Physical channel modeling by calcium signaling in molecular communication based nanonetwork

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ABSTRACT

Molecular communication is an emerging field of communication. It allows biological nanomachines to communicate through exchanging molecules in an aqueous environment and to perform collaborative tasks through integrating functionalities of individual biological nanomachines [1]. Traditional communication mechanism are not suitable for nanonetworks mainly due to the smaller dimensions of transmitters, receivers and other components [2,3,4]. Biological cells use molecular communication that involves both the intra-cellular or inter-cellular molecular communication using chemical signals to accomplish biological functions like respiration, nerve impulse conduction, hormone secretion, etc. One form of molecular communication is calcium (Ca$^{2+}$) signaling in which the concentration of a stream of Ca$^{2+}$ ions are modulated spatio-temporally to bring about processes like muscle contraction, cell differentiation, hormone secretion, etc. In this paper, we model the physical channel layer using Ca$^{2+}$ signaling and verify the protocol stack components of the physical channel defined by IEEE 1906.1 standard [5]. Next, we run the solution scheme for this model in MATLAB to evaluate the modulation and signal propagation of Ca$^{2+}$ signaling in an inter-cellular environment and discuss results to explain the behavior of physical channel.

Categories and Subject Descriptors


General Terms: Molecular Communication, Nano Network

Keywords

Calcium signaling, physical channel, protocol stack components, cell components, electro-diffusion, receptors.

1. INTRODUCTION

Molecular communication is a mode of communication where the information is encoded in terms of molecules and is the most common way of intra-cellular and inter-cellular communication. Molecular communication is advantageous as compared to electromagnetic communication due to its better noise immunity, low power consumption, easy to integrate the molecular transmitters and receivers, and to have better biocompatibility. There are many different mechanisms of molecular communication e.g., (i) communication using molecular motors, (ii) Ca$^{2+}$ signaling, (iii) communications using pheromones etc. Among all these molecular communication techniques, calcium signaling is the most flexible intra-cellular and inter-cellular communication and that is the reason why, we adopt the Ca$^{2+}$ signaling the way of communication in nanonetworks [6,7,8]. In multi-cellular organisms, Ca$^{2+}$ ions commonly act as the message carrier to regulate various cellular activities (e.g., chemical secretion, muscle contraction etc.) and the stimulus acts as the modulating signal. In Ca$^{2+}$ signaling, information is precisely encoded on amplitude or frequency of concentration changes of Ca$^{2+}$ ions often referred to as Ca$^{2+}$ spikes and oscillations. In section 2, we describe the protocol stack components of the physical channel defined by IEEE 1906.1 [5] and map this protocol stack into Ca$^{2+}$ signaling based nanonetwork. In section 3, we describe the mathematical model of cell components, the model of intra and inter-cellular propagation of Ca$^{2+}$ waves, and demodulation and detection mechanism of these Ca$^{2+}$ signaling by suitable receiver. Beside them, we describe their solution schemes. In section 4, we show results to observe the cell response and to verify the utility of Ca$^{2+}$ signaling in modeling of a nanonetwork based on 1906.1 standard. In section 5, the scope for further research on the physical channel for Ca$^{2+}$signaling in nanonetworks is discussed.
2. PROTOCOL STACK COMPONENTS OF PHYSICAL CHANNEL LAYER IN PERSPECTIVE OF CALCIUM SIGNALING

According to IEEE 1906.1 standard physical channel layer of a nanonetwork can be defined by five protocol stack components namely (i) message carrier, (ii) motion, (iii) field, (iv) perturbation and (v) specificity. We summarize the functionalities of the protocol stack components in Table 1.

Table 1. Protocol stack components of physical channel layer

<table>
<thead>
<tr>
<th>Specificity</th>
<th>Perturbation</th>
<th>Field</th>
<th>Motion</th>
<th>Message Carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific interaction to the intended receiver</td>
<td>Variation of carrier concentration according to the modulating signal</td>
<td>Concentration gradient and potential difference at different regions works as the controlling field for Ca²⁺ signaling</td>
<td>Ca²⁺ signals mainly propagate by diffusion</td>
<td>Mass and energy</td>
</tr>
<tr>
<td>Inositol trisphosphate (IP₃) receptors, ryanodine receptors, Ca²⁺ binding proteins serve this purpose</td>
<td>Amplitude modulation and Ca²⁺ spike generation by mitochondria, ER, ER pumps serve the purpose of perturbation</td>
<td>In Ca²⁺ signaling information is encoded in terms of Ca²⁺ concentration. So Ca²⁺ ions work as the message carrier</td>
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<td></td>
</tr>
</tbody>
</table>

The Figure 1 shows the functionalities of the physical channel layer in Ca²⁺ signaling based communication and maps the protocol stack components with them.

