Hindered convection-diffusion model of ion transport through nanometer-sized gap-junction biological pores

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Gap junctions are ubiquitous pores, roughly 1– 2 nm in diameter and 16 nm in length, that directly connect the interiors of neighboring cells and are responsible for the transfer of ions, small molecules and metabolites up to molecular weights of about 1.2kDa. They are key to normal intercellular molecular exchange and communication in tissues throughout the body. Defects in the proteins of which they are composed are responsible for a number of well-documented diseases, including cataract and deafness. Studies of electrical conductance, and intercellular transfer of fluorescent dyes and some natural metabolites, have revealed marked selectivity of these channels in both electro-migration of different ions driven by a voltage drop, and diffusion of different permeant molecules driven by a concentration difference. Although some of this selectivity derives from interactions with the pore related to size and charge of the permeant molecule, recent studies [1] have suggested that other types of interactions dependent on molecular structure are also critically important. This is an area where application of hindered diffusion theory at the pore scale can provide important insights into the underlying mechanisms of molecular interaction with the pore wall that influence transport. It will have high impact in advancing basic biological understanding, and ultimately, the understanding and treatment of certain disease states.

As a first step in developing a comprehensive permeability model, we report the development of a new theoretical model describing ion transport through gap junctions driven by a voltage drop. A realistic axisymmetric pore geometry, incorporating details of the observed double hourglass shape, is constructed using data on amino acid sequences and topology [2] together with latest determinations of the three-dimensional configuration of the protein domains lining the pore [3]. Our formulation of the governing equations, comprising coupled Poisson and convection-diffusion equations, addresses important phenomena not fully considered to date, including significantly hindered in-pore ionic mobility, as well as the fact that different fractions of the pore cross-section are geometrically excluded for ions of different sizes, making for a radially inhomogeneous electrical potential distribution inside the pore. A robust approximation to the solution of these equations is obtained via a regular perturbation procedure based on gradual variations in diameter progressing along the pore. Our model can incorporate the effects of charges on residues lining the pore, or in close proximity to it. The model is tested, and mechanistic conclusions are drawn, by assessing the match between calculated single-channel conductances with known experimental unitary conductances and ion selectivities for a number of specific gap junctions, including Cx43 pores, which occur in heart, brain and other tissues.

[1] Weber et al. (2004). *Biophys. J.* **87(2)**, 958-973.
[2] Skerrett et al. (2002). *J. Cell Biol*. **159(2)**, 349-359.
[3] Fleishman et al. (2004). *Molecular Cell* **15(6)**, 879-888.