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Applied Numerical Mathematics 15 (1994) 307–326

APPLIED NUMERICAL MATHEMATICS

Numerical treatment of the parameter identification problem for delay-differential systems arising in immune response modelling

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Abstract

We present an approach in this paper to the solution of parameter identification problem arising in immune response modelling. The models are formulated as stiff systems of nonlinear delay-differential equations (DDEs). The criteria for the best-fit solution are discussed, which are appropriate when the data to be fitted varies considerably in magnitude. The fitting procedures are based on a combination of crude but global methods of fitting the models to data and more accurate locally convergent techniques. An algorithm for sequential parameter identification is based on subdivision of the total fitting interval in order to reduce the complexity of an optimization problem. Poor initial estimates for some parameters are improved by short-cut procedures via adjusting the model with spline functions approximating the data on the whole observation time interval. The stiff DDEs are solved by a modification of the DIFSUB code. An example of the real-life parameter identification problem for the antiviral immune response model in the context of the modelling of hepatitis B virus infection is presented.

Keywords: Delay-differential equations; Parameter identification; Sequential fitting; Data approximation; Optimization, Stiff DDE solver; Immune response; Infectious disease

1. Introduction

The recent development of applied mathematics is characterized by increasing attempts to use mathematical modelling tools in biology and medicine. It is the integrated problem of dynamic response and optimization that brings into focus modern investigations in theoretical biology, operating with the concepts of adaptation and evolution of multilevel, multiparameter and multiloop biological systems. A particular interest to mathematical models has been established in theoretical studies of the immune system and infectious diseases. A number of mathematical models describing the immune response during infectious diseases are formu-

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SSDI 0168-9274(94)00007-4

lated as systems of nonlinear delay-differential equations (DDEs) characterized by multiple constant delays, moderate size and stiffness [14,34,37,38,40,42,57]. We note also a growing interest in delay effects and the use of DDEs in chemical kinetics modelling [19]. Derivation of mathematical models that are consistent with both prior knowledge and observations implies the development of effective computational tools for parameter identification in stiff nonlinear systems of DDEs. Considerable attention has been paid to the development of efficient methods for parameter estimation in stiff ordinary differential equations arising in chemical reaction modelling. The important issues of numerical identification of rate constants in chemical kinetics models formulated as systems of ODEs can be found in [1,8,10,17,26,47,54, 60,66]. These findings provide a solid basis for treating similar identification problems in immune response modelling.

This paper deals with some of the practical aspects of parameter identification in systems of nonlinear DDEs, with particular reference to modelling the immune response to viral and bacterial infections. An outline for modelling by DDEs the immune response to infections is presented in Section 2. The "best-fit" criteria and the algorithmic approaches to solving numerically the parameter identification problems in stiff nonlinear DDEs are described in Section 3. Section 4 presents a real-life application example of parameter estimation for the hepatitis B virus infection model. This example is general enough to illustrate the major difficulties associated with parameter identification for immune response models. Concluding remarks are presented in Section 5.

2. DDEs arising in immune response modelling

One of the clearly established functions of an immune system is the protection of a host against various infectious agents. To describe mathematically an immune response to viruses or bacteria, a conceptual model of the basic immune processes during an infectious disease is first elaborated, in which the interactions between cells and molecules are described in terms of positive and negative influences. The principal characteristic of a normal immune response is the generation of new lymphocytes and antibodies to deal efficiently with an infectious agent which also replicates. The response of an immune system, as well as the reaction of specific cell clones to a certain infection cannot be represented correctly without hereditary phenomena being taken into account. These include cell division and cell differentiation effects, residence time of cells in various compartments of the immune system, previous antigenic experiences, etc. In a number of ODE models the hereditary effects are modelled by introducing an additional "gearing up" state variable [18,53]. We consider the use of DDEs as a natural mathematical technique for representing the dynamics of the immune response in infectious diseases. Most of the DDE models used in immunology have constant delays, except for the threshold model of antigen-stimulated antibody production with time- and state-dependent delay [61] and the integro-delay differential equations model for coccidial infection in chickens [51]. Therefore, we focus here on models with constant delays.

Assuming that the kinetics of interactions between cells is governed by principles similar to the Law of Mass Action, and that durations of division processes of the immunocompetent cells are taken into account explicitly by introducing the time lags into corresponding equations, the

typical mathematical model of immune response during on infectious disease may be expressed as an N-dimensional system of DDEs with multiple constant delays:

$$\begin{aligned}
&\frac{dy}{dt} = f\big(t, \alpha, y(t), y^{[1]}(t-\tau_1), \ldots, y^{[m]}(t-\tau_m)\big),\\
&\alpha \in \mathbb{R}^L, \qquad y \in \mathbb{R}^N, \qquad y^{[i]} \in \mathbb{R}^{N_i},\\
&N_i \leqslant N, \quad i = 1,2,\ldots,m, \qquad t \in [t_0, t_0 + T],\\
&y(t_0) = \varphi^0, \qquad y^{[i]}(t) = \varphi^{[i]}(t), \quad t \in [t_0 - \tau_i, t_0],
\end{aligned} \tag{2.1}$$

with $y \equiv [y^{(1)}, \ldots, y^{((N)}]^{\mathrm{T}}$, $y^{[i]} \equiv [y^{(j_1)}, y^{(j_2)}, \ldots, y^{(j_{N_i})}]^{\mathrm{T}}$ and assigned initial functions φ^0 and $\varphi^{[i]}$.

This particular class of DDEs with several constant delays includes the mathematical models for antiviral and antibacterial immune responses developed during the last two decades by Marchuk [36,37] and the HIV infection model by Nelson and Perelson [42]. Another set of mathematical models formulated as linear multiple constant delay differential equations appears while studying the circulation of lymphocytes through the immune system [20,44]. The time delays appear in the transport of lymphocytes between certain compartments. These authors argue that the linear DDEs models are better approximations to the experimental data than the linear ODEs. The qualitative behavior of an immune network is studied by a nonlinear system of DDEs in [6]. A time lag is introduced to make the dynamics of the model richer.

The dimension of the state space (see (2.1)), N, is about 10, while L is about 10 to 50, and m ranges from 1 to 10. The right-hand side function f is usually k-linear, with $k = 1, 2, 3, 4$, with respect to the components of the state vector and linear in the parameter vector components α. The kinetic parameter of the model α characterizes the rate of immune process realization. It occurs over a time scale ranging from seconds (molecular interactions) to days (cellular interactions), and an observation interval is about 100 days. Therefore, the initial value problem (IVP) for the system of DDEs (2.1) appearing in immune response modelling is typically a *stiff* one [15,38,42,57].

An important problem for real-life applications in clinical immunology is how to make the models quantitatively consistent with experimental and clinical knowledge. To this end effective tools for assimilating the available data into the models are required. These tools include the numerical identification of model parameters, time delays and initial functions. The theoretical framework for estimation of various parameters in functional equations was developed in [4,41]. Practical aspects of developing efficient techniques for numerical fitting of stiff DDEs, which are characterized by severe nonlinearities, moderate state space dimension and a large number of parameters with poor initial estimates, have received little coverage in the literature as yet. This paper focuses on estimation of parameters in immune response models by fitting the model predictions to observed data.