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![Figure 1. Mapping of Ca²⁺ signaling with protocol stack components](image)

Any communication system consists of three basic phases: transmission, propagation and reception. To model a communication system, we have to model these in three phases. In Ca²⁺ signaling based communication, the functionalities of the defined protocol stack components (given in Table 1) of the physical channel can be integrated to achieve these three phases e.g., the functionality of the perturbation comes under transmission, the field and motion comes under propagation and the specificity is required for modelling the reception. In the next section we are modelling the physical channel to achieve these three phases to some extent.

3. PHYSICAL CHANNEL MODELING AND ITS SOLUTION SCHEME

Unlike conventional communication system in Ca²⁺ signaling based communication different cell components (organelles) mainly mitochondria and Endoplasmic Reticulum (ER) play active role Ca²⁺ signal modulation. This modulated Ca²⁺ waves finally reach to the intended receivers and are demodulated by ligand/receptor binding mechanisms in the receivers. So modelling of physical channel involves three subtasks: (i) modelling the cell components to modulate the Ca²⁺ waves, (ii) modelling the intra and inter-cellular propagation of these Ca²⁺ waves and (iii) modelling the receiver

3.1 Mathematical modeling of the components

To model the cell components mathematically, we consider five variables as discussed in [6]. These are cytosolic Ca²⁺ concentration (CaCyt), Ca²⁺ concentration present in ER (CaER), mitochondrial Ca²⁺ concentration (Caₘ), free Ca²⁺ binding sites (Pr) on cytosolic proteins and the concentration of bounded Ca²⁺ binding sites (CaPr) on cytosolic proteins. Mainly IP₃ works the binding of Ca²⁺ ions with these cytosolic proteins. First, by applying the conservation relation, we get,

\[
Ca_{tot} = Ca_{Cyt} + \rho_{ER} Ca_{ER} + \rho_{m} Ca_{m} + Ca_{Pr} \tag{1}
\]

where Ca_{tot} is the total cellular Ca²⁺ concentration. Similarly for total concentration of bound and unbound proteins we get,

\[
Pr_{tot} = Pr + Ca_{Pr} \tag{2}
\]

The terms \(\rho_{ER}\) and \(\rho_{m}\) represent the volume ratio between ER and cytosol, and between mitochondria and cytosol respectively. \(\beta_{ER}\) and \(\beta_{m}\) are constant factors for relating the concentration of free Ca²⁺ ions in ER and in mitochondria with respect to their total concentration [6]. The \(Pr_{tot}\) remains constant but when an external stimulus (modulating signal) is applied some Ca²⁺ bounded site on cytosolic proteins become dissociated producing free Ca²⁺ binding site and free Ca²⁺ ions which are released in the aqueous cytosol. Thus the cytosolic proteins work as transmitter in this Ca²⁺ based communication. Now we model mathematically the Ca²⁺ exchanges between the cytosol and ER, and the Ca²⁺ exchanges between the cytosol and mitochondria. Between ER and cytosol three exchanges takes place: i) the ATP-dependent calcium uptake from the cytosol into the ER (J_{ATP}), ii) the Ca²⁺ emission flux from the ER through channels following the calcium-induced calcium release (CICR) mechanism (J_{CICR}), and iii) an additional Ca²⁺ leak flux from the ER into the cytosol (J_{leak}). Between cytosol and mitochondria two exchanges take place: (i) active Ca²⁺ uptake by mitochondrial uniporters (J_{inh}), calcium release as the combined effect of Na⁺/Ca²⁺ exchangers and mitochondrial permeability transition pores (PTPs) in a very low conductance state, and (ii) a very small non-specific leak flux (J_{out}). The change of concentration of Ca_{Cyt} with
respect to time is dependent on fluxes across ER membrane, Ca$^{2+}$ exchange with the mitochondria and Ca$^{2+}$ binding with the cytosolic proteins. The basic equation of this phenomenon is

$$\frac{d\text{Ca}_{\text{Cyt}}}{dt} = J_{ch} + J_{\text{leak}} - J_{\text{pump}} - J_{\text{out}} - J_{\text{in}} + K_{\text{CaPr}} + K_{\text{CaCytPr}}$$  (3)

where $k_{\text{ch}}$ and $k_{\text{leak}}$ represent the on-rate and off-rate constants of Ca$^{2+}$ binding respectively.

