

## Exact Stochastic Simulation with Event Leaping

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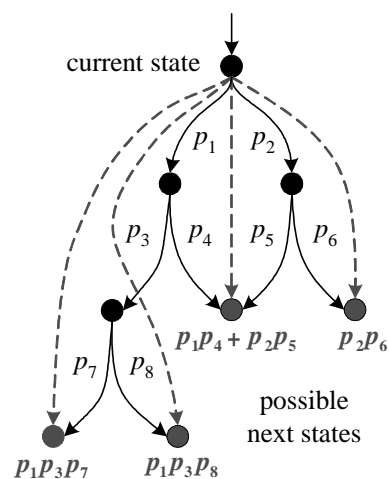
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Stochastic simulation has become the workhorse of computational biology. First proposed by Gillespie<sup>1</sup>, the mesoscopic framework for chemical kinetics assumes that a spatially homogenous mixture of reactants behaves as a discrete stochastic process. The simulation tracks integer quantities of the molecular species, executing reactions at random based on propensity calculations. Repeated trials are performed to characterize the evolution of the system.

The drawback of this approach is that many trials must be performed to obtain an accurate estimate. Each trial may consist of hundreds of thousands of reaction events. A separate random number must be generated for each event – a costly step from a computational standpoint. For networks with reversible reactions, it may be seen that the trajectories generally contain cycles; hence, the simulation loops through the same sequence of states repeatedly. This often contributes to prohibitively long simulation times. Several methods have been proposed to improve the efficiency, e.g., *time leaping*<sup>2</sup> and *partial equilibrium* analysis.<sup>3</sup> These methods are *inexact*, involving approximations that are not always applicable. Other improvements include optimized data structures.<sup>4</sup>

We propose a new *exact* algorithm that reduces simulation times through *event leaping*: multiple reactions are executed in a single step. This results in much more efficient utilization of random numbers. Furthermore, looping is eliminated.

Leaping is performed by analyzing the probabilities of different *sequences* of reactions occurring. As illustrated in the figure on the right, the reaction probabilities (denoted  $p_i$ ) are multiplicative along each sequence and additive when two sequences merge. Beginning at the current state, the sequences are extended – most probable first – until their probabilities drop below a threshold. Then, based on a single random number, the simulation leaps directly to one of the next states. (The possible leaps are indicated by dashed lines.) If a cycle is encountered, the *exit* probabilities are computed and the simulation leaps directly to one of the exit states.



We compare the simulation times required with event leaping vs. those with previous methods on several models. In all cases, the improvement is substantial – sometimes as much as an order of magnitude.

1. D. Gillespie, *J. Physical Chemistry*, Vol. 81, No. 25, 1977.
2. D. Gillespie, *J. Chemical Physics*, Vol. 115, No. 4, 2001.
3. Y. Cao, D. Gillespie and L. Petzold, *J. Computational Physics*, Vol. 206, No. 2, 2005.
4. M. Gibson and J. Bruck, *J. Physical Chemistry A*, Vol. 104, No. 9, 2000.