Estimation of the holding Time for Cytoplasmic Reactions in Stochastic Event Based Modeling of Complex Biological Networks

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Abstract

The complexity of biological networks motivates the use of computer or “in silico” stochastic event based modeling approach to better identify the dynamic interactions of different processes in the cell. This requires the computation of the time taken by different processes in the cell on a per molecule basis. We present a mathematical formulation for the estimation of the reaction time between two molecules within a cell. In particular, we propose two models: 1) The reactant molecules enter the system one at a time to initiate reactions, and 2) The reactant molecules arrive in batches of a certain size. We derive expressions for the average and second moment of the time for reaction that will be used by our stochastic event-based simulation for both models. Unlike rate equations, the proposed model does not require the assumption of concentration stability for multiple molecule reactions.

I. INTRODUCTION

The new research challenge of today is to develop a comprehensive modeling framework integrating molecular and genetic data for a quantitative understanding of physiology and behavior of biological processes at multiple scales that are close to experimental data. We need new modeling methods as well as simulation and emulation techniques for analyzing biological systems. There exist comprehensive mathematical models in the areas of mathematical physiology [16] and computational cell biology [4]. Although such models as Hodgkins-Huxley equation, work very well for specific problem domains like cell membrane current and conductance, they rarely address a biological system as a whole. Alongside, researchers from diverse disciplines have also focused on developing models to capture the dynamics of biological processes [2], [3], [5], [6]. These spatio-temporal models can be classified into four categories based on: (a) quantum mechanics (b) molecular dynamics (c) mesoscale dynamics and (d) cellular/organ-level stochastic simulation. The first two models are very limited in scope, as they cannot handle the complexity of an entire cell. For example, quantum mechanics based modeling captures the random environment of the cell at the level of electrons and can handle at most 1000 atoms; hence it is not suitable to model the cell dynamics. Similarly, the molecular mechanics model uses force field method that is based on Newtonian mechanics with mass and momentum. Although this model is suitable for macro-molecules like protein and can handle about a million atoms at a time, it results in an order of magnitude higher computational complexity for modeling the dynamics of a cell or biological network, and hence not practical.

The remaining two models have focused on a narrow range of biological components such as the wave model [2] for ventricular fibrillation in human heart, neural network signaling model [6] to control the onset of sleep in humans, or simulation frameworks like E-Cell [8] and Virtual Cell [7] for biological process modeling. The mesoscale dynamics deals with rate equation based kinetic models and uses continuous time deterministic techniques. Such model is closely related to a rate constant derived from measurements. This model solves complex differential equations corresponding to chemical reactions with the help of numerical integration. Since a biological system involves a very large number of differential equations, the mesoscale model is not suitable for our purpose. Stochastic simulation models are also based on rate equations, namely Gillespie technique [9] and its variations such as Kitano’s Cell Designer [13], DARPA’s BioSpice [12], Cell Illustrator [11] etc. Due to the large number of protein complexes in a cell, these models lead to combinatorial explosion in the number of reactions, thus making them unmanageable for complex signaling pathway problems. Moreover, many of these models focus mostly on the graphical user interfaces and do not capture the details of pertinent biological functions including the difference between membrane vs. cytoplasm reactions.

In our approach, we design a discrete-event [10] driven paradigm for modeling a composite biological system by combining the state variables in the spatio-temporal domain as events, and determine the immediate dynamics between the events by using statistical analysis or simulation methods [17], [18]. The key notion is that the dynamics of cell behavior is captured by discrete time (possibly a random variable) and space state variables, where an event is a combined process of a large number of micro-level state transitions between a set of state variables accomplished within event execution time. The underlying assumption is that it will be possible to segregate the complete state-space into such disjoint sets of independent events which can be executed simultaneously without any interaction. The goal is to model processes within the cell, tissue or organ and put them
together to model the entire functionality of a biological system in both bottom-up and top down approaches. Identifying the biological discrete events based on system knowledge, the set of resources involved and calculating the time taken to complete an event (which is termed in system modeling as the holding time of the discrete event) are key challenges in this approach. We propose to use and enhance existing analytical results based on chemical kinetics, stochastic models, and computational system biology to estimate these system algorithms and parameters. In this paper, we use a collision theory based approach to estimate the average holding time of reactions taking place inside the cytoplasm of the cell.