The rate of change of Ca$^{2+}$ concentration in ER is given by the following equation

$$\frac{d\text{Ca}_{\text{ER}}}{dt} = \frac{\text{Pr}_{\text{ER}}}{\text{K}_{\text{ER}}}(J_{\text{pump}} - J_{ch} - J_{\text{leak}})$$  (4)

The equation of Ca$^{2+}$ concentration in mitochondria is given as

$$\frac{d\text{Ca}_{\text{mt}}}{dt} = \frac{\text{Pr}_{\text{mt}}}{\text{K}_{\text{mt}}}(J_{\text{in}} - J_{\text{out}})$$  (5)

The ATPase-mediated Ca$^{2+}$ flux $J_{\text{pump}}$ is given as $J_{\text{pump}} = k_{\text{pump}}[\text{Ca}_{\text{Cyt}}]$, where $k_{\text{pump}}$ is the rate constant of ATPases. The channel flux $J_{ch}$ and leak flux $J_{\text{leak}}$ are given as

$$J_{ch} = k_{ch}\frac{\text{Ca}_{\text{Cyt}}}{K_{ch} + \text{Ca}_{\text{Cyt}}}$$  (6)

$$J_{\text{leak}} = k_{\text{leak}}([\text{Ca}_{\text{ER}}] - \text{Ca}_{\text{Cyt}})$$  (7)

where $k_{ch}$ represents the maximal permeability of the Ca$^{2+}$ channels in the ER membrane, $K_{ch}$ represents the half-saturation for Ca$^{2+}$ and $k_{\text{leak}}$ is the rate constant for Ca$^{2+}$ leak flux through the ER membrane [6]. The mitochondrial calcium uptake by uniporters is given as

$$J_{\text{in}} = k_{\text{in}}\frac{\text{Ca}_{\text{Cyt}}}{K_{\text{in}} + \text{Ca}_{\text{Cyt}}}$$  (8)

where $k_{\text{in}}$ represents the maximum permeability of uniporters in the mitochondrial membrane. The mitochondrial Ca$^{2+}$ efflux $J_{\text{out}}$ is given as

$$J_{\text{out}} = (k_{\text{out}}\frac{[\text{Ca}_{\text{Cyt}}]}{K_{\text{out}} + \text{Ca}_{\text{Cyt}}} + k_{\text{o}})\text{Ca}_{m}$$  (9)

By using stimulus, some bounded Ca$^{2+}$ binding sites (CaPr) on the cytosolic Ca$^{2+}$ binding proteins are dissociated, and are producing free Ca$^{2+}$ binding receptors (Pr) and free Ca$^{2+}$ ions. So the [Ca$^{2+}$] in the cytosol near the Ca$^{2+}$ binding proteins (transmitters) increases.

**Figure 2: Action of different cell-components during Ca$^{2+}$ signaling [6]**

This change of [Ca$^{2+}$] in the aqueous cytosol causes change of Ca$^{2+}$ exchanges between mitochondria and cytosol and Ca$^{2+}$ exchanges between ER and cytosol according to the mathematical equations discussed above. This cumulative effect gives rise a regenerative time variation of [Ca$^{2+}$] in the cytosol near the transmitters. As the rate of dissociation of CaPr is dependent on the nature of the stimulus so the ultimate time variation of cytosolic [Ca$^{2+}$] is dependent on the nature of the stimulus. This mechanism is displayed in Figure 2 graphically.

### 3.2 Solution Scheme

We model the different cell components e.g., mitochondria, ER etc., in the cell cytosol with their specific parameters (e.g., dimension, location, absorption rate etc.) and solve the above set of differential equations numerically by Runge-Kutta method to find out the time variation of the cytosolic [Ca$^{2+}$], [Ca$^{2+}$] in mitochondria and [Ca$^{2+}$] in ER. The parameters used in our model are given in Table 2.

