Verification of Biochemical Processes Using Stochastic Hybrid Systems

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***Abstract*— Modeling and analysis of biochemical systems are critical problems because they can provide new insights into systems which can not be easily tested with real experiments. One such biochemical process is the formation of sugar cataracts in the lens of an eye. Analyzing the sugar cataract development process is a challenging problem due to the highly-coupled chemical reactions that are involved. In this paper we model sugar cataract development as a stochastic hybrid system. Based on this model, we present a probabilistic verification method for computing the probability of sugar cataract formation for different chemical concentrations. Our analysis can potentially provide useful insights into the complicated dynamics of the process and assist in focusing experiments on specific regions of concentrations. The verification method employs dynamic programming based on a discretization of the state space and therefore suffers from the curse of dimensionality. To verify the sugar cataract development process we have developed a parallel dynamic programming implementation that can handle large systems. Although scalability is a limiting factor, this work demonstrates that the technique is feasible for realistic biochemical systems.**

I. Introduction

Modeling and analysis of biochemical systems are important tasks because they can unlock insights into the complicated dynamics of systems which are difficult 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 [8], [2]; however, analysis of these models has mainly been limited to simulation. Hybrid systems have also been used to model biochemical systems [1], [7]; 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 been used for simulations [20] or analysis of systems with simplified continuous dynamics [10].

In this paper we analyze the biochemical process of medication-controlled sugar cataract development in the lens of an eye. The enzyme sorbitol dehydrogenase catalyzes a reversible oxidation of sorbitol and other corresponding keto-sugars. An accumulation of sorbitol in the eye is theorized to be the main factor in the development of a sugar cataract. Medications exist which limit the effectiveness of the enzyme in the reactions which reduces the chance of developing cataracts, but also has other side effects.

The chemical reactions and kinetic coefficients for the model have been previously studied [17]. Understanding the exact conditions that lead to the development of sugar cataracts will help scientists better predict and prevent the condition [2]. Our analysis results can potentially provide useful insights into its complicated dynamics and assist in focusing experiments.

The stochastic dynamics of biochemical processes can be accurately modeled by the chemical master equation which, however, is impossible to solve for most practical systems [8]. 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 [20]. It is computationally intractable to enumerate all possible states of the model employed by the SSA for formal verification because the reaction rates depend on the concentrations and the SSA models individual molecules. Therefore, 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.

In this paper we use SHS to model a medication-controlled version of the sugar cataract development system. We then use a verification method based on dynamic programming to perform probabilistic safety verification to estimate the probability that the chemical concentrations will reach certain values. Early results of analysis of the sugar cataract development system without medication control are presented in [19].

The dynamic programming technique discretizes the continuous state space, so it suffers from the curse of dimensionality. Therefore, we have developed a parallel dynamic programming implementation of the verification algorithm. Although scalability continues to be a limiting factor, this work demonstrates that the technique is feasible for realistic biochemical systems.

The organization for the rest of the paper is as follows: Section 2 describes the related work, Section 3 describes modeling of biochemical systems and the sugar cataract development process using SHS, Section 4 describes the probabilistic verification method, Section 5 presents our experimental results, and Section 6 concludes the work.

II. Related Work

Many systems in the biological sciences can benefit from formal modeling and analysis methods. Hybrid systems have been used for modeling biological systems in order to capture the complicated dynamics using well-defined abstractions. Biomolecular network modeling is accomplished by using differential equations to model feedback mechanisms and discrete switches to model changes in the underlying dynamics [1]. Biological protein regulatory networks have been modeled with hybrid systems using linear differential equations to describe the changes in protein concentrations and discrete switches to activate or deactivate the continuous dynamics based on protein thresholds [7].

Stochastic hybrid systems further improve on the benefits of hybrid systems by providing a more realistic probabilistic framework for modeling real-world biochemical systems. A modeling technique that uses SHS to construct models for chemical reactions involving a single reactant specie is presented in [10]. A genetic regulatory network was modeled with a SHS model and compared to a deterministic model in [12]. SHS models of biochemical systems have been developed and simulated using hybrid simulation algorithms in [9], [20]. The modeling technique employed in this work is unique because it offers flexibility to include realistic system aspects such as medication or temperature.

