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An Application of Prony's Sum of Exponentials Method to Pharmacokinetic Data Analysis

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Abstract. We discuss the basic concept of compartmental modelling in pharmacokinetics and demonstrate that all the solutions admitted by multi-compartment models of classical pharmacokinetics are expressed as linear combinations of exponential functions of time. This lends itself to data analysis that depends on fitting exponential functions to finite size sets. A mathematical method developed a long time ago to deal with this type of problem is called Prony's method. We discuss the usefulness of this method in pharmacokinetic modeling and apply it to a particular data set obtained for the drug mibefradil. In spite of the method's power in dealing with well-behaved data sets, we indicate the existence of severe limitations since real concentration curves coming from pharmacokinetic data are seldom purely exponential.

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Key words: Data analysis, pharmacokinetics modelling, Prony's method.

1 Introduction to classical pharmacokinetics

In an attempt to interpret and quantify pharmacokinetic data, a commonly used model scheme, now termed "classical", was established. The biological model system under study is described by one, two, or more kinetically distinguishable interacting compartments. Each compartment represents a space of the body that is assumed to be kinetically distinct and homogeneously distributed with the drug [1–3]. The movement of drug between the compartments and the elimination of drug are assumed to follow the law of mass action to the first-order with time independent rate constants, $k_{i,j}$. Their mammillary structure is intended to correspond to biological model systems composed of organ arrangements that receive blood circulation in parallel, as in humans. Source terms, R,

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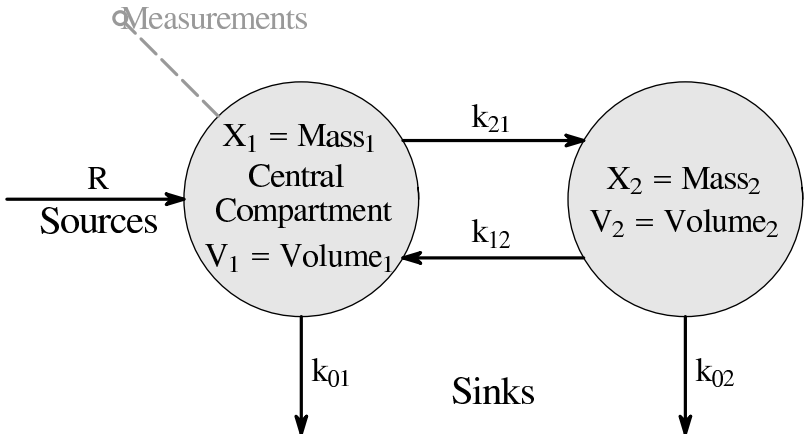

Figure 1: A schematic of a general 2-compartment model where the sources enter, and measurements are taken from, the central compartment. The ith-compartment is considered open if it looses drug to the environment ($k_{0i}>0$) and closed if it does not ($k_{0i}=0$). A multi-compartment model is considered mamillary if the secondary compartments are connected to the central compartment in a parallel arrangement and concatenary if the secondary compartments are connected in series.

are usually given as an initial condition for an effectively instantaneous bolus injection, as a zero-order (constant rate) i.v. infusion, or a first-order absorption of the drug from an oral dose (see Fig. 1). Ordinarily, measurements of drug plasma concentration are taken from the "central compartment" which is assumed to contain most or all of the blood [4–6].

The mass balance equations for a multi-compartmental system with m compartments are first-order differential equations that take the vector-matrix form

$$\begin{aligned} \frac{d\vec{X}}{dt} &= -\mathbb{K}\vec{X}+\vec{R}, \\ \vec{C} &= \mathbb{V}^{-1}\vec{X}, \end{aligned} \tag{1.1}$$

where $\vec{X}$ is a column vector of the m independent state variables (mass or concentration) of the system, $\mathbb{K}$ is a constant matrix composed of the first-order rate constants, $k_{i,j}$, such that, if the model is open (see Fig. 1) then $\mathbb{K}$ is non singular and invertible [2], $\vec{R}$ is the column vector describing the sources, $\vec{C}$ is the vector of compartment concentrations, and $\mathbb{V}$ is the distribution volume matrix. Solutions to this differential system are realized by standard matrix methods to be sums of exponentials with the form for each compartment following

$$C_j(t) = \sum_{i=0}^{m} A_{ij} e^{a_{ij}t}, \tag{1.2}$$

where A_{ij} and a_{ij} are both functions of the first-order rate constants, $f(k_{i,j})$. The form of the solution is the key reason that multi-compartmental modelling is so popular [7].

