Stochastic Modelling and Simulation of Biochemical Networks

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Introduction

Biochemical systems are inherently governed by stochastic laws. Consequently, stochastic models are an adequate choice for their thorough investigation. But due to the computational expense for their analysis, the considerations are often restricted to the averaged case and continuous models are used instead.

However, stochastic models are unavoidable if the stochastic noise is crucial for the behavioural properties to be investigated. In the light of this demand, substantial effort has been made to develop appropriate stochastic analysis techniques and to implement them by sophisticated data structures and efficient algorithms.

Analysis

Simulation

The stochastic simulation algorithm (SSA) creates a single finite path through the possibly infinite CTMC.

The probability that a transition $t_j \in T$ will occur in the infinitesimal time interval $[\tau, \tau + \Delta \tau)$ is given by:

 $P(\tau + \Delta \tau, t_j \mid s) = h_j(s) \cdot e^{-E(s) \cdot \Delta \tau}$

So, the enabled transitions in the net compete in a race condition. The fastest one determines the next state and the simulation time elapsed. In the new state, the race condition starts anew. The stochastic simulation algorithms implemented in MARCIE:

Modelling

A biochemically interpreted **Generalized Stochastic Petri Net** (\mathcal{GSPN}) is a tuple (P, T, f, h, s_0) . As usual, P denotes the set of places, modelling the biochemical species, T_s the set of stochastic transitions and T_i the set of immediate transitions, modelling the biochemical reactions, $f : ((P \times T) \cup (T \times P)) \rightarrow \mathbb{N}$ the arc weight function, and $s_0 : P \rightarrow \mathbb{N}$ the initial state (marking), defining the initial tokens on each place. Stochastic transitions have an exponentially distributed firing delay. The firing rates are typically transition-specific and state-dependent and defined by propensity (hazard) functions. We denote the propensity function for the stochastic transition t_j with h_j . Immediate transitions have a higher priority over stochastic transitions. The state of a Petri net can change by the firing of transitions.

The set of all states $s' \in \mathbb{N}^{|P|}$, reachable from s_0 by the firing of a transition word $w \in T^*$, written as $s_0 \xrightarrow{w} s'$, builds the state space and is denoted with S. A Continuous Time Markov Chain (CTMC) is a 3-tuple (S, \mathbf{R}, s_0) with S denoting the set of reachable states of the underlying net, $\mathbf{R} : S \times S \to \mathbb{R}_{\geq 0}$ the rate function, and s_0 the initial state.

Direct method by Gillespie (1977), computational complexity is O(T).
Next reaction method by Gibson & Bruck (2000), computational complexity is O(log T).



Phosphate Regulatory Network



Figure 1:

Petri net model of the phosphate regulatory network, along with a schematic representation of the membrane and of some relevant proteins [1]. Biomolecular components and their functional states are represented as places, (bio-) chemical reactions are represented as transitions. Stoichiometric reactions are represented as standard arcs, allosteric interactions of proteins by read arcs and inhibitory arcs. Organic and inorganic phosphate is supplied by the environment of the cell at constant concentration.

Figure 2:

Response of the phosphate regulatory network to step-wise changes in the supply of external inorganic phosphate. Traces were obtained by averaging 50,000 simulation runs [1].

Model checking

A more sophisticated analysis approach is model checking. It automatically determines whether a system satisfies a specific property expressed in some kind of temporal logic.

Transient analysis What is the probability to reach within time τ a state where the sum of molecules of the species A and B is not less than *threshold*?

 $\mathcal{P}_{=?}[\mathbf{F}_{[0,\tau]}(A+B \ge threshold)].$

Steady state analysis What is the probability the sum of molecules of the species A and B is not less than threshold at the steady state.

 $\mathcal{S}_{=?}[A+B \ge threshold].$

MARCIE

MARCIE [4] is a multi-threaded tool for the analysis of Generalized Stochastic Petri Nets. Its capabilities range from standard properties of Petri nets to CTL and CSL model checking, extended by rewards.

MARCIE provides the three base case techniques of stochastic analysis: exact numerical analysis, approximative numerical analysis, and stochastic simulation [3].



Snoopy [2] is set up as unifying Petri net framework, comprising a family of related Petri net models, sharing structure, but being specialized by their kinetic information: qualitative (time-free) place/transition Petri nets (QPN) as well as quantitative (time-dependent) Petri nets such as stochastic Petri nets (SPN), continuous Petri nets (CPN) and hybrid Petri nets (HPN). Furthermore it provides "colored" versions of the above mentioned net classes. Snoopy offers built-in animation (QPN) and simulation (SPN, CPN). This provides the grounds to investigate one and the same model in various complementary ways.

Snoopy supplies two features for the design and systematic construction of larger Petri nets. **Logical nodes** (places/transitions) serve as connectors and are used, e.g., for species involved in several reactions. **Macro transitions** (macro places) help to hide transition-bordered (place-bordered) subnets in order to design hierarchically structured nets.

The experimental results presented in [4] suggest that specifically for biological networks MARCIE is currently the most efficient model checking tool.

References

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