Lecture 4: Variational Approaches to Membrane Transport

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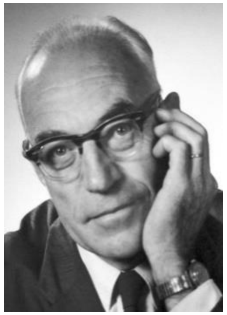
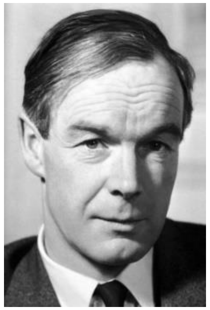
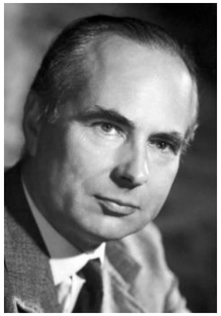
Part of Nobel Prizes on Ion Channels



John Carew Eccles

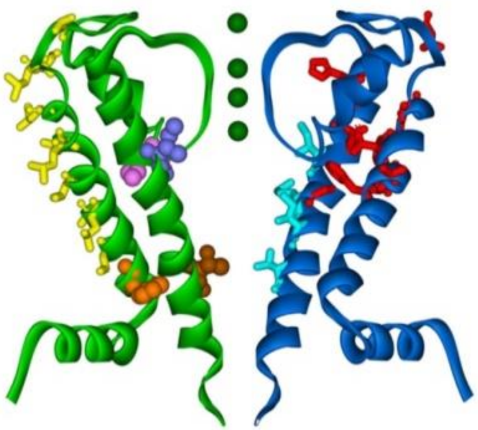


Alan Lloyd Hodgkin



Andrew Fielding Huxley

Nobel prize 1963 (ionic mechanisms)



Roderick MacKinnon

Nobel prize 2003 (Ion channel)

Erwin Neher

Bert Sakmann

Nobel prize 1991 (Ion Channel)

Role of Ion Channels

Acid-sensing ion channel (ASIC) in inflammatory pain hypersensitivity

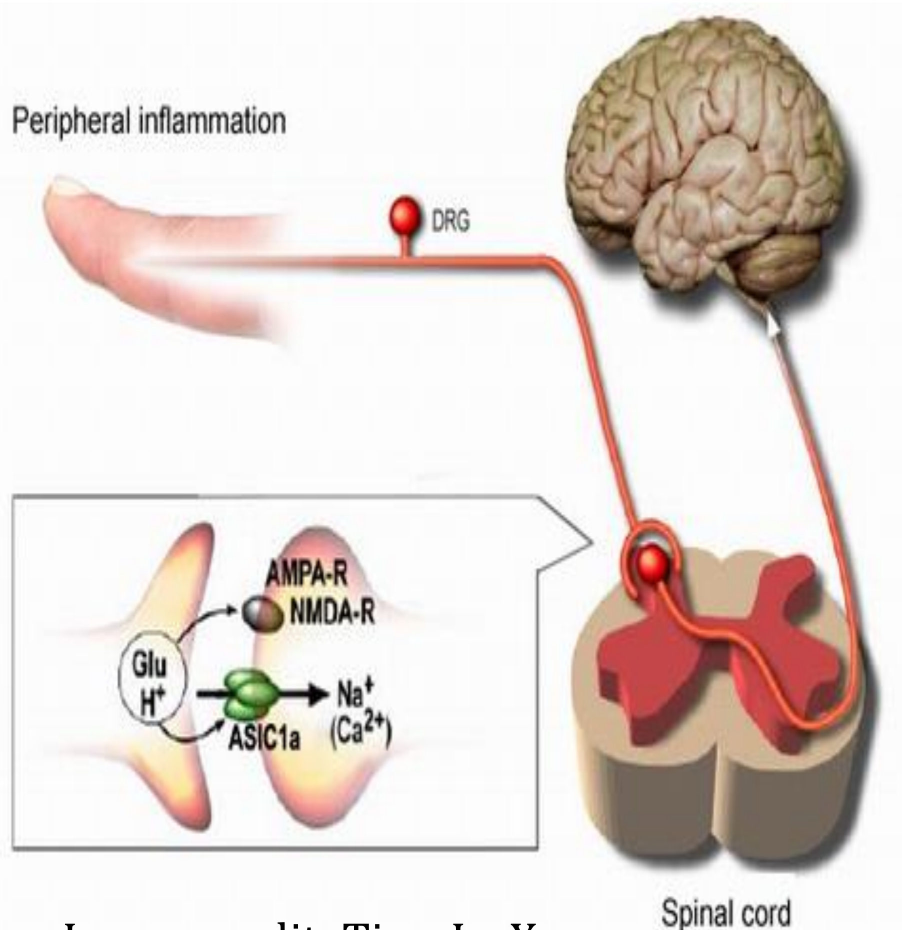
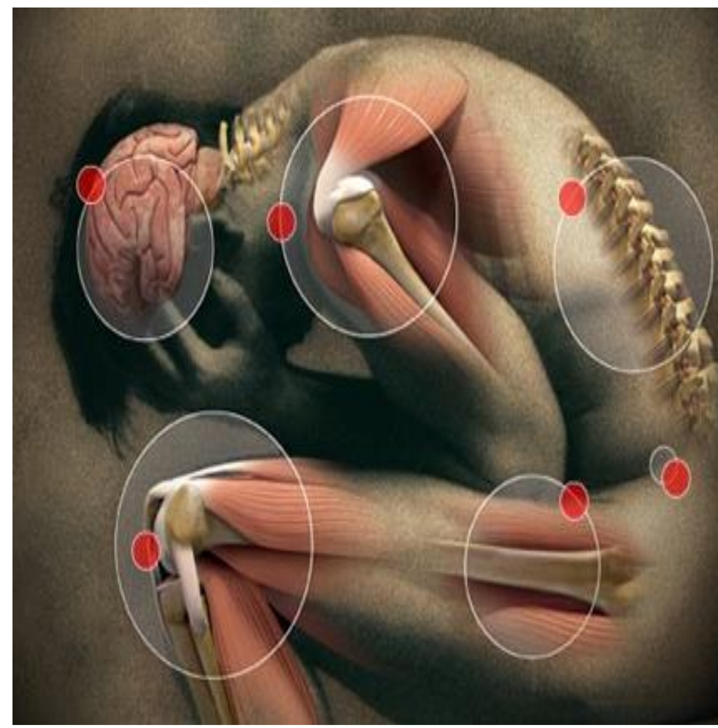


Image credit: Tian-Le Xu

Increased ASIC activity in spinal dorsal horn neurons promotes pain by central sensitization



Role of Ion Channels

The molecular mechanisms of inherited arrhythmia

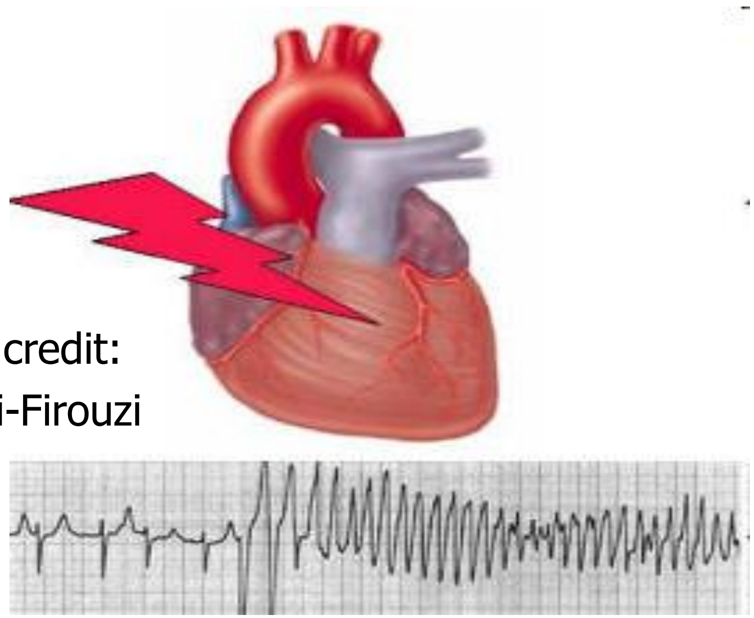
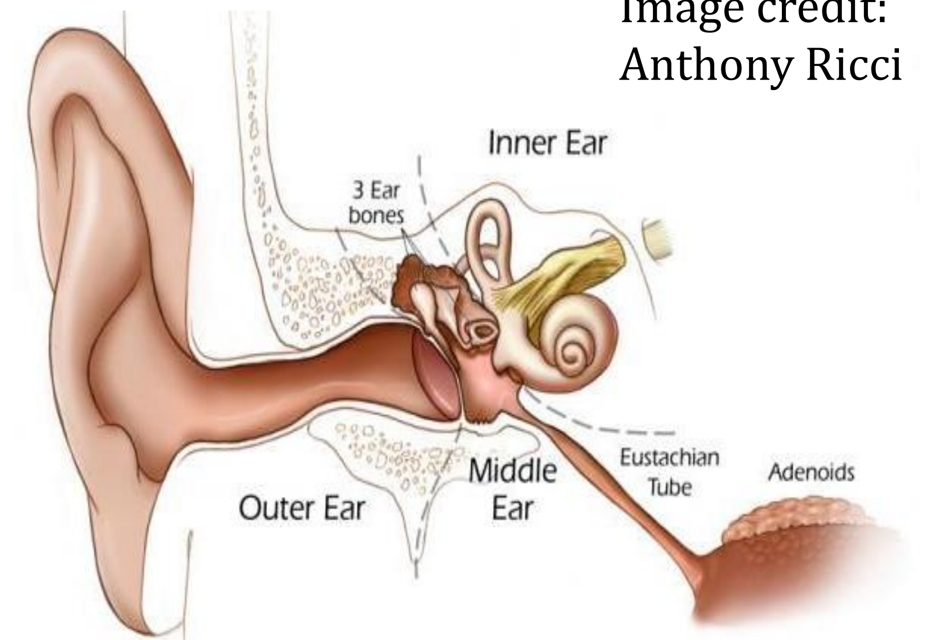


Image credit: Tristani-Firouzi

Mutations in K^+ channel cause a decreased outward K^+ current during the plateau phase of the cardiac action potential, and lead to cardiac arrhythmias and sudden death.

How human ear translates vibrations into sounds: Discovery of ion channel turns ear on its head

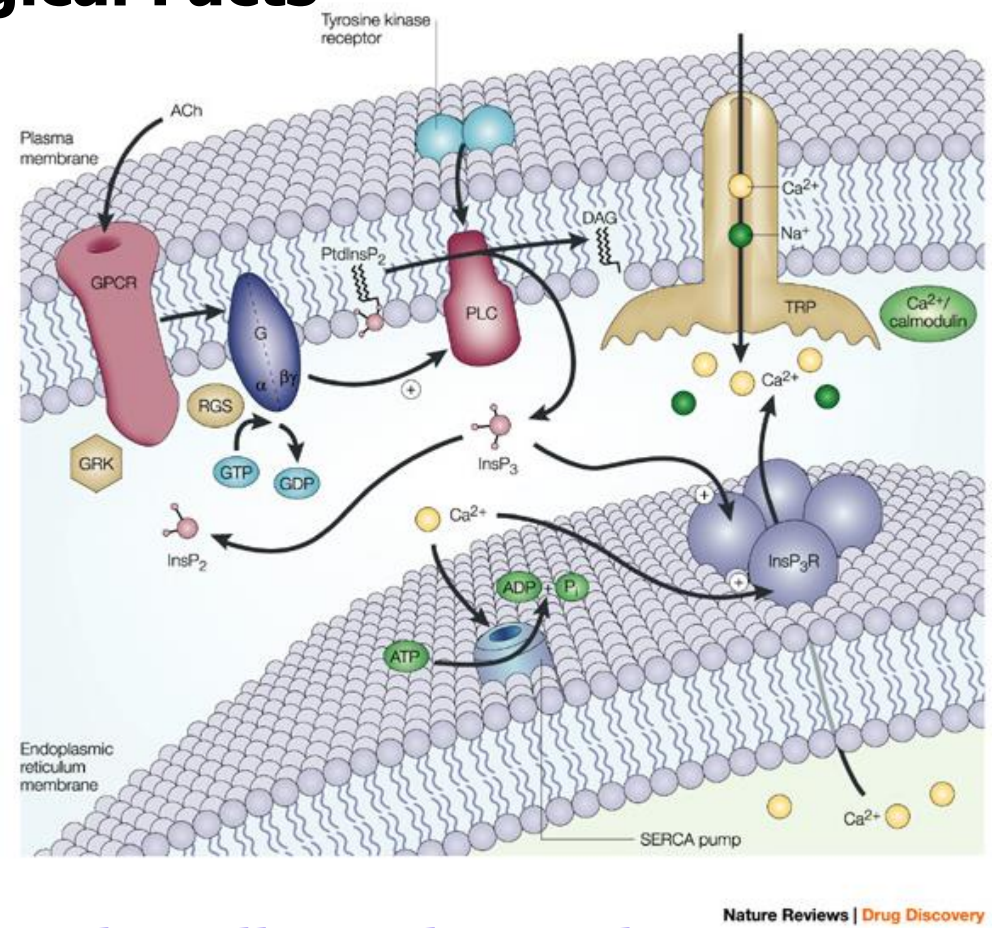
Image credit: Anthony Ricci



Inner hair cell mechanotransducer calcium channels turns sounds into electrical current.

Physiological Facts

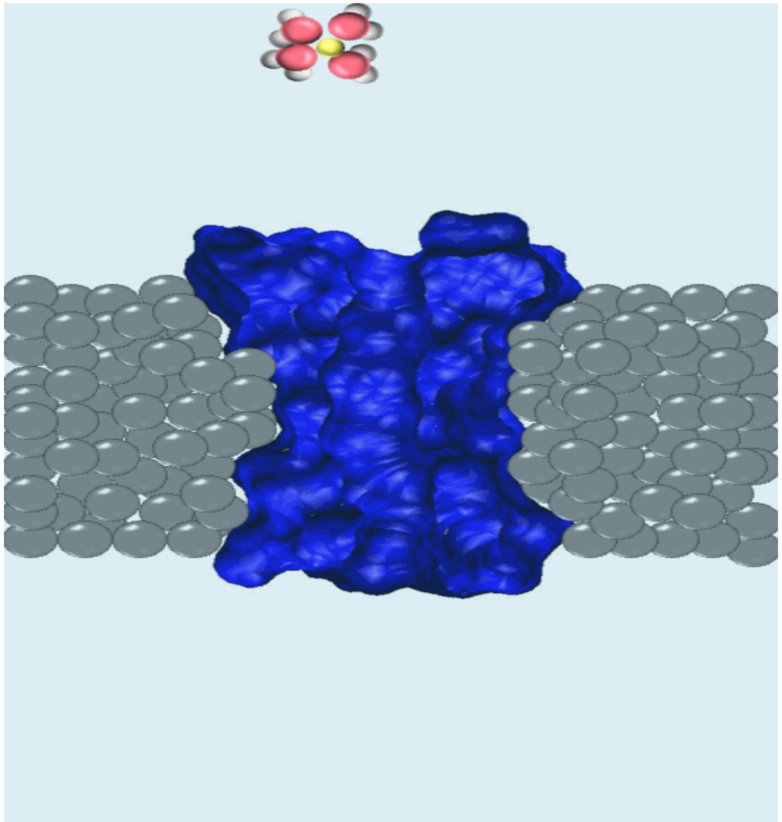
Human beings (and other living organisms) are run by electricity, and ion channels are the core of our electrical system.



