Effect of coarse-scale modeling on control outcome of genetic regulatory networks

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Abstract—Fine-scale models represented by stochastic master equations can provide a very accurate description of the real genetic regulatory system but inadequate time series data and technological limitations on cell specific measurements in cancer related experiments prevent the accurate inference of the parameters of such a fine-scale model. Furthermore, the computational complexity involved in the design of optimal intervention strategies to favorably effect system dynamics for such detailed models is enormous. Thus, it is imperative to study the effect of intervention policies designed using coarse-scale models when applied to the fine-scale models. In this paper, we map a fine-scale model represented by a Stochastic Master Equation to a coarse-scale model represented by a Probabilistic Boolean Network and derive bounds on the performance of the intervention strategy designed using the coarse scale model when applied to the fine-scale model.

I. INTRODUCTION

The sequencing of various genomes and technological advances in gene expression measurement over the last decade has provided tremendous opportunities for mathematical modeling of gene regulatory networks. There are two major objectives for modeling of genetic regulatory networks: first, to better understand the intergene interactions and relationships on a holistic level, thereby facilitating the diagnosis of disease; and second, to design and analyze therapeutic intervention strategies for shifting the state of a diseased network from an undesirable location to a desirable one. The first objective falls within the scope of the field known as Systems Biology, while the second objective falls within the scope of the field known as Systems Medicine.

The selection of a mathematical model to describe the dynamical behavior of a genetic regulatory network is dependent on the available data, estimation techniques, model complexity and specific purpose of constructing the model. From a Systems Biology point of view, the mathematical model must necessarily mimic the actual molecular biological interactions in as much detail as possible. A Stochastic Master Equation model can provide such detailed description of the dynamics of gene expression. However, the estimation of the parameters of the fine scale model requires larger data sets and preferably time series data. Furthermore, cell specific measurements instead of tissue averaged measurements are preferable for the inference of fine scale stochastic models. In the event of accurate inference of the parameters of the detailed model, the design of optimal intervention strategies for such a model possess a huge computational problem. From a Systems Medicine point of view, the network used for the purpose of design of intervention strategies can be a coarse representation of the biological phenomena occurring at the molecular level as long as it has the capability to faithfully capture the overall effects of intervention that are manifested at the phenotypic (observational) level. For intervention purposes, the effectiveness of drugs can usually be characterized by observing the expression levels of oncogenes, tumor suppressor genes and molecular markers of tumor progression represented by few discrete levels (mostly binary, ternary or quaternary). In one of our earlier case studies[1], [2], we were able to approximate our goal of intervention by the coarse-scale objective of minimizing the steady-state probability of mRNA molecules of a specific molecular marker of tumor progression (WNT5A) being higher than some threshold. In this context, an intervention approach designed from a coarse-scale model and producing the desired behavior in the coarse-scale model will be reasonable if the designed policy when applied to the fine scale model also produces similar coarse-scale behavior.

The basic systems approach to cancer therapy can be described as a series of steps shown in Fig. 1. Intervention in genetic regulatory networks has mainly been studied till date using the coarse scale Probabilistic Boolean Network model. In this paper, the detailed model is represented by a Stochastic Master Equation (SME) model and the coarse-scale model is represented by a Probabilistic Boolean Network (PBN). We use a mapping from SME to PBN that maintains the collapsed steady state probability distribution to explore the effect of the control policy designed using the PBN when applied to the SME model. The objective is to study
the conditions under which the desired control behavior can be attained in the fine-scale model by application of a control policy designed using coarse-scale models. We are assuming that the actual genetic regulatory network can be represented by a fine-scale stochastic master equation model but we are only able to infer a coarse-scale model due to limitations on experimental data. Our goal is to study the dynamic properties maintained by the coarse-scale model as compared to the fine scale model and the actual performance of the control strategy designed using the coarse-scale model.

The paper is organized as follows. We provide a brief description of the Stochastic Master Equation and the Probabilistic Boolean Network Model in Section II. Review of intervention is provided in Section III. The reduction mapping is presented in Section IV. We derived bounds on the control performance on Section V. Section VI contains a simulation example. Conclusions are provided in Section VII.