**Table 2: Input parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{in}}$</td>
<td>90μM</td>
<td>$\beta_{\text{ER}}$</td>
<td>0.0025</td>
<td>$K_{\text{out}}$</td>
<td>125s$^{-1}$</td>
<td>$K_{1}$</td>
<td>0.8μM</td>
</tr>
<tr>
<td>$P_{\text{ER}}$</td>
<td>120μM</td>
<td>$K_{p}$</td>
<td>4100 s$^{-1}$</td>
<td>$K_{m}$</td>
<td>0.00625s$^{-1}$</td>
<td>$K_{2}$</td>
<td>5μM</td>
</tr>
<tr>
<td>$\rho_{\text{ER}}$</td>
<td>0.01</td>
<td>$k_{\text{pump}}$</td>
<td>20s$^{-1}$</td>
<td>$k_{s}$</td>
<td>0.1μM$^{-}s^{-1}$</td>
<td>$\rho_{0}$</td>
<td>0.01s$^{-1}$</td>
</tr>
<tr>
<td>$\beta_{0}$</td>
<td>0.0025</td>
<td>$k_{\text{in}}$</td>
<td>300 μM$^{-}s^{-1}$</td>
<td>$K_{1}$</td>
<td>5μM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 3.3 Mathematical model for electro-diffusion

The modulated Ca$^{2+}$ waves propagate through the cellular space by electro-diffusion. Here we model the propagation of Ca$^{2+}$ in the intra- and inter-cellular space by electro-diffusion using electro neutral model [9]. We model a spherical cell as a three-dimensional space with a uniform spherical membrane. We consider a spherical cell structure surrounded by a cell membrane with uniform thickness. Through the external stimulus the calcium wave is generated within a cell; it propagates through the intra-cellular cytosolic medium towards the membrane. Upon reaching the membrane, these ions either add to the surface charge on the membrane or enter the extracellular space in the form of transmembrane current through the membrane ion channels. The membrane acts as a capacitor and maintains a membrane potential across it as described in [10]. In the electro neutral model, the ionic concentration follows ion conservation, drift-diffusion flux equation and electro neutrality condition given below:

$$\frac{\partial c}{\partial t} = -\nabla \cdot f$$  (10)

$$f = -D(\nabla c + \frac{qzc}{K_{B}T} \nabla \phi)$$  (11)

$$0 = \rho_{0} + qzc$$  (12)

Here, $f$ denotes the flux, $D$ is the diffusion coefficient, $qz$ is the amount of charge of Ca$^{2+}$, where $q$ is the elementary charge, i.e., the charge on a proton. $qD = k_{B}T$ is the mobility of Ca$^{2+}$ (Einstein relation), where $k_{B}$ is the Boltzmann constant, and $T$ is the absolute temperature. $\rho_{0}$ is the background charge density. The boundary condition for the membrane is given as below:

$$qD\frac{\partial \psi_{m}}{\partial t} + j$$  (13)

where $\psi_{m}$ is the membrane potential and $j$ is the transmembrane current.
3.4 Solution Scheme
To solve the coupled partial differential equations (PDEs), the numerical scheme is adopted [9], where a finite-volume method (FVM) is used to solve the PDEs. FVM is a method for representing and evaluating PDEs in the form of algebraic equations. A spherical boundary is incorporated to the computational domain that represents the cell membrane. Ca$^{2+}$ concentration is calculated in the intracellular region and its adjacent cell. A three-dimensional spherical mesh has been laid within this domain such that concentric finite volumes (FVs) are formed. Each FV (p) has a characteristic point (x), where the properties of that FV are defined. The divergence theorem is used to convert the volume integrals in a PDE that contains a divergence term to surface integrals. The flux through each face common to a pair of FVs, (p,p′) is then calculated. The flux entering a FV (p) is identical to that leaving adjacent FV (p). At x = x,

\[
\frac{\partial c}{\partial t} \approx \frac{1}{V} \int_{\text{finite volume}} \frac{\partial c}{\partial t} dV = -\frac{1}{V} \int_{\text{finite volume}} f \text{nd}A \approx -\frac{1}{V} \sum_{i} e_i \Gamma_i
\]

where F(p,p′) is the flux density approximation from FV p to p′ as. The ionic concentration is conserved when

\[
F(p,p') = F(p,p')
\]

\[
\frac{\partial c}{\partial t} = -\frac{1}{V} \sum_{i} e_i \Gamma_i
\]

