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Parameter estimation in kinetic reaction models using nonlinear observers is facilitated by model extensions

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Abstract: An essential part of mathematical modeling is the accurate and reliable estimation of the model parameters. In biology, the required parameters are particularly difficult to measure because of either shortcomings of the measurement technology or a lack of direct measurements. In both cases, parameters must be estimated from indirect measurements, usually in the form of time-series data. Here, we present a novel approach for parameter estimation that is particularly tailored to biological models consisting of nonlinear ordinary differential equations. By assuming specific types of nonlinearities common in biology, such as generalized mass action, Hill kinetics and products thereof, we can take a three step approach: (1) transform the identification into an observer problem using a suitable model extension that decouples the estimation of non-measured states from the parameters; (2) reconstruct all extended states using nonlinear observers; (3) estimate the parameters using the reconstructed states. The actual estimation of the parameters is based on the intrinsic dependencies of the extended states arising from the definitions of the extended variables, and solved via least squares approximation. An important advantage of the proposed method is that it allows us to identify suitable measurements and/or model structures for which the parameters can be estimated. In addition, the proposed identification approach is generally applicable to models of metabolic networks, signal transduction and gene regulation.

Keywords: parameter estimation, parameter identification, biological systems, biochemical systems, high-gain observers, reduced-order observers, observer Lyapunov function.

1. INTRODUCTION

In order to understand the dynamics and function of biomolecular networks, such as metabolic pathways, signal transduction and gene regulation, mathematical modeling presents an appropriate tool. These models depend crucially on kinetic parameters, whose accurate and reliable estimation still presents a bottleneck. However, recent advances in measurement technologies makes their indirect interference from time series data more and more feasible [Anguelova et al., 2007, Voit and Almeida, 2004].

The dynamics of cell biological processes are often modeled with reaction kinetic systems composed of ordinary differential equations. Thereby, the reaction rates $r$ as well as the measurements $y$ are represented by nonlinear functions that depend on the species concentrations $c$ and kinetic parameters $\rho$

$$\frac{dc}{dt} = Nr(c, \rho), \quad c(0) = c_0 \in \mathbb{R}^{n_c}, \quad y = h(c, \rho) \in \mathbb{R}^p \quad (1)$$

where $N \in \mathbb{R}^{n_r \times n_c}$ denotes the stoichiometric matrix and $c_0$ the initial condition for $t = 0$. The solution of this equation given a certain initial condition $c_0$ and parameter $\rho$ is called the trajectory of the system $c(t, c_0, \rho)$. From a mathematical perspective, measurements taken in an experiment somehow reflects such trajectories, and parameter estimation seeks for parameters that represent the data best based on some optimality criterion. A natural criterion, also used here, is to minimize the error between measured and simulated output $y = h(x(t, x_0, \rho))$. Note that we assume continuous measurement of the output, which can for instance be achieved by interpolation of time-course measurements obtained with sufficiently large resolution.

Often Monte-Carlo based methods, evolutionary strategies or other heuristic methods are utilized. These global methods can not guarantee to find the optimal solution, are computationally expensive and require a multitude of simulation runs that in turn depend on the parameters [Moles et al., 2003]. A method that tries to minimize problematic effects arising from this circular parameter dependence is for example multiple shooting [Peifer and Timmer, 2007]. Despite undoubtedly usefulness, multiple shooting methods do however not resolve the circular dependency. Further, heuristic methods do not allow to address the question of identifiability, which asks whether

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the parameters are theoretically obtainable under the assumptions of noise free measurements and error free model [Audoly et al., 2001]. The optimum is to choose a model structure and set of measurements for which all parameters are identifiable.

Here we present an approach to resolve the circular parameter dependency within the estimation process for kinetics composed of products of generalized mass action and Hill terms. A suitable model extension eliminates the kinetic parameters in the system and establishes a one-to-one correspondence between parameters and states. This decouples the parameter and the state estimation, and further, allows us to address identifiability in terms of observability. The present manuscript is organized as follows. First some results in the field of observability are given. Second, we present the model extension together with the state and parameter estimation methods. In order to provide a proof of concept, we test the method on a model of the circadian rhythm in Neurospora.

