ELECTRODIFFUSION WITH CALCIUM-ACTIVATED POTASSIUM CHANNELS IN DENDRITIC SPINE

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Abstract. Feedback of calcium signaling through calcium-activated potassium channels of a dendritic spine is investigated. To simulate such ion channels and the resulting spatial distribution of concentration, current, and membrane voltage within the dendritic spine, we apply the immersed boundary method with electrodiffusion. In this simulation method, the permeability to ion flow across the membrane is regulated by the amplitude of chemical potential barriers along the membrane. With spatially localized ion channels, chemical potential barriers are locally and stochastically regulated. This represents the ion channel gating with multiple subunits, the open and closed states of which are governed by a continuous-time Markov process. The model simulation recapitulates an inhibitory action on voltage-sensitive calcium channels by calcium-activated potassium channels in a stochastic manner with non-local feedback loop. The model also predicts higher calcium influx with more closely placed channel complexes, resolving a potential mechanism of differential calcium handling by locality of channel distribution. This work provides a foundation for future computer simulation studies of dendritic spine motility and structural plasticity.

Key words. the immersed boundary method, electrodiffusion, dendritic spine, voltage-sensitive calcium channel, calcium-activated potassium channel, continuous-time Markov process

AMS subject classifications. 92C20, 60J28, 76R50, 76R05, 35R35, 74F10

1. Introduction. Dendritic spines are small protrusions in postsynapse and dendritic tree of neurons [1], and crucial in learning and memory [2, 3, 4, 5, 6]. In developmental stages, they are highly motile in the course of neuronal wiring and pruning [7, 8, 9, 10]. However, dendritic spine motility and potentially involving structural plasticity are persistently observed even in matured stages [11] and also in psychiatric disorders, neuronal injury as well as aging [12, 13, 14]. There are several ion channels in dendritic spine [15, 16], and relevant modeling with electrodiffusion in the micro- and nano-domains is needful for reconstructing physiological ionic transports and understanding consequential motility and associated neuronal functions [17].

Previously we have studied electrodiffusion with stochastic voltage-sensitive calcium channels in one-dimensional setting using the immersed boundary method [18]. The interface conditions for membrane permeability to each species of ion are replaced by chemical potential barriers in a unified Cartesian domain without explicit dissection of computational domain between intracellular and extracellular domains. In this article, we extend this approach to two-dimensional domain considering spatial effects of stochastic channel gating and channel distribution. We focus on voltage-sensitive calcium channels and calcium-activated potassium channels. In the configuration of spatial expression of those two channels, they are mostly coupled together as “complex” with about 15 nm distance in nanodomain [19]. There are two types of calcium-activated potassium channels, small-conductance (SK) and large-conductance (BK) [20]. These potassium channels feed back to voltage-sensitive calcium channels with repolarization/hyperpolarization to inhibit further calcium influx [21], and regulate in the synaptic strength and short-term plasticity among many other roles [22, 23, 24].

The chemical potential barriers are chosen so that the membrane is permeable to $\text{Ca}^{2+}$ and $\text{K}^+$ locally in space when voltage-sensitive calcium channels and calcium-activated potassium channels are open, respectively. To recapitulate back-propagating

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action potential from soma, the membrane is also regulated uniformly in space to be semi-permeable to Na\(^+\) for membrane depolarization. The membrane is uniformly semi-permeable to Cl\(^-\) all the time of simulation.

We place 5 voltage-sensitive calcium channels and 5 calcium-activated potassium channels (BK) in the dendritic spine head. The opening and closing of the channels are modeled by lowering and raising the heights of the chemical potential barriers of calcium and potassium according to continuous-time Markov processes. The voltage-sensitive calcium channels have four independent subunits with inactivation from the intracellular local calcium concentration. The channels are open only when all four subunits are in the open state. The transitions between the open and closed states of the subunits are governed by voltage sensitive rate constants, and the transition to the inactivated state is governed by calcium concentration. The calcium-activated potassium channels also have four independent subunits with closed and open states dependent on membrane voltage, and each subunit activated by calcium.

As a whole, we have incorporated the immersed boundary method with electrodiffusion for ionic transport in dendritic spine of synapse on 2D, coupled to continuous-time Markov processes for ion channel gating of voltage-sensitive calcium channels and calcium-activated potassium channels possibly non-uniformly distributed in dendritic spine. The model simulation recapitulates an inhibitory action on voltage-sensitive calcium channels by calcium-activated potassium channels in a stochastic manner with non-local feedback loop. The model also predicts higher calcium influx with more closely placed channel complexes, resolving a potential mechanism of differential calcium handling by locality of channel distribution.

