Parameter Estimation in Canonical Biological Systems Models

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ABSTRACT

Dynamical models are the cornerstone of computational systems biology. While many methods are available for testing and simulating dynamical models, the estimation of their parameter values continues to be a difficult challenge. In recent years, this challenge has been addressed extensively for canonical models within Biochemical Systems Theory (BST), and while still no generally satisfactory solutions are available for the estimation of BST models, much has been learned. We use this recent expertise here to estimate parameter values in other canonical models, paying particular attention to Lotka-Volterra and linear-logarithmic models. The estimation itself is very simple in these cases, but the results are not always easy to interpret for systems of metabolic pathways.

Keywords: Biochemical Systems Theory, Canonical Model, Generalized Mass Action Model, Inverse Problem, Lin-Log Model, Lotka-Volterra Model, Parameter Estimation, S-system

INTRODUCTION

The central task of computational systems biology is the conversion of a biological system into a computational model. This conversion requires plenty of data and contextual information, as well as a mathematical model structure, along with computational methods that make the model fit the observations. Useful data can come from a variety of sources. In the context of modern systems biology, one might immediately think of gene expression data, but many other data types can be critical for the construction of a systems model. For an ecological system, the abundances of species in particular areas at particular times might be most important. Physiological systems models may benefit most from information on flow rates, forces, and electrochemical features. Metabolic pathway analysis depends on concentrations of metabolites and characteristics of enzymatic processes.

No matter which application area is being considered, most data fall into one of two categories: either they quantify the individual components of the system or they represent the overall dynamics of the system. In an ecological system, the former, “local” data could describe the birth and death rates within a population, while the latter, “global” data could represent the

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numbers of individuals in several cohabitating species as a set of time series. Similarly, molecular studies may generate “local” information on specific genes, proteins, metabolites, or the binding between two molecules, while “global” information might consist of time series of the expression of whole sets of genes or profiles of metabolite concentrations over a period of time.

Dense time series data often contain comprehensive information, because they reflect the collective dynamics of a biological system and its pertinent individual components under the specific investigated conditions. As a result, time series data have always been very appealing to biomathematical modelers. In the case of ecological systems, oscillations in the numbers of fish in the Adriatic Sea, interactions between plant populations and herbivores, and the famous data set on Canadian lynx and snowshoe hare, established for fur trade by the Hudson Bay Company, motivated Lotka, Volterra, and others to devise mathematical models that are now widely known as Lotka-Volterra models (see, e.g., [1-5]). Time series in molecular biology were rare until recently when advances in high-throughput methodologies began to create them with a rapidly increasing rate.

The extraction of numerical information from observed time series faces two obstacles. First, it is usually unknown which mathematical formulation might provide the best model representation. And second, standard computational methods often fail to find the optimal parameters for given data and a given model. It is useful to discuss these two obstacles in greater detail.

In contrast to physics or engineering, biological systems seldom obey simple physical laws. Of course, biology is a part of the physical world and therefore is in principle describable with the mathematical functions of physics. However, even in apparently simple biological systems, very many processes often act simultaneously and in concert with each other, so that the apparent behavior is the result of a complicated mixture of physical functions that is essentially impossible to deconvolute. Just imagine the response of a cell to receiving an external, chemical signal. The signal leads to a conformational change in a receptor anchored in the membrane. The physical change triggers a cascade of biochemical phosphorylation events, which is spatially and functionally constrained, for instance, by scaffolds. The last step of the cascade causes the translocation of a transcription factor from the cytosol through viscous, inhomogeneous cell plasma and through the nuclear membrane into the nucleus. There the transcription factor “finds” and attaches to the appropriate section of DNA and leads to altered gene expression. All component steps are bound by the laws of physics, but the signal transduction process in its complex entirety evades a succinct physics-based mathematical representation. Considering that the process furthermore requires energy, ribosomes, and amino acids, one might be ready to give up on mathematical modeling in biology.

