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Mathematical Biosciences 177&178 (2002) 147–160

Mathematical Biosciences

www.elsevier.com/locate/mbs

Parameter identification in dynamical models of anaerobic waste water treatment

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Received 14 December 2000; received in revised form 29 October 2001; accepted 12 November 2001

Abstract

Biochemical reactions can often be formulated mathematically as ordinary differential equations. In the process of modeling, the main questions that arise are concerned with structural identifiability, parameter estimation and practical identifiability. To clarify these questions and the methods how to solve them, we analyze two different second order models for anaerobic waste water treatment processes using two data sets obtained from different experimental setups. In both experiments only biogas production rate was measured which complicates the analysis considerably. We show that proving structural identifiability of the mathematical models with currently used methods fails. Therefore, we introduce a new, general method based on the asymptotic behavior of the maximum likelihood estimator to show local structural identifiability. For parameter estimation we use the multiple shooting approach which is described. Additionally we show that the Hessian matrix approach to compute confidence intervals fails in our examples while a method based on Monte Carlo Simulation works well.

Keywords: Parameter estimation; Structural identifiability; Practical identifiability; Confidence intervals; Waste water treatment processes

1. Introduction

Anaerobic waste water treatment processes are of interest for two main reasons: the ecological effect, including depollution of higher organic loading, and the energetical effect because the final product is methane. In recent years more and more complex mathematical models of anaerobic

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0025-5564/02/$ - see front matter
PII: S0025-5564(01)00098-0

digestion were introduced involving many biochemical processes. Yet, due to the scarcity of measured data, it is almost impossible to obtain reliable estimates of unknown dynamical parameters. Therefore either simpler, manageable models are needed or data acquisition has to be improved which is difficult especially for microorganisms [1].

In this work we investigate the parameter identification problem in second order models applied to two different experimental settings. These models describe the degradation of volatile fatty acids as the most important step, since it is assumed to be a limiting stage in waste water purification [2].

Many investigations concerning Monod models are available in the literature [2–7], but only for cases where substrate and/or microorganism concentrations are measurable. Yet in many experimental settings only biogas production rate data is available which complicates the parameter identification. Therefore, to make sure that all parameters of the model can be estimated, a structural identifiability analysis has to be carried out. After that, estimation of the parameters using experimental data is necessary which is still a huge problem when only few dynamical variables are observable and a priori information about the parameters and starting values is hardly available. A reliable method to overcome these problems is the multiple shooting technique [8] which we implemented in our investigations. We show that this algorithm is more stable than previously used fitting techniques. Furthermore, we address the problem of practical identifiability [3]. Since we are estimating parameters using measured data sets which are corrupted by observational noise, confidence intervals for the estimates have to be determined. We show that this can be done reliably with a method based on Monte Carlo Simulation (MCS) [9].

The paper is organized as follows: In Section 2 we describe the biochemical background and formulate the mathematical model. In Section 3 we summarize known results about structural identifiability and present a new method to show local structural identifiability. In the next section we deal with the problem of estimating parameters and starting values in non-linear ordinary differential equations (ODE). In this paragraph we describe the multiple shooting method. Section 5 summarizes results about practical identifiability and confidence intervals. In Sections 6 and 7 we present results and conclusions from the two experimental setups we have analyzed.

2. Experiments and modeling of waste water treatment processes

In this study, we used two experimental data sets. The first data set and the experimental methods used to obtain this data have been published previously [10]. The second data set is described in [11]. Here we briefly describe the experimental conditions: all experiments were conducted in a 5l automated-stirred fermenter. The working volume of the reactor was 2l. During all processes, the digester was maintained at a temperature of 34.0 ± 0.5 °C, that is, the processes were mesophilic. The monitoring of the methane reactor was conducted by a dedicated data acquisition system of on-line sensors, which provide measurements of pH, temperature, rH and biogas flow rate.

The complexity of mathematical models of anaerobic digestion processes is evident from the stoichiometry described in [12,13]. A complete mathematical treatment of the process would require the simultaneous solution of the mass balance equations for each individual substrate and bacterial population along with the interphase mass transfer between the slurry and the gas phases. Clearly, such a treatment is extremely complex, yielding equations with numerous parameters. Therefore, simpler treatments have been developed to predict the steady state and

dynamic behavior of digesters [4]. In our work we use simpler second order models and two different experimental data sets for batch processes from dairy farming waste waters. While for the first experiment a simple Monod model without decay coefficient ($b = 0$) is sufficient, the model for the second experiment is more complex due to the observed substrate inhibition during the process. We chose the non-competitive inhibition equation including the decay of methanogenic bacteria.

