Coarse-Grained Stochastic Particle-based Reaction-Diffusion Simulation Algorithm

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***Short Abstract* — The stochastic, diffusive motion of molecules influences the rate of molecular encounters and hence many biochemical processes in living cells. Tiny time steps are typically required to accurately resolve the probabilistic encounter events in a simulation of cellular signaling, creating the dilemma that only simplistic models can be studied at cell-biologically relevant timescales. Particular solutions of the diffusion equation, Green's functions, allow for larger time steps and more efficient simulations by detecting otherwise unnoticed encounter events. However, previous implementations of Green's functions based approaches were not generally applicable to reaction-diffusion problems. We generalized the method to reflect the physiologically relevant case of reversible, partially diffusion-controlled reactions. Here we discuss how the approach can be applied in computational cell biology, taking advantage of an efficient approximation technique that allows us to include the mathematically challenging case of 2D reaction-diffusion systems on membranes as well. The resulting algorithm is easily implementable, flexible and efficient and provides a coarse-grained but nevertheless detailed, stochastic representation of biochemical processes.**

I. Background

MANY biochemical processes in living cells are strongly influenced by the stochastic fluctuations governing the interactions among their molecular components. Also, cellular biochemical networks typically operate in environments that exhibit spatially intricate, highly heterogeneous organizations with aspects such as compartmentalization and molecular scaffolding playing important roles. In the case of diffusion-influenced reactions, the Brownian motion of the individual molecules becomes an important element of the theoretical description. In recent years, several particle-based stochastic simulation algorithms (PSSA) have been developed [1, 2] to study the spatially resolved dynamics of biochemical networks at a molecular scale. A challenge all these approaches have to address is to allow for simulations at cell-biologically relevant timescales without neither neglecting important spatial and biochemical properties of the simulated system nor introducing ad-hoc assumptions not based on physical principles. Here we describe a PSSA that addresses the typical disadvantage of Brownian dynamics, namely the need to use small time steps to resolve bimolecular encounters accurately, and permits large time steps while still retaining a high degree of accuracy.

II. Results

To correct for underestimating the number of encounters we employ the 3D and 2D analytical representations of the fundamental solutions of the associated Smoluchowski equation with absorbing, reflecting and radiation boundary conditions. These Green's functions can be used to compute the probability that particles that do not overlap after a time step nevertheless reacted at some intermediate time during the time step. The method has previously been proposed for the case of purely absorbing boundary conditions and irreversible reactions [3]. Here, we build on this approach to develop a general purpose simulation framework applicable to a broad class of reaction-diffusion systems by extending it to include reflective and radiation boundary conditions and reversible reactions [4]. Furthermore, we describe how to treat reaction-diffusion systems in 2D. In this case, the radial Green's functions cannot be expressed by elementary functions, in contrast to their 3D counterparts. As a consequence, their numerical approximation is more costly, an issue that becomes worse for smaller time steps. To address this problem, we derive small time expansions for the key expressions. These small time expansions permit to circumvent a numerical integration and should prove useful for any simulation algorithm employing 2D Green's functions.

References

[1] J. van Zon, P. ten Wolde (2005), Simulating Biochemical Networks at the Particle Level and in Time and Space: Green's Function Reaction DynamicsPhys, Rev. Lett. **94** 128103

[2] T. Opplestrup, et al. (2006), First-Passage Monte Carlo Algorithm: Diffusion without All the Hops, Phys. Rev. Lett. **97** 230602

[3] T. Barenbrug, E. F. Peters, J. Schieber (2002), Accurate method for the Brownian dynamics simulation of spherical particles with hard-body interactions, J. Chem. Phys. **117** 9202

[4] T. Prüstel, M. Meier-Schellersheim, Coarse-Grained Stochastic Particle-based Reaction-Diffusion Simulation Algorithm, arXiv:1107.0270 [q-bio.QM]

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