Mathematical models for intra- and inter-cellular Ca\textsuperscript{2+} wave propagations

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Abstract

Intra- and inter-cellular Ca\textsuperscript{2+} waves play key roles in cellular functions. Focal stimulation triggers Ca\textsuperscript{2+} wave propagation from the stimulation point to neighboring cells through the cytoplasm, which involves localized metabolism reactions and specific diffusion processes. Briefly, inositol 1,4,5-trisphosphate (IP\textsubscript{3}) is produced at membranes and diffuses into the cytoplasm, resulting in Ca\textsuperscript{2+} release from the endoplasmic reticulum (ER). Particularly, Ca\textsuperscript{2+} released from the ER is mediated by two principles, the IP\textsubscript{3}-induced Ca\textsuperscript{2+} and Ca\textsuperscript{2+}-induced Ca\textsuperscript{2+} releases. Ca\textsuperscript{2+} is diffused through the cytoplasm and, furthermore, transported into neighboring cells through gap junctions. These intra- and inter-cellular Ca\textsuperscript{2+} waves have been widely investigated using theoretical and experimental methods in various cell types. In this review we summarize the mathematical models used for the numerical simulation of intra- and inter-cellular Ca\textsuperscript{2+} wave propagations.

Keywords

Numerical simulation, Ca\textsuperscript{2+} wave, Ca\textsuperscript{2+}-induced Ca\textsuperscript{2+} release, IP\textsubscript{3}-induced Ca\textsuperscript{2+} release

Introduction

Ca\textsuperscript{2+} is one of the most important messengers in cells. Ca\textsuperscript{2+} signal is a result of a variety of stimuli and is a transient increase of the intracellular concentrations. Ca\textsuperscript{2+} relays the information arriving at the cell surface to intracellular targets or coordinate groups of cells through inter-cellular communications. Information is generally transmitted as a Ca\textsuperscript{2+} wave, which increased Ca\textsuperscript{2+} travels from a stimulus through the cytoplasm of a cell and group of cells. Currently, intra- and inter-cellular Ca\textsuperscript{2+} waves are recognized as important for intra- and inter-cellular communications. Therefore, Ca\textsuperscript{2+} waves have been widely investigated in various cell types using theoretical and experimental methods.

The related mechanisms and physiological functions were reviewed previously [1–4].

Ca\textsuperscript{2+} influx occurs via two pathways (Fig. 1): (i) inflow from the extracellular medium through Ca\textsuperscript{2+} channels in the plasma membrane and (ii) release from internal stores. There are several types of Ca\textsuperscript{2+} channels, such as voltage-controlled, receptor-operated, and mechanically operated channels. Ca\textsuperscript{2+} release from internal stores, such as the endoplasmic reticulum (ER), is mediated principally by two types of Ca\textsuperscript{2+} receptors (Fig. 1): the inositol 1,4,5-trisphosphate (IP\textsubscript{3}) receptor (IP\textsubscript{3}R) and the ryanodine receptor (RyR). In general, membrane receptors, such as G-protein-coupled receptors, are activated by an extracellular agonist. This results in the phospholipase Cβ (PLCβ) mediated hydrolysis of membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP\textsubscript{2}) into IP\textsubscript{3} and diacylglycerol (DAG). IP\textsubscript{3} is then released and diffused into the cytosol, leading to the opening of the IP\textsubscript{3}R and subsequent release of Ca\textsuperscript{2+} (IP\textsubscript{3}-induced Ca\textsuperscript{2+} release, IICR) and Ca\textsuperscript{2+}-induced Ca\textsuperscript{2+} release (CICR), respectively.

