Markovian Model of the Voltage Gating of Connexin-based Gap Junction Channels

A. Sakalauskaite, H. Pranevicius
Department of Business Informatics, Kaunas University of Technology, Studentu str. 56, LT-51424, Kaunas, Lithuania, phone: +370 37 300 376, e-mail: henrikas.pranevicius@ktu.lt

M. Pranevicius, F. Bukauskas
Department of Anesthesiology, Department of Neuroscience, Albert Einstein College of Medicine, 1300 Morris Park Ave. Bronx NY, 10461, USA, phone: 718 430-4130, e-mail: feliksas.bukauskas@einstein.yu.edu

Introduction

A major goal of this study was to describe gating of gap junction (GJ) channels formed of connexin (Cx) protein by using a discrete Markov chain. Gap junctions provide a direct pathway for electrical and metabolic signaling between cells. Each GJ channel is composed of two hemichannels (connexons), which in turn are composed from 6 connexins forming a hexamer with the pore inside. Twenty one Cx genes have been identified in humans. GJ channels vary highly in conductance, perm-selectivity and gating properties depending on Cx type. Mutations in Cxs have been shown to be responsible for several hereditary human diseases including the X-linked form of demyelinating disease, non-syndromic sensorineural deafness, erythropoietic protoporphyria, congenital cataractogenesis, oculodentodigital dysplasia and more. A number of studies have also demonstrated a correlation between reduced GJ-mediated communication and cancer or cardiac arrhythmias. Conductance and permeability of GJ channels can be modulated by transjunctional voltage ($V_J$) which induces channels transitions between open and closed states and this process is called as $V_J$-dependent gating. Gating of GJ channels can be modulated by intracellular ionic composition, pH, Ca$^{2+}$ and different pathological conditions, such as hypoxia, ischemia or epilepsy, causing significant dysregulation of electrical and metabolic cell-cell communication. In this study, we elaborated the algorithm for evaluation of gap junctional conductance dependence on $V_J$.

Conceptual model

Gap junctions form clusters of individual channels arranged in parallel in the junctional membrane of two adjacent cells. The GJ channel is composed of 2 hemichannels (left and right) arranged in series. Each connexin can be in 2 states (open – “o” or closed – “c”) and operates/gates between these two states (Fig. 1). For simplicity reasons, we assumed that only connexin in the left hemichannel gate, while all Cxs in the right hemichannel are always open (Fig. 2). The GJ channel gates in response to $V_J$ due to $o\leftrightarrow c$ transitions of each connexin. As reported earlier [1–3] probabilities of transitions between open and closed states are described as follows

$$p_{oc} = \frac{K \cdot k(A, P, V_{left}, V_0)}{1 + k(A, P, V_{left}, V_0)},$$

where $p_{oc}$ is the probability of transitions from open to closed state.

$$p_{oo} = 1 - p_{oc}(A, P, V_{left}, V_0),$$

where $p_{oo}$ is the probability to remain in an open state.

$$p_{co} = \frac{K}{1 + k(A, P, V_{left}, V_0)},$$

where $p_{co}$ is the probability of transitions from closed to open state.

$$p_{cc}(A, P, V_{left}, V_0) = 1 - p_{co}(A, P, V_{left}, V_0),$$

where $p_{cc}$ is the probability to remain in the closed state (Fig. 2) and

$$k(A, P, V_{left}, V_0) = e^{A(PV_{left} - V_0)},$$

where $P$ is the polarity of the voltage (+1 or -1); $A$ is a coefficient characterizing gating sensitivity to voltage (1/mV); $K$ is the constant of adjustment of states of connexins of left or right hemichannels (to modulate a probability of gating transitions; $V_0$ is a voltage across the hemichannel the half of a maximal conductance (mV).
Attributed to each connexin is a conductance $g$, which depends on a voltage across it ($V_{\text{left}/\text{right}}$), can gate by changing stepwise between open state with conductance $g_0 = 2$ arbitrary units in picosiemense (pS) and the closed state exhibiting some residual conductance $g_r = 0.25$ pS. In addition, it was assumed that $g_0$ and $g_r$ values rectifies, i.e., depends on $V_{\text{left}/\text{right}}$, exponentially:

$$g_0(V_{\text{left}/\text{right}}, P) = 2 \cdot \exp \left( \frac{PV_{\text{left}}}{800} \right),$$
$$g_r(V_{\text{left}}, P) = 0.25 \cdot \exp \left( \frac{PV_{\text{left}}}{300} \right),$$

where $V_{\text{left}/\text{right}}$ is a voltage across the left or right hemichannel.

