A Novel Channel Model for Molecular Communications Based on Inter-cellular Calcium Wave

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Abstract. Calcium signalling is a good bio-inspired method for molecular communication due to the advantages of biocompatibility, stability, and long communication range. In this paper, we investigate a few channel characteristics of calcium signaling transfer systems including propagation distance and time delay based on a novel inter-cellular calcium wave (ICW) propagation model. Our model is the first one that can investigate the impact of some exclusive parameters in ICW (e.g., the gap junction permeability). Understanding the channel transfer characteristics of ICW can provide a significant reference for the calcium signaling application in molecular communication. In the future, theoretical and simulation results in this paper can help in the design of molecular communication systems between nanodevices.

Keywords: Molecular communication · Inter-cellular calcium wave
Channel characteristics

1 Introduction

In recent years, the rapid development of nanotechnologies provides many new applications in biomedical, industrial, and military fields [1]. In nanometer scale, the most basic unit is called nano-machine [2] and each nano-machine can only perform simple tasks like sensing, computing, and drug delivery. Therefore, cooperation of different nano-machines is significant for nano-machines to do complex tasks. Nano-sized communication allowing nano-machines to pass instructions and sharing informations is an important part of cooperation of nano-machines.

Molecular communication is a type of promising nano-sized communication technology and can be a good compensation to traditional communication mode

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due to advantages of biocompatibility, small scale, and high energy efficiency [3]. In the molecular communication system, transmitted information is encoded in molecules and communicated by diffusion or molecular motor. By means of molecular communications, nano-networks between nano-machines can enable nano-machines to exchange messages and work cooperatively [4].

This paper concentrates on the bio-inspired molecular communication approach, which means that develop molecular communication from communication mechanism existing in biological structures. In nature, cells in organism transfer significant information to other cells using information objects. Bio-inspired approach utilizes communication mechanism existing in organism such as intercellular Ca^{2+}, Na^{+} wave propagation, and hormone traveling, to develop new advanced molecular communication technology. For this approach, bio-inspired molecular communication can work on both bio-organism and nano-machines that offer compatible solution for in-body communication scenario.

Calcium signal is a type of bio-inspired molecular communication method based on ICW [5]. Many studies suggested that this kind of communication method exists widely in nature [6,7]. As shown in Fig. 1, human smooth muscle coupling in intestines and stomach is mediated by Ca^{2+} release. In human astrocytes, the calcium wave plays an important role in information transfer in remote parts of the brain. Calcium signal is also a common phenomenon in epithelial cells, the calcium oscillation resulting from a simple regenerative is of vital importance for system equilibrium. In Ca^{2+} signaling, connected cells array can serve as a communication channel connecting the transmitter and receiver. The inter-cellular calcium wave can be transferred to the touching neighbor cells through the gap junctions, which results in the intercellular Ca^{2+} wave propagation.

Calcium signal have been studied by many researchers for a long time. In [10], a relay channel model based on ICW was proposed and communication capacity of a Ca^{2+} relay channel was computed. In [11], a linear channel model for intra/inter-cellular Ca^{2+} molecular communication based on Ca^{2+} signal was investigated and some channel characteristics were derived. However, these Ca^{2+} channel models mainly considered the effect of Ca^{2+} diffusion and Ca^{2+} induced Ca^{2+} release (CICR). Inositol 1, 4, 5-triphosphate (IP3) induced Ca^{2+} release was rarely taken into account in these channel models. According to the latest study [5], in some certain type of cells such as epithelial cells, ICW is mainly caused by transmission of IP3 between adjacent cells instead of calcium itself. This paper investigates the molecular communication channel model based on IP3 induced ICW. Close-form solutions for channel characteristics and channel capacity based on information theory are obtained, which will play important roles in communication system design and performance evaluation.

The rest of this paper can be divided in four parts. In Sect. 2, the mathematical model of cytosolic Ca^{2+} concentration oscillation and gap junction relevant to channel modeling is described and analyzed. In Sect. 3, some significant channel characteristics are analyzed based on a mathematical model. Binary channel capacity is computed in Sect. 4. Section 5 concludes the whole paper and points out the future works.