Fig. 1. Basic Steps involved in Modeling and Control of Genetic Networks : (A) Biological Experiments conducted to extract gene/ protein data (A1) Discretization of the Data (not required for continuous models) (B) Selection of a small set of genes relevant to the pathway of interest (C) Generation of the Network from the available data and prior biological knowledge (D) Intervention in the network with the objective of moving the network from undesirable to desirable states (E) Validation of the predictions arising from network analysis, validation of the intervention approach and closing the loop.

II. REVIEW OF GENETIC REGULATORY NETWORK MODELS

Given a set of genes/proteins, the evolution of their expression levels constitutes a dynamical system over time. A large number of approaches have been proposed to model the behavior of genetic regulatory networks, both deterministic and stochastic [3]. Nonlinear ordinary differential equations have been used in modeling molecular interactions [4]. Differential equation (DE) models assume that species concentration vary continuously and deterministically which is questionable in case of gene regulation [5]. Thus stochastic and discrete fine-scale models commonly known as stochastic master equation models have been proposed for modeling genetic regulatory networks [6]. To explain the stochastic master equation (SME) models for genetic regulatory networks, let us consider a system with \( n \) molecular species and \( m \) different reaction channels where the state of the system is defined by \( \mathbf{x} = [\phi_1, \phi_2, \ldots, \phi_i] \). \( \mathbf{x} \in \mathbb{N}^n \) is a vector of integers representing a specific population of each of the \( n \) molecular species. For such a system, given the probability density vector \( p(\mathbf{x}, t) \) at time \( t \), the probability that the system will be in the state \( \mathbf{x} \) at time \( t + dt \) is given by

\[
p(\mathbf{x}; t + dt) = p(\mathbf{x}; t)(1 - \sum_{\mu=1}^{m} a_{\mu}(\mathbf{x})dt) + \sum_{\mu=1}^{m} p(\mathbf{x} - v_{\mu}; t)a_{\mu}(\mathbf{x} - v_{\mu})dt
\]

where \( a_{\mu}(\mathbf{x})dt \) denotes the probability that the \( \mu \)th reaction will happen in a time step of length \( dt \) and \( v_{\mu} \) is the stoichiometric transition vector. From Eq. 1, the differential equation known as Chemical Master Equation (CME) [7] can be derived:

\[
\dot{p}(\mathbf{x}; t) = -p(\mathbf{x}; t) \sum_{\mu=1}^{m} a_{\mu}(\mathbf{x}) + \sum_{\mu=1}^{m} p(\mathbf{x} - v_{\mu}; t)a_{\mu}(\mathbf{x} - v_{\mu})
\]

By considering all the reactions beginning or ending at state \( \mathbf{x} \), the time derivative of the probability density of state \( \mathbf{x} \) can be written in vector form as [8]:

\[
\dot{\mathbf{p}}(\mathbf{x}; t) = [p(\mathbf{x}; t) \cdots p(\mathbf{x} - v_{m}; t)] \left[ -\sum_{\mu=1}^{m} a_{\mu}(\mathbf{x}) \cdots a_{m}(\mathbf{x} - v_{m}) \right] (3)
\]

As \( n \) is finite, the number of different possible vectors for \( \mathbf{x} \) is countable. Thus, we can map all the possible \( \mathbf{x}'s \in \mathbb{N}^n \) to a sequence \( x_1, x_2, \ldots \) of elements in \( \mathbb{N} \). Let us represent that enumeration as \( \mathbf{X} := [x_1, x_2, \cdots] \) and rewrite Eq. 3 as

\[
\dot{\mathbf{P}}(\mathbf{X}; t) = \mathbf{P}(\mathbf{X}; t) \mathbf{A}. (4)
\]

