Variational multiscale models for ion channel transport

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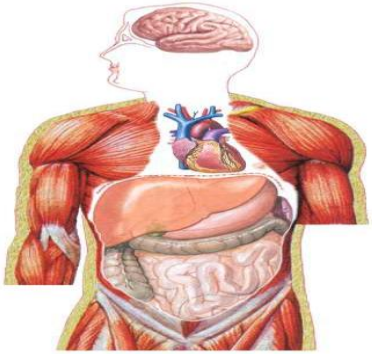
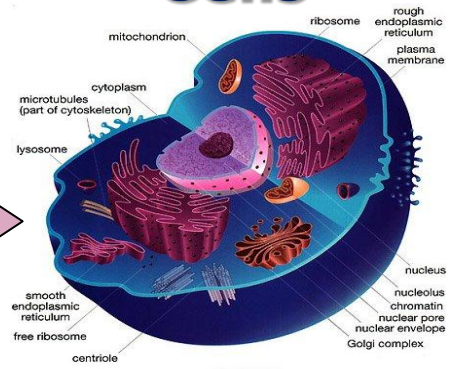
NIH R01GM, NSF DMS, NSF CCF

Species

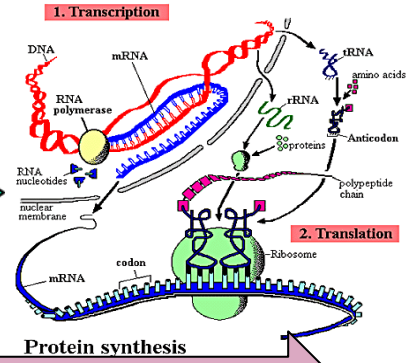
Organs



Cells



Molecules



About 20 orders in spatial scales

About 20 orders in time scales

Evolutionary biology

Reaction diffusion
Stochastic models
Kinetic models
Delayed ODEs
Discrete models
Homology models
Machine learning

Developmental biology
Physiology
Biomechanics

Continuum models
Mechanical models
Navier-Stokes
(Non-) linear elasticity
Maxwell's equation
Thermal models
Rheological models
Hodgkin-Huxley model
Lattice models
Neural networks
Geometric models
Topological models