The parameters of the models for immune response in infectious diseases may be subdivided into two groups: the first consists of the parameters for which sharp initial estimates are available from various experimental data. The second group consists of parameters, notably the kinetic rates of cell-to-cell interactions in lymphoid and pathogen-sensitive tissues, for which no experimental estimates are available. Their initial theoretical estimates range over several orders of magnitude. The parameters of the second group must be refined by seeking a

minimum difference between the model predictions and the observed data on the kinetics of the underlying processes.

3. Numerical solution of the parameter identification problem

3.1. Criteria for the best-fit solution

The identification of model parameters is generally performed by minimization of an objective function which represents a selected fitting criterion. It is known that observations are inexact, i.e. contain an uncertainty related to the measurement errors, random effects, nonlinear effects, unknown process contribution, etc. If the data displays statistically regular features, then the standard criteria of optimal estimation can be applied for parameter identification: the maximum likelihood method, Bayesian analysis, etc. [5]. The essential points for a correct use of this approach are the availability of a sufficient amount of data and the *ad hoc* stochastic frame for the analysis of data to characterize the structure of the errors in the data (see Kalman [33]). An example of this approach to the kinetic parameter estimation for mathematical models in immunology is presented in [7], with special experimental program developed to obtain the numerous and homogeneous sets of data. However, a number of immune response modelling problems are characterized by situations where, either the researchers have no reason to put forward the prior stochastic characterization of data, or the data itself are obtained by indirect estimates. In such cases the data is regarded as equally reliable.

To identify the parameters of immune response models, homogeneous and consistent data sets are derived in the form of Generalized Pictures [14,37], which represent the typical kinetics of a particular infectious disease. These data sets are not numerous and have uncertainties in their values which cannot be attributed to a certain stochastic mechanism. Therefore, they are believed to possess an equal value or have the same weight as the characteristics of the modelled process.

The problem of quantitative description of any data characterizing a process without *a priori* knowledge of their stochastic nature is usually solved by fitting of the model to data [5,33,65]. The objective function should be selected with due regard to the nature of particular observation data, the parametric nonlinearities of the model solutions, etc.

The classical least squares (LS) criterion is commonly used for fitting a model and data. A difference between the model predictions $y^{(i)}(t_j, \alpha)$ and the measured data $y^{(i)}_{\mathrm{obs}\,j}$, specified at certain points (t_j), is expressed via the residuals, i.e., the fitness function $\Phi(\alpha)$ has the following form:

$$\Phi(\alpha) = \sum_{j=1}^{M} \sum_{i=1}^{N} w_{ji} \left[y^{(i)}_{\mathrm{obs}\,j} - y^{(i)}(t_j, \alpha) \right]^2 \tag{3.1}$$

with the w_{ji} defined by the weighting procedure, and M being the total number of different observation times. For example, the parameters of the lymphocyte circulation model described by a system of linear DDEs were estimated by minimizing the residual LS criterion with reference to the experimental data [20].

Some limitations of the LS approach have been observed in several applications. It is known that the nonlinear LS fitting leads to a number of local minima. In an attempt to confront this problem, a nonlinear Chebyshev fitting was suggested in [65] to increase the possibility of unique global fits. It was pointed out in curve fitting problems that the ordinary LS method unduly weights the data points with the largest magnitude [16]. The last aspect of the residual LS approach becomes critical in our case, where the typical data representing the real processes varies considerably in magnitude. Indeed, the Generalized Picture data corresponding to hepatitis B (see Table 1) are characterized by an up to the 10^4 increase in concentration of cells and viruses in the course of the disease. The objective function (3.1) was modified to meet the following requirements: it should be equally sensitive to the same relative deviations of $y^{(i)}(t_j, \alpha)$ from $y^{(i)}_{\mathrm{obs}\,j}$ regardless of the magnitude of $y^{(i)}_{\mathrm{obs}\,j}$ and it should be equally sensitive to the same relative deviations of $y^{(i)}(t_j, \alpha)$ from $y^{(t)}_{\mathrm{obs}\,j}$ (and vice versa) no matter if $y^{(i)}(t_j, \alpha)$ is higher or lower than $y^{(i)}_{\mathrm{obs}\,j}$. To this end, we considered the *relative distance* least squares criterion, expressed in terms of the ratios $y^{(i)}_{\mathrm{obs}\,j}/y^{(i)}(t_j, \alpha)$ and $y^{(i)}(t_j, \alpha)/y^{(i)}_{\mathrm{obs}\,j}$, rather than the residuals $(y^{(i)}_{\mathrm{obs}\,j} - y^{(i)}(t_j, \alpha))$. The definition domain of the state vector is supposed to be $\mathbb{R}^N_+$.

If we adopt the LS form for the fitting function

$$\Phi(\alpha) = \sum_{j=1}^{M} \sum_{i=1}^{N} \left[F\left\{ \left(y^{(i)}(t_j, \alpha),\ y^{(i)}_{\mathrm{obs}\,j} \right) \right\} \right]^2,$$

then a number of opportunities exist to select a function of the ratios, $F(\cdot, \cdot)$, which should be summetric: $F(y^{(i)}_{\mathrm{obs}\,j},\ y^{(i)}(t_j, \alpha)) = F(y^{(i)}(t_j, \alpha),\ y^{(i)}_{\mathrm{obs}\,j})$. The following types of symmetric formulas for F were chosen, leading to the objective functions $\Phi(\alpha)$ given below, which have been used in our applications:

$$F(x) = x + \frac{1}{x}$$

$$\rightarrow \Phi(\alpha) = \sum_{j=1}^{M} \sum_{i=1}^{N} \left[\left(\frac{y^{(i)}_{\mathrm{obs}\,j}}{y^{(i)}(t_j, \alpha)} \right)^2 + \left(\frac{y^{(i)}(t_j, \alpha)}{y^{(i)}_{\mathrm{obs}\,j}} \right)^2 \right] - 2, \tag{3.2}$$

and

$$F(x) = \log x \rightarrow \Phi(\alpha) = \sum_{j=1}^{M} \sum_{i=1}^{N} \left[\log \left(\frac{y^{(i)}_{\mathrm{obs}\,j}}{y^{(i)}(t_j, \alpha)} \right) \right]^2. \tag{3.3}$$

The latter was proved to meet the distance requirements in $\mathbb{R}^N_+$ [34]. Note that some weighting procedure defined by a positive-definite matrix w_{ji} may be used to generalize the objective functions (3.2) and (3.3), similar to (3.1)

There is another important aspect of the identification procedure, which must be taken into account—the nonlinearity of the overall problem. Generally, only when regression models are linear in the parameter α, the residual LS approach generates a linear LS problem. Otherwise, one gets a nonlinear LS problem, especially in the case when the underlying mathematical model is a system of differential equations. Clearly, one should prefer those fitness functions $\Phi(\alpha)$, for which the minimization problem is characterized by a lesser degree of nonlinearity.

