Channel Capacity of Calcium Signalling Based on Inter-cellular Calcium Waves in Astrocytes

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Abstract—In this paper we investigate the channel capacity of the calcium signalling system based on an inter-cellular calcium wave model for astrocytes in the literature. Calcium signalling is a good candidate for molecular communication due to its long communication range, possible usage of existing cellular infrastructure, and its minimally invasive nature. Calcium waves are formed by the cytosolic oscillations of Ca\textsuperscript{2+} ion concentration, which propagates through neighbouring cells via secondary messenger molecules. Understanding the dynamics and physical properties of inter-cellular calcium waves is expected to produce an effective solution for the nano device communication problem. Thus, we extend the models developed in the literature to offer a calcium signalling scheme built on two cells and investigate the channel capacity depending on noise level and symbol duration. To the best of our knowledge, this is the first channel capacity analysis of calcium wave model that includes inter-cellular dynamics.

I. INTRODUCTION

Nano-scale devices, which are due to perform numerous tasks that their large-scale counterparts carry out, are predicted to be the future of interaction with the living organisms for their low invasiveness and non-restricting nature in terms of the habitual activities of the being. However, operating in the nano-scale is expected to require high cooperation among multiple devices to make an impact on the macro scale. Nano-communication, or nano-networking, is an emerging paradigm due to high level of collaboration needed by these devices. There is a variety of approaches in the literature for the establishment of the nano-communication. Most significant approaches in the biology domain are, molecular shuttles, communication via diffusion, and communication via Ca\textsuperscript{2+} oscillations.

The molecular shuttle model covers intra-cellular communication due to its infrastructure that is based on microtubules in the cytosol. Communication occurs via molecular shuttles which are basic molecules that can move on specific tracks, microtubules, in the cytoplasm. These shuttles can carry a large number of messenger molecules wrapped inside a container called a vesicle, to the receiver site [1].

In communication via diffusion (CvD), a number of micro- and nano-machines residing in a viscous environment communicate through molecules that are discharged into the communication medium. Communication via diffusion, absent of the need for infrastructural deployment, can be utilized for both intra- and inter-cellular communication. In CvD, molecules that are discharged for signalling are called messenger molecules. These molecules can be of many types of chemical compounds such as DNA fragments, proteins, peptides or specifically formed molecules as long as they are biocompatible with the inhabitant [7].

Calcium signalling is based on inter-cellular Ca\textsuperscript{2+} waves, which is a signalling method used by a wide variety of organisms in different types of cells and contexts. For example, it is argued that in legumes different types of Ca\textsuperscript{2+} oscillations are used to trigger a different set of events in response to different types of stimuli [4]. In mammals, for fertilization sperm is known to initiate a series of Ca\textsuperscript{2+} oscillations [12]. In human astrocytes it is believed that oscillations serve as a pathway for long range signalling and participate in information transport in remote parts in the brain [3].

Communication using Ca\textsuperscript{2+} oscillations has been demonstrated in various studies. Nakano et al. considered a molecular relay channel where transmission is propagated with Ca\textsuperscript{2+} oscillations from various transmitters to receivers [8]. However, they did not consider inter-cellular nature of the oscillations. In [9], a nano-scale communication using inter-cellular waves and solutions with possible extended functions, such as routing and self assembly, is proposed.

In [6], we discuss various properties of inter-cellular calcium waves (ICWs) and show that it can be a suitable candidate for the nano-scale communication paradigm. ICWs are found in many types of cells readily existing. Thus they can be considered as an already deployed infrastructure for in-vivo applications. Deployment scenarios of ICW-based systems enable coordination of large groups of cells, or nano-machines, with the possibility of triggering group reaction with a short delay. Use of ICWs enable communication with ranges up to a few hundreds of micrometers [10]. These properties make ICW-based systems a valuable candidate to be used in nano-communication.

In this paper, to be able to understand the complex nature of the ICWs on signalling, we focus on communication aspects of the inter-cellular Ca\textsuperscript{2+} oscillations. We evaluate their signalling capacity in astrocyte cell couples using the mathematical model derived in [3]. Their model involves agonist-evoked inositol tri-phosphate (IP\textsubscript{3}) concentration rise
with the calcium induced calcium release (CICR) for local Ca\(^{2+}\) spikes and dynamics created by IP\(_3\) and Ca\(^{2+}\) diffusion for inter-cellular wave spreading.