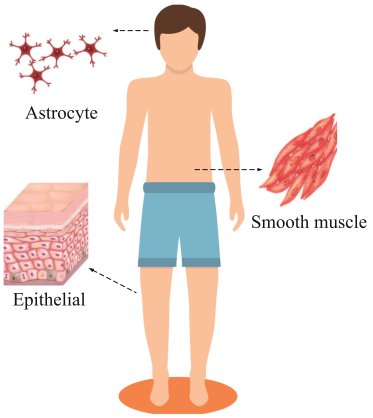

Fig. 1. Locations of cells having inter-cellular Ca^{2+} wave propagation.

2 Channel Models Based on ICW

2.1 Ca^{2+} Oscillation Model

Cytosolic Ca^{2+} serves as a kind of crucial second messenger in inter/inner cellular communications. The principle of this communication method has been studied by many researchers and different dynamic models have been proposed to explain the mechanism of ICW [8,9]. However, most communication channel models based on ICW mainly considered CICR to describe ICW communication mechanism, which dose not conform to the reality very well. In this paper, we refer to the ICW model proposed in [14], which takes IP3 as the main factor triggering the ICW, and apply this dynamic model to a molecular communication scenario, i.e. lots of cells connected with each other via gap junction. Then, we simulate the molecular communication process to get the ICW propagation characteristics based on the Ca^{2+} channel model.

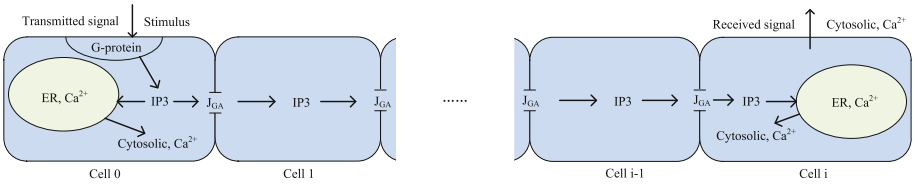

Fig. 2. Mechanism of inter-cellular Ca^{2+} wave propagation.

The basic mechanism of cytosolic Ca^{2+} oscillation is shown as Fig. 2 in Cell 0. Firstly, external stimulus applied on G-protein receptors induces the discharge of PLCβ molecules. Then, PLCβ molecules trigger the release of IP3 molecules initiating a rapid release of Ca^{2+} from the endoplasmic reticulum (ER) through IP3

and Ca^{2+} sensitive channels. Finally, with the repeated release and absorbtion of cytosolic Ca^{2+}, Ca^{2+} concentration in cytosol starts to perform an oscillation state.

This model contains three variables, namely, the concentrations of free Ca^{2+} in the cytosol (Z) and in ER (Y), and the IP3 concentration in the cytosol (A). The time evolution of these variables is governed by the following ordinary differential equations

$$\frac{dZ}{dt} = J_{\text{in}} + J_{\text{rel}} - J_{\text{pump}} - KZ + K_{\text{f}}Y \tag{1}$$

$$\frac{dY}{dt} = J_{\text{pump}} - J_{\text{rel}} - K_{\text{f}}Y \tag{2}$$

$$\frac{dA}{dt} = J_{\text{s}} + J_{\text{GA}} - \varepsilon A. \tag{3}$$

For cytosolic and ER Ca^{2+} concentration, J_{in} means the influx of Ca^{2+} from the extracellular media, J_{rel} and J_{pump} refer to IP3 induced Ca^{2+} release from ER and pumping of cytosolic Ca^{2+} into the ER, respectively, Ca^{2+} oscillation is mainly based on the balance between these two fluxes, KZ means the leak flux Ca^{2+} from cytosol to extracellular media which is proportional to cytosolic Ca^{2+} concentration, and $K_{\text{f}}Y$ is the leak flux of Ca^{2+} from ER to cytosol. For cytosolic IP3 concentration, J_{s} refers to stimulus induced IP3 release, ε refer to IP3 degration coefficient, and J_{GA} is the gap junction IP3 flux that will be discussed in next subsection. The function expressions of the participating fluxes are shown as follows:

$$J_{\text{s}} = \beta V_4 \tag{4}$$

$$J_{\text{in}} = V_0 + V_1\beta \tag{5}$$

$$J_{\text{pump}} = V_{\text{M2}}\frac{Z^2}{K_2^2 + Z^2} \tag{6}$$

$$J_{\text{rel}} = V_{\text{M3}}\frac{Z^m}{K_2^m + Z^m}\frac{Y^2}{K_{\text{Y}}^2 + Y^2}\frac{A^4}{K_{\text{A}}^4 + A^4}. \tag{7}$$

