It may seem that our problem is made more difficult by dealing with a biological system that may be complex and unknown. However, biological systems often exploit a single set of physical conditions to produce a robust input output relation. In bio-speak, evolution often discovers adaptations to produce a given function. Some properties of some important ion channels are in this category. In a series of some 40 papers (reviewed in [7], a model and approach introduced by Nonner and Eisenberg [32, 33] has been shown to describe the selectivity properties of three distinct ion channels of considerable importance, the $Ca_V$ channels that control the heart beat, the $Na_V$ channels that produce signaling in the nervous system, and the RyR channel that is the final common pathway controlling calcium signaling in nearly all cells, including cardiac and skeletal muscle. In the calcium and sodium channels a single model with three adjustable parameters, never adjusted in value, can account for the quite different selectivity properties in solutions of many monovalent and divalent cations over some 6 orders of magnitude of concentration, including mixtures. Crystal radii of ions are used and are never changed. The same set of parameter describe the quite different properties of sodium channels with selectivity sequence of amino acids DEKA = asp glu lys ala and calcium channels with selectivity sequence of amino acids EEEE=glu glu glu glu. The sodium vs. potassium selectivity of the DEKA channel arises automatically without adjustment of anything in this model, as the result of the depletion of potassium ions in the selectivity filter of the channel. The sodium vs. potassium selectivity is in fact set by ORTHOGONAL control variables in this model: the diameter of the channel controls the selectivity ONLY. (Diameter has no effect on the total ionic content of the channel.) The dielectric coefficient of the protein controls the the total ionic content of the channel. (The dielectric coefficient has no effect on the selectivity of the channel.) One could hardly imagine a simpler or more robust model. The model fits the selectivity properties of both types of channels over an enormous range of conditions and so it seems that it captures the physics used by evolution (i.e., the adaptation) to create the selectivity of these important channels. The RyR channel has been shown mostly by Gillespie et al [2-6, 11-15, 17-19, 40, 42] to be described by a closely related model. In this case current voltage relations have been fit in more than 120 solutions of many types of ions, including mixtures of two and three types of ions, and the results of drastic mutations involving removal of all (~17 molar) permanent charge have been predicted successfully before the experiments were done. The subtle anomalous mole fraction effect was predicted in a range of solutions by Gillespie's analysis before the experiments were done that showed it was there, as predicted within a few per cent.

Recently, the model introduced by Nonner and Eisenberg has been analyzed [8, 21, 24, 25, 29, 31] with the powerful methods of variational analysis using the energy variational approach introduced by Chun Liu [22, 23, 27, 28, 30, 39, 43], more than anyone else. These methods provide a mathematical foundation for the computational extension of the

Nonner/Eisenberg model and allow easy computation of the full range of current vs. voltage vs. time phenomena observed in ion channels [9, 21, 24], without the complexities and ambiguities of the more intuitive PNP-DFT [1, 10, 11, 14-16, 20, 26, 34-38, 41] theory used earlier.

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