Guaranteed Parameter Set Estimation for Exponential Sums: The Three-terms Case *

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June 29, 2006

Abstract. In this paper the problem of parameter estimation for exponential sums with three terms is considered. This task consists of finding the set of parameters (amplitudes as well as decay constants) such that the exponential sum attains values in specified intervals at prescribed time data points. These intervals represent uncertainties in the measurements. An interval variant of Prony's method is given by which intervals can be found containing all the consistent values of the respective parameters. By the use of interval arithmetic these enclosures can also be guaranteed in the presence of rounding errors.

Keywords: Parameter estimation, exponential sum, Prony's method, interval arithmetic.

1. Introduction

The problem of parameter estimation for exponential sums typically appears in pharmacokinetics, see, e.g., (Gibaldi and Perrier, 1982; Weiss, 1990). Pharmacokinetics is a branch of pharmacology dedicated to the study of the time course of absorption, distribution, metabolism, and excretion of drugs in the body. Often a multicompartment model is employed. To adequately obtain postintravenous injection data, a model with three compartments, called a mammillary system, is used, as illustrated in Figure 1. The central compartment, no. 1, contains organs such as the liver and kidney or tissues which, being highly perfused with blood, are in a rapid equilibrium distribution with the blood. The concentration of the drug in this compartment can be sampled through the blood (or plasma or serum). The central compartment communicates with two peripheral compartments. The shallow peripheral compartment, no. 2, consists of organs or tissues, e.g. muscles, which,

* Support from the Ministry of Education and Research of the Federal Republic of Germany under contract no. 1705803 and from the DAAD program PROCOPE under contract no. D/0205730 is gratefully acknowledged.

being less perfused with blood, are in a slow equilibrium distribution with the blood. The deep compartment, no. 3, contains poorly perfused tissue such as fat and bones. The two peripheral compartments are not susceptible to direct measurements. Drug excretion and transfer of drugs between the three compartments are assumed to obey first-order processes. So, after the intravenous injection of the drug into the central compartment, the excretion follows from compartment i with rate constant k_{i0}. Let $c_i(t)$ denote the drug concentration in compartment i. The flow rate of the drug from compartment i to compartment j is proportional to the concentration in the donor compartment i with rate constant k_{ij}. From mass balance we obtain the following system of governing equations

$$\begin{pmatrix} \dot{c}_1 \\ \dot{c}_2 \\ \dot{c}_3 \end{pmatrix} = \begin{pmatrix} -k_{11} & k_{21} & k_{31} \\ k_{12} & -k_{22} & 0 \\ k_{13} & 0 & -k_{33} \end{pmatrix} \begin{pmatrix} c_1 \\ c_2 \\ c_3 \end{pmatrix} + \begin{pmatrix} u \\ 0 \\ 0 \end{pmatrix}, \tag{1}$$

where $k_{11} := k_{10} + k_{12} + k_{13}$, $k_{ii} := k_{i0} + k_{i1}$, $i = 2, 3$. The eigenvalues λ_i, $i = 1, 2, 3$, of the coefficient matrix are real. Furthermore, they are distinct if

$$k_{21} \neq k_{31} \tag{2}$$

(Vaughan and Dennis, 1979). In this case the solution of the homogeneous system ($u = 0$) is given by a tri-exponential

$$c_i(t) = a_{1i}exp(\lambda_1 t) + a_{2i}exp(\lambda_2 t) + a_{3i}exp(\lambda_3 t), \quad i = 1, 2, 3, \tag{3}$$

e.g. (Anderson, 1983), p. 46.

If a mammillary model with p compartments (one central compartment communicating with $p - 1$ peripheral compartments) is considered, under similar conditions, the solution of the homogeneous system of the governing equations is given by a sum of p exponentials[1].

Irrespective of this application in pharmacokinetics (and analogous others such as electrical circuits (Sheppard and Householder, 1951)), we now consider a more general function

$$f(x, t) = \sum_{j=1}^{p} x_{2j-1} \exp(-x_{2j} t), \tag{4}$$

where $x = (x_1, \ldots, x_n), n = 2p$. Suppose that the measurements are performed at times t_i, $i = 1, \ldots, m$ (In the above application this would be measurements of the concentration of the administered dose in the central compartment). The problem of parameter estimation is now to

[1] This holds true for other multicompartment models such as the catenary model, where the compartments are arranged in a chain, see (Anderson, 1983), p. 63.

