SpatKin: spatially-resolved rule-based modeling of biochemical systems on the membrane

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***Short Abstract* — We present a rule-based algorithm and its implementation, SpatKin, designed for spatially-extended simulations of signaling on the plasma membrane. The software allows for the exact simulation of the time-continuous Markov process. Specific biochemical reactions and molecule movements are created on-the-fly based on rules defined by the user. In the limit of infinite diffusion, the method becomes equivalent to the NFsim algorithm. However, in realistic conditions the diffusion in the membrane is limited, and, as demonstrated with several examples, the diffusion coefficient qualitatively influences the dynamics of the signaling system.**

***Keywords* — stochastic simulation software, kinetic Monte Carlo, spatially extended system, rule-base modeling**

I. Motivation

Processes on the cell membrane are characterized by relatively small diffusivity ($D \approx 0.1$ μm^2/s), which together with high reaction rate constants (of order of $k \approx 1$/s) implies correlation length $L = (D/k)^{1/2} = 0.1$ μm, much smaller than the cell diameter. Consequently, the number of molecules in the area L^2 is small, and the cell membrane behaves as an intrinsically noisy biochemical reactor. The spatial distribution of reactants resulting from intracellular confinement and limited diffusion has a significant impact on the stochastic system dynamics. Independently, since biomolecules often comprise multiple components, their interaction networks suffer from inherent combinatorial complexity. Such systems can be modeled adequately only when the convenient abstraction of interactions is coupled to the spatial resolution of the simulated reactor. Motivated by this requirement, we developed a method dedicated to the rule-based modeling of spatially-extended membrane systems along with its software implementation, SpatKin.

II. Method

The algorithm ensures the exact state-to-state dynamics of the underlying time-continuous Markov process: competing reaction and molecule displacement events are selected from the catalog of possible events, and are fired with their propensities proportional to the corresponding rate constants. In one step, a molecule can move to an adjacent empty (unimolecular) lattice site or a bimolecular reaction can occur between molecules that are placed in adjacent sites. The catalog is always complete as, after performing any reaction, it is updated by considering every possible new event that may happen in the updated system. The network of possible interactions is evaluated on-the-fly for existing molecular species according to the rules specified by the user as in NFsim [1]. Complete updates are feasible due to the fact that the space is discretized using a triangular lattice. Local updates and global look-ups are efficient due to the hybrid use of hierarchical space-partitioning trees and hash tables. The method is rejection-free unless there are special regions of diminished diffusivity defined in the lattice. In the limit of infinite diffusion, the algorithmic approach is equivalent to the Gillespie algorithm; for fast diffusion and larger reactors, where the grain size becomes irrelevant, simulation results correspond to that obtained with PDEs.

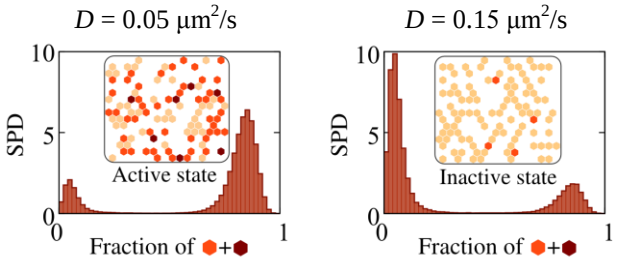

Figure 1. In the bistable kinase autoactivation system the stationary probability distribution of active kinase depends on the diffusivity, D.

III. Applications

The method is implemented as an application equipped with a graphical user interface and several tools for trajectory visualization and result analysis, offering a modest integrated desktop environment for the development of spatially-extended models. Rules are defined using the convention similar to the BioNetGen language.

SpatKin has been used to study a bistable kinase auto-activation model, leading to conclusions on the optimal diffusivity range required for efficient signal perception and transduction. The software is being currently applied to modeling early events of B cell receptor signaling with explicit handling of the dynamics of multivalent ligands and heterogeneous plasma membrane organization. Spatial effects such as cytoskeletal corralling, receptor clustering and molecular crowding can be analyzed within SpatKin.

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IV. References

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