Reduced Models of Calcium and Sodium Channels

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My collaborators and I have developed **reduced models** of channel function that allow computation of channel properties in the actual ionic conditions used in experiments. These reduced models at first received appropriate criticism and were met with skepticism (including from the authors of these models) because they include so little atomic detail.

This skepticism has declined (for three channel types) in the face of nearly 40 papers showing that these very simple models can ***quantitatively*** deal with the selectivity of the L type calcium channel, the voltage activated Na^+ channel, and the Ryanodine Receptor. Each of these channel types has received enormous experimental attention (hundreds of papers on each type; as seen in a Google Scholar Search) because they control the heart beat (L type calcium channel), signaling in nerve (Na^+ channel), and contraction in skeletal and cardiac muscle (Ryanodine Receptor).

In a particular success, a model with only two adjustable parameters can account for all the binding properties of the L type calcium channel in solutions of many types of ions, over concentration ranges of 10^{-7}M to 1 M using crystal radii of the ions and parameter values that are never changed.[1, 2] Amazingly (to the surprise of the authors) the same model and same parameters can account for the very different properties of the Na channel if the side chains of the channel protein are changed from EEEA (Ca channel) to DEKA (Na channel)[1, 2]. **No parameters are changed, yet the model changes properties entirely with this mutation,** just as the real channel is known to change.

The model is so successful we think—but we have not proven this yet—because the structure of the binding site of side chains and ions changes dramatically as bathing solutions change.

In each bathing solution, Monte Carlo and density functional methods capture the ensemble of structures that form the Boltzmann distribution at lowest free energy. **The binding site is self-organized into this structure; the binding site has an induced fit appropriate for these conditions [3, 4]**. The model is the ultimate version of the induced fit model of Koshland, in its modern formulation including protein motion (entropy) [5-12]. The only determinant of biological function in the model, and perhaps in some real channels, is the induced fit of the side chains, including their flexibility (i.e., entropy), and the thermodynamic driving forces.

Just as importantly, reduced models of the Ryanodine receptor [13-20] are able to account for current voltage relations in a large range of solutions and conditions with just a handful of parameters, never changes as solutions changed. The reduced models are particularly convincing because they predicted the existence of an anomalous mole fraction effect AMFE before it was measured, and of effects of drastic mutations of the chemical

nature of the channel protein, namely removing four acidic (i.e., negative) side chains and replacing them with neutral side chains.

Other laboratories working on selectivity have now adopted reduced models of different types and flavors to be sure, but all compute a small fraction of all the atoms in the protein.[21-33]

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