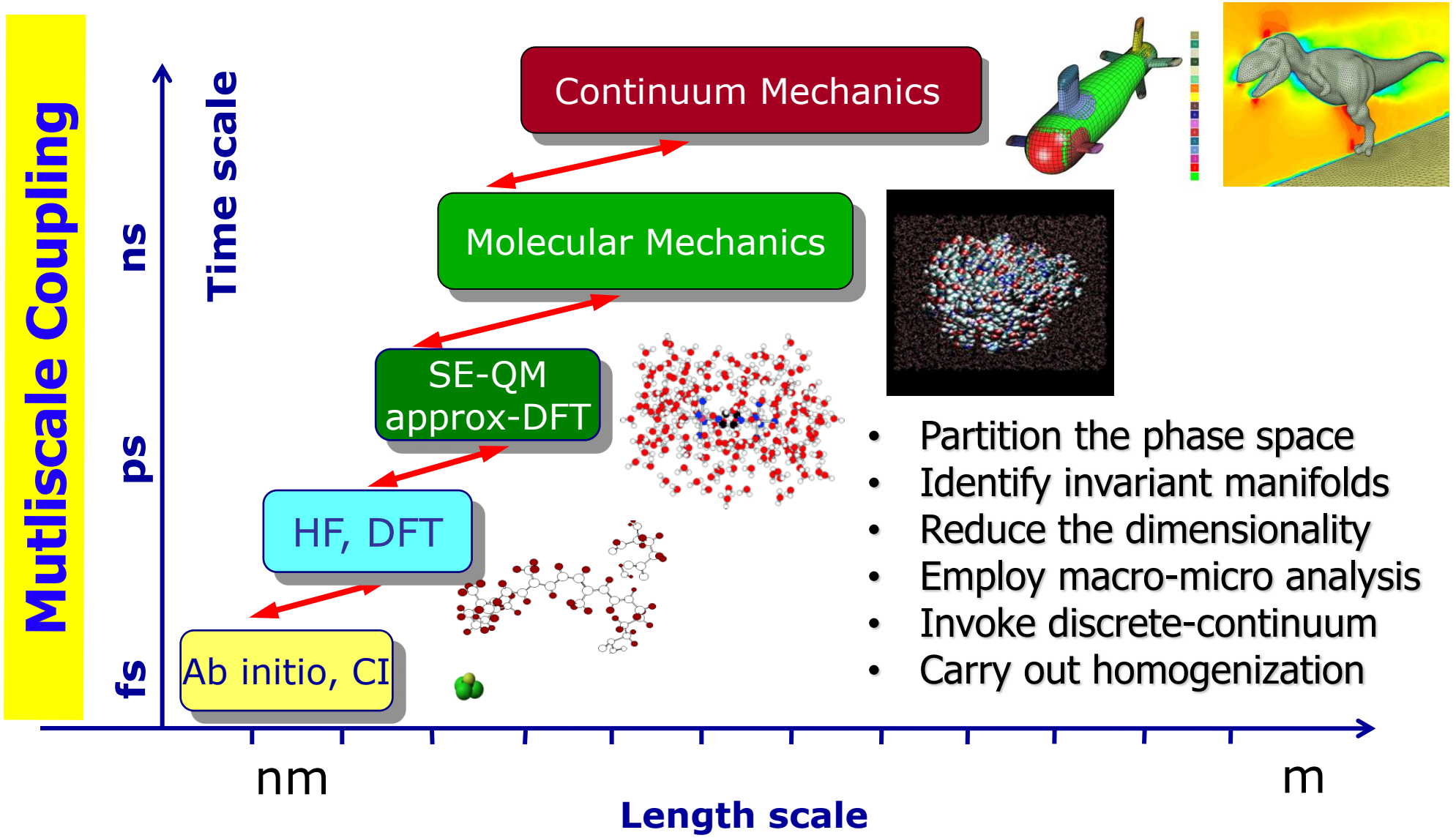
Cellular biology
Systems biology
Cellular mechanics

Chemical kinetics (ODEs)
Gene regulatory network
Protein network
Neural networks
Hodgkin-Huxley model
FitzHugh-Nagumo model
Mechanical models
Reaction diffusion
Phase field models
Stochastic models
Statistical models
Monte Carlo
Combinatory
Topological models
Machine learning

Molecular biology
Biochemistry
Biophysics

Molecular dynamics
Thermal dynamics
Brownian dynamics
Lagevin dynamics
Quantum models
QM/MM
Electrostatics
Implicit models
Boltzmann equation
Vlasov-Boltzmann
Fokker-Planck
Monte Carlo
Master equation
Homology models
Knot theory