Our contributions can be summarized as follows. We calculate the probability of reaction from concepts used in collision theory by considering the effects of activation energy. Next, we derive expressions for the average and second moment of the time for reaction that will be used by our stochastic event-based simulation for both models. We also derive expressions for the exact time for reaction assuming some simple chemical reactions. The proposed model does not require the assumption of concentration stability during the process of multiple molecule reactions as in rate equations. The stochastic event technique serializes the different events (i.e. if two different reactions have the same reactant we assume that one reaction occurs after the other). Our analytical results show that the adverse effect of this approximation is reduced with increasing number of reactant molecules in the system. We also show how to estimate the reaction time for more complex chemical reactions like different pathway processes that need to be incorporated in our simulation.

II. REACTION MODEL

We will present a simple reaction pair in this section to show how the discrete event modeling of chemical reactions brings in small approximations when the number of molecules of the reactants are large. Consider the elementary reaction pair:

\[
X_1 + X_2 \rightarrow X_3 \\
X_4 + X_2 \rightarrow X_5
\] (1)

To model these reactions analytically in the time domain, we consider two different models for the arrivals of \(X_1\) and \(X_4\) types of molecules in the system which, we assume, contains a fixed number \(n_2\) of \(X_2\) molecules. Our goal is to derive expressions for the average time and actual time required for chemical reactions. The discrete event scheme works with the average time for chemical reactions and we show that this is comparable to the actual time when the number of reactant molecules are large in the biological system.

A. Model 1

The molecules of \(X_1\) and \(X_4\) enter the system one at a time to start the reactions. From the principles of collision theory for hard spheres, we model each reactant molecule as rigid spheres with radii \(r_1, r_2, r_3, r_4, r_5\) respectively for molecules of type \(X_1, X_2, X_3, X_4, X_5\) (Fig 1). We define our coordinate system such that molecule \(X_2\) is stationary with respect to molecule \(X_1\), so that \(X_1\) moves towards molecule \(X_2\) with a relative velocity \(U_{12}\). Molecule \(X_1\) moves through space to sweep out a collision cross section \(A = \pi r_{12}^2\) (as illustrated in Fig 2), where \(r_{12}\) is the collision radius given by:

\[ r_{12} = r_1 + r_2 \]

If the center of an \(X_2\) molecule comes within a distance of \(r_{12}\) of the center of the \(X_1\) molecule, they will collide. In time
Now, the probability of $X_1$ molecules in the collision volume $\Delta V$ is $p_{X_1} = 1$ (it is given that one $X_1$ molecule arrived creating a collision volume of $\Delta V$).

Probability of at least one molecule of $X_2$ being present in an arbitrary uniformly distributed $\Delta V$ in $V$ is $p_{X_2} = \Delta V.n_2/V$. Thus, probability of the $X_1$ molecule to collide with an $X_2$ molecule during time $\Delta t$:

$$p_c = p_{X_1} \times p_{X_2} = \Delta V.n_2/V = \frac{n_2 \pi r_{12}^2 U_{12} \Delta t}{V}$$

(2)

We next assume that the colliding molecules must have free energy $E_{Act}$ or greater to react. Also, only the kinetic energy directed along the line of centers contributes to this reaction. The kinetic energy of approach of $X_1$ towards $X_2$ with a velocity $U_{12}$ is $E = \frac{m_{12} U_{12}^2}{2}$, where $m_{12} = \frac{m_1 m_2}{m_1 + m_2}$ is the reduced mass, $m_1$ = mass (in gm) of molecular species $X_1$, and $m_2$ = mass (in gm) of molecular species $X_2$. We also assume that as $E$ increases above $E_{Act}$, the number of collisions that result in reaction also increases. Thus the probability for a reaction to occur:

$$p_r = \begin{cases} \frac{E-E_{Act}}{E} & \text{for } E > E_{Act} \\ 0 & \text{otherwise} \end{cases}$$

(3)

and hence, the overall probability, $p$, for reaction given that a collision occurred is given by:

$$p = p(\text{Reaction}|\text{Collision}) = p_r \times p_c = \begin{cases} p_c \frac{(E-E_{Act})}{E} & \text{for } E > E_{Act} \\ 0 & \text{otherwise} \end{cases}$$

