Parameter Identification For Oscillating Chemical Reactions Modelled By Systems Of Ordinary Differential Equations

L. K. Babadzanjanz,* J. A. Boyle† D. R. Sarkissian‡ and J. Zhu §

January 13, 2002

Abstract

The Cauchy problem (also called the initial value problem) for the system of ordinary differential equations with right-hand sides depending on some unknown parameters is considered here. The noisy measurements of one of the variables at the given time moments are assumed to be known. A new algorithm for recovering (*identification*) the model parameters is proposed. The algorithm is based on the numerical integration of the gradient equations of some least-square functional. The right-hand sides of the gradient equations are obtained by the numerical integration of the Cauchy problem for the original equations and equations for their partial derivatives with respect to unknown parameters. Parameter identification for the well-known Lotka-Volterra model of oscillating chemical reaction demonstrates the robustness of the proposed algorithm when the measurements are corrupted with random multiplicative noise. All computations are performed using MATLAB® version 6.0.

1 Introduction

Mathematical modeling and computational simulations have now been widely used in the study of various chemical and biological processes [5, 7, 8]. In particular, systems of nonlinear ordinary differential equations have been used in the modeling of chemical reactions in many important bio-chemical pathways.

*Department of Applied Mathematics and Processes of Management, St. Petersburg State University, Russia, e-mail: Levon.Babadzanjanz@pobox.spbu.ru.

†Department of Biochemistry and Molecular Biology, Mississippi State University, MS, 39762, e-mail: jab@ra.msstate.edu.

‡Department of Mathematics and Statistics, P.O. Box MA, Mississippi State University, MS, 39762, e-mail: sarkiss@math.msstate.edu.

§Department of Mathematics and Computer Science, University of Akron, Akron, OH 44325, email: jzhu@math.uakron.edu.

For example, the following system of nonlinear ODEs has been used to model the signal transduction and second messenger systems in cell biology [8]:

$$\begin{aligned}
\frac{dx_1}{dt} &= \lambda(\gamma_0 + \gamma_1 x_4)(1 - x_1) - \frac{p_1 x_1^4}{p_2^4 + x_1^4}, \\
\frac{dx_2}{dt} &= k_1 I x_2 + k_{-1} x_3, \\
\frac{dx_3}{dt} &= -(k_{-1} + k_2 x_1) x_3 + k_1 I x_2 + k_{-2} x_4, \\
\frac{dx_4}{dt} &= k_2 x_1 x_3 + k_{-3} x_5 - (k_{-2} + k_3 x_1) x_4, \\
\frac{dx_5}{dt} &= k_3 x_1 x_4 - k_{-3} x_5
\end{aligned} \tag{1}$$

where λ, γ, k, p, and I are various parameters, such as reaction rates.

Many mathematical models, including the ones arising is such important areas as chemistry, biochemistry, cell biology, physiology, etc., have to include the concentrations of many "intermediate" reactants that are very hard to measure experimentally and many unknown constants (reaction rates) that can not be predicted theoretically with enough accuracy. However, some model variables (concentrations) might be much cheaper and easier to measure at different time moments by laboratory experiments then the other ones.

For example, when modeling bone loss in senior people one must track the evolution of chemical composition of the bones (which is very hard to measure in a living subject) and relate them to the evolution of the concentrations of the chemicals that are measured during the routine medical examinations and the intake of the drugs via the system of ODEs with the unknown reaction rates constants. It is, therefore, crucial for the practical applicability of such models to be able to identify the unknown parameters based the (noisy) measurements of just a few model variables that are easier to measure.

This paper presents an algorithm which robustly predicts the evolution of all model variables by identifying the unknown model parameters based on the measurements, usually corrupted with noise due to experiment errors, of some of the model variables.