The paper is organized in the following way; in Section 2 the mathematical formulation of electrodiffusion of ion species, ion-channel gating as a continuous-time Markov process, and the resulting regulation of the chemical potential barriers that model ion-channel selectivity are described. In Section 3 two-dimensional study with spatially localized channels are carried out, and the results are presented.

2. MATHEMATICAL FORMULATION. In this section we consider a fixed two-dimensional computational domain with dissolved ions. Immersed within the domain is a closed membrane, which is fixed in place. The membrane may be permeable or impermeable to each ion species, the permeability being controlled in a graded manner by its chemical potential barrier. We have the following notations:

\(D_i\): diffusion coefficient of the \(i\)th ion species
\(q\): the unit electrical charge (charge on a proton)
\(q_{z_i}\): charge of the \(i\)th species
\(K_B\): Boltzmann constant
\(T\): absolute temperature (degrees in Kelvin)
\(\Omega_E\): Eulerian domain
\(\Omega_L\): Lagrangian domain
\(\varepsilon\): dielectric constant

The notations for the variables are the following:
\(\mathbf{x} = (x_1, x_2)\): Eulerian coordinate
\(\mathbf{x} = \mathbf{X}(s)\): Lagrangian description
\(\psi_i(\mathbf{x}, t)\): chemical potential of the \(i\)th ion species
\(\Psi(\mathbf{x})\): chemical potential kernel
\(A_i(s, t)ds\): contribution of arc \((s, s + ds)\) of membrane to chemical potential of \(i\)th ion
2.1. The chemical potential. The chemical potential is expressed in the following way:

\[
\psi_i(x, t) = \int_{\Omega_i} \Psi(x - X(s), t, n) A_i(s, t) ds
\]

Here, \(X(s)\) is the configuration of the immersed boundary, where \(s\) is a Lagrangian parameter. The function \(A_i(s, t)\) describes the contribution of the membrane at \(X(s)\) to the chemical potential barrier for the \(i\)th species of ion. The chemical kernel \(\Psi\) defines how the contribution \(A_i(s, t)ds\) is to be spread out in space in the neighborhood of \(X(s)\). In the regulation of membrane permeability to the \(i\)th species of ion, the chemical potential amplitude \(A_i(s, t)\) is modulated locally or globally. When it is locally controlled, the localized area represents the domain of ion channel for the \(i\)th species of ion.

In general, any bell-shape function with compact support can be available for chemical potential kernel. For the one-dimensional kernel, a smoothed Dirac delta function \(\phi\) of the second order moment with compact support is used following the function suggested by Peskin [28]. The chemical potential kernel in two dimensional domain is as follows:

\[
\Psi_w(x, t, n) = \frac{1}{w^2} \phi\left(\frac{x \cdot t}{w}\right) \phi\left(\frac{x \cdot n}{w}\right)
\]

where \(w\) is a scaling factor such that \(\Psi_w\) has a support of a square of edge \(4w\). The coordinates used in the \(\phi\) are in the local frame from tangential and normal directions \(t\) and \(n\) with respect to the membrane at \(X(s)\).

2.2. The electrostatic potential: the Poisson equation. The electrical potential is a solution of the Poisson equation:

\[
-\nabla \cdot (\epsilon \nabla \varphi) = \sum_i q z_i c_i + \rho_0
\]
where $\rho_0$ represents the background electrical charge density. The two-dimensional domain is prescribed to be periodic in each direction, and the necessary condition for the existence of the solution of the Poisson equation requires the global electroneutrality. In the immersed boundary method with electrodiffusion, local electroneutrality is also satisfied except for the space charge layer around the membrane [26, 27]. The Poisson equation is solved by Fourier transformation with electrical density given by the computed concentration for each ionic species.

2.3. The electrodiffusion equations. The electrodiffusion equations are formulated in the following way:

$$\frac{\partial c_i}{\partial t} + \nabla \cdot J_i = 0$$ (2.4)

$$J_i = -D_i(\nabla c_i + c_i \frac{\nabla(\psi_i + qz_i\varphi)}{K_B T})$$ (2.5)

Eq. 2.4 is the conservation law (continuity equation) for the $i$th species of ion. In this equation $c_i$ is the concentration and $J_i$ is the flux per unit area of this ion species. Eq. 2.5 gives the flux per unit area as a sum of three terms: diffusion, drift caused by chemical potential, and drift caused by the electrical potential.