- Ion channels are small pores in the cell membrane that permeate ions or water
- Fast rate of transport 10^6 ions/s
- Transport is always down the gradient and non-equilibrium

Ion Channels

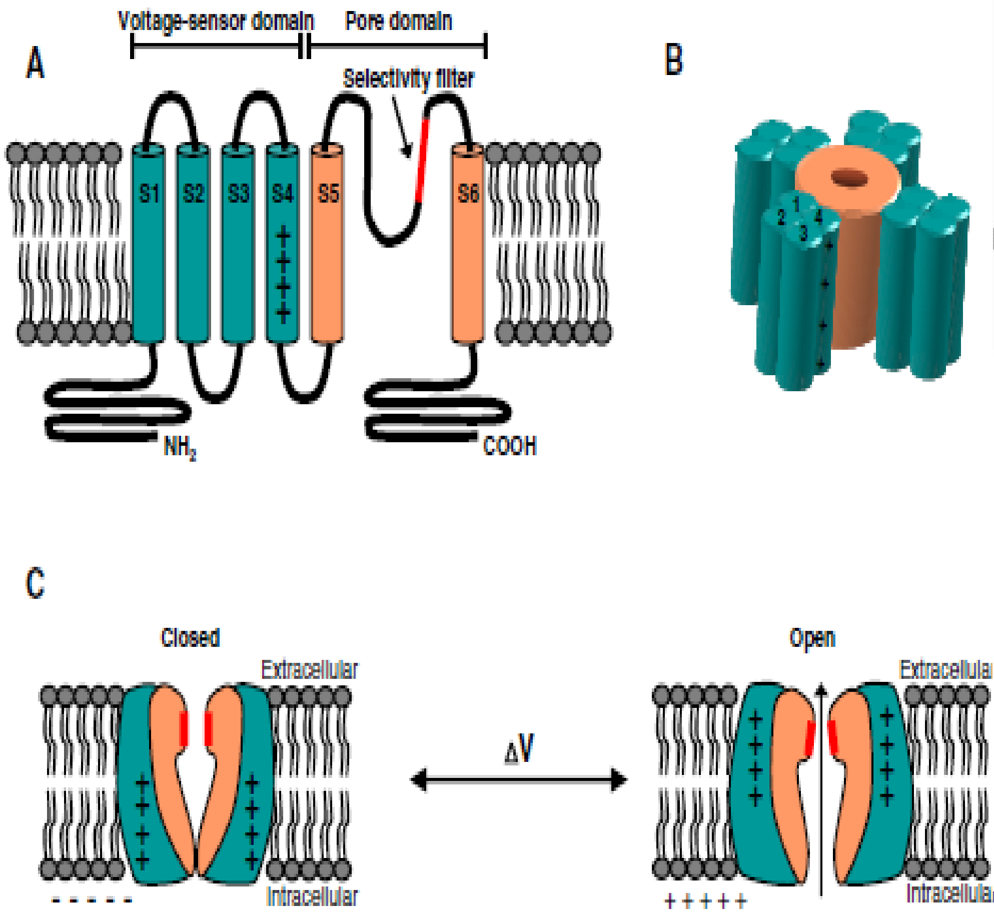
- Ion channels are molecular devices that self-assemble into reproducible arrays.
- Ion channels are highly selective: K channels select K^+ over N_a^+ by $\sim 10^4$.
- Ion channels gate/switch in response to thermal, chemical, photonic, acoustic, and mechanical stimuli.
- Ion channels admit mutation and evolution.
- Ion channels can be used as templates for nano-bio device and sensor design.

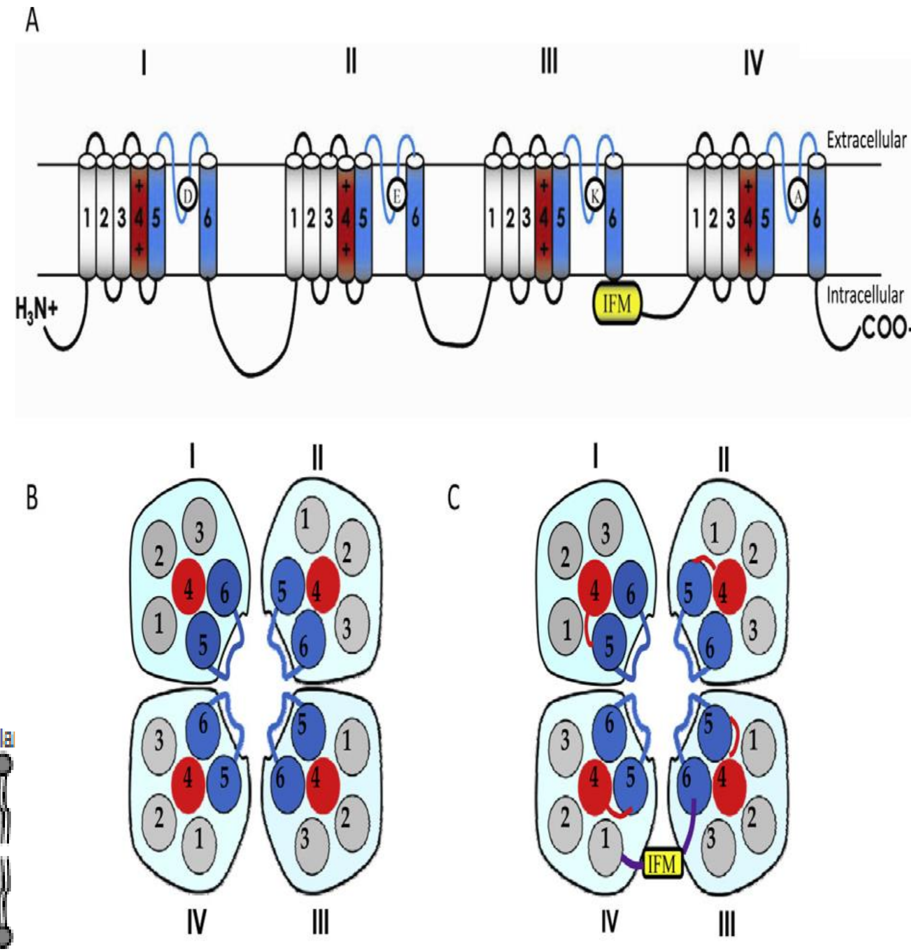


Sodium channels

Voltage sensor domain (VSD) and pore domain of sodium channel

- Structurally, the two domains are independent
- Functionally, energetic coupling of the VSD to the pore domain

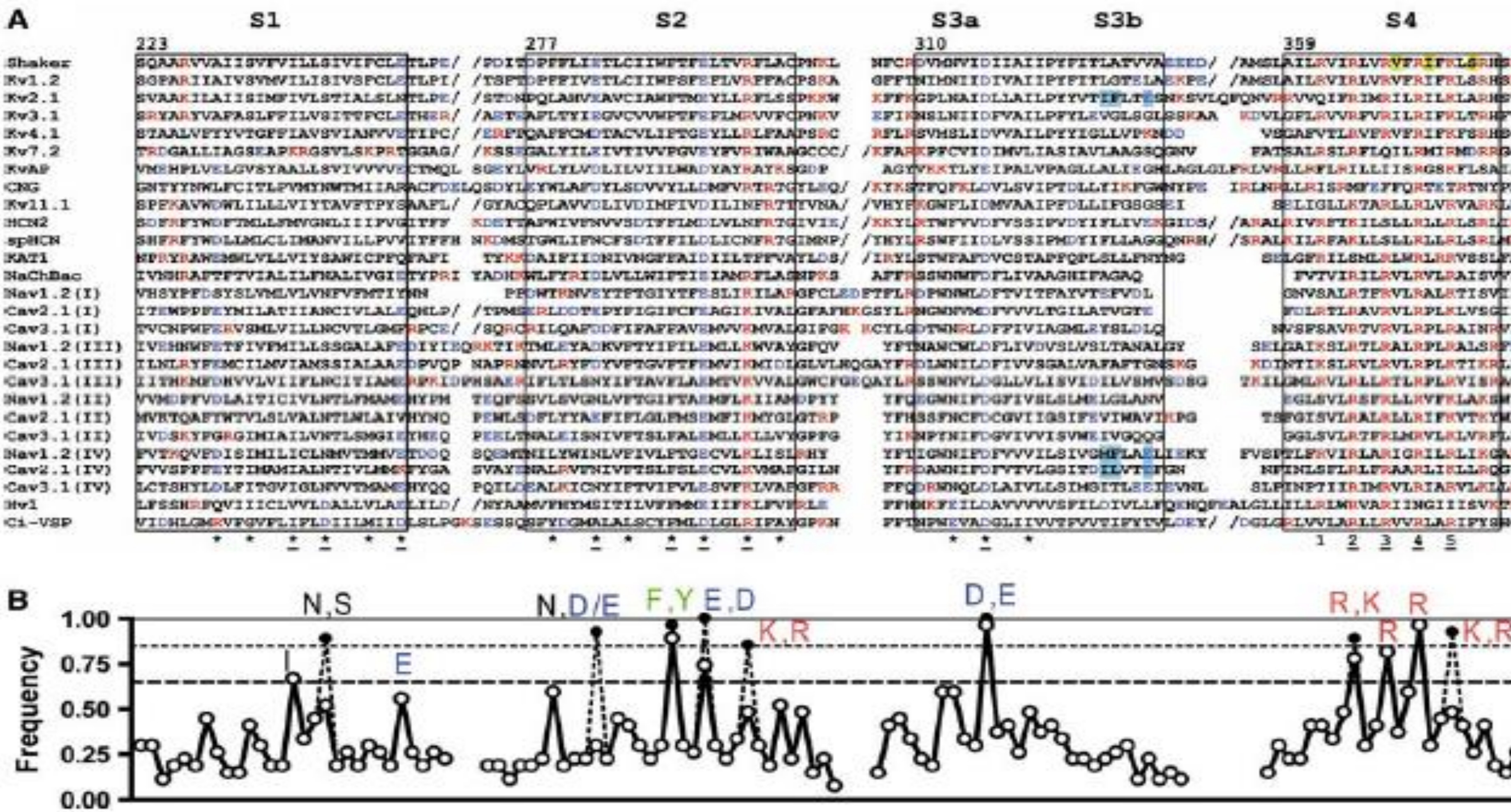




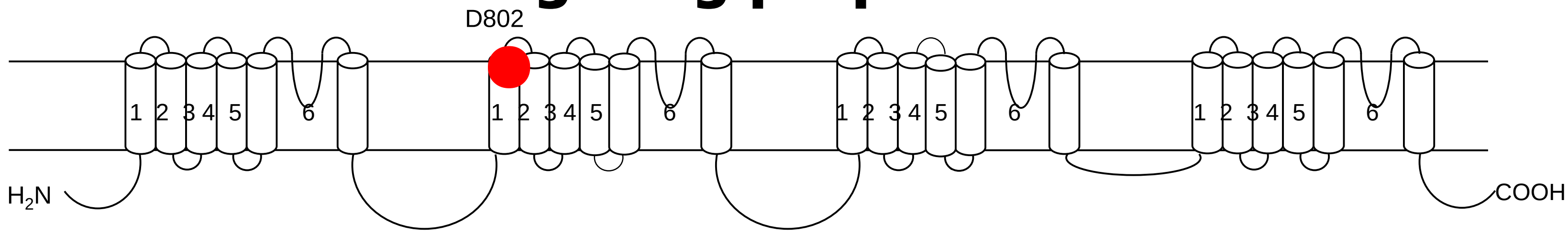
(Dong et al, IBMB, 2014)