This results from a superposition of the quadratic function, the function F of the ratios of predictions and observations and the solution function $y(t, \alpha)$, characterized by the exponential nonlinearities in t and α. Simple reasoning (in the scalar case) may be used to prove that if the underlying ODE is linear then, selecting the LS criterion with the logarithmic function of the ratios (3.3), one gets a linear LS problem.

It follows in turn that to treat efficiently the parameter fitting problem for nonlinear models the overall observation interval should be decomposed into a number of subintervals with clear exponential kinetics of the underlying processes.

3.2. Sequential parameter identification procedure

The formulate the parameter identification problem as follows. In the DDE model (2.1) some or all parameters appear to have poor initial estimates. Given the observed data we try to refine the parameters in (2.1) so that the residual LS fit-to-data criterion is minimized (the dimensions of the vectors and vector-valued functions are marked by the right upper indices):

Find

$$\min \Phi(\alpha^L),\ A^L \leqslant \alpha^L \leqslant B^L \tag{3.4}$$

determined by the following model (the single-delay case is examined for notational simplicity):

$$\frac{dy^N(t)}{dt} = f(\alpha^L,\ y^N(t),\ y^N(t-\tau)), \quad t_0 \leqslant t \leqslant t_0 + T,$$

$$y^N(t) = \varphi^N(t), \qquad t_0 - \tau \leqslant t \leqslant t_0.$$

The rather large dimension, complexity and nonlinearity of the DDE systems under consideration, the nonmonotonic initial functions $\varphi^N(t)$ of the initial value problems and the poor initial estimates for some of the model parameters α_0^L make it impossible to obtain a satisfactory fit of the model to the data just by searching for a minimum of an objective function $\Phi(\alpha^L)$ calculated over the full observation interval $t_1 \leqslant t \leqslant t_M$. Besides, in this case it is difficult to select the optimized parameters and to coordinate the biological meaning of an identified parameter with the sensitivity of the objective function to this parameter. Indeed, some parameters appear to be active over a limited time interval as compared to the time scale of the overall process. (It is similar to stiff and nonstiff parameters in chemical kinetics: the first are active in the boundary layer and the second are active outside it [1,58].) We have *decomposed* the total optimization problem, using the idea of recursive parameter estimation [56], within the full observation interval $T_{1,M} = \{t: t_1 \leqslant t \leqslant t_M\}$, into a sequence of manageable optimization subproblems in consecutive subintervals $T_{1,2}, T_{1,3}, \ldots, T_{1,M}$ to reduce the computational complexity of optimization problem (3.4). The decomposition had its bases in the observation data and the knowledge of biological processes which are active during a particular time subinterval. This makes it possible to associate the characteristics of observed data within the subintervals with the operation of a smaller number of processes from the whole set described by the models to make a grounded choice of optimized parameters. Information on the "natural history" for a particular infection [15,38] provides a natural biological guide for this subdivision and the choice of parameters to be fitted. It should be noted that fitting of a

model to data on larger time intervals may deteriorate the fitting quality for some variables as compared to smaller time intervals. Therefore, the coordination of fitting subproblems is required, which is performed for some of the state variables by introducing some linear relations to couple a number of model parameters.

Another important aspect in the solution of the optimization problem (3.4) is the initial localization of the parameter vector α_0^L in $\mathbb{R}_+^L$ with respect to the global minimum point(s). The classical minimization algorithms ensure local convergence for smooth convex functions, and the optimal solution is generally sensitive to a starting point in parameter space. Therefore, a computationally cheap procedure for improving the initial parameter estimates is to be involved in the solution process of problem (3.4). Short-cut iterative methods suggested in chemical kinetics modelling [26] and developed in [27,60,66] belong to this class of techniques. Now we formulate the algorithmic framework developed for solving the identification problem (3.4).

Algorithm I.

Step 1. Improve the starting estimates of the model parameters α_0^L by adjusting the model to functions approximating the observed data *globally* on $[t_1, t_M]$.

Step 2. Select the subinterval $[t_1, t_m]$ and the subset α^{l_m} of components of the parameter vector $\alpha^L \in \mathbb{R}^L$, which is to be fitted to data: $\alpha^{l_m} \in \mathbb{R}^{l_m} \subseteq \mathbb{R}^L$.

Step 3. Find numerically a solution $\alpha_*{}^{l_m}$ to the linearly constrained minimization problem

$$\alpha_*{}^{l_m} = \arg \min_{\alpha^{l_m} \in D} \Phi(\alpha_*{}^{l_m}),$$

where $\Phi_m(\alpha_*{}^{l_m}) \equiv F_m[\mathscr{Y}_{t_1,t_m}](\alpha^{l_m}), Y]$ is the objective function for given observation data Y on the interval $[t_1, t_m]$ and for the model solution

$$\mathscr{Y}_{[t_1,t_m]}(\alpha^{l_m}) = \left[y^{(1)}(t, \alpha^{l_m}), \ldots, y^{(N)}(t, \alpha^{l_m}) \right]^{\mathrm{T}}, \quad t_1 \leqslant t \leqslant t_m.$$

Step 4. Update the model's parameter vector:

$$\alpha_{m+1}^L = \left[\alpha^{L-l_m}, \alpha_*{}^{l_m} \right].$$

Return to Step 2 until $m < M$.

Let us consider the implementation of these steps in more detail.

3.3. Adjusting the model to functions interpolating the data

Simplified (short-cut) methods for the solution of inverse problems are based on globally adjusting over the observation interval any functions approximating continuously in time the observed data by a particular model written in the form of a differential equations system. Therefore, instead of a nonlinear programming problem for an objective function determined by an IVP for the differential system, a simpler LS problem is formulated for a linear or a non-linear algebraic system with respect to unknown parameters. Two extreme cases are to be analyzed.

3.3.1. Sufficient data case

An algorithm corresponding to the short-cut method may be formulated in the case of delay differential systems as follows. Let α_0^L be an initial guess for the parameter value, which is to

be refined; let $Y=\{\{\{y^{(i)}_{\mathrm{obs}\,j}\},\ j=J_{i_1},\ J_{i_2}\},\ i=1,\ldots,N\}$ be an observed data for each of the N model state variables $y^{(i)}(t)$, $i=1,\ldots,N$, at times $\{t_j\}_{j=J_{i_1},J_{i_2}}$, $t_0\leqslant t_1\leqslant t_{J_{i_1}}<t_{J_{i_2}}\leqslant t_M\leqslant t_0+T$, with $m_i=(J_{i_2}-J_{i_1})$ being the number of observations available for the ith variable.

Algorithm II.