The dynamical behavior of the system is described by

$$\begin{aligned} \dot{X} &= (\mu(S) - b)X, \\ \dot{S} &= -k_1\mu(S)X, \end{aligned} \tag{1}$$

with observation

$$y = k_2\mu(S)X$$

and where either

$$\mu(S) = \frac{\mu_m S}{(k_s + S)} \quad \text{(first model)}$$

or

$$\mu(S) = \frac{\mu_m S}{(k_s + S(1 + k_s/k_i) + S^2/k_i)} \quad \text{(second model)}.$$

Here S is the concentration of volatile fatty acids (mg/l), X is the concentration of total bacteria (mg/l), y is the biogas production rate (l/day), $\mu(S)$ is the specific growth rate of bacteria as a function of S (1/day), k_1^{-1} is the yield coefficient for bacteria (mg organism/mg total biodegradable organics), k_2 is the yield coefficient with respect to gaseous output (l^2/mg), b is the decay coefficient for bacteria (1/day), k_s is the saturation constant for bacteria (mg/l), μ_m is the maximum specific growth rate for the bacteria (1/day), k_i is the inhibition coefficient for the bacteria (mg/l).

In both models we assume the parameters μ_m and k_2 as known from previous investigations [10]. In this work μ_m was obtained under the assumption of no substrate inhibition so that it is possible to use this value in both of our models. In addition, the starting value $S(0)$ is known from direct measurement. With help of a literature review [11] we are able to obtain boundary values for all parameters and to use constrained optimization in our estimation.

3. Structural and local structural identifiability

There are several methods to show structural identifiability for a given ordinary differential equation (ODE) model [14]. To analyze our models we first transformed them to simpler forms, see Appendix A. After that we used the Taylor series expansion [15], implemented in MATHEMATICA, and the method of characteristic sets by Ritt [16] and Wu [17], implemented in MAPLE [18], to investigate structural identifiability.

The idea of the Taylor series approach [15] is that the observed output $y(t)$ and its successive time derivatives can be evaluated in terms of the dynamic parameters p and variables z at time t_0, usually $t_0 = 0$, using the observation equation, that is,

$$y(t) = g(z(t), p) = \sum_{k=0}^{\infty} g^{(k)}(z(t_0), p) \frac{(t - t_0)^k}{k!},$$

where

$$g^{(k)}(z(t), p) = \frac{\mathrm{d}^k g}{\mathrm{d}t^k}(z(t), p).$$

By calculating higher order derivatives, the problem reduces to determining the number of solutions for the parameters in a set of algebraic equations, since the coefficients in the Taylor series expansion are unique:

$$y^{(k)}(t_0) = g^{(k)}(z(t_0), p) \quad k = 0, 1, 2, \ldots \tag{2}$$

In general, Eqs. (2) are non-linear in the parameters. By definition the parameter set is globally structurally identifiable if there is a unique solution [3,15].

The method of characteristic sets, the Wu–Ritt method, aims at proving structural identifiability using differential-algebraic theory. As shown in [19], see also [16,17], a parameter θ is structurally identifiable if there exist functions Φ and Ψ, with Ψ of full rank, so that

$$\Phi(y, \dot{y}, \ddot{y}, \ldots, p) + \theta \Psi(y, \dot{y}, \ddot{y}, \ldots, p) = 0, \tag{3}$$

where p is a set of known parameters which do not have to be estimated and y is the observed variable. In principle, this method tries to simplify the original set of differential equations by eliminating unobserved variables (in our case S and X) and unknown parameters by rearranging the differential equations to get an equation of type (3).

Both the Taylor series approach and the Wu–Ritt method are working well for relatively simple models. As shown in [18–20], in more complex cases these methods can produce complicated and lengthy expressions which are difficult to solve even with the aid of modern symbolic manipulation packages. For example, in a first attempt, we were not able to prove structural identifiability even for the original Monod model using the Taylor series approach. This was the main reason for using the transformed model, presented in Appendix A, where structural identifiability can be shown. Because of these computational problems, we were not able to prove structural identifiability of the transformed inhibition model neither using the Taylor series approach nor with the Wu–Ritt method. For this reason we introduced a new method for investigating local structural identifiability, which we now describe.

Since we use the maximum likelihood approach for estimating parameters and starting values, the estimates $\hat{\theta}$ are asymptotically normally distributed with covariance matrix C_n, depending on the number of data points n, i.e., $\sqrt{n}(\hat{\theta} - \theta_{\text{true}}) \to N(0, C_n)$, $n \to \infty$. Although this is only valid for the limit case, we are able to investigate this situation by simulating many, say N experiments $E^i_{n_j}$, $(i = 1, \ldots, N)$, with a fixed number of data points n_j, using a vanishing noise level and the appropriate known error model from a biochemical expert analysis of the laboratory data thus assuming perfect data without measurement noise. Estimating parameters in all simulated experiments $E^i_{n_j}$ with the multiple shooting method one obtains an approximation of the joint probability distribution of the estimates depending on the number of data points n_j. Increasing the number of data points, $n_1 < n_2 < \cdots < n_k$, one obtains an approximation of the limit behavior of this distribution.