where \( \mathbf{P}(\mathbf{X}; t) = [p(x_1, t), p(x_2, t), \cdots] \) is the complete probability density state vector at time \( t \) and \( \mathbf{A} \) is the state reaction matrix. The matrix \( \mathbf{A} \) has the following properties : it is independent of \( t \), all of its diagonal elements are non-positive, and all of its off-diagonal elements are non-negative and all the rows sum to exactly zero. For the case of finite number of reachable states, the solution can be computed as \( \mathbf{P}(\mathbf{X}; t) = \mathbf{P}(\mathbf{X}, 0)e^{\mathbf{A}t} \) [8].
Discrete models with synchronous timing have been used since the late 1960s in the form of the Boolean network model [9]. In the Boolean model, the assumption of a single transition rule for each gene can be problematic with respect to inference. Thus, a new rule-based regulatory model, the probabilistic Boolean network (PBN) was developed [10]. A PBN is composed of a collection \( \{B_1, B_2, \cdots, B_r\} \) of finite-state-space networks having a small probability of perturbation \( p \) and a transition probability between the networks denoted by \( q \). The probabilistic structure of the PBN can be modeled as a Markov chain.

### III. Review of Intervention Using Genetic Regulatory Networks

A key objective of modeling genetic regulatory networks is to use them to design protocols for affecting network dynamics. To date, intervention studies have focused largely on BNs and PBNs [11], [12], [13] except few recent studies [14], [15] using detailed ordinary and stochastic differential equation models. The motivation behind application of control theory is to devise optimal policies for manipulating control variables that affect the transition probabilities of the network and can, therefore, be used to desirably affect its dynamic evolution. The initial control approaches utilized mean first passage times (MFPTs) [16] and stochastic control theory over finite-time horizon [17]. Subsequently, infinite-horizon control, with the goal of favorably altering the steady-state distribution of the network via a stationary control policy [1] was considered. In practice, intervention will be achieved by (a) targeted small molecule kinase inhibitors (Imatinib, Gefitinib, Erlotinib, Sunitinib etc.); (b) Monoclonal antibodies altering the protein concentrations (Cetuximab, Alemtuzumab, Trastuzumab etc.) or (c) gene knockdowns. The state desirability is determined by the values of genes/proteins associated with phenotypes of interest.

### IV. Reduction Mapping and Associated Transition Probabilities

If we consider the number of possible \( x_i \)'s to be finite, then the exact solution to the CME can be obtained through the exponential equation \( \mathbf{P}(X; t) = \mathbf{P}(X; 0)e^{At} \). This kind of situation can arise in biological systems where the number of mRNA/Protein molecules that can be generated are bounded. If for systems, the dimension of \( \mathbf{X} \) is infinite, we can apply the Finite State Projection approach [8] to arrive at a finite truncation of the state space. Henceforth, we will consider a CME with finite number of states \( M \) and our purpose is to transform that model to a smaller scale PBN model while maintaining some characteristics of the CME model. As the steady state distribution of the genetic regulatory network is considered representative of the phenotype, our objective will be to maintain the steady state distribution. The finite state continuous time CME model can be approximated by a discrete-time sampled Markov chain by using a suitable time period \( \Delta t \). The \( M \times M \) state transition probabilities of the discrete-time Markov Chain will be given by the equation \( \mathbf{P}_\Delta = e^{A\Delta t} \). We will map this transition probabilities to a \( N \times N \) transition probability matrix of a PBN where \( N = 2^n \) for binary levels and \( 3^n \) for the case of ternary levels. We will consider binary PBNs from now onwards but the derivation for more than 2 levels will be similar. Let \( T_i \) for \( i \in \{1, 2, \cdots, n\} \) denote the thresholds for binarization. For instance, if \( \mathbf{x}(t) = [\Psi_1, \Psi_2, \cdots, \Psi_n] \), then the corresponding state for the PBN is \( \mathbf{y} = [\psi_1, \psi_2, \cdots, \psi_n] \) where \( \psi_i = 1 \) if \( \Psi_i \geq T_i \) or \( \psi_i = 0 \) if \( \Psi_i < T_i \) for all \( i \in [1, 2, \cdots, n] \). As the states of the PBN will be \( n \)-dimensional vectors ranging from \( [0, 0] \) to \( [1, 1] \), we can represent them by the decimal equivalent state \( z(t) \) where \( z(t) \) ranges from 1 to \( 2^n \). Let us consider a sequence \( 0 = a_0, a_1, \cdots, a_N = M \) such that \( a_1 = a_i - 1 \) for \( i \in [1, 2, \cdots, 2^n] \) denote the number of states in the CME model that map to state \( i \) in the PBN model. The states of the CME model will be denoted by \( w(t) \) ranging from 1 to \( M \). The states will be re-ordered such that the states \( a_i = 1 \) to state \( a_i \) of the CME will be mapped to state \( i \) of the PBN for \( i = 1, \cdots, N \).