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Fig. 1 Diagram of the major fluxes of Ca\textsuperscript{2+} in the cytoplasm. Ca\textsuperscript{2+} influx occurs via two pathways: (i) inflow from the extracellular medium through Ca\textsuperscript{2+} channels and (ii) release from the endoplasmic reticulum (ER). There are two types of Ca\textsuperscript{2+} receptors on ER membranes, IP\textsubscript{3}R, and ryanodine receptors, which are involved in the IP\textsubscript{3}-induced Ca\textsuperscript{2+} release (IICR) and Ca\textsuperscript{2+}-induced Ca\textsuperscript{2+} release (CICR), respectively.
IICR). Furthermore, RyR is involved in the Ca\textsuperscript{2+}-induced Ca\textsuperscript{2+} release (CICR). Additionally, Ca\textsuperscript{2+} is removed from the cytoplasm in two principal ways: pumped out of the cell through the plasma membrane and reuptake from the cytosol to internal stores. On the other hand, inter-cellular Ca\textsuperscript{2+} waves were reportedly dominated by IP\textsubscript{3} and Ca\textsuperscript{2+} signaling through gap junctions and paracrine adenosine triphosphate (ATP) messaging [1]. The IICR/CICR models and one/two dimensional (1D and 2D) mathematical models of the intra- and inter-cellular Ca\textsuperscript{2+} waves in various cells have been proposed to study the metabolism and diffusion processes of Ca\textsuperscript{2+} [5–12]. In this review, we summarize the mathematical models for the numerical simulation of intra- and inter-cellular Ca\textsuperscript{2+} wave propagation.

IICR model

In the IICR model, IP\textsubscript{3}R is modulated by the binding of IP\textsubscript{3} and Ca\textsuperscript{2+}. Here, Ca\textsuperscript{2+} plays a dual role by activating and inactivating IP\textsubscript{3}R. Lebeau et al. [13] assumed that the IICR model is composed of four, functionally identical, independent subunits: (i) the shunt state S; (ii) open state O; and (iii, iv) two inactive states, I\textsubscript{1} and I\textsubscript{2} (Fig. 2A). Binding of IP\textsubscript{3} causes IP\textsubscript{3}R to be converted to the O state from the S state. The O state is relatively unstable and the subunits progress through to the more stable I\textsubscript{1} state, in which IP\textsubscript{3} is still bound but the channels do not conduct. IP\textsubscript{3}R recovers from the I\textsubscript{1} state to the S state, where IP\textsubscript{3} dissociates from its binding site. The receptor can then rebind IP\textsubscript{3} and repeat the cycle. In addition, a transition from the I\textsubscript{1} to I\textsubscript{2} state is included in this process. In this case, the I\textsubscript{2} represents a second inactive site where IP\textsubscript{3}R is no longer bound. The pathway is agonist specific and involves phosphorylation of the IP\textsubscript{3}R. The open probability of IP\textsubscript{3}R (P\textsubscript{IP3}) is given by the following:

\[
P_{IP3} = O^4
\]

\[
\frac{dO}{dt} = k_1[IP3]S - k_{-1}O - k_2O
\]

\[
\frac{dI_1}{dt} = k_2O - (k_1 + k_4)I_1
\]

\[
\frac{dI_2}{dt} = k_4I_1 - k_3I_2
\]

\[
S = 1 - O - I_1 - I_2
\]

\[
k_i = \frac{\alpha_i[Ca^{2+}]^j}{\beta_i + [Ca^{2+}]^j}
\]

where [Ca\textsuperscript{2+}] and [IP\textsubscript{3}] are intracellular Ca\textsuperscript{2+} and IP\textsubscript{3} concentration; and \(k_1, k_2, k_3, \) and \(k_4\) are constant; \(\alpha_i\) and \(\beta_i\) are the maximum rates of the S to O and the I\textsubscript{1} to the I\textsubscript{2} transitions, respectively; and \(\beta_j\) and \(\beta_k\) are Ca\textsuperscript{2+} and IP\textsubscript{3} concentrations at which the rate is half maximum, respectively. The model dose not explicitly incorporate the binding sites of Ca\textsuperscript{2+}, but instead incorporates the effect of Ca\textsuperscript{2+} through modulating the forward rate. Therefore, each transition between the states is also modulated by Ca\textsuperscript{2+} to improve the IICR model [14].