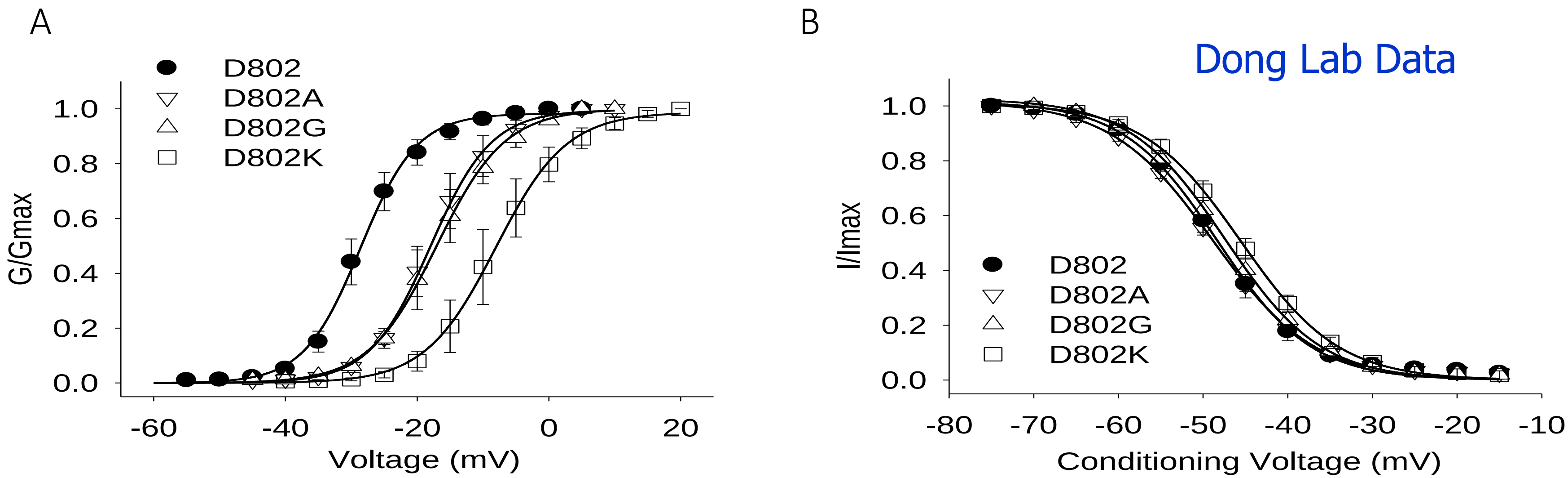
Insect sodium channel sequence analysis

Dong Lab Data

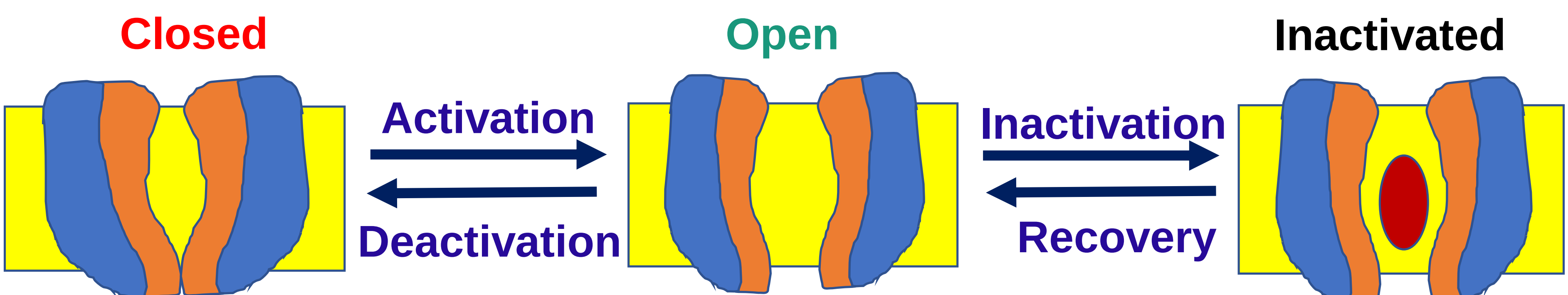


Effects of amino acid substitutions at D802 on channel gating properties



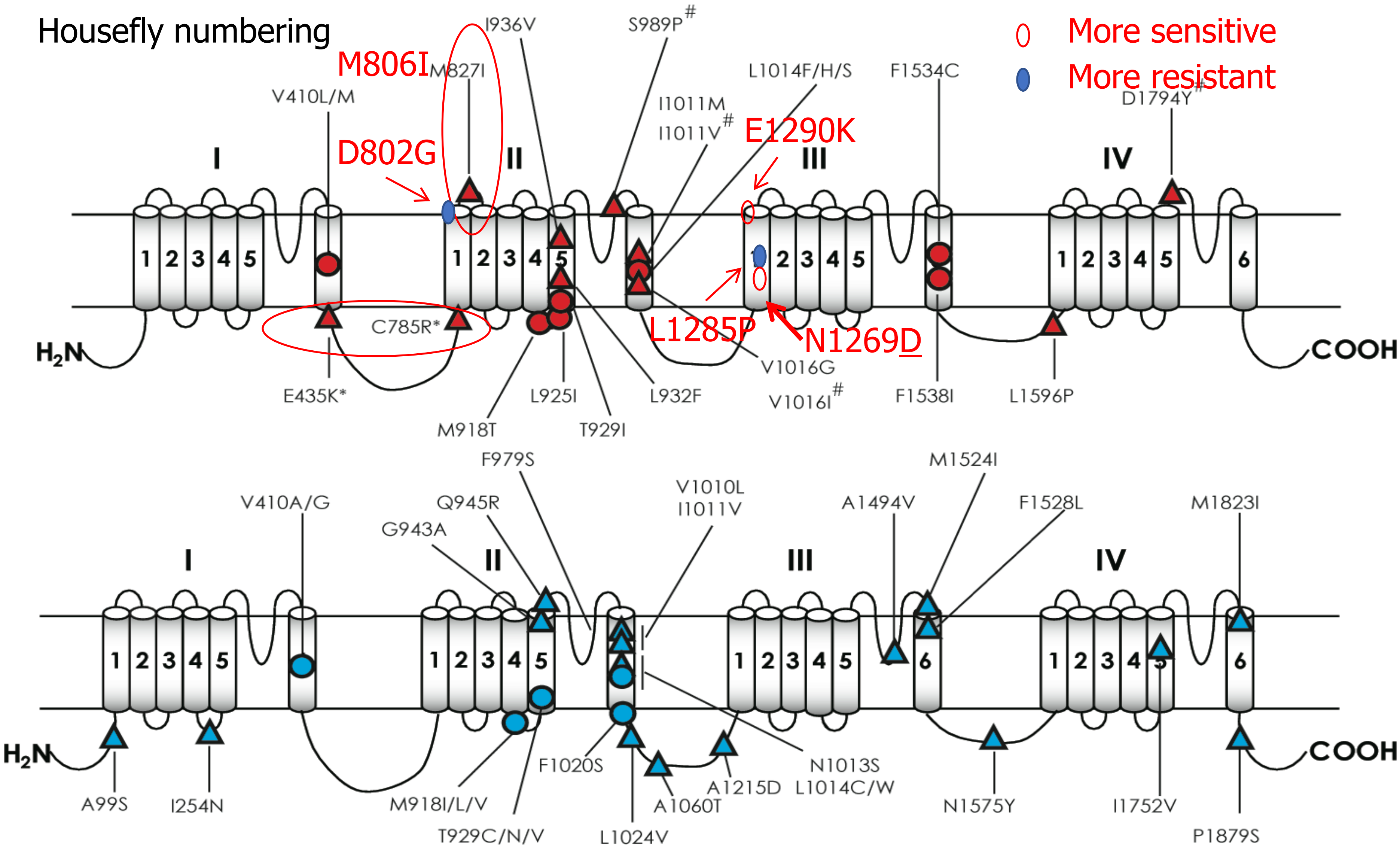


A. Normalized conductance curves. B. voltage dependence inactivation curves.

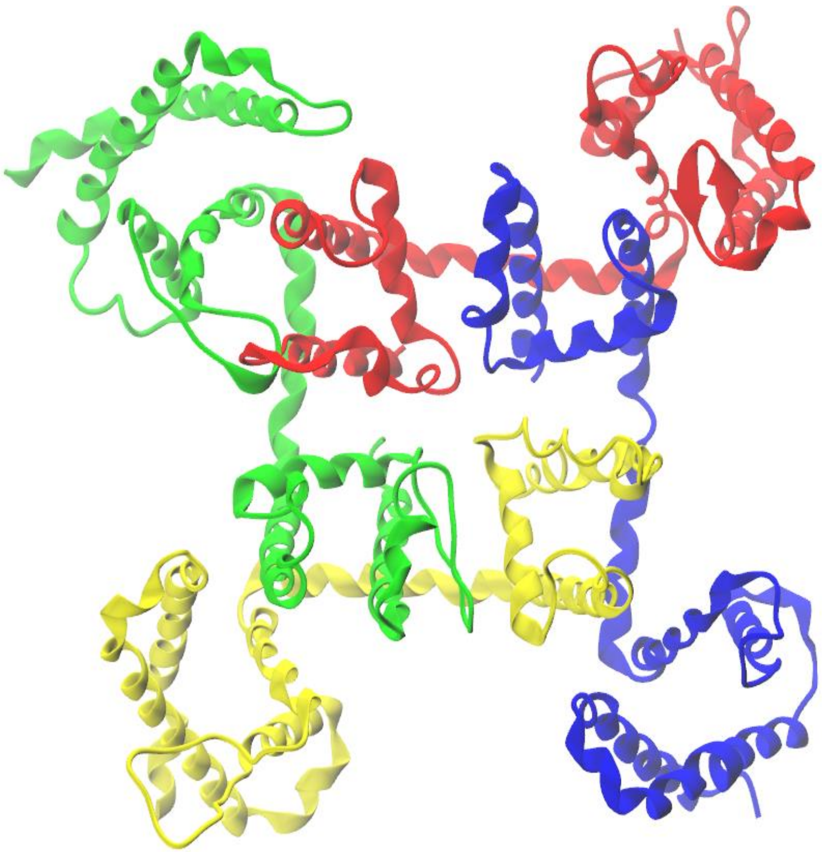


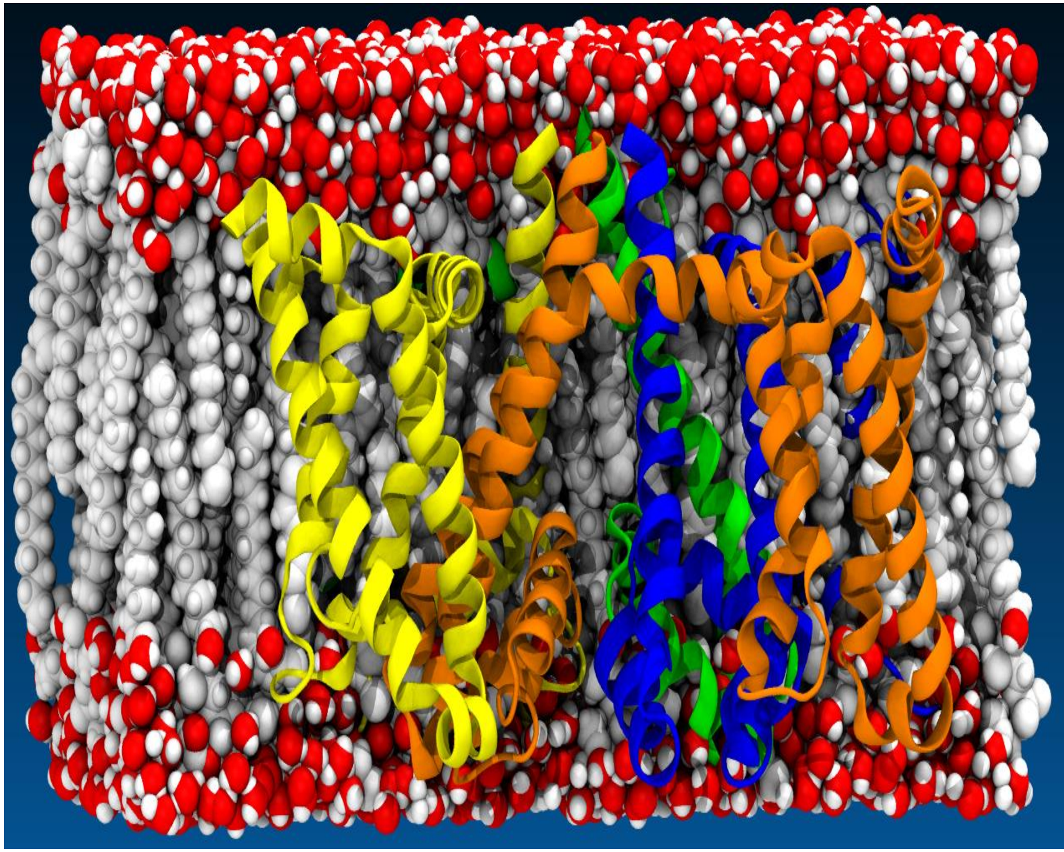
Mutation impact

Dong et al. (2014) IBMB



Homology structure of a sodium channel constructed from a mosquito sequence data



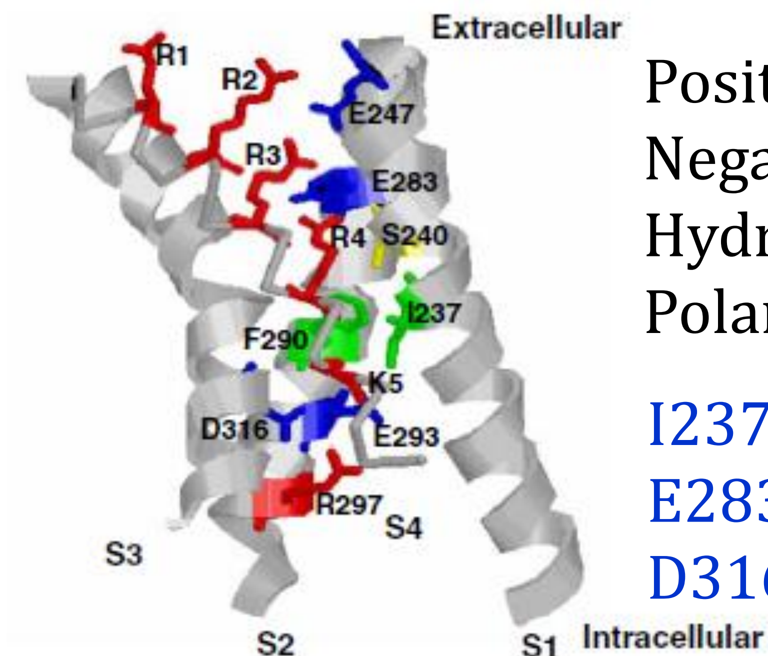


K. Opron

Wei Lab Data

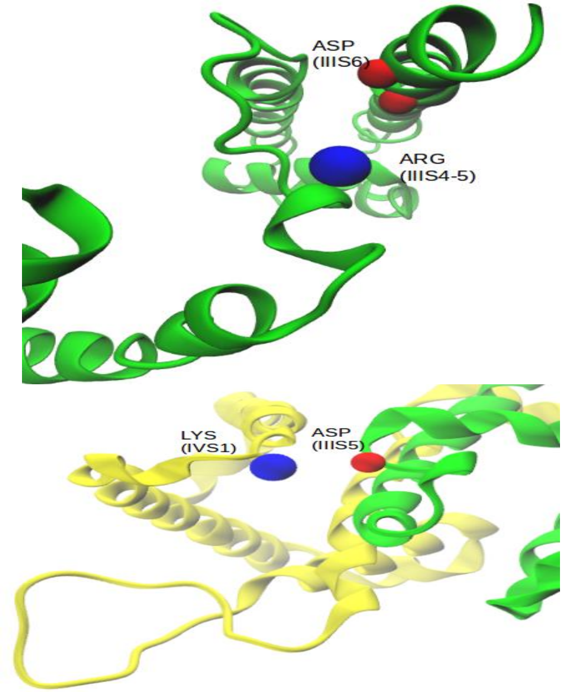
The VSD In the open (activated) state

Wei Lab Data

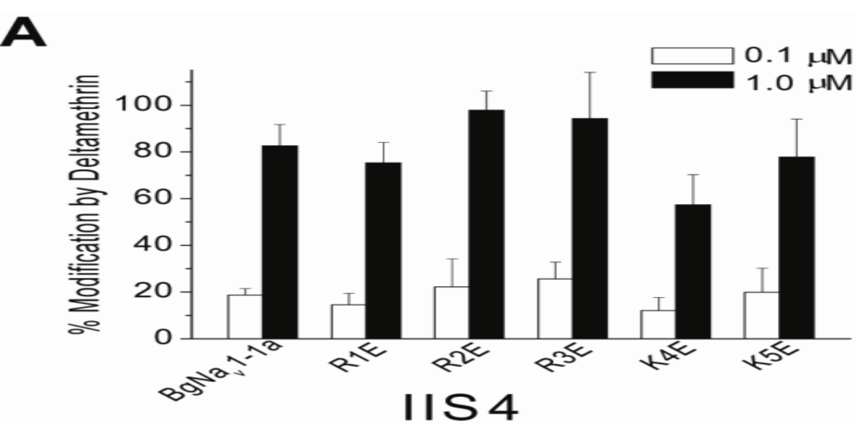


Positive charges in red.
Negative charges in blue.
Hydrophobic in green.
Polar in yellow.

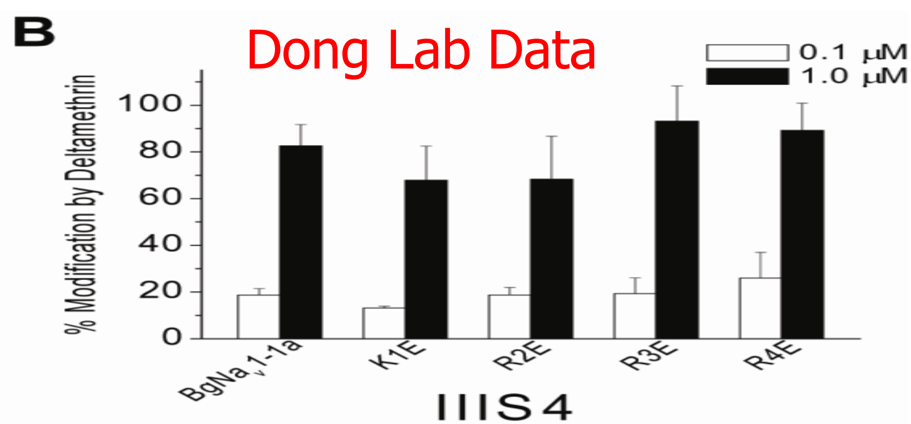
I237, S/N240, E247 in S1
E283, F290, E293 in S2
D316 in S3



- S1-S4 organized as anti-parallel helices.
- All the conserved residues are delineating a valley, called the gating pore.

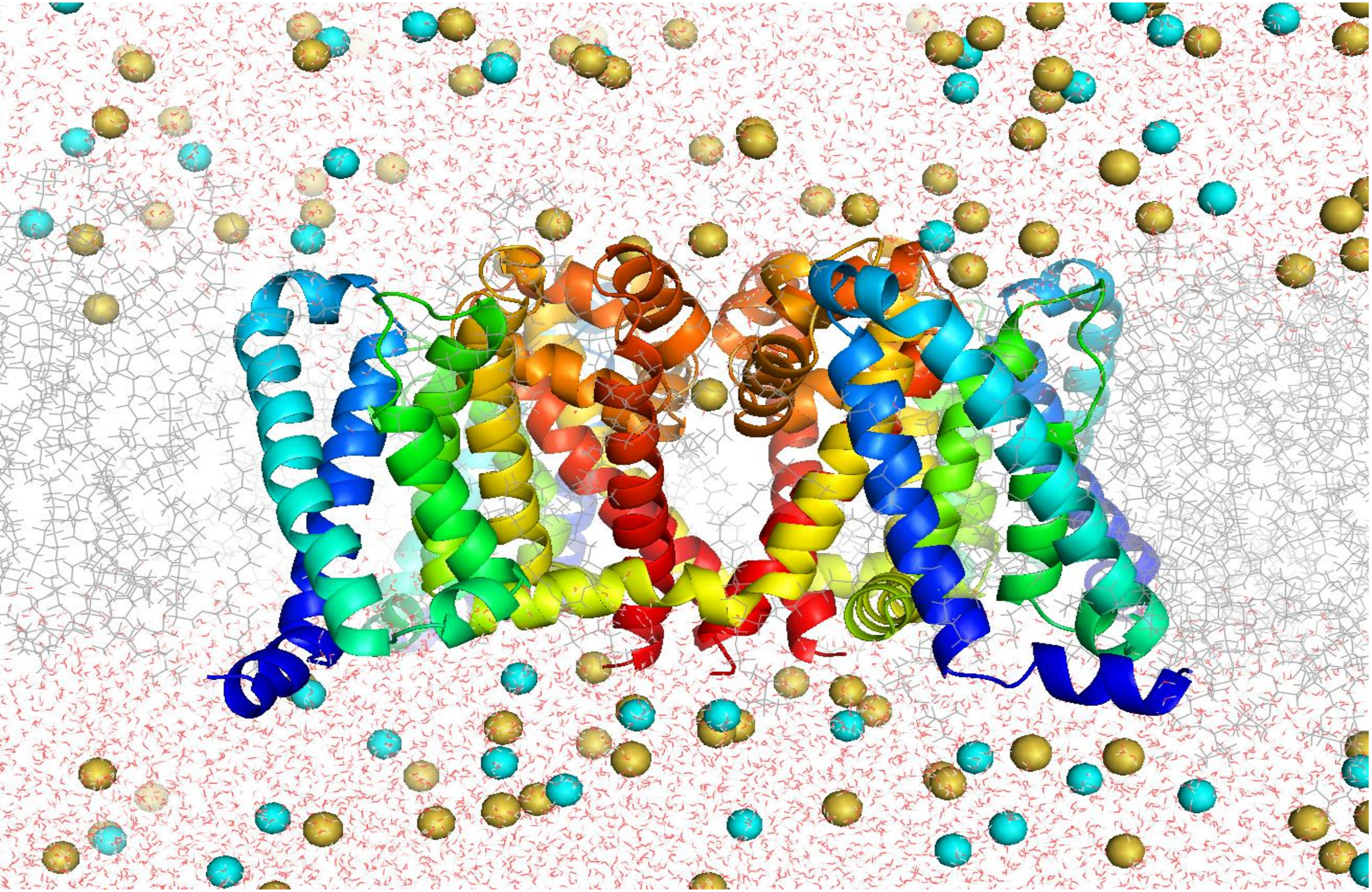


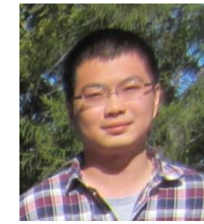
Dong Lab Data



Molecular dynamics simulation to seek for molecular mechanism of gating

Wei Lab Data



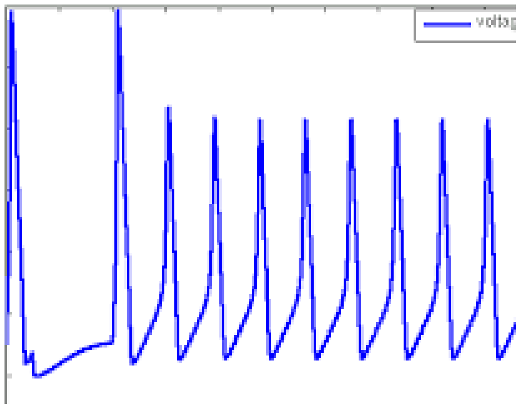


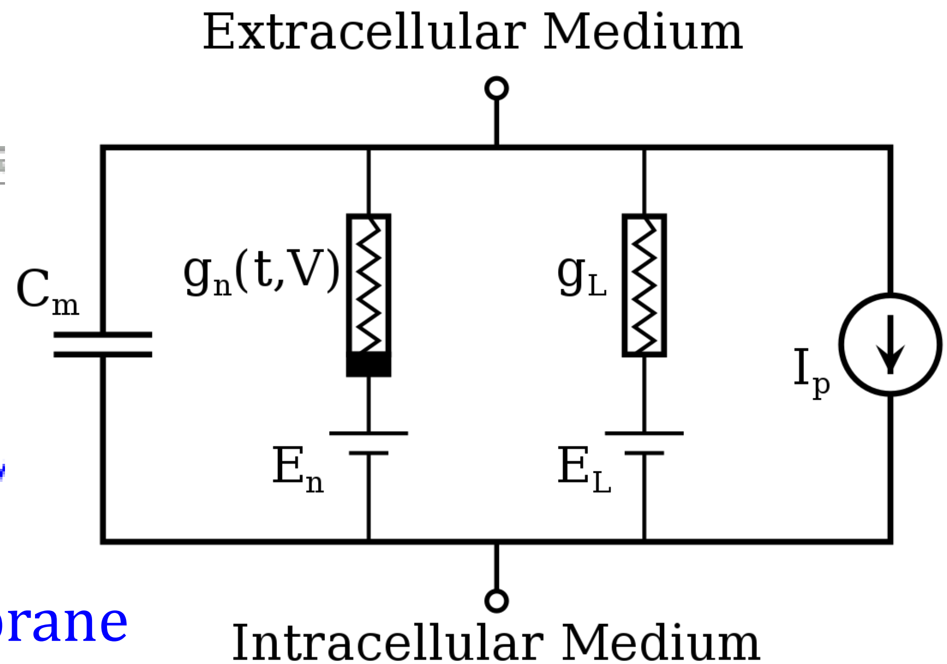
Zixuan Cang

It is difficult to reach the relevant timescale for I-V curves!

