Non-equilibrium Analysis of Stochasticity in Biochemical Reaction Networks

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***Short Abstract* — We describe a measure theoretic framework for describing temporal properties of Markov processes arising from models of biochemical reaction networks as well as sampling-based algorithms for estimating such properties for systems with vast numbers of states.**

***Keywords* —Biochemical networks, Low Copy Number.**

I. INTRODUCTION

THE chemical master equation for a system with a finite number of molecules yields a Markov Process [1] whose analysis can reveal the effects and possibilities of intrinsic noise [2]. This description is useful for modeling single cells, where low copy-numbers of some molecules can render a deterministic description incorrect. However, the number of states in the resulting Markov Process can be so exceedingly large that exhaustive enumeration of the states, required for exactly determining the properties of the process, is problematic or practically impossible.

Several techniques have been developed that allow one to probe such processes, most notably the stochastic simulation algorithm and its variations [3]. Recently, a method based on explicitly enumerating a large number of the states and grouping the rest into a *sink state* has been described [4]. These methods allow for certain properties to be obtained, such as the mean behavior and variance, or the probability of certain unlikely events. However, a general method for estimating general properties of Markov Processes that arise from biochemical models is not yet available. In this work, we propose (1) a framework based on measure theory that allows one to precisely capture every possible behavior of a system and (2) a set of sampling-based algorithms that allow one to estimate these properties for systems with vast numbers of states. Furthermore, we demonstrate the approach on several examples, both from the literature and using a testbed in our lab that allows us to examine variety of low-copy-number "chemical" reactions [5].

II. APPROACH

We consider Markov processes arising from biochemical networks with *outputs* such as the fluorescence intensity of certain molecules. The behavior is then captured by a measure on the set of all output sequences. If time is considered to be discrete, this results in the set Y^∞ of all infinite strings of outputs. If time is included, then infinite strings of alternating outputs and dwell times are produced. Several groups (e.g. [6]) define this measure by, for example, generating a σ-field with sets of the form

$$Y_0 \times [t_0, u_0] \times Y_1 \times [t_1, u_1] \times \ldots \times Y_n \times \infty .$$

This leads to several difficulties for our systems. In particular, the *distance* between two biochemical networks, determined by the difference between their measures, leads to the *discrete metric*. In contrast, we define a measure on the set of all finite behaviors (weighted by a function of their duration) that results in a metric on biochemical networks that is much more useful. For example, we can ask what the behavioral difference is between an actual system with intrinsic noise and ideal, noiseless system and use this to show some systems are less sensitive to noise than others.

The definition of distance between two systems is useful for analysis, but can also be estimated, even for large systems using either sampling or a directed stochastic simulation. We describe a family of such approximation algorithms that, given two biochemical reaction networks, compute an approximation of their distance.

We apply our approach to several examples from the literature and discuss, for example, their sensitivity to intrinsic noise. In addition, we have built a testbed that allows us to directly observe a class of chemical reactions in low-copy number environments [5]. To validate the approach, we compare the behavioral sensitivity of a variety of metabolic control techniques for controlling this system.

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Acknowledgements: This work was funded by NSF grant 0347955.

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