In the case of non-identifiability there exists a functional relationship for at least two parameters and the probability distribution does not follow a normal distribution. For example, if the parameters p_1 and p_2 are related by the functional relationship $p_1 = \alpha p_2$, then the joint probability distribution would be a straight line. In such cases the covariance matrix of the probability distribution does not have full rank and the condition number, the ratio of the largest to the smallest eigenvalue of this matrix tends to infinity. Therefore, local structural identifiability can be verified by investigating the limiting behavior of the condition number of the covariance matrix.

The assumption that the probability distribution of the observational noise $\eta_i(t)$ follows a normal distribution is certainly not always the case. But as long as it is of the exponential family all conclusions remain valid because all correction terms vanish asymptotically [21]. The method is applied first for initial parameter values, and after that for parameter estimates.

4. Parameter estimation in ODE models

The mathematical model of the dynamics of waste water treatment processes can be described generally by a set of non-linear ODEs

$$\dot{\vec{z}} = \vec{f}(\vec{z}, \vec{p}), \quad \vec{z} \in \mathbb{R}^n, \tag{4}$$

depending on a set of parameters $\vec{p} \in \mathbb{R}^p$ and starting values $\vec{z}_0 = \vec{z}(t_0)$. Since in our case we know the starting value $S(0) = \vec{z}_2(t_0)$, only the starting value $X(0) = \vec{z}_1(t_0)$ has to be estimated.

The observed biogas production rate is denoted by $y^D(t_i)$:

$$y^D(t_i) = g(\vec{z}, \vec{p})(t_i) + \eta(t_i),$$

where $g(\vec{z}, \vec{p})(t_i)$ is a known observation function. Observational noise $\eta(t_i)$ is assumed to be normally distributed with zero mean and known variance σ_i^2, known from expert analysis of the laboratory data.

With initial guesses for parameters and starting values of the variables one is able to integrate the ODE, e.g. with special integrators for stiff ODE problems, see [9], and to calculate the time course of the simulated $y^S(t, \vec{p}, \vec{z}_0)$. Our aim is to find the maximum likelihood estimators of $\vec{p}$ and $\vec{z}_0$, which amounts to globally minimizing the objective function

$$\chi^2(\vec{p}, \vec{z}_0) = \sum_{i=1}^{N} \frac{(y^D(t_i) - y^S(t_i, \vec{p}, \vec{z}_0))^2}{\sigma_i^2} \tag{5}$$

with respect to $\vec{p}$ and $\vec{z}_0$, (see [22]).

4.1. The initial value approach

In principle $\chi^2(\vec{p}, \vec{z}_0)$ can easily be minimized using state of the art optimization algorithms. Much has been accomplished in this field of research and many routines are readily available, see [9,23] for an overview.

Given initial guesses for $\vec{p}$ and $\vec{z}_0$, one integrates the ODE, calculates $\chi^2(\vec{p}, \vec{z}_0)$ via Eq. (4) and uses optimization routines to estimate $\vec{p}$ and $\vec{z}_0$. This is the so called initial value approach (IVA). Although this technique can be easily implemented, there exist many examples where the IVA does not work. As shown by [8] there are even examples where the IVA is determined to fail

always, independent of the minimization routine. Additionally $\chi^2(\vec{p},\vec{z}_0)$ will usually have many local minima in which the IVA is bound to run into, see [24].

4.2. The multiple shooting method

Originating from the context of boundary value problems in ODEs, [25], the multiple shooting method has been used as a parameter estimation technique first in [26]. In [27] this approach was analyzed thoroughly and convergence behavior was investigated.

The idea of the multiple shooting method is to subdivide the time interval into many smaller intervals. The parameter vector $\vec{p}$ is fitted simultaneously in each subinterval, while every interval gets different starting values. The advantage of this method is that much more information from the measured dynamics of the system can be used to estimate initial conditions since the trajectory stays close to the data. In contrast, the IVA effectively uses only the first data point to derive initial estimates.

On the other hand the trajectory is now discontinuous since the state variables at the end of a subinterval do not equal the state variables at the beginning of the next subinterval. To make sure that the minimization procedure will yield a continuous trajectory in the end, continuity constraints are imposed on the solution. This transforms the original minimization problem into a minimization problem of much higher dimension with additional constraints. Details of the mathematical and implementational aspects can be found in [8]. Fig. 1 shows the mechanism of the method with simulated data following closely the experimental data which we will analyze later.