This paper employs a reachability analysis method based on discrete approximations. Discrete approximation methods based on finite differences have been studied extensively in [16]. Based on discrete approximations, the reachability problem can be solved using algorithms for discrete processes [18]. The approach has been applied for optimal control of SHS given a discounted cost criterion in [13]. For verification, the discount term cannot be used and convergence of the value function can be ensured only for appropriate initial conditions. A related grid based method for safety analysis of stochastic systems with applications to air traffic management has been presented in [11]. Our approach is similar but using viscosity solutions we show the convergence of the discrete approximation methods [14].

III. Modeling Biochemical Reactions using SHS

A. Dynamics of Biochemical Reactions

All cellular function of living organisms is governed by complex systems of biochemical reactions. A reaction specifies all chemical species which react (reactants) and are produced (products). A kinetic coefficient k, associated with each reaction, numerically describes the affinity for the reactants to produce the products in constant temperature conditions.

Experimental analysis is used to physically measure the variation in individual concentrations of the chemical species in a biochemical system. However, understanding the dynamical behavior of biochemical systems requires running many experiments that can be time consuming, tedious, unsafe, or costly. Developing and analyzing dynamical models for capturing the evolution of individual chemical species concentrations can reduce the number of experiments needed.

Discrete models are a natural modeling paradigm for biochemical systems because reactions can be considered as occurring at specific points in time, and when a reaction occurs, individual molecules interact and produce new molecules. Discrete models update the concentrations of the involved reactants and products at a certain reaction rate based on the stoichiometry defined by the reaction.

Chemical reactions are inherently probabilistic because of the unpredictability of molecular motion [6], so their dynamics are best described by stochastic models. Discrete stochastic models of reactions can be created by describing a reaction j as firing at a rate a_j [5]. When the reaction fires, the concentrations of the reactants and products are reset to the appropriate updated values. Table I shows the rates and resets for several examples of different types of reactions. For example, when the reaction $X \rightarrow Z$ occurs, a molecule of X is consumed and a molecule of Z is produced denoted by $x- = 1$ and $z+ = 1$ respectively where x and z are the quantities of molecules of chemical species X and Z, and k_i is the kinetic coefficient for reaction i.

Reaction	a_j	Reset
$X \rightarrow Z$	$k_1 x$	$x- = 1;$ $z+ = 1;$
$X + Y \rightarrow 2Z$	$k_2 xy$	$x- = 1;$ $y- = 1;$ $z+ = 2;$
$2X \rightarrow Z$	$1/2 * k_3 x(x-1)$	$x- = 2;$ $z+ = 1;$
$2X + Y \rightarrow 2Z$	$1/2 * k_4 x(x-1)y$	$x- = 2;$ $y- = 1;$ $z+ = 2;$
$3X \rightarrow Z$	$1/6 * k_5 x(x-1)(x-2)$	$x- = 3;$ $z+ = 1;$

TABLE I
Example Reaction Rates and Resets

Reactions occur at different speeds depending on the concentrations of chemicals and the kinetic coefficient for each reaction. "Slow" reactions occur when reaction rates and concentrations are small enough and they can be modeled and simulated efficiently using discrete stochastic techniques. However, discrete simulations become inefficient when there are large concentrations of molecules and/or fast reaction rates. In such cases the reaction will occur very frequently and the discrete simulation will need to execute a large number of transitions in a short period of time. "Fast" reactions occur at a rate that is fast enough or in high enough concentrations. Such reactions can be modeled more efficiently as stochastic continuous models [20].

The rate of change of each chemical species is calculated using the dynamics from the biochemical reactions. Suppose that we have a system of M chemical reactions and N chemical species. We define x_i as the concentration of the ith chemical species in micro-Molarity (μM), M_{fast} as the number of fast reactions, a_j as the reaction propensity of the jth reaction, and W_j as a one-dimensional Wiener process. The stoichiometric matrix v is a (M_{fast} X N) matrix whose values represent the concentration of chemical species lost or gained in each reaction. Equation (1) describes the dynamics

for each of the i chemical species [20].

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

Discrete and continuous models consider only slow or only fast chemical reactions, but real biochemical systems often contain a mixture of both fast and slow reactions. In a such a situation it is most efficient to use a hybrid modeling approach to take advantage of the efficiency of continuous modeling while still keeping the accuracy of discrete modeling [20]. Stochastic hybrid systems are ideal for modeling biochemical systems with both fast and slow chemical reactions systems because they are able to model continuous and discrete dynamics in a stochastic framework. Fast reactions are modeled using the continuous stochastic dynamics techniques presented earlier, and slow reactions are modeled as discrete transitions with probabilistic rates and resets.