In these equations, V_0 refers to a constant input of Ca^{2+} from extracellular space and V_1 is the maximum rate of stimulus-induced influx of Ca^{2+} from the extracellular medium. Parameter β reflects the degree of stimulus that only varies between 0 and 1, V_4 is the maximum rate of stimulus-induced synthesis of IP3. V_{M2} and V_{M3} denote the maximum values of J_{pump} and J_{rel}, respectively. Parameters K_2, K_{Y}, and K_{A} are threshold constants for pumping, release, and activation of Ca^{2+} release by Ca^{2+} and by IP3, respectively. These parameter values are shown in Table 1.

2.2 Gap Junction Model

In the nature, one of the important cell-to-cell communication methods is the gap junction communication. In this way, the communication between different cells is achieved by the exchanges of message molecules like ions, protein,

Table 1. Simulation parameters.

Parameter	Value
Transport coefficient of cytosolic Ca^{2+}, k	$10\,s^{-1}$
Threshold constant for J_{pump}, K_2	$0.1\,\mu M$
Threshold constant for J_{rel} correlated to A, K_A	$0.2\,\mu M$
Coefficient of leak flux, K_f	$0.1\,\mu M$
Threshold constant for J_{rel} correlated to Y, K_Y	$0.2\,\mu M$
Threshold constant for J_{rel} correlated to Z, K_Z	$0.5\,\mu M$
Ca^{2+} from the extracellular medium, V_0	$2\,\mu M\,s^{-1}$
Maximum rate of stimulus-induced influx of Ca^{2+}, V_1	$2\,\mu M\,s^{-1}$
Maximum value of J_{pump}, V_{M2}	$6\,\mu M\,s^{-1}$
Maximum value of J_{rel}, V_{M3}	$60\,\mu M\,s^{-1}$
Maximum value of J_{in}, V_4	$2\,\mu M\,s^{-1}$
Coefficient of IP3 degration, ε	$0.3\,s^{-1}$
Hill coefficient, m	2

and organelles at the coupling channels of adjacent cells. This communication mechanism is a meaningful part of ICW propagation.

In our model, IP3 is transmitted by a transmitter cell, and then propagates through the gap junction crossing a few cells by means of diffusion. During this period, IP3 induces Ca^{2+} oscillation in passing cells and suffers decay in propagation process. Finally IP3 is received by the receiver cell and excites the Ca^{2+} oscillation. The IP3 flux between gap junction coupling cells is proportional to the IP3 concentration gradient and gap junction permeability [6]. Therefore, the IP3 gap junction transmitting mechanism is determined as

$$J_{GA} = P_{IP3}(Z^+ - Z) + P_{IP3}(Z^- - Z) \tag{8}$$

where Z^+ and Z^- are Ca^{2+} concentration in two different adjacent cells, P_{IP3} is the IP3 gap junction permeability and P_{IP3} is usually unaffected by the IP3 concentration. So, we consider that P_{IP3} is independent of IP3 concentration.

3 Results and Analysis

In this section, we study the ICW channel characteristics like maximum propagation distance, propagation time delay, and calcium oscillation frequency as the function of gap junction permeability P_{IP3} and stimulus intensity β using numerical and simulation methods.

3.1 Calcium Oscillation Condition

Refering to the model expression in Sect. 2.1, Ca^{2+} oscillation is mainly based on the balance between J_{pump} and J_{rel}. IP3 concentration increasing causes

the increasing of J_{rel} and breaks the steady state of cytosolic Ca^{2+}. Then CICR causes the positive feedback of J_{rel} and finally gives rise to Ca^{2+} oscillation. The condition of Ca^{2+} oscillation can be expressed as $J_{\text{pump}} > J_{\text{rel}}$, and substituting (6) and (7) into this condition we can get

$$V_{\text{M2}} \frac{Z^2}{K_2^2 + Z^2} > V_{\text{M3}} \frac{Z^m}{K_2^m + Z^m} \frac{Y^2}{K_{\text{Y}}^2 + Y^2} \frac{A^4}{K_{\text{A}}^4 + A^4} \tag{9}$$

$$\frac{A^4}{K_{\text{A}}^4 + A^4} > \max \left\{ \frac{V_{\text{M2}}({K_Z}^2 + Z^2)}{V_{\text{M3}}({K_2}^2 + Z^2)} \right\}. \tag{10}$$