In general, the more variables and parameters that are contained in the problem the harder the parameter identification problem becomes. One of the most widely known systems that captures the essence of the chemical oscillations is Lotka-Volterra system

$$\begin{aligned}
dx_1/dt &= -k_1 x_1 x_2, \\
dx_2/dt &= k_1 x_1 x_2 - k_2 x_2 x_3, \\
dx_3/dt &= k_2 x_2 x_3 - k_3 x_3, \\
dx_4/dt &= k_3 x_3,
\end{aligned} \tag{2}$$

where $x_1(t), x_2(t), x_3(t)$ and $x_4(t)$ are, respectively, the concentrations of the reactants A, X, Y and B at the time t, and k_1, k_2 and k_3 are the unknown rate

constants. This model was introduced by Lotka (see [6]) and its properties has been extensively studied (see [2] and references therein).

Despite being less complicated then (1), Lotka-Volterra system is of interest to many researchers because it is rich in content and is also useful as a model. That is why in this paper we apply our new parameter identification approach to the system (2) with the initial conditions

$$x_1(0) = x_{10}\,,\ \ldots\ ,\ x_4(0) = x_{40}\,. \tag{3}$$

The outline of the paper is as follows: The exact mathematical statement of the *parameter identification problem* for modeling chemical reactions is given in Section 2. The solution technique is described in Section 3. Section 4 provides numerical examples that attest to the robustness of the proposed algorithm. The directions of the future research, aimed to improve the proposed algorithm, are discussed in Section 5.

2 Mathematical Problem Statement

Let the Cauchy problem

$$\begin{aligned} dx_j(t)/dt &= f_j(x_1,\ldots,x_n;k_1,\ldots,k_m), &(4)\\ x_j(t_0) &= x_{j0}\,,\ j=1,2,\ldots,n, &(5)\end{aligned}$$

where $k_1,\ldots,k_m$ are unknown parameters and the M measurements

$$x_{q1},\ldots,x_{qM} \tag{6}$$

of the q^{th} component $x_q(t)$ of the model ($1 \le q \le n$) be given. Usually $x_q(t)$ is the one model variable which is the cheapest and/or easiest to make measurements for. Then the values $\hat{k}_1,\ldots,\hat{k}_m$ of the model parameters $k_1,\ldots,k_m$ are to be found to minimize

$$\Phi(k_1,\ldots,k_m) = \frac{1}{2}\sum_{i=1}^{M}\left(x_q(t_i,k_1,\ldots,k_m) - x_{qi}\right)^2\alpha_i\,. \tag{7}$$

Here α_i's are some given constant weights and $x_q(t,k_1,\ldots,k_m)$ is the q^{th} component of the solution of the Cauchy problem (4) and (5), considered as a function of both t and k_p's.

3 Solution Technique

Differentiating the j^{th} component of (4) and (5) with respect to k_r, one derives that the functions

$$y_{jr}(t) = \frac{\partial x_j(t,k_1,\ldots,k_m)}{\partial k_r}\,,\ j=1,\ldots,n,\ r=1,\ldots,m \tag{8}$$

satisfy the following Cauchy problem

$$dy_{jr}/dt = \frac{\partial f_j}{\partial k_r} + \sum_{p=1}^{n} \frac{\partial f_j}{\partial x_p}\, y_{pr}\,, \tag{9}$$

$$y_{jr}(t_0) = 0\,,\ j = 1, \ldots, n,\ r = 1, \ldots, m. \tag{10}$$

Next, we define the Cauchy problem

$$dk_r/d\tau = -\frac{\partial \Phi(k_1, \ldots, k_m)}{\partial k_r} = \\ -\sum_{i=1}^{M} \left(x_q(t_i, k_1, \ldots, k_m) - x_{qi}\right) y_{qr}(t_i)\, \alpha_i, \tag{11}$$

$$k_r(0) = k_r^0\,,\ r = 1, \ldots, m, \tag{12}$$

where τ is an internal time-like variable of autonomous system (11) and k_1^0, ..., k_m^0 are some constants, which we take as the initial approximation to $\hat{k}_1, \ldots, \hat{k}_m$. Equations (11) are called the *gradient equations* for the minimization of the functional $\Phi(k_1, \ldots, k_m)$.

