Multi-scale Modeling of Gas Transport through Channels in Living Cells

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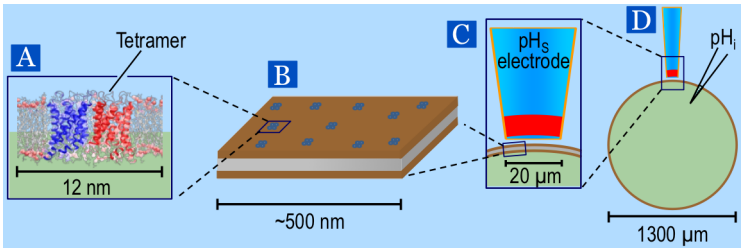
In this project, we develop a multi-scale model—at microscopic, mesoscopic, sub-macroscopic and macroscopic levels—to describe the movement of gases across cellular membranes, via either lipid phase of the membrane or protein "gas channels" embedded in the membrane. The result could be unprecedented insight into the pathways and mechanisms of gas transport across membranes, which would be invaluable for understanding both normal human physiology and pathogenesis of numerous diseases.

FIG 1. MULTI-SCALE ANALYSIS OF GAS TRANSPORT



At the **microscopic scale** (Fig 1A), we have employed extensive molecular dynamics simulations (explicit ligand sampling, implicit ligand sampling, umbrella sampling, and *in silico* mutagenesis) to characterize the permeability of O_2 and CO_2 across biological membranes. The impact of lipid composition of gas permeation was studied by simulation of lipid bilayers composed of various degrees of glycerolphospholipids, cholesterol, and sphinogomyelins, which are major constituents of mammalian membranes. The results show that membrane lipid composition modulates the permeability of nonpolar gases. We have also studied gas permeability of membrane-embedded tetrameric aquaporin (AQP) water channels, revealing how these membrane channels mediate permeation of gases—via the four monomeric pores and the central pore—with different degrees of selectivity. The simulations allowed for detailed characterization of the microscopic pathways, as well as quantitative description of free energies associated with gas transport and calculation of single-channel gas permeabilities to be used as input parameters in mathematical modeling (below).

At the **mesoscopic scale**, we first are developing a reaction-diffusion mathematical model of a single AQP tetramer and its surrounding lipid membrane. At the extracellular or intracellular face of the membrane, our model can either omit or include carbonic anhydrases—enzymes that catalyze the otherwise extremely slow buffer reaction $CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+$. We then will extend the model to the **full mesoscopic scale** (i.e., many tetramers, Fig 1B).

At the **sub-macroscopic scale** (Fig 1C), we are developing a reaction-diffusion model of the special microenvironment that exists between the cell membrane of the spherical *Xenopus* oocyte and the polished tip of a pH electrode that reports the time course of surface pH (pH_S)—the key physiological data that describe the permeability of the membrane to CO_2. The full mesoscopic model (Fig 1B) describes the gas permeability of the membrane beneath the pH_S electrode (Fig 1C). The boundary conditions for Fig 1C come from the macroscopic model (below, Fig 1D). We solve the reaction-diffusion equations for the sub-macroscopic model (Fig 1C) using the finite element method (FEM) with stiff solvers.

The full mesoscopic model (Fig 1B) also will provide the input to the **macroscopic model** of an oocyte (Fig 1D), at the greatest spatial scale. The pH electrode in Fig 1D reports the time course of intracellular pH (pH_i) at a certain depth in the oocyte. This pH_i record is a secondary piece of physiological data that describes the permeability of the membrane to CO_2. This macroscopic model is in hand.

Finally, we use the physiological pH_S and pH_i data—collected with different pH_S electrode diameters, different distances of the pH_S electrode from the membrane, and different mutants of AQP1 and AQP5—to inform and validate the model.