Mathematical models: Hodgkin–Huxley model

Wikipedia
The Free Encyclopedia





The total current through membrane

$$I = C_m \frac{dV}{dt} + g_K(V_m - V_K) + g_{Na}(V_m - V_{Na}) + g_l(V_m - V_l)$$

where I is the total membrane current per unit area, C_m is the membrane capacitance per unit area, g_K and g_{Na} are the potassium and sodium conductance per unit area, respectively, V_m, V_K and V_{Na} are the membrane, potassium and sodium reversal potentials, respectively, and g_l and V_l are the leak conductance per unit area and leak reversal potential, respectively.

Mathematical models: Poisson-Nernst-Planck model

The free energy functional G (Eisenberg *et al,* 1990s)

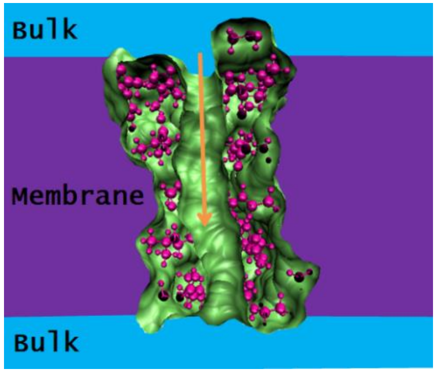
$$G = \int [\mathrm{Polar} + \mathrm{Chem}] d\boldsymbol{r}$$

Polar = electric field + solute charges + solevent charges:

$$\mathrm{Polar} = \left(-\frac{\varepsilon_m}{2}|\nabla\phi|^2 + \phi\sum_j Q_j\,\delta(\boldsymbol{r}-\boldsymbol{r}_j)\right) + \left[-\frac{\varepsilon_s}{2}|\nabla\phi|^2 + \sum_\alpha n_\alpha q_\alpha \phi\right]$$

Chem = Chemical potential + concentration effect

$$\mathrm{Chem} = (1-S)\sum_\alpha n_\alpha\left[\mu_{0\alpha} + kT\left(\ln\frac{n_\alpha}{n_0\alpha} - 1\right)\right]$$



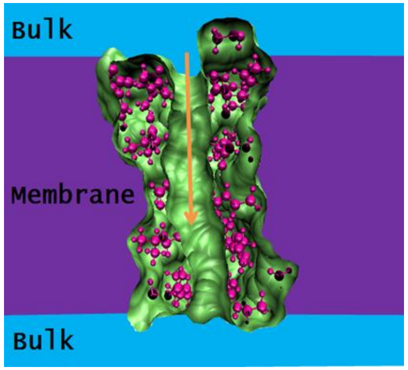
(Variational formulation: Fogolari and Briggs, 1997)

Poisson-Nernst-Planck model

The Poisson equation

$$-\nabla \cdot (\varepsilon(\boldsymbol{r})\nabla\phi) = \sum_j Q_j \delta(\boldsymbol{r} - \boldsymbol{r}_j) + \sum_\alpha q_\alpha n_\alpha$$

where $\varepsilon(\boldsymbol{r}) = \begin{cases} \varepsilon_m, & r \in \Omega_m \\ \varepsilon_s, & r \in \Omega_s \end{cases}$



Electrochemical potential

$$\frac{\partial G}{\partial n_\alpha} \Longrightarrow \mu_\alpha = \mu_{0\alpha} + kT \ln \frac{n_\alpha}{n_0 \alpha} + q_\alpha \phi + U_\alpha$$

Fick's first law: $J_\alpha = D_\alpha n_\alpha \frac{\nabla \mu_\alpha}{kT}$,

Conservation law: $\frac{\partial n_\alpha}{\partial t} = -\nabla \cdot J_\alpha$

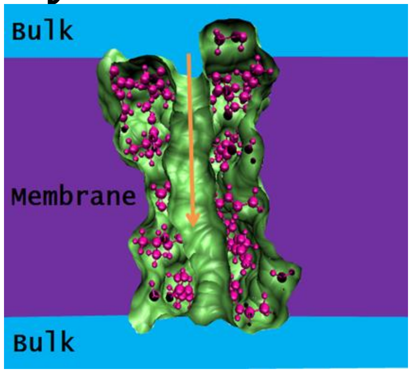
The Nernst-Planck equation

$$\frac{\partial n_\alpha}{\partial t} = \nabla \cdot \left[D_\alpha \left(\nabla n_\alpha + \frac{q_\alpha n_\alpha}{kT} \nabla(\phi + U_\alpha) \right) \right]$$

The Poisson-Nernst-Planck: Eisenberg et al, 1990s; Coalson, 2000s; Roux, 2000s; YC Zhou et al, 2008, WS Liu, 2000s; Chun Liu, 2010s; TC Lin, 2010s; JL Liu, 2010s; B Lu et al, 2000s; SB Dai et al, 2010s, and many others.

Poisson-Boltzmann-Nernst-Planck model

Motivation: In PNP, one needs to solve one NP equation for each of a multi-ion system ($N_a^+, Cl^-, K^+, C_a^{2+}, \ldots$). In BPNP, one only needs to solve NP equation for the targeted ions (say, N_a^+, Cl^-), then approximate the densities of other ions ($K^+, C_a^{2+}, \ldots$) by the Boltzmann distribution.



The free energy functional G

$$G = \int [\text{Polar} + \text{Chem}] d\boldsymbol{r}$$

Polar = electric field + solute charges + solevent charges:

$$\text{Polar} = \left(-\frac{\varepsilon_m}{2}|\nabla\phi|^2 + \phi\sum_j Q_j\,\delta(\boldsymbol{r}-\boldsymbol{r}_j)\right)$$

$$+\left[-\frac{\varepsilon_s}{2}|\nabla\phi|^2 + \sum_\alpha n_\alpha(\boldsymbol{r})q_\alpha\phi + \sum_\beta n_{0\beta}q_\beta\left(e^{-(q_\beta\phi-\mu_\beta)/kT}-1\right)\phi\right]$$

Chem = Chemical potential + concentration effect

$$\text{Chem} = \sum_\alpha n_\alpha\left[\mu_{0\alpha} + kT\left(\ln\frac{n_\alpha}{n_{0\alpha}} - 1\right)\right]$$

(Zheng and Wei, JCP, 2011)

Poisson-Boltzmann-Nernst-Planck model

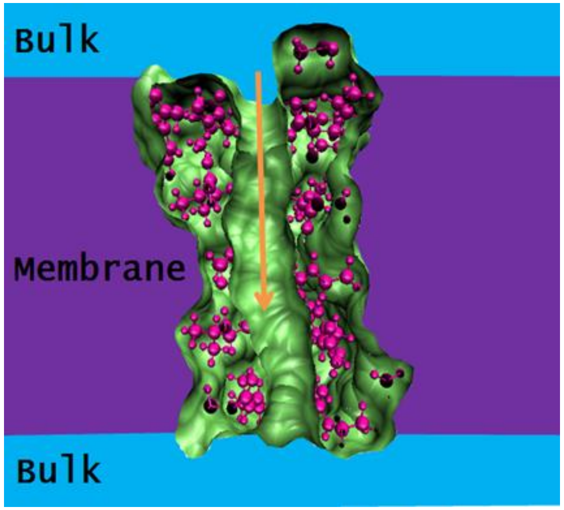
(Zheng and Wei, JCP, 2011)

The Poisson-Boltzmann equation

$$-\nabla\cdot(\varepsilon(\boldsymbol{r})\nabla\phi) = \sum_j Q_j\delta(\boldsymbol{r}-\boldsymbol{r}_j)$$

$$+\sum_\alpha q_\alpha n_\alpha + \sum_\beta q_\beta n_{0\beta} e^{-(q_\beta\phi-\mu_\beta)/kT}$$

where $\varepsilon(\boldsymbol{r}) = \begin{cases}\varepsilon_m, & r\in\ \Omega_m\\ \varepsilon_s, & r\in\ \Omega_s\end{cases}$



The Nernst-Planck equation

$$\frac{\partial n_\alpha}{\partial t} = \nabla\cdot\left[D_\alpha\left(\nabla n_\alpha + \frac{q_\alpha n_\alpha}{kT}\nabla(\phi+U_\alpha)\right)\right]$$

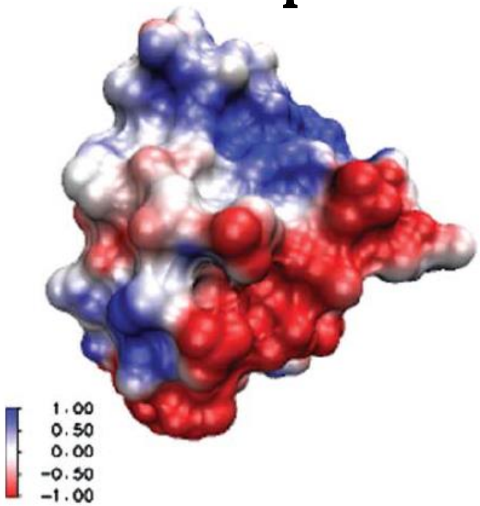
PBNP was confirmed by Kiselev *et al.* using the Monte Carlo method, JCP 135, 155103, 2011.

Poisson-Boltzmann-Nernst-Planck model

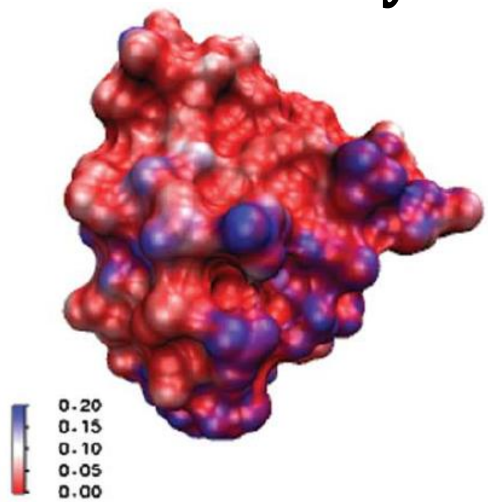
Validation: (Zheng and Wei, JCP, 2011)

Poisson-Boltzmann=Poisson-Nernst-Planck at equilibrium

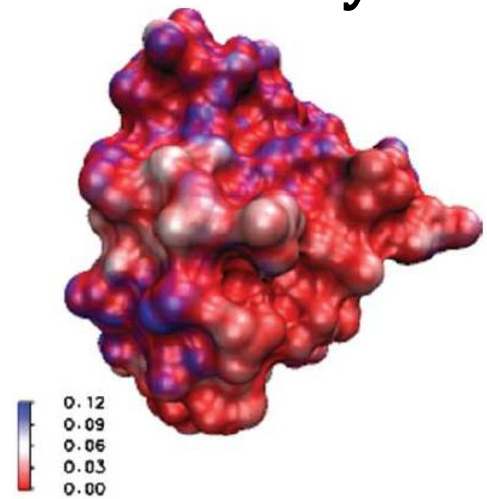
Electrostatic potential



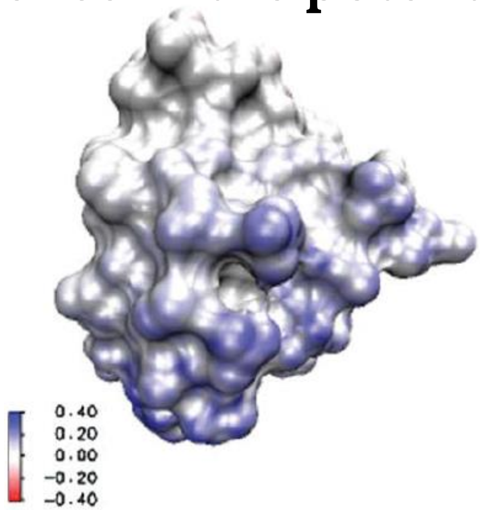
Na density



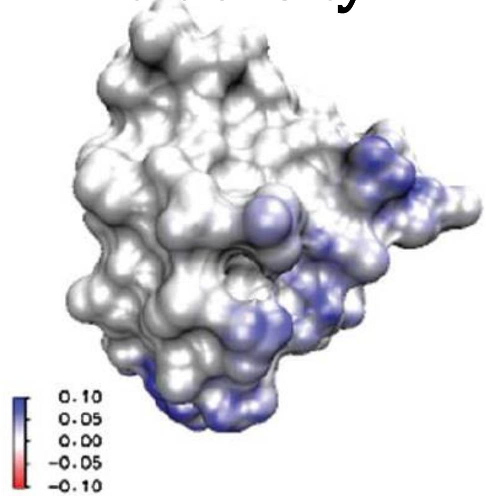
Cl density



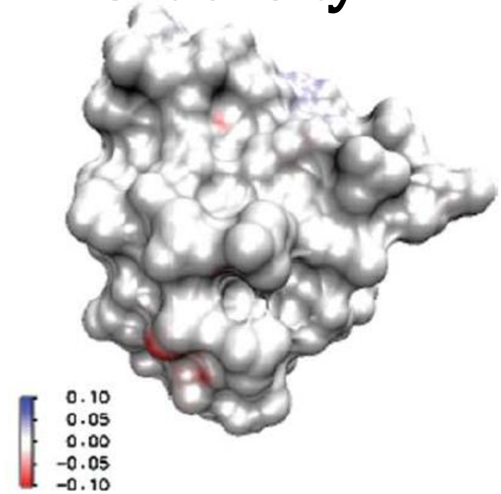
Difference in the potential



Na density

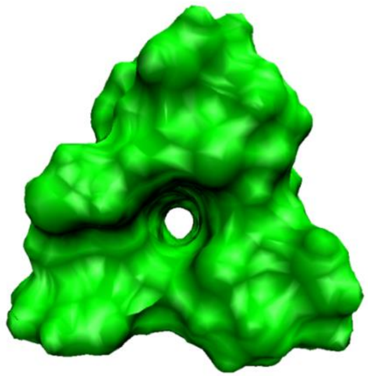


Cl density

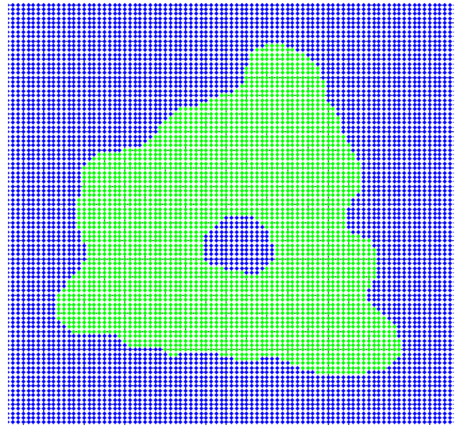


Computational issues

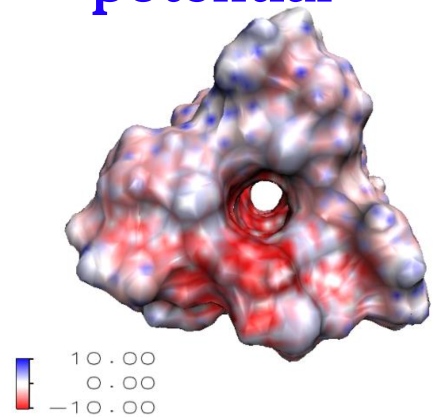
Channel surface



Computational domain



Electrostatic potential



Boundary conditions:

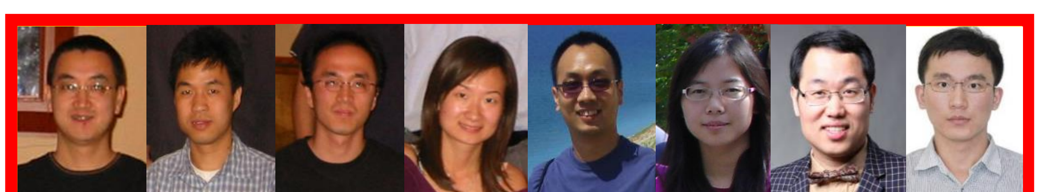
Poisson equation: Dirichlet and Neumann.