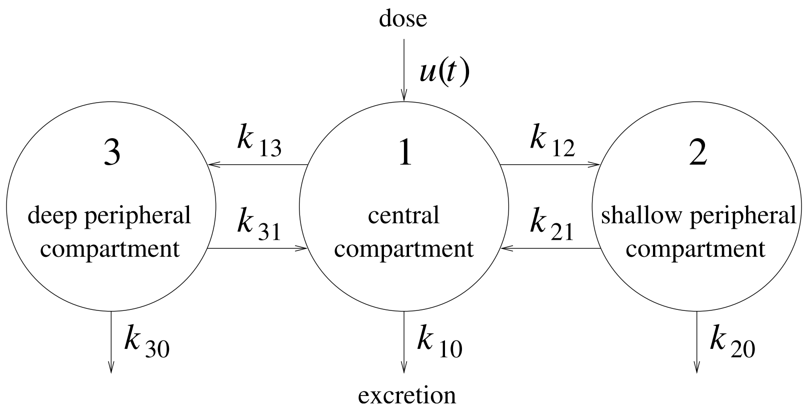

Figure 1. Mammillary three-compartment model in pharmacokinetics.

find the amplitudes x_{2j-1} and decay constants $x_{2j}, j = 1, \ldots, p$, which are consistent with the observations $\tilde{y}_i, i = 1, \ldots, m$, i.e., for which it holds that

$$f(x, t_i) = \tilde{y}_i, \quad i = 1, \ldots, m.$$

Unfortunately, this problem generally has no solution, since measurements may be imprecise and uncertain. Therefore, one tries to determine values of the model parameters that provide the best fit to the observed data. Often a least squares approach is employed, which results in minimizing the function

$$\sum_{i=1}^{m} w_i (f(x, t_i) - \tilde{y}_i)^2. \tag{5}$$

It is not uncommon for the objective function (5) to have multiple local optima in the area of interest. However, the standard techniques used to solve this problem are local methods that offer no guarantee that the global optimum, and thus the best set of model parameters, has been found. In contrast, methods from global optimization (Esposito and Floudas, 1998a,b; Gau and Stadtherr, 1999) are capable of localizing the global optimum of (5). However, this approach does not take into account that the observed data are affected by uncertainty. Therefore the resulting models may be inconsistent with error bounds on the data. To take uncertainty into account, we assume that the observed data are corrupted by errors, e.g. measurement errors, $\pm\varepsilon_i, \varepsilon_i \geq 0, i = 1, \ldots, m$. Then the correct value $y_i = f(x^*, t_i)$ is within the interval $[\tilde{y}_i - \varepsilon_i, \tilde{y}_i + \varepsilon_i], i = 1, \ldots, m$. More generally, we suppose that y_i is known to be contained in the interval $[a_i, b_i]$. The *parameter set estimation problem* consists of finding values of x subject to the following system of inequalities:

$$a_i \leq f(x, t_i) \leq b_i, \quad i = 1, \ldots, m. \tag{6}$$

The aim is to compute the set Ω of the consistent values of the parameters. This set may have a rather complicated structure in general. Interval arithmetic and inclusion functions for more general model functions are used in (Hofer, Tibken, and Vlach, 2001; Jaulin and Walter, 1993) to find boxes generated by bisection which are contained in Ω; the union of these boxes constitutes an inner approximation of Ω. Also, boxes are identified which contain part of the boundary of Ω or contain only inconsistent values; boxes of this second category can be used to construct an outer approximation of the set of inconsistent values. However, such an approach can not handle large initial boxes or problems with many parameters. Therefore, interval constraint propagation techniques are introduced in (Jaulin, 2000) to drastically reduce the number of bisections.

In (Garloff, Granvilliers, and Smith, 2005) the parameter set estimation problem is treated for bi-exponentials, i.e., $p = 2$, and equidistant $t_i = t_0 + ih, i = 1, \ldots, m$, by two different approaches: In a preprocessing step which is based on Prony's method (Prony, 1795) an enclosure for the set Ω is computed; this is accomplished without any prior information on the parameters sought. In a second step this enclosure is tightened by interval constraint propagation techniques using redundant constraints. The preprocessing step requires the enclosure of the zero set of an interval polynomial of order two and the solution sets of two systems of linear interval equations of order two with special structures. In (Garloff, Granvilliers, and Smith, 2005) it is shown how these two solution sets can be optimally bounded, i.e., the smallest axis aligned box can be constructed, which contains the solution set of the respective linear interval system, where the special structure of the system is taken into account. The bounds for the amplitudes and the decay rates are also guaranteed in the presence of rounding errors.

In the present paper we extend these results to the case of exponential sums with three terms. Three-compartment models appear, e.g., in pharmacokinetics (Gibaldi and Perrier, 1982). In the next section we recall Prony's method for three terms and extend it to the case of interval-valued data. Since exponential sums may be very sensitive to changes in their parameters, see, e.g., (Julius, 1972), special emphasis is put on finding tight bounds for the zero set of an interval polynomial of third degree and for the solution set of two structured linear systems of interval equations of order three.

