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

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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, erythrokeratodermia, congenital cataractogenesis, oculodentodigital displasia 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

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

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

$$p_{oo} = 1 - p_{oc}(A, P, V_{left}, V_0), \tag{2}$$

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

$$p_{co} = \frac{K}{1 + k\left(A, P, V_{left}, V_0\right)}, \tag{3}$$

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

$$p_{cc}(A, P, V_{left}, V_0) = 1 - p_{co}(A, P, V_{left}, V_0), \tag{4}$$

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

$$k\left(A, P, V_{left}, V_0\right) = e^{A \cdot \left(P \cdot V_{left} - V_0\right)}, \tag{5}$$

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 ($V_{left/right}$), can gate by changing stepwise between open state with conductance $g_o = 2$ 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_o and g_c values rectifies, i.e., depends on $V_{left/right}$, exponentially:

$$g_o(V_{left/right}, P) = 2 \cdot e^{\frac{P \cdot V_{left/right}}{800}}, \tag{6}$$

$$g_c(V_{left}, P) = 0.25 \cdot e^{\frac{P \cdot V_{left}}{300}}, \tag{7}$$

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

The conductance of the left hemichannel can be described as follows

$$g_{left} = n \cdot g_c\left(V_{left}(n), P\right) + (6-n) g_0\left(V_{left}(n), P\right), \tag{8}$$

where n – number of closed connexins.

The conductance of right hemichannel

$$g_{right} = 6 \cdot g_0\left(V_{left}(n), P\right). \tag{9}$$

The conductance of left side hemichannel at stationary time moment can be described as follows

$$g_{left} = \sum_{n=0}^{6} \left[\left(n \cdot P_n \cdot g_c\left(V_{left}(n), P\right) + (6-n) g_0\left(V_{left}(nf), P\right)\right)\right], \tag{10}$$

where p_n – stationary probability, when n connexins are closed and 6-n are open. For calculation of these probabilities Markov chain is created.

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

$$V_{left/right}(n) = \frac{g_{right/left}(n)}{g_{left}(n) + g_{right}} U. \tag{11}$$

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 $\leq 0{,}1\%$ accuracy.

Table 1. Calculation of steady voltage at connexins

i	$V_{left}(n,i)$	$V_{right}(n,i)$	$g_{left}(n,i,V)$	$g_{right}(i,V)$
0	$V_{left}(n,o)$	$V_{right}(n,o)$	$g_{left}(n,o,o)$	$g_{right}(o,o)$
1	$V_{left}(n,1)$	$V_{right}(n,1)$	$g_{left}(n,1,V_{left}(n,o))$	$g_{right}(1,V_{right}(n,o))$
2	$V_{left}(n,2)$	$V_{right}(n,2)$	$g_{left}(n,2,V_{left}(n,1))$	$g_{right}(2,V_{right}(n,1))$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$

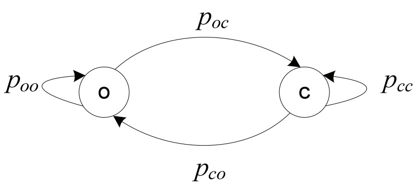

Fig. 1. The state graph of one connexin

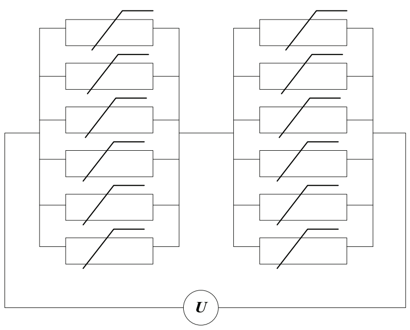

Fig. 2. Electrical scheme of *GJ* channel composed of two hemichannels each formed of 6 connexins

The construction of the Markov chain

The left hemichannel, which is composed of 6 connexins, is divided into two groups: open connexins (group I) and closed connexins (group II).

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

$$next\_states\_\mathrm{I}(n_c) = \{n_c, k : N | k \leq n_c \bullet (n_c - k, k)\} \tag{12}$$

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

$$next\_states\_\mathrm{II}(n_o) = \{n_o, l : N | l \leq n_o \bullet (l, n_o - l)\}. \tag{13}$$

If the current state is (n_c, n_0) and during one step k closed connexins will open and l open conexins will close, then the hemichannel will pass into the state $(n_c - k + l, n_0 + k - l)$ with probability, which is calculated using Bernoulli distribution

$$q_{kl} = C_{n_c}^{k} \cdot P_{co}^{k} \cdot P_{cc}^{n_c - k} \cdot C_{n_o}^{l} P_{oo}^{l} \cdot P_{oo}^{n_o - l}. \tag{14}$$

For example, for *the_state* (1,5):

$$next\_states\_\mathrm{I}(1) = \{k : N | k \leq 1 \bullet \cdot (1-k, k)\}, \tag{15}$$

$$next\_states\_\mathrm{II}(5) = \left\{l : N\right|' l \leq 5 \bullet (l, 5-l)\right\}. \tag{16}$$

Fig. 3 illustrates the process of transitions into new states for the *state* (1,5).