Nernst-Planck equation: Non-flux at the interface and Dirichlet.

Laplace-Beltrami equation: Dirichlet.

Numerical methods

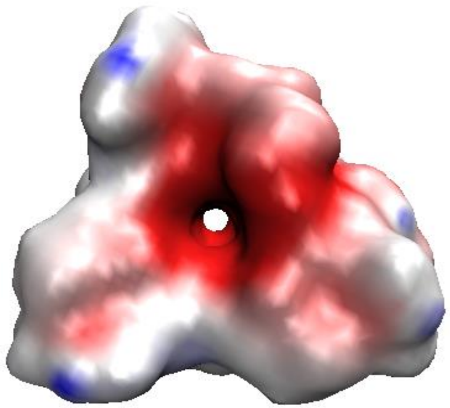
- Matched interface and boundary (MIB, 2nd order method!)
- Dirichlet to Neumann mapping
- Gummel iterations

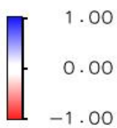


Simulation of Gramicidin A

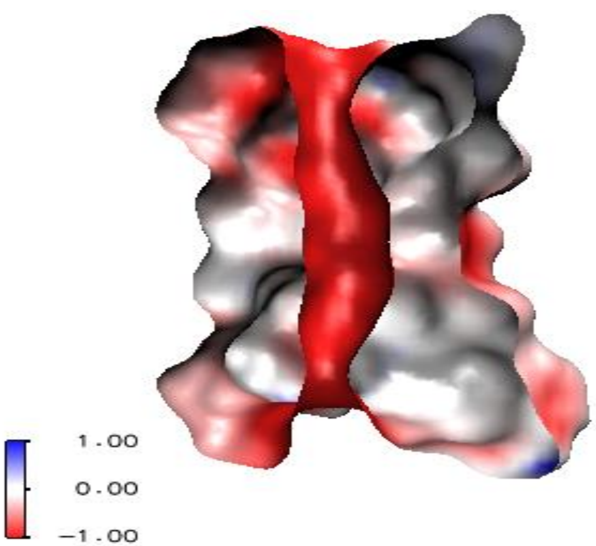
Poisson-Nernst-Planck equations

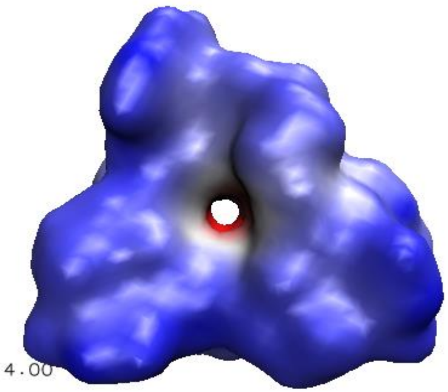
(Zheng and Wei, JCP, 2011)

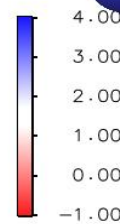




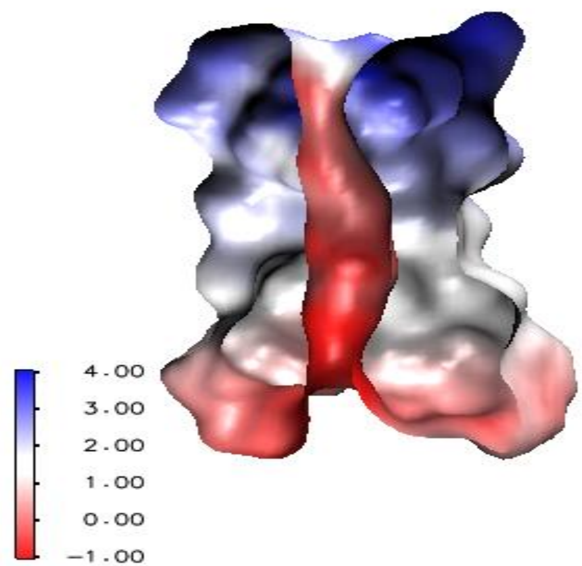
Surface electrostatic potential at 0mV







Surface electrostatic potential at 150mV

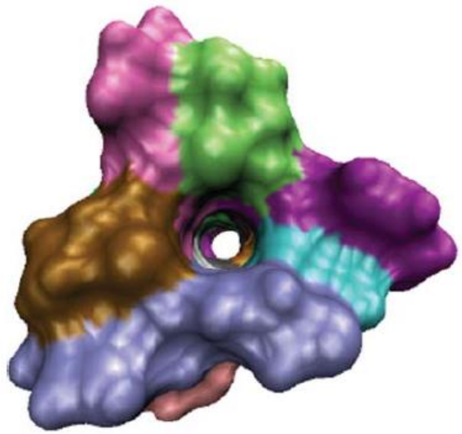


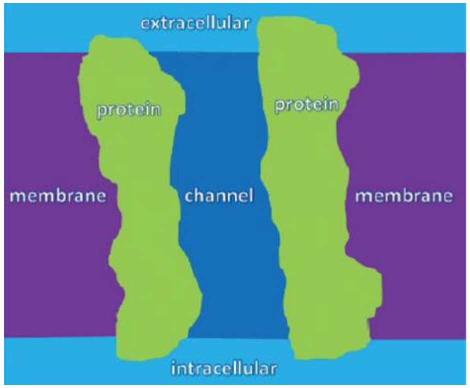
Poisson-Boltzmann-Nernst-Planck model

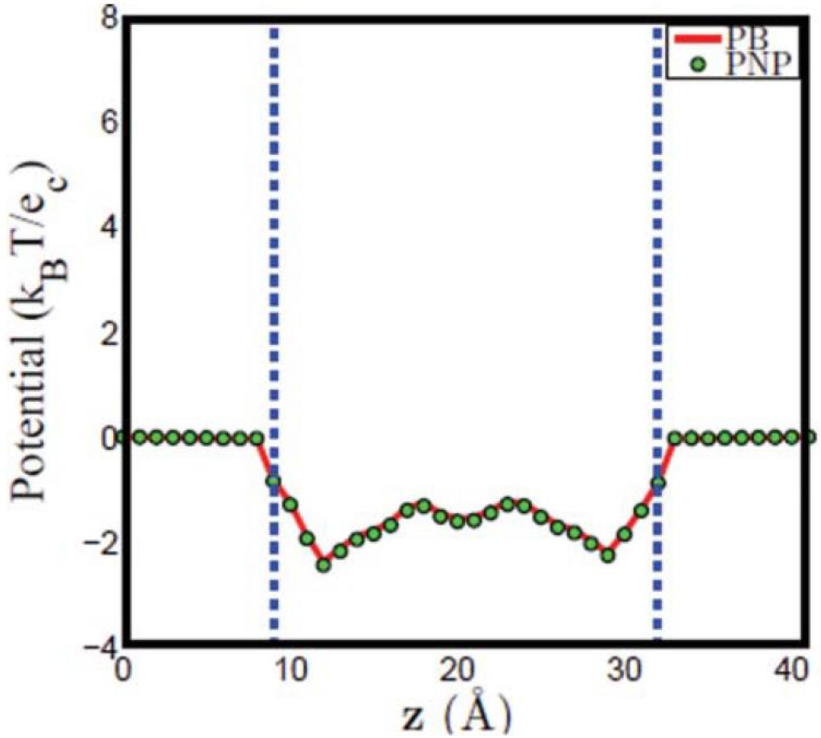
Validation:

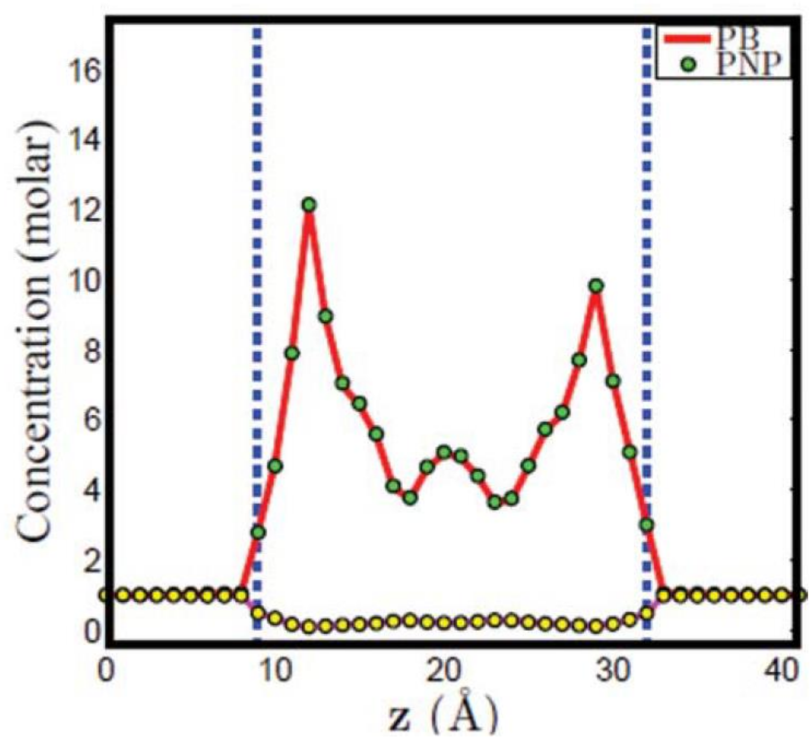
(Zheng and Wei, JCP, 2011)

PB=PNP at equilibrium





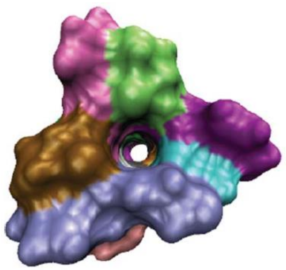


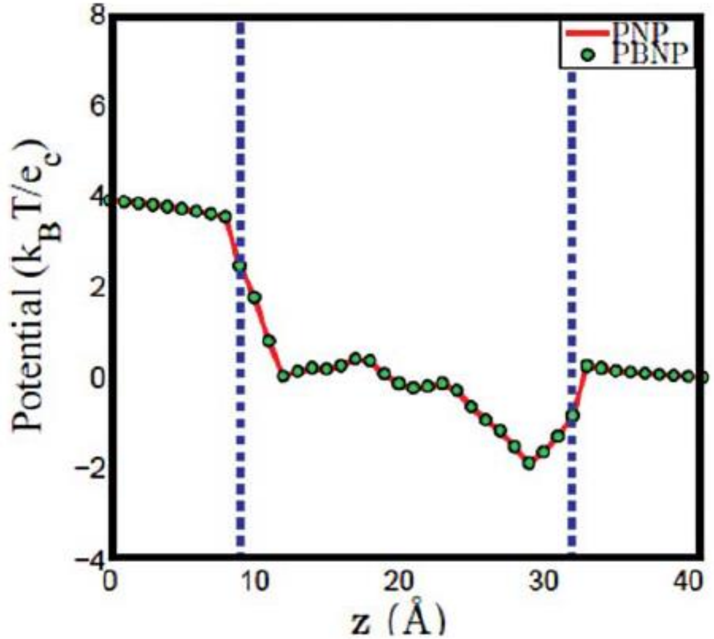


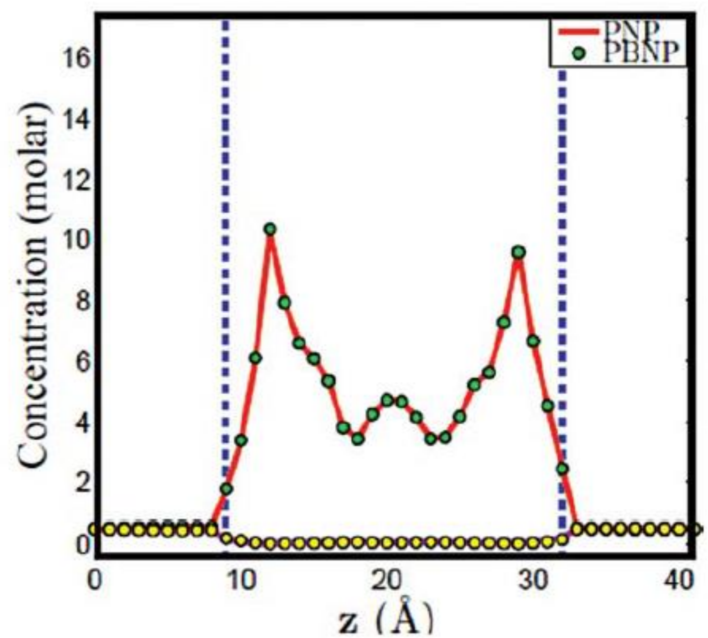
Poisson-Boltzmann-Nernst-Planck model

Validation:

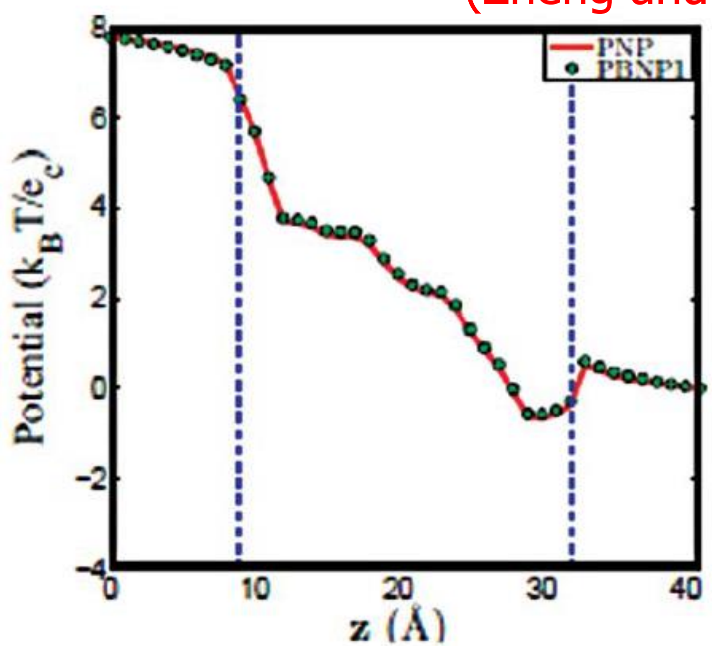
PBNP=PNP

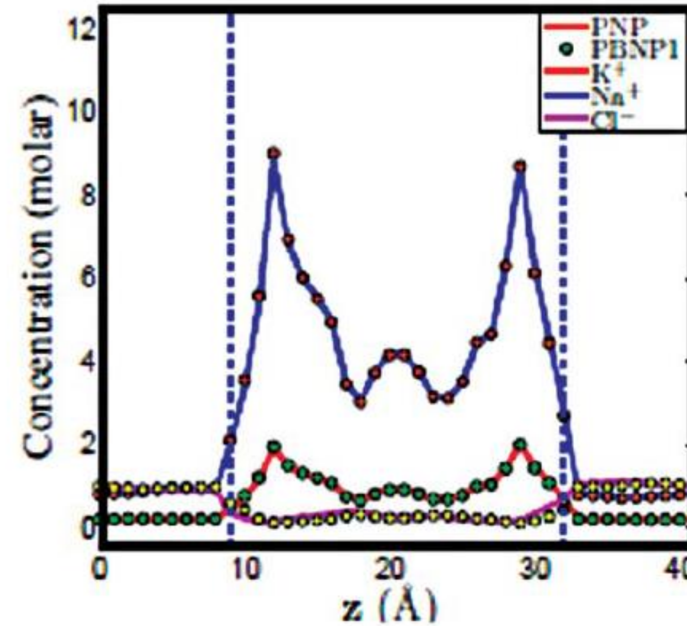






(Zheng and Wei, JCP, 2011)





Differential geometry based Poisson-Nernst-Planck model

The free energy functional G

$$G = \int [\text{Nonpolar} + \text{Polar} + \text{Chem}] d\boldsymbol{r}$$

Nonpolar=area, volume and solvent-solute interaction:

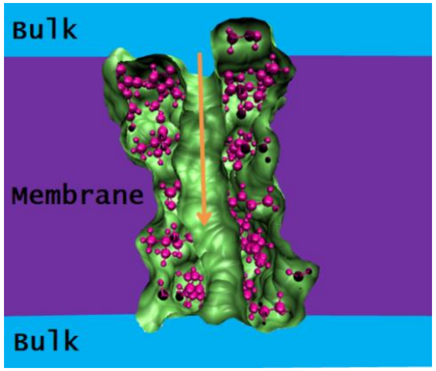
Nonpolar=$\gamma|\nabla S| + Sp + (1-S)\sum_\alpha n_\alpha U_\alpha$

Polar = electric field + solute charges + solevent charges:

$$\text{Polar} = S\left(-\frac{\varepsilon_m}{2}|\nabla\phi|^2 + \phi\sum_j Q_j\,\delta(\boldsymbol{r}-\boldsymbol{r}_j)\right) + (1-S)\left[-\frac{\varepsilon_s}{2}|\nabla\phi|^2 + \sum_\alpha n_\alpha q_\alpha \phi\right]$$