5. Practical identifiability and confidence intervals

After fitting parameters $\vec{p}$ and starting values $\vec{z}_0$ to data, it is desirable to obtain some measure of the quality of the estimates which is related to uncertainty analysis [28]. Unfortunately, in nonlinear systems an analytical description of the probability distribution of the parameters exists only in the limit of large number of data points, [22]. In this case, the Hessian at the convergence point $\theta = (\vec{p},\vec{z}_0)$

$$H_{ij} = \frac{\partial^2 \chi^2(\vec{\theta})}{\partial\theta_i \partial\theta_j}$$

is half of the inverse of the covariance matrix $\mathbf{C}$. Then parameters are normally distributed with the 95% confidence interval at $\pm 1.96\sqrt{\mathbf{C}_{jj}}$ for parameter θ_j. As mentioned above, this approach works only in the limit of large number of data points and is normally not feasible with small sample sizes like in our experiments where the number of data points is roughly 50. A different approach to practical identifiability which does not depend on a large number of data points is the sensitivity analysis [3,29–33]. The main problem with this approach is related to the fact that it is difficult to include all information from the graphical analysis of sensitivity functions into quantitative criteria. There are such attempts [32,34], but no clear way to overcome these problems could be established and work in this direction still has to be improved.

In order to solve these problems practically, we use a MCS method, see [9]. The idea of the MCS is that the probability distribution $P(\vec{p},\vec{z}_0)$ at the convergence point does not differ substantially

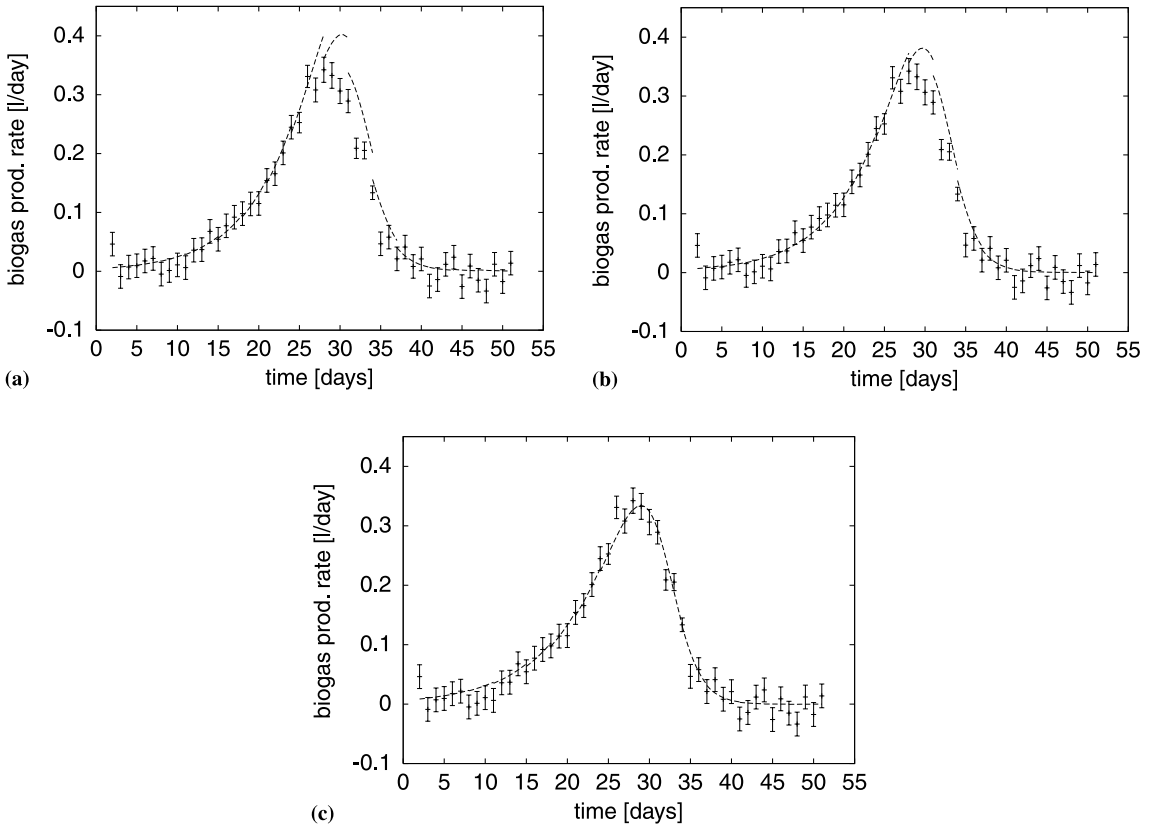

Fig. 1. Convergence of the multiple shooting algorithm applied to simulated data similar to the experimental data: after the initialization of the method the trajectory is discontinuous. After several iterations the fitting procedure leads to a smaller distance to the data while forcing the trajectory to become continuous.

from the probability distribution at the true values, since we assume that our estimate is close to the true parameters. Keeping in mind that we know the variance of the measurement error at every time point, we are able to use our estimate to simulate many data sets closely related to the original data set. By using these simulated data sets to estimate $\vec{p}$ and $\vec{z}_0$ many times, we obtain a probability distribution for the estimates and hence can calculate 95% confidence intervals for all parameters.

In this way data dependent non-identifiability of parameters and starting values of dynamical variables can be detected reliably. Moreover, interdependencies between two or more parameters can be analyzed with help of the estimated joint probability distributions.

6. Results

6.1. Results for the first model

Proving structural identifiability for the simpler model is possible using the Taylor series expansion as well as the Wu–Ritt method, see Appendix A.