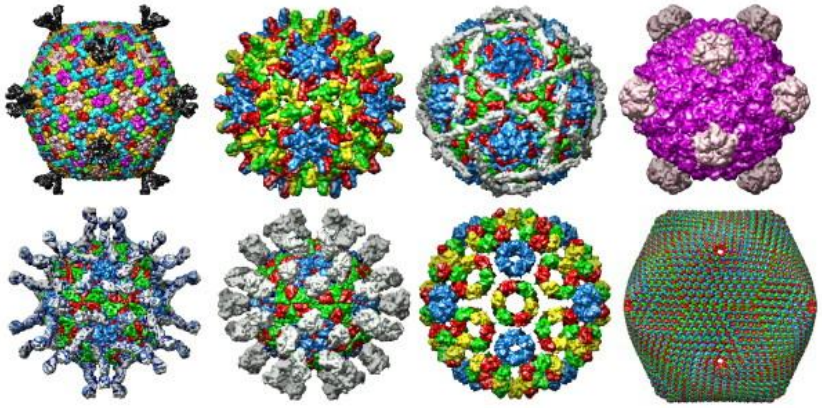
Hierarchy of Methods



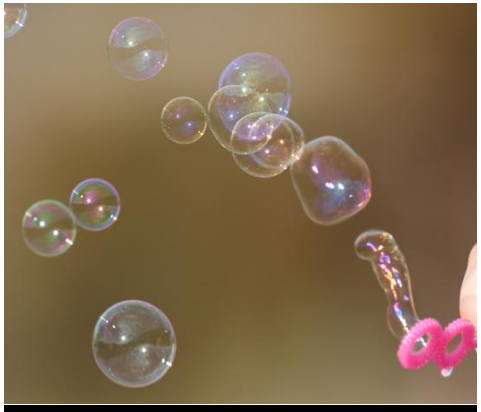
- Partition the phase space
- Identify invariant manifolds
- Reduce the dimensionality
- Employ macro-micro analysis
- Invoke discrete-continuum
- Carry out homogenization

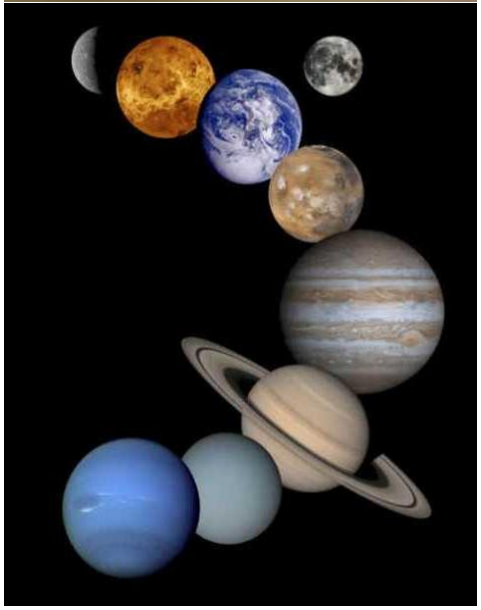
Minimal Surfaces

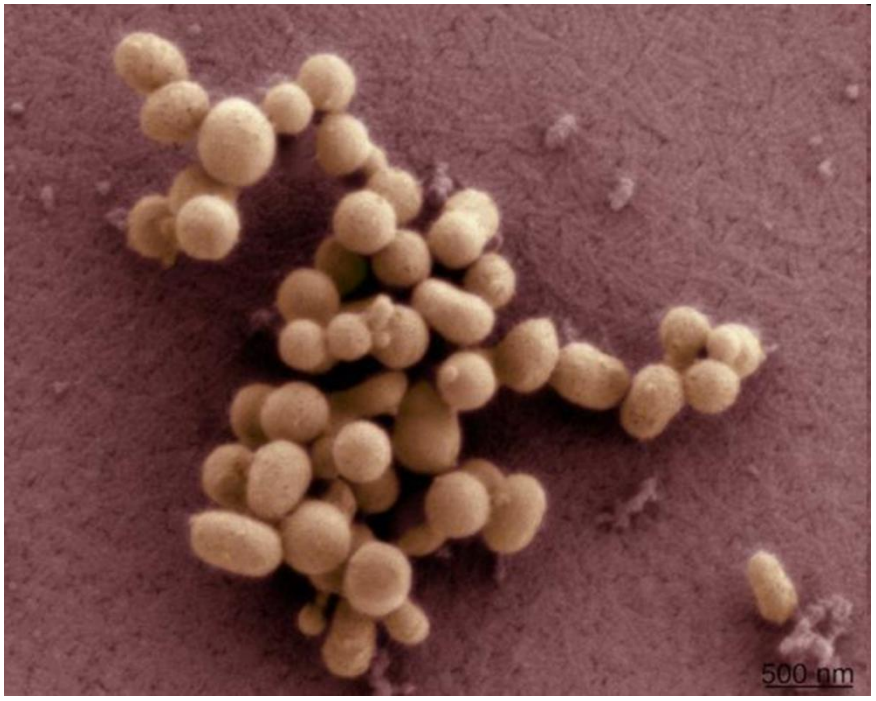
A way to minimize energy and maximize stability