Chem = Chemical Potential + concentration effect

$$\text{Chem} = (1-S)\sum_\alpha n_\alpha\left[\mu_{0\alpha} + kT\left(\ln\frac{n_\alpha}{n_0\alpha} - 1\right)\right]$$



(Wei, BMB, 2010; Zheng, Chen, & Wei, JCP, 2011)

Differential geometry based Poisson-Nernst-Planck model

Generalized Poisson equation:

$$-\nabla \cdot (\varepsilon(S)\nabla\phi) = S\sum_j Q_j\delta(\boldsymbol{r}-\boldsymbol{r}_j) + (1-S)\sum_\alpha q_\alpha n_\alpha$$

The Nernst-Planck equation:

$$\frac{\partial n_\alpha}{\partial t} = \nabla \cdot \left[D_\alpha\left(\nabla n_\alpha + \frac{q_\alpha n_\alpha}{kT}\nabla(\phi + U_\alpha)\right)\right]$$

Generalized Laplace-Beltrami equation:

$$\frac{\partial S}{\partial t} = |\nabla S|\left[\nabla \cdot \left(\frac{\gamma\nabla S}{|\nabla S|}\right) + V_{\mathrm{LB}}\right]$$

where $V_{\mathrm{LB}} = -p + \sum_\alpha n_\alpha U_\alpha$

$$-\phi\sum_j Q_j\delta(\boldsymbol{r}-\boldsymbol{r}_j) + \frac{\varepsilon_s}{2}|\nabla\phi|^2 + \sum_\alpha n_\alpha q_\alpha\phi - \frac{\varepsilon_s}{2}|\nabla\phi|^2$$

$$-\sum_\alpha n_\alpha\left[\mu_{0\alpha} + kT\left(\ln\frac{n_\alpha}{n_0\alpha} - 1\right)\right]$$

(Wei, Zheng, Chen, Xia, SIAM Review, 2012)

Differential geometry based Poisson-Nernst-Planck model

Generalized Laplace Beltrami equation

$$\frac{\partial S}{\partial t} = |\nabla S| \left[\nabla \cdot \left(\frac{\gamma \nabla S}{|\nabla S|} \right) \quad + V_{\mathrm{LB}} \right]$$

where

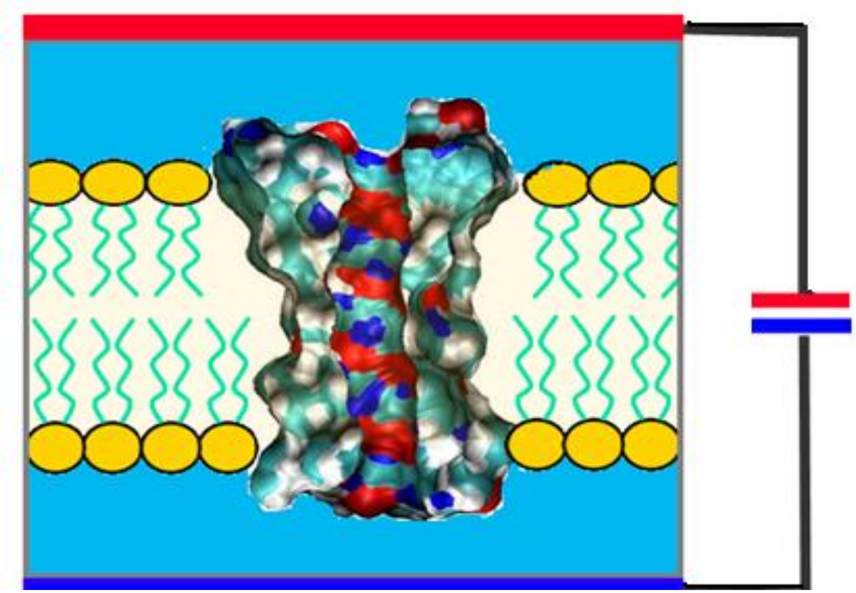
$$V_{\mathrm{LB}} = -p + \sum_{\alpha} n_{\alpha} U_{\alpha}$$

$$-\phi \sum_{j} Q_j \delta(\boldsymbol{r} - \boldsymbol{r}_j) + \frac{\varepsilon_s}{2} |\nabla \phi|^2 + \sum_{\alpha} n_{\alpha} q_{\alpha} \phi - \frac{\varepsilon_s}{2} |\nabla \phi|^2$$

$$-\sum_{\alpha} n_{\alpha} \left[\mu_{0\alpha} + kT \left(\ln \frac{n_{\alpha}}{n_0 \alpha} - 1 \right) \right]$$

(Wei, Zheng, Chen, Xia, SIAM Review, 2012)

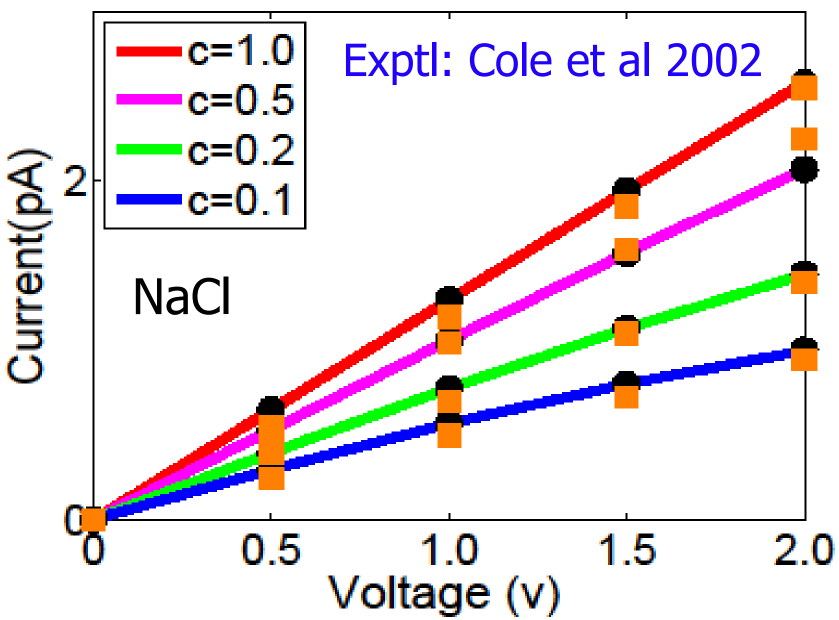
Differential geometry based Poisson-Nernst-Planck model

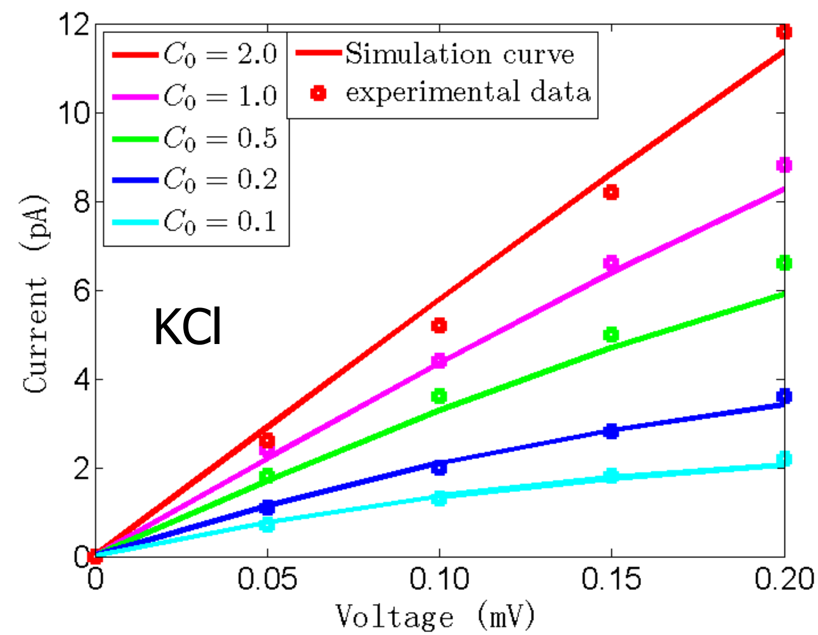


Simulation of Gramicidin A

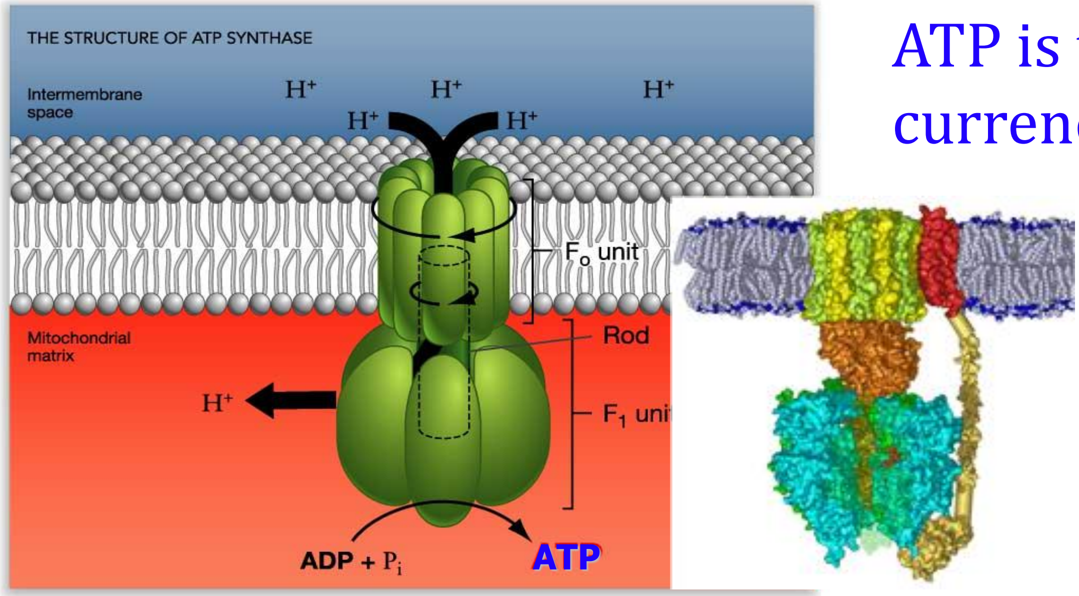
Laplace-Beltrami and Poisson-Nernst-Planck equations

(Zheng, Chen, Wei, JCP, 2011;
Wei, Zheng, Chen, Xia, SIAM Review, 2012)



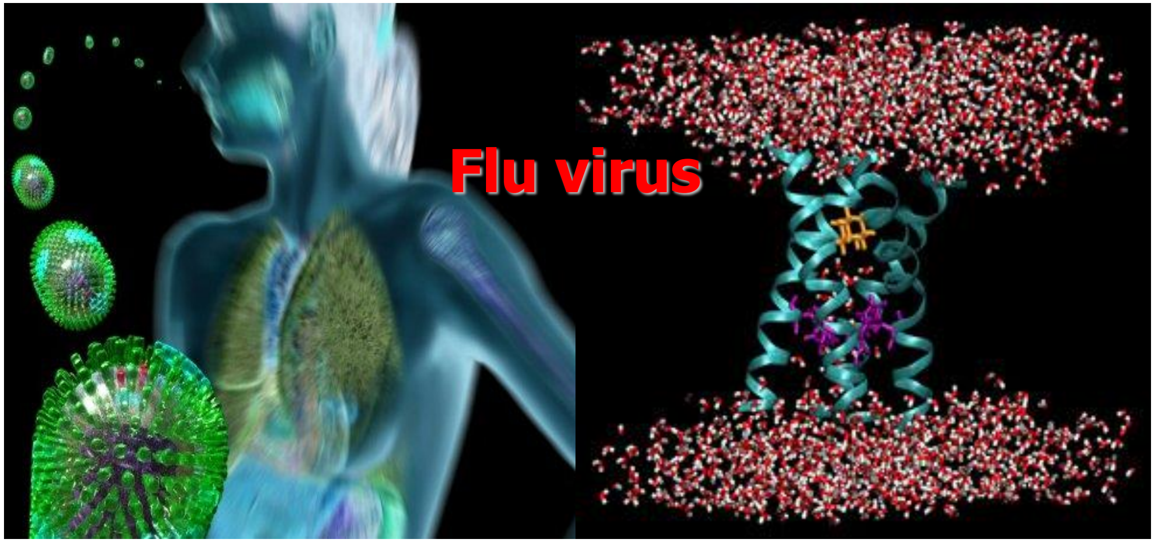


Proton transport



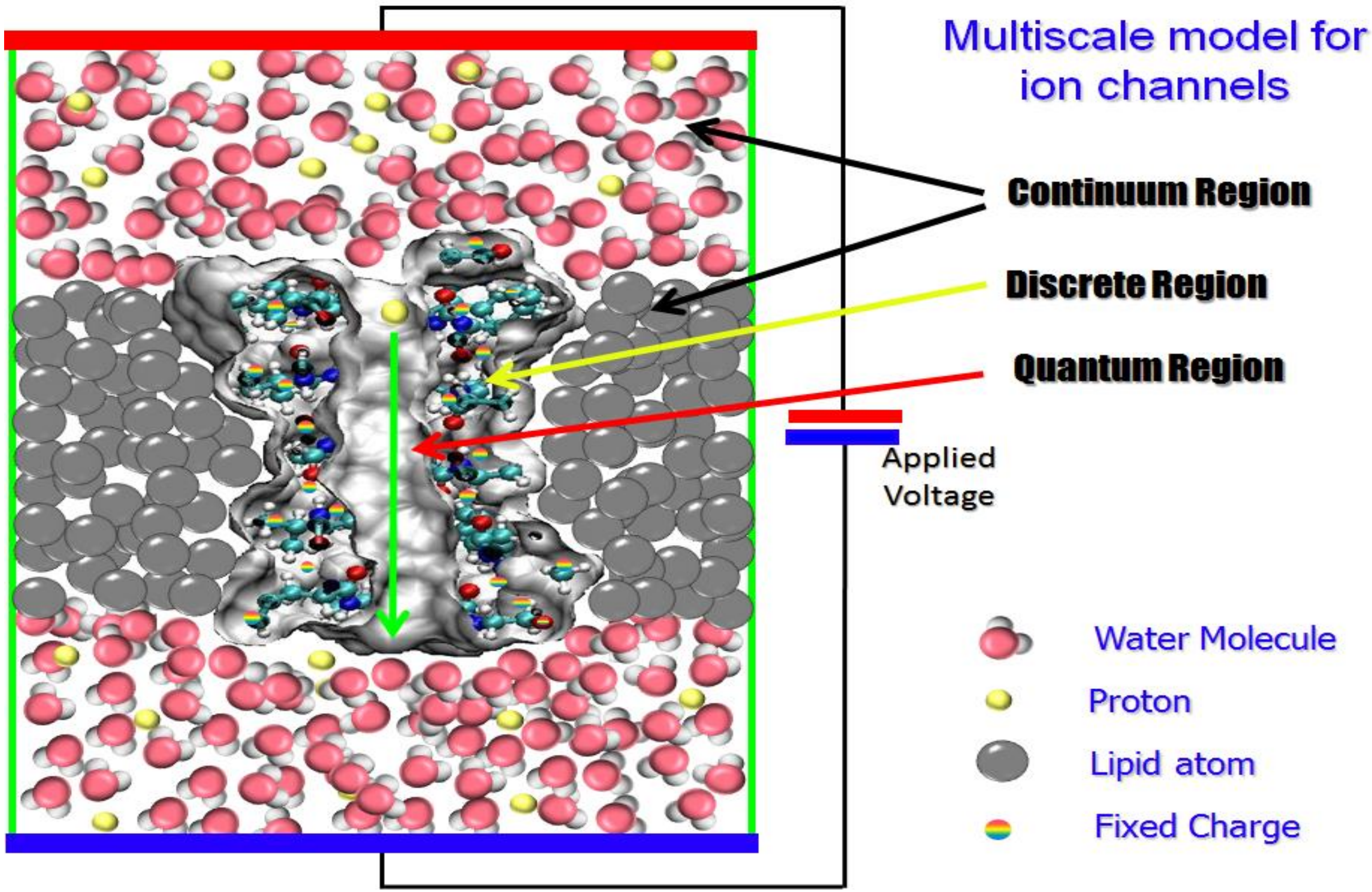
https://www.expii.com/t/atp-synthase-5735

ATP is the energy currency in human body



Influenza M2 proton channel regulates viral replication process in a host cell (internet images).