Newton-type methods based on equations (4), (5), (9) and (10) are usually used to minimize the functional Φ with the derivatives $\partial\Phi/\partial k_1, \ldots, \partial\Phi/\partial k_m$ being calculated by some numerical method (see [9]). The other approach to minimization is to solve the Cauchy problem (11) and (12). By integrating this Cauchy problem numerically, we will move along the gradient curve $k(\tau)$. We have even more reasons then in the case of Newton-type methods which attempt to follow the same gradient curve to expect that $k(\tau) \to k^*$ when $\tau \to +\infty$, where k^* is the point of local minimum of Φ. In fact, along the gradient curve $k(\tau)$, we have

$$d\Phi/d\tau = -\left(\nabla\Phi(k_1(\tau), \ldots, k_m(\tau)), \nabla\Phi(k_1(\tau), \ldots, k_m(\tau))\right) < 0\,, \tag{13}$$

which implies that Φ is a monotone decreasing function along this curve.

In literature the approach based on numerical integration of gradient equations and its generalizations is also known as the "relaxation method" and the "heavy ball with friction" (see [4, 1]).

Thus, in this paper a local minimum is sought by the numerical integration of the Cauchy problem (11) and (12), computing the values of the right-hand sides of (11) by the numerical integration of the problem (4), (5), (9) and (10). In this paper the numerical integration is performed using the function `ode45` from MATLAB, which is based on an explicit Runge-Kutta $(4, 5)$ formula, the Dormand-Prince pair.

4 Numerical Examples

In this section Lotka-Volterra model of oscillating chemical reaction is considered. We demonstrate the performance of the proposed algorithm as follows:

1. The arbitrary values $k_1, \ldots, k_m$ of the unknown parameters and arbitrary initial conditions $x_{10}, \ldots, x_{n0}$ are chosen.

2. For the uniformly spaced time moments $t_0 < t_1 < \ldots < t_M$, the values $x_4(t_i, k_1, \ldots, k_m)$, $i = 1, \ldots, M$ are computed by solving Cauchy problem (4) and (5). Adding $0\%, 5\%, 10\%$ and 15% multiplicative noise to simulate the experimental error, the measurements x_{4i}'s are taken as

$$x_{4i} \quad = \quad (1 + \xi_i)\, x_4(t_i, k_1, \ldots, k_m), \quad i = 1, \ldots, M \tag{14}$$

   where ξ_i are independent uniformly distributed random variables.

3. Fixing arbitrary initial approximations $k_1^0, \ldots, k_m^0$, the local minimum k_1^*, ..., k_m^* is computed using the proposed algorithm. The efficiency of the parameter estimation is judged by the distance between the local minimum $k_1^*, \ldots, k_m^*$ and the original values $k_1, \ldots, k_m$.

The numerical experiments are illustrated with the figures given in the next sections. The MATLAB® program, implementing these examples, is available upon request.

4.1 Ordinary Differential Equations of Parameter Identification Method for Lotka-Volterra Model Of Oscillating Chemical Reaction

The general Cauchy problem (2) and (3) for Lotka-Vortera model was introduced in Section 1. Here, we repeat these equations with specific initial values along with other equations of the parameter identification method proposed in this paper.

Consider the Cauchy problem

$$\begin{array}{rcl} dx_1/dt & = & -k_1 x_1 x_2, \\ dx_2/dt & = & k_1 x_1 x_2 - k_2 x_2 x_3, \\ dx_3/dt & = & k_2 x_2 x_3 - k_3 x_3, \\ dx_4/dt & = & k_3 x_3, \end{array} \tag{15}$$

$$x_1(0) = 3\,,\ x_2(0) = 0.9\,,\ x_3(0) = 2.1\,,\ x_4(0) = 0, \tag{16}$$

where $x_1(t), x_2(t), x_3(t)$ and $x_4(t)$ are, respectively, the concentrations of the reactants A, X, Y and B at the time t, and k_1, k_2 and k_3 are the unknown rate constants. The initial values (16) are taken from [2].