CICR model

Friel [15] proposed the simple CICR model to simulate Ca\textsuperscript{2+} oscillation. Many cell types respond to various stimulations with oscillations in the Ca\textsuperscript{2+} concentration. The periodic fluctuations of cell membrane potentials, and the associated periodic Ca\textsuperscript{2+} entry through the Ca\textsuperscript{2+} membrane channels, are involved in this complicated mechanism of Ca\textsuperscript{2+} oscillation [3, 15]. In other words, Ca\textsuperscript{2+} oscillations are also dominated by the balance between the uptake and release by the ER. This model is assumed to be a single ER in a cell, and the ER exchanges Ca\textsuperscript{2+} with the cytoplasm (\(J_{L2}:Ca^{2+}\) release, \(J_{P2}:Ca^{2+}\) uptake), which in turn exchanges Ca\textsuperscript{2+} with external...
medium ($J_{L+}: \text{Ca}^{2+}$ entry, $J_{P+}: \text{Ca}^{2+}$ extrusion). The equations for this phenomenon are as follows:

$$\frac{d[\text{Ca}^{2+}]}{dt} = J_{L1} - J_{P1} + J_{L2} - J_{P2}$$

$$\frac{d[\text{Ca}^{2+}]}{dt} = \gamma(-J_{L2} + J_{P2})$$

$$J_{L1} = k_1 \left([\text{Ca}^{2+}]_o - [\text{Ca}^{2+}]_e\right)$$

$$J_{P1} = k_2 [\text{Ca}^{2+}]_e$$

$$J_{L2} = k_3 \left([\text{Ca}^{2+}]_o - [\text{Ca}^{2+}]_e\right)$$

$$J_{P2} = k_4 [\text{Ca}^{2+}]_e$$

where and $k_1$, $k_2$, $k_3$, and $\gamma$ are constant. Additionally, $[\text{Ca}^{2+}]_o$ and $[\text{Ca}^{2+}]_e$ are $\text{Ca}^{2+}$ concentration in the ER and extracellular space, respectively. Particularly, $\text{Ca}^{2+}$ oscillation can be described simply by defining the $k_i$ as an increasing sigmoidal function of the $[\text{Ca}^{2+}]$ as follows:

$$k_i = k_i^{-} + \frac{k_i^{+} [\text{Ca}^{2+}]^n}{K_i^{n} + [\text{Ca}^{2+}]^n}$$

and $k_i^{-}$, $k_i^{+}$, $K_i$, and $n$ are based on the experimental data.

On the other hand, the RyR activation occurs within milliseconds, whereas inactivation occurs on a timescale of a few seconds [16]. This adaptation occurs during the slow, spontaneous decrease in the open probability of a channel after it has been rapidly activated by $\text{Ca}^{2+}$. Keizer and Levine [17] proposed a simplified model to mimics RyR adaptation using an open probability state ($P$), as follows:

$$\frac{d[P C_1]}{dt} = -k_{P C_1}^{-} [\text{Ca}^{2+}]^n P_{C_1} + k_{P C_1} P_{O_1}$$

$$\frac{d[P O_1]}{dt} = k_{P O_1}^{-} [\text{Ca}^{2+}]^n P_{O_1} - k_{P O_1} [\text{Ca}^{2+}]^n P_{C_1} + k_{P O_2} P_{O_2} - k_{P C_2} P_{C_2} + k_{P C_1} P_{C_1}$$

$$\frac{d[P O_2]}{dt} = k_{P O_2}^{-} [\text{Ca}^{2+}]^n P_{O_2} - k_{P O_2} [\text{Ca}^{2+}]^n P_{C_3} + k_{P C_2} P_{C_2}$$