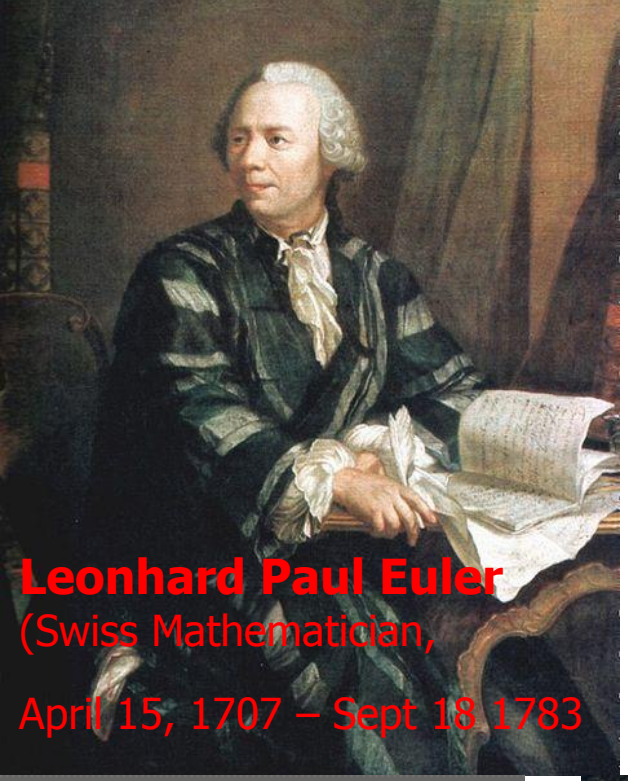
Viral morphology





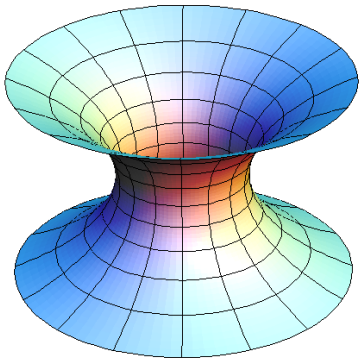


The first man-made life, Bacterium, *M. mycoides*, based on information from a computer



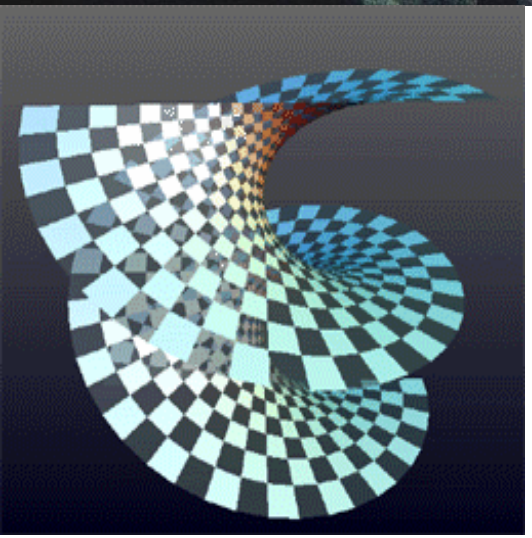
Leonhard Paul Euler
(Swiss Mathematician,
April 15, 1707 – Sept 18 1783