Through proper simplification, the condition can be written as

$$A > (\frac{EK_A^4}{1-E})^{\frac{1}{4}} = K'_{\text{A}} \tag{11}$$

$$E = \begin{cases} V_{\text{M2}}{K_Z}^2 / V_{\text{M3}}{K_2}^2, & K_Z > K_2 \\ V_{\text{M2}}/V_{\text{M3}}, & K_Z \leq K_2 \end{cases} \tag{12}$$

which means that the sum of cytosolic Ca^{2+} fluxes forms the positive feedback and E is the critical condition of oscillation state and steady state for variable $\frac{A^4}{K_{\text{A}}^4 + A^4}$.

We take IP3 induced Ca^{2+} release threshold as K'_{A}. In order to prove that a certain IP3 concentration K'_{A} excites the calcium concentration oscillation, numerical method is used to simulate IP3 induced calcium oscillation. We use the system parameters from [14] and assume that all the cells in the system have the same biological parameters. Utilizing Runge-Kutta method, we get three variables time evolution of IP3 induced Ca^{2+} oscillation of different cells. Figure 3 indicates that the existence of Ca^{2+} oscillation is controlled by IP3 concentration. The same IP3 concentration threshold enable the oscillation in different cells. The relationship between IP3 concentration and Ca^{2+} oscillation amplitude or frequency is shown in Fig. 4. From this numerical simulation, Ca^{2+} oscillation amplitude Z_{AM} and frequency f_o are related with IP3 concentration and once IP3 concentration surpasses the threshold value K'_{A}, Z_{AM} and f_o tend to be a constant.

3.2 Intercellular IP3 Concentration Propagation

Since cytosolic Ca^{2+} oscillation is mediated by IP3 concentration in our model, ICW propagation time delay and distance can be calculated based on IP3 propagation differential equations. The variation of IP3 concentration due to the gap junction IP3 exchanging between Cell i and Cell i-1 can be illustrated as

$$\frac{dA_{\text{i}}}{dt} = \begin{cases} P_{\text{IP3}}(A_{\text{i-1}} - A_{\text{i}}) - \varepsilon A_{\text{i}} - P_{\text{IP3}}(A_{\text{i}} - A_{\text{i+1}}), & i \neq 0 \\ \beta V_4 - P_{\text{IP3}}(A_{\text{i}} - A_{\text{i+1}}) - \varepsilon A_{\text{i}}, & i = 0. \end{cases} \tag{13}$$

The IP3 in each cell can be described by steady-state and transient-state based on (13). Setting time derivative of A_{i} to 0, the steady-state of IP3 concentration

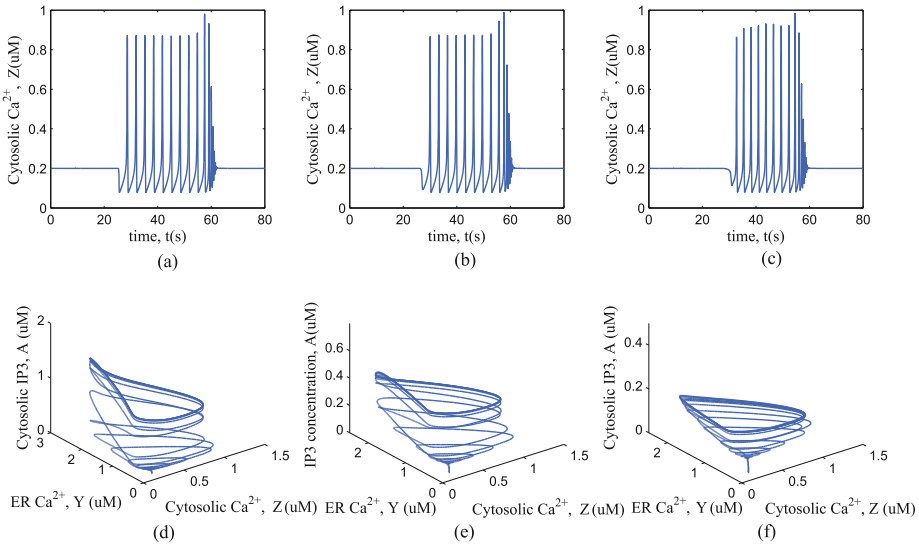

Fig. 3. Time evolutions of cytosolic Ca^{2+} concentration, (a) in Cell 2, (b) in Cell 4, and (c) in Cell 8 with transmitter cell subject to agonist stimulus representing the sequence '010' and symbol duration of 25 s. The relationships of three variables (A, Z, Y) are shown as (d) in (a), (e) in (b), and (f) in (c), respectively. Simulation parameters are the same as Table 1.

