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

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Abstract: An essential part of mathematical modelling is the accurate and reliable estimation of model parameters. In biology, the required parameters are particularly difficult to measure due to 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, resulting from generalised 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 suitable 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. An important advantage of the proposed method is that it allows to identify suitable measurements and/or model structures for which the parameters can be estimated. Furthermore, 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, observability, 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 networks, mathematical modelling and analysis presents an appropriate tool. The derived models depend crucially on kinetic parameters, whose accurate and reliable estimation still presents a bottleneck. However, recent advances in measurement technologies make 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 modelled by systems of biochemical reactions composed of ordinary differential equations:

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

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 ρ. Here $N \in \mathbb{R}^{n_c \times n_r}$ denotes the stoichiometric matrix and c_0 the initial condition for $t = 0$.

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The aim of parameter estimation seeks to determine the parameters ρ from experimental data. Naturally cell biological models (1) are nonlinear, which is why optimal parameter estimation often uses Monte-Carlo based methods, evolutionary strategies or other heuristic methods. These optimisation methods all share a common problem: The simulations necessary for parameter estimation depend on the parameters, thus creating a circular parameter dependency. As a consequence, these global search methods can not guarantee to find the optimal solution and are computationally expensive (Moles *et al.*, 2003). A method reducing the computational load is for example multiple shooting (Peifer and Timmer, 2007). Despite undoubted usefulness, multiple shooting methods do however not resolve the circular dependency. Further, heuristic methods do not address the question of identifiability, which asks whether the parameters are theoretically obtainable under the assumptions of noise free measurements and error free model (Audoly *et al.*, 2001).

Here we present an approach to resolve the circular parameter dependency within the estimation process for kinetics composed of products of generalised 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 extended states.

This decouples the parameter and the state estimation, and further, allows us to address identifiability in terms of observability. The method assumes continuous measurements, which can be achieved by interpolation of time course data obtained with sufficiently fine resolution.

The present manuscript is organised as follows. Section 2 presents the parameter estimation method in three steps, and Section 3 provides a proof of concept, by testing the method on a simplified model of the circadian rhythm in *Neurospora*. Finally Section 4 gives the conclusions and points to non-resolved issues.

2. METHODS

Generally, the reaction rates in (1) may consist of any nonlinear function. For most biochemical reactions however, the kinetics possess a particular form. We assume:

Assumption 1. The reaction rates can be written as

$$r_i = \hat{r}_i \prod_{j=1}^{n_c} \frac{c_j^{\nu_{i,j}}}{K_{i,j}^{\eta_{i,j}} + c_j^{\eta_{i,j}}}, \tag{2}$$

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

Remark 3. 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 $\eta_{i,j} = 0$), generalised mass-action ($\nu_{i,j} \in \mathbb{R}_+$ and $\eta_{i,j} = 0$), Michelis-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 to (2) 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 r_i and their denominators $m_{i,j} = K_{i,j}^{\eta_{i,j}} + c_j^{\eta_{i,j}}$, 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 by solving the definitions of the extended variables for the parameters. 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, parameter independent form.
2) Estimate all (non-measured) states using an appropriate (nonlinear) observer.
3) Calculate the parameters from the extended state estimate.

In the following, details concerning each one of the steps are presented.

2.1 Model extension

A crucial part of the proposed method is to reformulate the system in a parameter independent form by introducing new state variables (Farina *et al.*, 2006).

Assumption 4. The concentrations c_i and the parameters $\hat{r}_i$ and $K_{i,j}$ are strictly positive.

Theorem 5. Under Assumption 4 the reaction kinetic model (1) and (2) is equivalent to the parameter independent system

$$\frac{d}{dt} c_i = \sum_{k=1}^{n_r} N_{i,k} r_k, \tag{3a}$$

$$\frac{d}{dt} m_{i,j} = \eta_{i,j} c_j^{\eta_{i,j}-1} \sum_{k=1}^{n_r} N_{j,k} r_k, \tag{3b}$$

$$\frac{d}{dt} r_i = r_i \sum_{j=1}^{n_c} \left(\left(\nu_{i,j} \frac{1}{c_j} - \frac{\eta_{i,j} c_j^{\eta_{i,j}-1}}{m_{i,j}} \right) \sum_{k=1}^{n_r} N_{j,k} r_k \right), \tag{3c}$$

where $m_{i,j}$ is the *Hill variable*

$$m_{i,j} = K_{i,j}^{\eta_{i,j}} + c_j^{\eta_{i,j}}, \tag{4}$$

which is defined for all nonzero $\eta_{i,j}$.