2. PRELIMINARIES

Before discussing observability and observers, it is useful to outline some important results in that field. For a detailed discussion of nonlinear observability considering multiple outputs we refer to Birk and Zeitz [1988].

Consider the dynamical system with output $y$

$$\dot{x} = f(x), \quad x(0) = x_0 \in \mathbb{R}^n, \quad y = h(x) \in \mathbb{R}^p. \quad (2)$$

The **observability space** consists of the outputs and Lie-derivatives thereof

$$\mathcal{O} = \{ h_1(x), L_f h_1(x), L_f^2 h_1(x), \ldots, h_p(x), L_f h_p(x), L_f^2 h_p(x), \ldots \}. \quad (3)$$

Note that on a trajectory $x(t)$ Lie derivatives and time derivatives are equivalent $\frac{du}{dt} = L_f h(x(t)) = \frac{dh}{dx} f(x(t))$.

The **observability map** $q : \mathbb{R}^n \mapsto \mathbb{H}^n \subseteq \mathcal{O}$ is a selection of $n$ functions in that space

$$q(x) = \begin{bmatrix} q_1(x) \\ q_2(x) \\ \vdots \\ q_p(x) \end{bmatrix}, \quad q_i(x) = \begin{bmatrix} L^1 f_i(h_1(x)) \\ L^2 f_i(h_2(x)) \\ \vdots \\ \sum_{i=1}^p n_i = n. \quad \Gamma^i f_j h_i(x) \end{bmatrix} \quad (3)$$

If $q$ is smooth and has a continuous inverse ($\hat{z}$ semi-diffeomorphism) it can be used to transform the system (2) with $z = q(x)$ into observer normal form

$$\dot{z} = \hat{f}(z), \quad z(0) = q(x_0), \quad y = \hat{C} z, \quad (4)$$

with

$$\hat{f}(z) = \begin{bmatrix} z_2 \\ \vdots \\ \phi_{n_1}(z) \\ z_{n_1+2} \\ \vdots \\ z_{n_1+n_{p-1}+2} \\ \phi_{n_p}(z) \end{bmatrix} \quad, \quad \hat{C} = \frac{\partial}{\partial z} \begin{bmatrix} z_1 \\ z_{n_1+1} \\ \vdots \\ z_{n_1+n_{p-1}+1} \end{bmatrix}$$

which is structured into $p$ modules consisting of integrator chains summarizing the nonlinearity in $\phi_i(z)$

$$z_{n_1+1} + \ldots + z_{n_1+n_{p-1}+1} = \hat{y}, \quad \hat{z}_j = z_{j+1}, \quad \hat{z}_{n_i} = \phi_i(z).$$

To check whether an observer exists, the system is analyzed for observability:

**Definition 1.** System (2) is **locally observable** iff the observability matrix $Q = \frac{\partial}{\partial z} f(x(t))$ has full rank. It is called **observable** in a region $\mathcal{R} \subset \mathbb{R}^n$ if it is locally observable for all $x \in \mathcal{R}$.

For observer design, often Lipschitz continuity of $\hat{f}$ is postulated, since it guarantees uniqueness of solutions of (4) given a certain initial condition. This can be relaxed, using the following definition.

**Definition 2.** System (2) is **trajectory observable** iff $q$ is a semi-diffeomorphism and (4) exhibits only one solution that generates the same output as (2) [Vargas and Moreno, 2005].

3. METHODS

Generally, the reaction rates in (1) may consist of any nonlinear function. For most biological models however, the kinetics possess a particular form.

**Assumption 3.** The reaction rates can be written as

$$r_i = \hat{r}_i \prod_{j=1}^n c^i_{\nu_j} \prod_{j=1}^n c^{\nu_j}_{\eta_j}, \quad (5)$$

where the parameters are the nominal reaction rates $\hat{r}_i \in \mathbb{R}_+$ and the Hill-constants $K_{i,j} \in \mathbb{R}_{+}$, which describe a regulatory influence of species $j$ on reaction $i$.