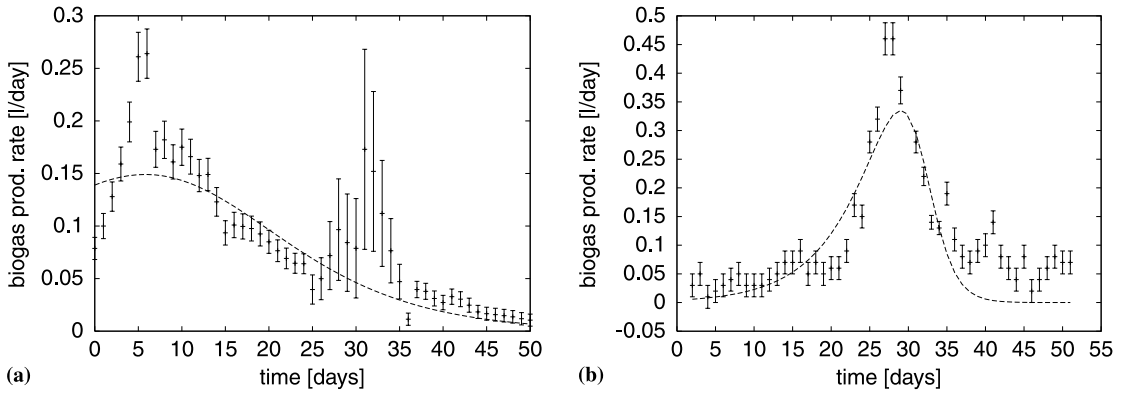

Fig. 2. (a) Best fit of the Monod model to the biogas production rate of data set 1. (b) Best fit of the model with non-competitive inhibition to the biogas production rate of data set 2.

Parameter estimation was done with the multiple shooting method which needed seven iterations to converge at the minimum of $\chi^2 = 103.7$. Fig. 2(a) shows the fitted trajectory for the first model. It turns out that the model is too simple and is not able to describe the dynamics. Table 1 lists all estimates of parameters and starting values and their confidence intervals. Fig. 3 shows examples of the probability distributions of some parameters and starting values determined by a MCS with 200 simulations as explained in Section 5. Every simulation consists of 50 time points as in our experiment and noise with the appropriate error distribution was added. The estimated parameters and starting values of the simulations approximate the true probability distribution. In the limit case we would expect a normal distribution but due to the small number of data points this is not the case. The probability distribution as displayed in Fig. 3(a) is asymmetric and the calculation of confidence intervals with the Hessian matrix would yield inappropriate results. From the joint probability distribution, as displayed in Fig. 3(b), it can be seen that $X(0)$ and k_s of the first model estimated with data set 1 are highly correlated with correlation coefficient $r^2 = 0.98$. This non-identifiability can be also be seen in Table 1, left column. Confidence intervals for both estimates are quite large which means that these parameters are practically non-identifiable.

Table 1
Estimated parameters and starting values and their 95% confidence intervals for both models

	Model 1 with data set 1	Model 2 with data set 2
$S(0)^*$ (mg/l)	3.0	6.0
b^* (1/day)	–	0.004
μ_m^* (1/day)	0.4	0.4
k_2^* (l^2/mg)	75.0	75.0
$\widehat{X}(0)$ (mg/l)	$0.054^{+0.024}_{-0.010}$	$(4.5^{+2.5}_{-1.5})10^{-4}$
$\hat{k}_s$ (mg/l)	$27.6^{+11.1}_{-4.6}$	$4.13^{+0.63}_{-0.52}$
$\hat{k}_i$ (mg/l)	–	$17.2^{+32.1}_{-4.3}$
$\hat{k}_1$	56.2 ± 1.9	102.6 ± 5.1

Confidence intervals were computed with a MCS. Parameters and starting values marked with '$*$' are known from other experiments or from direct measurement.