The membrane voltage, $V_m(s)$, intracellular concentration, $c_i(s)$, and ionic current, $I_i(s)$ for the ion channel with the center at $X(s)$ are collected from the following:

$$V_m(s) = \int_{\Omega_e} \left( \Psi_h(x - X(s) + 2wn) - \Psi_h(x - X(s) - 2wn) \right) \varphi(x) dx$$ (2.6)

$$c_i(s) = \int_{\Omega_e} \Psi_h(x - X(s) + 2wn)c_i(x) dx$$ (2.7)

$$I_i(s) = qz_i \int_{\Omega_e} \Psi_h(x - X(s) + 2wn)J_i(x) \cdot n dx$$ (2.8)

where $4w$ is mostly the width of the membrane, and $n$ is the normal unit vector at $X(s)$ outward from the membrane. In interpolating those quantities with $\Psi$ in Eulerian domain, the grid size $h$ is used for regularizing on a compact support. The electrodiffusion equations are solved by backward Euler method with a second-order Godunov upwind method, the details of which are described in [27].

2.4. Continuous-time Markov process for the stochastic ion channel gating. First, let us describe the voltage-sensitive calcium channel gating. The transition between closed and open states of each subunit is expressed as follows:

$$C_S \xrightarrow{\alpha(V_m)} O_S$$ (2.9)

where $C_S$ and $O_S$ represent closed and open states of a subunit. The rate constants of $\alpha$ and $\beta$ are functions of membrane voltage $V_m$.

We describe the states of subunits and ion channel in on/off way:

$$\chi_i = \begin{cases} 1 & \text{subunit open} \\ 0 & \text{subunit closed} \end{cases}$$ (2.10)

$$S = \begin{cases} C_{i-1} & i - 1 \text{ subunits are open} \\ O & \text{ion channel open} \\ I & \text{inactivated state} \end{cases}$$ (2.11)
Fig. 2.2. *Markov chain of voltage-sensitive calcium channel*: The calcium channel has 4 subunits. In the state of $C_i$, $i-1$ subunits are open. In the state of $I$, the channel is in inactivation and closed. The ion channel is open only when it stays on the state of $O$. The rate constants for the opening and closing of each subunit are denoted by $\alpha$ and $\beta$. Courtesy of Cox [25].

where $\chi_i$ indicates the open/closed state of $i^{th}$ subunit, and $S$ the state of ion channel. When we express the transition probability between open and closed state of each subunit based on Eq. (2.9),

\[
P(\chi_i(t+dt) = 1|\chi_i(t) = 0) = \alpha(V_m)dt \tag{2.12}
\]

\[
P(\chi_i(t+dt) = 0|\chi_i(t) = 1) = \beta(V_m)dt \tag{2.13}
\]

\[
\alpha(V_m) = \alpha_0 e^{q_{\text{forward}} V_m/26.7} \tag{2.14}
\]

\[
\beta(V_m) = \beta_0 e^{-q_{\text{backward}} V_m/26.7} \tag{2.15}
\]

where $\alpha_0 = 3.0 \text{ ms}^{-1}$, $\beta_0 = 0.241 \text{ ms}^{-1}$, $q_{\text{forward}} = 1.16$, and $q_{\text{backward}} = 1.94$, where $V_m$ is in mV. Eq. (2.12) represents the probability of $i^{th}$ subunit to take transition from closed state at $t$ to open state at $t + dt$ in the infinitesimal time interval $dt$. For the individual ion channel gating, a continuous-time Markov process is applied [29]. The ion channel is assumed to have 4 independent subunits; each of them has open and closed states.

The channel as a whole is open only when all 4 subunits are in the open state, and when the channel is not inactivated. The diagram for the Markov process with discrete states is presented in Fig. (2.2). In the discrete states labeled $C_i$, $i-1$ represents the number of subunits in the open state. The state with all 4 subunits open, however, is given the special symbol $O$. The ion channel is open when all those subunits are open, i.e. when it is in the state $O$. In the state of $I$, the channel is in inactivation and closed.

Fig. 2.3. *Markov chain of calcium-activated potassium channel*: The channel has 4 subunits, and calcium binding rate to each subunit is calcium dependent. The rate constants for the opening and closing in 5 different calcium bound states are denoted by $k_i$ and $k_{-i}$, each of which dependent on membrane voltage. Courtesy of Cox [25].