Determining which reactions are fast or slow is based on analysis of the rates using the kinetic coefficients and quantities of each reactant involved. The reaction rate range can be determined by analyzing the rate a_j from Table I over the entire range of possible chemical concentrations. To determine the smallest rate, the smallest concentrations for each chemical species should be used. Similarly, the largest rate can be determined by using the highest concentrations in the range. Reactions are classified as fast or slow depending on their relative speed differences [20].

B. Sugar Cataract Development

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. Often these cataracts are formed in the eyes of diabetes patients who do have highly fluctuating blood sugar levels. Several factors affect the accumulation of sorbitol including the amount of the enzyme Sorbitol Dehydrogenase (SDH). SDH catalyzes the reversible oxidation of sorbitol and other polyalcohols to the corresponding keto-sugars [17].

Reactant	Variable	[Min, Max] (μM)	Res (μM)
$NADH$	x_1	[0.0005, 10.0005]	1
$E-NADH$	x_2	[0.0005, 10.0005]	1
NAD^+	x_3	[0.0009, 10.0009]	1
$E-NAD^+$	x_4	[0.0009, 10.0009]	1
SDH (E)	x_5	[0.0002, 1.0002]	.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 II

CHEMICAL SPECIES PROPERTIES FOR THE SUGAR CATARACT MODEL

The chemical species and concentration ranges for the sugar cataract development process for bovine lens are described in Table II. The bovine lens data is used as a standard model for human cataract development. 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 [17]. Table III describes the seven reactions and rates involved in sugar cataract development. The rate is calculated based on the average concentrations in Table II and the kinetic coefficients presented in Table III. The average rate of the last reaction ($E \rightarrow Z$) is several orders of magnitude slower than the other reactions, so it is classified as a slow reaction.

The slow reaction describes the conversion of the enzyme (E) into its inactive form (Z) at a rate of $k_7 x_5$ according to Table I. When the reaction occurs, the number of molecules of E will be decreased by one and the concentration will be decreased by $d_1 = 10^{-21}$ μ Molar.

The rate of change of the concentrations of each chemical species are modeled using the SDE (1) and are given below. The inactive form of E (Z) is not a reactant in any of the chemical equations, so its concentration is not included.

$$\begin{aligned}
dx_1 &= (-k_1x_1x_5 + k_2x_2)dt - \sqrt{k_1x_1x_5}dW_1 + \sqrt{k_2x_2}dW_2 \\
dx_2 &= (k_1x_1x_5 - k_2x_2 - k_3x_2x_6 + k_4x_4x_7)dt + \sqrt{k_1x_1x_5}dW_1 - \sqrt{k_2x_2}dW_2 - \sqrt{k_3x_2x_6}dW_3 + \sqrt{k_4x_4x_7}dW_4 \\
dx_3 &= (k_5x_4 - k_6x_3x_5)dt + \sqrt{k_5x_4}dW_5 - \sqrt{k_6x_3x_5}dW_6 \\
dx_4 &= (k_3x_2x_6 - k_4x_4x_7 - k_5x_4 + k_6x_3x_5)dt + \sqrt{k_3x_2x_6}dW_3 - \sqrt{k_4x_4x_7}dW_4 - \sqrt{k_5x_4}dW_5 + \sqrt{k_6x_3x_5}dW_6 \\
dx_5 &= (-k_1x_1x_5 + k_2x_2 + k_5x_4 - k_6x_3x_5)dt - \sqrt{k_1x_1x_5}dW_1 + \sqrt{k_2x_2}dW_2 + \sqrt{k_5x_4}dW_5 - \sqrt{k_6x_3x_5}dW_6 \\
dx_6 &= (-k_3x_2x_6 + k_4x_4x_7)dt - \sqrt{k_3x_2x_6}dW_3 + \sqrt{k_4x_4x_7}dW_4 \\
dx_7 &= (k_3x_2x_6 - k_4x_4x_7)dt + \sqrt{k_3x_2x_6}dW_3 - \sqrt{k_4x_4x_7}dW_4
\end{aligned} \quad (2)$$

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 [3]. It has been shown that fructose (x_6) and SDH (x_5) play a significant role in the accumulation of sorbitol (x_7) in the eye which in turn begins the formation of sugar cataracts.

C. Medication Control

Medications exist which can help patients who are at high risk of developing sugar cataracts. These medications work by inhibiting the effectiveness of the enzyme SDH. The end result is a reduction in the rate at which the enzyme (E) reacts with other molecules in the system resulting in less sorbitol production; however, since the reversible reactions are tightly coupled, the results can have side effects.