Step 1. Transform the initial value problem for a system of DDEs into an equivalent integral system of equations:

$$y^N(t)=y^N(t_0)+\int_{t_0}^{t} f^N\bigl(\alpha^L,\ y^N(\theta),\ y^N(\theta-\tau)\bigr)\,\mathrm{d}\theta. \tag{3.5}$$

Step 2. Interpolate the observed data pairs for each of the model state variables

$$\bigl\{y^{(i)}_{\mathrm{obs}\,j},\ t_j\bigr\}_{j=J_{i_1},J_{i_2}},\quad i=1,\ldots,N,$$

using an appropriate spline function $S^{(i)}_Y(t)$ which is to be selected for particular aims. These aims depend on the character of available data; smoothing (when all m_i are large), least squares approximation (all m_i are large), monotonic interpolation by quasi-Hermite polynomials (m_i are small), etc. In this way the N-dimensional vector spline function $S^N_Y(t)$ is generated. We consider the $S^N_Y(t)$ as a prototype (quasi-solution) of these model solution $y^N(t)$, which corresponds to the unknown best-fit parameter values. The model parameter estimates may be improved using this quasi-solution.

Step 3. Substitute the quasi-solution $S^N_Y(t)$ for $y^N(\theta)$ and project the system of integral equations (3.5) on given set of observation times,

$$\Bigl\{\{t_k\}_{k=k_1,\ldots,k_2}\colon t_{k_1}=\max_{i_1}\bigl(t_{J_{i_1}}\bigr),\ t_{k_2}=\min_{i_2}\bigl(t_{J_{i_2}}\bigr)\Bigr\},$$

to obtain a nonlinear algebraic system of equations with respect to unknown parameters α^L:

$$\Psi_{S_Y}(\alpha^L)=\Delta Y^J,$$

where the vectors ΔY^J and $\Psi_{S_Y}(\alpha^L)$ have the components

$$(\Delta Y^J)_j=y^{(i)}_{\mathrm{obs}\,k}-y^{(i)}_{\mathrm{obs}\,k_1},$$

$$\bigl(\Psi^J_{S_Y}(\alpha^L)\bigr)_j=\int_{t_{k_1}}^{t_k}\bigl(f^N\bigl(\alpha^L,\ S^N_Y(\theta),\ S^N_Y(\theta-\tau)\bigr)\bigr)_i\,\mathrm{d}\theta,$$

$$i=1,2,\ldots,N,\quad k=k_1,k_1+1,\ldots,k_2,\quad j=(k-1)\times(N+i),\quad J=\max(j).$$

Step 4. Find the solution to the overdetermined system of algebraic equations with respect to α^L: $\alpha^L=\Psi^{-1}_{S_Y}(\Delta Y^J)$.

If parameters α^L appear linearly in the right-hand side of the differential system, then we obtain a linear overdetermined system of algebraic equations with respect to α^L (or to some subset α^l, $l<L$, depending on the number of observations and the value of L). It may be solved easily by a number of algorithms for linear LS problems [35] to get the best LS solution $\alpha^L=(\Psi^{m*L}_{S_Y})^+\times\Delta Y^m$, where $(\Psi^{m*L}_{S_Y})^+$ is a generalized inverse matrix.

The corresponding code, suitable for fitting the DDE models to data, makes use of the following algorithms of the IMSL package [28]: the one-dimensional quasi-cubic interpolation

based on Hermite polynomials IQH SCU (Step 2), the one-dimensional adaptive quadrature procedure DCADRE (Steps 1 and 3) and the LINPACK algorithm for the linear LS problems (Step 4). This makes it possible to refine the crude estimates for some components of the parameter vector α_0^L providing that there are enough observation data to construct the spline functions $S_Y^N(t)$ for all components of the state vector $y^{(i)}(t)$, $i = 1, \ldots, N$.

3.3.2. Deficient data case

The typical situation in mathematical modelling of infectious diseases is when the available observation data allow one to construct the spline function $S_Y^n(t)$ only for a number (n) of the N model state variables ($n < N$). In this case, the model system of the DDEs is decomposed into two subsystems with dimensions n and $N-n$. The second subsystem is used to generate the "quasi-solution" for data-deficient variables. To this end, the components of the spline function $S_Y^n(t)$ are substituted instead for $y^n(t)$ in the following reduced system of DDEs:

$$\frac{\mathrm{d}y^{N-n}(t)}{\mathrm{d}t} = f\big(\alpha^{l_{N-n}}, S_Y^n(t), y^{N-n}(t), S_Y^n(t-\tau), y^{N-n}(t-\tau)\big), \quad t_0^* \leqslant t \leqslant t_0^* + T,$$

$$\alpha^{l_{N-n}} \in \mathbb{R}^{l_{N-n}} \subset \mathbb{R}^L, \qquad y^{N-n}(t) = \varphi^{N-n}(t), \quad t_0^* - \tau \leqslant t \leqslant t_0^*.$$

The interval $[t_0^*, t_0^* + T^*]$ is chosen according to available observations at times $\{t_k: k = k_1, \ldots, k_2\}$. Integrating numerically the IVP for the reduced DDE system we obtain a solution, which is used instead of the unavailable $(N-n)$ continuous functions $S_y^{N-n}(t)$. The N-dimensional quasi-solution vector-function is obtained then by combining the data-generated quasi-solution and the model-generated one: $S_{Y,y}^N(t) = [S_Y^n(t), S_y^{N-n}(t)]^{\mathrm{T}}$. Now, using the $S_{Y,y}^N(t)$, the initial estimates for the model parameter α_0^L may be refined by applying Steps 3 and 4 of algorithm II. In this way the model DDEs are used to fill in the data set and the applicability of Himmelblau's method is extended.

It must be noted that it is quite common in chemical kinetics modelling for the parameters used in a full set of equations to be obtained from reduced data on subsystems. A sequential equation procedure based on the singular perturbation approach to estimate the nonstiff and stiff parameters in chemical reaction systems [58] gives an example of the attempt to reduce the number of equations which are used to generate good initial parameter estimates for subsequent refinement.

Spline functions approximating continuously an observed data for the n state variables, $S_Y^n(t)$, give a similar opportunity for the simplification of the parameter refinement process. Indeed, the vector-function $S_Y^n(t)$, or some of its components may be used to reduce the dimension of the model differential system by excluding (via direct substitution) those equations, which do not contain the parameters varied to solve a particular minimization problem in Step 3 of Algorithm I, i.e., α^l, $l < L$. This leads to the following problem of reduced complexity:

Find

$$\min F\big(y^{N-d}(\alpha^l), Y^{N-d}\big), \quad A^l \leqslant \alpha^l \leqslant B^l,$$

$$\frac{\mathrm{d}y^{N-d}(t)}{\mathrm{d}t} = f^{N-d}\big(\alpha^l, S_Y^d(t), y^{N-d}(t), S_Y^d(t-\tau)y^{N-d}(t-\tau)\big), \quad t_0 \leqslant t \leqslant t_0 + T,$$

$$y^{N-d}(t) = \varphi^{N-d}(t), \quad t_0 - \tau \leqslant t \leqslant t_0.$$

This technique is helpful in decreasing the sensitivity of partial optimization subproblems with respect to the dimension of the model. The particular choice of the state vector components $y^{(i)}(t)$ is to be fixed and replaced by the data-derived spline functions depending on the particular fitting subproblem to be solved.