Next, for the calcium-activated potassium channel gating, the channel is also constituted with 4 independent subunits. Each subunit is activated by calcium, with
binding and unbinding rate constants \( K_0[\text{Ca}] \) and \( K_{-0} \) in the open state, and \( K_c[\text{Ca}] \) and \( K_{-c} \) in the closed state. The constants \( K_0, K_{-0}, K_c, \) and \( K_{-c} \) are 1.0 nM\(^{-1}\)s\(^{-1}\), 1.065 ms\(^{-1}\), 1.0 nM\(^{-1}\)s\(^{-1}\), and 11.917 ms\(^{-1}\), respectively. With \( i \) subunits activated by calcium, the open and closed states are determined by forward and backward rate constants, \( K_i \) and \( K_{-i} \):

\[
K_i(V_m) = \alpha_{0,i} e^{q_{\text{forward}} V_m / 26.7}
\]

\[
K_{-i}(V_m) = \beta_{0,i} e^{-q_{\text{backward}} V_m / 26.7}
\]

where \( \alpha_{0,0} \) through \( \alpha_{0,4} \) are 5.5, 8.0, 2.0, 884, 900 s\(^{-1}\), and \( \beta_{0,0} \) through \( \beta_{0,4} \) are 8.669, 1.127, 0.0252, 1.013, 0.1257 ms\(^{-1}\), respectively. The rate constants of forward and backward are 1.16 and 1.94. The numerical algorithm for the ion channel gating is basically based on the Monte Carlo method, determining first whether to transit, and secondly the state to transit if needed. The details are described in [18].

### 2.5. Regulation of chemical potential.
As described in the previous section, the continuous-time Markov process for voltage-sensitive calcium channel is applied with the membrane voltage and intracellular calcium concentration adjacent to each ion channel, and the chemical potential for \( \text{Ca}^{2+} \) is modulated in the on/off way with the channel state variable \( S \) from the Markov process. In the two-dimensional scheme, the chemical potential of calcium is locally regulated. Let the width of the ion channel be \( w_{ch} \). For the \( j \)th ion channel in the state \( S_j \), with the Lagrangian parameter \( s_j \) for the location of the center of the channel, we do spatial regulation of chemical potential in the following way:

\[
A_{\text{Ca}^{2+}}(s, t) = \begin{cases} 
A_{\text{Ca}^{2+},\text{open}} & S_j = O, s \in [s_j - w_{ch}/2, s_j + w_{ch}/2] \\
A_{\text{Ca}^{2+},\text{closed}} & \text{otherwise}
\end{cases}
\]

where \( A_{\text{Ca}^{2+},\text{closed}} \) and \( A_{\text{Ca}^{2+},\text{open}} \) are specified chemical potential amplitudes to make the membrane mostly impermeable or semi-permeable to calcium ions (Table 3.2). For the domain of membrane without ion channels, the chemical potential for calcium is fixed. The regulation for calcium-activated potassium channels are mostly the same, but the regulated chemical potential is of potassium, and not calcium ionic species.

### 3. RESULTS AND DISCUSSION.
The membrane changes its permeability to \( \text{Ca}^{2+} \) and \( \text{K}^+ \) in a voltage- and calcium-dependent manner according to the continuous-time Markov process described above with spatially localized ion channels. For 2D simulation, a periodic square domain with dimensions 2 \( \mu \text{m} \times 2 \mu \text{m} \) is covered by a Cartesian grid containing 256 \( \times \) 256 points with the uniform grid size \( h \) in each direction. The model dendritic spine has a diameter 1 \( \mu \text{m} \) and is centered within the computational domain. A timestep \( \Delta t = 30 \mu \text{s} \) is used for all computations, including both the electrodiffusion and the Markov process that controls the opening and closing of membrane channels. For the simulation, 5 voltage-sensitive calcium channels and 5 calcium-activated potassium channels are uniformly distributed on the upper half circle of the head representing a postsynaptic density (PSD) with 15 nm distance between two types of channels as a complex. These complexes are labeled indices from 1 to 5 counter-clockwise. Four ion species and background charge are considered with initial concentrations different between extracellular and intracellular domains as shown in Table 3.1.