Fortunately, biology is organized in a hierarchical and often modular fashion, which permits the establishment of models with different degrees of granularity and coarseness. At an atomic level, existing models are able to shed light on the details of binding between a protein and a ligand. At higher levels, we have models describing enzyme catalyzed reactions, and at even higher levels, models are capable of capturing the functioning of a muscle and the interactions among populations. These higher-level models no longer account for every involved molecule,
but instead use averaging and approximation to represent the dynamics of biological systems, often with sufficient accuracy.

If physical laws cannot be used for describing complex biological processes, how is it possible to find appropriate mathematical representations? The question has no answer that is generally true for all scenarios. Instead, modelers have pursued two strategies or their combination. The first strategy aims at developing semi-mechanistic representations. A good example is the Michaelis-Menten rate law, which uses mechanistic concepts of the formation and dissolution of chemical complexes and combines them with a number of assumptions that lead to a simple, yet often quite accurate mathematical representation of an enzyme catalyzed process. The main problem with this strategy in general is that there is usually no guidance for how to design these types of functions. The second strategy is the use of generic approximations. The advantage of this strategy is that there are certain mathematical guarantees of correctness and quality, but the disadvantage is that these guarantees only extend over a small—or even infinitesimally small—range of variation in the involved variables and parameters. In spite of this potential drawback, approximative models have turned out to be very useful and often bring forth satisfactory results even over extended ranges of variation.

Pursuit of the latter, generic strategy requires the choice of an approximation scheme. The first default to come to mind might be a linear approximation, but it is well known that most biological systems contain significant nonlinearities, which render linear descriptions too restrictive. Alternatives are nonlinear, “canonical” representations that consist of different variations of approximations, which typically happen to include logarithmic transformations [6, 7]. While many options are available in principle, only a few classes of canonical models have so far proven truly useful. Most prevalent among them are Lotka-Volterra (LV) models [1, 5] and power-law models under the umbrella of Biochemical Systems Theory (BST) [8-13]. Much newer and so far less exposed to the scrutiny of actual different data are logarithmic-linear (log-lin) and linear-logarithmic (lin-log; LL) [14, 15], as well as saturable-cooperative (SC) models [6]. In the next section we will discuss these models in some more detail.

The second obstacle to the efficient extraction of numerical information from observed time series is technical. In principle, the task is a straightforward optimization problem, in which the residual error between model and data is to be minimized. However, experience has shown that this optimization problem, which involves sets of nonlinear ordinary differential equations with quite a few parameters, is everything but trivial, and in spite of considerable effort, no generally satisfactory solutions have been found. Even within the relatively limited realm of metabolic pathway analysis, generic gradient methods like nonlinear regression, many variations of genetic algorithms, and other evolutionary methods such as particle swarm and ant colony optimization have been employed, but their success rates have been inconsistent and often disappointing (for a recent review, see Chou and Voit [16]).

Three methodological strategies have been shown to possess the potential of moving the field forward. First, it seems beneficial to preprocess the data, in order to tame experimental noise and to identify clear interactions—or the lack of interactions—between pairs of system components. Second, the estimation of slopes from observed time courses can tremendously speed
up the estimation, because it converts the estimation of systems of differential equations into an estimation task consisting solely of systems of algebraic equations. Finally, taking advantage of the specific form of canonical models can greatly increase the efficiency of estimation algorithms.