$$P_{C_1} + P_{C_2} + P_{O_1} + P_{O_2} = 1$$

where states $C_1$ and $C_2$ are closed states, and $O_1$ and $O_2$ are open states (Fig. 2B). Transitions from $C_1$ to $O_1$ and from $O_2$ to $O_2$ are assumed to be $\text{Ca}^{2+}$ dependent. In addition, the transition from $O_1$ to $C_2$ is to adapt for the slow inactivation, and the transition from $O_1$ to $O_2$ is also to adapt for the plateau open states of RyR as $\text{Ca}^{2+}$ concentration increases. As a result, they are written as depending on the binding of $n$ and $m \text{Ca}^{2+}$, respectively. The subscripts $a$, $b$, and $c$ show each transition, and $k_i^{\pm}$ are constants. In particular, transitions $a$ and $b$ should be fast, whereas transition $c$ should be slow.

**1D and 2D model of intra- and inter-cellular $\text{Ca}^{2+}$ wave propagation**

As mentioned above, $\text{Ca}^{2+}$ diffuses through the cytoplasm and propagates into neighboring cells via gap junctions. Höfer et al. [7] considered the linear array of cells coupled by gap junctions and proposed a simple mathematical model for intra- and inter-cellular $\text{Ca}^{2+}$ wave propagation through gap-junctional $\text{Ca}^{2+}$ diffusion, as follows:

$$\frac{\partial[\text{Ca}^{2+}]_i}{\partial t} = h(x) f([\text{Ca}^{2+}]_i) + D \frac{\partial^2[\text{Ca}^{2+}]_i}{\partial x^2}, 0 \leq x \leq L$$

