A Diffusion Model to Estimate the Inter-arrival Time of Charged Molecules in Stochastic Event based Modeling of Complex Biological Networks

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Abstract

With biological experiments generating lots of empirical data, the challenge is to develop a modeling paradigm that integrates structural, molecular and genetic data for a quantitative understanding of physiology and behavior of biological processes at multiple scales - starting from cell, to tissues and finally to the whole organism. The complexity of the problem motivates the use of computer or "in silico" stochastic event based modeling approach. We focus on the signal transduction cascade triggered by extra-cellular Mg^{2+} concentration in the two component PhoPQ regulatory system of Salmonella Enterica serovar Thphimurium, and present the mathematical formulation for the estimation of statistical parameters of inter-arrival time of molecules/ions to a cell receptor as external signal.

1. Discrete Event Modeling Concept

We develop a discrete-event based "in silico" model [1] for complex biological dynamic systems. This requires the development of mathematical models to capture the defined biological processes and obtain statistical parameters for analyzing the "in silico" models. 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 the challenges in this approach. We first identify the biological processes involved in the PhoPQ regulatory network (from the sensing of magnesium at the cell membrane to the expression of virulent genes) [2]. The schematic block diagram of the processes capturing these sequence of actions is shown in Fig 1. Each process block, has some input signal(s) and output signal(s) which can trigger one or more processes. These signals, acting as drivers for various resources used in the processes, together with the different holding times capture the dynamic behavior of the system.

2. Diffusion Model 1

The actual diffusion process of Mg^{2+} ions inside the cell membrane is illustrated in Fig 2 [3]. Diffusion takes place through an ion-channel at the surface of the cell membrane. This is captured by the following hypothetical mathematical model: an infinitely long capillary (open at one end)

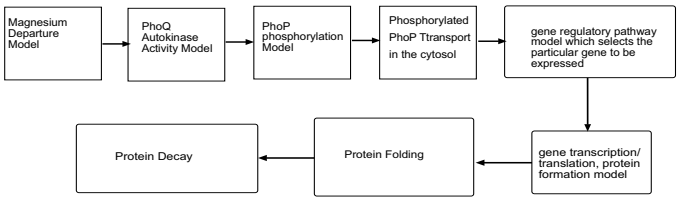

Figure 1. Biological Processes involved in the PhoPQ Regulation Process in Salmonella

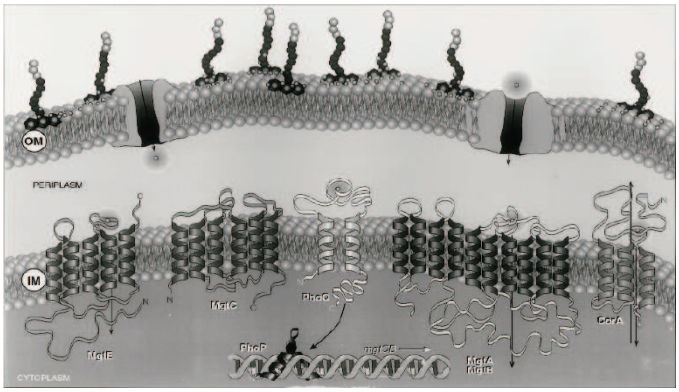

Figure 2. Membrane topography of Mg^{2+} transport systems and other relevant proteins.

filled with water is inserted into a solution of known chemical concentration C_0. The concentration of the chemical species depends only on the distance down the tube and so is governed by the diffusion equation:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}, \qquad 0 < x < \infty, \quad t > 0 \tag{1}$$

Here D is the diffusion constant having units $length^2/time$, c is the concentration of the chemical, t is time and x is the distance traversed inside the capillary by the chemical. The boundary conditions are $C(0,t) = C_0$, $C(x,0) = 0$ and the solution is: $C(x,t) = 2C_0[1 - \frac{1}{2\pi}\int_{-\infty}^{y} exp(-\frac{s^2}{2})ds]$ where $y = \frac{x}{\sqrt{2Dt}}$ (from [4]). We can compute the inter-arrival time between the diffused molecules from the following theorem:

Theorem 1 *The inter-arrival time between the diffusion of the $(i+1)^{th}$ and i^{th} molecules/ions (diffusion is based on the concentration gradient only) is given by:*

$$I_{i+1} - I_i = \frac{\pi(2i+1)}{4C_0^2 G^2 D} \tag{2}$$

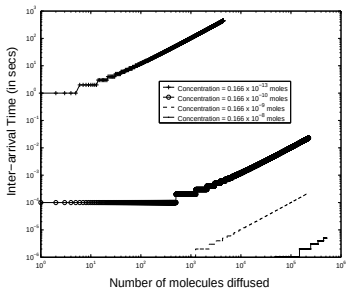

Figure 3. Inter-arrival time Vs no. of molecules for Diffusion Model 1

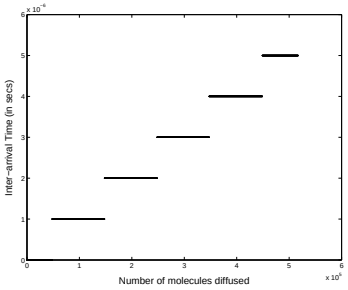

Figure 4. Inter-arrival time against no. of molecules plot for Diffusion Model 1 with concentration 0.166×10^{-8} moles