The corresponding equations (9) and their initial conditions (10) for the

Cauchy problem (15) and (16) become

$$\begin{aligned}
dy_{11}/dt &= -k_1x_2y_{11} - x_1(x_2 + k_1y_{21}),\\
dy_{12}/dt &= -k_1(x_2y_{12} + x_1y_{22}),\\
dy_{13}/dt &= -k_1(x_2y_{13} + x_1y_{23}),\\
dy_{21}/dt &= x_1x_2 + k_1y_{11}x_2 - k_2y_{31}x_2 + (k_1x_1 - k_2x_3)y_{21},\\
dy_{22}/dt &= (k_1x_1 - k_2x_3)y_{22} - x_2(x_3 - k_1y_{12} + k_2y_{32}),\\
dy_{23}/dt &= (k_1x_1 - k_2x_3)y_{23} + x_2(k_1y_{13} - k_2y_{33}),\\
dy_{31}/dt &= k_2x_3y_{21} + (k_2x_2 - k_3)y_{31},\\
dy_{32}/dt &= x_2x_3 + k_2y_{22}x_3 + (k_2x_2 - k_3)y_{32},\\
dy_{33}/dt &= x_3(k_2y_{23} - 1) + (k_2x_2 - k_3)y_{33},\\
dy_{41}/dt &= k_3y_{31},\\
dy_{42}/dt &= k_3y_{32},\\
dy_{43}/dt &= x_3 + k_3y_{33},
\end{aligned} \tag{17}$$

$$y_{11}(0) = y_{12}(0) = y_{13}(0) = y_{21}(0) = \ldots = y_{43}(0) = 0. \tag{18}$$

Using the parameters $k_1 = 1$, $k_2 = 1.5$ and $k_3 = 0.1$, the "measurements" of the concentration of the reactant B are simulated as follows

$$x_{4i} = (1 + \xi_i)\, x_4(25i/M, 1, 1.5, 0.1), i = 1, 2, \ldots, M,$$

where ξ_i are independent uniformly distributed random variables. The time interval $0 < t_i \leq 25$ for the measurements is chosen because in this interval the variable $x_4(t)$ changes significantly.

Choosing the weights $\alpha_i = 1$, $i = 1, 2, \ldots, M$, the functional (7) becomes

$$\Phi(k_1, k_2, k_3) = \frac{1}{2}\sum_{i=1}^{M} \left(x_4(25i/M, k_1, k_2, k_3) - x_{4i}\right)^2. \tag{19}$$

Thus, the gradient equations (11) and (12) become

$$\begin{aligned}
dk_1(\tau)/d\tau &= -\textstyle\sum_{i=1}^{M}(x_4(25i/M, k_1(\tau), k_2(\tau), k_3(\tau)) - x_{4i})y_{41}(25i/M),\\
dk_2(\tau)/d\tau &= -\textstyle\sum_{i=1}^{M}(x_4(25i/M, k_1(\tau), k_2(\tau), k_3(\tau)) - x_{4i})y_{42}(25i/M),\\
dk_3(\tau)/d\tau &= -\textstyle\sum_{i=1}^{M}(x_4(25i/M, k_1(\tau), k_2(\tau), k_3(\tau)) - x_{4i})y_{43}(25i/M),
\end{aligned} \tag{20}$$

Taking

$$k_1(0) = k_1^0 = 0.5\,,\ k_2(0) = k_2^0 = 0.7\,,\ k_3(0) = k_3^0 = 0.4. \tag{21}$$

as the initial approximation, in the following figures we give the results of four numerical experiments for Lotka-Volterra problem with the measurements $x_{4,1}, \ldots, x_{4,M}$ corrupted with multiplicative noise of $0\%, 5\%, 10\%$ and 15%, respectively.