The membrane is stochastically permeable to calcium by the voltage-sensitive calcium channel. The amount of influx through the channel is regulated by controlling
Table 3.1

Initial concentrations in all simulations (mM). $X^-$ denotes fixed background charge and the concentrations stated for $X^-$ refer to the concentration of background charges, not the concentration of the molecules that carry the background charges.

| Ion species | extracellular concentration | intracellular concentration |
|-------------|-----------------------------|-----------------------------|
| Ca$^{2+}$  | 2.0                         | 0.0002                      |
| Cl$^-$      | 150                         | 13                          |
| Na$^+$      | 150                         | 15                          |
| K$^+$       | 5                           | 100                         |
| X$^-$       | 9                           | 102.0004                    |

The chemical potential with two parameter of $A_{Ca^{2+\text{,open}}}$ and $A_{Ca^{2+\text{,closed}}}$ as prescribed in Table 3.2. Similarly, the membrane is stochastically permeable to potassium by the calcium-activated potassium channel. The amount of influx through the channel is regulated by controlling the chemical potential with two parameter of $A_{K^{+\text{,open}}}$ and $A_{K^{+\text{,closed}}}$.

With the membrane voltage in the range of depolarization, there comes calcium ionic influx from the extracellular domain. The depolarization of the membrane is implemented by lowering the chemical potential of sodium to $42.7422 K_B T$ at $t=3$ ms. The membrane is repolarized by raising the sodium chemical potential to the initial level, $53.4278 K_B T$ at $t=21$ ms. The locally regulated chemical potential of Ca$^{2+}$ around the area of ion channels are shown in Fig.2.1 with its dynamic changes in amplitude.

The calcium concentration distributions in y-section are shown when calcium ions are flowed in, and does electrodiffusion at $t=4.8$ ms and $t=5.4$ ms (Fig.3.1 (a)). The calcium concentration distribution on 2D are also shown zoomed in at $t=4.8$ ms in Fig.3.1 (b). The electrical potential distributions in y-section and 2D are shown at $t=7.8$ ms and $t=8.4$ ms (Fig.3.2). At $t=7.8$ ms, two voltage-sensitive calcium channels are open, and the associated chemical potential is locally lowered. Accordingly the membrane is locally more depolarized showing two spikes. At $t=8.4$ ms, a calcium-activated potassium channel is open, and the corresponding chemical potential is locally decreased. There follows a huge upstroke of electrical potential adjacent to the open BK channel, and the expected membrane repolarization does appear far away non-locally unexpectedly.

The ionic current and membrane voltage in the time course of channel gating are presented in Fig.3.3. When the membrane is depolarized and the channels are open, calcium currents are evidently observed. Interestingly even when the membrane is repolarized, it takes a while for the calcium channels are all closed. The stochastic calcium-activated potassium channel 1 is shortly open around $t=4$ ms before calcium concentration are elevated enough. The evident response of calcium-activated potassium channel after calcium inflow by voltage-sensitive calcium channels is shown for complexes 3 and 5 with some persistent outflow of potassium ionic current. Here one interesting aspect of membrane voltage change is that local membrane voltages are increased around complexes 3 and 5 (red circled), and decreased around complexes 1 and 2 (blue circled). This shows that the ionic current from BK ion channel gating is influential non-locally with fast redistribution of electrical potential by electrodiffusion as shown in Fig.3.2 (c) and (d).

Finally we have tested whether different distribution of complex channels generate different calcium influx, and whether BK channel inhibition drives more calcium in-
flux. We compare the averaged intracellular calcium concentration at t=30 ms for the non-uniformly distributed case with that of channel complexes uniformly distributed in the whole dendritic spine head (Fig. 3.4, first two datasets). The two-sample t-test shows a significantly higher calcium level for the non-uniformly distributed case. It is supposed that calcium influx induces membrane depolarization and this provides a positive feedback to adjacent voltage-sensitive calcium channels for them to have higher probability to open channels. This interaction is thought to be stronger than repolarizing effects from adjacent calcium-activated potassium channels. Based on the model simulation result of Fig. 3.2 (c) and (d), once intracellular calcium concentration around a voltage-sensitive calcium channel is elevated when the channel is open, the adjacent calcium-activated potassium channel gradually responds by opening the channel. What happens here is local depolarization and non-local repolarization. Thereafter, this might enhance the coupled voltage-sensitive calcium channel to stay in open state, and the only action of channel inhibition is by calcium-sensitive inactivation in the channel itself.