where $[\text{Ca}^{2+}]_i$ is $\text{Ca}^{2+}$ concentration in $i$th cell, and $L$ is the cell length and $x$ is mapped for each cell individually. $[\text{Ca}^{2+}]_i$ is governed by the $\text{Ca}^{2+}$ release from ER and removal from cytoplasm, $f([\text{Ca}^{2+}]_i)$, and by cytoplasm diffusion with an efficient coefficient, $D$. The function, $h(x)$, refers to the spatial distribution of ER sites, and $i$ is the time. In addition, this model hypothesizes that $\text{Ca}^{2+}$ spreads through the CICR and gap-junctional $\text{Ca}^{2+}$ diffusion. Meanwhile, the inter-cellular $\text{Ca}^{2+}$ fluxes are assumed to be proportional to the concentration differences across the gap junctions and permeability. As the results, they reported that the effective gap-junction $\text{Ca}^{2+}$ permeability in this model agreed with experimental data. Edwards and Gibson [5] proposed a 2D model for intra- and inter-cellular $\text{Ca}^{2+}$ waves in a network of glial cells that incorporates a simplified IICR and inter- and extracellular pathways. ATP binds to membrane receptor, initiating G-protein cascade that results in the IP$_3$ production involving PLC$.\beta_i$. IP$_3$ diffuses within the cell, leading to the $\text{Ca}^{2+}$ release from ER and to the ATP release in the extracellular space. This $\text{Ca}^{2+}$ release subsequently produces IP$_3$. The 2D space is discretized by 1 μm squares grid for extracellular space with the cells superimposed over this grid, and the model consists of 4 components: the extracellular space, cell somata, protruding processes of cells and gap junctions. These cells are individually connected through gap junctions in addition to extracellular communication, and IP$_3$ and ATP subsequently diffuse through gap junctions and extracellular spaces, respectively. Finally, the concentrations of ATP, IP$_3$, $\text{Ca}^{2+}$, and G-protein in each component are calculated by solving the reaction-diffusion equations. The model showed that extracellular pathway increased the extend and duration of $\text{Ca}^{2+}$ wave but did not change the propagation speed, and that the speed was alternatively increased by the amount of gap junctions. Kobayashi et al. [8] proposed a 2D model for inter-cellular $\text{Ca}^{2+}$ waves in keratinocytes, which included IICR, CICR, diffusion of $\text{Ca}^{2+}$, and IP$_3$ through gap junctions and ATP-mediated paracrine communications (Fig. 3), and modeled...
the ATP concentration in culture medium, the \([\text{IP}_3]\) and
\([\text{Ca}^{2+}]\) in \(i\)th cell, the gap-junction activity, and influx from
extracellular \(\text{Ca}^{2+}\). They considered a 2D space, where the
circles were randomly distributed and any two cells were
connected through gap junctions, and reported the consist-
ency of \(\text{Ca}^{2+}\) wave between experiment and simulation
(Fig. 4). In addition, they demonstrated the utility of the
mathematical model in various skin diseases by blocking
the paracrine and gap junction communications. Warren et
al. \cite{18} also developed the mathematical model for IICR
\cite{13}, CICR \cite{17}, and extracellular paracrine pathways for
the intra- and inter-cellular \(\text{Ca}^{2+}\) wave propagations in air-
way epithelium. In this model, mechanical stimulus triggers
the release of ATP from the simulated cell and opens of the
membrane \(\text{Ca}^{2+}\) channels of the stimulated cell (autocrine)
and non-simulated cells (paracrine) to allow the \(\text{Ca}^{2+}\)
influx from the extracellular space. The release of ATP results in
the activation of the G-protein at the membrane and IP\(_3\)
production. IP\(_3\) can diffuse through the cytoplasm to initiate
the release of \(\text{Ca}^{2+}\) from the ER or diffuse through gap junc-
tion to initiate \(\text{Ca}^{2+}\) release from the ER in adjacent cell.
The strength of mechanical stimulus was described by the
relationship fitted to match the dose-response curve for air-
way epithelium to ATP, and the effective conductance of the
membrane \(\text{Ca}^{2+}\) channel was parameterized based on the
experimental data. The flux of IP\(_3\) between cells was
assumed to be proportional to the concentration difference
across the boundary. The reaction/diffusion equations were
solved on a 2D mesh consisting of rectangular cells measur-
ing 25 \(\mu\)m \(\times\) 25 \(\mu\)m, and each cell consists of 81 nodes with
an accompanying 64 elements. They considered the various
cases in \(\text{Ca}^{2+}\) wave propagation, such as a \(\text{Ca}^{2+}\)-free extra-
cellular space, physical gap in culture (Fig. 5), and different
amounts of released ATP for extracellular communication.
The comparison with experimental study showed that the
decay in the magnitude of \(\text{Ca}^{2+}\) with increasing radius was
much flatter in experiment than numerical simulation,
suggesting that an additional mechanism might exist for
regenerative release of ATP from cells downstream of the
stimulated cell (Fig. 5). Long et al. \cite{9} assumed the
intercellular \(\text{Ca}^{2+}\) wave is transported between cells by
diffusion through gap junctions and established the one-
dimensional chains of endothelial cells. The fundamental
equation of \(\text{Ca}^{2+}\) is expressed as follows:

\[
\frac{\partial [\text{Ca}^{2+}]}{\partial t} = D \frac{\partial^2 [\text{Ca}^{2+}]}{\partial x^2} + f ([\text{Ca}^{2+}])
\]

where \(D\) is a coefficient representing diffusion between
cells through gap junctions, and \(f\) is the rate of change of
intracellular \(\text{Ca}^{2+}\). \(x\) and \(t\) are the position and time varia-
bles, respectively. In addition, to model IICR and CICR, \(f\) is
simply expressed by a simple \(\text{Ca}^{2+}\) dependent non-linear
reaction function:

\[
f ([\text{Ca}^{2+}]) = -k ([\text{Ca}^{2+}]) \times [\text{Ca}^{2+}]
\]

![Figure 3](image3.png) Schematic diagrams of IICR, CICR, diffusion of \(\text{Ca}^{2+}\) and IP\(_3\)
through gap junctions, and ATP-mediated paracrine communications \cite{8}.