3.4. Numerical solution of the function minimization problem

It has been noted above that the problem of identifying model parameters was reduced to a sequence of minimization subproblems for the nonlinear function $\Phi(\alpha^{l_m})$ subject to simple two-sided bound constraints:

$$\alpha^{l_m}_{*} = \arg\min \Phi(\alpha^{l_m}), \quad A^{l_m} \leqslant \alpha^{l_m} \leqslant B^{l_m}. \tag{3.6}$$

It should be pointed out that the two-sided inequality constraints improve the convergence of minimization algorithms, because they allow the scaling of variables to pass from primary units of parameters to new ones which are of the same order and, therefore, suitable from a computational point of view [24].

A search for a minimum was performed by a two-step procedure: (1) searching for a crude estimate of the minimum point by a simplex method and (2) precise localization of the minimum by a quasi-Newton (QN) method.

Smoothness properties of the objective function $\Phi(\alpha^{l_m})$ are the major characteristic required to decide whether higher-order optimization methods can be applied. Using the results on the differentiability of the solutions of IVP DDEs with respect to parameters, it can be shown that for the twice continuously differentiable right-hand side function, $f(t, \alpha, y(t), y(t-\tau))$, with respect to all arguments and for strongly positive initial conditions to objective function, $\Phi(\alpha)$, given by (3.2) or (3.3) and determined by an IVP for DDEs is also twice continuously differentiable in $\mathbb{R}^L_+$. Therefore, the gradient $g(\alpha)$ and the Hessian matrix $H(\alpha)$ exist and are continuous in $\mathbb{R}^L_+$. Two algorithms—the simplex method and quasi-Newton method—realized in the MINUIT system [31], as well as the QN method for nonlinear function minimization with the specified accuracy of function evaluation, ZXMIN [28], have been used to solve the minimization problem (3.6). The MINUIT package provides a comfortable environment for function minimization, even though it requires the objective function to be calculated with the full accuracy. If the two-sided linear constraints were imposed on parameters, then the following transformation was used to make the optimization problem unconstrained; $y^{(l)} = \arcsin(2(\alpha^{(l)} - A^{(l)})/(B^{(l)} - A^{(l)}) - 1)$.

The simplex method is a derivative-free heuristic method, which uses only the information of the minimized function values and is less sensitive to the errors in the function evaluations. It was started first for obtaining better estimates of parameter values followed by the launching of the more efficient QN method. The QN method is considered to be very efficient for unconstrained minimization of nonlinear functions, when the dimension of the parameter space is not too high. It requires, however, more precise evaluation of the objective function. For evaluation of the gradients and the hessian matrix of the objective function, a finite-difference approximation was used. In this case, the smoothness of the numerical solution of the IVP for DDEs, $y_h(t, \alpha)$, which is used for evaluations of $\Phi(\alpha)$ with respect to α becomes a delicate problem. Indeed, it determines the differentiability of $\Phi_h(\alpha^L)$ and, hence, the precision of the approximations $g_h(\alpha)$ and $H_h(\alpha)$ and, consequently, the behavior of the minimization code.

The most effective numerical methods for systems of differential equations are the adaptive variable step/variable order algorithms. However their smoothness properties are poor, because two slightly different values of any parameter of the IVP can generate different sequences of integration steps and approximation orders, resulting in small jumps, about O(tolerance), of solution values [5,23]. Generally, the discontinuities arise as the change of a parameter causes the code to employ a different execution path. As a result, the numerical solution $y_h(t, \alpha)$ is a piecewise smooth function of the parameter α with frequent jump discontinuities. There are a number of approaches to handle the smoothness problem of the numerical solution [5,23,24,39,47]: using an equally spaced integration mesh, or using a fixed mesh/order sequence; integration of a set of variational equations; simultaneous integration of both the perturbed and basic system of equations; the more accurate solution of the IVP to decrease the level of noise in the estimation of the objective function, etc. We used the last of these approaches because it is easier to implement for multiparameter models.

It was shown in [23,24] that to estimate the partial derivatives

$$\partial^s y(t, \alpha)/\partial \alpha^s, \quad s = 1,2,$$

of the IVP solution with the precision $O(\delta)$ using the finite-difference interval $\Delta\alpha$, the corresponding IVP should be solved numerically with tolerance $O((\Delta\alpha)^s\delta)$. Therefore, an adaptive and robust code for the numerical integration of stiff IVP DDEs within a wide range of tolerances is required. The description of our approach to the numerical solution of the IVP for stiff DDEs is given below.

3.5. Algorithm for solving numerically the stiff IVP for DDEs

A conventional approach to numerical integration of IVP DDEs is based on adapting the standard techniques developed for ODEs. Two major concerns are the inherent derivative jump discontinuities of the analytical solution [45,46,52,64] and the need for continuous approximation of delayed variables by an interpolation method which should be consistent with an ODE-related discretization scheme being adapted [3,25,29,45,63]. A variety of numerical methods have been proposed for solving the IVP for DDEs, mainly for nonstiff problems. The first widely available code for finite-difference equations was the DMRODE [43,44]; then, experimental solvers based on Runge–Kutta methods, including the DELAY-2, STRIDE, etc., have been proposed [3,11,25,48–50,59]. The multistep integrators for DDEs based on the composite methods, as well as the Adams or BDFs, were developed in [9,32,55,62]. The recent contribution in this field is the general-purpose Adams-formulas-based code DELSOL developed according to NAG standards [63].

For treating a stiff IVP for DDEs, an adaptation of the A-, $A(\alpha)$- or stiffly stable methods is required. An IVP for DDEs is referred to as stiff if, for a given tolerance, the stepsize taken by a numerical method is restricted by stability rather than accuracy requirements [9,30,62]. There are a number of references to codes suitable for solving stiff DDEs [9,32,55]; however the codes themselves are not readily available [19].

For numerical integration, in a wide range of tolerances, of a stiff IVP for DDEs having several constant delays we developed an adaptive code, the DIFSUB-DDE [12,13], using Gear's DIFSUB [21,22]. The Nordsieck history arrays are utilized as natural interpolating polynomials,

being locally consistent with the underlying ODE's method, for continuous approximation of the delayed variables. To approximate delayed variables in the vicinity of the mesh point t_n, Nordsieck's p_nth-order polynomial is applied as follows:

$$y(t-\tau) = C(\alpha)\cdot \bar{y}_n + \mathrm{O}\big((\alpha\cdot h_n)^{p+1}\big) + C(\alpha)\cdot \bar{\varepsilon}_n, \qquad y\in\mathbb{R}, \quad (t-\tau)\in(t_{n-1}, t_n),$$

with

$$\bar{y}_n = \left[y_n, h_n y'_n, \ldots, \frac{h_n^{p_n}\cdot y_n^{(p_n)}}{p_n!} \right]^{\mathrm{T}},$$

$$C(\alpha) = \mathrm{diag}[1, \alpha, \ldots, \alpha^{p_n}], \qquad \alpha = \frac{(t-\tau-t_n)}{t_n - t_{n-1}}, \quad |\alpha| < 1.$$

Because only constant delays are considered, the derivative discontinuities points, up to the order $(p+1)$, are calculated in advance and are included amongst the integration meshpoints. A stepsize/order selection strategy employed in the DIFSUB code is kept unmodified except for an additional control of stepsize and order to pass smoothly trough the jump points. The original DIFSUB's error control criterion was modified to be based on a relative error criterion above a certain threshold. Integration stepsizes are not limited explicitly by particular delay values within those time intervals in which the corresponding analytical solution is sufficiently smooth. Test calculations are given in [13].