Let the state of the PBN at time \( t \) be \( z(t) = i \) and the state at time \( t + 1 \) be \( z(t + 1) = j \). The transition probability of going from state \( i \) to state \( j \) is given by [18]:

\[
P_r(i, j) = P(z_{t+1} = j | z_t = i) = \frac{\sum_{j_1 = a_{i-1}+1}^{a_i} \sum_{j_2 = a_{i-1}+1}^{a_i} P_{\Delta}(i_1, j_1)P(w_t = i_1)}{\sum_{j_2 = a_{i-1}+1}^{a_i} P(w_t = i_2)}
\]

We next show that if we use the steady state probabilities of the CME model for \( P(w_t = i_1) \) in Eq. 5, then the steady state probabilities of the resultant PBN, \( P_r \), will be the same as the collapsed steady state probabilities of the CME model. Here collapsing refers to the summation of the state probabilities of the detailed model that map to a certain state of the PBN model. For instance, if \( \eta \) represents the \( M \) dimensional steady state probability vector for the CME model, then the collapsed steady state vector will be a \( N \) dimensional vector represented by \( \zeta \) where \( \zeta(i) = \sum_{c=a_{i-1}+1}^{a_i} \eta(c) \) for \( i = 1, \cdots, N \). We next provide a theorem for the equivalence of \( \zeta \) and the steady state probabilities of the PBN represented by the...
following state transition probabilities:

\[ P_r(i,j) = \frac{\sum_{j_1=a_{j-1}+1}^{a_j} \sum_{i_1=a_{i-1}+1}^{a_i} P_\Delta(i_1,j_1) \eta(i_1)}{\sum_{i_2=a_{i-1}+1}^{a_i} \eta(i_2)} \]  

(6)

**Theorem IV.1.** With Eq. 6 denoting the transition probabilities of the PBN, the steady state probability distribution vector, \( \pi \), of the PBN is given by

\[ \pi(i) = \sum_{i_2=a_{i-1}+1}^{a_i} \eta(i_2) = \zeta(i) \]  

(7)

for \( i = 1, \ldots, N \).

The proof is available in [18].

We have established that if the transition probabilities of the PBN are decided based on Eq. 6, then the steady state probabilities of the generated PBN is same as the collapsed steady state probabilities of the original detailed network. Thus, we are able to maintain the collapsed steady-state probabilities which might be indicative of a phenotype. If we revisit Eq. 6, we notice that \( P_r(i,j) \) can be calculated from the transitions of the network once it has reached the steady state. If we observe the steady-state transitions of the genetic regulatory network accurately modeled by the CME for a long time and generate the state-transition probabilities of the PBN \( P_r(i,j) \) based on the number of transitions occurring from state \( i \) to state \( j \) divided by the total number of transitions from state \( i \), we will arrive at Eq. 6.