Catenoid



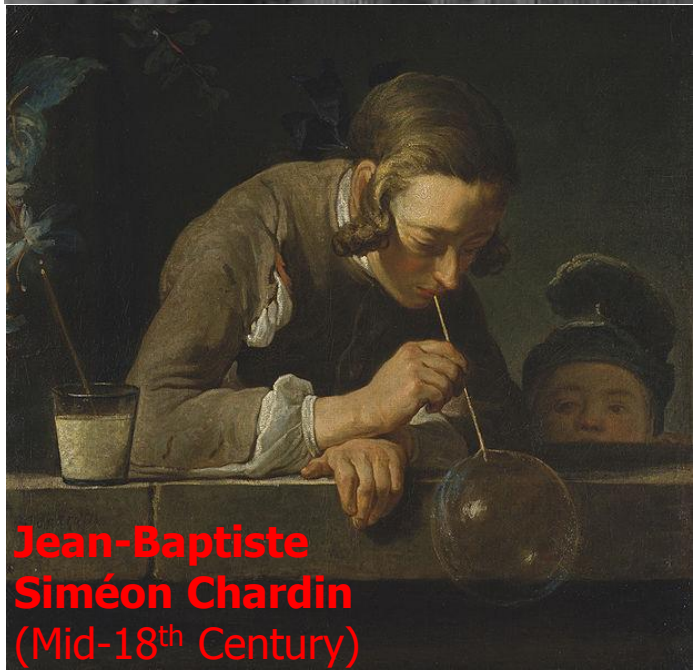
Minimal Surfaces

Joseph-Louis Lagrange
(Italian Mathematician,
January 25 1736 – April 10, 1813)



Helicoid

Jean Baptiste Meusnier
(French, June 19, 1754-June 13, 1793)



Jean-Baptiste Siméon Chardin
(Mid-18th Century)

Free energy functional of a surface model

$$G = \gamma(Area) = \int_U \gamma \sqrt{g}\, du_1 du_2$$

where gamma is the surface tension and g is the Gram determinant: $g = 1 + S_1^2 + S_2^2$ of matrix $(g_{ij}) = \begin{pmatrix} 1+S_1^2 & S_1 S_2 \\ S_2 S_1 & 1+S_2^2 \end{pmatrix}$

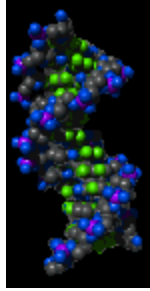
Minimizing the surface free energy with the Euler-Lagrange equation, we arrive at the generalized mean curvature equation:

$$\Delta_\Xi S = \frac{1}{\sqrt{g}} \sum_{ij} \frac{\partial}{\partial x_i} \left(\gamma \sqrt{g} g^{ij} \frac{\partial}{\partial x_j} S \right) = \frac{1}{\sqrt{g}} \nabla \bullet \left(\frac{\gamma}{\sqrt{g}} \nabla S \right) = 0$$

where $\Delta_\Xi S$ is the Laplace-Beltrami operator. We solve the Laplace-Beltrami equation below to generate minimal molecular surfaces:

$$\frac{\partial S}{\partial t} = \sqrt{g} \left[\nabla \cdot \left(\frac{\gamma \nabla S}{\sqrt{g}} \right) \right]$$

(Bates, Wei & Zhao, 2006)