4. Applications in immune response modelling

The presented approach to treating the parameter identification problem was elaborated in applications of mathematical models to quantitative description of immune response in a number of infectious diseases: acute hepatitis B virus infection [38], uncomplicated influenza A virus infection [15], acute pneumonia [34] and T cell proliferation [57].

We present here an example: we apply the methods developed in the previous section to the identification of several parameters in a mathematical model of antiviral immune response by the data on the kinetics of acute hepatitis B. The following notation is used for the state variables of the model; free virus population, $V_{\mathrm{f}}(t)$; antigen-presenting cell population, $M_V(t)$; helper Th1 cell population, $H_E(t)$; helper Th2 cell population, $H_B(t)$; cytotoxic T cell population, $E(t)$; B cell population, $B(t)$; plasma cell population, $P(t)$; antibody population, $F(t)$; virus-infected sensitive tissue cell population, $C_V(t)$; destroyed sensitive tissue cells, $m(t)$. The interactions in which these species participate are represented by the model, which is a system of ten nonlinear DDEs with several constant delays:

$$\mathrm{d}V_{\mathrm{f}}/\mathrm{d}t = \nu C_V + nb_{CE}C_V E - \gamma_{VF}V_{\mathrm{f}}F - \gamma_{VM}V_{\mathrm{f}} - \gamma_{VC}V_{\mathrm{f}}(C^* - C_V - m),$$

$$\mathrm{d}C_V/\mathrm{d}t = \sigma V_{\mathrm{f}}(C^* - C_V - m) - b_{CE}C_V E - b_m C_V,$$

$$\mathrm{d}m/\mathrm{d}t = b_{CE}C_V E + b_m C_V - \alpha_m m,$$

$$\xi(m) = 1 - m/C^*,$$

$$
\begin{aligned}
\mathrm{d}M_V/\mathrm{d}t &= \gamma_{MV} M^* V_\mathrm{f} - \alpha_M M_V,\\
\mathrm{d}H_E/\mathrm{d}t &= b_H^E\left[\xi(m)\rho_H^E M_V(t-\tau_H^E)H_E(t-\tau_H^E) - M_V H_E\right]\\
&\quad - b_p^{H_E} M_V H_E E + \alpha_H^E(H_E^* - H_E),\\
\mathrm{d}H_B/\mathrm{d}t &= b_H^B\left[\xi(m)\rho_H^B M_V(t-\tau_H^B)H_B(t-\tau_H^B) - M_V H_B\right]\\
&\quad - b_p^{H_B} M_V H_B B + \alpha_H^B(H_B^* - H_B),\\
\mathrm{d}E/\mathrm{d}t &= b_p^E\left[\xi(m)\rho_E M_V(t-\tau_E)H_E(t-\tau_E)E(t-\tau_E) - M_V H_E E\right]\\
&\quad - b_{EC} C_V E + \alpha_E(E^* - E),\\
\mathrm{d}B/\mathrm{d}t &= b_p^B\left[\xi(m)\rho_B M_V(t-\tau_B)H_B(t-\tau_B)B(t-\tau_B) - M_V H_B B\right] + \alpha_B(B^* - B),\\
\mathrm{d}P/\mathrm{d}t &= b_p^P\xi(m)\rho_P M_V(t-\tau_P)H_B(t-\tau_P)B(t-\tau_P) + \alpha_P(P^* - P),\\
\mathrm{d}F/\mathrm{d}t &= \rho_F P - \gamma_{FV} F V_\mathrm{f} - \alpha_F F.
\end{aligned}
$$

To describe the onset and development of an infectious disease in a healthy organism following virus exposure the following initial conditions are specified:

$$
\begin{aligned}
&V_\mathrm{f}(0) = V_\mathrm{f}^0, \quad M_V(0) = M_V^0, \quad H_E(0) = H_E^*, \quad H_B(0) = H_B^*, \quad E(0) = E^*,\\
&B(0) = B^*, \quad P(0) = P^*, \quad F(0) = \rho_F \cdot P^*/\alpha_F, \quad C_V(0) = 0, \quad m(0) = 0,
\end{aligned}
$$

$$
\begin{aligned}
&M_V(t)H_E(t) = 0, && \text{for } -\tau_H^E \leqslant t \leqslant 0,\\
&M_V(t)H_B(t) = 0, && \text{for } -\tau_H^B \leqslant t \leqslant 0,\\
&M_V(t)H_E(t)E(t) = 0 && \text{for } -\tau_E \leqslant t \leqslant 0,\\
&M_V(t)H_B(t)B(t) = 0, && \text{for } -\max(\tau_B, \tau_P) \leqslant t \leqslant 0.
\end{aligned}
$$

In this type of immune response modelling, experimental data is never taken on all variables of interests in a single set of experiments. Available sets of data, partial and incomplete, are

Table 1
Data of the Generalized Picture of acute hepatitis B virus infection

T	V_f (pt/ml)	$\frac{C_V}{C^*}$	$\frac{m}{C^*}$	$\frac{M_V}{M^*}$	$\frac{H_E}{H_E^*}$	$\frac{H_B}{H_B^*}$	$\frac{E}{E^*}$	$\frac{B}{B^*}$	$\frac{P}{P^*}$
0	$1 - 10^6$	0	0	0	1	1	1	1	1
60	$0.5\cdot 10^8$	–	–	–	–	–	–	–	–
70	$0.2\cdot 10^9$	–	–	–	–	–	–	–	–
80	$0.8\cdot 10^9$	0.02	–	–	–	–	–	–	–
90	–	–	0.008	0.1	–	–	–	–	–
100	$0.5\cdot 10^{10}$	0.15	0.06	–	10	10	2	1.5	–
105	–	–	–	0.5	100	100	20	15	10
110	$0.6\cdot 10^{10}$	0.04	0.2	–	10^3	10^3	$2\cdot 10^4$	$0.15\cdot 10^5$	10^4
120	10	–	0.09	–	–	–	–	–	–
130	–	–	0.02	–	–	–	–	–	–

Table 2
The set of the model parameters allowing to simulate quantitatively the kinetics of acute hepatitis B virus infection ("d" denotes day)

