

ENERGETIC VARIATIONAL ANALYSIS of ions in calcium and sodium channels

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Energy Variational Principle

EnVarA (in general)

$$\frac{\delta E}{\delta x} - \frac{1}{2} \frac{\delta \Delta}{\delta u} = 0$$

Conservative 'force' is a variation of a familiar action integral with respect to position x . Dissipative 'force' is a variation of the Dissipation Functional (defined by Rayleigh and used by Onsager) with respect to velocity u , not position. Variations are taken with respect to different variables written in the same Eulerian framework. Resulting **Euler-Lagrange equations specify the system**. Their solutions satisfy both variational principles simultaneously and **include all interactions of the components of the energy and dissipation**.

The energy variational principle has been used successfully by Chun Liu and his collaborators to analyze solid balls in liquids; deformable electrolyte droplets that fission and fuse [1,2]; and suspensions of ellipsoids, including the interfacial properties of these complex mixtures, such as surface tension and the Marangoni effects of 'oil on water' and 'tears of wine' [1,3,4,5], as well as liquid crystals, polymer fluids [6,7], colloids and suspensions [1,5] and electrorheological fluids [8,9], and magnetohydrodynamic systems [10].

Solid charged spheres like sodium and chloride ions in water seem to be a simpler fluid than deformable fissioning droplets and so we wondered if energy variational methods could help us understand these ionic solutions. We try to create a **FIELD THEORY OF IONIC SOLUTIONS** from an energy variational principle that uses only a few fixed parameters to calculate most properties in flow and in traditional thermodynamic equilibrium, both in bulk and in spatially complex domains like pores in channel proteins.

Variational methods involving dissipation functions give the 'final' time dependence as the system relaxes to equilibrium. A calculation of the response of a sodium channel to a step voltage shows a fast time dependent current **even though the conformation of the channel does not change**. The change in current resembles a gating current but its detailed properties have not yet been studied. Uncertainty also arises because the time scale depends linearly on the actual mobility of ions in channels and that is not well known.

ABSTRACT

Selective binding in calcium and sodium channels can be described (in many solutions and concentrations: Biophys J 2007 93:1960) by the same reduced model with two unchanging parameters (dielectric coefficient and diameter) despite very different primary structure of the two proteins (Ca channel EEEE/EEEE; Na channel DEKA) and properties, even though amino-acid side-chains (E, D, etc.) are represented only as charged spheres. Monte Carlo MC simulations, reported in ~30 publications, work well (we think) because they do not specify structure as an input, independent of conditions. Rather, MC calculates structure as an output, as a self-organized, induced fit of side-chains to ions (and vice-versa). Structure is different in different solutions in self-organized systems.

Self-organized systems can be analyzed using the calculus of variations, **energetic variational analysis (EnVarA)**. We optimize both action and dissipation integrals (*Least Action* and *Maximum Dissipation* Principles), motivated by Rayleigh, then Onsager who optimized just one, or the other. The resulting systems of coupled partial differential equations automatically satisfy the First and Second Laws of Thermodynamics and electrostatic Poisson equations, with physical boundary conditions that can produce flow. **EnVarA** extends Navier-Stokes equations to complex fluids containing deformable droplets (J Fluid Mechanics 2004 515: p.293).

EnVarA provides a seamless extension of conservative Hamiltonian systems to dissipative systems, perhaps at thermodynamic equilibrium. **EnVarA** is a field theory of ions in channels and solutions with entropy, friction, and flow. **EnVarA** computes current where MC computes only binding. **EnVarA** applied to EEEE/DEKA channels gives binding like real calcium/sodium channels. Currents computed with **EnVarA** vary with time although the **EnVarA** model has only one unchanging conformation and the time dependence shows charge storage (i.e., "gating current") and some features of activation and inactivation.

EnVarA

$$E(t) = \int \left\{ \frac{1}{2} \rho |\vec{u}_{IP}|^2 + w(\rho) \right\} d\vec{x}$$

Generalization of Chemical Free Energy

Hydrodynamic Kinetic Energy Hydrodynamic Potential Energy Equation of State

Macroscopic (hydrodynamic)

$$+ \lambda \left[\frac{1}{2} \epsilon |\nabla \phi|^2 + k_B T (c_n \log c_n + c_p \log c_p) + E(\text{Solid Spheres}) \right] d\vec{x}$$

Lagrange Multiplier

Electrostatic Entropy Finite Size Effect

Microscopic (atomic)

Euler Lagrange Equations: Solvent Water Phase

$$\frac{\partial \rho_f}{\partial t} + \vec{u}_f \cdot \nabla \rho_f = 0 \quad \nabla \cdot \vec{u}_f = 0$$

$$\rho_f \frac{\partial \vec{u}_f}{\partial t} + \rho_f \vec{u}_f \cdot \nabla \vec{u}_f + \nabla p_f = M_f \nabla^2 \vec{u}_f + k(\vec{u} - \vec{u}_f)$$