Figure 1 shows the original functions $x(t) = (x_1(t), \ldots, x_4(t))$ computed by the numerical integration of the Cauchy problem (15) and (16) with "true parameters" $k_1 = 1$, $k_2 = 1.5$ and $k_3 = 0.1$ as solid lines and with initial approximation k_1^0, k_2^0 and k_3^0 as dashed lines.

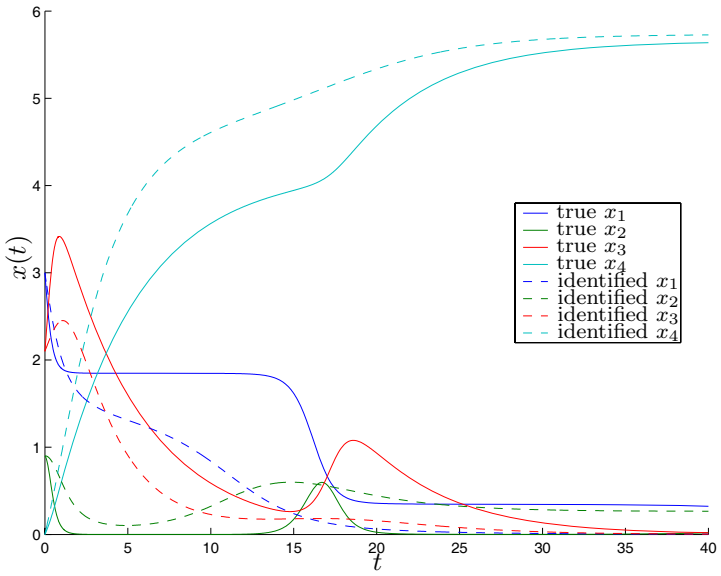

Figure 1: The true model (solid lines) and its initial approximation (dashed lines).

The trajectory of $k(\tau) = (k_1(\tau), k_2(\tau), k_3(\tau))$ of the Cauchy problem (20) and (21) is displayed in Figures 2, 3, 5 and 7, respectively.

The identified model and the measurements it was identified from are shown in Figures 4, 6 and 8 for the multiplicative noise of 5%, 10% and 15%, respectively, along with the true model. The similar figure for the case of noiseless measurements is not included here. In this case, $M = 10$ measurements are enough to identify the parameters with less then 1% error, and the graphs of true and identified models can not be distinguished visually.

5 Future Research

To improve the proposed algorithm, the following directions of research seem to be promising:

1. Our numerical experiments showed that to ensure enough accuracy of parameter identification most of the computer time is usually spent during the repeated numerical integration of the Cauchy problem (4), (5), (9) and (10). Thus, a fast and highly accurate parallel method of numerical integration is of vital importance.

   To achieve this, we suggest computing the right-hand side of the gradient equations (11) in the polynomial form using Aggregative Taylor Series method [3] to integrate the Cauchy problem (4), (5), (9) and (10).

