Safety Analysis of Sugar Cataract Development Using Stochastic Hybrid Systems

Derek Riley[+], Xenofon Koutsoukos[+], and Kasandra Riley[*]

[+]ISIS/EECS Vanderbilt University [*]Mayo Foundation
Nashville, TN 37235, USA Rochester, MN 55905, USA
Derek.Riley, Xenofon.Koutsoukos@vanderbilt.edu;riley.kasandra@mayo.edu

1 Introduction

Modeling and analysis of biochemical systems are important tasks because they can unlock insights into the complicated dynamics of systems which are difficult or expensive to test experimentally. A variety of techniques have been used to model biochemical systems, but the effectiveness of the analysis techniques is often limited by tradeoffs imposed by the modeling paradigms. Stochastic differential equations have been used to model biochemical reactions [5, 2]; however, analysis of these models has mainly been limited to simulation. Hybrid systems have also been used to model biochemical systems [4]; however, verification methods based on deterministic hybrid systems fail to capture the probabilistic nature of some biochemical processes and therefore may not be able to correctly analyze certain systems. Stochastic Hybrid Systems (SHS) have been used to capture the stochastic nature of biochemical systems but have previously only been used for simulations [10] or analysis of systems with simplified continuous dynamics [6].

In this paper we model Sugar Cataract Development (SCD) as a SHS, and we present a probabilistic verification method for computing the probability of sugar cataract formation for different chemical concentrations. An accumulation of sorbitol in the eye is theorized to be the main factor in the SCD process. Understanding the exact conditions that lead to the development of sugar cataracts will help scientists better predict and prevent the condition [2]. The chemical reactions and kinetic constants for the system have been previously studied [8].

The stochastic dynamics for biochemical processes can be accurately modeled by the chemical master equation which, however, is impossible to solve for most practical systems [5]. The Stochastic Simulation Algorithm (SSA) is equivalent to solving the master equation based on a discrete model by simulating one reaction at a time, but if the number of molecules of any of the reactants is large, the SSA is not efficient [10]. For verification, it is computationally intractable to enumerate all possible states of the model employed by the SSA. Our approach suggests starting with the continuous stochastic dynamics and generating discrete approximations with coarser (and variable) resolution unlike the fixed, overly-fine resolution of the SSA. The discrete approximations can then be used for verification of reachability properties [7].

The proposed verification method employs dynamic programming based on a discretization of the state space and suffers from the curse of dimensionality. To verify the SCD process, we have developed a parallel dynamic programming implementation of the verification algorithm that can handle large systems. Although scalability is a limiting factor, this work demonstrates that the technique is feasible for realistic biochemical systems.

2 Modeling SCD using SHS

A sugar cataract is a type of cataract which distorts the light passing through the lens of an eye by attracting water to the lens when an excess of sorbitol is present. The reactions involved in SCD are given in Table 1. The chemical species and concentration ranges for the SCD process are described in Table 2. The ranges are bounded and are estimated using realistic concentration values derived from experimental data and Michaelis-Menten constants (Km) defined as the rate of the reaction at half-maximal velocity [8].

Reaction	Kinetic constant	Rate
$E + NADH \rightarrow E - NADH$	$k_1 = 6.2$	Fast
$E - NADH \rightarrow E + NADH$	$k_2 = 33$	Fast
$E - NADH + F \rightarrow E - NAD^+ + S$	$k_3 = 0.0022$	Fast
$E - NAD^+ + S \rightarrow E - NADH + F$	$k_4 = 0.0079$	Fast
$E - NAD^+ \rightarrow E + NAD^+$	$k_5 = 227$	Fast
$E + NAD^+ \rightarrow E - NAD^+$	$k_6 = .61$	Fast
$E \rightarrow Z$	$k_7 = 0.0019$	Slow

Table 1. SCD reactions and kinetic constants

Following [10] we classify the reaction rates as either fast or slow. The slow reaction firing is described by a probabilistic rate function [10]. The dynamics of the fast reactions are described by the equation

$$dx_i = \sum_{j=1}^{M_{fast}} v_{ji} a_j(x(t))dt + \sum_{j=1}^{M_{fast}} v_{ji} \sqrt{a_j(x(t))} dW_j, \quad i = 1, ..., 7 \qquad (1)$$

where x_i is the concentration of the i^{th} chemical species, M_{fast} as the number of fast reactions, a_j as the reaction propensity of the j^{th} reaction, and W as an M_{fast}-dimensional Wiener process. The stoichiometric matrix v is a (M_{fast} X N) matrix which holds values representing the concentration of chemical species lost or gained in each reaction.