The above equations assumed a fixed relative velocity $U_{12}$ for the reaction. We will use the Maxwell-Boltzmann distribution of molecular velocities for a species of mass $m$ given by:

$$f(U,T)dU = 4\pi \left(\frac{m}{2\pi k_b T}\right)^{3/2} e^{-\frac{m U^2}{2k_b T}} U^2 dU$$

where $k_b$ = Boltzmann’s constant = $1.381 \times 10^{-23} m^2/s^2/K/molecule$. Replacing $m$ with the reduced mass $m_{12}$ of the molecules $X_1$ and $X_2$, we get,

$$f(U,T)dU = 4\pi \left(\frac{m_{12}}{2\pi k_b T}\right)^{3/2} e^{-\frac{m_{12} U^2}{2m_{12} k_b T}} U^2 dU$$

(4)

The term on the left hand side of the above equation denotes the fraction of $X_1$ molecules with relative velocities between $U$ and $(U + dU)$. Summing up the collisions for the $X_1$ molecules for all velocities we get the probability of reaction, $p$, as a function of temperature only as follows:

$$p(T) = \int_0^\infty p(U,T)dU$$

Now, recalling $E = \frac{m_{12} U^2}{2}$, i.e., $dE = m_{12} U_{12} dU$ and substituting into Eqn 4, we get:

$$f(U,T)dU = 4\pi \left(\frac{m_{12}}{2\pi k_b T}\right)^{3/2} \frac{2E}{U m_{12}^2} e^{\frac{-E}{k_b T}} dE$$

Thus we get:

$$p = \int_{E_{Act}}^\infty \frac{(E - E_{Act})4n_2 \pi r_{12}^2 \tau}{V k_B T} \frac{1}{2\pi k_B T m_{12}} e^{-\frac{E}{k_B T}} dE$$

$$= \frac{n_2 \pi r_{12}^2 \tau}{V} \sqrt{\frac{8\pi k_B T}{m_{12}}} e^{-\frac{E_{Act}}{k_B T}}$$

(5)

Let us now compute the time taken to complete the reaction with this probability. Let us assume that the molecule composition does not change during the reaction time. Let $\Delta t = \tau = $ an infinitely small time step. The molecules try to react through collisions. If the first collision fails to produce a reaction, they collide again after $\tau$ time units and so on.

We can interpret $p$ as the probability of a successful reaction in time $\tau$. Thus can formalize the average time of reaction for discrete event modeling for reaction $R_1$, $T_{avg1}$, and the corresponding second moment, $T_{2ndmoment1}$, by the following theorem:

**Theorem 1:** The average and the second moment of reaction times of type $R_1$ for one molecule of $X_1$ reacting with $n_2$ molecules of $X_2$ is given by:

$$T_{avg1}^{DE} = \frac{\tau}{p}$$

$$T_{2_{ndmoment1}}^{DE} = \frac{(2-p)\tau^2}{p^2}$$
**Proof:** The average time of reaction can be approximated by summing up the times taken for reaction with the first collision, second collision and so on. Thus we get:

\[ T_{avg}^{DE} = p\tau + (1-p)p\cdot 2\tau + (1-p)^2 p\cdot 3\tau + ... \\
\[ = p\tau[1 + 2(1-p) + 3(1-p)^2 + ...] \\
\[ = \frac{\tau}{p} \]  

(6)

Similarly, for the second moment we have:

\[ T_{2nd\ moment}^{DE} = p\tau^2 + (1-p)p\cdot (2\tau)^2 + (1-p)^2 p\cdot (3\tau)^2 + ... \]
\[ = p\tau^2[1 + 2^2(1-p) + 3^2(1-p)^2 + ...] \]
\[ = \frac{(2-p)\tau^2}{p^2} \]  

(7)

The detailed derivation is shown in the appendix.