The rest of the paper is organized as follows. In Section 2, we explain the mathematical model behind the ICWs and its application to our two-cell system. We define the metrics used to distinguish correct and erroneous detection and give the formulation for channel capacity. In Section 3, in the light of the results obtained from the simulations, we discuss the effects of input noise and symbol duration on channel capacity. Section 4 concludes the paper and cites future directions.

II. MODELLING OF AGONIST EVOKED CALCIUM WAVES

The underlying mechanism for ICWs has been debated over a long time in biology literature [11]. Different models depicting the behaviour of these waves have been proposed. In [2], calcium waves in hepatocytes are modelled. The authors demonstrated cell coupling in terms of Ca\(^{2+}\) oscillation frequency and amplitude with and without presence of IP\(_3\). Dupont et al. experimented and modelled inter-cellular oscillations under agonist stimulation of hepatocyte triplets and showed a phase difference between corresponding oscillations. In [3], ICWs in airway epithelium are investigated. In this model in addition to IP\(_3\) dynamics, the authors include the effect of extracellular secondary messengers (e.g. ATP) for triggering ICWs. In [5], complex Ca\(^{2+}\) oscillations are modelled via a chaotic model in response to agonist stimulation in a single cell.

Although all of these models agree on basic understanding of signalling in calcium waves, they differentiate which molecules take part in oscillation formation and wave propagation. In this paper we select the model proposed in [3], which models the ICWs in the astrocytes in response to an agonist stimulation. The model best describes the characteristics of the waves in terms of signalling for short and long range, therefore it is an excellent basis for our communication study regarding ICWs.

According to the designated model, an ICW is initiated by the external agonist acting on G-protein coupled receptors, which enable the release of PLC\(_{\beta}\) molecules. The increase in PLC\(_{\beta}\) concentration triggers the release of IP\(_3\) molecules, which initiates a rapid discharge of Ca\(^{2+}\) from the sarcoplasmic reticulum (SERCA) through IP\(_3\) sensitive receptor channels (IP\(_3\)R’s). The ICW is initiated by stimulating only the first cell. The rise in the Ca\(^{2+}\) concentration is carried through the cell array by means of direct diffusion of IP\(_3\) and activation of PLC\(_{\beta}\) by the increased concentration of Ca\(^{2+}\) in the next cell as a consequence of diffusion. Figure 1 depicts a simple propagation scheme.

A. Mathematical Model

The model we base our simulations on is given in [3], where the flow equations are formulated as follows:

$$\frac{\partial S}{\partial t} = \beta(v_{SERCA} - v_{rel})$$

$$\frac{\partial R}{\partial t} = v_{rec} - v_{inact}$$

$$\frac{\partial I}{\partial t} = v_{PLC\beta} + v_{PLC\delta} - v_{deg} + D_{IP3}(\partial^2 I/\partial x^2 + \partial^2 I/\partial y^2)$$

where C denotes the cytoplasmic Ca\(^{2+}\) concentration, S sarcomplasmic Ca\(^{2+}\) concentration, R active fraction of IP\(_3\)R, I concentration of IP\(_3\) and v\(_{PLC\beta}\), v\(_{PLC\delta}\), v\(_{deg}\), v\(_{rel}\), v\(_{SERCA}\), v\(_{in}\), v\(_{out}\) denote the rates of PLC\(_{\beta}\), PLC\(_{\delta}\), IP\(_3\) degradation, Ca\(^{2+}\) release from the SERCA, Ca\(^{2+}\) pumping into the SERCA, Ca\(^{2+}\) influx across the plasma membrane, and Ca\(^{2+}\) extrusion, respectively. The rates of receptor activation and recovery are denoted by v\(_{inact}\) and v\(_{rec}\). Equations 1 and 2 incorporate the effects of calcium flux in and out of SERCA. Equation 3 accounts for active receptor density variation during the calcium spikes and Equation 4 reflects the effects of PLC\(_{\beta}\) and PLC\(_{\delta}\) on IP\(_3\) concentration.

$$v_{rel} = (S - C)[k_1 + k_2 R C^2 I^2/(K_a^2 + C^2)/(K_{IP3}^2 + I^2)]$$

$$v_{rec} - v_{inact} = k_6[(K_I^2 + C^2) - R]$$

$$v_{PLC\beta} = v_8 C^2/(K_{C^2}^2 + C^2)$$

where Equation 5 depicts the positive feedback in CICR, Equation 6 determines the rate of active fraction IP\(_3\) receptors, Equation 7 and 8 give positive feedback values for IP\(_3\) concentration. The values for the constants used for the modelling and the simulation is given in Table I.