The model parameters k_{ij} may be found directly from these solutions while the decaying exponential functions serve as a power basis set for describing the normally declining concentration time-course pharmacokinetic data.

Classical mammillary multi-compartmental models possess the properties of constant clearance, linearity, time invariance, and a terminal mono-exponential phase. Linearity and time invariance of this model are due to the linearity and time invariance of the differential operator, d/dt, and the constant matrix $\mathbb{K}$. The systemic clearance, CL_S, is the extraction rate (rate of elimination), dX_e/dt, divided by the plasma concentration of drug, such that for an i.v. bolus dose,

$$CL_S = \frac{dX_e/dt}{C(t)} = \frac{\int_0^\infty dX_e}{\int_0^\infty C(t)dt} = \frac{X_e|_0^\infty}{\int_0^\infty C(t)dt} = \frac{0 - X_e(0)}{\text{AUC}} = \frac{-\text{Dose}}{\text{AUC}} = \text{const}, \tag{1.3}$$

where AUC stands for the area under the curve. Finally, the terminal mono-exponential phase occurs, since beyond some time, t_z, all but one exponential term, say $i=m$, will be approximately zero, such that

$$C_j(t) \approx A_{mj} e^{a_{mj} t} \quad \forall t > t_z. \tag{1.4}$$

Consequently, the coefficients a_{ij} must be negative in order to lead to an asymptotic trend of $C_j(t)$ to zero as $t \to \infty$.

2 Prony's method applied to pharmacokinetics

The equations generated by classical compartmental models, and sometimes used by non-compartmental techniques, are sums of exponentials. Prony's method is a mathematical routine to fit said equations to data [8, 9] and was studied for its merits in pharmacokinetic applications. Broadly described, the approach of Prony's method is to convert exponential expressions to nonlinear algebraic equations and then transform those to a larger number of linear algebraic equations that can be easily solved by the method of least squares. So, presuming that drug concentration time-course data is to be fit to an approximation with $2M$ unknowns of the form

$$C(t) \approx A_1 e^{a_1 t} + A_2 e^{a_2 t} + \cdots + A_M e^{a_M t}, \tag{2.1}$$

let $\mu_k = e^{a_k}$, to put the exponential relation into the more convenient configuration of

$$C(t) \approx A_1 \mu_1^t + A_2 \mu_2^t + \cdots + A_M \mu_M^t. \tag{2.2}$$

Now Prony's method demands that ordinate values of $C(t)$ are specified on a set of $N \geq M$ equally spaced points, and that a linear change of variables has been introduced in advance in such a way that the abscissa datum points are at $t \to k = 0, 1, 2, \ldots, N-1$. Therefore, the real data must be translated in time so that the first meaningful datum is at time $t = 0$,

and then scaled by a lowest common denominator and mapped onto the natural numbers. If the data set is incomplete at this point, then the only known option is to complete the data set by interpolation between the actual datum points. By successive substitution of each transformed datum (k,C_k), each relation of the following group

$$\begin{aligned}
C_0 &\approx A_1\mu_1^0 + A_2\mu_2^0 + \cdots + A_M\mu_M^0, \qquad \mu_k^0 = 1\\
C_1 &\approx A_1\mu_1^1 + A_2\mu_2^1 + \cdots + A_M\mu_M^1\\
C_2 &\approx A_1\mu_1^2 + A_2\mu_2^2 + \cdots + A_M\mu_M^2\\
&\vdots\\
C_{N-1} &\approx A_1\mu_1^{N-1} + A_2\mu_2^{N-1} + \cdots + A_M\mu_M^{N-1}
\end{aligned} \tag{2.3}$$

necessarily would be met, such that the exponential approximation may be based on the result of satisfying these N algebraic expressions as nearly as possible.