The conductance of the left hemichannel can be described as follows

$$g_{\text{left}} = n \cdot g_c(V_{\text{left}}(n), P) + (6 - n)g_0(V_{\text{left}}(n), P),$$

where $n$ – number of closed connexins.

The voltages on the left and right connexins, when $n$ connexins are closed is as follows

$$U_{\text{left/\text{right}}} = \frac{g_{\text{left/\text{right}}}(n,V)}{g_{\text{left}}(n) + g_{\text{right}}(n)} \cdot U.$$

Initially conductances of connexins are calculated at $V = 0$. In the next iteration conductances of connexins are calculated at the voltage from a previous iteration, and so on. The calculation scheme is presented in Table 1, where $i$ is the number iterations. Calculation shows that after 3-4 iterations the value of voltage is settled with $\pm 0.1\%$ accuracy.

<table>
<thead>
<tr>
<th>$i$</th>
<th>$V_{\text{left}}(n,i)$</th>
<th>$V_{\text{right}}(n,i)$</th>
<th>$g_{\text{left}}(n,i,V)$</th>
<th>$g_{\text{right}}(l,V)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>$V_{\text{left}}(n,o)$</td>
<td>$V_{\text{right}}(n,o)$</td>
<td>$g_{\text{left}}(n,o,o)$</td>
<td>$g_{\text{left}}(n,o,o)$</td>
</tr>
<tr>
<td>1</td>
<td>$V_{\text{left}}(n,1)$</td>
<td>$V_{\text{right}}(n,1)$</td>
<td>$g_{\text{left}}(n,1,V_{\text{left}}(n,o))$</td>
<td>$g_{\text{right}}(1,V_{\text{right}}(n,o))$</td>
</tr>
<tr>
<td>2</td>
<td>$V_{\text{left}}(n,2)$</td>
<td>$V_{\text{right}}(n,2)$</td>
<td>$g_{\text{left}}(n,2,V_{\text{left}}(n,1))$</td>
<td>$g_{\text{right}}(2,V_{\text{right}}(n,1))$</td>
</tr>
</tbody>
</table>

The set of states into which $n_c$ closed connexins can pass is as follows

$$\text{next\_states} \_\text{I}([n_c]) = \left\{ n_c, k : N \mid k \leq n_c \cdot (n_c - k, k) \right\}.$$ (12)

and the set of states into which $n_o$ opened connexins can pass is as follows

$$\text{next\_states} \_\text{II}([n_o]) = \left\{ n_o, l : N \mid l \leq n_o \cdot (l, n_o - l) \right\}. $$ (13)

If the current state is $(n_c, n_o)$ and during one step $k$ closed connexins will open and $l$ open connexins will close, then the hemichannel will pass into the state $(n_c - k + l, n_o + k - l)$ with probability, which is calculated using Bernoulli distribution

$$q_{kl} = C_{n_c}^k \cdot p_{cc}^k \cdot p_{cc}^{n_c-k} \cdot C_{n_o}^l \cdot p_{oo}^l \cdot p_{oo}^{n_o-l}. $$ (14)

For example, for the state (1,5):

$$\text{next\_states} \_\text{I}(1) = \left\{ 1 : N \mid 1 \leq 1 \cdot (1 - k, k) \right\}, $$ (15)

$$\text{next\_states} \_\text{II}(5) = \left\{ 5 : N \mid 5 \leq 5 \cdot (5 - l) \right\}. $$ (16)