1) **Generalization of the Reaction Event:** The discrete event technique assumes that all events are time serialized. Thus no two events occur at exactly the same time, and if they do happen at the same time, one event will be considered to occur before the other one. Let us consider the following three reactions:

\[ R_1 : X_1 + X_2 \rightarrow X_3 \]
\[ R_2 : X_4 + X_2 \rightarrow X_6 \]
\[ R_3 : X_6 + X_5 \rightarrow X_7 \]

We next illustrate the different possible event scenarios in Fig 3. The events are shown along the time axis. There is a conflict in the first event because the \( X_2 \) molecules are shared by both reactions \( R_1 \) and \( R_2 \) and thus they have to be serialized. There are no conflicts between events \( R_1 \) and \( R_3 \) as they do not share any molecules. Similarly, there is conflict between \( R_2 \) and \( R_3 \) because of \( X_6 \) molecules. Also, there are no conflicts between reaction pairs \( R_1, R_2 \) and \( R_2, R_3 \) events if the reactions do not occur at the same time. The concept of serialization in discrete event modeling requires that these conflict scenarios should be approximated as one reaction occurring only after the completion of another one. Thus, in Case III above, we assume that the molecule of \( X_6 \) is available to \( R_3 \) only after the completion of \( R_2 \). These assumptions will work well as long as the number of molecules in the system is large. Thus, this marginal adjustment will not significantly distort the reaction time. We next show the analytical modeling of Case I as presented above to calculate the exact way in which the reaction time should be calculated so as to show how the number of molecules in the system affect this marginal distortion.

2) **Analytical Modeling of Case I:** In Case I (Fig 4), molecules of \( X_2 \) are shared by reactions \( R_1 \) and \( R_2 \). Thus when \( R_2 \) starts, there is faster depletion of molecule \( X_1 \). This will obviously result in a larger average time of reaction, \( T_{avg} \), for reactions \( R_1 \) and \( R_2 \). In this section, we will estimate \( T_{actual}^{avg} \), which is the actual time for reaction \( R_1 \). Similar analysis can also be done for \( R_2 \).
Let, \( n_1 \) = number of molecules of \( X_1 \) at time \( t_0 \), \( n_2 \) = number of molecules of \( X_2 \) at time \( t_0 \) and \( n_4 \) = number of molecules of \( X_4 \) at time \( t_1 \). Also, let \( p_1 \) = probability of reaction of \( X_1 \) and \( X_2 \) during time \( t_1 \) - \( t_0 \). Thus as calculated before, we have,

\[
p_1 = \frac{n_2 r_{12}^2}{V} \sqrt{\frac{8\pi k_B T}{m_{12}}} e^{-\frac{E_{A12}}{k_B T}}
\]

where \( E_{A12} \) is the activation energy required for \( R_1 \). Let,

\[
q = \left\lfloor \frac{t_1 - t_0}{\tau} \right\rfloor
\]

Now, the average number of \( X_2 \) molecules in the system at time \( t_1 \) is \( n_{21}^{t_1} = n_2 - \sum_{k=1}^{q} p_1 (1 - p_1)^{k-1} \). Also, let \( p_2 \) = probability of reaction between \( X_4 \) and \( X_2 \) molecules. Then:

\[
p_2 = \frac{n_2 r_{12}^2}{V} \sqrt{\frac{8\pi k_B T}{m_{12}}} e^{-\frac{E_{A12}}{k_B T}}
\]

where \( r_{42}, m_{42} \) and \( E_{A42} \) are defined as before for reaction \( R_2 \). Now, the probability of reaction \( R_1 \) changes from the \((q+1)^{th}\) step onwards as \( R_2 \) can reduce the number of \( X_2 \) molecules in the system. Thus, we get:

\[
p_{11}^{t_1+h\tau} = (n_{21}^{t_1} - \sum_{k=1}^{h} p_2 (1 - p_2)^{k-1}) r_{12}^2 \sqrt{\frac{8\pi k_B T}{m_{12}}} e^{-\frac{E_{A12}}{k_B T}} (1 - p_{11}^{t_1+k\tau}) Q(r, p, \tau, \tau, \tau)
\]

Thus, the exact average time for reaction \( R_1 \), \( T_{avg1}^{actual} \), is given by:

\[
T_{avg1}^{actual} = \sum_{i=1}^{q} p_1 (1 - p_1)^{i-1} i \tau + \sum_{j=1}^{\infty} p_{11}^{t_1+j\tau} (1 - p_1) p_{11}^{t_1+j\tau} \sum_{k=1}^{j} (1 - p_{11}^{t_1+k\tau}) Q(r, p, \tau, \tau, \tau)
\]

Similarly, the average time for \( R_2 \) can be calculated. Also, the actual second moments for reactions \( R_1 \) and \( R_2 \) can be calculated easily following the same concepts.