Acceleration Convective Acceleration Pressure Gradient Viscosity Coupling Drag

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\vec{u} \rho) = 0$$

Macroscopic and Atomic Scale Combined

$$\rho \left(\frac{\partial \vec{u}}{\partial t} + \vec{u} \cdot \nabla \vec{u} \right) + \nabla p$$

$$= M \nabla^2 \vec{u} + \overbrace{k(\vec{u} - \vec{u}_f)}^{\text{Coupling Drag}} + \overbrace{(c_n(\vec{x}) - c_p(\vec{x})) \nabla \phi}^{\text{Coulomb Force}}$$

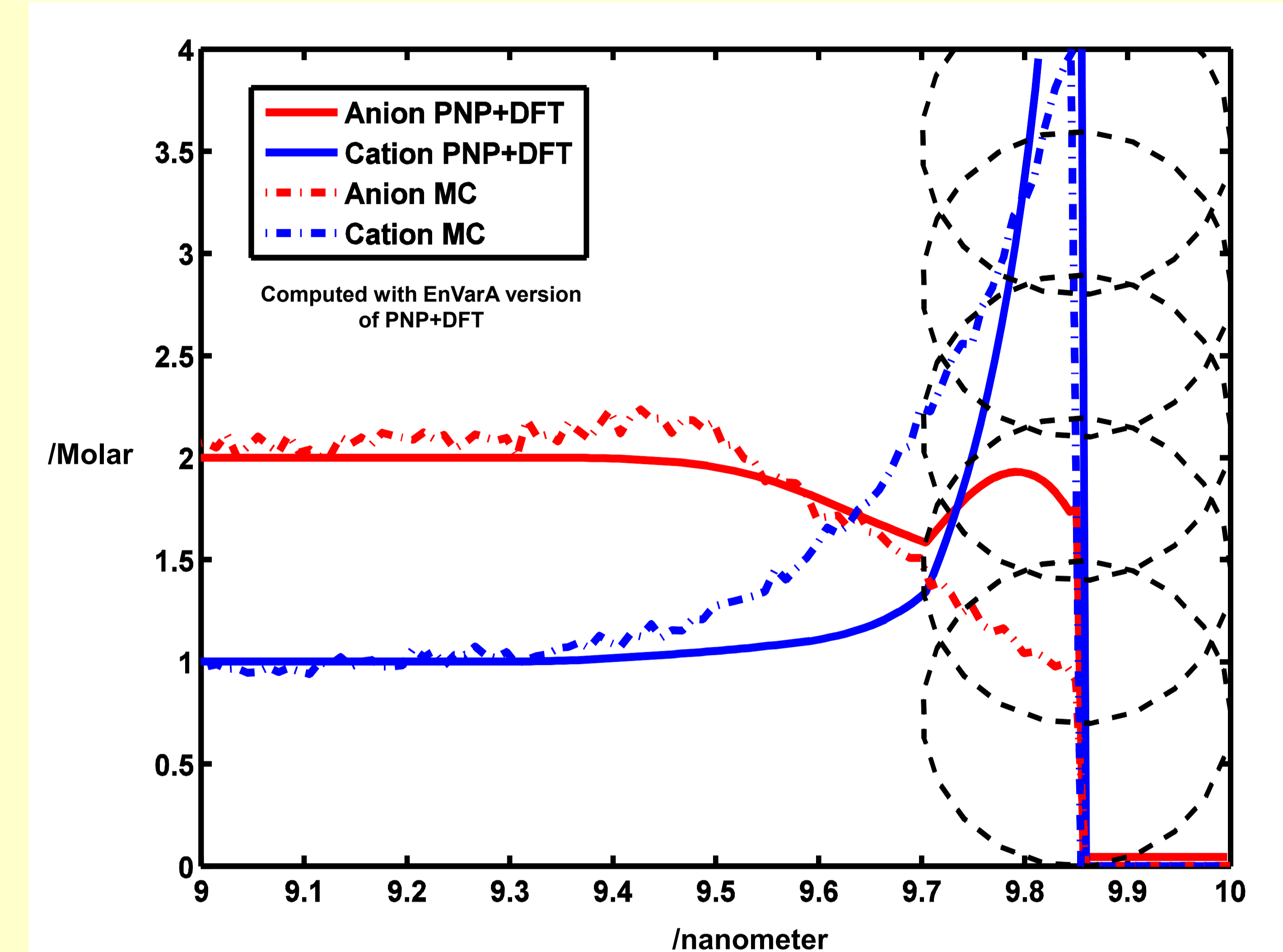
Lennard Jones Solid Sphere

$$\left\{ \begin{array}{l} -c_n(\vec{x}) \nabla \cdot \int \chi(|\vec{x} - \vec{y}|) (c_n(\vec{y}) + \frac{1}{2} c_p(\vec{y})) d\vec{y} \\ -c_p(\vec{x}) \nabla \cdot \int \chi(|\vec{x} - \vec{y}|) (\frac{1}{2} c_n(\vec{y}) + c_p(\vec{y})) d\vec{y} \end{array} \right.$$

$$\chi(|\vec{x} - \vec{y}|) = \epsilon_{i,j} \left(\frac{a_i + a_j}{|\vec{x} - \vec{y}|} \right)^{12}$$