To help solve this group of mostly nonlinear *algebraic* relations, introduce a temporary variable μ and construct the equation

$$(\mu-\mu_1)(\mu-\mu_2)\cdots(\mu-\mu_M)=0, \tag{2.4}$$

where $\mu_1,\mu_2,\ldots,\mu_M$ are the roots of the expanded algebraic equation

$$\alpha_0\mu^M+\alpha_1\mu^{M-1}+\alpha_2\mu^{M-2}+\cdots+\alpha_{M-1}\mu^1+\alpha_M\mu^0=0, \tag{2.5}$$

where $\alpha_i=f(\mu_1,\mu_2,\ldots,\mu_M)$ and $\alpha_0=1$ without loss of generality. The strategy is to temporarily isolate the nonlinearity of the system within the single polynomial and transform it into a set of linear algebraic equations. In order to determine the coefficients $\alpha_1,\alpha_2,\ldots,\alpha_M$, the first equation in (2.3) is multiplied by α_M, the second equation by α_{M-1}, …, the Mth equation by α_1, and the $(M+1)$th equation by α_0, and then the results are added as follows:

$$\begin{aligned}
C_0 &\approx A_1\mu_1^0 + A_2\mu_2^0 + \cdots + A_M\mu_M^0 \times \alpha_M\\
C_1 &\approx A_1\mu_1^1 + A_2\mu_2^1 + \cdots + A_M\mu_M^1 \times \alpha_{M-1}\\
C_2 &\approx A_1\mu_1^2 + A_2\mu_2^2 + \cdots + A_M\mu_M^2 \times \alpha_{M-2}\\
&\vdots \qquad\qquad\qquad\qquad \vdots\\
C_{N-1} &\approx A_1\mu_1^M + A_2\mu_2^M + \cdots + A_M\mu_M^M \times \alpha_0,
\end{aligned} \tag{2.6}$$

$$\begin{aligned}
&C_0\alpha_M + C_1\alpha_{M-1} + \cdots + C_M\alpha_0\\
&\quad\approx 0 = (\alpha_0\mu^M + \alpha_1\mu^{M-1} + \cdots + \alpha_M\mu^0)\times(A_1+\cdots+A_M).
\end{aligned}$$

Notice, since $N \geq 2M$, the above démarche does not include all of the N equations in (2.3). But, with the same approach, by starting instead successively with the second, third, …, $(N-M)$th equation, all of the equations of (2.3) are used, and $N-M-1$ additional equations of similar form to (2.6) are obtained. Together, the above treatment implies the

set of $N-M$ linear algebraic equations

$$\begin{aligned} C_M\alpha_0+C_{M-1}\alpha_1+C_{M-2}\alpha_2+\cdots+ \quad C_0\alpha_M \quad &\approx 0,\\ C_{M+1}\alpha_0+ \ C_M\alpha_1 \ +C_{M-1}\alpha_2+\cdots+ \quad C_1\alpha_M \quad &\approx 0,\\ \vdots& \\ C_{N-1}\alpha_0+C_{N-2}\alpha_1+C_{N-3}\alpha_2+\cdots+C_{N-M-1}\alpha_M &\approx 0. \end{aligned} \tag{2.7}$$

Since the ordinates C_k are determined from the real data, the above set generally can be solved using the method of least-squares.

From this course of action, after the α's are determined, the M μ's, and subsequently the unknown parameters $a_1,\ldots,a_M$, are found as the roots of a single polynomial equation. After substitutions, equations (2.3) then become linear equations in the M A's with known coefficients μ_k. Finally, the unknown parameters $A_1,\ldots,A_M$ are determined again by applying the least squares technique to this set of equations to complete the process of obtaining values for all of the sought after pharmacokinetic parameters.

For data sets that are not in the form required, additional datum points can be synthesized by linearly interpolating between real data points. Once obtained, the resulting new set of data could be mapped onto the natural numbers by division by the lowest common denominator.