Differential geometry based Density Functional Theory for proton transport



Differential geometry based Density Functional Theory

Duan Chen

The free energy functional G

$$G = \int [\text{Nonpolar} + \text{Polar} + \text{QM}] d\boldsymbol{r}$$

Nonpolar=area, volume and solvent-solute interaction:

Nonpolar$=\gamma|\nabla S| + Sp + (1-S)\,U$

Polar = electric field + solute charges + solevent charges:

Polar

$$= \mathrm{S}\left(-\frac{\varepsilon_m}{2}|\nabla\phi|^2 + \phi\sum_j Q_j\,\delta(\boldsymbol{r}-\boldsymbol{r}_j)\right) + (1-S)\left[-\frac{\varepsilon_s}{2}|\nabla\phi|^2 + nq\phi\right]$$

QM = Kinetic + Potential + Lagrange multiplier

$$\mathrm{QM} = (1-\mathrm{S})\left[\int\left(-f\frac{\hbar^2}{2m}|\nabla\psi_E|^2 - E_{GC}[n]\right)dE - \lambda\left(\int f|\psi_E|^2 dE - \frac{N}{V}\right)\right]$$

Proton density: $n = \int|\psi_E|^2 f dE$, Boltzmann factor $f = e^{-\frac{(E-\mu)}{\mathrm{kT}}}$

(Chen & Wei, JCP, 2012, IJNMBE 2011)

Differential geometry based Density Functional Theory

Generalized Poisson equation

$$-\nabla \cdot (\varepsilon(S)\nabla\phi) = S\sum_j Q_j\delta\left(\boldsymbol{r}-\boldsymbol{r}_j\right) + (1-S)qn$$

Generalized Kohn-Sham equation

$$-\frac{\hbar^2}{2m}\nabla^2\psi_E + (U_{GC}[n] - q\phi)\psi_E = E_E\psi_E, \quad U_{GC}[n] = \frac{\delta E_{GC}[n]}{\delta n}$$

Generalized Laplace-Beltrami equation

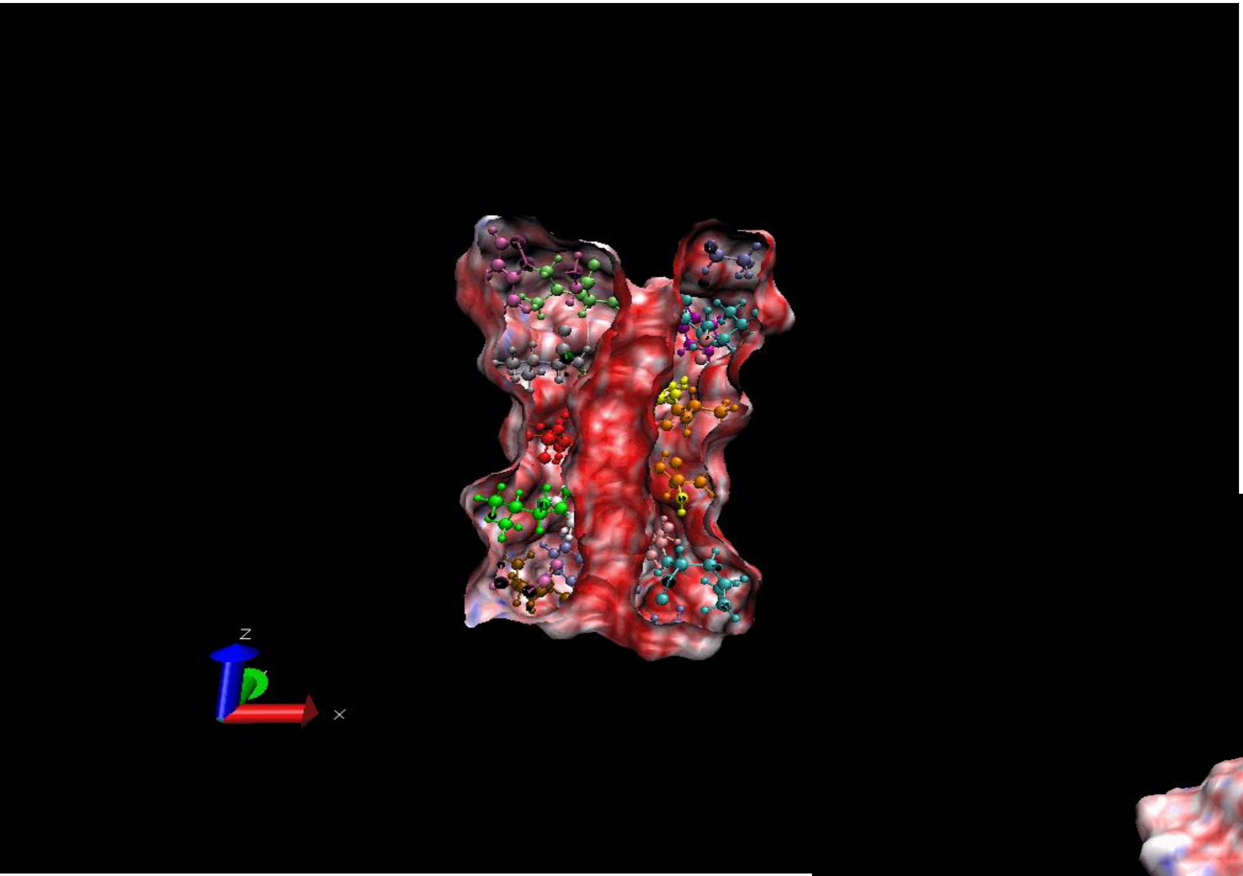
$$\frac{\partial S}{\partial t} = |\nabla S|\left[\nabla \cdot \left(\frac{\gamma\nabla S}{|\nabla S|}\right) + V_{\mathrm{LB}}\right]$$

where $V_{\mathrm{LB}} = -p + U$

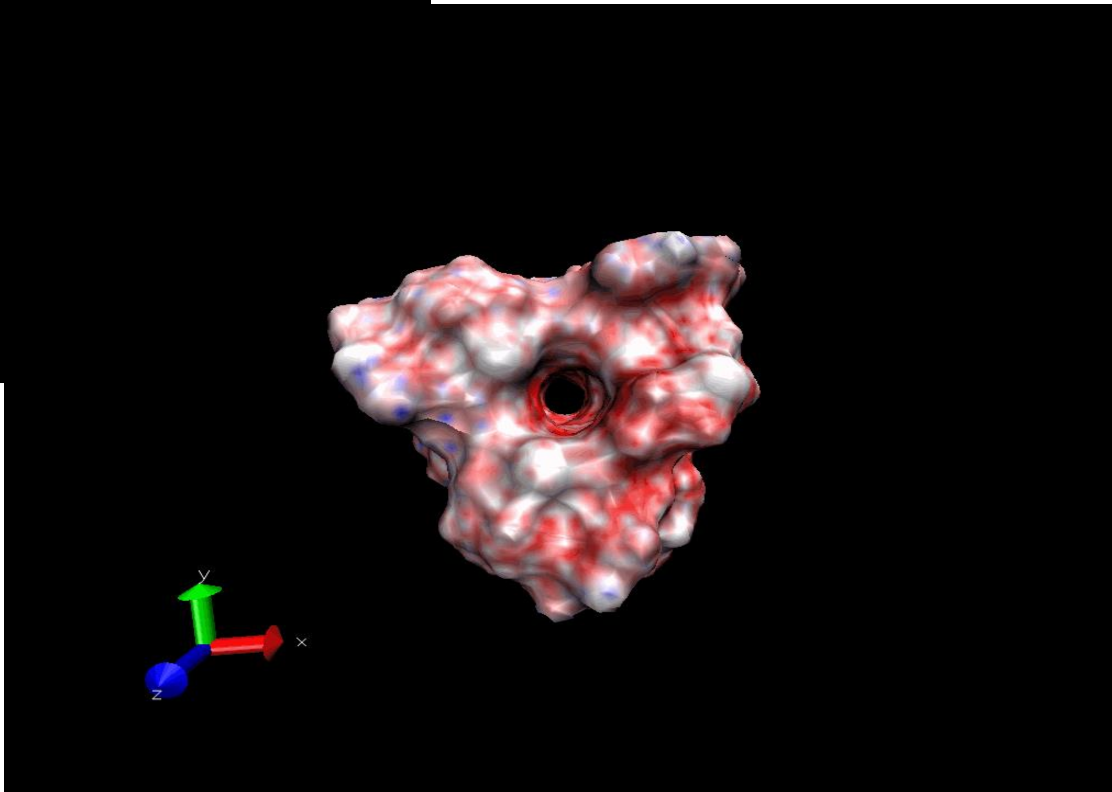
$$-\phi\sum_j Q_j\delta\left(\boldsymbol{r}-\boldsymbol{r}_j\right) + \frac{\varepsilon_s}{2}|\nabla\phi|^2 + nq\phi - \frac{\varepsilon_s}{2}|\nabla\phi|^2$$

$$+\int\left(-f\frac{\hbar^2}{2m}|\nabla\psi_E|^2 - E_{GC}[n]\right)dE - \lambda\left(\int f|\psi_E|^2 dE - \frac{N}{V}\right)$$

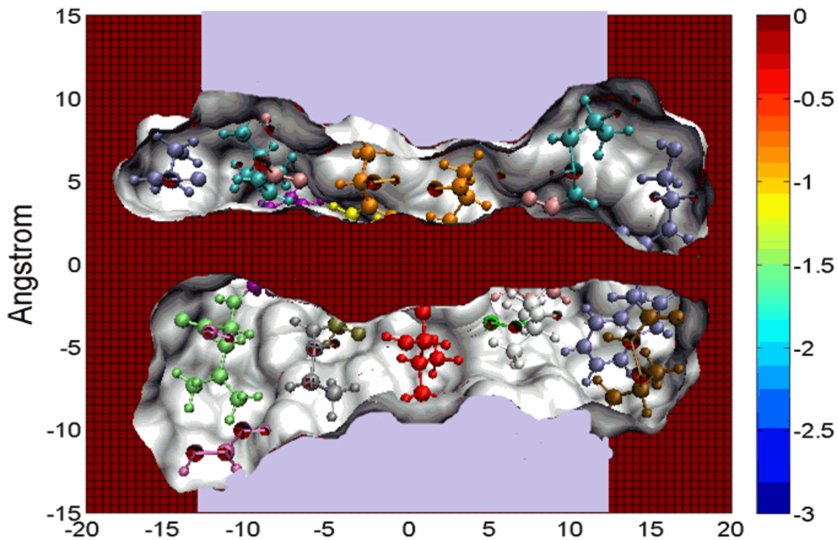
Differential geometry based Density Functional Theory



(Chen, Wei, IJNMBE, 2011; JCP, 2012)



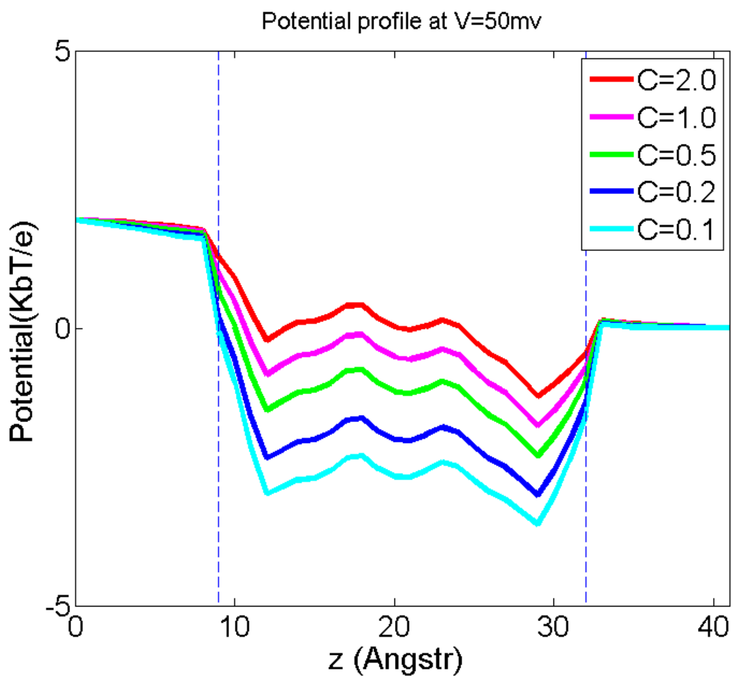
Differential geometry based Density Functional Theory

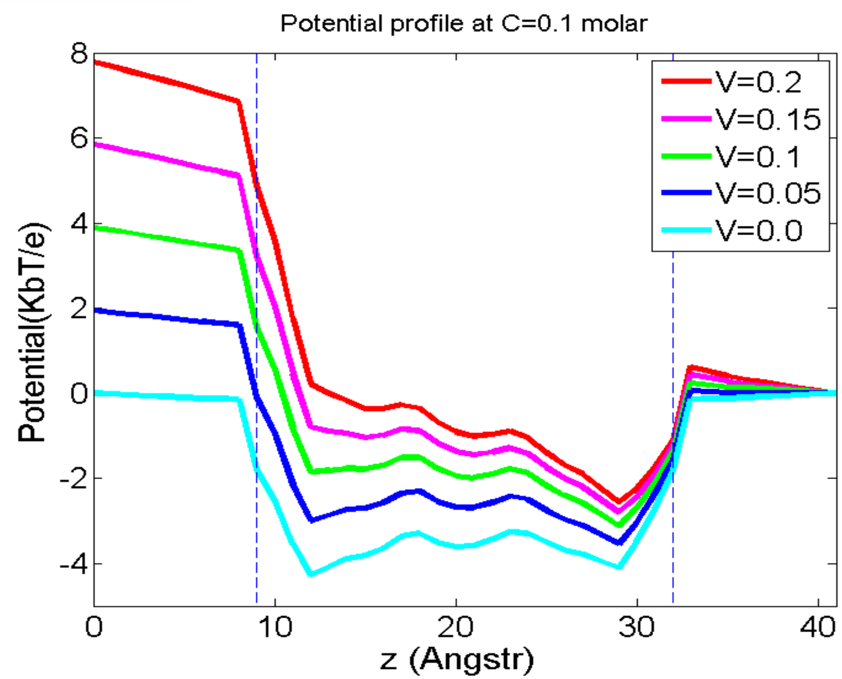


Simulation of Gramicidin A

Laplace-Beltrami and Kohn-Sham equations

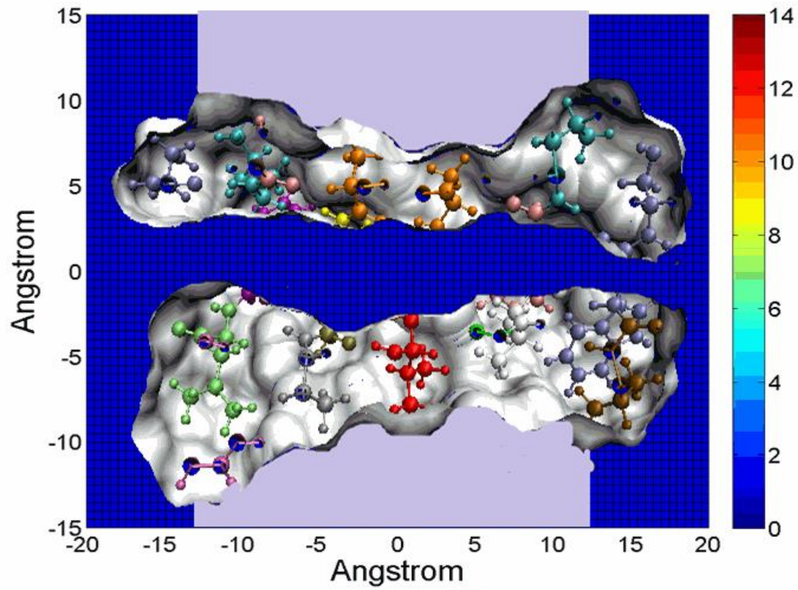
(Chen, Wei, INJNMBE, 2011; JCP, 2012)