Fig. 3 illustrates the process of transitions into new states for the state (1,5).
The probabilities of transitions from the state \((1,5)\) to the remaining states are as follows:

\[
P_{(1,5)(06)} = C_0^1 \cdot P_{cc}^0 \cdot P_{co}^1 \cdot C_5^0 \cdot P_{oc}^0 \cdot P_{oo}^5, \tag{17}
\]

\[
P_{(1,5)(15)} = C_1^1 \cdot P_{cc}^1 \cdot P_{co}^0 \cdot C_5^0 \cdot P_{oc}^0 \cdot P_{oo}^5 + \ldots, \tag{18}
\]

\[
P_{(1,5)(24)} = C_1^1 \cdot P_{cc}^1 \cdot P_{co}^0 \cdot C_5^1 \cdot P_{oc}^1 \cdot P_{oo}^4 + \ldots, \tag{19}
\]

\[
P_{(1,5)(33)} = C_1^1 \cdot P_{cc}^1 \cdot P_{co}^0 \cdot C_5^1 \cdot P_{oc}^1 \cdot P_{oo}^4 + \ldots, \tag{20}
\]

\[
P_{(1,5)(42)} = C_1^1 \cdot P_{cc}^1 \cdot P_{co}^0 \cdot C_5^2 \cdot P_{oc}^2 \cdot P_{oo}^3 + \ldots, \tag{21}
\]

\[
P_{(1,5)(53)} = C_1^1 \cdot P_{cc}^1 \cdot P_{co}^0 \cdot C_5^2 \cdot P_{oc}^2 \cdot P_{oo}^3 + \ldots, \tag{22}
\]

\[
P_{(1,5)(60)} = C_0^1 \cdot P_{cc}^0 \cdot P_{co}^1 \cdot C_5^3 \cdot P_{oc}^3 \cdot P_{oo}^2 + \ldots, \tag{23}
\]

\[
P_{(1,5)(4,2)} = C_1^1 \cdot P_{cc}^1 \cdot P_{co}^0 \cdot C_5^3 \cdot P_{oc}^3 \cdot P_{oo}^2 + \ldots, \tag{24}
\]

\[
P_{(1,5)(3,3)} = C_1^1 \cdot P_{cc}^1 \cdot P_{co}^0 \cdot C_5^4 \cdot P_{oc}^4 \cdot P_{oo}^1 + \ldots, \tag{25}
\]

\[
P_{(1,5)(4,2)} = C_1^1 \cdot P_{cc}^1 \cdot P_{co}^0 \cdot C_5^4 \cdot P_{oc}^4 \cdot P_{oo}^1 + \ldots, \tag{26}
\]

\[
P_{(1,5)(5,0)} = C_0^1 \cdot P_{cc}^0 \cdot P_{co}^1 \cdot C_5^5 \cdot P_{oc}^5 \cdot P_{oo}^0. \tag{27}
\]

Stationary probabilities were calculated using Kolmogorov-Chapman equations:

\[
P_j = \sum_{i=1}^{7} p_{ij} \cdot p_i, \quad j = 1, 7, \tag{29}
\]

\[
\sum_{i=1}^{7} p_i = 1.
\]

The system of equations (29) has been resolved using Greville method [4, 5].

### The results of modeling

To perform calculations of conductances according to (14) and (29) equations, we used the following values of parameters describing gating properties of connexins (Table 2):  

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A)</td>
<td>0.1 (V/m²)</td>
</tr>
<tr>
<td>(P)</td>
<td>1 (const.)</td>
</tr>
<tr>
<td>(V)</td>
<td>-100–100 (mV)</td>
</tr>
<tr>
<td>(V_0)</td>
<td>40 (mV)</td>
</tr>
</tbody>
</table>

\[
g_{oc}(V_{left/right}, P) \cdot P_{V_{left/right}} \cdot 2 \cdot e^{-800} \quad \text{(pS)}
\]

\[
g_{cc}(V_{left}, P) \cdot P_{V_{left}} \cdot 0.25 \cdot e^{-300} \quad \text{(pS)}
\]

\(K\) | 0.1 (const.) |

Stationary probabilities of the gap junction channel at transjunctional voltages from -100 mV to 100 mV are shown in Fig. 4.

![Fig. 4. Stationary probabilities of different states of the left hemichannel depending on transjunctional voltage in the range from -100 mV to 100 mV](image)

At \(U = -100\) mV, the probability for all connexins to be open is equal to 1. At \(U = 100\) mV, all 6 connexins are closed. At \(U\) values in between -100 and 100 mV, all intermediate states are probable.