Proof.

a) Equation (3a) follows directly from (1).
b) The dynamic description of m is obtained by differentiation along the trajectory of (1) and using (3a)
$$\frac{d}{dt} m_{i,j} = \eta_{i,j} c_j^{\eta_{i,j}-1} \dot{c}_j = \eta_{i,j} c_j^{\eta_{i,j}-1} \sum_{k=1}^{n_r} N_{i,k} r_k.$$
c) We multiply both sides of (2) with the denominator and take the logarithm
$$\sum\nolimits_{j=1}^{n_c} \log\left(K_{i,j}^{\eta_{i,j}} + c_j^{\eta_{i,j}}\right) + \log\left(r_i\right) = \log\left(\hat{r}_i\right) + \sum\nolimits_{j=1}^{n_c} \nu_{i,j} \log\left(c_j\right).$$
Again taking the time derivative and using (4) yields
$$\sum_{j=1}^{n_c} \frac{\dot{m}_{i,j}}{m_{i,j}} + \frac{\dot{r}_i}{r_i} = \sum_{j=1}^{n_c} \nu_{i,j} \frac{\dot{c}_j}{c_j}.$$
Rearranging yields the differential equations for the reaction rates
$$\dot{r}_i = r_i \left(\sum_{j=1}^{n_c} \nu_{i,j} \frac{\dot{c}_j}{c_j} - \sum_{j=1}^{n_c} \frac{\dot{m}_{i,j}}{m_{i,j}} \right).$$
Substituting $\dot{c}_j$ and $\dot{m}_{i,j}$ using (3a) and (3b) respectively yields in (3c). □

The advantage of the description (3) is that the right-hand-side does not depend on the parameters $\hat{r}_i$ and $K_{i,j}$.

Further, in the context of intracellular signalling and gene regulation, measurements usually concern protein and mRNA levels, i.e. species concentrations, whereas for metabolic pathways usually fluxes are measured (Costenoble *et al.*, 2007). Therefore, we require the following assumption.

Assumption 6. Measurements consist of linear combinations of species concentrations and/or reaction rates.

Using Assumption 6, the extended system (3) is not only parameter independent, but also linear in the output. By defining $x = [c^T \ \mathrm{vec}(m)^T \ r^T]^T$, the extended system is of the form

$$\frac{d}{dt}x = f(x), \quad x(0) = x_0 \in \mathbb{R}^n, \quad y = h(x) = \bar{C}x, \quad (5)$$

where the parameters $\rho = [\hat{r}^T \ \mathrm{vec}(K)^T]^T$ are hidden in the initial condition $x_0 = [c_0^T \ \mathrm{vec}(m(c_0, \rho))^T \ r(c_0, \rho)^T)]^T$.

The somewhat artificial introduction of additional states similar to Farina *et al.* (2006) induces dependencies between the extended states. From (1) follows that the trajectories lie on a manifold $\mathcal{M}$ of dimension smaller or equal to n_c. The model extension describes the system in a higher dimensional state-space of dimension $n > n_c$, inducing $n - n_c$ dependencies within the extended trajectory. Section 2.3 uses these dependencies to infer the parameter values. First however, the extended state trajectory must be reconstructed from the output measurement.