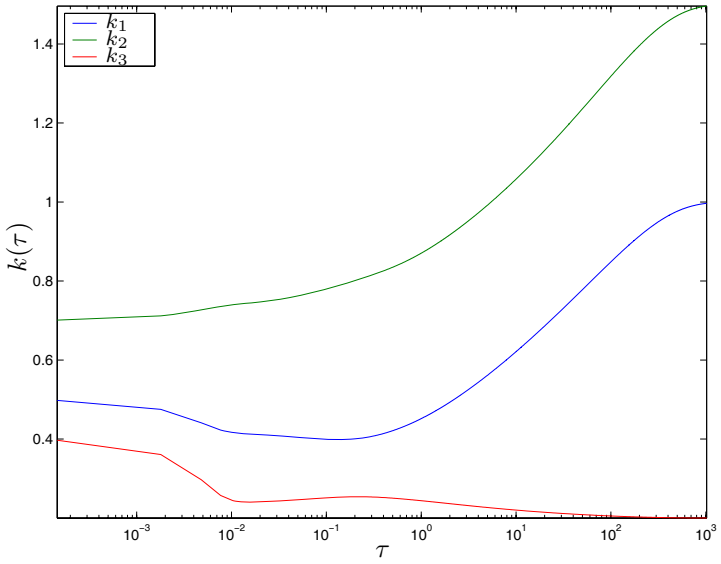

Figure 2: The trajectory $k(\tau)$ recovered from $M = 10$ noiseless measurements.

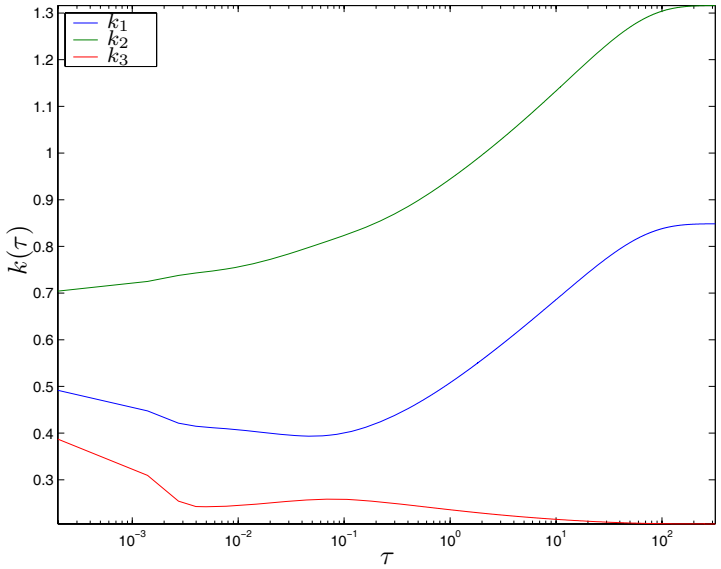

Figure 3: The trajectory $k(\tau)$ recovered from $M = 30$ measurements with 5% multiplicative noise.

2. When the initial approximations $k_1^0, \ldots, k_m^0$ are not too far away (around 50%) from the "true" values of the parameters, our algorithm recovers

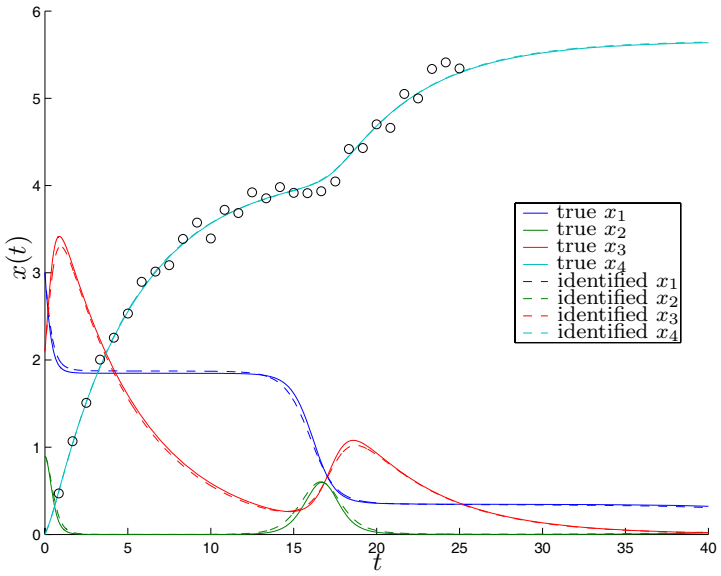

Figure 4: The true model, $M = 30$ measurements with 5% multiplicative noise (circles) and the model identified from them (dashed lines).