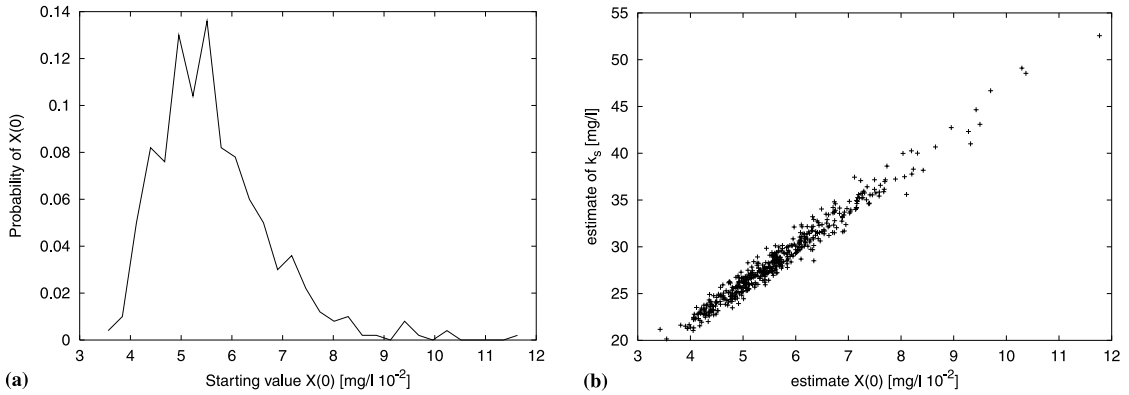

Fig. 3. Sample probability distributions of the fit of model 1 to data set 1: (a) Probability distribution of estimated starting value $X(0)$. (b) Joint probability distribution of estimated starting value $X(0)$ and parameter k_s. Both distributions do not follow a normal distribution.

6.2. Results for the second model

To the best of our knowledge, there is no proof that the parameters k_1, k_s and k_i and the starting value $X(0)$ in the second model are structurally identifiable. Additionally both methods for proving identifiability, Taylor series expansion and the Wu–Ritt approach, fail due to the algorithmic complexity of the problem. Therefore we applied the local structural identifiability test as introduced in Section 3 choosing parameters k_i and b from the literature [13] and taking all other parameters from the first experiment. Fig. 4 shows the condition number and its convergence behavior for increasing number of data points. We find that the condition number decreases for increasing number of data points. If structural non-identifiability would be the case we would

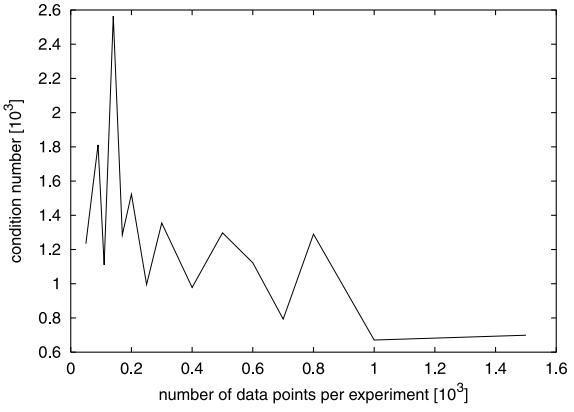

Fig. 4. Behavior of the condition number of the estimated covariance matrix for increasing number of data points. While in the case of non-identifiability the condition number would tend to infinity, in our case the condition number decays.

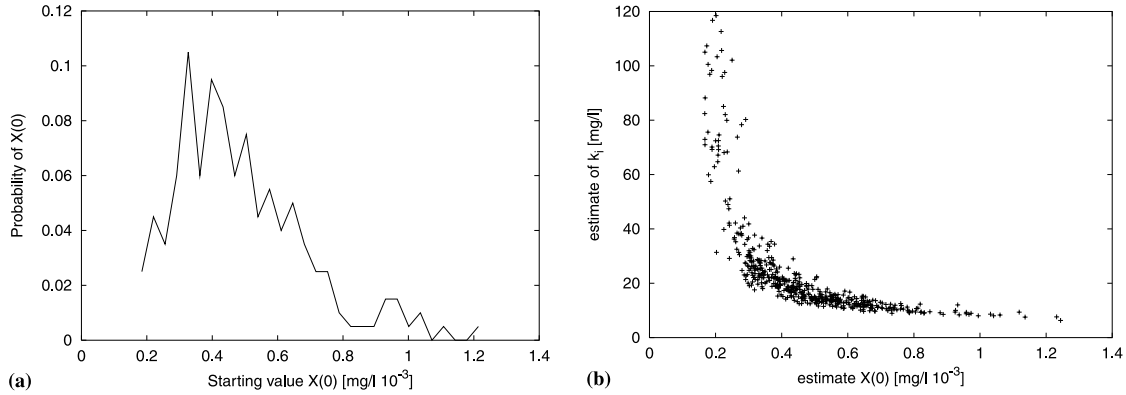

Fig. 5. Sample probability distributions of the fit of model 2 to data set 2: (a) Probability distribution of estimated starting value $X(0)$. (b) Joint probability distribution of estimated starting value $X(0)$ and parameter k_i. Both distributions do not follow a normal distribution.

expect the condition number tend to infinity, with the number of data points having no effect at all.

Therefore we assume local structural identifiability and estimate parameters and starting values as in the first experiment. Local structural identifiability was then also tested for the estimated parameters leading to similar results. The condition number also decreases for increasing number of data points. The fitted trajectory for model 2 with data set 2 is displayed in Fig. 2(b), the estimates with confidence intervals are displayed in Table 1.

In experiment two, as in the first experiment, the probability distributions do not allow the computation of confidence intervals with the Hessian matrix, see Fig. 5. Again we obtain an asymmetric probability distribution for the estimated starting value $X(0)$, see Fig. 5(a). Moreover, parameter k_s and starting value $X(0)$ are highly dependent, this time in a non-linear way. Therefore practical identifiability of these values cannot be established. This can be also seen in Table 1, right column. Parameter k_i and starting value $X(0)$ cannot be estimated reliably and are therefore not practically identifiable; confidence intervals of both are very large.

