Accumulation and Depletion near Ion Channels

We investigate the interaction of particle-based models of ion-channels and reduced continuum models of the surrounding baths under physiological conditions. In particular, we study the sensitivity of the main characteristics of the channel (mostly the current-voltage, or I-V, relation) to the size of the bath treated with particle methods and the proximity of the continuum bath to the channel.

We assume a particle-based description of the permeation of the channel—a Brownian dynamics or a Transport Monte-Carlo dynamics of solid charged spheres. With this approach a large ambient bath cannot be resolved using contemporary computing power. Instead, a relatively small portion of the bath is typically treated "microscopically", that is with atomic detail for the ions, using particles. The rest of the bath is treated as a "macroscopic" object described by continuous functions describing the density of each type of ion and the (macroscopic) electrical potential. The densities and electrical potential satisfy a macroscopic Nernst-Planck equation coupled to the Poisson's equation for the electrostatic potential—the Poisson-Nernst-Planck equation (PNP). The boundary conditions are applied at the edge of this macroscopic bath and the interface between the "macroscopic" and "microscopic" baths. It is this coupling that is of interest to us.

Typically, particle control mechanisms (injection and removal protocols) are used to implement the boundary conditions for a particle simulation of the channel \cite{}. It is well-known, at least in the case of uncharged point particles, that the typical controls produce spurious boundary layers on the microscopic side of the micro/macro interface \cite{}. The effect of these spurious inhomogeneities on the behavior of the channel has not been quantified. The boundary layers of **un**charged systems disappear away from the interface and the concentrations approach the intended boundary values. It is assumed that placing an interface sufficiently far from the channel reduces undesirable effects of the interface to 'zero'. This assumption is reasonable for uncharged particles but is unreasonable for charge particles because even one particle changes the electrical potential substantially.

We seek to quantify how such spurious phenomena affect the I-V characteristics of the channel obtained from the simulation. The effects are quantified as a function of the size of the microscopic bath, the method of coupling across the macro/micro interface, and the precise macroscopic model actually used (e.g., PNP or PNP/DFT). In the simplest case the macroscopic bath can be treated as a resistor and a battery, the resistor representing the conductance of the bath and the battery representing the

chemical potential associated with the number density of the ion. This description is a particular limit of the PNP equations. In this case the particle control will implement a general Robin-type boundary condition by appropriate injection and removal of particles at the interface. We investigate the limits of validity of such a model THE MODEL HAS TO BE DESCRIBED PRECISELY IN MATHEMATICAL DETAIL SOMEWHERE by comparison to an all-particle simulation of a charged channel of simple structure (i.e., geometry). The all-particle simulation will include a sizable ambient bath with Dirichlet boundary conditions applied at the lateral boundary. This will be compared to a particle simulation of a channel with a small bath coupled to a resistor and battery by a Robin-type boundary condition.

This set up will be used to describe a number of biological systems of considerable significance, namely, K^+, Na^+, and Ca^{2+} channels of (for example) nerve fibers. Each of these channels has function that depends on the change of ion concentration nearby (caused by current flow through the channel), but the dependence is very different because the concentrations of the permeable ions is very different in biological systems.

	Na^+	K^+	Ca^{2+}	Cl^-	Comment
	Units: moles/liter				
Outside the cell	1.60×10^{-1}	4.0×10^{-3}	1.5×10^{-3}	1.67×10^{-1}	*Without pH buffer*
Inside the cell	3×10^{-2}	1.37×10^{-1}	5×10^{-7}	1.40×10^{-1}	2.7×10^{-2} *univalent impermeable anions make inside electroneutral*

$\underline{\textbf{Na}^\pm \ \textbf{Channels}}$ of nerve cells typically carry current inwards from $[Na^+]_{out} = 1.60 \times 10^{-1}$ M to $[Na^+]_{in} = 3 \times 10^{-2}$ M. During a single action potential, or for voltage clamp pulses < 5 msec, the current flow does not significantly change the intracellular or extracellular concentrations, so the baths behave 'ideally' whether one is dealing with a single channel or many channels in parallel. During trains of (repeated) action potentials, or during prolonged pulses of Na^+ channels that have been modified so they do not turn off spontaneously (i.e., do not 'inactivate'), the concentrations can change ~1×10^{-2} M.

$\underline{\textbf{K}^\pm \ \textbf{Channels}}$ of nerve cells typically carry current outwards from 1.37×10^{-1} M to 4.0×10^{-3} M. The macroscopic current densities (from all the channels in a macroscopic patch of membrane) are nearly equal to the Na^+ currents mentioned above so the change

in concentration on the outside (for example) is $160/4 = 40\times$ more important for $[K^+]_{out}$ than for $[Na^+]_{in}$ Thus, significant changes of $[K^+]_{out}$ occur during single action potentials or voltage clamp pulses < 5 msec. Trains of action potentials or longer voltage clamp pulses can produce dramatic effects on $[K^+]_{out}$. These effects are intimately involved with epilepsy and so models are of considerable interest.

Ca^{2+} channels typically conduct current from outside where $[Ca^{2+}]_{out} = 1.5 \times 10^{-3}$ M to inside where $[Ca^{2+}]_{in} = 5 \times 10^{-7}$ M. The current is somewhat smaller than Na^+ currents thus changes in $[Ca^{2+}]_{in}$ are $(3 \times 10^{-2})/(5 \times 10^{-7}) = 6\times10^4$ more important than changes in $[Na^+]_{in}$. Indeed, currents through ensembles of Ca^{2+} channels always produce significant even dramatic changes in $[Ca^{2+}]_{in}$ and so Ca^{2+} channels operate in an environment of changing concentration, whereas the classical treatments (i.e., Hodgkin Huxley) of Na^+ and K^+ channels assume unvarying concentrations of ions.

Notice that the effects of current on concentration depend strongly on the number of channels. Thus effects measured from a single *isolated* channel will be very different from effects measured from an ensemble of channels or from one channel in the presence of an (unperturbed) ensemble of channels.

Each channel type corresponds to a different domain of accumulation/depletion. Thus, each channel type will live in a different domain of the mathematics. This means that a mathematical analysis of each domain will be of immediate biological, medical, and experimental importance.