To capture the discrete dynamics due to the slow chemical reaction, it is sufficient to consider a hybrid system with one discrete state and with a self-transition representing an occurrence of the slow reaction. As time progresses, the state $x_i, i = 1, ..., 7$ evolves according to (1). When the discrete transition occurs, the concentration of E (x_5) jumps instantaneously according to the assignment

Reactant	Var.	[Min, Max] (μM)	Resolution (μM)
$NADH$	x_1	[0.0005, 10.0005]	1.0
$E - NADH$	x_2	[0.0005, 10.0005]	1.0
NAD^+	x_3	[0.0009, 10.0009]	1.0
$E - NAD^+$	x_4	[0.0009, 10.0009]	1.0
sorbitol dehydrogenase (E)	x_5	[0.0002, 1.0002]	0.1
fructose (F)	x_6	[0.2, 500.2]	20
sorbitol (S)	x_7	[0.2, 500.2]	20
Inactive form of E (Z)	-	[0.000002, 0.200002	-

Table 2. Chemical species properties for the SCD model

$x_5 := x_5 - d$ where d is a constant representing the Molar volume which the discrete transition consumes.

Biologists have determined that a ratio of sorbitol to fructose that is greater than one is correlated to the beginning stages of sugar cataract formation [2]. Therefore, we define the set of safe states as the set of all concentrations that satisfy $x_7 - x_6 < 1$, and we can then perform safety analysis on the system to determine the probability that a patient will develop a sugar cataract from any starting state.

3 Probabilistic Verification of SCD

In this section, we analyze the safety probability for the SCD model using the technique presented in [7]. The resolution parameters for the SCD system result in a discrete Markov Chain (MC) with approximately 800 million states. Storing the values at each state alone requires several gigabytes of memory, so we developed a parallel value iteration implementation to improve the performance of the algorithm. Assuming that the value at each state is updated periodically, the value iteration algorithm is guaranteed to converge in a parallel implementation [3]. The MC has a regular structure which improves the efficiency of the value iteration algorithm and allows us to implement a fairly straitforward partitioning technique for parallel implementation [9].

To visualize our results we plot projections of the data which show the safety probability for fixed values of the first five variables and the entire range for sorbitol and fructose. Figure 1 shows a projection of the value function along the safety boundary where $x_1 = 1.0, x_2 = 1.0, x_3 = 1.0, x_4 = 1.0, x_5 = 0.1$. This data could possibly be used to help better predict sugar cataracts by demonstrating where the safest and most unsafe concentrations exist. It could also give guidance for choosing the most effective of economical treatment to avoid the cataract development.

The SCD experiment took approximately 10 hours using 32 processors of the ACCRE computing cluster [1]. Currently, the bottlenecks of this approach are memory size and speed.

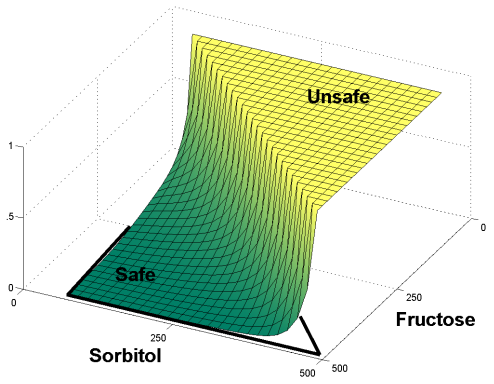

Fig. 1. Projection of the value function

Acknowledgements This research is partially supported by the National Science Foundation (NSF) CAREER grant CNS-0347440. We would like to thank Howard Salis and Yiannis Kaznessis from the University of Minnesota for their help with this project.

References

1. ACCRE computing cluster, http://www.accre.vanderbilt.edu
2. R. Barbuti, A. Maggiolo-Schettini, P. Milazzo, A. Triona, An Alternative to Gillespie's Algorithm for Simulating Chemical Reactions, *Computational Methods in Systems Biology 2005*, Edinburgh, 2005.
3. D. Bertsekas, J. Tsitsiklis, Parallel and Distributed Computation: Numerical Methods, Prentice-Hall, 1989.
4. R. Ghosh, C. Tomlin, Symbolic Reachable Set Computation of Piecewise Affine Hybrid Automata and its Application to Biological Modeling: Delta-Notch Protein Signalling, *Systems Biology*, 1:170-183, 2004.
5. D. Gillespie, A General Method for Numerically Simulating the Stochastic Time Evolution of Coupled Chemical Reactions. *J Comp. Phys.*, 22:403-434, 1976.
6. J. Hespanha, A. Singh. Stochastic Models for Chemically Reacting Systems Using Polynomial Stochastic Hybrid Systems, *Int. J. on Robust Control, Special Issue on Control at Small Scales*, 15:669689, 2005.
7. X. Koutsoukos and D. Riley, Computational Methods for Reachability Analysis of Stochastic Hybrid Systems, *Hybrid Systems: Computation and Control 2006* LNCS 3927, pp. 377-391, 2006.
8. I. Marini, L. Bucchioni, P. Borella, A. Del Corso, U. Mura, Sorbitol Dehydrogenase from Bovine Lens: Purification and Properties, *Archives of Biochemistry and Biophysics*, 340:383-391, 1997.
9. D. Riley, X. Koutsoukos, K. Riley, Safety Analysis of Sugar Cataract Development Using Stochastic Hybrid Systems, ISIS Technical Report ISIS-06-708.
10. H. Salis and Y. Kaznessis, Accurate hybrid stochastic simulation of a system of coupled chemical or biochemical reactions, *The Journal of Chemical Physics*, v122, pp. 54-103, 2005.