A symbolic approach to the simulation of biochemical models: application to circadian rhythms

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Abstract

Symbolic rewriting systems are gaining interest as tools for simulating biochemical dynamics. Compared to traditional methods based on differential equations, the symbolic approach allows a straightforward translation of a signal transduction network into a system of rewriting rules capable of describing the network dynamics by means of a proper application of these rules. Coherently with this design approach, our algorithm applies rewriting rules proportionally to the values assumed by specific reaction maps. Such maps are nonlinear functions of the state of the system. Preliminary results obtained using this algorithm in the simulation of a known model of circadian rhythms in Drosophila *envision its potential applicability in reproducing complex biochemical networks, such as that presented here.*

1. Introduction

We propose a symbolic method for the representation and the simulation of biochemical models. In an aim to overcome the limits shown by traditional methods based on differential equations in representing the complex, heterogeneous, and discrete nature of biological systems, our method translates the evolutionary and transductional aspects of a model into a system of rewriting rules [5]. The application of these rules is governed by specific nonlinear functions, called reaction maps, that are informed with kinetic and quantitative model parameters such as Michaelis constants and biochemical concentrations. An algorithm manages step-by-step the dynamic evolution of the resulting formal system [1].

Advantages in choosing this method arise due to i) simple but accurate description of biomolecular reactions: complex formation ($AB \rightarrow C$), dissociation ($C \rightarrow AB$), and enzyme activity ($CA \rightarrow CB$); ii) absence of discretization stages: the method inherently represents biomolecules as populations of symbols, conversely it embeds continuous phenomena within the reaction maps; iii) variable resolution: as a natural consequence of the way the evolution algorithm works, individual molecules are treated as more accurately, as fewer of them populate the system; iv) scalability: new types of molecules and reactions can be straightforwardly included in a system.

Successful validations of our method in representing the Lotka-Volterra population dynamics, the Brusselator model of the Belousov-Zhabotinskii reaction [1], and the PKC activation, foster its application in computational systems biology. In this poster a synthetic description of the method is given along with results obtained by the simulation of a known model of circadian rhythms in *Drosophila* [3].

2. The algorithm: a quick overview

Let our system be made of a set $R = \{r, s, \ldots, w\}$ of rewriting rules working over strings on an alphabet $\mathcal{A} = \{X, Y, \ldots\}$ containing k symbols:

$$r : \alpha_r \rightarrow \beta_r\,, \quad s : \alpha_s \rightarrow \beta_s\,, \quad \ldots, \quad w : \alpha_w \rightarrow \beta_w$$

in which α_ρ and β_ρ are strings respectively denoting consumed and produced objects for each rule $\rho \in R$.

Let the state of our system be a k-uple $\langle q(X), q(Y), \ldots \rangle$ containing the number of objects $X, Y, \ldots$ in the system at every temporal step. To every rule we associate a corresponding *reaction map* $F_r, F_s, \ldots, F_w$, i.e., a real function of the state of the system.

By denoting with $\alpha(i)$ the ith symbol in a string α, with $|\alpha|$ the length of the same string, and with $|\alpha|_X$ the number of occurrences of the symbol X in α, then we define the *reaction weight* $W_r\big(\alpha_r(i)\big)$ for $r : \alpha_r \rightarrow \beta_r$ with respect

to the symbol $\alpha_r(i)$:

$$W_r\big(\alpha_r(i)\big) = \frac{F_r}{\sum\limits_{\rho \in R \,|\, \alpha_r(i) \in \alpha_\rho} F_\rho} \quad , \quad i = 1, \ldots, |\alpha_r|$$

Note that at the denominator we sum only over the rules containing the symbol $\alpha_r(i)$ in their left part.

If we, at this point, consider that every rule r cannot consume more than the amount of the symbol (called also *reactant*) whose availability in the system is lowest, then for every rule we have to minimize among all reactants—each one taken with its own multiplicity in α_r—participating to the reaction. In this way we find the (minimum) number of applications of a rule during a transition of the system:

$$\Lambda_r = \min_{i=1,\ldots,|\alpha_r|} \left\{ W_r\big(\alpha_r(i)\big) \frac{q\big(\alpha_r(i)\big)}{|\alpha_r|_{\alpha_r(i)}} \right\}$$

In the end, during any transition, for every symbol $X \in \mathcal{A}$ the change in the number of objects due to r is equal to $|\beta_r|_X - |\alpha_r|_X$ times Λ_r:

$$\Delta_r(X) = \Lambda_r \left(|\beta_r|_X - |\alpha_r|_X \right)$$

A detailed explanation of the algorithm structure, in particular the way it works with populations rather than concentrations and its extension to multiple reaction environments made using membrane systems, is given in [1].

2.1. Application to circadian rhythms

We have applied the algorithm discussed in section 2 to the simulation of a known model of circadian cycles (or *rhythms*) in *Drosophila melanogaster*, involving the oscillation of the Period (PER) and Timeless (TIM) proteins [3]. Symbolic rewriting allows to describe this model by means of a set of rules, avoiding the classical approach based on differential equations.

Figure 1 depicts the salient result we have obtained by our simulation. The stable oscillatory dynamics generated by the numerical solution of the differential equations is achieved also using the symbolic approach, moreover the relative temporal shifts between concentrations obtained using the differential equations are respected in our simulation, meaning that comparable dynamic behaviors exist for the two approaches. In particular, the sequence of concentration peaks exhibited by the phosphorilating PER protein (P_0, P_1 and P_2) is correctly followed by the peak in the concentration of the cytosolic PER-TIM complex C and, finally, by its nuclear counterpart C_N.

3 Concluding remarks

The symbolic approach has already obtained promising results in the simulation of known dynamics as those reported in Section 1. These results, along with those coming out in the analysis of the PKC activation process, by all means suggest to further test the symbolic algorithm in models of biochemical dynamics.

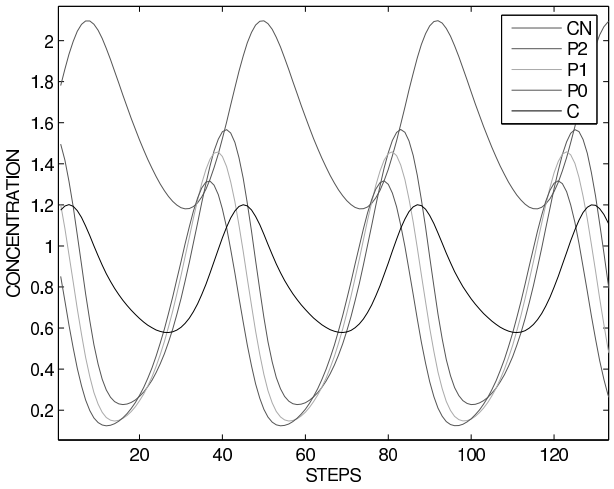

Figure 1. Plots for nuclear PER-TIM complex (C_N), phosphorilating PER (P_2, P_1, P_0), and PER-TIM complex (C). Elements are ordered starting from the highest to the lowest maximum peak value, as in the legend at the top-right corner.

Even more interesting will be comparing our symbolic algorithm to some well-known stochastic simulation methods, that are used when the molecules involved in a biochemical process are few in a way that the deterministic approach turns out to be no longer suitable. Surprising analogies exist in fact between the symbolic and the stochastic approach to the simulation of circadian rhythms when our algorithm is set to work over population (i.e., discrete) rather than concentration (i.e., continuous) domains [4, 2].

References

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