At a late stage of our work we became aware of the paper (Goodman, 1970a) in which a basic interval version of Prony's method is already discussed, mainly with the aim of finding an appropriate degree p of (4) in the case of interval-valued data. To the best of our knowledge it is the first paper on interval interpolation, treating a highly nonlinear problem, appearing two years before the paper (Rokne, 1972) on a linear interval interpolation problem was published. This early paper already addresses some of the salient issues here such as overestimation when interval Gaussian elimination is applied to determinant evaluation. At the time of writing, it seems (as with two other papers (Goodman, 1970b; Goodman and Hiller, 1971) of this author) to be completely unknown to the interval computations community[2].

2. Extension of Prony's method in the tri-exponentials case for interval-valued data

For real data, Prony's method (Prony, 1795), cf. Chap. IV, §23 of (Lanczos, 1956), for finding $x \in \mathbf{R}^6$ such that[3]

$$f(x,t) = \sum_{j=1}^{3} x_{2j-1} \exp(x_{2j}t) \tag{7}$$

satisfies

$$f(x, t_0 + ih) = y_i, \; i = 1, \ldots, 6, \tag{8}$$

is as follows:
If the linear system

$$\begin{pmatrix} y_1 & y_2 & y_3 \\ y_2 & y_3 & y_4 \\ y_3 & y_4 & y_5 \end{pmatrix} \begin{pmatrix} \zeta_1 \\ \zeta_2 \\ \zeta_3 \end{pmatrix} = - \begin{pmatrix} y_4 \\ y_5 \\ y_6 \end{pmatrix}. \tag{9}$$

has a unique solution $\zeta = (\zeta_1, \zeta_2, \zeta_3)^T$ and if the zeros u_1, u_2, u_3 of the cubic

$$u^3 + \zeta_3 u^2 + \zeta_2 u + \zeta_1 \tag{10}$$

are distinct and positive then the decay constants are given by

$$x_{2j} = \ln(u_j)/h, \; j = 1, 2, 3.$$

The amplitudes can be computed from the solution of the Vandermonde system

$$\begin{pmatrix} 1 & 1 & 1 \\ u_1 & u_2 & u_3 \\ u_1^2 & u_2^2 & u_3^2 \end{pmatrix} \begin{pmatrix} z_1 \\ z_2 \\ z_3 \end{pmatrix} = \begin{pmatrix} y_1 \\ y_2 \\ y_3 \end{pmatrix}. \tag{11}$$

[2] As the present versions of the bibliographies at http://www.cs.utep.edu/interval-comp/ show.

[3] For simplicity, we neglect the minus sign in (4) and the tilde on y_i.

with $x_{2j-1} = e^{-(t_0+h)x_{2j}} z_j,\ j = 1,2,3.$
If the matrices

$$\begin{pmatrix} y_1 & y_2 & y_3 \\ y_2 & y_3 & y_4 \\ y_3 & y_4 & y_5 \end{pmatrix} \quad \text{and} \quad \begin{pmatrix} y_2 & y_3 & y_4 \\ y_3 & y_4 & y_5 \\ y_4 & y_5 & y_6 \end{pmatrix} \tag{12}$$

are positive definite, then the above procedure is feasible, in particular, the amplitudes x_{2j-1} are positive and the decay constants x_{2j} are distinct, $j = 1,2,3$, (Karlin, 1968) p. 75[4].
The matrix in (9) is a Hankel matrix; furthermore the Hankel structure is continued at the right-hand side. An algorithm which is suited to solve such systems is the Berlekamp-Massey algorithm, cf. Sect. 11.3 in (Blahut, 1985). If the equations of (9) are ordered in reverse, then the matrix becomes a Toeplitz matrix, i.e., the entries along the main and the lower and upper diagonals are equal. Algorithms for the solution of Toeplitz systems are given in, e.g., (Bareiss, 1969; Trench, 1964).
We now consider the case of interval data

$$f(x, t_0 + ih) \in [a_i, b_i],\ i = 1, \ldots, 6. \tag{13}$$

In the case of the system of linear interval equations resulting from (9) we can restrict the solution to Hankel matrices and to the special right-hand sides; for a discussion of the different *structured* solution sets cf. (Garloff, Granvilliers, and Smith, 2005). The structured solution set of the interval extension of (9) can be enclosed by interval versions of the algorithms of Trench and Bareiss if they are feasible. These interval variants are investigated in (Garloff, 1986). However, in the case of systems of order three both algorithms need at least as many arithmetic operations as Gaussian elimination. So, it is not surprising that often the bounds computed by these algorithms are not tight enough. Also, the bounds calculated by an interval version of the Berlekamp-Massey algorithm, by interval Gaussian elimination[5], see, e.g., Sect. 4.5 in (Neumaier, 1990), and the solver provided in (Popova, 2004) are often too wide. But the worse the bounds become, the sooner zeros of the interval extension of the cubic polynomial (10) become negative or cannot be separated.
Therefore, we have chosen a different approach. Note that each of the three components of the solution of (9) is a rational function of the entries $y_i, i = 1, \ldots, 6$, e.g.,

$$\zeta_1 = \frac{2y_3y_4y_5 - y_4^3 - y_2y_5^2 + y_6(y_2y_4 - y_3^2)}{y_1(y_3y_5 - y_4^2) - y_2^2y_5 + 2y_2y_3y_4 - y_4^3}.$$