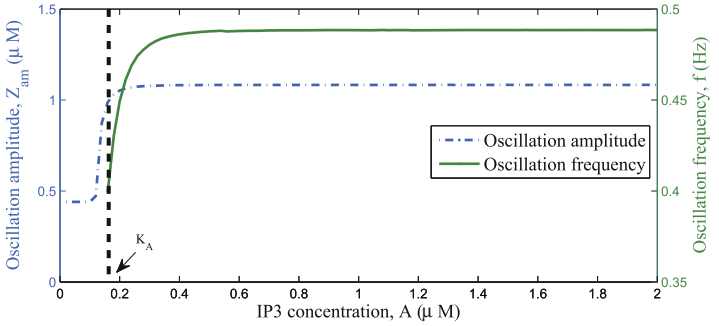

Fig. 4. Ca^{2+} oscillation amplitude or frequency affected by IP3 concentration.

in Cell i, A_i', can be obtained by solving the first order linear equations in matrix formation as below

$$\mathbf{Ax} = \mathbf{b} \tag{14}$$

where $\mathbf{A}$ is an infinite matrix with the formation

$$\mathbf{A} = \begin{bmatrix} (P_{\mathrm{IP3}}+\varepsilon) & -P_{\mathrm{IP3}} & 0 & \cdots & \\ -P_{\mathrm{IP3}} & (2P_{\mathrm{IP3}}+\varepsilon) & -P_{\mathrm{IP3}} & 0 & \cdots \\ 0 & -P_{\mathrm{IP3}} & (2P_{\mathrm{IP3}}+\varepsilon) & -P_{\mathrm{IP3}} & 0 \ \cdots \\ \vdots & \ddots & \ddots & \ddots & \end{bmatrix}.$$

Here, $\mathbf{x}$ and $\mathbf{b}$ are infinite vectors, i.e. $\mathbf{x} = \begin{bmatrix} A'_0 & A'_1 & A'_2 & \cdots \end{bmatrix}^T$, $\mathbf{b} = \begin{bmatrix} \beta V_4 & 0 & 0 & \cdots \end{bmatrix}^T$. By solving these equations, it can be found that steady-state IP3 concentration attenuation a_{in} between Cell i and Cell i+1 is a function of P_{IP3} and ε, and can be expressed as

$$a_{in} = 1 - \frac{\sqrt{\varepsilon^2 + 4\varepsilon P_{\mathrm{IP3}}} - \varepsilon}{2P_{\mathrm{IP3}}}. \tag{15}$$

Therefore, steady-state of IP3 in each cell can be obtained as

$$A'_i = a_{in} A'_{i-1} = a_{in}^i A'_0 \tag{16}$$

and A'_0 is written as

$$A'_0 = \frac{\beta V_4(\sqrt{\varepsilon^2 + 4\varepsilon P_{\mathrm{IP3}}} - \varepsilon)}{2\varepsilon P_{\mathrm{IP3}}}. \tag{17}$$

Once the IP3 concentration steady-states in each cell is determined, IP3 induced ICW propagation distance N can be determined as

$$N \log a_{in} = \log \frac{\mathrm{K_A}}{\mathrm{A'_0}}. \tag{18}$$

Because of the time consumption of IP3 diffusion in the cytosol, we assume that inter cellular IP3 propagation starting from cytosolic IP3 concentration is equal to steady state. Then, the overall response of IP3 concentration in each cell can be written as

$$A_i(t) = \begin{cases} 0, & t \le (i-1)\tau_{in} \\ P_{\mathrm{IP3}} A'_{i-1}(1 - \exp(-\lambda (t - (i-1)\tau_{in}))/\lambda, & (i-1)\tau_{in} < t \le i\tau_{in} \\ a_{in} A'_{i-1}, & t > i\tau_{in} \end{cases} \tag{19}$$

where $\lambda = P_{\mathrm{IP3}} + \varepsilon$ is the time coefficient and τ_{in} is the IP3 propagation time delay for each cell that can be written as

$$\tau_{in} = \frac{1}{\lambda} \ln\left(\frac{\mathrm{P_{IP3}} - a_{\mathrm{in}}\lambda}{\mathrm{P_{IP3}}}\right). \tag{20}$$