2.2 Observer design

For the reconstruction of all extended variables from time course measurements y_i, $i = 1, \cdots, p$, nonlinear observers provide a natural tool. Particularly suited for observer design is the observability canonical form, based on the observability map

$$q(x) = \begin{bmatrix} q_1(x) \\ q_2(x) \\ \vdots \\ q_p(x) \end{bmatrix}, \quad q_i(x) = \begin{bmatrix} \mathrm{L}_f^0 h_i(x) \\ \mathrm{L}_f^1 h_i(x) \\ \vdots \\ \mathrm{L}_f^{n_i-1} h_i(x) \end{bmatrix}, \quad \sum_{i=1}^{p} n_i = n. \quad (6)$$

Assuming that the observability map of the extended system is smooth with a continuous inverse, $z = q(x)$ transforms the extended system into observability canonical form (Xia and Zeitz, 1997)

$$\frac{d}{dt}z = Az + B\phi(z), \quad z(0) = q(x_0), \quad y = Cz \in \mathbb{R}^p, \quad (7)$$

where

$$A = \begin{bmatrix} A_1 & & \\ & \ddots & \\ & & A_p \end{bmatrix} \text{ with } A_i = \begin{bmatrix} 0 & 1 & \\ & \ddots & 1 \\ & & 0 \end{bmatrix} \in \mathbb{R}^{n_i \times n_i},$$

$$B = \begin{bmatrix} B_1 & & \\ & \ddots & \\ & & B_p \end{bmatrix} \text{ with } B_i = \begin{bmatrix} 0 \\ \vdots \\ 1 \end{bmatrix} \in \mathbb{R}^{n_i},$$

$$C = \begin{bmatrix} C_1 & & \\ & \ddots & \\ & & C_p \end{bmatrix} \text{ with } C_i = \begin{bmatrix} 0 & \cdots & 1 \end{bmatrix} \in \mathbb{R}^{n_i},$$

which is structured into p modules corresponding to each output component. The characteristic nonlinearity $\phi(\cdot)\left[\phi_1(\cdot), \cdots, \phi_p(\cdot)\right]$ captures all the nonlinearities of the system.

We consider Luenberger observers of the form

$$\frac{d}{dt}\tilde{z} = A\tilde{z} + B\phi(\tilde{z}) + L(\theta) \cdot [y - C\tilde{z}], \quad (8)$$

consisting of a simulation term $A\tilde{z} + B\phi(\tilde{z})$ (a copy of the system) and a correction term that feeds back the error of measured y and estimated output $\tilde{y} = C\tilde{z}$ through the gain matrix $L \in \mathbb{R}^{n \times p}$, which depends on a gain-parameter θ used to tune the convergence of the observer (Gauthier *et al.*, 1992). In order to ensure that such an observer exists, trajectory observability is required.

Preliminary 7. The extended system is *trajectory observable*, i.e. q is smooth with a continuous inverse, and the system in observability coordinates (7) has only one solution exhibiting the same output trajectory as the system in physical coordinates (5).

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 $\phi(\cdot)$ is Lipschitz, whereby the Lipschitz constant can be interpreted as the maximal slope of $\phi(\cdot)$ according to which the minimal observer gain has to be chosen. Because the observability canonical form consists of p semi-independent modules only coupled through the characteristic nonlinearity, the observer gain matrix L can be calculated independently for each module, by solving for each output y_i, $i = 1, \cdots, p$ the Lyapunov equation

$$0 = -\theta S_{\infty,i} - S_{\infty,i}A_i - A_i^T S_{\infty,i} + C_i^T C_i.$$

The gain matrix $L(\theta)$ is then calculated with the block-diagonal matrix of all inverse solutions

$$L(\theta) = \begin{bmatrix} S_{\infty,1}^{-1} & & \\ & \ddots & \\ & & S_{\infty,p}^{-1} \end{bmatrix} \cdot C^T.$$

Some additional calculations are 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 $Q = \frac{\partial q}{\partial x}$, Vargas *et al.* (2003). Then the observer is given by
$$\frac{d}{dt}\tilde{x} = f(x) + Q^{-1}(x) \cdot L(\theta) \cdot [y - h(x)]. \quad (9)$$
The proof is presented in the Appendix.
2) Transform the observed trajectory back into original coordinates. Then the observer consists of a dynamic part in observability canonical form and an algebraic part (Vargas and Moreno, 2005)
$$\frac{d}{dt}\tilde{z} = A\tilde{z} + B(\tilde{z}) + L(\theta) \cdot [y - C\tilde{z}], \quad (10)$$
$$\tilde{x} = q^{-1}(\tilde{z}).$$

Remark 8. The calculation of the characteristic nonlinearity ϕ and the inverse observability matrix q^{-1} involves symbolic manipulation and might be infeasible for large nonlinear systems. Considering the computational effort, the first observer strategy seems advantageous, since only the inverse of the observability matrix Q^{-1} must be calculated, which can even be done point-wise.