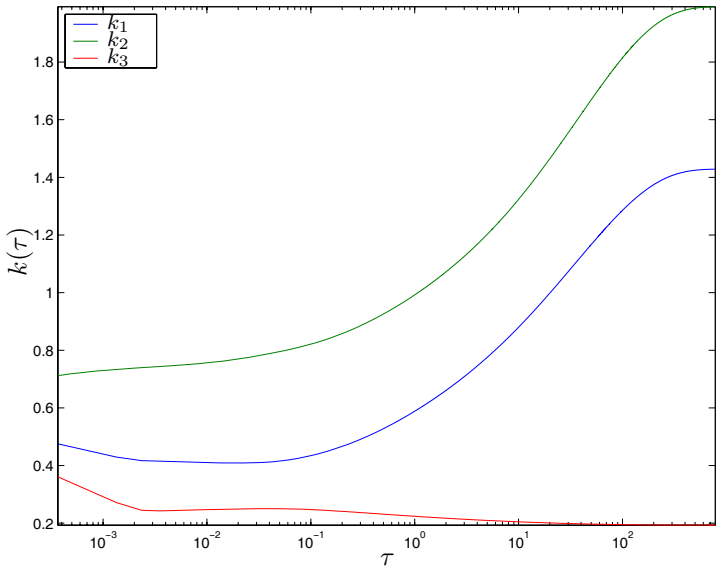

Figure 5: The trajectory $k(\tau)$ recovered from $M = 50$ measurements with 10% multiplicative noise.

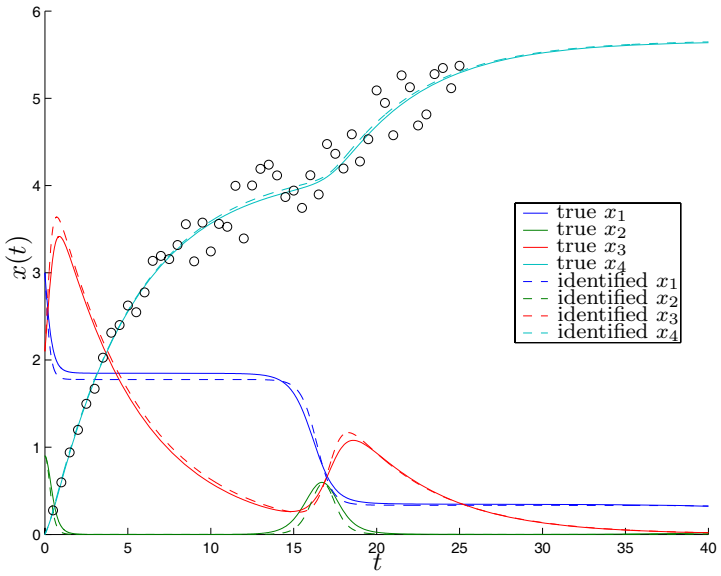

Figure 6: The true model, $M = 50$ measurements with 10% multiplicative noise (circles) and the model identified from them (dashed lines).

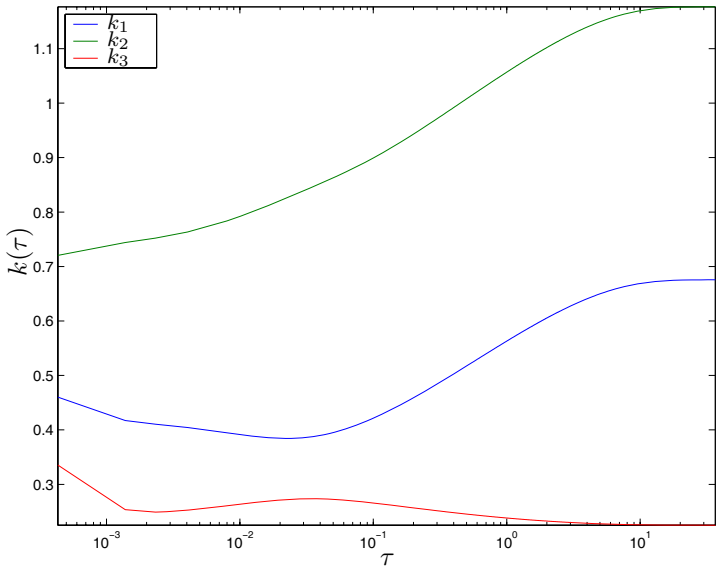

Figure 7: The trajectory $k(\tau)$ recovered from $M = 70$ measurements with 15% multiplicative noise.