7. Conclusions

The applicability of dynamical models in waste water treatment processes strongly depends on two types of identifiability: the structural identifiability of parameters inherent in the model structure, and the practical identifiability of parameters depending on the quality of the measured data.

For the first type, many problems are still not solved since currently available methods fail even in simple models due to the algorithmic complexity of the problems. The introduced new method, based on the asymptotic behavior of the maximum likelihood estimator, is able to overcome some of these limitations and is a promising tool to show local structural identifiability for complex problems.

In contrast, practical identifiability relates to the problem of assessing the quality of an estimate in case of noisy data and/or unobserved components, and detecting interdependencies between variables. The new method, based on computing joint probability distributions for estimated parameters and starting values of dynamic variables with help of MCSs, is able to present this information in a convenient way.

Using two mathematical models applied to different experimental situations, we showed the applicability of both methods in a realistic setting. Applying the methods in more complex situations will be an interesting topic of further research.

Acknowledgements

We are grateful to Assoc. Prof. Ivan Simeonov for the opportunity to use the experimental datasets, obtained at the Central Laboratory of Bioinstrumentation and Automation, BAS, Sofia.

N.N. has received financial support from the Graduate School in Computational Biology, Bioinformatics and Biometry (ComBi).

T.G.M. has received financial support from the Graduate School 'Nonlinear Differential Equations' of the Deutsche Forschungsgemeinschaft (DFG).

The research of M.G. is supported by the Academy of Finland.

Appendix A

Starting from the biochemical description of Eq. (1), we apply the following transformation to obtain a simpler representation of the mathematical models:

$$x = k_2 X \qquad s = \frac{k_2}{k_1} S$$
$$\alpha = \frac{k_s k_2}{\mu_{max} k_1} \qquad \beta_1 = \frac{1}{\mu_{max}}$$
$$\gamma = \frac{k_1}{k_2 k_i \mu_{max}} \qquad \beta_2 = \frac{k_i + k_s}{k_i \mu_{max}}$$

We get the following simpler ODEs, on the left for the Monod model, on the right for the more complex model, describing the same dynamical behavior with less parameters:

$$\dot{x} = \frac{s}{\alpha + \beta_1 s} x \qquad \dot{x} = \left(\frac{s}{\alpha + \beta_2 s + \gamma s^2} - b \right) x$$
$$\dot{s} = -\frac{s}{\alpha + \beta_1 s} x \qquad \dot{s} = -\left(\frac{s}{\alpha + \beta_2 s + \gamma s^2} \right) x$$
$$y = \dot{x} \qquad y = \dot{x}$$

Theoretically, all information about $y(t)$ is available which allows us to compute $y'(t) := \int_0^t y(t')\,dt' = \int_0^t \dot{x}(t')\,dt'$. This simplifies the proof of structural identifiability for the simple model due to the new observable $y'(t)$:

$$y'(t) = x(t) - x(0)$$

with

$$\dot{y}'(t) = \dot{x}(t)$$

and with

$$x(0) = \dot{y}'(0)\left(\frac{s(0)}{\alpha + \beta_1 s(0)}\right)^{-1}.$$

A.1. Structural identifiability analysis of the simpler Monod model

Using both Taylor series expansion and the Wu–Ritt method it can be shown that the dynamical parameters k_1 and k_s and the starting value $X(0)$ in the simpler Monod model are structurally identifiable. Here we present the results from the Taylor series expansion approach.

Let $x^{(i)} = \mathrm{d}^i x(0, \mathbf{p})/\mathrm{d}t^i$, then the transformed simpler model takes the form

$$x^{(1)} = \frac{s^{(0)}x^{(0)}}{\alpha + \beta_1 s^{(0)}} \tag{A.1}$$

$$s^{(1)} = -\frac{s^{(0)}x^{(0)}}{\alpha + \beta_1 s^{(0)}} \tag{A.2}$$

$$y^{(0)} = x^{(1)}. \tag{A.3}$$

Using the Taylor series approach, firstly we need to determine the first three derivatives of the model output y:

$$y^{(1)} = x^{(0)}s^{(0)}\left[s^{(0)}(\alpha + \beta_1 s^{(0)}) - \alpha x^{(0)}\right]\left[\alpha + \beta_1 s^{(0)}\right]^{-3} \tag{A.4}$$

$$y^{(2)} = x^{(0)}s^{(0)}\left[s^{(0)^2}(\alpha + \beta_1 s^{(0)})^2 - 4\alpha s^{(0)}x^{(0)}(\alpha + \beta_1 s^{(0)}) + \alpha(\alpha - 2\beta_1 s^{(0)})x^{(0)^2}\right]\left[\alpha + \beta_1 s^{(0)}\right]^{-5} \tag{A.5}$$

