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Transitions States of Stochastic Chemical Kinetic Systems

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Abstract. Based on Transition Path Theory (TPT) for Markov jump processes [1, 2], we develop a general approach for identifying and calculating Transition States (TS) of stochastic chemical reacting networks. We first extend the concept of probability current, originally defined on edges connecting different nodes in the configuration space [2], to each sub-network. To locate sub-networks with maximal probability current on the separatrix between reactive and non-reactive events, which will give the Transition States of the reaction, constraint optimization is conducted. We further introduce an alternative scheme to compute the transition pathways by topological sorting, which is shown to be highly efficient through analysis.

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Key words: Transition path theory, Markov chain, reacting network.

1 Introduction

Biochemical switches are nowadays widely found in gene regulatory networks and signal transduction pathways, in the form of networks of chemical reactions with multiple steady states such that transitions between different metastable states can occur due to stochastic fluctuations. From the modeling point of view, a biochemical network can be described by a set of chemical reactions with certain topological structures and rate functions, the latter of which, in the stochastic setting, provide transition probabilities between different states on fixed time horizons [3]. A hierarchy of models on different time and space scales have been applied to the understanding of intra-cellular bio-chemical systems. Graph based logic and kinetic models can be constructed from gene expression data through inductive or reverse engineering approaches, e.g., a variety of clustering algorithms have been used to group together genes with similar temporal expression

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patterns. A search for graph paths between two genes, for instance, would reveal interactions and functionings of network components. Dynamical behaviors of gene regulatory systems can be described using Ordinary and Partial Differential Equations (ODE/PDE), where interactions are represented as functional and differential relations between concentrations of reacting species.

Stochastic effects in biochemical reacting networks can be incorporated by specifying how probabilities of the system being in certain states evolve with time, which follows the master equation. The stochastic processes governing the dynamics of a reacting system therefore have the form of a Stochastic Differential Equation (SDE) driven by Brownian or Poisson noises. The challenge is that it is especially difficult to analytically solve the master equation involved in stochastic gene regulatory networks, which is often of high dimensions [6]. Direct simulation of the SDE's is also limited by the time scale separation between the fast relaxation to local steady states and rare transitions between metastable states.

A fundamental fact is that dynamics in nature works on very disparate time scales. Atomic vibration occurs on femto- to pico-second time scales (10^{-15} to 10^{-12} sec.), whereas our daily lives are organized on the time scale of hours or days. Although many physical or biological processes occur on intermediate time scales, there are still huge gaps between the different time scales. Consequently, most dynamic processes proceed in the form of rare events. The system under consideration spends most of its time in localized regions in configuration space. Only very rarely, it hops from one localized region to another. These localized regions are called metastable states. Chemical reactions, conformation changes of molecules, nucleation events in a first order phase transition are all examples of rare events, and so are many other dynamic processes in material science, biology and chemistry.

Intuitively, one can think of the dynamics of a system as the process of navigation over its potential or free energy landscape, under the action of small amplitude noise. The metastable states are the local minima of the energy, or the basins of attraction of the local minima, all called potential wells. Without the noise, the system will simply be stuck at the local minima. Noise makes it possible to move between different local minima. However, transition events are rare because the system has to overcome some barriers. These barriers can either be of an energetic nature or an entropic nature. An entropic barrier will arise for example when a diffusing particle tries to find a narrow exit over a flat but vast landscape.

Our objective is not to keep track of the detailed dynamics of the system, but rather to capture statistically the sequence of hops or transitions between different local minima or metastable states. This means that effectively, the dynamics of the system is modeled by a Markov chain: the metastable states are the states of the chain and the hopping rates are the transition rates between different states. When designing algorithms for accelerating molecular dynamics, our purpose is not to reproduce the detailed dynamics, but rather to capture the effective dynamics of the Markov chain.