The application of the medication can be represented as a new discrete mode in the hybrid model that captures the dynamics introduced by such a medication. In the medication application mode the reaction rates, where the enzyme is a reactant (k_1,k_6, and k_7), are reduced. The amount that the rates are reduced is directly proportional to the concentration of the medication administered, so we use a 50 percent reduction to model realistic behavior.

Since the amount of sorbitol is difficult to measure, we have modeled the medication administration based on an elevated level of fructose (as is the current practice). When the amount of fructose in the blood rises above 250 μMolar, we introduce the effect of the drug, and when the level drops below 250, we remove the effect of the drug, see Fig. 1. The guards ensure that the medication is administered according to the proper protocol, and the reset models the incrementing or decrementing of the fructose by $d_2 = 5$.

The analysis of this system will help the understanding of the conditions that could lead to a patient developing cataracts given a medication administration protocol and possibly identify better thresholds for drug prescription.

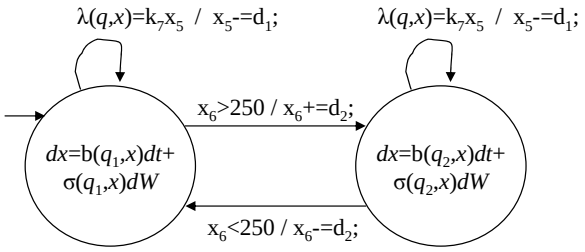

Fig. 1. SHS model of medication-controlled sugar cataract development

D. SHS Model of Sugar Cataract Development

The SHS model for medication-controlled sugar cataract development is shown in Fig. 1. In each discrete mode, the continuous state evolves according to the corresponding SDE where the solution is understood using the Itô stochastic integral. The drift vector $b(q, x)$ and the dispersion matrix $\sigma(q, x)$ are defined by Equation (2) and are bounded and Lipshitz continuous in x, and thus, the SDE has a unique solution for a fixed q.

Two types of discrete transitions can be used to define switching between the discrete modes: guarded transitions and probabilistic rate transitions. A guarded transition fires the instant when the guard becomes true. The firing of a probabilistic rate transition is governed by an exponential distribution characterized by the state-dependent transition rate $\lambda(q, x)$ which is assumed to be a bounded and measurable function that is integrable for every sample path.

Reaction	Kinetic coefficient	Rate
$E + NADH \rightarrow E - NADH$	$k_1 = 6.2$	31.1
$E - NADH \rightarrow E + NADH$	$k_2 = 33$	151
$E - NADH + F \rightarrow E - NAD^+ + S$	$k_3 = 0.0022$	6
$E - NAD^+ + S \rightarrow E - NADH + F$	$k_4 = 0.0079$	19.5
$E - NAD^+ \rightarrow E + NAD^+$	$k_5 = 227$	998
$E + NAD^+ \rightarrow E - NAD^+$	$k_6 = .61$	3.2
$E \rightarrow Z$	$k_7 = 0.0019$	0.002

TABLE III
SUGAR CATARACT REACTIONS AND KINETIC COEFFICIENTS

In general, the reset map is defined as a transition measure $R(s, A)$ that defines the probability distribution of the state after the jump and is assumed to be defined so that the system cannot jump directly into the set of safe states [14]. In the SCD system, the reset maps are deterministic and represent the increasing or decreasing of the corresponding chemical concentration (d_1 or d_2).

The SHS for the sugar cataract development is a special case of the SHS model described in [15]. In particular, this model has two discrete states, two probabilistic discrete transitions, two guarded discrete transitions, and deterministic reset maps. It is assumed that the expected number of discrete transitions in a finite time interval $[0, t]$ is finite; see [15] for sufficient conditions. Further, as described in Table II, the concentrations of the SCD system are assumed to be bounded.

We define the set of safe states as the set of all concentrations that satisfy $x_7 - x_6 < 1$ denoted by

$$\begin{aligned} B &= \cup_{q\in\{q_1,q_2\}}\{q\} \times B^q \\ &= \{(q, x)|x_7 - x_6 < 1,\ q \in \{q_1, q_2\}\}. \end{aligned}$$

Our problem is to determine what is the probability that the SHS will exit the safe set assuming an arbitrary initial condition inside the safe set.