where h is the area of the face common to finite volumes p and p′ and G(p,p′) is the flux from a finite volume p to another finite volume p′ that share a membrane of area γp,p′, so G(p,p′) is termed as the membrane flux will make an effect only for the boundary FVs of the cell. For ordinary FVs in the intra-cellular space, γp,p′ = 0, so the second term is zero. The ordinary flux F(p,p′) is calculated using the equation

\[
F = D \left[ \frac{c_p - c_{p'}}{h} + \frac{q(z(c_p + c_{p'}) - q_p - q_{p'}}{2k_BT} \right]
\]

where D is the diffusion coefficient. The expression qp − q_{p'} gives the potential difference between the representative points x for the finite volumes p and p′. z = 2 for Ca$^{2+}$ as it is divalent. To calculate the concentration in the (n+1)th instant from that in the nth instant of time we use the relation:

\[
\frac{c_{p,n+1} - c_{p,n}}{\Delta t} = -\frac{1}{V} \sum_{p} e_p \Gamma_i [hF(p,p',n)]
\]

where Δt should have a value long enough for the ions to move over from one FV to an adjacent FV in this time period. However, it should not be so long that ions can move over more than one FV.

The membrane flux is calculated numerically by the equation given as below:

\[
qzG_i(p,p') = \frac{c_{p,n}}{\Delta t} \frac{q_{p,n+1} - q_{p,n}}{\Delta t} + i_j(p,p')
\]

3.5 Modelling of the receiver
The modulated Ca$^{2+}$ signals reach to the receiver and are demodulated by ligand-receptor binding mechanism where Ca$^{2+}$ ions work as ligand. We adopt a cell kinetic model of this binding mechanism [11]. We consider that the receptors reside on the cell-surface (i.e., the external side of the cell-membrane) of the receiver-cell. After reaching to receiver, the Ca$^{2+}$ ions are bound to free receptors forming ligand/receptor complexes [11]. Depending on the formation of these ligand/receptor complexes, the modulated Ca$^{2+}$ signal is decoded at the receiver cell. To model these ligand/receptors bindings mathematically, we consider a set of variables: the number of free receptors on the cell-surface (R_s), the number of receptor/ligand complexes on the cell-surface (C_s), the total number of free plus bound receptors in endosomes (R_{T}), the total number of intra-cellular Ca$^{2+}$ ions (L_{s}) i.e., which are generated from the receiver cell internally, the Ca$^{2+}$ concentration in the medium (L) and the rate of new receptor synthesis (V_{s}). The binding of Ca$^{2+}$ ions with the receptors can be represented by a set of differential equations [11]:

\[
a \frac{dR_s}{dt} = -k_{d}R_s + k_{c}C_s - k_{n}R_s + k_{n}C_{11}(1-f_{s})R_{T} + V_{s}
\]

\[
a \frac{dC_s}{dt} = k_{d}R_s - k_{c}C_s - k_{c}C_s
\]

\[
a \frac{dR_{11}}{dt} = k_{n}R_s + k_{c}C_s + [k_{n}C_{11}(1-f_{s}) + k_{n}C_{11}f_{s}]R_{T}
\]

\[
a \frac{dL_s}{dt} = k_{c}C_s + [k_{n}C_{11}(1-f_{s}) + k_{n}C_{11}f_{s}]L_{s} + k_{n}N_{s}L_{s}
\]

The terms k_d and k_c are reaction rate constants of receptor/ligand binding and dissociation respectively. We assume that each receptor has one binding site (i.e., one receptor can bind one Ca$^{2+}$ ion) and the binding is simple bimolecular non-cooperative binding [11]. Rate constants describing the internalization of receptor/ligand complexes and free-receptors are k_{c} and k_{n} respectively. k_{c} represents the intrinsic rate constant for transport of material via vesicles from the endosome back to the cell-surface. (1-f_{s}) and (1-f_{s}) are the fraction of endocytosed receptors and ligands respectively. k_{n} represents a lumped rate constant for the routing of ions from the endosome to the lysosome, degradation in the lysosome, and the release of fragments in the extracellular medium.

3.6 Solution scheme
The above equations (20), (21), (22), (23) are solved by Runge-Kutta method in MATLAB that will show how the rate of change of bounded ligand/receptor complexes occur. This rate of change of the number of bounded ligand/receptor complexes represent demodulated signal.