![Figure 4](image4.png) Simulation results of \(\text{Ca}^{2+}\) wave propagation \cite{8}. The cell located at the center is stimulated at time = 0, and \(u\) is the dimensionless \(\text{Ca}^{2+}\)
concentration, and. (A): Snapshots in 2 time units. (B): Changes in \(\text{Ca}^{2+}\) concentration of the cells which are labeled in left figure.
with $k([\text{Ca}^{2+}])$ representing a Ca$^{2+}$ dependent calcium release/intake rate constant. The reaction/diffusion equation above is discretized in space and time using finite differences as followed:

\[
\begin{align*}
\left[\text{Ca}^{2+}\right]_{i,t+1} &= \left[\text{Ca}^{2+}\right]_{i,t} + D^\ast \left[\text{Ca}^{2+}\right]_{i,t} - 2\left[\text{Ca}^{2+}\right]_{i,t} + \left[\text{Ca}^{2+}\right]_{i-1,t} \\
&- k^\ast \left(\left[\text{Ca}^{2+}\right]\right) \times \left[\text{Ca}^{2+}\right]
\end{align*}
\]

where $\left[\text{Ca}^{2+}\right]_{i,t+1}$ is Ca$^{2+}$ concentration in cell “$i$” at time $t_{n+1}$. $D^\ast$ and $k^\ast([\text{Ca}^{2+}])$ are a dimensionless diffusion coefficient and calcium release/intake rate constant, respectively.

They examined multicellular structures composed of a single chain of cells and demonstrated inter-cellular Ca$^{2+}$ wave propagated from the stimulated cell in experimental and theoretical studies (Figs. 6 and 7). In addition, they demonstrated inter-cellular Ca$^{2+}$ wave propagations in the different chain of cells with a side branch, “T” structure cells, and suggested the importance of the architecture of multicellular structures. Additional models for Ca$^{2+}$ oscillation have been proposed but are not covered in our review [19, 20].

### Three-dimensional (3D) model of intra- and inter-cellular Ca$^{2+}$ wave propagation

In almost all previous models for intra- and inter-cellular Ca$^{2+}$ wave propagation, cells are assumed to be a single computational domain. In other words, all metabolic reactions occur homogeneously in cells. However, in living cells metabolic components, such as proteins and enzymes, are not homogeneously present in subcellular compartments. In addition, the cytosol, membrane localizations, diffusion within cell spaces, and their related reactions must also be
localized in cells. Moreover, certain ions and proteins can diffuse in 3D cell spaces. Ca\(^{2+}\) wave propagation is mainly dominated by Ca\(^{2+}\) diffusion, and so, to some extent, the simulation may be sufficient in 1D and 2D model. However, strictly, metabolic components, such as proteins and enzymes, are not homogeneously present in subcellular compartments, resulting that the cytosol, membrane localizations, diffusion within cell spaces, and their related reactions must also be localized in cells. Intra- and inter-cellular Ca\(^{2+}\) waves are recognized as important for intra- and intercellular communications and are involved in various signal transductions, such as protein kinase Ca (PKCa) and Ca\(^{2+}\)/calmodulin-dependent protein kinase (CaMK) signals. For example, in PKCa signal, DAG diffuses through the plasma membrane and PKCu is activated by both Ca\(^{2+}\) and DAG, as indicated by translocation from the cytosol to the membrane [21], and PKCu is translocated to different areas of the cell membrane depending on the Ca\(^{2+}\) influx from extracellular space [22]. Additionally, recent studies show that PKCa was translocated toward wounded cells following destruction of cell-cell connections by single cell wounding [23, 24] and that PKCa accumulated at points of mechanical stimulus [25]. 1D and 2D homogenous numerical simulations of Ca\(^{2+}\) wave propagation make it impossible to investigate these heterogeneous signals. Therefore, 3D heterogeneous metabolic reaction/diffusion framework of Ca\(^{2+}\) wave propagation could inform investigations of inter- and intracellular communications and functions.