IV. PROBABILISTIC VERIFICATION

A. Reachability Analysis

Given the set of safe states B, we consider the verification problem of computing the probability that the system execution from an arbitrary (safe) initial state will exit the safe set indicating the beginning stages of sugar cataract development. We denote ∂B and $\bar{B} = B \cup \partial B$ the boundary and the completion of B respectively. Consider the stopping time $\tau = \inf\{t \geq 0 : s(\tau^-) \in \partial B\}$ which is the first hitting of the boundary ∂B. Let $s = (q, x)$ be an initial state in B, then we define the function $V : \bar{B} \rightarrow \mathbb{R}$ by

$$V(s) = \begin{cases} E_s[I_{(s(\tau^-)\in\partial B)}], & s \in B \\ 1, & s \in \partial B \end{cases}.$$

where I denotes the indicator function.

The function $V(s)$ can be interpreted as the probability that a trajectory starting at x will reach the boundary ∂B of the safe set, i.e. the probability that the system is unsafe and sugar cataract formation may begin.

The value function V that characterizes the safety of sugar cataract formation can be described as the viscosity solution of a system of coupled Hamilton-Jacobi-Bellman (HJB) equations. This function is similar to the value function for the exit problem of a standard stochastic diffusion, but the running and terminal costs depend on the function itself. The coupling between the equations arises because the value

function in a particular mode depends on the value function in the adjacent modes and is formally captured by the dependency of the running and terminal costs on the value function V.

Proposition 1 We define a bounded function $c : \bar{B} \to \mathbb{R}_+$ continuous in x such that

$$c(q,x) = \begin{cases} 1, & \text{if } x \in \partial B^q \\ 0, & \text{otherwise} \end{cases}.$$

and denote $L^V(q,x) = \lambda(q,x)\int_\Gamma V(y)R((q,x),dy)$ and $\psi^V(q,x) = c(q,x) + \int_\Gamma V(y)R((q,x),dy)$. Then, V is the unique viscosity solution of the system of equations

$$b(q,x)D_xV + \frac{1}{2}\text{tr}(a(q,x)D_x^2V) + \lambda(q,x)V + L^V(q,x) = 0$$

in $B^q,\ q \in Q$, with boundary conditions $V(q,x) = \psi^V(q,x)$ on $\partial B^q,\ q \in Q$. The proof is a straightforward application of the results presented in [15] to the SHS of the sugar cataract development.

B. Numerical Methods Based on Dynamic Programming

One of the advantages of characterizing reachability properties using viscosity solutions is that for computational purposes we can employ numerical algorithms based on discrete approximations. We employ the finite difference method presented in [16] to compute locally consistent Markov chains (MCs). We consider a discretization of the state space denoted by $\bar{S}^h = \cup_{q\in Q}\{q\} \times \bar{S}_q^h$ where $\bar{S}_q^h$ is a set of discrete points approximating B^q and $h > 0$ is an approximation parameter characterizing the distance between neighboring points. By the boundness assumption, the approximating MC will have finitely many states which are denoted by $s_n^h = (q_n^h, \xi_n^h),\ n = 1, 2, \ldots, N$. The transition probabilities $p^h((q,x),(q',x'))$ of the Markov chain are computed to approximate the SHS while preserving local mean and variance.

Concentrations of chemical species are constrained to be non-negative, and therefore, reflective boundaries are introduced to approximate such constraints. For the approximating process, the constraints are modeled as reflective boundaries equipped with reflections directions that point into the state space. The process is reflected back when it tries to violate the constraints. Local consistency can be satisfied in a straitforward manner [16].

The value function V of the SHS can be approximated by

$$V^h(s) = E_s\left[\sum_{n=0}^{\nu_h} c(q_n^h, \xi_n^h) I_{(n=n_i)}\right].$$

The function V^h can be computed using a value iteration algorithm. The results in [15] show that the algorithm converges for appropriate initial conditions, and further, the solution based on the discrete approximations converges to the one for the original stochastic hybrid system as the discretization becomes finer ($h \to 0$). Regarding the efficiency of the computational methods, the iterative algorithm is polynomial in the number of states of the discrete approximation process. Although scalability is a limiting factor, using parallel methods the approach is feasible for realistic systems as the sugar cataract development, a seven-dimensional biochemical system for which the approximating process has approximately 800 million states.

V. Experimental Results

In this section we analyze the safety probability for the medicated SHS sugar cataract model. The chemical concentration ranges used are presented in Table II, and the resolution of each range is presented in Table II. We assume that the system includes reflective boundaries at the upper and lower limits of each range. This is reasonable since it is assumed that the ranges given include all possible states which are reachable, and the resolutions are sufficiently small for realistic approximation. We chose the resolution parameters to be similar to the resolution that measurement equipment can achieve in actual experiments. For example, the concentration of sorbitol can be experimentally measured with sub μMolar resolution.

