic tests. Analysis of real biological data may not allow the refined precision of spectral intervals defined in our exponential basis set, due to the presence of noise, and the data acquisition procedures. Noise analysis will be performed to determine the limitations of the spectral technique, specifically due to the effects of noise. Model covariance matrices which include the variance of the data will be computed to assess the uniqueness of model parameter estimates.

Table 1. Fonts sizes to be used for various types of text. All fonts are Computer Modern Roman or an equivalent.

Article title	16 pt, bold, centered
Author names and affiliations	12 pt, normal, centered
Section heading	11 pt, bold, centered (all caps)
Subsection heading	11 pt, bold, left justified
Sub-subsection heading	10 pt, bold, left justified
Normal text	10 pt, normal
Footnote text	9 pt, normal

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