Transition paths of genetic switches from string-based weighted ensemble sampling

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***Short Abstract* — Gene regulatory networks with dynamics characterized by multiple stable states underlie cellular decision-making. Efforts to characterize global dynamics and switching mechanisms in these non-equilibrium systems have been motivated by studies of cellular development, reprogramming, and carcinogenesis. Numerical methods for sampling simulated stochastic trajectories can give insight to complex dynamics, while explicitly accounting for intrinsic molecular fluctuations. We use the weighted ensemble-based string method developed by Adelman and Grabe [1] to study pathways of transitions between stable states for a class of genetic switches. We find that the method can efficiently uncover detailed mechanisms of rare switching events in gene regulatory networks.**

***Keywords* — Gene regulatory network, dynamics, stochastic process, sampling algorithm**

I. Background

MULTI-stability in gene regulatory networks has been proposed as the basis for the existence of diverse cell states [2]. In this view, transitions between attractor basins represent observable changes in gene expression programs corresponding to critical cellular processes, including developmental fate decisions, carcinogenesis, cellular reprogramming, and phenotypic plasticity. As such, there is interest in characterizing the global dynamics of complex multi-stable networks, in order to gain insight into the stochastic fluctuations or environmental perturbations that drive transitions between cell states.

Approaches for describing dynamical landscapes and transition pathways of multi-stable biochemical networks have included large deviation theory [3], vector field decomposition [4], and direct numerical sampling of simulated trajectories [5,6]. Of these, direct sampling methods have the advantage of explicitly accounting for intrinsic molecular fluctuations, e.g., by the Chemical Master Equation via the Gillespie algorithm [7].

So-called string methods restrict sampling of simulated dynamic trajectories around a one-dimensional path ("string") through a high-dimensional state-space, by an adaptive partitioning. Combined with the weighted ensemble (WE) method from Molecular Dynamics, the WE-string algorithm allows efficient sampling of rare events in non-equilibrium (non-gradient) systems. Moreover, the simulation converges on the most probable transition pathway connecting two states, giving insight into processes involving collective dynamics of many variables.

II. Methods and Results

The WE-string method was applied to a class of biochemical network models for the genetic toggle switch. The sampling algorithm [1] was coupled to Gillespie simulations by the Stochastic Simulator Compiler [8].

Detailed mechanisms of rare switching between stable states (representing two alternative stable expression levels of mutually repressive transcription factors) were revealed by the WE-string method. Differences between forward and backward transition pathways between two states were observed, in agreement with previous results [4,5]. The converged transition path showed qualitative agreement with the transition state ensemble found by Forward Flux Sampling [5]. Furthermore, the WE-string method resolved additional intermediate states, involving transient unbinding of transcription factors from regulatory DNA sites. The ability of the method to uncover collective dynamics in gene regulatory networks was found to depend heavily on the choice of distance metric used to partition the state space.

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