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HYBRID EXECUTION OF DYNAMIC RULE-BASED MULTI-LEVEL MODELS

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ABSTRACT

Hybrid algorithms are a promising approach to speed-up the execution of multi-scale biochemical reaction networks, i.e., networks with reactions that operate on different time scales. The basic idea is to use the quasi-steady state distribution of the fast reactions, computed either analytically or empirically, to update the propensities of slow reactions and to apply a stochastic simulation algorithm to compute the slow reactions. We apply this approach to multi-level models. Executing multi-level models that are characterized by dynamic nested structures by these hybrid algorithms poses specific challenges. For example, all reactions, even fast reactions, can change the structure of the model and consequently the set of reactions. To evaluate our approach, we use the rule-based multi-level language ML-Rules.

1 INTRODUCTION

The execution of biochemical multi-scale models, i.e., models with different temporal scales, can be improved significantly by using hybrid variants of the stochastic simulation algorithm (SSA) (Gillespie 1977), e.g., the slow-scale SSA (Cao, Gillespie, and Petzold 2005) or the nested SSA (E, Liu, and Vanden-Eijnden 2005). Basically, these algorithms firstly partition the set of reactions and species into slow and fast reactions and species. Afterwards, a quasi-steady state approximation is used to approximate the behavior of the fast reactions and species as well as to adapt the propensities of the slow reactions. To apply the approximation, two stochastic stiffness conditions must be satisfied: the fast reactions and species must be stable, i.e., a quasi-steady-state distribution must exist and this distribution must be reached fast, i.e., much faster compared to the firing time of the next slow reaction. Finally, a normal SSA step is executed with the set of slow reactions and the whole procedure is repeated until a simulation end criterion is fulfilled.

Many variations of this algorithm exist to improve its performance or enhance its applicability, but to our knowledge non of these deal with multi-level models. Multi-level models describe systems at different organizational levels and support upward and downward causation, i.e., direct interaction between such levels. Such models play an important role within the realm of molecular and cell biology (Noble 2008), e.g., to describe models with intercellular and intracellular entities and dynamics. ML-Rules is one rule-based multi-level formalism to describe such cell biological models (Maus, Rybacki, and Uhrmacher 2011). It allows the modeler to describe models with a dynamic structure and interaction between different organizational levels, e.g., the diffusion of proteins into and out of cells. Entities in ML-Rules are represented in a discrete population-based manner, i.e., entities have amount variables and identical entities are merged. Entities are identical if and only if they have the same name, the same attributes and they contain an identical set of sub entities. To speed up the execution time of multi-scale models written in ML-Rules, we develop a hybrid SSA for multi-level models.

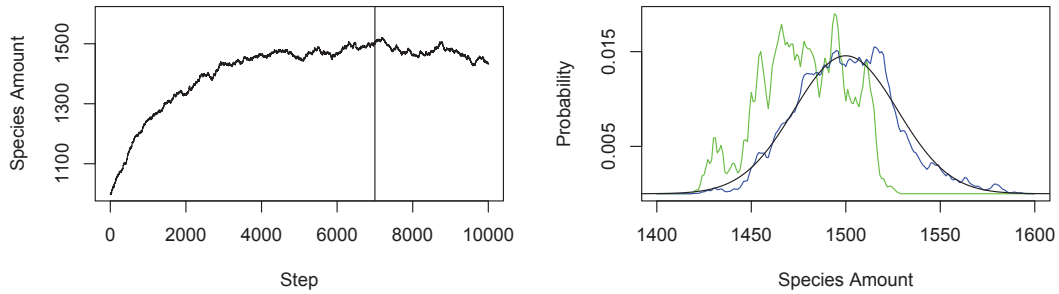

Figure 1: Suppose a simple model with a cell and a species diffusing into the cell and out of the cell with the same rate. The results of one replication are shown. The figure on the left illustrates the species amount within the cell. The used steady state estimator estimates the start of a steady state at step 7000. The figure on the right represents the approximated stationary distribution of this species after 10000 steps (green) and 100000 steps (blue) compared to the analytical result (black).

2 RESULTS

The structure of our hybrid SSA for ML-Rules is similar to the structure of the hybrid algorithms described above. Initially, the set of reactions is computed at the beginning of each step. Afterward, the reactions and species are partitioned into slow and fast reactions and species. Besides both stochastic stiffness conditions, fast reactions and species must additionally satisfy a third condition: they are not allowed to change the structure of the model, i.e., the species tree is not allowed to change due to fast reactions. Structural changes lead to a variable set of reactions and species and consequently are not practicable to be applied for the quasi-steady state approximation. Due to multi-level rules, it is usually not possible to compute one quasi-steady state approximation for each context, so that currently one approximation is computed for the whole model. So far, we approximate the stationary distribution by initially executing the fast process until it reaches a steady state (see Figure 1 left) and afterward execute a specific number of fast steps. During each fast step, the amount of each species is observed and used to calculate its stationary distribution (see Figure 1 right). The number of fast steps is adapted during the simulation. After approximating the stationary distribution, the slow reactions are changed accordingly, one normal SSA step is executed with the set of slow reactions and the next step is computed. Thereby, a challenge is represented by the discrete population-based execution of ML-Rules models, because all reactions within a context species could lead to a change of the species tree due to merging identical species. To solve this problem, we introduce another hybrid scheme: species which do not contain other species (leaf species) are treated population-based, whereas species which contain other species (context species) are now treated individual-based. All in all, we already achieve a speed-up about two orders and more with a negligible loss of accuracy by using our hybrid approach for initial benchmark multi-level models.

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