NONLINEAR CANONICAL MODELS AND THEIR ESTIMATION

Biochemical Systems Theory (BST): Within the realm of molecular systems, power-law models within BST have received the most attention. The BST modeling framework was originally devised for the analysis of biochemical and gene regulatory systems, but has subsequently found much wider application in various biomedical and other areas (cf. [13]). The hallmark of BST models is the formulation of each process \( v_i \) as a product of power-law functions of the form

\[
v_i = \gamma_{ik} \cdot X_1^{f_{i1}} \cdot X_2^{f_{i2}} \ldots \cdot X_n^{f_{in}}.
\]

These terms contain two types of parameters: the rate constant \( \gamma_{ik} \) represents non-negative turnover and each kinetic order \( f_{ij} \) is a real number quantifying the direct influence of its associated variable. Positive kinetic orders signify positive or augmenting effects, while negative kinetic orders signify inhibitory or diminishing effects. A kinetic order of zero in effect eliminates the associated variable from the process \( v_i \). BST comes in three variations, which differ in their numbers of terms in each equation. The format of a generalized mass action (GMA) model with \( n \) dependent and \( m \) independent variables, which are not affected by the dynamics of the system, is

\[
\dot{X}_i = \sum_{k=1}^{T_i} \pm \gamma_{ik} \prod_{j=1}^{m} X_j^{f_{ij}},
\]

where \( T_i \) is the number of terms in the \( i \)th equation. The second BST variant is the so-called S-system format. Here, the focus is on pools (dependent variables) rather than on fluxes: all fluxes entering a pool are represented by only one collective power-law term and all fluxes leaving a pool are represented by one collective power-law term. As a consequence, S-systems have at most one positive and one negative term in each equation, and their general format is

\[
\dot{X}_i = \alpha_i \prod_{j=1}^{m} X_j^{\gamma_{ij}} - \beta_i \prod_{j=1}^{m} X_j^{\delta_{ij}} \quad i = 1, 2, \ldots, n,
\]

where the parameters are defined in analogy with GMA systems.

It is furthermore mathematically possible to aggregate all fluxes affecting a given variable, so that each equation contains only one term [17]. This format is interesting, because it is very simple and because parameter estimation becomes a matter of linear regression, upon a straightforward logarithmic transformation [18]. However, the single-term format is inconvenient for most modeling purposes, for instance, because it does not permit non-trivial steady states, where all variables assume non-zero values. This format will therefore not be considered further here. Surprisingly, it has been shown that GMA and S-systems, as well as systems with only one power-law term, are capable of modeling virtually any differentiable nonlinearities, if sufficiently
many auxiliary variables are included in the system [17].

Essentially all standard methods have been used for estimating the parameters in GMA and S-systems. In addition, the special format of S-systems has led to efficient, germane estimation methods. Most of these are based on the technique of slope estimation and decoupling [13, 19, 20]. Suppose for simplicity of discussion that the observed time series for each system variable is so dense and uncorrupted by noise that it is easy to draw smooth curves through the data points. The slope of such a curve for variable $X_i$ at time $t_k$ is equivalent to the derivative $dX_i/dt$ at $t_k$. If one obtains the slopes at many ($K$) time points, it is possible to replace the one differential equation for variable $X_i$ with $K$ algebraic equations of the type

$$\text{Slope of } X_i \text{ at time } t_k = S_{ik} = \frac{dX_i}{dt}$$

The set of equations contains on the left-hand sides the slopes, which are obtained directly from the data. Each right-hand side contains some or all of the variables, whose values are also obtained from the data, as well as the parameters that need to be estimated. The slope-estimation-decoupling strategy has two advantages. First, it avoids the need to integrate differential equations numerically, which tremendously speeds up the estimation [19]. And second, each equation may be estimated separately, thus allowing parallel or sequential analysis. Most recent methods of parameter estimation for BST models from time series have used this strategy.

For the specific case of S-systems, the strategy of Alternating Regression (AR) is very efficient in combination with slope estimation and decoupling [21]. In the first step of AR, the parameters $\beta_i$ and $h_{ij}$ in Eq. (4) are guessed based on generic experience with S-systems ([13]: Ch. 5). This guess converts the term on the far right in Eq. (4) into a single numerical value. This value is moved to the left-hand side of the equation, and a logarithmic transformation reduces the estimation to a multiple linear regression step, yielding estimates of $\alpha_i$ and $g_{ij}$. In the second step, these estimates are entered into the first term on the right-hand side of Eq. (4), making it into a number, which is merged with the slope on the left-hand side. Log transformation and regression now yields improved guesses for $\beta_i$ and $h_{ij}$. In this manner, the method switches between the two terms and parameters are iteratively updated. Outside possible convergence issues, this process is very fast, because every step consists of a simple linear regression.

