Stochastic Transitions in a Bistable Reaction System on the Membrane

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***Short Abstract* — We studied the interplay between stochastic switching and traveling wave propagation for a prototype bistable system of kinase–phosphatase interactions on the plasma membrane. Within microscopic kinetic Monte Carlo (KMC) simulations on the hexagonal lattice, we observed that for finite diffusion the behavior of the spatially extended system differs qualitatively from the behavior of the same system in the well-mixed regime. Even when a small isolated sub-compartment remains mostly inactive, the chemical traveling wave may propagate, leading to the activation of a larger compartment. The activating wave can be induced after a small subdomain is activated as a result of a stochastic fluctuation. Such a spontaneous onset of activity is radically more probable in subdomains characterized by slower diffusion. A local immobilization of substrates can thus lead to the global activation of membrane proteins by the mechanism that involves stochastic fluctuations followed by the propagation of a semi-deterministic traveling wave.**

***Keywords* — multistability, spatially extended system, Markov process, kinetic Monte Carlo on the lattice**

I. Methods

In order to understand the principal mechanisms of state-to-state transitions in spatially extended systems, we employed KMC simulations on the 2-D lattice. We consider a model of auto-activating kinases. Each kinase molecule can be in one of three states: unphosphorylated k (yellow), monophosphorylated k_p (orange) and bisphosphorylated k_{pp} (brown). Catalytic activity of a kinase grows with its phosphorylation status. Kinase molecules can trans-phosphorylate when they occupy adjacent lattice sites, and can be dephosphorylated by adjacent phosphatases. All molecules diffuse with the same motility M, which can vary across the reactor.

II. Results

We demonstrated that, even if the system in the well-mixed compartment is mainly inactive, the activating traveling waves may propagate in larger compartment (see Fig. 1). For sufficiently large diffusion, these waves propagate in a semi-deterministic manner, and can be well approximated by solutions of corresponding reaction–diffusion equations. We also found that, depending on the reaction rate constants, either activating or inactivating waves may propagate. Interestingly, these waves can arise spontaneously because of local stochastic switching and this mechanism becomes the dominant mode of macroscopic state-to-state transitions in spatially extended systems. Accordingly, we found that macroscopic state-to-state mean first-passage times (MFPTs) increase exponentially with the volume of the reactor but only in the well-mixed regime, and then decrease as volume^{-1} for larger reactors, which is in stark contrast to perfectly mixed reactors. Since at large diffusivities more molecules are communicated, MFPTs are longer (Fig. 2). Furthermore, spatially extended reactors of similar volumes but different geometries can have vastly different times to activation.

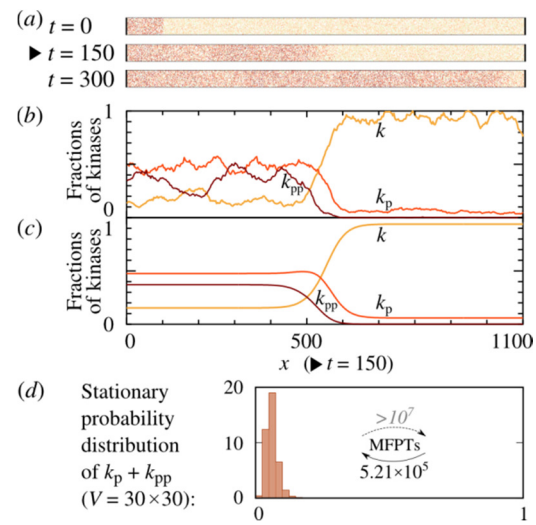

Figure 1. (a) Three snapshots from kinase activity wave propagation on the cylindrical domain 30×1100, motility M = 3000. (b) Kinase activity profile across the domain at t = 150, averaged using the sliding window of width w = 11. (c) Kinase activity profile obtained from corresponding PDEs. (d) In the well-mixed (M = ∞) isolated chamber 30×30 the system is inactive.

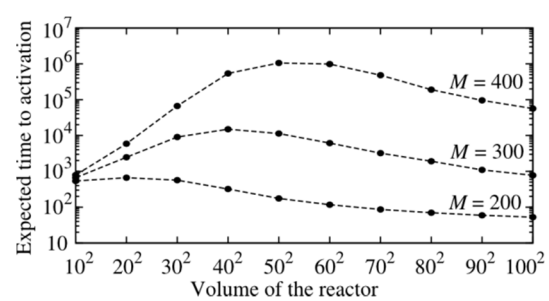

Figure 2. MFPTs for activation as a function of the volume of the square-shaped reactor with periodic boundary conditions, obtained in on-lattice KMC simulations for three values of motility M.

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IV. References

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