4. EVALUATION AND RESULTS
First, we model the cell-components (mitochondria, ER) to modulate the Ca$^{2+}$ waves. To test the solution scheme, we assume that there is a single transmitter for the sake of simplicity, and mitochondria and ER are uniformly distributed throughout the cell and their individual dimension negligible compared to the dimensions of entire cell. Figure 3 demonstrates the Ca$^{2+}$ concentration inside the cell components and the aqueous cytosol as well in an equilibrium condition (i.e., in absence of any stimulus).
When stimulus is applied Ca\(^{2+}\) ions are emitted in the aqueous cytosol from the transmitter. So, the time variation of [Ca\(^{2+}\)] in the cytosol near the transmitter occurs. Figure 4.1 and Figure 4.2 show the variation of [Ca\(^{2+}\)] near the transmitter for Ca\(^{2+}\) emission from the transmitter for two type of stimuli namely train of pulses and single pulse respectively. For two types of stimuli, two types of [Ca\(^{2+}\)] patterns are observed.

In our simulation, we consider a space consisting of two adjacent cells, and the whole space consisting of these two cells are divided into seven FVs. The transmitter is situated at the 1\(^{st}\) FV, say FV1, and the inter-cellular membrane is situated at the boundary of 3\(^{rd}\) FV, say FV3 and 4\(^{th}\) FV, say FV4. The receptors are located on the membrane. The first cell contains the transmitter and the second cell works as the receiver. The transmitter transmits the modulated calcium waves and this modulated wave propagates through the aqueous cytosol by electro-diffusion mechanism. Figure 5.1 and Figure 5.2 show the time variation of calcium concentration in the seven FVs for train of pulses and single pulse type emission pattern.

From the above two figures, we observe that due to Ca\(^{2+}\) emission from the transmitter, the time variation of [Ca\(^{2+}\)] i.e., Ca\(^{2+}\) waves occurs in all the FV which explains the field and motion protocol components are justified and Ca\(^{2+}\) waves acts as a message carrier. The another observation is that the time variation of Ca\(^{2+}\) waves decreases from the first FV to the last (seventh) FV i.e., the time variations of Ca\(^{2+}\) waves decrease with the increase of the distance from the transmitter which may be analogous to attenuation due to distance in conventional communication system. In Figure 6.1 and Figure 6.2, we show the concentration in different FVs at discrete time instants for the same two emission patterns.
Figure 6.2. $[\text{Ca}^{2+}]$ at different finite volumes at discrete instants of time for single pulse type stimulus
From the figures (6.1 and 6.2), it is observed that there is an abrupt change in concentration at 4th FV, say FV4. This phenomenon can be explained by the capacitive action of the membrane. Due to this capacitive action, a jump in electrostatic potential (membrane potential) is maintained across the cell membrane [9]. Therefore, there is a thin space charge layer on both sides of the membrane which causes this abrupt change in concentration.

Figure 7. Variation of space-charge concentration across the membrane with respect to time
The above Figure 7 shows the space charge concentration variation across the membrane with respect to time. These propagated $\text{Ca}^{2+}$ waves ultimately reach to the intended receiver and the modulating signal is decoded in the receiver from these received modulated $\text{Ca}^{2+}$ waves. Some certain receivers (specific to the ligand) are situated in the system for these purpose. So we can say that specificity is also maintained. As we have mentioned before that the inter-cellular membrane is situated at the boundary of FV3 and FV4, so we have placed the receiver on the cell membrane.

Figure 8.1. $[\text{Ca}^{2+}]$ Variation in 3rd FV3 with time
Figure 8.2. Variation of rate of formation of ligand/receptor complexes with respect to time
Figure 8.3. Variation of Difference between rate of formation of ligand/receptor complexes and actual $[\text{Ca}^{2+}]$ in FV3 with time

5. CONCLUSION
Our ongoing work has focused to model the physical channel by using the electro-diffusion model. We have observed the $\text{Ca}^{2+}$ concentration at different points in adjacent cells at each time instance and finally observed the pattern of received signal estimated by the receiver. The next task remains to implement the decoding scheme at the receiver i.e., the mapping between the received $[\text{Ca}^{2+}]$ estimated by the receiver corresponding to different biological phenomena that will help to design of the protocol stack components of the physical channel layer. Then the different metrics defined for the protocol stack
components stated 1906.1 [5] can be analyzed to determine the performance of the components of physical channel.

6. REFERENCES