Then, the time delay τ_i for ICW propagation of Cell i can be calculated by solving $A_i(\tau_i) = K_{\mathrm{A}}$ and the solution is

$$\tau_i = (i-1)\tau_{in} - \frac{1}{\lambda} \ln\left(1 - \frac{\mathrm{K_A}}{\mathrm{A'_i}}\right), \quad \mathrm{i} \le \mathrm{N}. \tag{21}$$

ICW propagation distance and delay can be calculated base on (18) and (21), respectively.

3.3 Effect of Gap Junction Permeability and Stimulus Intensity

In this subsection, we examine the ICW propagation distance and time delay with the variation of both junction permeability and stimulus intensity. The propagation distance for the ICW process is computed with both theoretical and numerical methods. It can be seen that theoretical and numerical values match well as shown in Fig. 5. Propagation distance is shown with respect to both the gap junction permeability and stimulus intensity. Increase of gap junction permeability and stimulus intensity can enhance the ICW propagation distance obviously.

ICW propagation time delay of Cell i is calculated in (21) as a function of number of cells along the path and simulated with Euler algorithm. From Fig. 6, ICW propagation time delay, τ_i, increases proportionally with the rising number

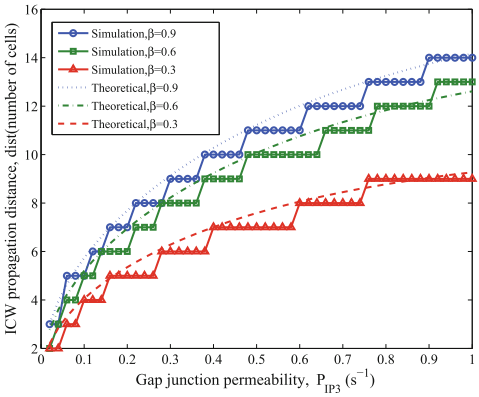

Fig. 5. ICW transmit distance with varying stimulus intensity and gap junction permeability.

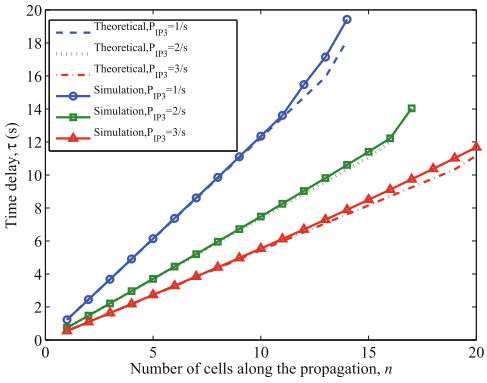

Fig. 6. ICW transmission delay with varying propagation distance and gap junction permeability.

of cells along the propagation. Meanwhile, gap junction permeability increase causes the decrease of time delay, indicating that gap junction permeability is another crucial factor affecting the calcium wave propagation delay. Therefore, it is a reasonable approach to optimize the communication channel by increasing the gap junction permeability.

4 Channel Capacity

Channel capacity can be calculated as the maximum mutual information value between the transmitter and the receiver. Considering a binary channel in our system, mutual information can be calculated as

$$\mathrm{I}(X;Y) = \sum_{\mathrm{X}} \sum_{\mathrm{Y}} \mathrm{P(x,y)} \log_2 \frac{\mathrm{P(x,y)}}{\mathrm{P(x)P(y)}}. \tag{22}$$

A symbol '1' is transmitted when continuous stimulus is applied to the transmitter cell. Detection of symbols at the receiver side is realized by detection of Ca^{2+} concentration pulses number. If the cytosolic Ca^{2+} concentration shows more than $M/2$ pulses within a symbol duration at receiver cell (M is the total number of pulses in a symbol duration with oscillation state, $M = f_0 T_s$), then we judge the received signal as '1'. If not, the received symbol will be detected as '0'. A symbol '0' is transmitted when no stimulus to transmitter cell and if the cytosolic Ca^{2+} concentration shows more than $M/2$ pulses without IP3, received symbol will be judged false as '1'. If not, the received symbol will be judged correctly as '0'. The probability of Ca^{2+} pulse occurring in unit time can be calculated as [12]