3 Application of the method to mibefradil data sets

Mibefradil is a calcium antagonist designed for the treatment of hypertension and angina since it has the useful effects of being able to relax blood vessels allowing more blood and oxygen to reach the heart but at the same time not reducing the performance of the heart [11–13]. Experiments on chronically instrumented dog model systems exhibited nonlinear pharmacokinetics for mibefradil as dose was increased, and the liver was identified as the major organ for elimination of the drug [14, 15]. Plasma concentration time-course data sets were collected for different dogs at different oral and i.v. dosages.

Because the uncertainties of the concentration measurements were never explicitly stated and perhaps never calculated in either [11] or [12], the values were directly calculated from the documented concentration calibration chromatograms of HPLC assays of mibefradil in the dog plasma from [11]. The percentage errors of measured concentration values of the known test standards were assumed to be Gaussian distributed, such that the standard deviation of the distribution, to randomly account for the discrepancies 90% of the time, was 9%. The uncertainty in the documented measurements of the independent time variable likewise was not stated in [11] or [12], but is assumed to be small for the purposes of this article.

Since the declared nonlinear behaviour of mibefrdail after higher oral doses is at least partially attributed to a possible increase in the gut absorption [11], only the data for the i.v. trials were considered. It was additionally concluded in [11] that the observed nonlinear kinetics was mainly due to dose- and/or time-dependent reductions in hepatic

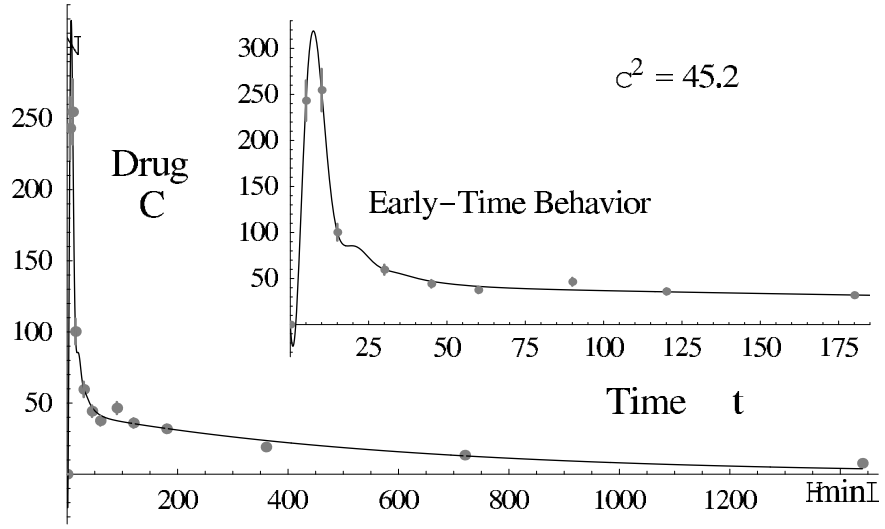

Figure 2: A curve generated using a sum of six exponential terms fit by the standard Prony's method compared to a representative concentration verses time data set from the dog model system studied with a characteristic sharp peak and elongated tail. The measured concentrations are of mibefradil in the plasma of the number two dog taken at various times from the portal vein after an intravenous dose (IV-PV-D2). The uncertainty of the concentration measurements was calculated to be 9%.