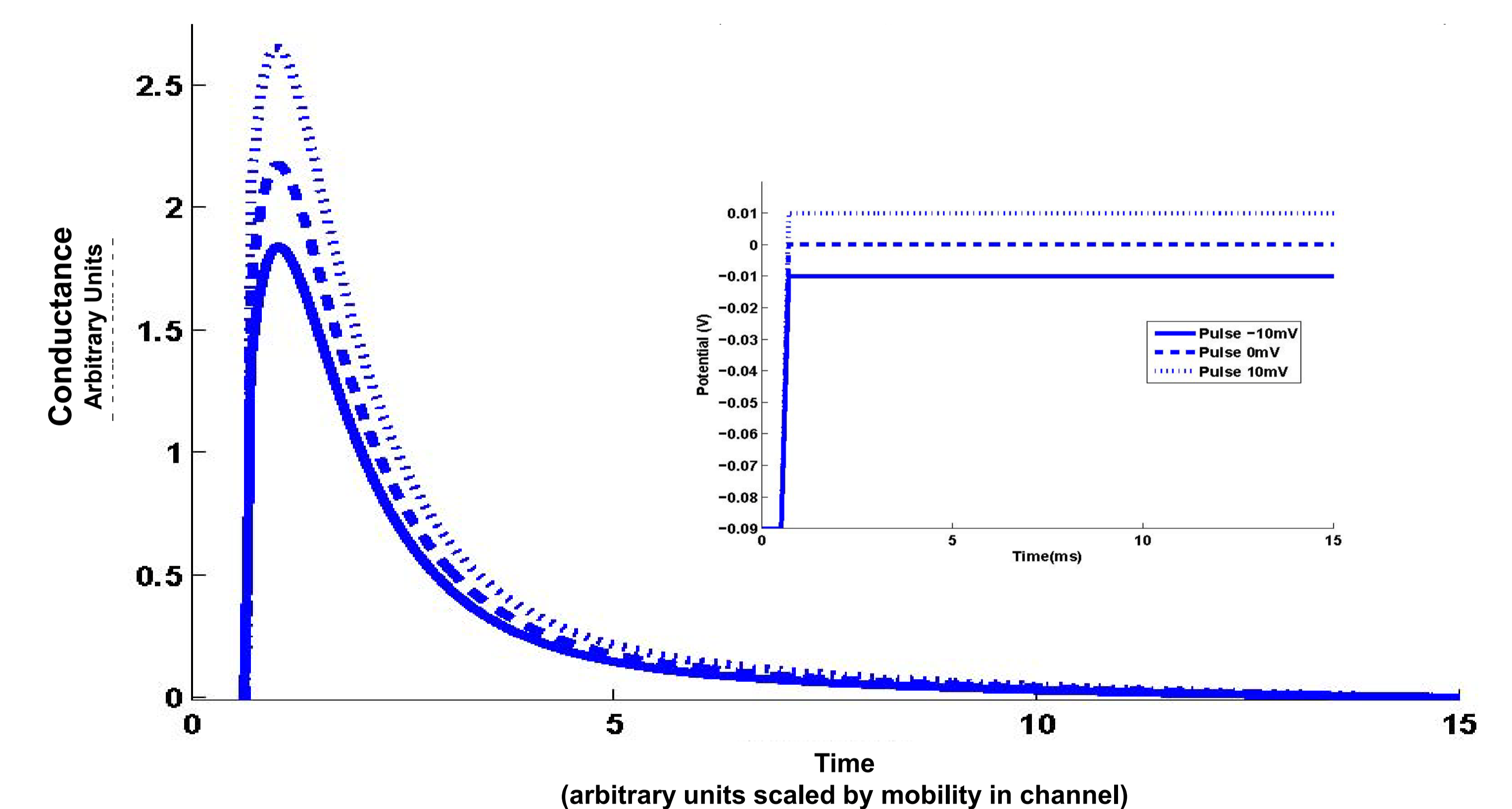
Layering Against Charged Wall

Classical Interaction Effect



Cation 'Ca⁺⁺' 3Å, 1 M; Anion 'Cl⁻' 3Å, 2 M; Charge on Wall = 0.1 C/m²; Dielectric Constant 78

Transient Currents without Conformation Change in voltage clamped channels



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A variational approach to osmotic water flow (and electrodiffusion) was presented by Yoichiro Mori, et al, in Poster 511.