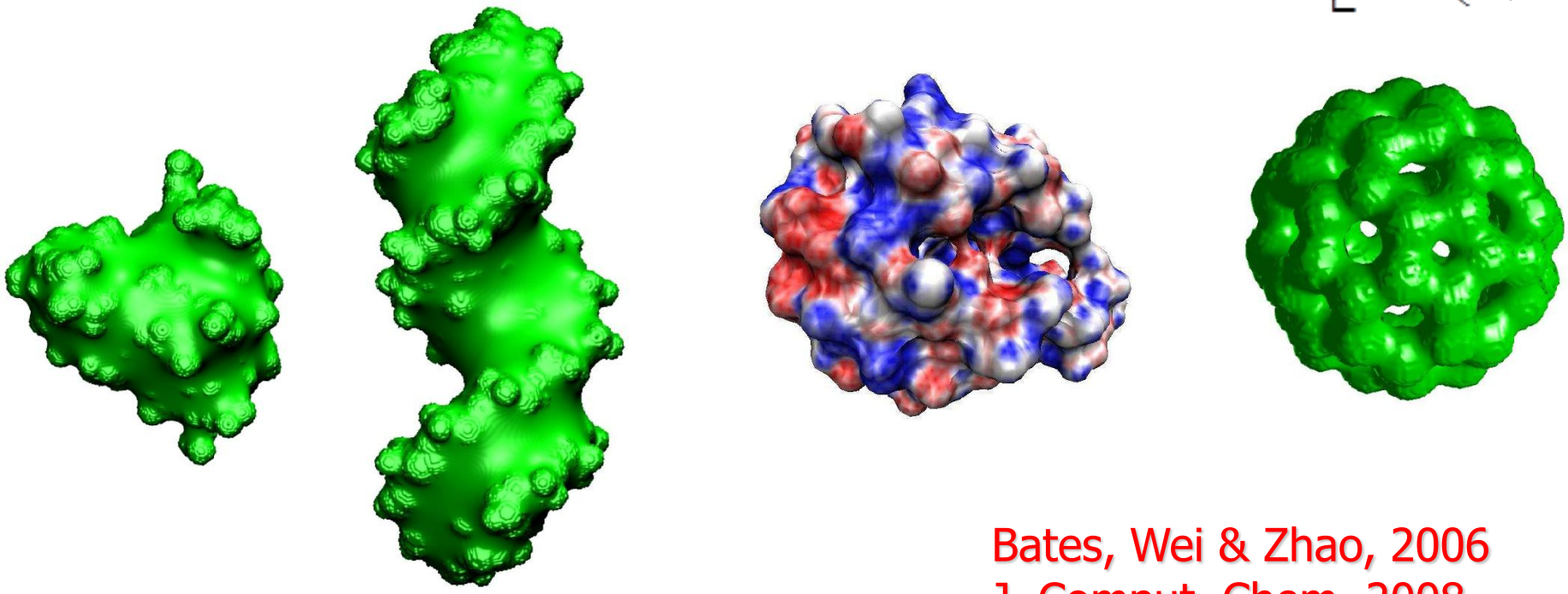


Minimal Molecular surface

The first biomolecular surface constructed with the variational principle

Generalized Laplace-Beltrami flow:

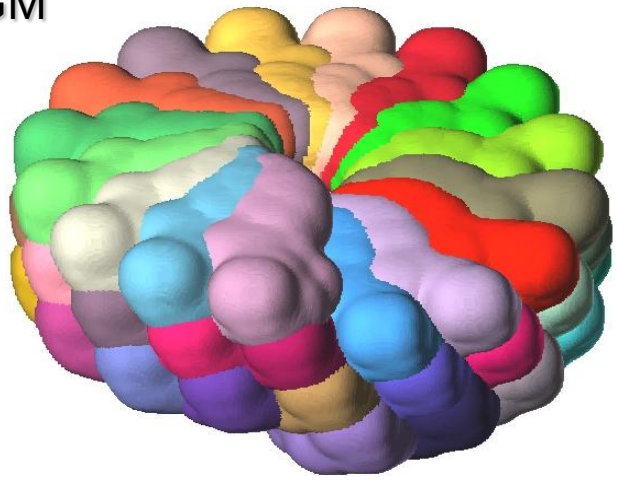
$$\frac{\partial S}{\partial t} = \sqrt{g}\left[\nabla \cdot \left(\frac{\gamma \nabla S}{\sqrt{g}}\right)\right]$$



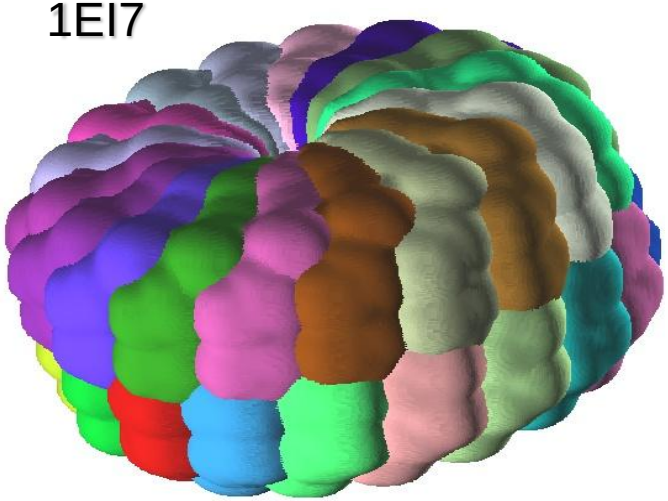
Bates, Wei & