Diffusion- and Geometry-Influenced Stochastic Switching in a Reaction Network with Positive Feedback

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***Short Abstract* — In signal transduction, cells propagate information in response to various stimuli by means of biochemical reaction networks. Positive feedback between two molecular species in a network can lead to bistability, and spontaneous fluctuations in numbers of molecules can lead to stochastic switching between the two states. In this work, we use stochastic simulations [1] to investigate the role of spatial confinement and diffusion on stochastic switching in a simple reaction network with positive feedback. Characteristics of the bistability and stochastic switching depend on system shape, reaction volume, and diffusion coefficients.**

***Keywords* — Bistability, positive feedback, stochastic switching, signal transduction**

I. Purpose

STOCHASTICITY and spatial organization can each play important roles in the emergent behavior of biochemical reaction networks with positive feedback. Fluctuation-induced transitions between stable steady states may occur in the bistable regime by a phenomenon known as stochastic switching. Unlike well-mixed systems, in a spatially resolved system, such transitions may occur by spatially inhomogeneous pathways. For example, fluctuations in the local concentration can nucleate a cluster of active molecules that then spreads in space [2]. Spatial clustering often leads to fast nucleation of active molecules and thus a rapid transition to the active steady state [3]. Biologically, we are interested in the difference between stochastic switching in the cytoplasm and stochastic switching in confined regions such as the membrane.

A simple and well-studied two-component reaction network that exhibits bistability by means of positive feedback can be described by the following reactions:

$$A \leftrightarrow X$$

$$A + 2X \leftrightarrow 3X$$

Here, we say that X is the molecular species that prompts system activation and that a system with high X molecule concentration is in the active state. The rate constants allow for bistability under reasonable reaction conditions.

II. Results

We utilize the Gillespie algorithm to generate many spatially resolved stochastic trajectories under various conditions [1]. In the well-mixed case, the initial concentration of each species influences the distribution of steady states sampled within a fixed time window. In the spatially extended case, the molecular diffusion coefficients as well as the system size and shape also influence the distribution of stable steady states sampled within a fixed time window.

In the well-mixed case, we observe unidirectional stochastic switching from the active to inactive state in cases in which the system is in the bistable regime near the bifurcation point. To gain insight into stochastic switching from the inactive to active state in the spatially resolved system, we perturb the system with a pulse of X molecules in a localized region. The probability that the system is in the active state at a given time depends on the diffusion coefficient, and it increases when the initial X distribution is spatially clustered rather than homogeneously distributed. In three dimensions, the system shape plays a key role in the emergent dynamics. Systems of equal volume that have small aspect ratios are more likely to switch to the active state. Faster diffusion also results in faster activation and a larger steady state value of X molecule population.

III. Conclusion

Faster diffusion and larger concentrations promote the active steady state in the positive feedback network considered in this work. In a spatially resolved system, stochastic switching from the inactive to the active state often occurs as a result of nucleation of clusters of X molecules. Such clusters can form naturally by means of localized fluctuations or artificially by implementation of a pulse of desired size and concentration.

References

[1] Gillespie DT (2007) "Stochastic Simulation of Chemical Kinetics." *Annu. Rev. Phys. Chem.* **58**, 35-55.

[2] Das J, Kardar M, and Chakraborty AK (2009) "Positive Feedback Regulation Results in Spatial Clustering and Fast Spreading of Active Signaling Molecules on a Cell Membrane." *J. Chem. Phys.* **130**, 245102.

[3] Kochanczyk M, Jaruszewicz J, and Lipniacki T (2013) "Stochastic Transitions in a Bistable Reaction System on the Membrane." *J. R. Soc. Interface* **10**, 20130151.

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