**B. Model 2 (Batch Arrival)**

Now, we consider that the \( X_1 \) molecules arrive in batches of size \( b_1 \) and \( X_4 \) molecules arrive in batches of size \( b_4 \) in the system. We will again try to model analytically the average time for reaction \( R_1 \) for both the discrete event modeling and actual scenario, \( T_{avg1}^{batch} \) and \( T_{avg1}^{batch/actual} \) considering such batch arrivals. Fig 5 depicts the scenario. Let, \( p_{11}^{b1} \) be the probability of the first reaction of \( X_1 \) between one \( X_1 \) molecule and an \( X_2 \) molecule resulting from the first collision. Thus we have,

\[
p_{11}^{b1} = \frac{b_1 n_2 r_{12}^2}{V} \sqrt{\frac{8\pi k_B T}{m_{12}}} e^{-\frac{E_{A12}}{k_B T}}
\]

The numerator on the right hand side of the above equation gets multiplied by \( b_1 \) to sum up the probability of reaction for all the \( b_1 \) molecules that arrived in a single batch. Similarly, let \( p_{12}^{b1} \) be the probability of the first reaction of \( X_2 \) between \( X_4 \) and \( X_2 \) from the first collision. So, we have,

\[
p_{12}^{b1} = \frac{b_4 n_2 r_{42}^2}{V} \sqrt{\frac{8\pi k_B T}{m_{42}}} e^{-\frac{E_{A42}}{k_B T}}
\]

The black circles in Fig 5 signify the reaction \( R_1 \) occurring from the first collision, second collision and so on. Hence, probability of the first reaction of \( R_1 \) from the \( i^{th} \) collision (\( 2 \leq i \leq \infty \)), is given by:

\[
p_{1i}^{b1} = p_{11}^{b1}
\]
We can calculate the probability of reaction from \( p \) solving for \( \tau \):

\[
\tau = \frac{8\pi k_B T}{m_{12}} e^{-\frac{E_{A_{12}}}{k_B T}}
\]

Similarly, the probabilities of the \( u^{th} \) reaction of types \( R_1 \) and \( R_2 \) from the \( i^{th} \) collision are denoted by \( p_{1i}^{1w} \) and \( p_{2i}^{2w} \) as follows:

\[
p_{1i}^{1w} = p_{1i}^{1w} \\
p_{2i}^{2w} = p_{2i}^{2w}
\]

Hence, the average time for reaction \( R_1 \) to occur, \( T_{\text{avg1}}^{\text{batch/DE}} \), and corresponding second moment, \( T_{2nd,moment1}^{\text{batch/DE}} \), in the approximated model is given by the following theorem:

**Theorem 2**: The average and second moment of reaction times of type \( R_1 \) for a batch of size \( b_1 \) molecules of \( X_1 \) and \( n_2 \) molecules of type \( X_2 \) is given by:

\[
T_{\text{avg1}}^{\text{batch/DE}} = \frac{\sum_{k=1}^{b_1} \sum_{i=1}^{\infty} (p_{1i}^{1k} \tau \prod_{j=1}^{i-1} (1 - p_{1j}^{1k}))}{b_1}
\]

\[
T_{2nd,moment1}^{\text{batch/DE}} = \frac{\sum_{k=1}^{b_1} \sum_{i=1}^{\infty} (p_{1i}^{1k} (i\tau)^2 \prod_{j=1}^{i-1} (1 - p_{1j}^{1k}))}{b_1}
\]

**Proof**: The proof is very similar to that of Theorem 4 and is omitted.

### C. Probability of Collision Calculation for Large \( \tau \)

The probability of collision, \( p_c \), as calculated in Eqn 2 also accounts for the estimated number of collisions of the \( X_1 \) molecule with a molecule of \( X_2 \), \( Est_{\text{coll}} \). This is because the number of collisions of one molecule of \( X_1 \) (under Model 1) with molecules of \( n_2 \) in the area \( \Delta V \) is given by \( n_2 \frac{\Delta V}{V} \), where \( \Delta V = \pi \tau r_2^2 U_{12} \). Also, we have:

\[
Est_{\text{coll}} = p_c (1 + p_c)^2 + p_c (1 + p_c)^3 + \ldots = \frac{p_c}{(1 - p_c)^2} = n_2 \frac{\Delta V}{V}
\]

Solving for \( p_c \) from the above quadratic equation and noting that \( p_c \leq 1 \), we get:

\[
p_c = \frac{1 + 2 n_2 \frac{\Delta V}{V} - \sqrt{1 + 4 n_2 \frac{\Delta V}{V}}}{2 n_2 \frac{\Delta V}{V}} \tag{10}
\]

We can calculate the probability of reaction from \( p_c \) as before.