The resolution parameters for the sugar cataract system result in an MDP 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. The value iteration algorithm is still guaranteed to converge in a parallel implementation as long as updated values are used periodically [4]. Parallel dynamic programming algorithms are well-defined and easy to implement [4]. Our MDP has a regular structure which improves the efficiency of the value iteration algorithm and allows us to implement a fairly straitforward partitioning technique for the parallel implementation.

To partition the problem for multiple processors we select five of the seven dimensions of the MDP to divide in half. Each processor only analyzes half of the total range for each of five divided ranges and the entire range for the other two dimensions. The two range divisions in five dimensions create $2^5 = 32$ range combinations that must be considered. The processors are each specifically assigned a combination of the ranges to ensure that the entire range for each dimension is computed, and all range values are arranged to minimize communication. Processors with neighboring range values regularly update their neighbors to ensure the value iteration converges.

To visualize our results we can plot projections of the data for different concentrations of the chemicals involved. Specifically, these projections show the safety probability for entire range of sorbitol and fructose levels for certain values of the five other variables. Multiple selections of the five other variables are chosen to show a more comprehensive view of the data.

Figure 2 shows a projection of the value function for the medicated SCD system along the safety boundary where $x_1 = 1.0$, $x_2 = 1.0$, $x_3 = 1.0$, $x_4 = 1.0$, and $x_5 = 0.1$. Near the boundary of the safe and unsafe regions, the value function varies significantly depending on the projection variables chosen. The results imply that certain chemical

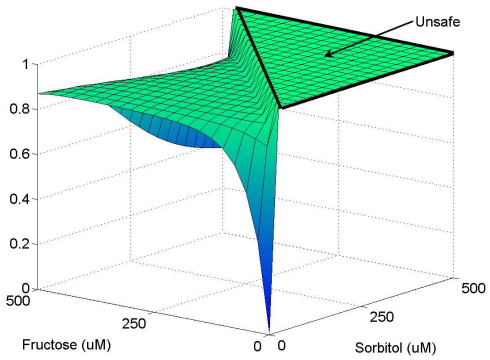

Fig. 2. Projection of the value function

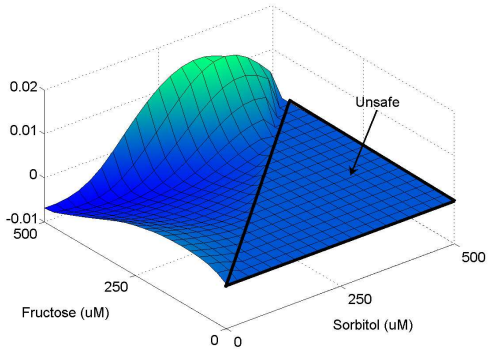

Fig. 3. Difference between medicated and non-medicated value functions

concentrations are more prone to developing cataracts than others.

Figure 3 shows the difference between the value functions of the medicated and non-medicated models. It demonstrates that the effectiveness of the medication is variable depending on the patient's current condition. This information could be used to help doctors and patients decide whether or not the benefits of the medication justify the costs or side effects.

The Advanced Computing Center for Research and Education (ACCRE) at Vanderbilt University provides the parallel computing resources for our experiments (www.accre.vanderbilt.edu). The computers form a cluster of 348 JS20 IBM PowerPC nodes running at 2.2 GHz with 1.4 Gigabytes of RAM per machine. We use C++ as the implementation language because ACCRE supports Message Passing Interface (MPI) compilers for C++. We use the MPI standard for communication between processors because it provides an efficient protocol for message passing middleware for distributed memory parallel computers. The sugar cataract experiment took approximately 10 hours on the 32 processors. Currently, the bottlenecks of this approach are the memory size and speed.

VI. Conclusions

Biochemical system modeling and analysis are important but challenging tasks which hold promise to unlock secrets of complicated biochemical systems. SHS are an ideal modeling paradigm for biochemical systems because they incorporate probabilistic dynamics into hybrid systems to capture the inherent stochastic nature of the biochemical systems. The sugar cataract development problem is excellent example of a system that is modeled effectively using the presented modeling methods. Our dynamic programming analysis technique provides verification results for realistic systems using parallel computing techniques to lessen the effect of the curse of dimensionality.

Acknowledgements This work is partially supported by the National Science Foundation CAREER grant CNS-0347440.

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