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Stochastic switching in a spatially extended, bistable kinase autoactivation model

In this study we consider a spatially extended kinase autoactivation model with underlying bistability. We assume that kinases may diffuse on the cell membrane (or its restricted domain) and can be in one of three states: unphosphorylated, single or doubly phosphorylated. Catalitic activity of the kinase is regulated by its phosphorylation level; unphosphorylated kinases have the lowest activity, doubly phosphorylated – the highest. The emerging reactions are following:
$K_p \xrightarrow{d} K$, $K_{pp} \xrightarrow{d} K_p$ – dephosphorylation,
$K + K \xrightarrow{c_1} K + K_p$, $K + K_p \xrightarrow{c_1} K + K_{pp}$ – phosphorylation by K,
$K_p + K \xrightarrow{c_2} K_p + K_p$, $K_p + K_p \xrightarrow{c_2} K_p + K_{pp}$ – phosphorylation by K_p,
$K_{pp} + K \xrightarrow{c_3} K_{pp} + K_p$, $K_{pp} + K_p \xrightarrow{c_3} K_{pp} + K_{pp}$ – phosphorylation by K_{pp},
where d and $c_3 > c_2 > c_1$ are dephosphorylation and phosphorylations coefficients. Let us notice that for $c_1 = 0$ the state in which all kinases are unphosphorylated is absorbing.

We consider two limits:

(1) infinite diffusion for which the system can be considered as perfectly mixed and its dynamics is described by the two-dimensional Markov process, and simulated using the Gillespie algorithm,
(2) continuous limit in which evolution of concentrations is given by the system of partial differential equations.

We numerically investigated the activation process in the original model in SpatKin, a program designed to simulate reaction-diffusion processes on a triangular lattice. We observed that for biologically justified values of parameters the behavior of the system cannot be described in any of the two limits even qualitatively. In particular, we found that probability density distributions depend on the diffusion coefficient: bimodal distributions observed in the infinite diffusion limit become unimodal with decreasing diffusivity. We also found that in the bistable case the expected extinction time (i.e. the time in which the absorbing state is reached when $c_1 = 0$) grows with diffusivity and only in the infinite diffusion limit it becomes exponentially proportional to the number of molecules.

We conclude that the original Gillespie algorithm is not appropriate for simulations of spatially extended systems.

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