As a variation on AR, it was shown that the two steps in each iteration may be merged. This strategy results in an Eigenvector Optimization (EO) task that often has favorable convergence features [22]. Both AR and EO are tightly connected to the structure of S-systems, and even GMA systems are not trivially addressed with these methods.

The quality of fit clearly depends on the noise in the time courses and accuracy with which the slopes can be obtained. Numerous methods, including splines, various filters, and artificial neural networks have been proposed for smoothing time courses and subsequently computing slopes [23-31].

**Lotka-Volterra (LV) Models**: LV models are the canonical models with by far the longest
history. Interestingly, they were independently proposed in the 1920’s by Lotka, a pioneer in mathematical biology, and Volterra, an applied mathematician [1, 5]. The concept and structure of LV models are simple. Each dependent variable is assumed to interact potentially with every other variable in the system. Furthermore, one linear term in the variable itself is permitted in each equation; it could represent birth, death, degradation or transport out of the system. Using the basic principles of mass-action kinetics, each differential equation of an LV model thus has the format

\[ \dot{X}_i = a_i X_i + \sum_{j=1}^{n} b_{ij} X_i X_j \]  

(5)

Obviously some (or many) of the parameters may have values of 0. LV models have a rich history in ecology, where interactions between populations are easily mapped onto the binomial terms of the equations. But even though Lotka [1] himself referred to these equations as “kinetic,” and they are special cases of GMA systems, LV models are not well suited for the kinetics of metabolic pathway systems. For instance, it is not directly possible to represent a simple conversion of a substrate \( X_1 \) into a product \( X_2 \), because the equation of \( X_2 \) must not include variable \( X_1 \) with a rate constant by itself.

Nevertheless, LV equations are very interesting, especially for the modeling of different populations in the same environment that affect each other. First, it is easy and intuitive to set up the equations and to compute the steady state of the system, which requires simple linear algebra. Secondly, these equations are extremely flexible. Just like BST systems, LV models were shown to be capable of modeling any type of differentiable nonlinearities, including different kinds of oscillations and chaos, if sufficiently many equations and artificial, auxiliary variables, are included in the system [4, 17, 32]. As an example, Fig. 2 later in this section shows a four-variable LV systems exhibiting deterministic chaos.

Many methods of parameter estimation have been applied to LV systems, including nonlinear regression with the differential equations [33], multiple shooting algorithms with subsequent optimization [34], and statistical methods based on nonlinear Kalman filtering [35]. However, it seems that none of the published estimation methods has taken advantage of the very special structure of these models. The only exception is apparently a method of preprocessing data for structure identification [36]. This omission is quite puzzling, because the methods of slope estimation and decoupling discussed above are not only immediately applicable to LV models, but they result in a straightforward linear regression task. As a small example from systems ecology, consider the interactions between an herbivore species \( N_1 \) and a predatory species \( N_2 \) of carnivores. A typical LV description is

\[ \dot{N}_1 = N_1 \cdot \left( a_1 - b_1 N_1 - b_2 N_2 \right) \]
\[ \dot{N}_2 = N_2 \cdot \left( a_2 N_1 + a_3 - b_3 N_2 \right) \]

(6)

The model equations indicate that \( N_1 \) grows exponentially with rate \( a_1 \). Death comes in two forms. First, intrinsic death (with rate \( b_1 \)) is commonly represented with the square of \( N_1 \). Second, \( N_2 \) feeds on population \( N_1 \) and the rate for this predation is \( b_2 \); it is common practice to formulate this process as the product of \( N_1 \) and \( N_2 \). \( N_2 \) grows by virtue of predation \( (a_2 N_1 N_2) \) as
well as intrinsically \((a_iN_i)\) and dies with rate \(b_j\).