Usually, local observability, i.e. $\det(Q) \neq 0$, everywhere on the manifold is a prerequisite for designing the above observers. If some points on the trajectory are not locally

observable, the observers may fail, because Q^{-1} does not exist, and $\phi(\cdot)$ may not be Lipschitz. However, if the system is trajectory observable, (10) is an approximative observer converging into an ϵ-band around the true trajectory (Vargas and Moreno, 2005).

Clearly, the observer (9) fails in the case of a local loss of observability. However, Vargas *et al.* (2003) propose modifications to resolve this issue. Consider an event as the set of time points along a trajectory where the inversion of Q is numerically ill conditioned:

$$T_{\text{Event}} = \{t \in \mathbb{R} : \quad \left|\frac{\lambda_{\min}(Q)}{\lambda_{\max}(Q)}\right| < \delta\}$$

where $\lambda_{\min}(Q)$ and $\lambda_{\max}(Q)$ are the absolute smallest and largest eigenvalue of $Q(x(t,x_0))$ respectively, and $\delta > 0$ is some predefined value. During such an event, Q is close to singular, the inversion of Q is numerically infeasible and the correction term in (9) gets very large. A solution that enables to simulate (9) despite the ill-conditioned Q is to switch the correction term $Q^{-1}(x)L(\theta)$ in (9) to zero for the time of the event T_{event}. Therewith, the event based observer is given by

$$\frac{d}{dt}\tilde{z} = A\tilde{z} + B\phi(\tilde{z}) + Q^{inv}(\tilde{z}) \cdot L(\theta) \cdot [y - h(\tilde{z})],$$

whereby

$$Q^{inv} = \begin{cases} Q^{-1} & \text{if } \left|\frac{\lambda_{\min}}{\lambda_{\max}}\right| \geq \delta, \\ 0 & \text{if } \left|\frac{\lambda_{\min}}{\lambda_{\max}}\right| < \delta. \end{cases} \tag{11}$$

In the case of local observability on the entire trajectory, both observers (9) and (10) converge to the true trajectory $x(t,x_0)$, whereby the convergence region depends on the gain parameter θ. Further, both observers are applicable even if local observability is lost for some points on the trajectory. Then, (9) is modified according to (11), and numerical difficulties in (10) only concern the algebraic part and do not effect the simulation.

2.3 Inferring the parameters

After the estimation of the extended states, the final step of the approach is obtaining the parameters. We solve the definition of the model extensions for the parameters, leading to the following formulas for the parameter estimate

$$K_{i,j} = \sqrt[\eta_{i,j}]{m_{i,j}(t) - c_j(t)}, \tag{12}$$

$$\hat{r}_i = r_i(t) \prod_j^{n_c} \frac{m_{i,j}(t)}{c_j(t)^{\nu_{i,j}}}. \tag{13}$$

Using (12) and (13) with the estimated states $\tilde{x}(t,\tilde{x}_0)$ instead of the true states $x(t,x_0)$ gives estimates of the parameters, which converge to the true values in the same way as the observer.

Summarising, the proposed parameter estimation method presents an observer based approach in three steps. First, the system is transformed into an extended, parameter independent form. Second, the extended states are reconstructed from continuous time course measurement using an appropriate nonlinear observer. Finally, the parameters are obtained by applying the inverse transformation of the model extension. The resulting parameter estimate is time dependent, but converges to the true values as the observer converges.