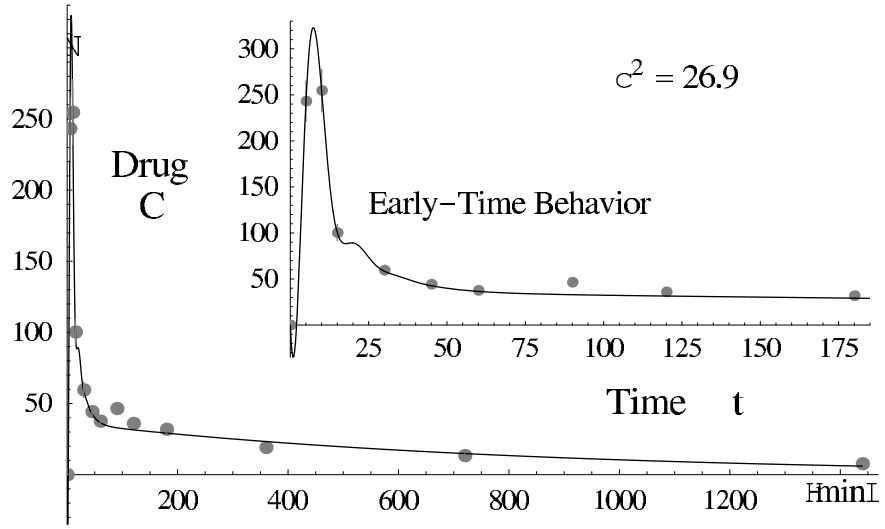

Figure 3: A curve generated using a sum of six exponential terms determined by the weighted Prony's method to the IV-PV-D2 concentration time-course data exhibiting an improved fit.

clearance. A major objective of this paper is to propose a novel physical mechanism that helps explain the observed nonlinear behaviour of mibefradil in dogs.

The results of Prony's method as applied to fitting the mibefradil data are illustrated in Figs. 2 and 3. The first seven datum points of the concentration peak were matched re-

markably well considering the rapidly changing, and broad range of, drug concentration values over a narrow domain of time. The global fit of the data was generally not as successful as indicated by a rather large figure-of-merit chi-square function value. A view of the statistical residuals, $R_i=|C_i-C(t_i)|$, of the data indicated that most of the discrepancy as measured by the figure-of-merit function between the curve fit and the data was due to the datum points in the long shallow sloped tail (see Fig. 4). This was not surprising since the standard Prony's method must perform with all the data, real and synthesized, without discrimination, while the chi-square figure-of-merit function is only concerned with the agreement between the fitted curve and the real experimental data. Whereas the chi-square function weights all absolute deviations between the fitted curve and the real datum points inversely proportional to the uncertainty (previously shown to be 9%) of the measured concentration at that point ($w_i=1/\sigma_i^2$), thus demanding greater absolute accuracy at the low concentrations of the tail, the standard Prony's method has no abilities to take into account weighted datum points and considers the absolute deviation of all datum points equally. An amelioration of Prony's method appeared necessary for the statistical technique to be influenced by the real datum points to a larger extent than the interpolated datum points and, since the range of the ordinate data spans 4.3 orders of magnitude (relative to base e), to consider absolute residuals differently for each datum point.

From the theory of approximation by the method of least-squares for discrete data, a system of equations can be used to manufacture a set of M normal equations with which the M unknowns $\alpha_1,\alpha_2,\ldots,\alpha_M$, can be exactly solved for using matrix methods. Establishing the rth normal equation entails multiplying each relation of (2.6) by the coefficient of α_r in that equation, and by the weight associated with that equation, and summing the results, as follows

$$\begin{aligned}
-C_M \approx & C_{M-1}\alpha_1+C_{M-2}\alpha_2+\cdots+C_0\alpha_M && \times C_{M-r} \times w_?\\
-C_{M+1}\approx & C_M\alpha_1+C_{M-1}\alpha_2+\cdots+C_1\alpha_M && \times C_{M+1-r}\times w_?\\
& \vdots &&\\
-C_{N-1}\approx & C_{N-2}\alpha_1+C_{N-3}\alpha_2+\cdots+C_{N-M-1}\alpha_M\times C_{N-1-r}\times w_? &&
\end{aligned} \tag{3.1}$$

where $r=1,2,\ldots,M$, $\alpha_0=1$, and w_i are the unknown weights. Besides possessing the appropriate form to be susceptible to solution by the method of least-squares through the use of normal equations, the above group of relations possesses the critical difference, compared to groups of relations formed by an approximation to data with a linear model, of each of the relations not being dependent on a single discrete datum value. An examination of the individual relations shows that the coefficients and constants are dependent on a train of $M+1$ ordered ordinate datum values.