**V. EFFECT ON INTERVENTION PERFORMANCE**

Let us consider the case that we have two control actions at each time step and \( P_{\Delta_1} \) and \( P_{\Delta_2} \) represent the stochastic master equation / chemical master equation models corresponding to the two control actions. In practice, \( P_{\Delta_1} \) might represent the model of the network with no drug delivery and \( P_{\Delta_2} \) represent the model of the network following a drug delivery. Let, \( P_{r_1} \) and \( P_{r_2} \) represent the transition probability matrices of the PBNs generated from models \( P_{\Delta_1} \) and \( P_{\Delta_2} \) respectively using Eq. 6. Since, we will design the control policy based on the reduced model, our control design will be based on \( P_{r_1} \) and \( P_{r_2} \). Let the goal of our control action be to alter the steady state probability distribution of the network and we design a stationary control policy using dynamic programming approaches based on \( P_{r_1} \) and \( P_{r_2} \). A stationary control policy for the case of 2 control actions for the PBN will be a binary vector of length \( N \) where 0 at location \( i \) denotes no control action when at state \( i \) (the model of the network for state \( i \) will then be based on \( P_{r_1} \)) and a 1 at location \( i \) denotes control action when at state \( i \) (the model of the network for state \( i \) will then be based on \( P_{r_2} \)). To illustrate it further, let us consider a simple example where \( N = 2 \),

\[
P_{r_1} = \begin{bmatrix} .2 & .8 \\ .65 & .35 \end{bmatrix}
\]

\[
P_{r_2} = \begin{bmatrix} .45 & .55 \\ .25 & .75 \end{bmatrix}
\]

and stationary control policy = [0 1]. Then the designed controlled network model \( P_{r_c} \) will have its first row from \( P_{r_1} \) and second row from \( P_{r_2} \) i.e.

\[
P_{r_c} = \begin{bmatrix} .2 & .8 \\ .25 & .75 \end{bmatrix}
\]

Thus, we will represent the designed controlled model as \( P_{r_c} = TP_{r_1} + (I_N - T)P_{r_2} \) where \( I_N \) represent the identity matrix of size \( N \times N \) and \( T \) is a \( N \times N \) matrix with all entries zero except the diagonal entries corresponding to no control action equal to 1. For the example earlier, \( T = \begin{bmatrix} 1 & 0 \\ 0 & 0 \end{bmatrix} \). When a control policy designed using the PBN is applied to the fine-scale stochastic network models, the control policy corresponding to states \( a_{i-1} + 1, \ldots, a_i \) of the stochastic master equation model will be the same as the control policy for state \( i \) of the PBN. Thus, the controlled fine scale model will be \( P_{\Delta_c} = T\Delta P_{\Delta_1} + (I_M - T\Delta)P_{\Delta_2} \), where \( T\Delta \) is a \( M \times M \) matrix of all zeros except the states that map to PBN states with no control action, equal to 1. For the example before, if we consider \( M = 4 \) and the states 1 and 2 of the fine-scale model map to state 1 of the PBN, then \( T\Delta = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \). Let \( P_{r_c} \) represent the PBN generated from \( P_{\Delta_c} \) according to Eq. 6. Let \( \pi_d \) and \( \pi_c \) represent the steady-state probability distribution vector for \( P_{r_d} \) and \( P_{r_c} \) respectively. Let \( \eta_c \) be the length \( M \) steady state probability distribution vector of \( P_{\Delta_c} \) and \( \zeta_c \) be the length \( N \) collapsed steady state probability distribution vector of \( P_{\Delta_c} \). Due to Theorem 7, \( \pi_c \) is equal to \( \zeta_c \).

Our control objective is to alter the steady state probabilities of the network which in our control design is represented by \( \pi_d \). When the designed control policy is applied to the actual network represented by the fine-scale model, the resulting coarse-scale steady state probability vector is \( \pi_c \). We would like to study the conditions for \( \pi_c \) to be close to \( \pi_d \) so that our control designed on a reduced network when applied to the fine-scale network will have similar coarse-scale performance.

Let

\[
u(i) = \begin{cases} 1 & \text{if } T(i,i) = 1 \\ 2 & \text{if } T(i,i) = 0 \end{cases}
\]
Then,
\[
P_{rc}(i,j) = \sum_{j_1=a_{i-1}+1}^{a_i} \sum_{i_1=a_{j-1}+1}^{a_j} P_{\Delta u(i)}(i_1,j_1) \eta_c(i_1) / \zeta_c(i) \]
and
\[
P_{rd}(i,j) = \sum_{j_1=a_{i-1}+1}^{a_i} \sum_{i_1=a_{j-1}+1}^{a_j} P_{\Delta u(j)}(i_1,j_1) \eta_c(i_1) / \zeta_c(i) \]
(8)

Let \( \beta_1(i_1,j) = \sum_{j_1=a_{j-1}+1}^{a_j} P_{\Delta u(i)}(i_1,j_1) \) and \( \beta_2(i_1,j) = \sum_{i_1=a_{i-1}+1}^{a_i} P_{\Delta u(j)}(i_1,j_1) \).