**Remark 4.** The orders of the reactions $\nu_{i,j}$ and the Hill exponents $\eta_{i,j}$ are assumed to be known a priori, and are therefore not considered as parameters.

**Remark 5.** The description comprises zero order (constant reaction rates, i.e. $\nu_{i,j} = \eta_{i,j} = 0$), mass-action kinetics ($\nu_{i,j} \in \mathbb{N}_0$ and $\eta_{i,j} = 0$), generalized mass-action ($\nu_{i,j} \in \mathbb{R}_{+}$ and $\eta_{i,j} = 0$), Michaelis-Menten ($\nu_{i,j} = \eta_{i,j} = 1$) as well as activating ($\nu_{i,j} = \eta_{i,j} \in \mathbb{R}_{+}$) and inhibitory Hill kinetics ($\nu_{i,j} = 0, \eta_{i,j} \in \mathbb{R}_{+}$).

Restricting the nonlinearity in the reaction rates as above allows us to reformulate (1) into a more suitable form for addressing the identification problem. By introducing new ordinary differential equations for the reaction rates $\hat{r}_i$ and their denominators $m_{n_{i,j}} = K_{n_{i,j}}^{\nu_{i,j}} + c^{\nu_{i,j}}$, we eliminate the dependency of the system on the parameters. These are now hidden in the initial conditions, and can be obtained by either identifying the correct initial conditions or applying a regression scheme on the extended variables. For the latter case a analytical solution minimizing the least squares criterion can be stated regardless of particular system under consideration. Thus, the problem of parameter estimation is transformed into a problem of state estimation, whereupon appropriate non-linear observers can be used.

The proposed approach can be structured into the following three steps:

1. Transform the model into its extended form.
2. Estimate all (non-measured) states using an appropriate (nonlinear) observer.
The great advantage of this description is that the right-hand-side does not depend on the parameters \( \hat{r}_i \) and \( K_{i,j} \) and that the output is linear (which follows directly from Assumption 7). By defining \( x = [c^T \ \text{vec}(m)^T \ r^T]^T \) (7) is of the form
\[
\frac{d}{dt} x = f(x), \quad x(0) \in \mathcal{M} \subset \mathbb{R}^n, \quad y = C \cdot x \in \mathbb{R}^p.
\]

The somewhat artificial introduction of additional states induces dependencies within the trajectories of the extended model. From (1) follows that the trajectories move on a manifold \( \mathcal{M} \) of dimension \( \leq n_c \), which is then, through the model extension, embedded in a state-space of dimension \( n > n_c \). In Section 3.3 we will make use of the arising dependencies to infer the parameter values.

### 3.2 Observer design

For the reconstruction of all extended variables from time course measurements \( y_i, i = 1, \ldots, p \), a natural tool is provided by nonlinear observers. Assume that the system is trajectory observable and that we can transform it into observability normal form with \( \bar{f}(z) = (Q \cdot f) \circ q^{-1}(z) \).

\[
\frac{d}{dt} \bar{z} = \bar{f}(\bar{z}), \quad \bar{z}(0) = \varphi(x_0) \in \mathcal{H}^n, \quad y = C \cdot z \in \mathbb{R}^p. \tag{8}
\]

**Definition 11.** A high gain observer with the gain parameter \( \theta \in \mathbb{R}^p \) in observer normal coordinates is of the form
\[
\frac{d}{dt} \bar{z} = \bar{f}(\bar{z}) + L(\theta) \cdot [y - C\bar{z}]. \tag{9}
\]

It consists of a simulation term \( \bar{f} \) (a copy of the system) and a correction term \( L(\theta) \) that feedbacks the error of measured \( y \) and estimated output \( \hat{y} = C\bar{z} \) and depends on a high gain-parameter \( \theta \).

Some observers involve a state dependent correction term \( L(x) \), whose design requires extensive symbolic manipulations that might not be feasible for large nonlinear systems [Birk and Zeit, 1988]. Here, for simplicity, the correction term \( L \) is designed independently of the actual states of the system taking a Lyapunov based approach [Gauthier et al., 1992]. Global convergence can be guaranteed if \( f \) is Lipschitz, whereby the Lipschitz constant can be interpreted as the maximal slope of \( f \) according to which the minimal observer gain has to be chosen. In the following, we extend the method for systems with multiple outputs \( y_k, k = 1, \ldots, p \).