In Equation 8, v\(_8\) determines the rate of PLC\(_{\beta}\), which is a product of interaction of the cell with the agonist. The model assigns v\(_8\) a constant value for a period of time to create the Ca\(^{2+}\) spike assuming a simple collision scheme.
B. Wave Propagation Model For an Adjacent Cell Pair

For our two-cell system, we hypothesise an environment where the first cell is stimulated by the agonist for some fraction of total symbol duration and the second cell is stimulated by the initial Ca$^{2+}$ oscillation formed in the first cell via the internal characteristics of the oscillation model mentioned above.

In the model by Höfer et al. the stimulation is assumed to have constant amplitude for a period of time, which results in a well-formed Ca$^{2+}$ spike that propagates along the cell array. Figure 2 represents calcium levels of two cells stimulated by an agonist under noise-free conditions. The constant amplitude assumption is appropriate for modelling purposes. However, it is unrealistic for the modelling of a communication application. For the purposes of understanding the channel dynamics, we assume the concentration of the applied agonist varies over time subject to additive white Gaussian noise (AWGN).

The diffusion of IP$_3$ and Ca$^{2+}$ is taken into account differently in our two-cell system. We first convert the partial differential equations to ordinary differential equations by separating diffusion related variables and calculate the concentration of these diffused molecules at a distance of $d$. Concentrations are calculated as it is found by the general one dimensional solution for Fick’s second law:

$$c(d, t) = c_d + c_d erf \left( \frac{d}{\sqrt{D t}} \right)$$

where $d$ is the distance between two points, $D$ is the diffusion constant of that particular molecule, $c(d, t)$ is the concentration at distance $d$ at time $t$ and $c_d$ is the concentration difference between two points. By using this approach, we discretize the continuous cell space into two separate cells and make the assumption that the concentration level of IP$_3$ and Ca$^{2+}$ are uniform inside a single cell.

C. Reception Probabilities

In our system, a signal represents a single bit value. The input and output signals are represented by the amplitude of agonist and the amplitude of the cytosolic Ca$^{2+}$ concentration of the second cell, respectively. To send a bit value of “1” we apply an elevated agonist concentration to the first cell for the first 5 seconds of the total symbol duration, and to send a bit value of “0” no agonist is applied throughout the symbol duration. Detection of the symbol in the second cell is performed using a thresholding mechanism. If the cytosolic calcium level exceeds a certain threshold on the positive ongoing direction within a symbol duration, the output is accounted as “1”, if not as “0”. For simplicity, we assume exact cytoplasmic Ca$^{2+}$ concentration measurement by the second cell communication unit.

The correct reception depends on the Ca$^{2+}$ state (i.e., presence or absence of a Ca$^{2+}$ spike) of the second cell within a symbol duration. The presence of a Ca$^{2+}$ spike represents a bit value of “1”. Similarly absence of such spike represents a bit value of “0”. Based on the transmitted bit value, if an appropriate Ca$^{2+}$ state is observed at the receiver, then the transmission of the current symbol is considered to be successful. The probability of error for a given bit value is defined as the number of erroneous receptions of that bit value divided by the total number of transmitted bits. Thus;

$$P_{E(s)} = \frac{N_{Error_s}}{N_{Total_s}}$$

and

$$P_{S(s)} = \frac{N_{Success_s}}{N_{Total_s}}$$

where $s \in \{0, 1\}$, $P_{E(s)}$ stands for the probability of erroneous transmission of symbol $s$, and $P_{S(s)}$ stands for the probability of successful transmission.

Since a calcium spike keeps the cytosolic Ca$^{2+}$ level elevated for some duration, consecutive transmissions create
inter-symbol interference (ISI). Smaller symbol durations are expected to result in higher ISI by nature. However, increasing the symbol duration increases the duration of being exposed to the channel noise. In order to understand the effects of ISI on the detection, we separate the time between two consecutive inputs by varying the symbol duration.

D. Channel Capacity Formulation

\[
\begin{pmatrix}
X & Y \\
0 & 0 \\
1 & 1
\end{pmatrix}
\]

Fig. 4. Graphic representation of a binary channel

A binary channel is a common channel model, in which the transmitter sends and the receiver receives a single bit. Each sent bit is subject to a set of probabilities that determine correct or faulty reception. As Figure 4 suggests, a bit value of \(s\) has a correct reception probability \(P_{S(s)}\) and an erroneous reception probability of \(P_{E(s)}\) where \(s\) is either a “0” or a “1”.