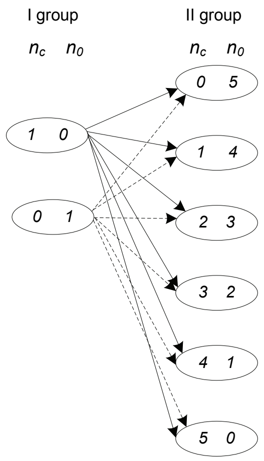

Fig. 3. Scheme illustrating transitions of the state (1,5) into six new states

The probabilities of transitions from the state $(1,5)$ to the remaining states are as follows:

$$p_{(1,5)(06)} = C_1^0 \cdot p_{cc}{}^0 \cdot p_{co}{}^1 \cdot C_5^0 \cdot p_{oc}{}^0 \cdot p_{oo}{}^5, \quad (17)$$

$$p_{(1,5)(1,5)} = C_1^1 \cdot p_{cc}{}^1 \cdot p_{co}{}^0 \cdot C_5^0 \cdot p_{oc}{}^0 \cdot p_{oo}{}^5 + \ldots, \quad (18)$$

$$C_1^0 \cdot p_{cc}{}^0 \cdot p_{co}{}^1 \cdot C_5^1 \cdot p_{oc}{}^0 \cdot p_{oo}{}^4, \quad (19)$$

$$p_{(1,5)(2,4)} = C_1^1 \cdot p_{cc}{}^1 \cdot p_{co}{}^0 \cdot C_5^1 \cdot p_{oc}{}^1 \cdot p_{oo}{}^4 + \ldots, \quad (20)$$

$$C_1^0 \cdot p_{cc}{}^0 \cdot p_{co}{}^1 \cdot C_5^2 \cdot p_{oc}{}^2 \cdot p_{oo}{}^3, \quad (21)$$

$$p_{(1,5)(3,3)} = C_1^1 \cdot p_{cc}{}^1 \cdot p_{co}{}^0 \cdot C_5^2 \cdot p_{oc}{}^2 \cdot p_{oo}{}^3 + \ldots, \quad (22)$$

$$C_1^0 \cdot p_{cc}{}^0 \cdot p_{co}{}^1 \cdot C_5^3 \cdot p_{oc}{}^3 \cdot p_{oo}{}^2, \quad (23)$$

$$p_{(1,5)(4,2)} = C_1^1 \cdot p_{cc}{}^1 \cdot p_{co}{}^0 \cdot C_5^3 \cdot p_{oc}{}^3 \cdot p_{oo}{}^2 + \ldots, \quad (24)$$

$$C_1^0 \cdot p_{1cc}{}^0 \cdot p_{1co}{}^1 \cdot C_5^4 \cdot p_{1oc}{}^4 \cdot p_{1oo}{}^1, \quad (25)$$

$$p_{(1,5)(5,1)} = C_1^1 \cdot p_{cc}{}^1 \cdot p_{co}{}^0 \cdot C_5^4 \cdot p_{oc}{}^4 \cdot p_{oo}{}^1 + \ldots, \quad (26)$$

$$C_1^0 \cdot p_{cc}{}^0 \cdot p_{co}{}^1 \cdot C_5^5 \cdot p_{oc}{}^5 \cdot p_{oo}{}^0, \quad (27)$$

$$p_{(1,5)(6,0)} = C_1^1 \cdot p_{cc}{}^1 \cdot p_{co}{}^0 \cdot C_5^5 \cdot p_{oc}{}^5 \cdot p_{oo}{}^0. \quad (28)$$

Stationary probabilities were calculated using Kolmogorov_Chapman equations:

$$\begin{cases} p_j = \sum_{i=1}^{7} p_{i,j} \cdot p_i; \; j = \overline{1,7}, \\ \sum_{i=1}^{7} p_i = 1. \end{cases} \quad (29)$$

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 2. Table of chosen values of parameters

Parameters	Values (units)
A	0.1 (1/mV)
P	1 (const.)
V	-100:10:100 (mV)
V_0	40 (mV)
$g_o\left(V_{left/right}, P\right)$	$2 \cdot e^{\frac{P \cdot V_{left/right}}{800}}$ (pS)
$g_c\left(V_{left}, P\right)$	$0.25 \cdot e^{\frac{P \cdot V_{left}}{300}}$ (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.