Suppose the population sizes have been measured at subsequent time points, starting at time \(t = 1\) (Fig. 1). It is now easy to compute the parameters. First, the time courses allow us to estimate slopes \(S_1(t_k)\) and \(S_2(t_k)\), either directly or upon smoothing. With these quantities, we can formulate the estimation task for the first differential equation as a set of \(K\) algebraic equations of the type

\[
S_1(1.1) = \frac{N_1(1.1)}{a_1 - b_1N_1(1.1) - b_2N_2(1.1)}
\]

\[
S_2(1.2) = \frac{N_1(1.2)}{a_1 - b_1N_1(1.2) - b_2N_2(1.2)}
\]

Furthermore, \(N_i\) is never 0, so that we can divide both sides by \(N_i(t_k)\) and substitute \(N_i(t_k)\) and \(S_i(t_k)\) with numerical values from the observed time courses. The result is a linear system with unknown quantities \(a_i, b_i,\) and \(b_2\):

\[
S_1(1.1)/N_1(1.1) = a_1 - b_1N_1(1.1) - b_2N_2(1.1)
\]

\[
S_1(1.2)/N_1(1.2) = a_1 - b_1N_1(1.2) - b_2N_2(1.2)
\]

Simple linear regression immediately yields the correct parameter values \((a_i = 40, \ b_i = 0.008, \ b_2 = 1.0)\), within the accuracy of the computation (results not shown). The parameter

![Figure 1: Estimation and simulation of a two-variable predator-prey model. The light grey line indicates the “true” model. Random noise is added to the true model (grey data points). The noisy data are smoothed as shown with the grey dashed line. Simulated data (black line) were generated using parameter values obtained by linear regression as described in the Text.](image-url)
values for the equation of $N_2$ are computed in exactly the same fashion as ($a_2 = 0.05$, $a_3 = 0.01$, $b_3 = 0.18$). Even with moderate noise, this estimation is simple, and the result is excellent (Fig. 1). As an additional advantage, the estimation permits application of the large repertoire of diagnostic tools that have been developed for linear regression analysis [37].

The most intriguing aspect of the proposed estimation is that the LV system may exhibit very highly nonlinear responses and yet, the estimation becomes a simple task of linear regression. To illustrate this surprising fact with a more complex example, consider the following LV system with non-zero variables, which exhibits deterministic chaos [38, 39]:

Figure 2: Responses of the chaotic system in Eq. (9) with parameter values estimated from data without and with noise. In each case, the slopes were assumed to be error free. Panel a: Noise-free data; panels b-d: 2%, 5%, 20% noise, respectively. Symbols and lines: Black circle and solid line: $X_1$; grey square and solid line: $X_2$; black triangle and dashed line: $X_3$; grey diamond and dashed line: $X_4$.
The parameter values for the example are taken directly from the literature and presented in the second column of Table 1.

Table 1

<table>
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<tr>
<th>Parameter</th>
<th>True parameter value</th>
<th>0%</th>
<th>1%</th>
<th>2%</th>
<th>5%</th>
<th>10%</th>
<th>20%</th>
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<td>1.53</td>
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<td>1.09</td>
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</table>

* Parameter values were obtained per simple linear regression.

Under the assumption that the data are accurate enough to obtain good slope values, either directly or upon smoothing [30], the parameter estimation is again a simple task of linear regression with four variables. For noise free data, the correct parameters are obtained without any problem (Table 1). As the data become noisier, the accuracy of the parameter values begins to degrade, and given that the system is chaotic, the predicted behavior may quickly deviate...
from the true time courses. This divergence is not surprising and would happen with any other estimation approach. At any rate, the ease with which decent parameter estimates are obtainable is quite intriguing. For 1% or 2% noise, the results are still quite similar to the true model (Fig. 2). For 5% noise, the system still seems chaotic, but the time courses are noticeably different, as it is to be expected for a chaotic system. For 20% noise, the system loses its chaotic characteristics and approaches a limit cycle instead (Fig. 3).

Figure 3: Limit cycle of system (9) with parameters estimated from noisy data. If the data are corrupted by 20% noise, the LV system loses its chaotic characteristics and instead approaches a limit cycle (here shown for $X_1$ and $X_2$).

**Linear-Logarithmic (Lin-Log) Models:** Log-lin and lin-log models grew out of Metabolic Control Analysis (MCA), an analytical approach to understanding the shared control within metabolic pathways close to a steady state [40-42]. For a long time, MCA only permitted infinitesimally small variations about the normal operating state of a pathway, but the restriction was later relaxed, ultimately leading to a dynamic pathway formulation that is now known as the *lin-log model* [15, 43].

For a pathway with $n$ dependent metabolites, $X_1, X_2, \ldots, X_n$, $m$ independent variables $X_{n+1}, X_{n+2}, \ldots, X_{n+m}$, and $r$ reactions $v_1, v_2, \ldots, v_r$, catalyzed by enzymes with activity $e_i$, the lin-log model describes the rate of the $i$th enzyme catalyzed reaction as

$$\frac{v_i}{J_i} = \frac{e_i}{e_i^0} \left(1 + \sum_{j=1}^{n+m} \frac{e_j}{e_j^0} \log \left(\frac{X_j}{X_j^0}\right)\right).$$

(10)
One characteristic tying the lin-log model to MCA is the consideration of a reference (steady) state at which $X_j^0$ is the concentration of species $X_j$, $J_i^0$ is the flux through the $i$th reaction, $e_i^0$ is the reference level of the enzyme activity and $E_j^0$ is the reference elasticity, which corresponds to a kinetic order in BST [44, 45]. Methods of MCA have been used to estimate the parameters in these models of single reactions (e.g., [43]).

For purposes of parameter estimation from time series data, the parameters characterizing the reference state are merged with other parameters, and embedding of the individual reactions into a system of differential equations yields

$$X_j = b_{j0} + \sum_{j=1}^{n} b_{j} \log X_j + \sum_{j=1}^{m} b_{j} \log X_j.$$

This system has nonlinear characteristics but is entirely linear in its parameters. In other words, if time courses of sufficient quality are available, the logarithmic terms and the derivatives (slopes) can be obtained directly from the data and the estimation consists of a simple linear estimation task (cf. [46, 47]). Indeed for pathway systems that adhere to the lin-log format or whose variables remain within relatively close ranges, the estimation is trivial.

As an example, consider the simple branched pathway model in Fig. 4, whose dynamics is modeled as the S-system

$$\begin{align*}
\dot{X}_1 &= 12X_3^{-0.8} - 10X_1^{0.5} \\
\dot{X}_2 &= 8X_1^{0.5} - 3X_2^{0.75} \\
\dot{X}_3 &= 3X_2^{0.75} - 5X_1^{0.5}X_4^{0.2} \\
\dot{X}_4 &= 2X_1^{0.5} - 6X_4^{0.8}
\end{align*}$$

[19] and suppose three datasets are available for parameter estimation (Table 2). Even though the time courses were produced with an S-system, rather than a lin-log model model, the estimation of lin-log parameters is simple and the result is excellent for Dataset 1 (Fig. 5; Table 3).

The main limitation of the lin-log estimation is that the model structure may not be able to capture the dynamics of the time courses adequately. For instance, if the same S-system is used

Figure 4: Didactic system with four variables and two regulatory signals. This pathway model [19] has been used for demonstrations of parameter estimation methods. Here it is used for parameter estimation with lin-log models. See Text for details.
with different initial conditions, the dynamics of the estimated lin-log model may be deviating from the data slightly (Dataset 2) or lead to unreasonable results (Dataset 3) (see Fig. 6).