Since weights are normally applied to a single relation as functions based on the one corresponding datum point determining the coefficients and constants of the single relation, the same weighting scheme for Prony's method is unworkable. An altered weighting scheme based on the entire ordered series of ordinate concentration values of an individual equation was devised ad hoc. Because any ordered sequence of ordinate data

implies an ordered sequence of abscissate data, the weight assigned to each equation was considered to be the average weight attributed to each datum point as a function of time.

Using aggregate weights as define above effectively smears in time the influence of the weight function, w, around each abscissal datum value, t_k, over a domain $t\in[t_{k-M-1}, t_{k+M+1}]$. This occurs because each equation that is used to calculate the aggregate weight is a train in time, $M+1$ cars long, that requires $2M+1$ units of time to pass. Therefore, this weighting scheme performs most like a regular linear least-squares weighting procedure when the number of parameters, M, is small and the short train is more like a point along the abscissa than a long line. Illustrative results of the process can be discerned from Fig. 5.

An advantage of the described weighting system for Prony's method for fitting pharmacokinetic data is that much of the influence of the interpolated datum points, introduced because of an incomplete data set as a necessity of the procedure, can be removed by setting the weight function to be zero for all interpolated data, such that $w(t_k)=0\forall(k,C_k)\in\{\text{interpolated data}\}$. This results in the interpolated data mostly being diminished to valueless placeholders that the method requires, but that affect the final fit diminutively. The nonzero weights assigned to real datum points were the same as those for the normal linear least-squares method: $w(t_k)=1/\sigma_k^2\ \forall\ (k,C_k)\in\{\text{real data}\}$, where $\sigma_k=9\%C_k$. Because Prony's method uses a least-squares fit a second time, in a more conventional format, the weights of the individual datum points are used again to calculate for the A's.

Finally, to calculate the rth normal equation contributing to a direct solution as described above, as a first step in Prony's method, for the unknowns $\alpha_1,\alpha_2,\ldots,\alpha_M$, the aggregate weights were implemented explicitly as follows

$$\begin{aligned}
-C_M &\approx C_{M-1}\alpha_1+C_{M-2}\alpha_2+\cdots+C_0\alpha_M && \times C_{M-r} \times w(t_M,\ldots,t_0)\\
-C_{M+1} &\approx C_M\alpha_1+C_{M-1}\alpha_2+\cdots+C_1\alpha_M && \times C_{M+1-r}\times w(t_{M+1},\ldots,t_{N-M-1})\\
&\ \ \vdots\\
-C_{N-1} &\approx C_{N-2}\alpha_1+C_{N-3}\alpha_2+\cdots+C_{N-M-1}\alpha_M\times C_{N-1-r}\times w(t_{N-1},\ldots,t_0),
\end{aligned}$$

which yields

$$\zeta_{r,1}\alpha_1+\zeta_{r,2}\alpha_2+\cdots+\zeta_{r,M}\alpha_M=\eta_r \quad (r\text{th normal equation}), \tag{3.2}$$

where $\zeta_{r,j}$ are the constant coefficients of the unknown parameter variables α_j described by

$$\zeta_{r,j}=\sum_{i=M}^{N-1} w(t_i,t_{i-1},\ldots,t_{i-M})\,C_{i-r}\,C_{i-j} \tag{3.3}$$

and η_r are constants described in terms of known values by

$$\eta_r=-\sum_{i=M}^{N-1} w(t_i,t_{i-1},\ldots,t_{i-M})\,C_{i-r}C_i. \tag{3.4}$$

