Parameter Estimation in Biochemical Reaction Networks
- Observer Based Prediction Error Minimization

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Introduction

Estimating parameters in dynamic systems is an important and challenging part of modeling of biochemical and biological processes. Parameter estimation can be seen as a subset of system identification - to build dynamic models from measurement data, which is a discipline with a large number of existing techniques and applications in particular in engineering [1].

It is common to formulate the parameter estimation problem as an optimization problem with an associated cost function. In the systems biology community the 'standard' choice of cost function seems to be the sum of (possibly weighted) squared errors between measurement data and simulated response. Cost functions of this type are known to have many local minima and usually efficient gradient based methods will fail if no good initial guesses of the parameter values can be given. Hence, one usually resorts to global optimization schemes with slow convergence but still without any guarantee that the global minimum actually will be found. In this work we demonstrate the power of employing concepts from non-linear filtering in setting up parameter estimation problems, which give more nicely behaving cost functions.

Prediction Error Minimization

The basic idea of so called prediction error minimization (PEM) is to construct a predictor and compare its predictions with available data using some suitable measure [1]. In general the predictor is not just a simulation of the system but also take measurement data into account, which substantially reduce the prediction error. The PEM framework can be considered both from a probabilistic and deterministic point of view [3, 1]. The dynamic system is assumed to be described as

$$\begin{aligned} \tfrac{d}{dt}x(t) &= f(x(t), u(t), \theta) + w(t) \\ y(t_k) &= g(x(t_k), u(t_k), \theta) + v(t_k) \end{aligned} \tag{1}$$

and the optimization problem to be solved is given by

$$
\begin{aligned}
\varepsilon(t_k,\theta) &= y(t_k) - \hat{y}(t_k|\theta) \\
V_N(\theta) &= \frac{1}{N}\sum_{t=1}^{N} \tfrac{1}{2}\varepsilon(t_k,\theta)^2 \\
\hat{\theta}_N &= \underset{\theta\in\Theta}{\operatorname{argmin}}\, V_N(\theta)
\end{aligned}
\tag{2}
$$

where y and $\hat{y}$ are the measured and predicted output at time, t_k respectively, ε the prediction error, and V_N the cost function.

Employing a probabilistic framework it can be shown (under some additional assumptions) that the optimal predictor corresponds to continuous integration of the original set of ordinary differential equations describing the system between sample data points but where the state is updated discretely at sample time instants based on the prediction error, see Figure 1. This behavior resembles the multiple shooting method [4], which is formulated in a deterministic framework. For non-linear systems the implementation of optimal predictors is very computationally demanding and one usually resorts to approximate schemes, e.g., the extended Kalman filter. In the deterministic case so called observers can be used to utilize both model and data to compute good predictions.

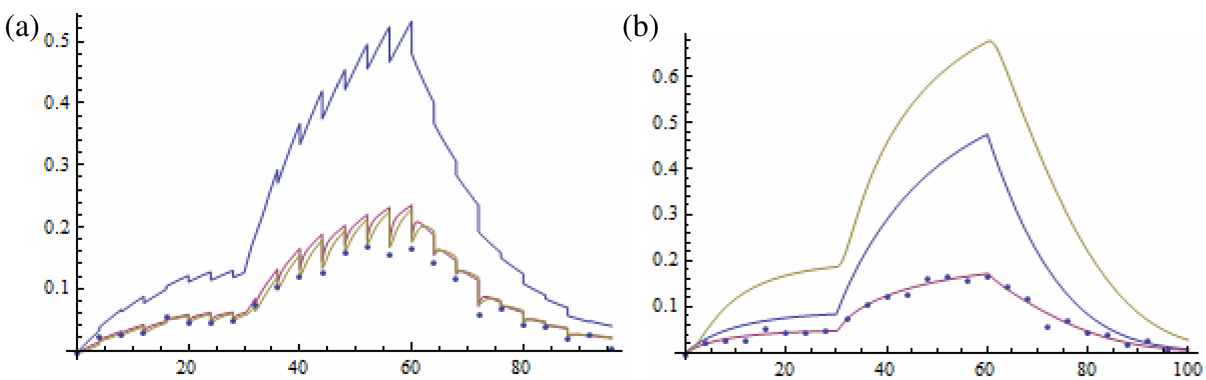

Figure 1. The behavior of the predictor is illustrated both with (a) initially guessed parameters and (b) their values at convergence of the optimization algorithm.

A Continuous-Discrete Observer

In this work we investigate the feasibility of using a simplified predictor, which retains the continuous-discrete structure of the optimal predictor but use a much simplified scheme for computing the measurement update equation. For a system of the form (1) this observer is

$$
\begin{aligned}
\tfrac{d}{dt}\widehat{x}(t|\theta) &= f(\widehat{x}(t|\theta), u(t), \theta),\ t_{k-1} \le t < t_k, k = 1, \ldots, N \\
\widehat{x}(t_k^{+}|\theta) &= \widehat{x}(t_k^{-}|\theta) + K_\theta \left(y(t_k) - g(\widehat{x}(t_k^{-}|\theta), u(t), \theta) \right) \\
\widehat{y}(t_k|\theta) &= g(\widehat{x}(t_k^{-}|\theta), u(t), \theta)
\end{aligned}
\tag{3}
$$

In the linear system case the above predictor is known as the directly parameterized continuous-discrete Kalman filter. To illustrate the PEM approach to parameter estimation we use this predictor structure and apply it to some small biochemical systems.

References

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