The situation becomes particularly troublesome if concentrations are close to zero, which can cause problems with rates becoming negative [47]. Problems may also arise if the model
exhibits truly nonlinear features, such as stable oscillations. For example, the system
\[
\begin{align*}
\dot{X}_1 &= 1.01 \cdot (X_1^{-3.368} \cdot X_2^{-3.059} - X_1^{-6.894} \cdot X_2^{-22.814}) \quad X_1(t_0) = 1 \\
\dot{X}_2 &= X_1^{4.761} \cdot X_2^{-4.034} - X_1^{1.4902} \cdot X_2^{1.903} \quad X_2(t_0) = 1.05
\end{align*}
\] (13)
describes a limit cycle oscillation [48]. The parameter values of the corresponding lin-log model
\[
\begin{align*}
\dot{X}_1 &= b_1 + b_2 \log X_1 + b_3 \log X_2 \\
\dot{X}_2 &= b_4 + b_5 \log X_1 + b_6 \log X_2
\end{align*}
\] (14)
are easily computed from noise-free data per linear regression. Their values are \(b_1 = -0.0923, \ b_2 = 6.0355, \ b_3 = 20.7249, \ b_4 = 0.0308, \ b_5 = -2.9675, \ b_6 = -6.6309\), and the resulting model captures the general trends but not the exact dynamics. Worse, the model loses its characteristics of a limit cycle and instead exhibits damped oscillations (Fig. 7). It is unclear whether this example constitutes a singular problem, caused by the fact that the lin-log model is used as an approximation to a different model type (cf. [49]), or whether the lin-log model structure is principally unable to capture limit cycle behaviors.

While the estimation of lin-log models from time series data is a matter of straightforward

![Figure 5](image)

**Figure 5:** Estimation of a lin-log model of the pathway in Figure 4. Even though the original model was in S-system form (12), the lin-log model captures Dataset 1 (Table 2) very well.
Figure 6: Estimation of a lin-log model of the pathway in Figure 4. In contrast to Dataset 1 (Figure 5), Datasets 2 (panel a) and 3 (panel b) of Table 2 are not modeled well by the lin-log model.
linear regression, one must note that the result is not well suited for typical simulation studies. For instance, suppose we intend to study the response of the pathway in Fig. 4 to a 50% increased input. The corresponding term in the first equation of the system seems to be \( b_{\text{w}} \). However, this parameter not only represents the input but also contains contributions associated with the inhibitor \( X_3 \) and with the degradation of \( X_1 \), and it is not possible to dissect the relative contributions by the input and by variables \( X_1 \) and \( X_3 \). In more general terms, it seems impossible to associate the parameters to particular fluxes without further biological information. In the bottom-up approach, the combination of parameters is not an issue [43], but it does become a serious problem in top-down estimations from time series.

**Saturable-Cooperative (SC) and More Complicated Models:** The hallmark of SC models is that all individual processes are s-shaped with zero slope for zero concentrations and saturation toward high values of their variables [6]. The particular format of SC models can be rationalized in two ways. On one hand, they may be seen as a generalization of BST models, in which each power-law function is replaced by a Hill function of the type

\[
H(X) = \frac{V_{\text{max}} X^h}{K_m^h + X^h},
\]

where \( V_{\text{max}} \) describes the upper limit of the process, \( K_m \) is the Michaelis constant, and the positive real number \( h \) is a generalized, real-valued Hill coefficient. On the other hand, similar to BST, LV, and lin-log models, SC models can also be derived directly as a Taylor approximation in some log-transformed space. In this particular case, a process

\[
v = f(X_1, \ldots, X_n)
\]

is first transformed by introduction of the new variables \( w = v^{-1} \) and \( Z_i = X_i^{m_i} \), resulting in

\[
w = \varphi(Z_1, \ldots, Z_n).
\]

