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

J. Fuite, R. E. Marsh and J. A. Tuszyński*

Department of Physics, University of Alberta, Edmonton, Alberta, T6G 2J1, Canada.

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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,

*Corresponding author. *Email addresses:* jfuite@phys.ualberta.ca (J. Fuite), rmarsh@ualberta.ca (R. E. Marsh), jtus@phys.ualberta.ca, (J. A. Tuszyński)

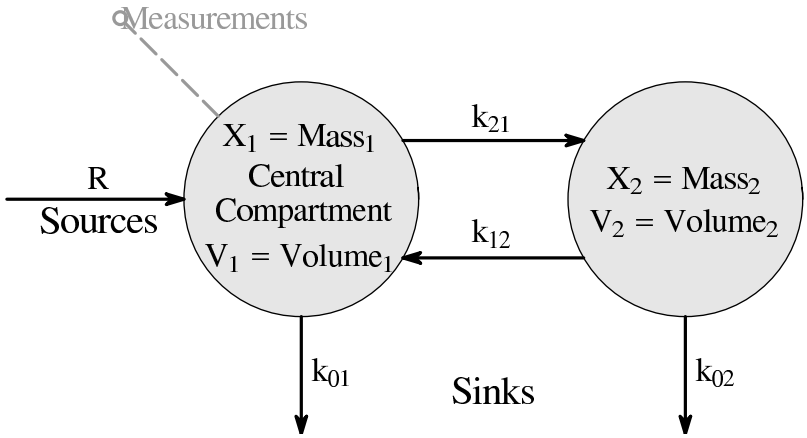

Figure 1: A schematic of a general 2-compartment model where the sources enter, and measurements are taken from, the central compartment. The ith-compartment is considered open if it looses drug to the environment ($k_{0i}>0$) and closed if it does not ($k_{0i}=0$). A multi-compartment model is considered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