Regarding intracellular Ca\(^{2+}\) dynamics, if the waves are initialized in a small region near the cell surface, they will spread as a roughly spherical wave through the cell and will provide the distribution of the ER uniformly in a cell. However, concave waves are found experimentally in some species, such as sea urchins [26], which may be due to enhanced distribution of the peripheral ER structures [27]. Hunding and Ipsen [28] distributed the small spheres containing ER randomly inside the cell and simulated a Ca\(^{2+}\) wave in a simple 3D sphere based on the CICR from homogenous and heterogeneous ERs through channels activated by IP\(_3\). On the other hand, we derived computational domains for membrane and cytoplasmic processes to achieve the heterogeneous metabolic reactions (Fig. 8) based on the diagram of the major fluxes involved in the cytoplasmic Ca\(^{2+}\) (Fig. 1) [29]. In this framework, we divided metabolic reactions into each domain according to a previous study of endothelial cells [30]. Finally, the intra- and inter-cellular Ca\(^{2+}\) wave propagations were induced using microscopic stimulation and were compared between numerical simulations and experiments. In simulation, we assume that Ca\(^{2+}\), IP\(_3\), PKC, and Ca\(^{2+}\) bound PKC (PKC.Ca\(^{2+}\)) diffuse across the cell. For example, Ca\(^{2+}\) dynamics is modeled according to the following equation:

\[
\frac{\partial [\text{Ca}^{2+}]}{\partial t} = V_{rel} - V_{ER} - V_{com1} - V_{out} + \nabla \cdot D_{Ca} \nabla [\text{Ca}^{2+}]
\]

where \(V_{rel}\) is the Ca\(^{2+}\) release rate from the ER, \(V_{ER}\) is the Ca\(^{2+}\) influx rate into the ER, \(V_{com1}\) is the Ca\(^{2+}\) consumption rate in the cytoplasm, \(V_{out}\) is the Ca\(^{2+}\) release rate into extracellular spaces, and \(D_{Ca}\) is a diffusion coefficient for Ca\(^{2+}\).

Similarly, the IP\(_3\) dynamic, PKC, and PKC.Ca\(^{2+}\) are also modeled based on reaction/diffusion equations. In intracellular Ca\(^{2+}\) wave propagations, we excluded extracellular communication and modeled the diffusion of IP\(_3\) and Ca\(^{2+}\) into neighboring cells via gap junctions. The resulting metabolic reactions and Ca\(^{2+}\) flux into neighboring cells is simply described by the following equation:

\[
f_{Ca} = K_{Ca} \left( [\text{Ca}^{2+}]_{st} - [\text{Ca}^{2+}]_{nei} \right)
\]

where \(f_{Ca}\) is Ca\(^{2+}\) flux through gap junctions, \(K_{Ca}\) is the permeability rate, and \([\text{Ca}^{2+}]_{st}\) and \([\text{Ca}^{2+}]_{nei}\) are Ca\(^{2+}\) concentrations in stimulated and neighboring cells, respectively. Similarly, the flux of IP\(_3\) is also defined. Geometries of the cells in which Ca\(^{2+}\) waves were observed experimentally were segmented from confocal microscopic images. Cartesian computational grids with 0.5-μm pitch were then generated using segmented surface data and membrane was assumed to be 0.01 μm height of the surface, and gap junctions were set at the surfaces of connecting voxels between stimulated and neighboring cells. The experiment (Fig. 9) and simulations (Fig. 10) of intra- and inter-cellular Ca\(^{2+}\) waves show that Ca\(^{2+}\) waves propagate from a focal stimulated point to neighboring cells, indicating the utility of our 3D model for investigations of intra- and inter-cellular messaging in endothelial cells. However, we modeled the IICR mechanism only, which simply depended on the IP\(_3\) concentration and not the open probability of IP\(_3\)R. Hence, although our 3D heterogeneous metabolic reaction/diffusion model is the first to simulate intra- and inter-cellular Ca\(^{2+}\) waves, further simulations need to be designed to improve Ca\(^{2+}\) release from internal store.