Taylor linearization of this function and transformation back to the original space yields
Clearly, this format contains a larger number of parameters than other canonical models, which endows it with a higher degree of flexibility in shape. Parameter estimation has so far been performed only for individual processes but not for time series of integrated systems. Extending the flexibility of rate laws further, other authors have proposed more complex kinetic formulae, which may or may not be considered canonical. For instance, Hadlich et al. [50] suggested the following rate law, which accounts for activators $a_1, \ldots, a_m$ and inhibitors $d_1, \ldots, d_n$ and contains the kinetic parameters $\alpha_1, \ldots, \alpha_j$:

$$v = b_0 \frac{\prod_{j=1}^{n} X_j^{m_j}}{\prod_{j=1}^{n} X_j^{m_j} + b_0 \sum_{k=1}^{n} b_k \prod_{j=1, j \neq k}^{n} X_j^{m_k}}. \quad (18)$$

Even more complicated in terms of their structure and number of parameters are rate laws of “convenience kinetics” [51], which therefore allow for further increased flexibility in shape. In these cases of not truly canonical models, the estimation of parameters from time series data becomes rapidly more complicated as the complexity of the metabolic system grows.

**DISCUSSION**

Biological systems operate within the physical world. However, the processes governing these systems are often too complex to permit truly mechanic, physics-based representations. Alternatives are canonical models, which are based on some specific type of approximation that leads to a well-defined, characteristic mathematical structure. Biological systems that are modeled within such a structure are always represented by the same symbolic equations and differ exclusively in the number of variables and the values of the model parameters. The use of canonical models is particularly advantageous for inverse problems, where observations on the biological system consist of time courses of system responses. In this case, it is very difficult to determine the optimal mechanistic model, while it is comparatively easy to set up a canonical model.

Among many options, Lotka-Volterra (LV) systems and models designed under the auspices of Biochemical Systems Theory (BST) have received the most attention, but other options, such as the linear-logarithmic (lin-log) and the saturable-cooperative (SC) model, are available. With regard to parameter estimation from time series, by far the most attention has been paid to BST models. In fact, essentially all standard methods, including nonlinear regression, genetic and other evolutionary algorithms, and some customized methods have been applied to BST models (for a recent review, see [16]). While no clear winner among these methods has emerged, it has become evident that one preprocessing step is particularly useful, namely the estimation of slopes from the time series data. This step circumvents the very costly numerical integration of systems of differential equations and permits optimization of parameters for one variable at a
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time. In the case of BST models, the estimation task is therewith reduced to an optimization of systems of nonlinear algebraic equations. Interestingly, it seems to have gone unnoticed that the same strategy leads to a straightforward linear regression task in the case of LV systems. The only mention of a related strategy has apparently been a method for inferring the connectivity of networks from time series data [36]. We show here that a direct estimation of LV models per linear regression is possible and essentially trivial even for highly nonlinear cases, including systems exhibiting deterministic chaos. The linear regression has the added advantage of making the rich repertoire of diagnostic methods available, with which statisticians have been analyzing the quality of linear regression results for a long time (e.g., [37]).

The same advantage of leading to a linear regression task is present for lin-log models. For systems operating close to a non-zero steady state, or within a small window of variation in its variables, the inverse problem is therefore simple. The main drawback is that this estimation does not associate mathematical terms with particular fluxes. As a consequence, the fit is almost like a black-box fit, where it is difficult to map a biological experiment or a change in pathway structure onto the mathematical model. It seems that this problem can only be resolved with additional, independent biological information. In many cases, a lin-log model will give sufficiently good results, but it needs to be determined whether this model structure is rich enough to capture all relevant types of nonlinear behaviors, including limit cycles and deterministic chaos. It also needs to be seen whether it might be useful to execute a pre-fitting with lin-log models and to use the results as a starting point for the estimation of more flexible power-law models within BST or for the even more complex SC models.

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