Let us represent \( \beta_1(i_1,j) \) and \( \beta_2(i_1,j) \) for \( i_1 \in [a_{i-1}+1, a_{i-1}+2, \ldots, a_i] \) as summation of two terms with the first one independent of \( i \) and dependent on \( j \) and the second term dependent on \( i_1 \) and \( j \). \( \beta_1(i_1,j) = \beta_1(i,j) + \epsilon_1(i_1,j) \) and \( \beta_2(i_1,j) = \beta_2(i,j) + \epsilon_2(i_1,j) \).

Let \( \epsilon \) denotes the maximum of \( |\epsilon_1(i_1,j)| \) and \( |\epsilon_2(i_1,j)| \) i.e. \( -\epsilon \leq \epsilon_1(i_1,j) \leq \epsilon \) and \( -\epsilon \leq \epsilon_2(i_1,j) \leq \epsilon \) \( \forall i_1 \in [1,2,\ldots,M], j \in [1,2,\ldots,N] \). The value of \( \epsilon \) can be calculated as
\[
2\epsilon = \max_{i,j \in [1,\ldots,N]} \max_{u \in [1,2]} \max_{i_1 \in [a_{i-1}+1,\ldots,a_i]} \beta_u(i_1,j) - \min_{i_1 \in [a_{i-1}+1,\ldots,a_i]} \beta_u(i_1,j) \]
(10)

The following theorem bounds the difference between the transition probabilities of \( P_{rc} \) and \( P_{rd} \) in terms of \( \epsilon \).

**Theorem V.1.** \( |P_{rc}(i,j) - P_{rd}(i,j)| \leq 2\epsilon \ \forall i,j \in [1,2,\ldots,N] \)

The proof is available in [19].

A low value of \( \epsilon \) signifies that the probabilities of leaving the state \( i \) from the states mapping to state \( i \) (i.e. \( i_1 \ldots i_d \)) are very similar.

Based on theorem V.1, we can study the difference between the actual steady state distribution \( \pi_c = \zeta_c \) after application of stationary control policy \( T \) and the simulated steady state probability distribution \( \pi_d \) based on the reduced PBN model.

The steady-state probability distribution \( \pi_c \) of \( P_{rc} \) is the solution to the following linear equation
\[
x(P_{rc} - I_N) = 0 \]
(11)
where \( I_N \) is the identity matrix of size \( N \times N \) and the solution vector \( x \) is equal to \( \pi_c \). The residual for the approximate solution \( \pi_d \) is given by \( \kappa = \pi_d(P_{rc} - I_N) \) where the norm of \( \kappa \) provides a measure of closeness of the approximate solution as compared to the true solution [20].

\[
|\kappa|_\infty = |\pi_d(P_{rc} - I_N)|_\infty = |\pi_d(P_{rd} - P_{rd})|_\infty \\
\leq 2\epsilon \quad \text{(from Theorem V.1)} \quad (12)
\]

**VI. Example I**

Our mapping procedure is applied to a model representing the life cycle of bacteriophage-\( \lambda \) [21], [22] which involves five proteins \( U_1, U_2, \ldots, U_5 \). The decay reactions \( U_i \rightarrow \phi \) for \( i = 1,2,\ldots,5 \) are taken from [21] as:

1. \( \phi \rightarrow U_1 \) with propensity \( a_1(b_1/(b_1 + \Psi_2)) \)
2. \( \phi \rightarrow U_2 \) with propensity \( (a_2 + \Psi_5)b_2/(b_2 + \Psi_1) \)
3. \( \phi \rightarrow U_3 \) with propensity \( a_3b_3\Psi_2/(b_3\Psi_2 + 1) \)
4. \( \phi \rightarrow U_4 \) with propensity \( a_4b_4\Psi_3/(b_4\Psi_3 + 1) \)
5. \( \phi \rightarrow U_5 \) with propensity \( a_5b_5\Psi_3/(b_5\Psi_3 + 1) \)

