

Stochastic dynamics in biological ion channels

Tuesday, September 5, 2017 4:00 PM (30 minutes)

The passage of ions through biological cell membranes [1] is essential for life at all levels. It occurs via ion channels through proteins embedded in the membrane, and involves Brownian motion under the influence of powerful electrostatic forces. The permeation process is highly selective, e.g. in valence selectivity a calcium channel selects Ca^{2+} over Na^+ by up to 1000:1. There is still no general agreement on the physical mechanism(s) underlying selectivity, but it is known to be associated with fixed negative charge Q_f in a narrow part of the channel called the selectivity filter. There are persuasive arguments [2] that valence selectivity arises from ionic Coulomb blockade (ICB), a phenomenon that is closely analogous to electronic Coulomb blockade in semiconductor devices such as quantum dots and which gives rise to distinct conduction bands and stop-bands as Q_f is varied. We report the first systematic tests [3] of the ICB picture based on experimental, analytical and numerical investigations of the influences of the fixed charge and bulk ionic concentrations on conduction and selectivity in the bacterial NaChBac channel and its mutants. Site-directed mutagenesis and voltage clamp recordings were used to investigate its $\text{Na}^+/\text{Ca}^{2+}$ selectivity, divalent blockade and anomalous mole fraction effect (AMFE). We show that an enhanced ICB model can describe well both the main experimental observations (divalent blockade and AMFE) and the results of Brownian dynamics simulations including the conduction bands and concentration-dependent shifts of the Coulomb staircase of channel occupation. We take account of multi-ion effects, the discreteness of the ionic energy levels, their occupation statistics, and the density of states in the channel, and we consider a generalisation of the theory to encompass selectivity between alike charges [4,5]. These results are not only extending the understanding of ion channel selectivity but also promise applications to biomimetic nanopores with charged walls.

[1] J. Zheng and M. C. Trudeau (eds.), *Handbook of Ion Channels*, CRC Press, Boca Raton, 2015.

[2] I. Kh. Kaufman, P. V. E. McClintock, and R. S. Eisenberg, "Coulomb blockade model of permeation and selectivity in biological ion channels", *New J. Phys.* **17**, 083021 (2015).

[3] I. Kh. Kaufman, O. A. Fedorenko, D. G. Luchinsky, W. A. T. Gibby, S. K. Roberts, P. V. E. McClintock, and R. S. Eisenberg, "Ionic Coulomb blockade and anomalous mole fraction effect in the NaChBac bacterial ion channel and its charge-varied mutants", *EPJ Nonlinear Biomed. Phys.*, in press (2017).

[4] D. G. Luchinsky, W. A. T. Gibby, I. Kh. Kaufman, D. A. Timucin, and P. V. E. McClintock, "Statistical theory of selectivity and conductivity in biological channels", *arXiv preprint arxiv:1604.05758* (2016).

[5] W. A. T. Gibby, D. G. Luchinsky, I. Kh. Kaufman, A. Ward, and P. V. E. McClintock, "Kinetic model of selectivity and conductivity of the KcsA filter", *International Conference on Noise and Fluctuations*, IEEE, doi 10.1109/ICNF.2017.7985935 (2017).

Primary author: MCCLINTOCK, Peter (Department of Physics, Lancaster University)

Co-authors: LUCHINSKY, Dmitri (Department of Physics, Lancaster University); KAUFMAN, Igor (Department of Physics, Lancaster University); FEDORENKO, Olena (Department of Biomedical and Life Sciences, Lancaster University); EISENBERG, Robert (Department of Molecular Biophysics, Rush University, Chicago); ROBERTS, Stephen (Department of Biomedical and Life Sciences, Lancaster University); GIBBY, William (Department of Physics, Lancaster University)

Presenter: MCCLINTOCK, Peter (Department of Physics, Lancaster University)

Session Classification: Session 7