3. EXAMPLE

In order to provide a proof of concept, the presented approach is tested on a simple gene regulation model of the circadian rhythm in *Neurospora*. The model describes day-night oscillations of the frequency protein (FRQ) by a nonlinear feedback loop within its gene expression (Leloup *et al.*, 1999)

$$\begin{aligned} \dot{M} &= r_3 - r_5 & r_1 &= k_s M & r_3 &= v_s \frac{K_1^4}{K_1^4 + F_n^4} \\ \dot{F}_c &= r_1 - r_4 - r_2 + r_{2'} & r_2 &= k_1 F_c & r_4 &= v_d \frac{F_c}{K_d + F_c} \\ \dot{F}_n &= r_2 - r_{2'} & r_{2'} &= k_2 F_n & r_5 &= v_m \frac{M}{K_M + M}. \end{aligned}$$

Here M denotes the concentration of FRQ mRNA, F_c and F_n the concentration of FRQ protein in the cytosol and nucleus respectively, r_1 denotes the rate of translation, r_2 and $r_{2'}$ of transport in and out the nucleus, r_3 of transcription, r_4 and r_5 of degradation. By using the above reaction rates and defining the Hill variables

$$m_1 = K_1^4 + F_n^4, \quad m_2 = K_d + F_c, \quad m_3 = K_M + M,$$

the model is extended as described in the previous section.

We explore different designs of $q(\cdot)$, i.e. different combinations of outputs and their derivatives, to analyse observability (Table 1). Thereby it is advisable to limit the order of the derivatives for two reasons. First, to keep the observer design simple, and second to minimise numerical errors. If for a particular choice of $q(\cdot)$ the corresponding observability matrix $Q = \frac{\partial q}{\partial x}$ has full rank $n = 12$, the extended *Neurospora* model is observable and thus identifiable.

Outputs & their degree n_i									
M	F_c	F_n	r_1	r_2	$r_{2'}$	r_3	r_4	r_5	rank(Q)
3	2	3	-	-	-	-	2	2	12
-	2	3	-	-	-	3	2	2	11
1	2	3	-	-	-	2	2	2	12
5	3	4	-	-	-	-	-	-	11
5	4	3	-	-	-	-	-	-	12
-	2	3	3	-	-	-	2	2	11
3	2	-	-	-	3	-	2	2	12
-	2	-	2	1	3	-	2	2	10

Table 1. Selection of the observability analysis of the *Neurospora* model, each row corresponds to one particular design of q with the entries being the degree n_i as in (6). Observability and thus identifiability is achieved for full rank of $Q = \frac{dq}{dx}$, i.e. rank(Q) $= n = 12$.

A biologically feasible output, which also enables a simple observer design, is for example measuring the species concentrations (Leloup *et al.*, 1999) and degradation rates (Shu and Hong-Hui, 2004):

$$y = \begin{bmatrix} M & F_c & F_n & r_4 & r_5 \end{bmatrix}^T.$$

A suitable choice of q for this output with invertible $Q = \frac{\partial q}{\partial x}$ is for instance given by (see Table 1 row 1)

$$q = \left[M \ \dot{M} \ \ddot{M} \ F_c \ \dot{F}_c \ F_n \ \dot{F}_n \ \ddot{F}_n \ \dot{r}_4 \ r_5 \ \dot{r}_5 \right]^T .$$

Remark 9. Note that the system is also observable if only the concentrations are measured $y = [M \ F_c \ F_n]$ (see Table 1 row 5).

The observer design has to be performed carefully, because there is a loss of local observability if one of the following conditions holds:

$$r_2 = r_{2'}, \ r_3 = r_5, \ r_1 + r_{2'} = r_2 + r_4,$$
$$F_c(r_2 - r_{2'}) = F_n(r_1 + r_{2'} - r_2 - r_4).$$

Despite the fact that at these points q^{-1} is non-Lipschitz, q^{-1} is still continuous under the image of q since $q \circ q^{-1} = id$, thus permitting the observer design.

Both observer structures, (9) and (10), were implemented, whereby for (9) the modified version of Q^{-1} as in (11) was used. A trial and error procedure revealed best results for a condition number in (11) of $\delta = 10^{-4}$.

In a simulation study with the originally published parameters, artificial data was generated, initialising the non-measured observer states with 100% deviation from the true initial condition, i.e. $\tilde{x}_i(0) = 2 \cdot x_i(0)$ for $i = 4, \cdots, 10$. For this initial condition, the event based observer (9) fails (Figure 2a), whereas the ϵ-approximative observer (10) converges (Figure 2b). There are time intervals where the observer error increases due to the reduced observability property of the system (Figure 2 Row 3).