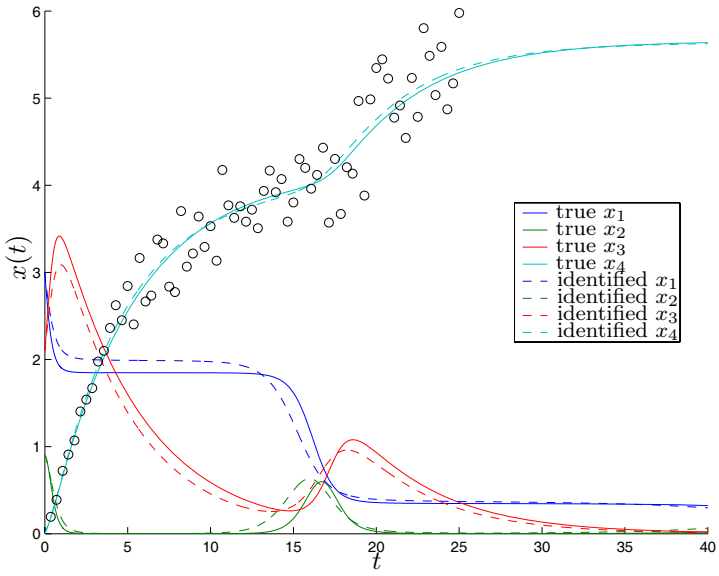

Figure 8: The true model, $M = 70$ measurements with 15% multiplicative noise (circles) and the model identified from them (dashed lines).

the values of parameters for the above examples successfully. If the initial approximations are taken too far away, then the algorithm might converge to other local minimum.

Thus, if the initial approximation is not known precisely, the well-known methods for the global minimization have to be used. Note that the global minimization method usually uses repeated local minimizations. It is advisable to use the proposed algorithm in parallel to perform these local minimizations simultaneously.

References

[1] A.S. Antipin, *Minimization of convex functions on convex sets by means of differential equations*, Differential Equations **30** (1994), no. 9, 1365 – 1375.

[2] P.W. Atkins, *Physical Chemistry*, 6$^{\text{th}}$ ed., W.H. Freeman Company, New York, 1998.

[3] L. K. Babadzanjanz, D. R. Sarkissian, *Step size and error estimates for Taylor series and aggregative Taylor series methods for mildly stiff ordinary differential equations*, Proc. 5th Mississippi State Conference on Differential Equations and Computational Simulations (2001)

[4] N.S. Bakhvalov, N.P. Zhidkov, G.M. Kobelkov, Numerical Methods, Nauka, Moscow, 1987.

[5] J. M. Bower and H. Bolouri, *Computational modeling of genetic and biochemical networks*, The MIT Press, Cambridge, MA, 2001.

[6] A. J. Lotka, *Undamped oscillations derived from the law of mass action*, J. Amer. Chem. Soc. **42** (1920), 1595 – 1599.

[7] J. D. Murray, *Mathematical biology*, Springer-Verlag, Berlin, 1993.

[8] H. G. Othmer, F. R. Adler, M. A. Lewis, and J. C. Dallon, *Case studies in mathematical modeling – ecology, physiology, and cell biology*, Prentice Hall, Upper Saddle River, NJ, 1997.

[9] K. Schittkowski in X. Yang et al. eds., *Progress in Optimization*, Kluwer Academic Publishers, Dordrecht, Boston, 2000, pp. 183 - 204