For batch arrivals (Model 2), the estimated number of collisions should be added up for the \( b_1 \) molecules of \( X_1 \) arriving in a single batch. Thus, we have:

\[
Est_{\text{batch}} = b_1 n_2 \frac{\Delta V}{V} = \frac{p_c}{(1 - p_c)^2} \tag{11}
\]
and hence:

\[ p_{c_{\text{batch}}} = \frac{1 + 2b_1n_2 \frac{\Delta V}{V} - \sqrt{1 + 4b_1n_2 \frac{\Delta V}{V}}}{2b_1n_2 \frac{\Delta V}{V}} \]  

(12)

In the numerical results section we shall show that the difference between actual and average reaction times is minimal as \( \tau \) grows large. But, we cannot have \( \tau \) excessively large because that would violate our assumption of only one collision in this time period.

D. Generalization for Other Types of Reactions

We have considered simple reactions of type \( R_1 \) for the analysis of our discrete event based chemical reactions. The mathematics become a little cumbersome for reactants having more than one molecules participating in the reaction. Nevertheless, such situations can also be modeled with our scheme. Let us consider the following reaction \( R_4 \):

\[ R_4 : X_1 + yX_2 \rightarrow X_3 \]

Hence, the probability of collision, \( p_c \) for Model 1, and \( p_{c_{\text{batch}}} \) for Model 2 can be written as:

\[ p_c = \frac{n_2}{y} \frac{\Delta V}{V} \]

\[ p_{c_{\text{batch}}} = b_1 \frac{n_2}{y} \frac{\Delta V}{V} \]

If more than one \( X_1 \) molecule is involved in the reaction, then we can only consider batch arrivals of Model 2. Thus for reaction \( R_5 \):

\[ R_5 : xX_1 + yX_2 \rightarrow X_3 \]

we have:

\[ p_{c_{\text{batch}}} = \left( \frac{b_1}{x} \right) \frac{n_2}{y} \frac{dV}{V}, \quad b_1 \geq x \]

III. Numerical Results

In this section, we present the numerical results for our diffusion and chemical reaction models. Figs 6-9 plot the performance of our chemical reaction models. The graphs are generated considering the following reaction:

\[ R_1 : H + O_2 \rightarrow OH + O \]

\[ R_2 : H + Cl_2 \rightarrow HCl + Cl \]  

(13)  

(14)

The reactions are assumed to occur at 273\(^0\) K with both \( R_1 \) and \( R_2 \) having activation energy, \( E_{\text{Act}} = 7 \text{ Kcal/mol} \). All the results have been generated assuming 50\% overlap between the reactions, i.e., \( q = \left\lfloor \frac{T_{\text{avg}} \times 0.5}{1} \right\rfloor \).

Fig 6 plots the average and actual times of reaction for Model 1 against \( \tau \). We find that initially the two differ, but after a certain interval they are both the same. So, our discrete event simulation should consider the time step \( \tau \) to fall in this range. But \( \tau \) cannot be increased indefinitely because that would violate our assumption of one collision taking place in one time step. A similar nature is observed for the batch arrival case in Fig 7. In this plot, we only show the average time taken for
reactions of type $R_1$, occurring in a single batch. The actual time of reaction for Model 2 is hard to compute. In Fig 7, the average time of reaction increases with $\tau$ as more time is required for every single collision of the reactant molecules resulting in increases average reaction time. A point to note is that the actual time of reaction should be more than the average time because it captures the actual scenario of reduction in probabilities for conflicting reactions.

Figs 8 and 9 plot the average and actual times for reaction with increase in the number of molecules in the system for Model 1 and just the average time for Model 2. For both plots we find that the time for reaction reduces with increasing number of molecules. Initially, there is substantial difference between the actual and average results, but the difference quickly reduces as the number of molecules is increased in the system as illustrated in Fig 8. For micro-molar concentrations of the reactant molecules, we find a negligible difference between the actual and average results that point to the efficacy of the serialization process in discrete event simulations. Also, we observe that average time of reaction for Model 2 is higher than that for Model 1. This is again intuitive as in in the batch model, the time taken for the reaction of the last few molecules of a single batch increases appreciably because of reduction in the number of of both $X_1$ and $X_2$ molecules resulting in a higher average time for reaction than Model 1.

