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Ion selectivity in the ryanodine receptor and other calcium channels.

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Biological ion channels passively conduct ions across cell membranes, some with great specificity. Calcium channels are selective channels that range in their Ca^{2+} affinity depending on the channel's physiological role. For example, the L-type calcium channel has micromolar affinity while the ryanodine receptor (RyR) has millimolar affinity. On the other hand, both of these channels have the chemically-similar EEEE and DDDD amino acid motifs in their selectivity filters. An electrodiffusion model of RyR that reproduces and predicts >50 data curves will be presented. In this model, ions are charged, hard spheres and the chemical potential is computed using density functional theory of fluids. Ion selectivity arises from a competition between the need for cations to screen the negative charges of the channel and the crowding of ions in the tiny space of the channel. Charge/space competition implies that selectivity increases as the channel volume decreases (thereby increasing the protein charge density), something that has recently been experimentally confirmed in mutant channels. Dielectric properties can also increase selectivity. In Monte Carlo simulations, Ca^{2+} affinity is much higher when the channel protein has a low dielectric constant. This counterintuitive result occurs because calcium channel selectivity filters are lined with negatively-charged (acidic) amino acids (EEEE or DDDD). These permanent negative charges induce negative polarization charge at the protein/lumen interface. The total negative charge of the protein (polarization plus permanent) is increased, resulting in increased ion densities, increased charge/space competition, and there in increased Ca^{2+} affinity. If no negative protein charges were present, cations would induce enough positive polarization charge to prevent flux.