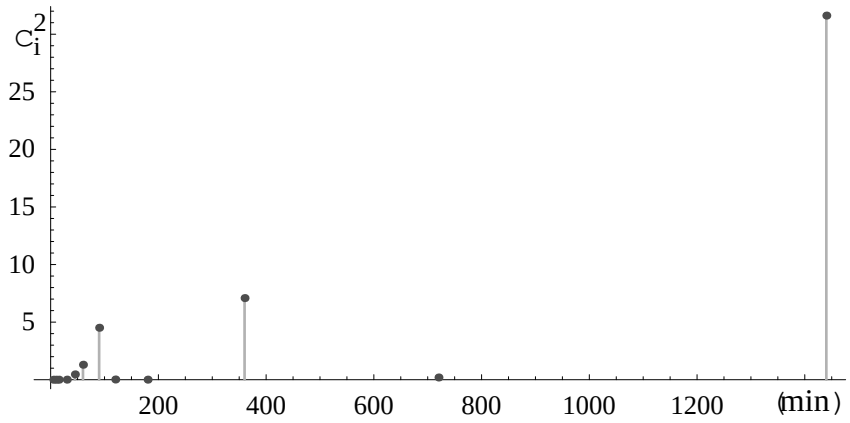

Figure 4: A plot of the weighted residual squared for each of the real datum points separated in time to indicate their relative contribution to the disparity with the curve produced by Prony's method as measured by the chi-squared figure-of-merit function for the trial IV-PV-D2.

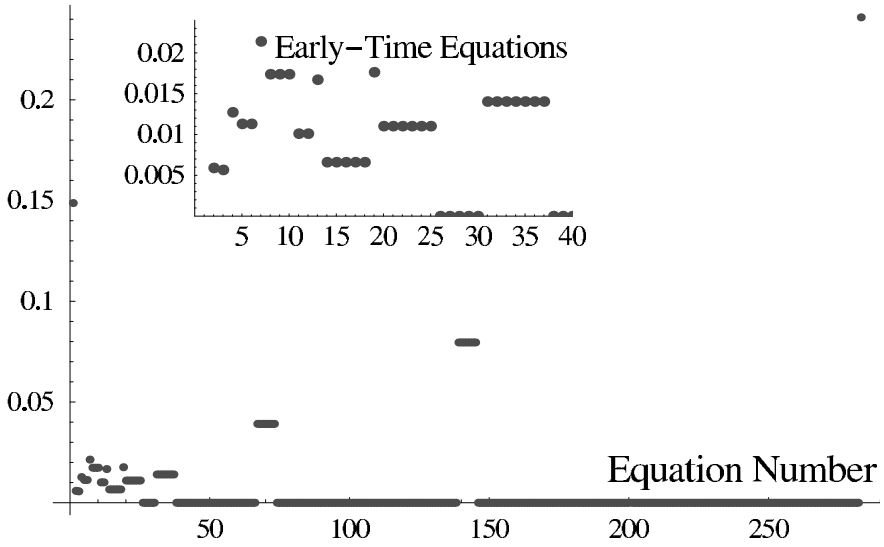

Figure 5: A plot of the calculated aggregate weight values assigned to each of the $N-M$ equations for the IV-PV-D2 data. Large values cluster around real data and are assigned large weights whereas zero values indicate equations constituted entirely of interpolated data given no weight.

The consequences of the utilization of the weights can be appreciated in Figs. 2 and 3.

The improvement of the curve fit to the pharmacokinetic data was most clear by the observed reduction in the calculated chi-square merit function value from 45.2 to 26.9, (see Figs. 2 and 3). However, we expect the regular Prony's method was fortunate to fit the real data so well in the first place. Although it did not weigh the calculated residual values from the tail any more than the residual values from the peak, as it should have because of the smaller variances there ($w \propto 1/\sigma^2$), the nature of the incomplete data set conspired to provide hundreds of interpolated datum points along the shallow extended

tail that compensated for this neglect. We predict that the improvements of the weighted Prony's method would be even greater if the original data contained gaps more evenly spread or contained no interruptions at all.

Regardless of the improved accuracy of a weighted Prony's method for fitting pharmacokinetic concentration-time course data, apparently the method cannot be used to assist in any kind of standard interpretation of results in connection with classical compartmental models. The actual expression is

$$\begin{aligned} C(t) \approx & 37e^{-0.001t} + 250e^{-0.08t} \\ & + (9-132\mathrm{i})e^{(-0.2+0.2\mathrm{i})t} + (9+132\mathrm{i})e^{(-0.2-0.2\mathrm{i})t} \\ & - (152-181\mathrm{i})e^{(-0.2+0.4\mathrm{i})t} - (152+181\mathrm{i})e^{(-0.2-0.4\mathrm{i})t}. \end{aligned} \tag{3.5}$$