The results of conductance at different \(U\) obtained with the described model are compared with those obtained using the results of a simulation [3]. As illustrated in Table 3 and Fig. 5, both models produce identical results.

<table>
<thead>
<tr>
<th>Voltage, mV</th>
<th>Conductance, pS</th>
<th>The results of a simulation</th>
<th>The results of Markov model</th>
</tr>
</thead>
<tbody>
<tr>
<td>-100</td>
<td>5,5736</td>
<td>5,6365</td>
<td></td>
</tr>
<tr>
<td>-90</td>
<td>5,6082</td>
<td>5,6718</td>
<td></td>
</tr>
<tr>
<td>-80</td>
<td>5,643</td>
<td>5,7074</td>
<td></td>
</tr>
<tr>
<td>-70</td>
<td>5,6779</td>
<td>5,7431</td>
<td></td>
</tr>
<tr>
<td>-60</td>
<td>5,7131</td>
<td>5,7791</td>
<td></td>
</tr>
<tr>
<td>-50</td>
<td>5,7476</td>
<td>5,8153</td>
<td></td>
</tr>
<tr>
<td>-40</td>
<td>5,7583</td>
<td>5,8515</td>
<td></td>
</tr>
<tr>
<td>-30</td>
<td>5,7983</td>
<td>5,8876</td>
<td></td>
</tr>
</tbody>
</table>
in addition, introducing a third state, so-called the deep closed (dc) state with a linear transition scheme: 0→c→dc. This is stimulated by our latest experimental data demonstrating an existence of the dc state, which has the same conductance as the c state, but with the restriction for the 0→dc transitions.

Conclusions

The Markovian model allows evaluation of the conductance of the gap junction channel at steady-state conditions at different transjunctional voltages.

The validity of the proposed Markovian model was verified by comparing it to results obtained using a stochastic simulation of voltage gating.

References


Received 2011 02 15


Gap junction (GJ) channels, which are formed of a connexin (Cx) protein provide pathways through which ions and small molecules are exchanged between adjacent cells. GJs co-ordinate the cellular activity in tissues by synchronizing their electrical activity and allowing a direct cell-to-cell chemical signaling. Electrically gap junctions present nonlinear conductance that depends on transjunctional voltage and can be modulated by chemical reagents and ions, such as pH, Ca$^{2+}$, etc. Here, we describe the model of the voltage gating of gap junctions using Markovian formalism. The results obtained using a stationary Markov model are well comparable with those obtained using a stochastic/imitational model of voltage gating. Ill. 5, bibl. 5, tabl. 3 (in English; abstracts in English and Lithuanian).


Płyšinės jungties (PJ) kanalai, sudaryti iš koneksinių (Cx) baltymų – tai kelių, kuriais greitimos įstalelių keičiasi jonais ir mažomis molekulėmis. PJ reguliuoja įstalelių veiklą audiniuose derinant jų elektrinį veikimą ir leidžiant tiesioginį cheminį srautą į įstalelę į įstalelę. Fizikine prasme plynines jungties atitinka neteisinią laidumą, kuris priklauso nuo įstalelių įstalelių ir gali būti reguliuojamas cheminiais reagentais įstalelių, tokiais kaip pH, Ca$^{2+}$ ir t. t. Šiame straipsnyje, naudojantis Markovo formalizmu apibūdintos plynines jungties, sudarytų iš įkaitočio individualių plynines jungties kanalų skaičius, įstalelių įstalelių ir gali būti reguliuojamos cheminiais reagentais įstalelių, tokiais kaip pH, Ca$^{2+}$ ir t. t. Šiame straipsnyje, naudojantis Markovo formalizmu apibūdintos plynines jungties, sudarytų iš įkaitočio individualių plynines jungties kanalų skaičius, įstalelių įstalelių ir gali būti reguliuojamos cheminiais reagentais įstalelių, tokiais kaip pH, Ca$^{2+}$ ir t. t. Šiame straipsnyje, naudojantis Markovo formalizmu apibūdintos plynines jungties, sudarytų iš įkaitočio individualių plynines jungties kanalų skaičius, įstalelių įstalelių ir gali būti reguliuojamos cheminiais reagentais įstalelių, tokiais kaip pH, Ca$^{2+}$ ir t. t.