Simulating rare events in cell cycle regulation

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Short Abstract — Rare events become relevant when they have drastic consequences. For example, a rare failure in cell cycle regulation may result in tumor formation. Simulations of exponentially rare events generally require enhanced sampling techniques. While an arsenal of efficient methods are available for equilibrium systems, rare-event sampling schemes for driven systems such as gene-regulatory networks are relatively recent. We employ a generalized Forward-Flux Sampling method to investigate a simplified model of cell cycle regulation.

Rare events are ubiquitous in nature, but mostly go rightfully unnoticed. In rare cases, they trigger large-scale consequences and thereby become extremely relevant. Well-known examples include activated processes such as crystal nucleation and stress-induced crack formation but also stock market crashes. In biology, rare events on the single-cell level may get amplified by exponential growth and then lead to important consequences on the population or organism level. For example, a rare beneficial mutation can take over an entire bacterial population, rare switching into sporulation influences bacterial population survival [Veening,Smits & Kuipers 2008] and rare failure of cell cycle regulation can lead to tumor formation [Riley,Sontag,Chen & Levine 2008].

By definition, rare events differ significantly from the average behavior of a system; this makes them hard to study using analytic tools such as mean-field or perturbation theory. At the same time they are notoriously hard to simulate since the system dynamics generates an exponentially large number of irrelevant common events while very few of the interesting rare events occur in the available simulation time.

To cope with this problem, a number of enhanced sampling techniques have been developed in statistical physics, such as umbrella sampling [Torrie & Valleau 1977] , flat-histogram [Wang & Landau 2001] and multicanonical [Berg & Neuhaus 1992] methods, and transition-path sampling [Bolhuis,Chandler,Dellago & Geissler 2002] . These methods rely on the knowledge of the canonical distribution for re-weighting system states and are thus suitable only for equilibrium systems.

Forward-flux sampling (FFS) is a technique which allows simulation of rare events also in non-equilibrium systems, such as biochemical networks operating in living cells. FFS enhances those stochastic trajectories which are judged more likely to lead to a rare event of interest, based on a pre-defined progress coordinate. Since the steady-state distribution in phase space is not needed, FFS can simulate rare transitions in driven systems, and has been applied successfully to the study of bistable switches in biochemical networks, see [Allen,Valeriani & ten Wolde 2009] .

In adult non-regenerative tissues, the cell cycle is collectively regulated such that cell division occurs at an extremely low rate per cell. We employ a generalized FFS method to study rare events in simplified models [Tyson & Novak 2008] of cell cycle progression.

References

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