We also compare the intracellular calcium concentrations with two cases of BK channels expressed with their non-uniform distribution or knocked out (Fig. 3.4, second and third datasets). The paired-sample t-test shows a significant elevation of calcium influx by BK channel inhibition or knock-out. The significant difference in calcium concentration shows the inhibitory mechanism on calcium influx by the interaction purely between voltage-sensitive calcium channels and calcium-activated potassium channels.

4. Conclusions. By proposing the immersed chemical potentials, we realize the regulation of membrane permeability to each species of ion, and consequently ion selectivity of membrane. With the continuous-time Markov process in the stochastic feature of the voltage-sensitive ion channel, the ion channel gating and the corresponding ionic current are observed dependent on the membrane voltage. In the chemical potential barrier landscape for the ion channel, there are several local minima by a number of subunits of the ion channel. In our approach, that kind of feature is embedded in the finite discrete states of the Markov chain, and bell-type shape without local minima is applied for the chemical potential. The shape of these chemical potential barriers also influences the current-voltage relationship of the membrane, the investigation of which remains for the future.

In two dimensional study, the stochastic ion channel gating with discretely placed ion channels were considered. Individual ion channel gating is observed with spatiotemporally changing chemical potential distributions. In comparison to the point cell modeling, this kind of approach makes it available for us to consider spatially nonuniform distribution of ion channels and their spatial effects on the physiology. Accordingly, in the sense of synaptic plasticity, we can implement the change in the ion channel density.

The non-local interaction between voltage-sensitive calcium channels and calcium-activated potassium channels is thought to be captured by treating the electrophysiology in nano- to micro-scale electrodiffusion, and surely not feasible by drift-diffusion. At the same time, positive feedback among local channel complexes for calcium influx is also predicted for further validation by experiments. Currently the back-propagating action potential was treated by one-time event of phasic train. In real neuronal activities, the frequency of this back-propagating action potential spikes may induce differential response from calcium-activate potassium channels [30, 31]. Of course, we expect to reconstruct 3D electrodiffusion [32, 33] with the formalism.
we exposed here.

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Table 3.2
Chemical potential ($K_B T$) prescribed for each ionic species.

| Ion species | chemical potential high | chemical potential low |
|-------------|-------------------------|------------------------|
| Ca$^{2+}$   | 53.4278                 | 8.0142                 |
| Cl$^{-}$    | 45.4136                 | 45.4136                 |
| Na$^+$      | 53.4278                 | 42.7422                 |
| K$^+$       | 53.4278                 | 18.6997                 |
| X$^-$       | 53.4278                 | 53.4278                 |

Fig. 3.1. Concentration distribution with ion channels open on 2D: (a) The calcium concentration distribution in y-section at $t=0$ ms (red), $t=4.8$ ms (black-dotted), $t=5.4$ ms (black-solid). The chemical potential distribution is also shown (blue) at $t=4.8$ ms. (b) The calcium concentration is zoomed in to resolve the low level concentration in µM in intracellular domain at $t=4.8$ ms.
Fig. 3.2. Electrical potential distribution on 2D: (a) The electrical potential in y-section at $t=0.2$ ms (red) and $t=7.8$ ms (black). The chemical potential for calcium is also shown in y-section at $t=7.8$ ms (blue). (b) The electrical potential on 2D at $t=7.8$ ms. (c) The electrical potential in y-section at $t=0.2$ ms (red) and $t=8.4$ ms (black). The chemical potential for potassium is also shown in y-section at $t=8.4$ ms (blue). (d) The electrical potential on 2D at $t=8.4$ ms.
Fig. 3.3. Voltage-sensitive calcium channel and calcium-activated potassium channel activities; The columns represent (a) calcium ionic currents by voltage-sensitive calcium channels, (b) potassium ionic currents by calcium-activated potassium channels, (c) membrane voltage, and (d) intracellular calcium concentration adjacent to each voltage-sensitive calcium channel. The rows represent 5 individual complexes of voltage-sensitive calcium channel and calcium-activated potassium channel. These electrophysiological activities are from non-uniform distribution channel complexes.
Fig. 3.4. Calcium ion concentration comparison; 10 samples are collected for comparison of averaged intracellular calcium ion concentrations for three cases, 1) ion channel complexes are uniformly distributed, 2) ion channel complexes are non-uniformly distributed, 3) ion channel complexes are non-uniformly distributed and BK channels are knocked out. The activity of BK channel shows an inhibiting function in calcium inflow. Non-uniform distribution of ion channel complexes induce higher intracellular calcium concentration. * p < 0.05 two sample t-test, ** p < 0.05 paired-sample t-test.