The channel capacity of a communication system is defined as the maximum mutual information value of the channel. Mutual information measures the dependency of the two variables to each other. In other words, it gives us a formal method for guessing to which extend we can identify a certain variable \(Y\) when we are given the value of variable \(X\), or vice versa.

The mutual information for a binary channel is formulated as:

\[
I(X; Y) = \sum_{y \in Y} \sum_{x \in X} p(x, y) \log_2 \left( \frac{p(x, y)}{p(x)p(y)} \right)
\]

where \(X \in 0, 1\) and \(Y \in 0, 1\). The probability of a bit value of “0” and “1” are equally selected as \(1/2\) for the simulation, where reception probabilities are calculated as:

\[
P(y = 1) = P(x = 1) \cdot P_{S(1)} + P(x = 0) \cdot P_{E(0)}
\]

and

\[
P(y = 0) = P(x = 1) \cdot P_{S(0)} + P(x = 0) \cdot P_{E(1)}
\]

III. RESULTS

A. Metrics and Simulation Parameters

The model by Höfer et al. requires a set of parameters, which define the behaviour of the system accordingly. The values of these parameters are given in Table I. In addition to parameters defined in [3], we elaborate on the effects of three system parameters, namely the level of agonist noise (\(\sigma_n\)), symbol duration (\(t_s\)), and signal detection threshold (\(\tau\)).

The simulations use a Bernoulli random number generator with equal probabilities for “0” and “1”, over 20,000 bits. The mutual information between the input and the output for bit values of “0” (\(P_{E(0)}\)) and “1” (\(P_{E(1)}\)) are calculated under different agonist (input) noise levels \(\sigma_n = 0.05, 0.1, 0.2 \ \mu M\). Different values of \(\tau\) ranging from 0.2 to 0.5 \(\mu M\) are selected to determine under which detection threshold the mutual information for the channel is maximized. Each combination is carried for different \(t_s\) equal to 10, 13, 15, 20, 25, 40, 50 seconds, where agonist stimulation (in the case of input “1”) is held elevated for a constant duration of 5 seconds at the beginning of the symbol duration.

B. Effect of Noise on Capacity

The cells react to subsequent increases in the agonist levels with elevated cytosolic \(Ca^{2+}\) levels. Thus, Gaussian noise on the input agonist concentration vary resulting in \(Ca^{2+}\) spike

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate constant of calcium leak from ER</td>
<td>(k_1)</td>
<td>0.0004 sec(^{-1})</td>
</tr>
<tr>
<td>Rate constant of calcium release through IP(_3)R</td>
<td>(k_2)</td>
<td>0.08 sec(^{-1})</td>
</tr>
<tr>
<td>Rate constant of SERCA pump</td>
<td>(k_3)</td>
<td>0.5 sec(^{-1})</td>
</tr>
<tr>
<td>Rate of calcium leak across plasma membrane</td>
<td>(v_{40})</td>
<td>0.025 (\mu M/\text{sec})</td>
</tr>
<tr>
<td>Maximal rate of activation dependent calcium influx</td>
<td>(v_{41})</td>
<td>0.2 (\mu M/\text{sec})</td>
</tr>
<tr>
<td>Rate constant of calcium extrusion</td>
<td>(k_5)</td>
<td>0.5 sec(^{-1})</td>
</tr>
<tr>
<td>Rate constant of IP(_3) inactivation</td>
<td>(k_6)</td>
<td>4 sec(^{-1})</td>
</tr>
<tr>
<td>Maximal rate of PLC(_3)</td>
<td>(v_7)</td>
<td>0.05 (\mu M/\text{sec})</td>
</tr>
<tr>
<td>Rate constant of IP(_3) degradation</td>
<td>(k_9)</td>
<td>0.08 sec(^{-1})</td>
</tr>
<tr>
<td>Half-saturation constant for IP(_3) activation of IP(_3)R</td>
<td>(K_{IP_3})</td>
<td>0.3 (\mu M)</td>
</tr>
<tr>
<td>Half-saturation constant for calcium activation of IP(_3)R</td>
<td>(K_a)</td>
<td>0.2 (\mu M)</td>
</tr>
<tr>
<td>Half-saturation constant for calcium inhibition of IP(_3)R</td>
<td>(K_i)</td>
<td>0.2 (\mu M)</td>
</tr>
<tr>
<td>Half-saturation constant for calcium activation of PLC(_3)</td>
<td>(K_{Ca})</td>
<td>0.3 (\mu M)</td>
</tr>
<tr>
<td>Half-saturation constant for agonist-dependent calcium entry</td>
<td>(K_r)</td>
<td>1 (\mu M)</td>
</tr>
<tr>
<td>Diffusion coefficient of IP(_3)</td>
<td>(D_{IP_3})</td>
<td>280 (\mu m) sec(^{-2})</td>
</tr>
<tr>
<td>Effective diffusion coefficient of calcium</td>
<td>(D_{Ca})</td>
<td>20 (\mu m) sec(^{-2})</td>
</tr>
<tr>
<td>Ratio of the effective volumes for (Ca^{2+}) of cytoplasm and ER</td>
<td>(\beta)</td>
<td>20</td>
</tr>
</tbody>
</table>
concentration. For a non-elevated agonist input corresponding to bit value of “0”, input noise occasionally creates an elevated level of stimulation, which consequently results in an unexpected Ca\(^{2+}\) spike. On the other hand an elevated agonist input corresponding to bit value of “1” results in a Ca\(^{2+}\) spike, which has higher or lower concentration than the noise-free adaptation. Higher concentration does not contribute much to bit error since it is readily detectable by lower thresholds. However, lower amplitude spikes fail to be detected if the selected threshold is high.

