Modelling biochemical networks with intrinsic time delays

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Modelling of biochemical reactions involves the incorporation of different reaction-time scales into one modelling framework, i.e.: reactions that run much faster than the time scale of the model are assumed to be in quasi steady-state, reactions that last much longer are neglected [1], see Fig. 1. The incorporation of time delays into a model becomes necessary either when a process takes an intrinsic discrete time to be accomplished, i.e. some reactions, like translational or transcriptional reactions take a discrete time to be completed [1, 2], or as a consequence of the modelling approach used, i.e. lumping a sequence of events might lead to an apparent time delay [2]. This means that the delay dynamics are an intrinsic property of the system which needs to be accounted for.

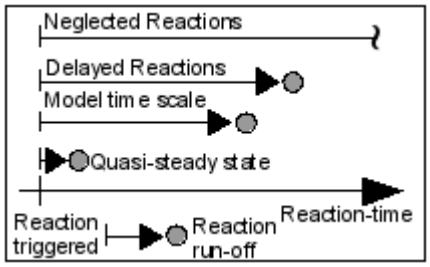

Figure 1: Reaction Times

Retarded Functional Differential Equations (RFDE) provide a mathematical construct for the integration of delays into the modelling framework [3]. Simplifications of this general framework can for instance result in neutral delay differential equations, state-dependent delay differential equations, delay differential equations or integro-differential equations. The latter two approaches, which assume either discrete delays or distributed delays in the state variables, respectively, are maybe most frequently applied in systems biology [2, 4-6].

The complexity of the system under study is usually high in systems biology and moreover fundamental knowledge is many times missing. Attempts to convert data into knowledge while using mechanistic modeling techniques is laborious and hampered by several factors, such as large scale, poorly defined kinetic parameters and limited generalization capacity. In such a context the mechanisms that cause time delays are not likely to be known.

A cost-effective alternative to model biochemical networks with intrinsic time delays is posed through hybrid semi-parametric mathematical systems. Hybrid semi-parametric systems combine fundamental (parametric) biological constraints with more empirical data-based techniques. The arrangement can be either parallel or serial. The serial concept, which is chosen in this study (see Fig. 2), bases on material balances, in which the kinetic terms are described by data-driven techniques, i.e. an Artificial Neural Network (ANN). The incorporation of time delays into this system is accomplished through choosing the concept of discrete delays, i.e. the ANN inputs are augmented by lagged values of the state variables, see Fig. 2, resulting in delay differential equations. The type of delay chosen is not limiting the applicableness of the model concept since it is mathematically clear that a sum of a weighted series of discrete delayed states is somewhat equal to the concept of distributed delays, i.e. the integral of the kernel function for distributed delays is approximated by the ANN.

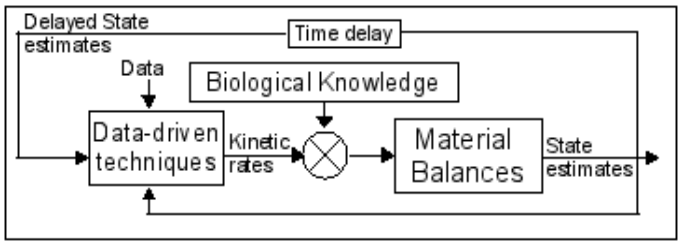

Figure 2: Semi-parametric hybrid model with discrete delayed states

The proposed hybrid model was applied to a typical gene regulatory system where the transport of macromolecules between the cytosol and nucleus introduce strong delay dynamic effects. The strong delay dynamics are in [7] accounted for through the application of the concept of discrete delays, namely a single discrete delay governs the network dynamics. Therefore their model equations where chosen as a first simulation case.
In the hybrid approach various delays in the vicinity of the "true" delay were studied in order to (i) analyze the sensitivity of the hybrid model towards the delayed states and (ii) to investigate whether the incorporation of lagged states leads to reinforced prediction performance. Additionally, simultaneously 2 or 3 numbers of different delays were studied in order to determine the influence that time series of discrete delayed states have on the prediction. It was observed that (a) the predictions were the better the closer the incorporated delay was to the "true" delay; (b) the prediction performance peaked when the incorporated and the true delay coincided; and (c) the estimated dynamics were only similar to the "true" dynamics in cases were delays in the vicinity to the "true" delays were used, enabling to identify the system underlying delay.

In addition, heterologous protein expression by recombinant Pichia pastoris was studied by assuming a hypothetical network with distributed time delays. It is assumed that specific growth and product formation are delayed regarding the substrate uptake. A strong delay kernel is assumed with a hypothetical mean delay of 5 hours. The resulting equations constitute a second simulation case with which it was intended to verified that the applicability of the proposed hybrid model is not limited to discrete delay cases.
For the hybrid model, series with different numbers of delays in the state variables, which are inputs to the ANN, were studied. It was observed that (a) the performance of those series which comprised the mean delay of 5 hours were enhanced when compared to series which did not; and (b) in general the incorporation of series of discrete delayed states led to enhanced performance when compared to hybrid models with no delay at all.

These results lead to the conclusions that:

1. delays are important intrinsic properties of biochemical networks.
2. the proposed hybrid approach can mimic the biochemical network and its underlying delay dynamics, where the principal is probing from the outside.
3. both types of delayed dynamics, i.e. posed through discrete or distributed delays, can be modelled.
4. therefore the identification of intrinsic time delays in biochemical networks is enabled.

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