Parameter	Value	Parameter	Value	[Initial estimate]
M^*	10^{-15} M	ρ_E, ρ_B	16	
H_E^*	10^{-18} M	ρ_P	3	
H_B^*	10^{-19} M	ρ_F	1.7×10^{8} molec.(cell $*$ d)$^{-1}$	
E^*	10^{-18} M	b_H^E	2.7×10^{16} M^{-1}d^{-1}	[10^{15}]
B^*	10^{-18} M	b_H^B	2.7×10^{16} M^{-1}d^{-1}	[10^{15}]
P^*	4.3×10^{-22} M	b_p^E	5.3×10^{33} M^{-2}d^{-1}	[10^{32}]
F^*	8.3×10^{-14} M	b_p^B	8.0×10^{32} M^{-2}d^{-1}	[10^{32}]
C^*	0.5×10^{-12} M	b_p^P	1.7×10^{30} M^{-2}d^{-1}	[10^{32}]
α_M	1.2 d^{-1}	γ_{MV}	9.4×10^{9} M^{-1}d^{-1}	[10^{8}]
α_H^E	1.0 d^{-1}	γ_{FV}	8.6×10^{11} M^{-1}d^{-1}	
α_H^B	1.0 d^{-1}	σ	2.3×10^{9} M^{-1}d^{-1}	[2.5×10^{8}]
α_E	0.4 d^{-1}	b_{CE}	6.6×10^{14} M^{-1}d^{-1}	[1.6×10^{15}]
α_B	0.1 d^{-1}	b_m	0.052 d^{-1}	[0.01]
α_P	0.4 d^{-1}	α_m	0.15 d^{-1}	[0.12]
α_F	0.043 d^{-1}	ν	83 d^{-1}	[6×10^{3}]
τ_H^E	0.6 d	γ_{VC}	2.5×10^{7} M^{-1}d^{-1}	
τ_B^H	0.6 d	γ_{VM}	0.4 d^{-1}	
τ_E	2.0 d	γ_{VF}	3×10^{11} M^{-1}d^{-1}	
τ_B	2.0 d	$b_p^{H_E}$	5.3×10^{27} M^{-2}d^{-1}	
τ_P	3.0 d	$b_p^{H_B}$	8.0×10^{28} M^{-2}d^{-1}	
ρ_H^E	2	ρ_H^B	4	
b_{EC}	1.6×10^{11} M^{-1}d^{-1}	n	5	[2×10^{4}]
V_f^0	2.9×10^{-16} M			

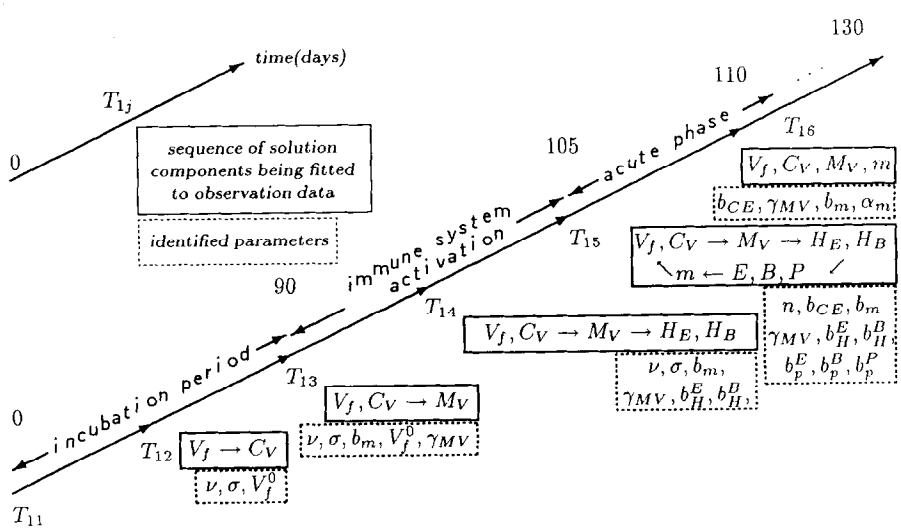

Fig. 1. The flowchart of sequential model parameter identification based on the "natural history" of an infection.

specially organized to represent the kinetics of an infection under modelling in the state space of the model. Table 1 lists the data points representing the typical kinetics (Generalized Picture) of immune response in hepatitis B virus infection.

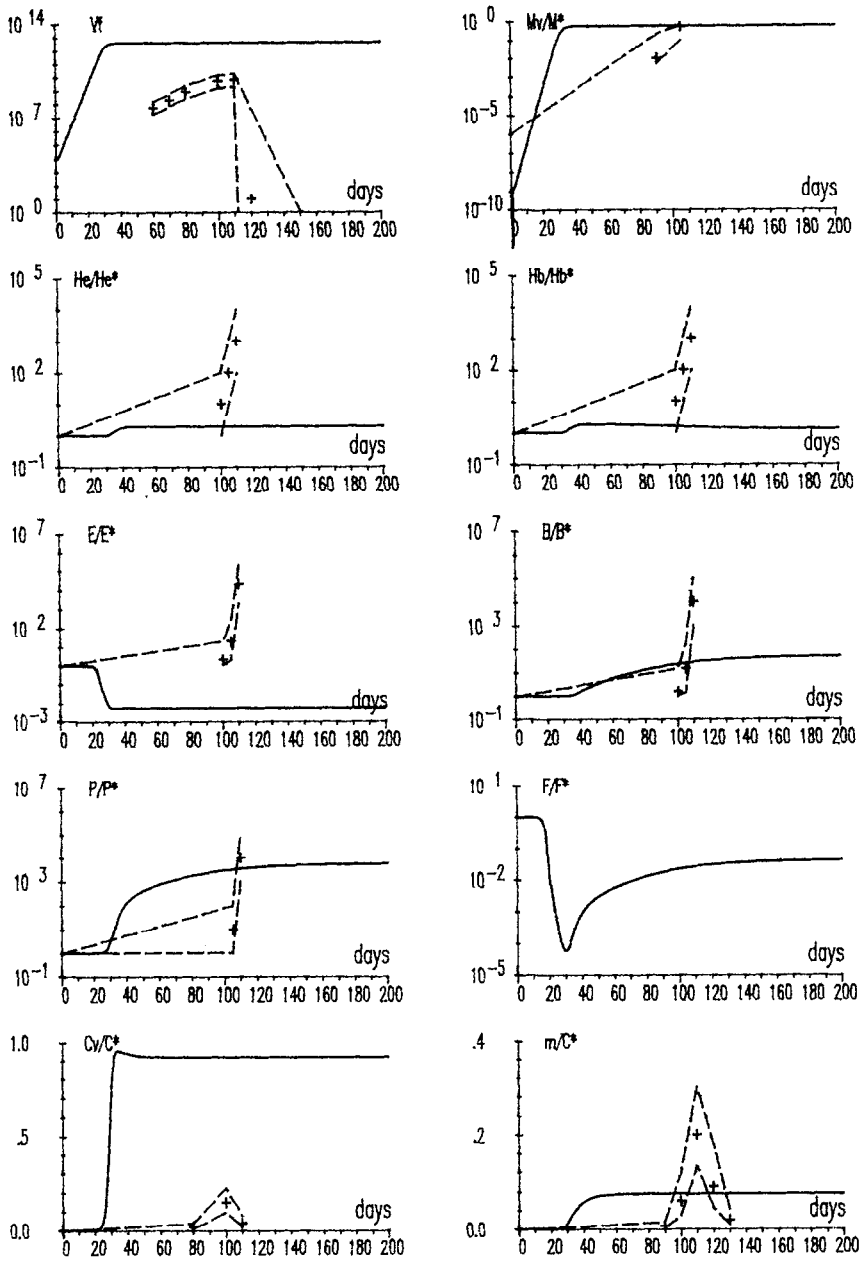

Fig. 2. Model solution for the initial parameter guess and the data on kinetics of the acute hepatitis B virus infection. The uncertainty boundaries for the data points are marked by the dotted line.