The parameters \( a_i, b_i, c_i \) are taken from [21] as:

<table>
<thead>
<tr>
<th>( i )</th>
<th>( a_i )</th>
<th>( b_i )</th>
<th>( c_i )</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>0.12</td>
<td>0.0025</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0.6</td>
<td>0.0007</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
<td>0.1</td>
<td>0.0231</td>
</tr>
<tr>
<td>4</td>
<td>0.3</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>5</td>
<td>0.3</td>
<td>0.3</td>
<td>0.01</td>
</tr>
</tbody>
</table>

The maximum number of protein molecules for \( U_1, U_2, U_3, U_4 \) and \( U_5 \) are truncated to be at 3, 24, 3, 2 and 2 respectively so that the total number of possible states for the CME is \( 4 \times 25 \times 4 \times 4 \times 3 = 4800 \). Using the above propensity functions and values for parameters \( a_i, b_i, c_i \) the state reaction matrix, \( A_1 \) is computed and the continuous Markov Chain is approximated by a discrete chain using equation \( P_{\Delta t} = e^{A_1\Delta t} \) with a time step of \( \Delta t = 0.1 \) seconds. The discretization of the proteins is achieved using thresholds 2, 8, 2, 1 and 1, respectively. The transition probabilities of the reduced model (PBN \( P_{r1} \)) are calculated using Eq. 6. The equivalence of the steady state probability distribution \( \pi_1 \) of \( P_{r1} \) and the collapsed steady state probability distribution \( \zeta_1 \) of \( P_{\Delta 1} \) is shown in Figure 2.
Next, we proceed to study the effect of the control policy designed on the reduced network being applied to the original network. The control input is assumed to increase the decay of the proteins by increasing the values of the decay parameters $c_1, c_2, c_3, c_4, c_5$ to 0.05, 0.1, 0.231, 0.4 and 0.7 respectively. We consider the control objective of reducing the steady state masses of the high states in Fig. 2. Thus the undesirable states are 16, 32 (corresponding to binary states $[0,1,1,1,1]$ and $[1,1,1,1,1]$ respectively) and all other states are desirable. The cost of control is assumed to be 0.2 and the discount factor $\alpha$ is taken to be 0.9. Using Dynamic Programming, we generated the following optimal stationary control policy: application of control when in states 16 and 32 and no control when in all other states. The designed control policy is applied to both the reduced PBN model and the detailed CME model. The steady state distribution $\pi_d$ of the PBN and the collapsed steady state distribution $\zeta_c = \pi_c$ of the CME model after application of the control policy are shown in Figure 3. Similar to the two gene case, we notice that the collapsed probability distribution $\zeta_c$ and the controlled PBN probability distribution $\pi_c$ are very close to each other, though not exactly the same. We see that the steady state mass of the undesirable states have reduced in Fig. 3 as compared to Fig. 2 while many of the desirable states have increased steady state masses, indicating that the control is effective. The $\epsilon$ for this example is 0.1487, the maximum of $|P_d(i,j) - P_d(i,j)|$ for all $i,j \in [1, \cdots, N]$ is 0.0335 and $|\pi_c - \pi_d|_\infty$ is 0.0365.

![Fig. 3. Steady State Probability Distributions $\pi_d$ and $\zeta_c$ ($\zeta_c = \pi_c$)](image)

**VII. CONCLUSIONS**

In this paper, we formulated a mapping from fine scale stochastic models represented by CMEs to coarse-scale models represented by PBNs and studied the effect of control policy designed using PBNs when applied to the CME models. We derived bounds on the difference in the steady state behavior of the fine scale model and the coarse-scale model after application of control policy designed using the coarse-scale model. The effect of the control policy designed using the reduced network when applied to the fine scale model was evaluated through a biological example. The simulation showed that the result of the control policy application on the fine-scale model was not far away from the result observed with the PBN model.

**REFERENCES**