Applying (12) and (13) on the state estimate for each time point gives the parameter estimate. As Figure 1 shows, this parameter estimate is time dependent, converging towards the true values. Spikes occur where local observability and thus local identifiability is lost. Consequently, a readout of the parameter values outside of these spiky regions is preferable to e.g. least squares fitting (Table 2).

	k_s	k_1	k_2	v_s	v_d	v_m	K_1	K_d	K_m
True	0.5	0.5	0.6	1.6	1.4	0.505	0.5	0.13	0.5
15h	0.50	0.50	0.60	1.63	1.39	0.505	0.55	0.13	0.50
25h	0.50	0.50	0.60	1.62	1.40	0.504	0.53	0.13	0.50

Table 2. True parameters that generated the simulated data for testing the method, and readout of the estimated parameters at 15h and 25h. Units: k_i (h^{-1}), v_i (nMh^{-1}), K_i (nM).

4. 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 strength of the presented method lies in the model extension, which establishes a one-to-one correspondence between parameters and extended states. Therewith, the main challenge of the proposed parameter estimation is the reconstruction of the extended trajectory from the measurements. Here, we use Lyapunov based observers and demonstrate that their design is tricky if local observability is not given on the entire trajectory. The example shows that ϵ-approximative observers are coping with such impaired observability.

The method holds the potential of further improvements dealing with real world biological data. Noise for example

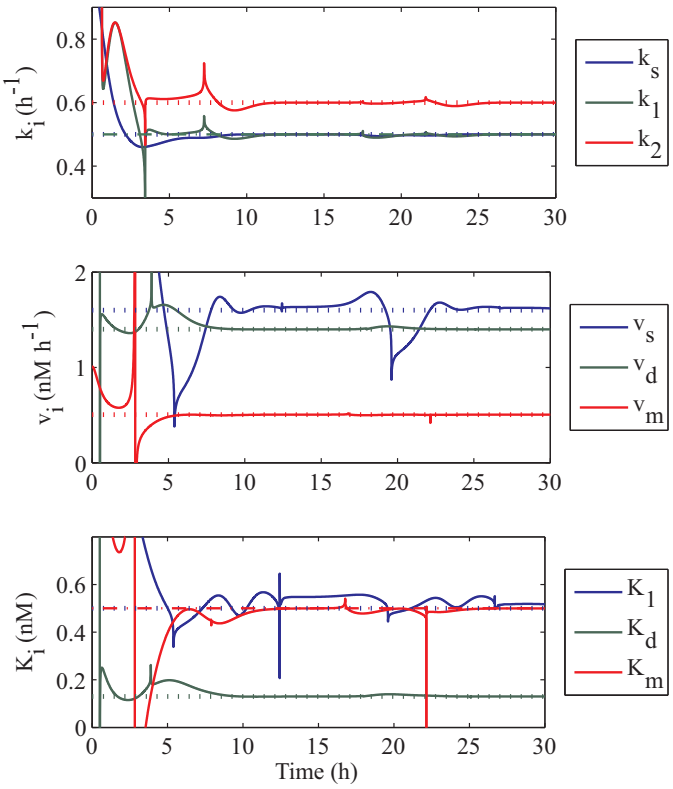

Fig. 1. As the observer converges, the parameter estimates based on the ϵ-approximative observer (10) converge to the true values (dotted, constant).

can be dealt with by borrowing techniques from particle or Bucy-Kalman filters. Modifications are however necessary to cope with the possible loss of local observability at some points on the trajectory. Concerning sampling issues, hybrid observers composed of a continuous simulation part updated at discrete time points should be developed. In addition, all benefits arising from the extended system representation have probably not yet uncovered.