[4] For a more general statement if only nonsingularity of the matrices (9) is presupposed, see Theorem 7.2c on p. 574 in (Henrici, 1974).
[5] This was used in (Goodman, 1970a) in the interval variant of Prony's method.

The ranges of the numerator and denominator of these three functions over the box $[a_1, b_1] \times \ldots \times [a_6, b_6]$ can be tightly enclosed if both polynomials are expanded into Bernstein polynomials (Garloff, 1993; Zettler and Garloff, 1998). Division of both enclosures gives an upper and a lower bound for the respective component of the solution. In the examples we have tried, the bounds obtained in this fashion were always superior to the bounds provided by interval Gaussian elimination. We have had a similar experience with the interval extension of the Vandermonde system (11). So, the approach based on Bernstein expansion might be recommended for structured systems up to order about four.
If the zeros of the cubic interval polynomial stemming from (10) are positive and separated, a tight enclosure for the zero sets can be computed by an interval variant of Cardano's formula (Weiß, 2004).
We mention a possibility for tightening the enclosures for the parameters: choose another group of six time data points, compute again enclosures for the parameters and intersect with the enclosures obtained for the first group. Continuing in this way, we successively improve the quality of the enclosures. If an intersection becomes empty, we have then proven that there is no exponential function of the form (7) which solves the real interpolation problem with data taken from the interval given in (13).

3. An example

We present an example with data which were chosen randomly. The amplitudes are

$$x_1 = 2.751045354, \ x_3 = -0.1283402602, \ x_5 = -4.149664312$$

and the decay constants are given by

$$x_2 = 0.04857438013, \ x_4 = 0.9455500478, \ x_6 = 0.5427153956.$$

We choose $t_0 = 2.252796652$, $h = 2.960316177$, and $m = 10$.
The intervals $[a_i, b_i]$ were created by multiplying $f(x, t_0 + ih)$ by $[0.999999, 1.000001], \ i = 1, \ldots, 10$.
We first check whether there is an interpolating single exponential term or a bi-exponential. In both cases the program reports that the set Ω of the parameters which are consistent with the data intervals is empty.
In the case of three exponentials, interval Gaussian elimination applied to the interval variant of the linear system (9) results in the following enclosure for its solution set (rounded to six digits after the decimal point)

$$[-100.779868, -88.435118] \times [105.635714, 107.665818] \times [-22.691417, -22.450984].$$

In contrast, application of Bernstein expansion results in the following bounds for the structured solution set

$$[-95.743989, -93.434371] \times [106.337024, 106.958709] \times [-22.607016, -22.534697].$$

These intervals provide the coefficients of the interval extension of the cubic (10), i.e. they present bounds on ζ_1, ζ_2, and ζ_3. The use of these tighter bounds gives the following enclosure for the decay constants

$$[0.040799, 0.056418] \times [0.943651, 0.947420] \times [0.537105, 0.548244].$$

The bounds for the amplitudes computed by Bernstein expansion applied to the structured solution set of the interval Vandermonde system (11) are

$$[1.527609, 4.213951] \times [-0.136666, -0.120530] \times [-4.571274, -3.769826].$$

If instead we were to use Gaussian elimination to enclose the solution set of the interval variant of (11) then the span of the resulting interval for x_1 would be more than 21.5, i.e. more than eight times larger than the span provided by Bernstein expansion.

4. Conclusion

A salient feature of the approach presented in this paper is that if this method works, in particular, if the two interval systems contain only nonsingular real matrices and the roots can be separated, we obtain an enclosure for the parameters of an exponential sum with three terms without any prior information on the decay constants and amplitudes. Such prior informaton is normally required for the use of interval methods, e.g., (Jaulin, Kieffer, Didrit, and Walter, 2001). Often one has to choose an unneccessarily wide starting box which is assumed to contain all feasible values of interest. Application of a subdivision method then results in a large number of subdivision steps. Therefore, Prony's method is well suited for use as a preprocessing step for more sophisticated methods such as interval constraint propagation, e.g., (Garloff, Granvilliers, and Smith, 2005; Granvilliers, Cruz and Barahona, 2004). The amount of computational effort is negligible.
The approach presented in this paper can be extended to exponential sums (4) with $p = 4$ at the expense of greater computational effort.

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