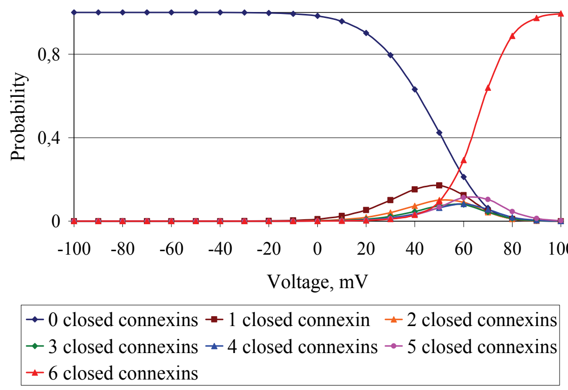

Fig. 4. Stationary probabilities of different states of the left hemichannel depending on transjunctional voltage in the range from -100 mV to 100 mV

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 3. Comparison of results obtained using a stochastic simulation and Markov model, used gating parameters are shown in Table 2

Voltage, mV	**Conductance, pS**	
	The results of a simulation	**The results of Markov model**
-100	5,5736	5,6365
-90	5,6082	5,6718
-80	5,643	5,7074
-70	5,6779	5,7431
-60	5,7131	5,7791
-50	5,7476	5,8153
-40	5,7583	5,8515
-30	5,7983	5,8876

Voltage, mV	Conductance, pS	
	The results of a simulation	The results of Markov model
-20	5,8018	5,9228
-10	5,857	5,9556
0	5,8276	5,9814
10	5,7269	5,9899
20	5,7916	5,9585
30	5,6241	5,8447
40	5,2061	5,5769
50	5,1357	5,0158
60	3,987	3,942
70	2,4979	2,6196
80	1,8875	1,906
90	1,7121	1,7322
100	1,5811	1,7277

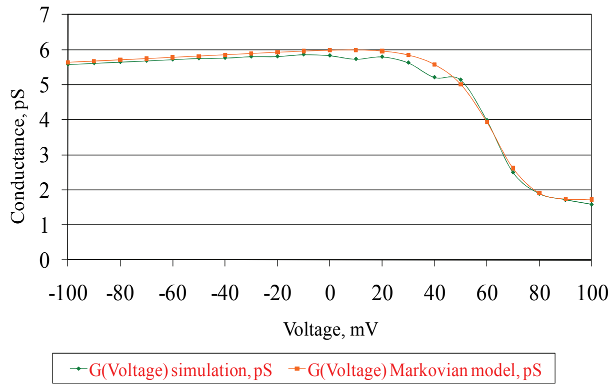

Fig. 5. Superposition of Conductance–Voltage plots obtained using stochastic simulation and Markov model

This Markov model will be further developed by allowing gating for both, left and right hemichannels, and, in addition, introducing a third state, so-called the deep closed (*dc*) state with a linear transition scheme: *o*↔*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 *o*↔*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.

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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).

A. Sakalauskaitė, H. Pranevičius, M. Pranevičius, F. Bukauskas. Plyšinės jungties savybių modeliavimas naudojant Markovo grandines // Elektronika ir elektrotechnika. – Kaunas: Technologija, 2011. – Nr. 5(111). – P. 103–106.

Plyšinės jungties (PJ) kanalai, sudaryti iš koneksinų (Cx) baltymų – tai keliai, kuriais gretimos ląstelės keičiasi jonais ir mažomis molekulėmis. PJ reguliuoja ląstelių veiklą audiniuose derinant jų elektrinį veikimą ir leidžiant tiesioginį cheminį srautą iš ląstelės į ląstelę. Fizikine prasme plyšinės jungtys atitinka netiesinį laidumą, kuris priklauso nuo kintančios įtampos ir gali būti reguliuojamas cheminiais reagentais ir jonais, tokiais kaip pH, Ca^{2+} ir t. t. Šiame straipsnyje, naudojantis Markovo formalizmu apibūdintos plyšinių jungčių, sudarytų iš kintančio individualių plyšinės jungties kanalų skaičiaus, įtampos kitimo modelis. Rezultatai, gauti naudojant stacionarų Markovo modelį, sutampa su rezultatais, gautais naudojant stochastinį ir imitacinį įtampos kitimo modelį. Il. 5, bibl. 5, lent. 3 (anglų kalba; santraukos anglų ir lietuvių k.).