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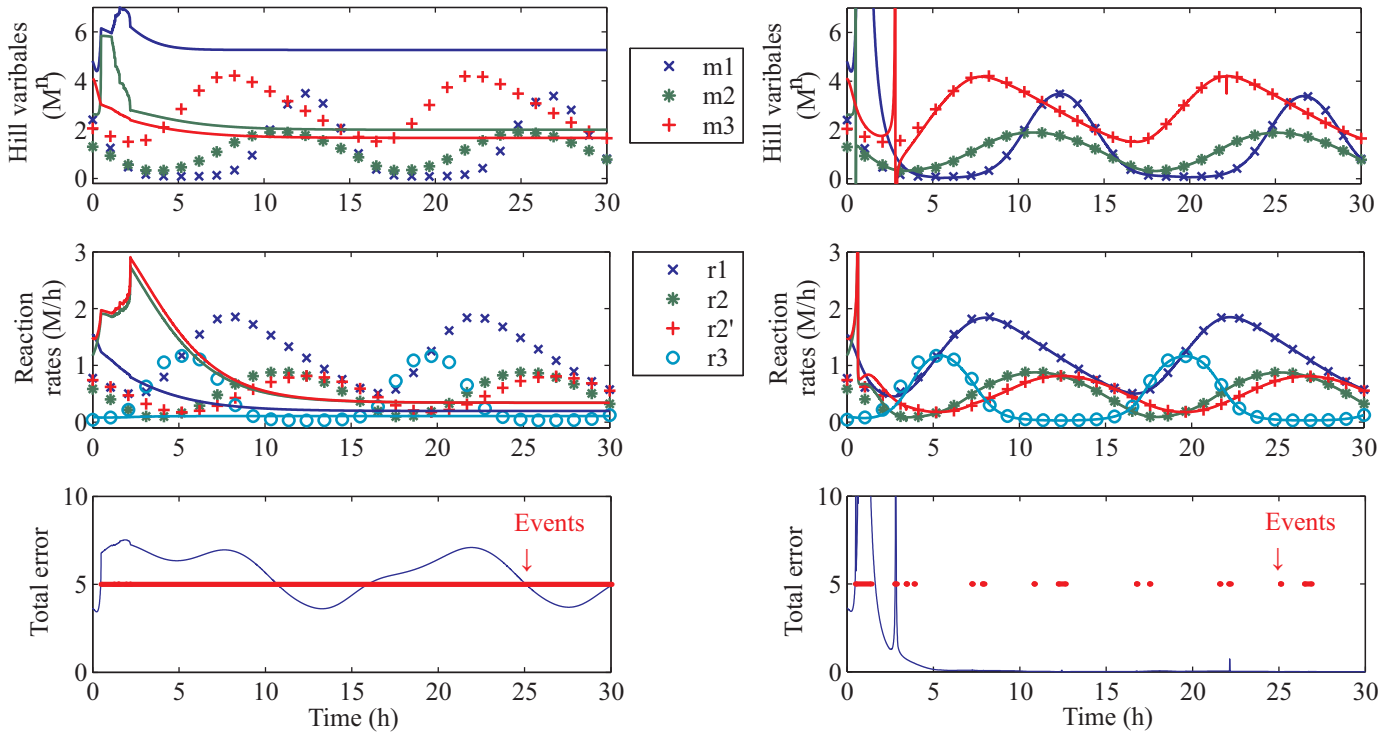

Fig. 2. (1) - (2) The real (markers) and estimated (solid) trajectories of the non measured states for both observer structures with gain parameter $\theta = 1.5$. (3) The Euclidean error of the estimated states. The red markings indicate where events occur on the observed trajectory. Note that the estimation error can increase during an event.

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

Consider a continuous observer in observability canonical form (Birk and Zeitz, 1988)

$$\frac{d}{dt}\tilde{z} = A\tilde{z} + B\phi(\tilde{z}) + L[y - \tilde{y}],$$

with a constant gain matrix L. The observer states are transformed back into the original coordinates by differentiating $\tilde{x} = q^{-1}(\tilde{z})$

$$\frac{d}{dt}\tilde{x} = \frac{\partial q}{\partial \tilde{z}}\frac{d\tilde{z}}{dt} = \left[Q^{-1}[A\tilde{z} + B\phi(\tilde{z})] + Q^{-1}L[y - \tilde{y}]\right]_{\tilde{z}=q(\tilde{x})}.$$

As $f = Q^{-1}\bar{f} \circ q$ with $\bar{f}(\tilde{z}) = A\tilde{z} + B\phi(\tilde{z})$, it follows that

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