In our simulations it is evident that lower levels of noise is subsidized in the first cell by the internal dynamics of Ca\(^{2+}\) oscillations. At noise level of \(\sigma_n = 0.05 \mu M\), one can observe that the Ca\(^{2+}\) spikes created at the first cell due to system noise are completely eliminated or shrunk to a non-effective amplitude by system dynamics in the second cell. The smoothing effect of the system makes ICW-based communication more robust against detection errors under small noise values (Figure 3).

For noise level of \(\sigma_n = 0.1 \mu M\) there is no substantial increase in the signal impairment. The resulting Ca\(^{2+}\) level deviates more as a result of the increased noise. However, it is still possible to find a clever choice of threshold which eliminates most of the contribution of noise.

However, as the noise level is increased to \(\sigma_n = 0.2 \mu M\), we start observing much larger deformations in Ca\(^{2+}\) concentrations of the first cell. These deformations are transmitted to the second cell and result in erroneous detections. Increases due to noise in the cytosolic Ca\(^{2+}\) levels when transmitting bit value “0” are more visible because sudden increases in the noise level contributes to the formation of a spike in the first cell. The spike propagates to the second cell and is detected as a bit value “1”. However, when transmitting a bit value of “1”, instantaneous decreases of the input due to noise is less likely to suppress the formation of Ca\(^{2+}\) spike in the first cell. Even though ill-formed, a Ca\(^{2+}\) spike can be correctly detected by appropriately selected threshold levels (Figure 5).

Increase in the noise level increases the bit error rate of the system as expected. The overall increase in the error contributes to a decrease in the mutual information. However, by selecting an appropriate threshold value as suggested in Figure 6 the effect of noise can be minimized. For each of the three noise levels, there is a threshold that maximizes the mutual information through minimizing the relative symbol error rates in the system.

As seen in the Figure 7, the effect of the reduction in symbol duration on channel capacity, the system is more prone to error when it is transmitting a zero, therefore optimum threshold is expected to be above the average level to compensate for this effect.

C. Effect of Symbol Duration on Channel Capacity

The cytosolic calcium concentration rises from a steady 0.1 \(\mu M\) to 0.6 \(\mu M\) in the presence of a Ca\(^{2+}\) spike. The detector, therefore, must identify changes ranging between 0.1 \(\mu M\) and 0.6 \(\mu M\). As can be observed from Figure 6 the optimum thresholds are around the level 0.40 - 0.45 \(\mu M\). This result is expected in the sense that higher threshold values contribute to errors due to false negatives, and lesser thresholds increase the amount of false positives. The reason behind that the optimum threshold is not 0.35 \(\mu M\) (i.e. the mean of concentration range) is that the effect of noise is more prevalent when there is a transmission of bit value “0” rather than “1” because of Ca\(^{2+}\) oscillation dynamics. Even for the smaller levels of noise, it is easier to initiate a Ca\(^{2+}\) spike than to suppress a spike that is already there. The system is more prone to error when it is transmitting a zero, therefore optimum threshold is expected to be above the average level to compensate for this effect.
A future theoretical work may be the investigation of the range of communication via inter-cellular waves. In this work we have only tested for a small distance of two cells. However, it is known that ICWs have a capability of reaching longer distances. It is worthwhile to investigate the effective communication range, which in turn may elucidate the theoretical limitations of the ICW communication paradigm.

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