The observer gain matrix \( L \) is obtained by solving for each of the outputs \( y_k \) the Lyapunov equations

\[
0 = \Theta_0 S_{\infty, k} - S_{\infty, k} A_k - A_k^T S_{\infty, k} + C_{T,k}^T C_k,
\]

where \( S_{\infty, k} \in \mathbb{R}^n, A_k \in \mathbb{R}^{n \times n_k} \) with \( A_{i,j} = \delta_{i,j-1}^1 \), \( C_k^T \in \mathbb{R}^{n_k} \) with \( C_k = \delta_{1,k} \) and \( n_k \) denotes the highest derivative of \( y_k \) present in the observability map. The matrix \( L \in \mathbb{R}^{n \times p} \) is then calculated with the block-diagonal matrix of all inverse solutions

\[
L = \text{diag}(S_{\infty, k}^{-1}) \cdot C_{T}, \quad C_{T} \in \mathbb{R}^{n \times p}, \quad C_{T,k}^T = \delta_{k,n_k}.
\]

Some additional calculation is necessary to obtain the observed states in the original (physically meaningful) coordinates. There are basically two possibilities:

1. Transform the differential equations of the observer back into original coordinates using the inverse of the observability matrix \( Q^T = Q^{-1} \). Then the observer is a system of ordinary differential equations (proof see Appendix)

\[
\frac{d}{dt} \hat{z} = f(x) + Q^{-1}(x) \cdot L \cdot [y - h(x)]. \tag{10}
\]

\[1 \text{ Here } \delta \text{ denotes the Kronecker symbol with } \delta_{i,j} = \begin{cases} 1 & \text{if } i = j \\ 0 & \text{if } i \neq j \end{cases}. \]
\(\lambda\) eigenvalue of \(Q\). During an event, the determinant of (10) becomes very large. To resolve this whereby 
\[ \delta > L, \] 
\(\delta\) must be large enough to be significant for the observer (see Vargas and Moreno [2005] for a detailed discussion).

Definition 16. The least squares cost functions are
\[ \Theta_m = \sum_{k=1}^{n_t} (r_m(t_k))^2, \quad \Theta_r = \sum_{k=1}^{n_t} (r_r(t_k))^2. \] (13)

Theorem 18. An optimal estimate for the parameters minimizing the cost functions (13) is
\[ K_{i,j} = \frac{1}{n_t} \sum_{k=1}^{n_t} (m_{i,j}(t_k) - c_{i,j}(t_k))^2. \] (14)
\[ \hat{r}_i = \frac{\sum_{k=1}^{n_t} r_i(t_k) \chi(k)}{\sum_{k=1}^{n_t} \chi(k)}, \quad \chi(k) = \prod_{j=1}^{n_t} m_{i,j}(t_k)^{\nu_{i,j}}. \] (15)

Proof. We start with the sum of squared errors of the reaction rates
\[ \Phi_r = \frac{1}{n_t} \sum_{k=1}^{n_t} (r_i(t_k) - \hat{r}_i \sum_{j=1}^{n_t} m_{i,j}(t_k)^{\nu_{i,j}})^2. \]
For the sake of simplicity, set \(\chi(t_k) = \prod_{j=1}^{n_t} m_{i,j}(t_k)^{\nu_{i,j}}\), and expand the square
\[ \Phi_r = \frac{1}{n_t} \sum_{k=1}^{n_t} \left( r_i(t_k) - r_i \hat{r}_i \sum_{j=1}^{n_t} m_{i,j}(t_k)^{\nu_{i,j}} + \frac{\hat{r}_i^2}{n_t} \chi(t_k)^2 \right). \]
Then the minimum is obtained by setting the partial derivative \(\frac{\partial \Phi_r}{\partial \hat{r}_i}\) equal to zero
\[ 0 = \frac{1}{n_t} \sum_{k=1}^{n_t} r_i(t_k) \chi(t_k) - \frac{\hat{r}_i^2}{n_t} \sum_{k=1}^{n_t} \chi(t_k) \sum_{k=1}^{n_t} r_i(t_k) \chi(t_k). \]
Simple manipulation solves this for \(\hat{r}_i\), resulting in (15).