The complex exponential coefficients arise naturally when the μ's are solved for as the roots of a polynomial. Since the exponential coefficients are a function of the μ's, $\mu_k = e^{a_k}$, the a's and the A's from subsequent calculations have imaginary components generally. The result is a concentration curve that is oscillatory and that possesses physically impossible negative concentration values at very early times. The fit ostensibly utilises 20 adjustable parameters. However, since $C(t)$ must be a real function, the complex terms appear as complex conjugate pairs, reducing the number of adjustable parameters to 12. The data sets used to generate the fit contained 13 points and Prony's method is valid for $2M \leq N$ which is the case here.

Yet if classical multi-compartmental models are generalized somewhat to similarly include linear interactions, based on the amount of drug in a compartment with other compartments, that do not imply a direct transfer of material, then control systems based on positive or negative feedback signals can be represented by compartmental analysis [16–19]. We speculate the means of this may be from the induction of metabolism in one compartment due to the presence of drug in another compartment via one of the signalling systems of the body. Prony's method could then serve a useful purpose when describing a system from this new perspective.

4 Discussion

In this section we give additional comments regarding the fitting. Initial estimates of the macro-constants, A_i and a_i, were conducted by an exponential curve stripping process from the original program Model Maker to reduce the potential domains of the parameters, corresponding computing times, and any resulting chances for bias (see Fig. 6). The equations were then fitted by minimizing weighted sum of squares within Model Maker for a one, two, and three term sum of exponentials to obtain the macro-parameters, A_i and a_i, $i = 1,2,$or 3.

As the number of terms in the sum of exponential functions was increased the deviation of the curve from the data decreased, as measured by the chi-squared merit function. The data seemed to be closely fit with a three-term sum of exponentials requiring six free

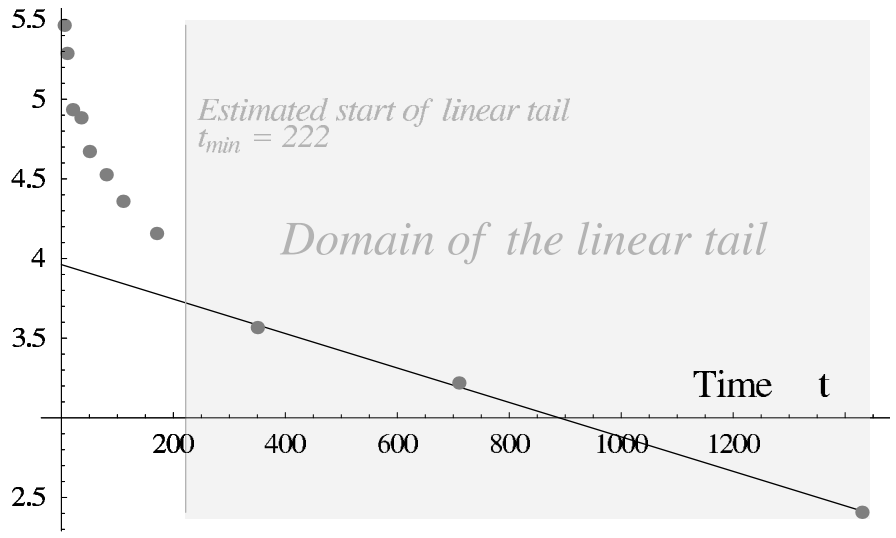

Figure 6: A semi-log plot of mibefradil concentration versus time shows an intuitive estimation of the domain of the linear elimination before curve stripping for the IV-PV-D2 data.

parameters, yet the domain where the slope of the graph subjectively changed from the early-time behaviour of the peak to the late-time behaviour of the tail, was estimated to be $[5,25)$ where few data points reside. Observations of the residuals for those data points in this domain for all of the dog trials, intuitively revealed a non-normal distribution indicating an unrealized pattern. The inability of the exponential functions to describe this transition was unsatisfying. This in turn implied that an interpretation of the pharmacokinetics of mibefradil based on a classical compartmental model would also be disappointing.

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