$$P_w = 1 - \exp(-\frac{P_{\max} Z_{\mathrm{init}}^2}{K_p^2 + Z_{\mathrm{init}}^2} T_u) \tag{23}$$

where $P_{\max}$ is the maximum probability of Ca^{2+} pulse occurrence in unit time T_{u}, $\mathrm{Z_{init}}$ is the initial Ca^{2+} concentration in cytosol, and K_p is the threshold constant. Here, we take $Z_{\mathrm{init}} = 0.2\,\mu\mathrm{M}$, $T_{\mathrm{u}} = 1\,\mathrm{s}$, $T_s = 25\,\mathrm{s}$, $f_o = 0.44\,\mathrm{Hz}$, and $K_p = 0.6\,\mu\mathrm{M}$. The error probability P_E of transmitting '0' and receiving '1' can be calculated as probability of more than $M/2$ pulses occurring in a symbol duration, i.e.

$$P_E = \Pr(m > \frac{M}{2}). \tag{24}$$

The pulse number without the IP3 in a symbol duration, m, can be approximated by poisson distribution as

$$m \sim \mathrm{Pois}(\frac{T_{\mathrm{s}} P_{\mathrm{w}}}{T_{\mathrm{u}}}). \tag{25}$$

The probability of Ca^{2+} oscillation occurring at receiver cell P_s due to ICW can be represented by probability of IP3 successful propagation. As mentioned in [13], gap junctions may be blocked due to virous factors such as connexin protein phosphorylation, which causes the ICW propagation to fail to transmit. We assume that different gap junctions have the same probability P_{block} to be blocked. Thus, the probability of IP3 induced ICW occurring at Cell n can be represented as

$$P_S(n) = \begin{cases} (1 - P_{\text{block}})^n, & n \leq N \\ 0, & n > N \end{cases}. \tag{26}$$

The joint probability distribution of the transmitted symbol and received symbol from Cell 0 to Cell n can be obtained as equation below

$$P_n(X, Y) = \begin{cases} P_0(1 - P_E), & X = 0, Y = 0 \\ P_0 P_E, & X = 0, Y = 1 \\ P_1(1 - P_S(n))(1 - P_E), & X = 1, Y = 0 \\ P_1 P_S(n) + P_1(1 - P_s)P_E, & X = 1, Y = 1 \end{cases} \tag{27}$$

where P_0 and P_1 are probabilities of transmitted symbols to be '0' and '1', respectively. Finally, the channel capacity can be calculated as maximum of mutual information value shown in Fig. 7. It can be seen that channel capacity reduce with the increase of propagation distance and maximum probability of Ca^{2+} pulse occurrence. Gap junction blocking greatly decreases the channel capacity in the long range ICW communication.

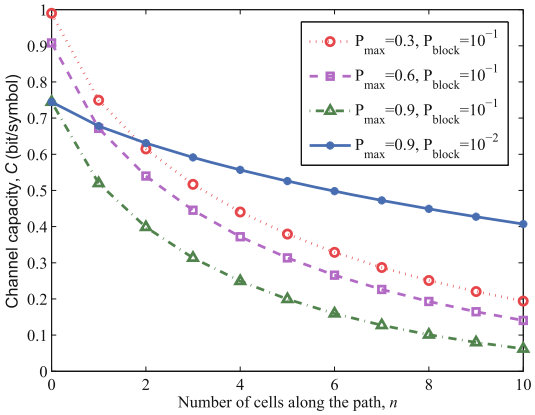

Fig. 7. Channel capacity between transmitter cell and receiver cell. $P_{\max}$ is set to be 0.3, 0.6, 0.9 and effect of P_{block} is also tested from 10^{-1} to 10^{-2} with $P_{\max} = 0.9$.

5 Conclusions

In this study, the mechanism of molecular communication via ICW has been illustrated and a few channel characteristics have been investigated based on the theory of IP3 induced inter-cellular calcium wave. The main contributions of this paper is offering close-form solutions for channel characteristics like IP3 propagation attenuation, ICW propagation distance, and ICW propagation time delay. Besides, channel capacity considering the binary channel has also been calculated. A few parameters affecting ICW propagation have been analyzed. We believe that theoretical and simulation results in this paper can offer significant reference to the design of ICW based molecular communication systems. However, most parameters in this study were set to be ideal which do not accord with the practical conditions. More practical parameters and models will be investigated in our future works.

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