Parameters of the model are listed in Table 2. They span thirty orders of magnitude. Some of them are taken directly from experiments, the others are derived from theory (see [14,37] for details). The last estimates can be incorrect by orders of magnitude and need to be refined by fitting to the data.

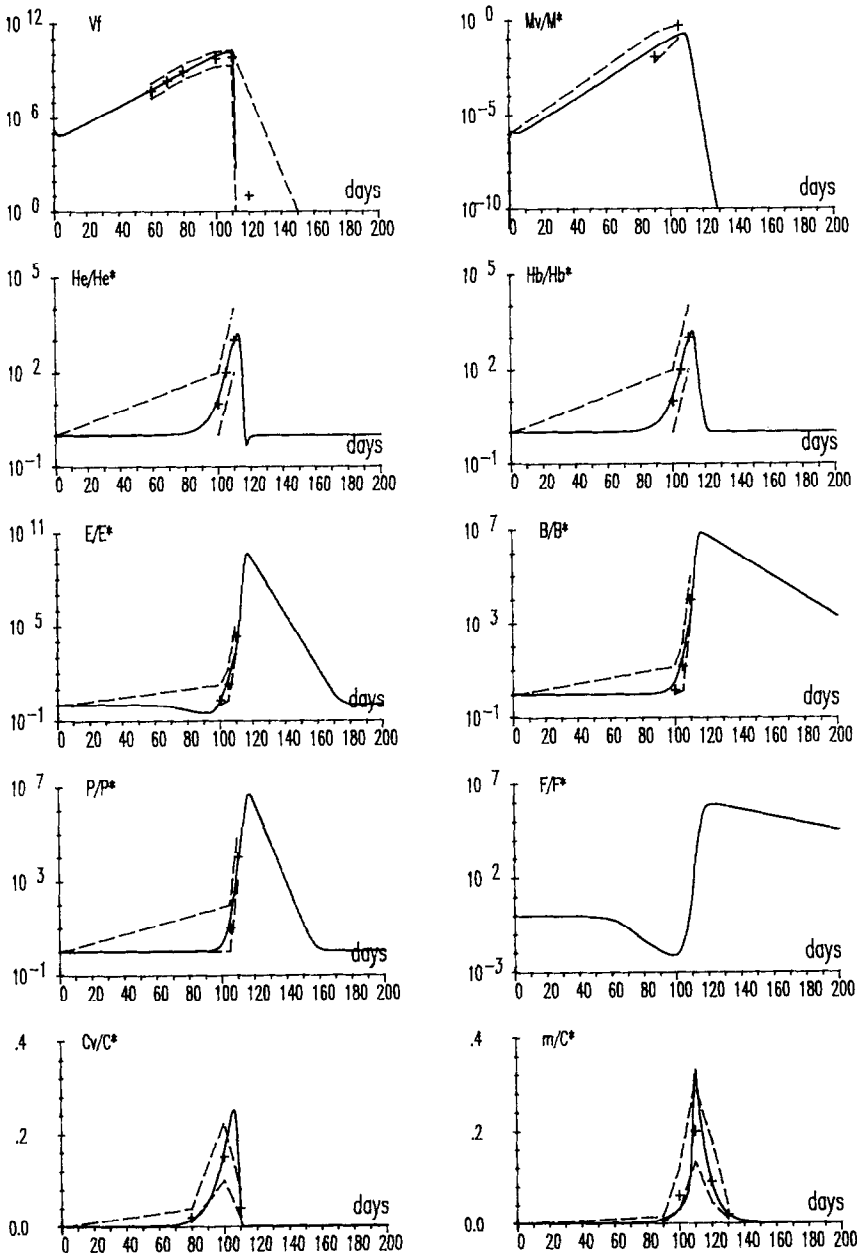

Fig. 3. Model solution fitted to the observed data on kinetics of the acute hepatitis B virus infection. The uncertainty boundaries for the data points are marked by the dotted line.

In this particular example, twelve parameters characterizing the rates of immune precesses in lymph nodes and viral spread in liver, were identified. A detailed fitting protocol is given in [38], and the sketch of the sequential parameter identification approach is displayed on Fig. 1. The identified parameters in Table 2 are distinguished by their initial estimates given in square brackets. The solution of the antiviral immune response model for the initial guess parameter values is pictured in Fig. 2. The fitted-to-data parameters give the solution shown in Fig. 3.

Calculations were performed in double precision on HP-1000. The IVP for DDEs was solved with a relative tolerance of about 10^{-8} by the stiff version of the DIFSUB-DDE. As large as 3000 times the IVP was solved to identify several parameters, giving the quality of fit shown on Fig. 3. Simplex and quasi-Newton procedures implemented in the MINUIT package [31] were utilized for numerical minimization of an objective function over the sequential subintervals.

Another example of parameter identification for an immune response to influenza A virus infection, which is a faster process as compared to hepatitis B, is given in [14,15]. A combination of crude but global fitting methods (Algorithm II) and locally convergent techniques was required to identify ten model parameters.

The presented strategy of treating the parameter identification problem for nonlinear multiparameter DDE models gives, in a strict sense, nonunique parameter estimates or may involve ill-conditioned stages. Therefore, parameter identification results need further biological validation [38,57]. Nevertheless, this approach allows the allocation of the iterative process of model fitting between the crude but computationally cheap "global fitting" method and exact but computationally expensive "local" optimization methods to be made more effectively. Usually, a stochastic sensitivity analysis was performed to obtained a measure of confidence with respect to certain characteristics of model solutions for the identified parameters [15,38]. The ill-conditioning results from the character of the data are available for the processes under study: they are valuable from a biological viewpoint and poor from a formal or statistical point of view. We have addressed the problem of homogeneous data requirement to reliably estimate the model parameters in [14,38].

5. Concluding remarks

Heavy computational work is inherent to parameter identification problems for stiff nonlinear DDEs with constant delays arising in immune response modelling. They could be effectively solved by carefully developing the tools and experience from another branches of computational mathematics. In turn, the methodology elaborated in treating complex immunological processes may be useful for other problems in mathematical biology, as well as for these studies in chemical kinetics which use the delay effects and the DDEs for representing the dynamics of reactions [19].

Acknowledgement

The authors would like to thank Professor J.C. Butcher for an opportunity to take part in the SCADE 93 Conference and visit the Department of Mathematics and Statistics of the

Auckland University. The authors are indebted to the referees for their help in improving the presentation of the material of the paper. The advice of the Editor, Dr. P.W. Sharp, concerning the exposition of the content of the manuscript is also highly appreciated.

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