Dear Colleagues,

We would like to offer a web-accessible voltage-gating model (available at http://connexons.aecom.yu.edu/Applet.htm) to facilitate analysis of gating properties of gap junction (GJ) channels and unapposed/nonjunctural hemichannels formed from connexins, innexins or pannexins.

Boltzmann formalism, originally proposed by Drs. Bennett, Harris and Spray (Spray et al., 1979 & 1981; Harris et al., 1981), is used commonly to fit the dependence of junctional conductance (gj) on transjunctional voltage (Vj). This method assumes that one hemichannel of the GJ channel “sees” Vj when the hemichannel in series with it is open. Furthermore, it has become evident that both apposed hemichannels contain ‘fast’ and ‘slow/loop’ gates with rectifying unitary conductances, and that closing one gate changes the profile of the electrical field in the channel pore, which, in turn, influences gating of the series gates. By integrating these new findings and experience in modeling of voltage gating of GJs by other groups (Harris et al., 1981; Vogel et al., 1998; Ramanan et al., 1999; Chen-Izu et al., 2001), we elaborated a model using a stochastic approach to describe voltage gating of GJ channels containing one voltage sensitive gate per hemichannel (Paulauskas et al., 2009). This model allows the simulation of Vj-gating in homotypic and heterotypic GJ channels at the single channel level or macroscopically. The model presented here extends the published version in that each apposed hemichannel is composed of two conductances in series: a conductance ascribed to open and closed states of the gate region (Go↔Gc) and a constant conductance (Gn) ascribed to the non-gated region. This is based on the assumption that the gate occupies only a fraction of the hemichannel pore and another fraction remains unmodified during the gating process. If Gn>>Go, where Go is the conductance of the open gate, then the effect of Gn on Vj-gating is negligible. However, if Gn is comparable to Go (a case that is probably true for many Cxs), then it can ‘absorb’ a substantial fraction of Vj and effectively reduce Vj–gating of GJs even though Vj sensitivity of the gate itself remains unchanged.

This model can be used to simulate gating properties of unapposed hemichannels (uHCs) by assigning very high unitary conductances to the open and closed states of one hemichannel (e.g., Go=Ge=10,000,000 pS). As an alternative, you can assign left and right hemichannels to two halves of uHCs and simulate voltage gating of the uHC containing both fast and slow gates in series.

We fully appreciate that the current model has limitations, and we are working to upgrade it by including a second gate in each apposed hemichannel in order to permit simulation of fast and slow gating, arbitrary user specified Vj protocols and modulation of gating parameters over time to imitate effect of different factors on gj and Vj-gating. In addition, in collaboration with Dr. Mockus (Institute of Mathematics and Informatics, Lithuania), we are developing Global Optimization methods that will allow for the automated evaluation of gating parameters of GJs from gj-Vj plots (see Movies in http://connexons.aecom.yu.edu/Research.htm) and from dynamics of junctional current in response to Vj. At this point, the model allows for the adjustment of eight independent
parameters characterizing each gate of homotypic or heterotypic junctions and calculates the steady-state $g_j-V_j$ dependence as well as changes of junctional current and conductance over time in response to selected voltage protocols. Simulated $g_j-V_j$ dependence can be saved in text format and transferred to other programs such as Excel, Sigma Plot, etc.

If you decide to use the model in your research or teaching topics related to gating processes of channels, we would appreciate the citation of Paulauskas et al. (2009) and http://connexons.aecom.yu.edu. We readily welcome and appreciate comments and suggestions about the function of the model or propositions to improve it. User feedback can be provided via the Comments Area.

I write on behalf of all coauthors of Paulauskas et al., 2009 (Paulauskas, N., Pranevicius, M., Pranevicius, H., Bukauskas, F. A stochastic four-state model of contingent gating of gap junction channels containing two ‘fast’ gates sensitive to transjunctional voltage. Biophysical J. 96:3936-48). We also thank a graduate student at the Kaunas University of Technology (Lithuania), Saulius Vaiceliunas, who was working side-by-side with PhD student Nerijus Paulauskas in designing this page when he was visiting my laboratory at Albert Einstein College of Medicine during the winter semester of 2010-11.

I cordially thank my closest colleagues/collaborators, Dr. Michael Bennett and Dr. Vytas Verselis, for highly valuable and enjoyable discussions on voltage gating of GJ channels and hemichannels that stimulated these studies.

Finally, I thank Dr. Luc Leybaert for his kind suggestion to use the list of e-mail addresses of approaching conference in Ghent to distribute this information among members of Gap Junctional Community.

Sincerely,

Feliksas Bukauskas