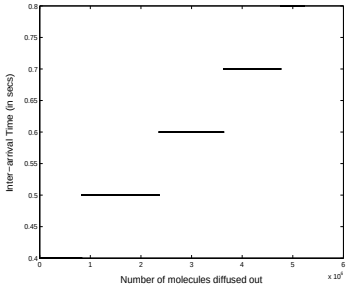

Figure 5. Inter-arrival time against no. of molecules plot for Diffusion Model 2 with concentration 0.166×10^{-8} moles

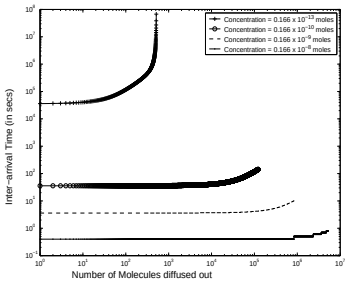

Figure 6. Inter-arrival time against no. of molecules plot for Diffusion Model 2

where I_{i+1} and I_i are times taken for diffusion of the $(i+1)^{th}$ and i^{th} molecules respectively, and G is the cross-sectional area of the capillary.

PhoP-P transport to cytosol process can be modeled using Theorem 1, but it is not suited for diffusion of charged ions.

3. Diffusion Model 2

We need to consider the ion flux through the membrane of width l (supposing a potential difference exists across it with $\phi(0) = \phi_1$ and $\phi(l) = \phi_2$) created due to movement of positively charged Mg^{2+} ions. We assume that the potential gradient through the channel is constant:

$$\frac{\partial \phi}{\partial x} = \frac{\phi_1 - \phi_2}{l} = \frac{V}{l}, \quad V = \phi_1 - \phi_2 \tag{3}$$

The total flux, $J = -D[\frac{\partial c(x,t)}{\partial x} + \alpha c(x,t)\frac{V}{l}]$, where, $\alpha = zF/RT$, z = total number of positive charges in Mg^{2+}, F = Faraday's constant, T = absolute temperature and R = gas constant. The diffusion equation becomes:

$$\frac{\partial c}{\partial t} == -D\frac{\partial^2 c}{\partial x^2} - aD\frac{\partial c}{\partial x}, \quad 0 < x < \infty, \quad t > 0 \tag{4}$$

where, $a = \alpha V/l$. We now consider diffusion out of a plane sheet of thickness l through which the diffusing substance is initially uniformly distributed and the surfaces of which are kept at zero concentration. Thus the ion channel of length l is assumed to contain the entire diffusing substance. Each molecule coming out of this sheet is assumed to enter the cell membrane (Mg^{2+} arrival process). The corresponding boundary conditions are $C(x,0) = C_0, C(0,t) = 0, C(l,t) = 0, 0 < x < l$. The solution is:

$$C(x,t) = \sum_{m=1}^{\infty} \frac{2C_0 m\pi(1-(-1)^m e^{-\frac{zFV}{2RT}})}{(\delta)}\, e^{\frac{\delta Dt}{l^2} - \frac{zFVx}{2RTl}}\, \sin\frac{m\pi x}{l}$$

where, $\delta = m^2\pi^2 + \frac{z^2F^2V^2}{4R^2T^2}$. The inter-arrival time between diffused molecules is given by Theorem 2:

Theorem 2 *The inter-arrival time between the diffusion of the $(i+1)^{th}$ and i^{th} molecules/ions when the diffusion is based on both concentration and potential gradients across the cell is given by $I_{N-i} - I_{N-i-1}$, where I_{N-i} and I_{N-i-1} are the times taken for diffusion of the i^{th} and $(i+1)^{th}$ molecules respectively, and G is the area of the plane sheet and can be solved from the following equations:*

$N-i-1 = 2C_0G\sum_{m=1}^{\infty} m^2\pi^2\{\frac{1-(-1)^m e^{-\frac{zFV}{2RT}}}{\delta}\}^2\, e^{\frac{\delta DI_{N-i-1}}{l^2}}$

$N - i = 2C_0G\sum_{m=1}^{\infty} m^2\pi^2\{\frac{1-(-1)^m e^{-\frac{zFV}{2RT}}}{\delta}\}^2\, e^{\frac{\delta DI_{N-i}}{l^2}}$.

4. Numerical Results

The cross-sectional area of the capillary is taken in the range of μm, and $D = 10^{-5}cm^2/s$. Fig 3 shows that larger the initial concentration, lesser is the inter-arrival time. Fig 4 shows a stair-case function for the inter-arrival times. With high initial concentration, the inter-arrival time remains fixed for a few molecules before increasing to the next level. Figs 5 and 6 incorporates the potential gradient. We assume a constant potential gradient of 60mV for the diffusing molecules to overcome. Length of an ion channel is taken as 1 mm (we add up the lengths for the ion channels present on the cell membrane). Fig 5 shows the same stair-case functionality and Fig 6 shows the increasing trend of inter-arrival times. Instead of the linear increase of model 1, we now see an exponential increase in the inter-arrival times. The inter-arrival times are higher than the first model because the molecules have to overcome the potential gradient as well in order to diffuse.

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