A similar procedure for the sum of squares error of the Hill variables resulting in (14) is
\[ \frac{1}{n_t} \sum_{k=1}^{n_t} m_{i,j}(t_k)^{2} - 2m_{i,j}(t_k) \left( K_{i,j}^{\nu_{i,j}} - c_{i,j}(t_k)^{\nu_{i,j}} \right) + \left( K_{i,j}^{\nu_{i,j}} + c_{i,j}(t_k)^{\nu_{i,j}} \right)^2 \]
\[ = \min. \]
Now we set the partial derivative to zero and solve for \(K_{i,j}\)
\[ \frac{1}{n_t} \sum_{k=1}^{n_t} \left( -2m_{i,j}(t_k) + 2K_{i,j}^{\nu_{i,j}} + C_{i,j}(t_k)^{\nu_{i,j}} \right) = 0 \]
\[ K_{i,j}^{\nu_{i,j}} + \sum_{k=1}^{n_t} \left( -m_{i,j}(t_k) + c_{i,j}(t_k)^{\nu_{i,j}} \right) = 0 \]
\[ K_{i,j}^{\nu_{i,j}} = \sum_{k=1}^{n_t} m_{i,j}(t_k) - c_{i,j}(t_k)^{\nu_{i,j}}. \] □

4. EXAMPLE

In order to provide a proof of concept for our approach, it is tested on the circadian clock of neurospora modeled by a nonlinear feedback loop in the gene expression of the so called frequency protein (FRQ) [Leloup et al., 1999].
that the species concentrations as well as the transcription for simplicity of the design, we assume in the following errors. An invertible observer design simple, and second to minimize numerical combinations of chosen output derivatives, to analyze and dominant tells us that local observability is lost if

\[ r_2 = r_2' \lor r_3 = r_5 \lor r_1 + r_2' = r_2 + r_4 \lor F_c(r_2 - r_2') = F_n(r_1 + r_2' - r_2 - r_4), \]

and \( q^{-1} \) is non-Lipschitz (see Appendix), but continuous under the image of \( q \) since \( q \circ q^{-1} = id \).

Both observer structures, (10) and (11), were implemented. The limit for the condition number of Observer (10) is chosen to \( \delta = 10^{-4} \).

In a simulation study with the originally published parameters and the corresponding initial conditions for the extended system, the observers are initialized with \( \tilde{x}_i(0) = 2x_i(0) \) for all non-measured variables \( i = 4, \ldots, 9 \). For the given initial condition, the event based observer fails (Figure 1a), whereas the \( \epsilon \)-approximative observer (15) converges (Figure 1b). There are periods where observer error increases due to the reduced observability properties of the system (Figure 1.3). Calculation of the parameters using the state estimates of (15) for \( t > 10 \) h to ensure convergence of the observer, does not exhibit errors > 0.5\% (Table 4), proving the applicability of the method. Note that biological measurements usually exhibit errors about one order of magnitude larger or worse.

5. CONCLUSIONS

This paper proposes a novel method for kinetic parameter estimation that is particularly tailored to biological models consisting of ordinary differential equations. Basically, the potential of the presented method lies in the model extension, which establishes a one-to-one correspondence between parameters and states. Therewith, the main task of the method becomes to reconstruct the extended trajectory from the measurements. Here, we used Lyapunov based observers, however, since biological data is usually discrete and noisy, other techniques might be useful, such as Kalman filters or hybrid observers composed of a continuous simulation part \( f(x) \) updated at discrete timestamps. The inherent dependencies of the observed trajectory given by the definition of the extended states allows us to solve a least squares criterion for the parameters. Note that estimation of the parameters could in principle also be achieved by identifying the true initial conditions of the observer, which is however a hard problem. In addition, the benefits that might arise from the extended system being parameter independent are not yet fully explored.