$$\begin{aligned} y^{(3)} = x^{(0)}s^{(0)}\Big[&s^{(0)^3}(\alpha + \beta_1 s^{(0)})^3 - 11\alpha s^{(0)^2}x^{(0)}(\alpha + \beta_1 s^{(0)})^2 + \alpha s^{(0)}(11\alpha - 14\beta_1 s^{(0)})(\alpha + \beta_1 s^{(0)})x^{(0)^2} \\ &- \alpha(\alpha^2 - 8\alpha\beta_1 s^{(0)} + 6\beta_1^2 s^{(0)^2})x^{(0)^3}\Big]\left[\alpha + \beta_1 s^{(0)}\right]^{-7}. \end{aligned} \tag{A.6}$$

We then have to solve the system of algebraic equations (14)–(17) with respect to the parameters α, β_1 and starting values $s^{(0)}$ and $x^{(0)}$. The solutions of the system which could be found using MATHEMATICA are

$$\begin{aligned} Ps^{(0)} = y^{(0)^2}\Big[&-6y^{(1)^3} + 7y^{(0)}y^{(1)}y^{(2)} - y^{(0)^2}y^{(3)} \mp \Big(18y^{(1)^6} - 54y^{(0)}y^{(1)^4}y^{(2)} + 55y^{(0)^2}y^{(1)^2}y^{(2)^2} \\ &- 18y^{(0)^3}y^{(2)^3} - 2y^{(0)^3}y^{(1)}y^{(2)}y^{(3)} + y^{(0)^4}y^{(3)^2}\Big)^{1/2}\Big]\Big[3y^{(1)^4} - 2y^{(0)}y^{(1)^2}y^{(2)} \\ &- 3y^{(0)^2}y^{(2)^2} + 2y^{(0)^2}y^{(1)}y^{(3)}\Big]^{-1}, \end{aligned}$$

$$x^{(0)} = y^{(0)^2}\Big[6y^{(1)^3} - 7y^{(0)}y^{(1)}y^{(2)} + y^{(0)^2}y^{(3)} \pm \Big(18y^{(1)^6} - 54y^{(0)}y^{(1)^4}y^{(2)} + 55y^{(0)^2}y^{(1)^2}y^{(2)^2} - 18y^{(0)^3}y^{(2)^3} - 2y^{(0)^3}y^{(1)}y^{(2)}y^{(3)} + y^{(0)^4}y^{(3)^2}\Big)^{1/2}\Big]\Big[3y^{(1)^4} - 2y^{(0)}y^{(1)^2}y^{(2)} - 3y^{(0)^2}y^{(2)^2} + 2y^{(0)^2}y^{(1)}y^{(3)}\Big]^{-1},$$

$$\alpha = 2y^{(0)^3}\Big[9y^{(1)^6} - 30y^{(0)}y^{(1)^4}y^{(2)} + 31y^{(0)^2}y^{(1)^2}y^{(2)^2} - 9y^{(0)^3}y^{(2)^3}3y^{(0)^2}y^{(1)^3}y^{(3)} - 5y^{(0)^3}y^{(1)}y^{(2)}y^{(3)} + y^{(0)^4}y^{(3)^2} + \Big(3y^{(1)^3} - 4y^{(0)}y^{(1)}y^{(2)} + y^{(0)^2}y^{(3)}\Big)\Big(18y^{(1)^6} - 54y^{(0)}y^{(1)^4}y^{(2)} + 55y^{(0)^2}y^{(1)^2}y^{(2)^2} - 18y^{(0)^3}y^{(2)^3} - 2y^{(0)^3}y^{(1)}y^{(2)}y^{(3)} + y^{(0)^4}y^{(3)^2}\Big)^{1/2}\Big]\Big[3y^{(1)^4} - 2y^{(0)}y^{(1)^2}y^{(2)} - 3y^{(0)^2}y^{(2)^2} + 2y^{(0)^2}y^{(1)}y^{(3)}\Big]^{-1},$$

$$\beta_1 = 2y^{(0)}\Big[3y^{(1)^3} - 4y^{(0)}y^{(1)}y^{(2)} + y^{(0)^2}y^{(3)}\Big]\Big[3y^{(1)^4} - 2y^{(0)}y^{(1)^2}y^{(2)} - 3y^{(0)^2}y^{(2)^2} + 2y^{(0)^2}y^{(1)}y^{(3)}\Big]^{-1}.$$

According to the definition of structural identifiability this means that the transformed model is locally structurally identifiable with respect to α, β_1, $s^{(0)}$ and $x^{(0)}$.

If we assume the parameter values μ_m and k_2 and the starting value $S(0)$ in the original Monod model to be known, then using the transformation (A.4) enables us to determine the parameter values k_1 and k_s and the starting value $X(0)$ in the original model. Hence we conclude that the simpler Monod model is locally structurally identifiable with respect to k_1, k_s and $X(0)$.

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