Differential geometry based Density Functional Theory

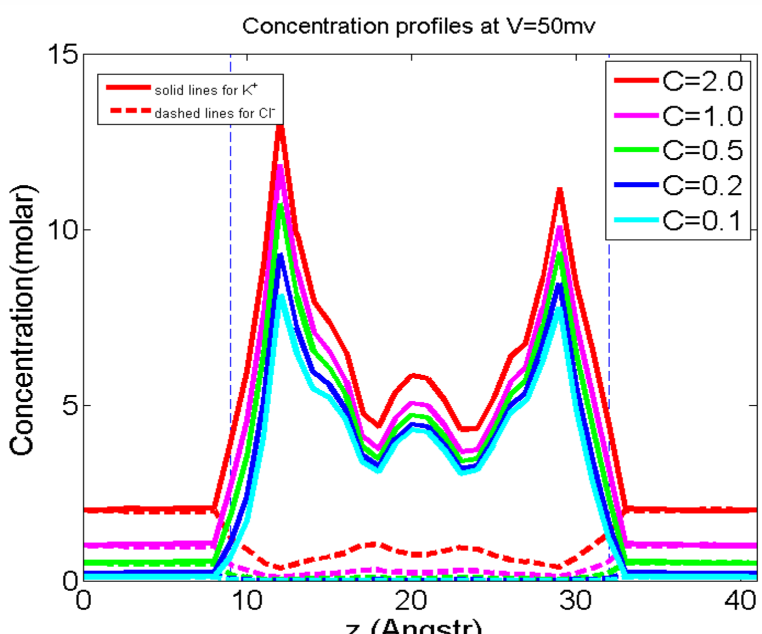
Concentration profile

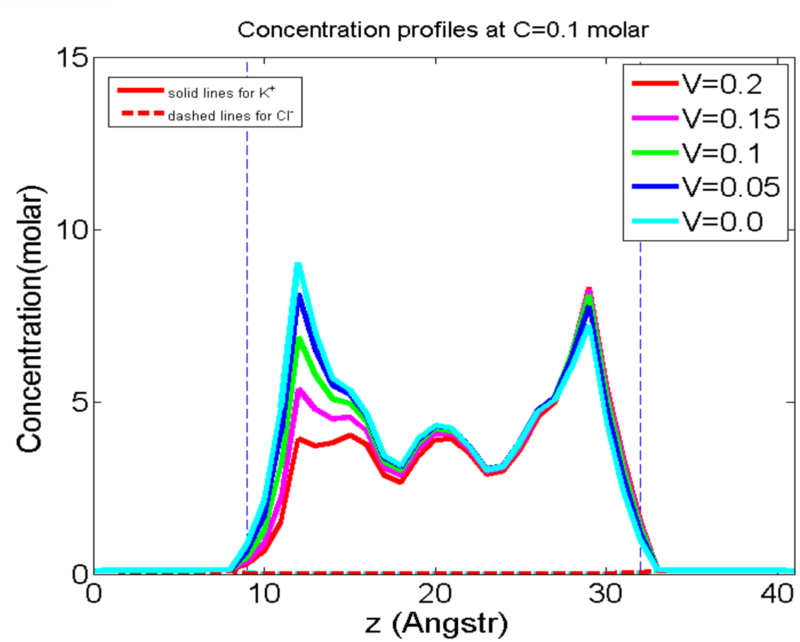


Simulation of Gramicidin A

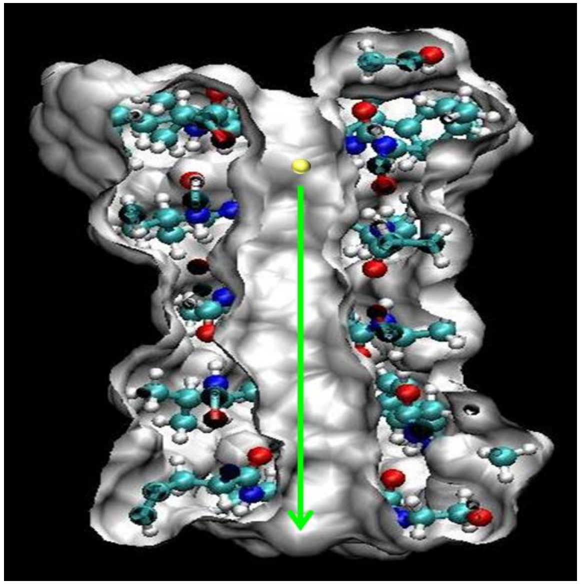
Laplace-Beltrami and Kohn-Sham equations

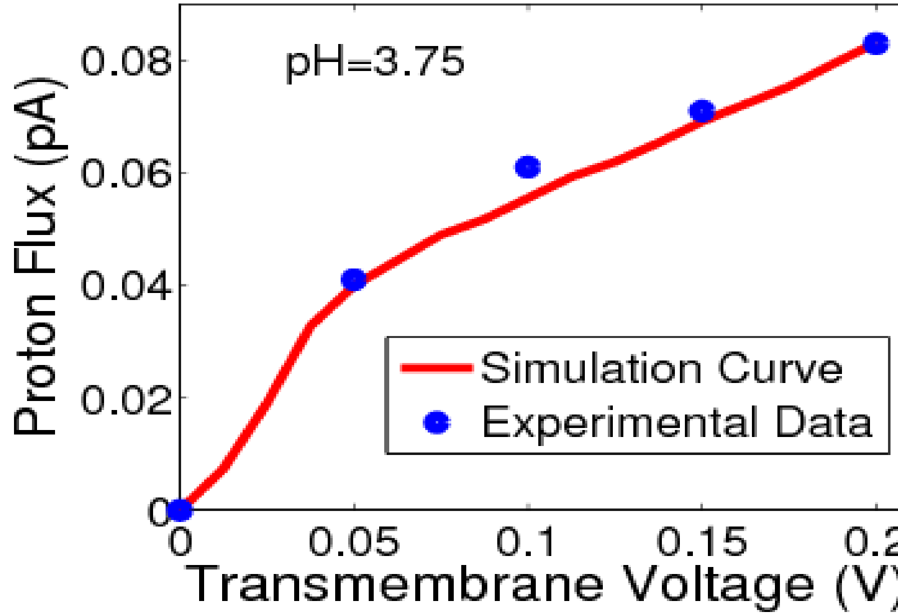
(Chen, Wei, CiCP, 2013)





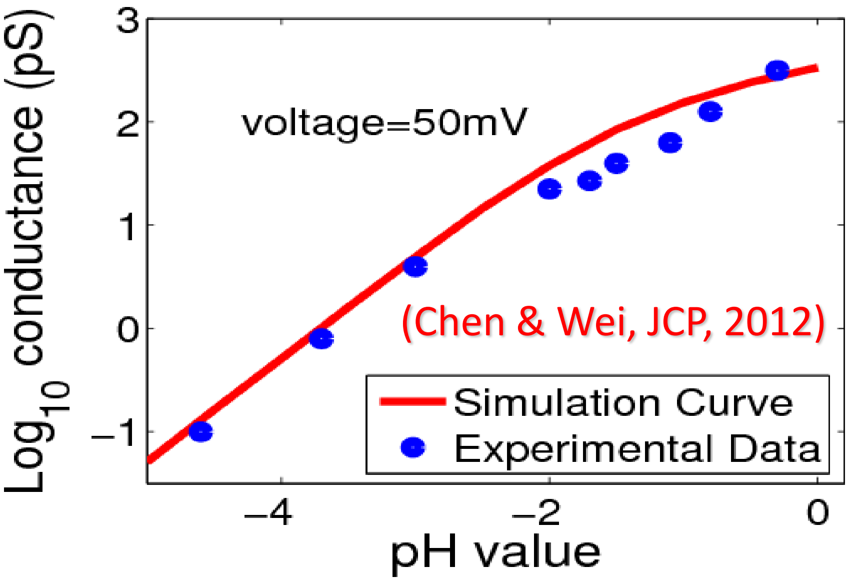
Differential geometry based Density Functional Theory

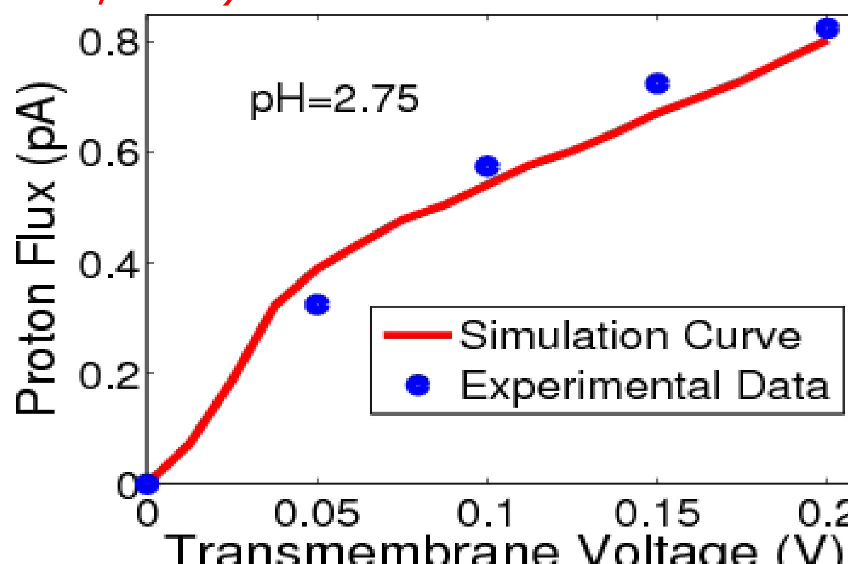




Proton transport of Gramicidin A

(Expl: Eisenman et al., 1980)





To improve variational multiscale models

- Need to describe the configurational changes due to receipt binding
- Need to account for the structural response to the ion permeation
- Need to reflect water flow due to the cellular material balance
- Need to account for ion-ion and ion-water correlations

Electro-Chem-Fluid-MM model

$$G = \iiint \left[Nonpolar + Electro + Chemical + Fluid + MM \right] dxdzdt$$

$$G_{Nonpolar} = \gamma |\nabla S| + Sp + (1-S)\sum_{\alpha} n_{\alpha} U_{\alpha}$$

$$G_{Electro} = S\left[\phi \rho_m - \frac{\varepsilon_m}{2} |\nabla \phi|^2 \right] + (1-S)\left[\phi \sum_{\alpha} n_{\alpha} q_{\alpha} - \frac{\varepsilon_s}{2} |\nabla \phi|^2 \right]$$

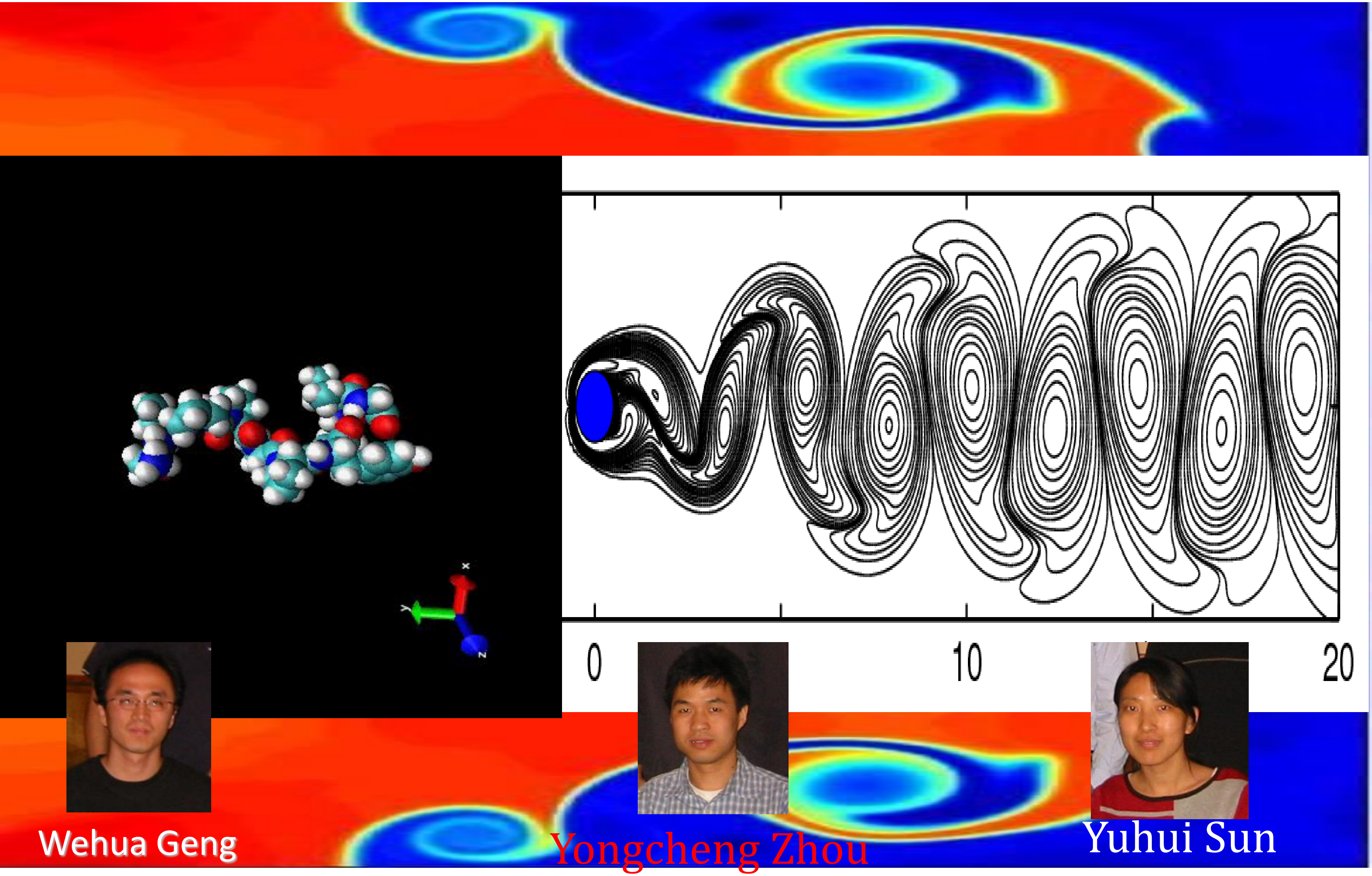
$$G_{Chemical} = (1-S)\sum_{\alpha} n_{\alpha} \left[\mu_{0\alpha} + kT\left(\ln \frac{n_{\alpha}}{n_{\alpha 0}} - 1 \right) \right]$$

$$G_{Fluid} = -(1-S)\left[\rho_s \frac{v^2}{2} - p + \frac{\mu}{8} \int^t \left(\frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right)^2 dt' \right]$$

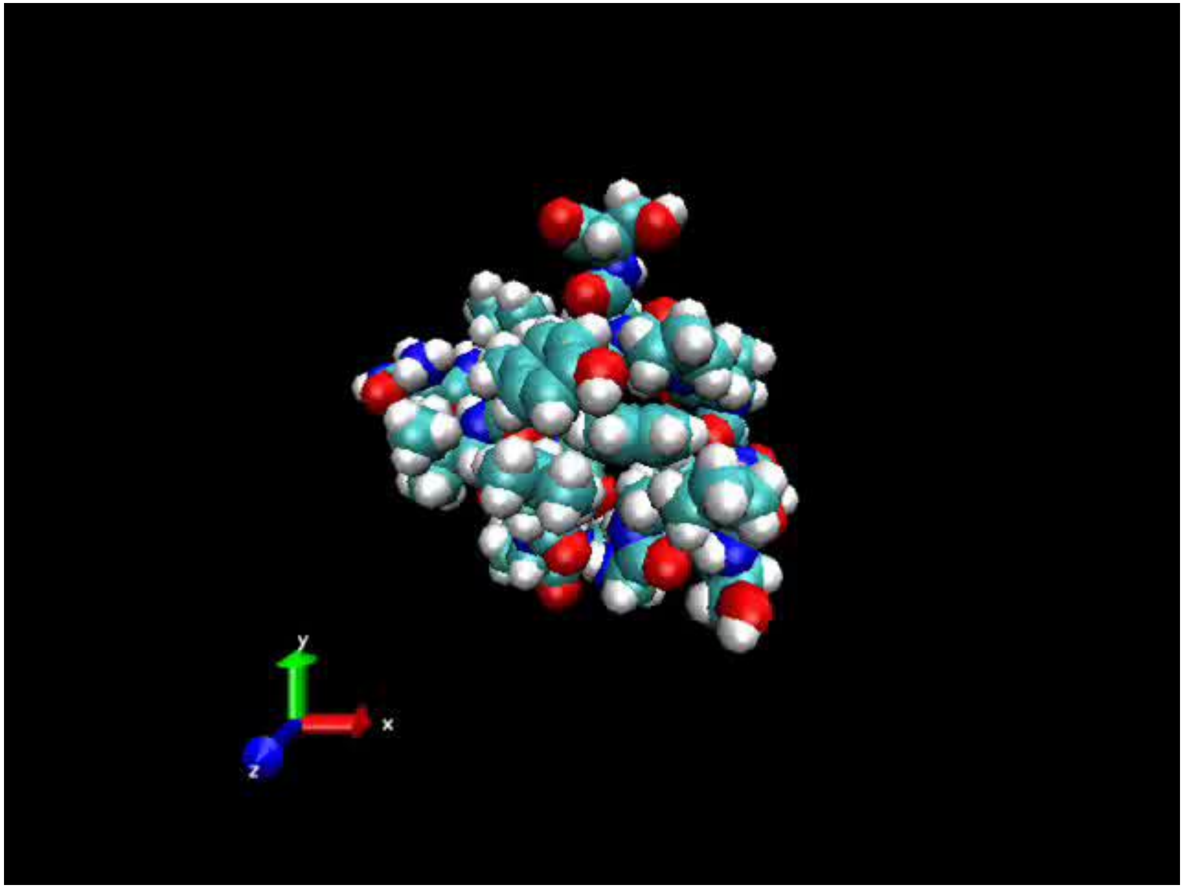
$$G_{MM} = -S \sum \left[\rho_j \frac{\dot{z}_j^2}{2} - U(z) \right]$$

(Wei, BMB, 2010;
Chun Liu et al 2010s)

Coupling of molecular dynamics & fluid dynamics



MIBPB Based Multiscale Molecular dynamics



Wehua Geng

Multiscale MD of Trp-cage miniprotein (1L2Y)

(Geng & Wei, JCP, 2011)

Further topics and future directions

- Ion size-effects and (de)protonation effects.
- Stochastic analysis of ion transport.
- Transmembrane (ATP-binding cassette) transporters.
- Drug permeation rate analysis.
- Coupling of structural change and ion permeation.
- Mechanotransducers.
- Proton-coupled ion/electron transport, ATP production.
- Multiscale multiphysics based discrete-continuum modeling of transmembrane dynamics and transport.
- Mathematical modeling of membrane dynamics and associated organelle function.
- Mathematical modeling of membrane dynamics and associated cellular function.
- Interaction of membrane, protein, receptor, and inhibitor.
- Modeling of G-protein-coupled receptors (GPCRs) dynamics and transport.
- Mathematical modeling of protein-membrane interactions in endoplasmic reticulum and mitochondrial ultrastructure, etc.


thank you