In this section of 3D Ca\(^{2+}\) wave propagation, we focused
Fig. 8 Schematic of Ca\textsuperscript{2+} wave signaling in heterogeneous metabolic reaction/diffusion model [29]. The computational domain is divided into the membrane and cytoplasm. The divided metabolic reactions were also further divided into each domain according to a previous study [30]. Membrane receptors are activated by caged ATP (A), resulting in PLC mediated hydrolysis of the membrane phospholipid PIP\textsubscript{2} into IP\textsubscript{3} and DAG (B&C). IP\textsubscript{3} is then released into the cytosol and stimulates Ca\textsuperscript{2+} release from the ER (F) during degradation (E). In this study, we assumed that ER distributed homogenously in cells. Ca\textsuperscript{2+} then activates membrane PLC to induce further Ca\textsuperscript{2+} release from the ER [34]. At this point, Ca\textsuperscript{2+} returns to the ER (G), is bound by CaM (H) and PKC\textalpha{} (I), and is released into extracellular spaces (J). Finally, PKC. Ca\textsuperscript{2+} is bound by DAG at membrane (D). Membrane thickness is assumed to be 0.01 μm and that IP\textsubscript{3} and Ca\textsuperscript{2+} are assumed to be diffused through the cytoplasm in the stimulated cell and into neighboring cells via gap junctions. Extracellular communication is excluded.

Fig. 9 Microscopic images of intra- and inter-cellular Ca\textsuperscript{2+} waves in endothelial cells based on experimental analysis [29]. In this experiment, caged ATP was used to stimulate a single cell microscopically and trigger a Ca\textsuperscript{2+} wave. Here, the stimulus point is indicated by a white circle in A. The EGTA (Dojindo, JAPAN) and Apyrase (Sigma-Aldrich Corp., MO, USA) were loaded to ignore the Ca\textsuperscript{2+} influx from the extracellular space and paracrine pathway, respectively. Rhod-4–AM (AAT Bioquest, CA, USA) was used as a Ca\textsuperscript{2+} indicator. The dotted line and white arrow indicate the cell geometry and gap junction, respectively. The white line in G demonstrates the Ca\textsuperscript{2+} wave direction, and inter-cellular Ca\textsuperscript{2+} wave propagates from the stimulus point.
on the heterogeneous metabolic reaction models. On the other hand, not heterogeneous reactions, additional 3D frameworks of Ca\textsuperscript{2+} waves are proposed, such as for cardiomyocytes [31] and coupled of endothelial cells and smooth muscle cells [32]. In particular, in myocytes, not only Ca\textsuperscript{2+} wave propagations but also active contraction can be achieved by the finite element method [31].

**Summary**

Ca\textsuperscript{2+} is one of the most important messengers in cells, and intra- and inter-cellular Ca\textsuperscript{2+} waves are widely recognized as an important factor for intra- and inter-cellular communications. These waves have been investigated using theoretical and experimental methods in various cell types. In this review, we summarize the mathematical models for numerical simulations of the intra- and inter-cellular Ca\textsuperscript{2+} wave propagations. Various 1D and 2D mathematical models are proposed and validated by experimental studies.

Indeed, Ca\textsuperscript{2+} wave propagation is mainly influenced by Ca\textsuperscript{2+} diffusion, and so, to some extent, the numerical simulation may be sufficient in 1D and 2D model. However, strictly, metabolic components are not homogenously present in subcellular compartments, resulting that their related reactions must also be localized in cells. Intra- and inter-cellular Ca\textsuperscript{2+} waves are recognized as important for intra- and inter-cellular communications and involved in various signal transductions. Therefore, 3D heterogeneous metabolic reaction/diffusion framework will be useful for investigations of these communications and functions.

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