REFERENCES


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Table 1. Selection of the observability analysis of the neurospora model, each row corresponds to one particular construction of \( q \) with the entries being the \( n_i - 1 \) in Equation 3. Observability is given if \( Q = \frac{\partial q}{\partial x} \) has full rank = 12.

For simplicity of the design, we assume in the following that the species concentrations as well as the transcription and degradation rates are measured [Shu and Hong-Hui, 2004]. (Note however, that the system is also observable if only the concentrations are measured \( y = [M F_c F_n] \).

\[
y = [M F_c F_n r_3 r_4 r_5]^T.
\]

We explored different constructions of \( q \), i.e. different combinations of chosen output derivatives, to analyze observability (Table 1). Thereby it is advisable to limit the order of that derivatives for two reasons. First, to keep the observer design simple, and second to minimize numerical errors. An invertible \( Q = \frac{\partial q}{\partial x} \in \mathbb{R}^{n \times n} \) is for example obtained using (Table 1 row 1)

\[
q = [M F_c \dot{F}_c F_n \dot{F}_n F_n r_3 r_4 r_5 r_3 r_4 r_5 r_3 r_4]^T.\]

However, there are singular points. Looking at the determinant tells us that local observability is lost if

\[
r_2 = r_2' \lor r_3 = r_5 \lor r_1 + r_2' = r_2 + r_4 \lor F_c(r_2 - r_2') = F_n(r_1 + r_2' - r_2 - r_4),
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REFERENCES


\[
\begin{align*}
\text{Max. rates} & : k_1_k_2_ v_1_v_2_v_3_v_4_v_5_v_6_v_7_v_8_v_9_v_{10} \\
\text{Obs. (11)} & : 0.5000 0.5000 0.6000 0.4000 1.0000 0.5000 \\
\text{Hill const.} & : K_1 K_2 K_3 K_4 K_5 \\
\text{Obs. (11)} & : 0.4999 0.4988 0.5985 0.4994 1.4004 0.5045
\end{align*}
\]

Table 2. True and estimated parameter values.

Units are \( k_i \) (h\(^{-1}\)), \( v_i \) (nm\(^{-1}\)), \( K_i \) (nm).

Appendix A. (BACK-)TRANSFORMATION FROM THE OBSERVER INTO ORIGINAL COORDINATES

Consider a continuous observer in observer normal form [Birk and Zeitz, 1988]

\[
\frac{d}{dt} \tilde{z} = f(\tilde{z}) + L(y - \tilde{y}),
\]

with a constant gain matrix L. We transform back into original coordinates by differentiating \( \hat{x} = q^{-1}(\tilde{z}) \).

\[
\frac{d}{dt} \hat{x} = \frac{dq}{d\tilde{z}} \frac{d\tilde{z}}{dt} = \left[ Q^{-1}(\tilde{z})g(\hat{z}) + Q^{-1}(\tilde{z})L(y - \tilde{y}) \right] \tilde{z} = q(\tilde{z}).
\]

Remind that \( f = Q^{-1}g \circ q \), wherewith follows

\[
\frac{d}{dt} \hat{x} = f(\hat{x}) + Q^{-1}(\hat{x})L(y - \tilde{y}).
\]

Appendix B. INVERSE OBSERVABILITY MAP OF THE NEUROPORA MODEL

\[
q^{-1} = \begin{bmatrix}
    z_1 \\
    z_4 \\
    z_2 \\
    -2z_7 z_4 z_5 / z_8 \\
    -z_9 z_2 z_3 / (z_10 z_2 - z_9 z_3) \\
    z_11 z_1 (z_11 - z_7) / (z_11 z_1 + z_11 + z_12 z_1) \\
    z_5 + z_9 + z_3 \\
    -z_4 (-z_5 z_3 + z_6 z_2) / (-z_4 z_3 + z_2 z_5) \\
    -z_2 (z_6 z_4 - z_5) / (-z_4 z_3 + z_2 z_5) \\
    z_7 \\
    z_9 \\
    z_{11}
\end{bmatrix}
\]