IV. Conclusion

We have proposed an “in silico” modeling technique which captures the dynamics of biological systems at multiple scales – from cell, to tissue, to organ and finally to the process level. We have presented the cytoplasmic reaction model as an illustration of the event modeling method that are required for characterizing the events of the simulation of a biological process. Other mathematical models are under development to estimate the event duration of processes like gene expression time, protein docking time and transportation time of various biological entities. The modeling framework presented in this paper is flexible enough to be extended to create the other models listed in this paper. The fidelity of the “in-silico” model proposed in this paper is closely coupled with “in-vitro” and “in-vivo” validations. We are exploring the definition of custom wet-test configurations and instrumentation techniques using atomic scale measurement tools to collect experimental data to validate the models wherever possible. In addition, we are exploring the use of Force Field based atomic level simulation for very restrictive cases to validate the reaction models.

REFERENCES

V. APPENDIX

Derivation of \( T_{avg1}^{DE} \): We have:

\[
T_{avg1}^{DE} = p\tau S
\]

where,

\[
S = 1 + 2(1 - p) + 3(1 - p)^2 + \ldots
\]

Also, multiplying both sides of this equation by \((1-p)\) we get:

\[
(1 - p)S = (1 - p) + 2(1 - p)^2 + 3(1 - p)^3 + \ldots
\]

Subtracting \(\text{Eqn 17 from Eqn 16}\) we get:

\[
pS = 1 + (1 - p) + (1 - p)^2 + (1 - p)^3 + \ldots
\]

\[
\Rightarrow S = \frac{1}{p^2}
\]

Substituting \( S \) in \(\text{Eqn 15}\) we get:

\[
T_{avg1}^{DE} = \frac{\tau}{p}
\]

Derivation of \( T_{2nd\text{moment}}^{DE} \):

\[
T_{2nd\text{moment}}^{DE} = p\tau^2 + (1 - p)p(2\tau)^2 + (1 - p)^2p(3\tau)^2 + \ldots
\]

\[
= p\tau^2 S
\]

where,

\[
S = 1 + 2^2(1 - p) + 3^2(1 - p)^2 + \ldots
\]

Similarly,

\[
S(1 - p) = (1 - p) + 2^2(1 - p)^2 + 3^2(1 - p)^3 + \ldots
\]

Subtracting \(\text{Eqn 22 from Eqn 21}\) we get:

\[
pS = 1 + (2^2 - 1^2)(1 - p) + (3^2 - 2^2)(1 - p)^2 + (4^2 - 3^2)(1 - p)^3 + \ldots
\]

Now, we can substitute the terms of the form \(a^2 - (a - 1)^2\) in the above equation by \(2a - 1\) as follows:

\[
pS = 1 + (2.2 - 1)(1 - p) + \ldots
\]

\[
= [1 + 2\{(2(1 - p) + 3(1 - p)^2 + 4(1 - p)^3 + \ldots\}] - [(1 - p) + (1 - p)^2 + (1 - p)^3 + \ldots\]

\[
= 1 + 2Y - Z
\]

where, \(Y = \{2(1 - p) + 3(1 - p)^2 + 4(1 - p)^3 + \ldots\}\) and \(Z = (1 - p) + (1 - p)^2 + (1 - p)^3 + \ldots\)

\(Z\) forms an infinite geometric series and we simply have:

\[
Z = \frac{1 - p}{p}
\]
Next we multiply \((1 - p)\) to \(Y\) and subtract it from the expression of \(Y\) to get:

\[
pY = 2(1 - p) + (1 - p)^2 + (1 - p)^3 + ...
\]

\[
= 2(1 - p) + \frac{(1 - p)^2}{p}
\]

\[
\Rightarrow Y = \frac{1 - p^2}{p^2}
\]  \hspace{1cm} (26)

Substituting the values for \(Y\) and \(Z\) in Eqn 24 we get:

\[
S = \frac{2 - p}{p^3}
\]  \hspace{1cm} (27)

\[
\Rightarrow T_{2,x,y}\text{moment1} = \frac{(2 - p)\tau^2}{p^2}
\]  \hspace{1cm} (28)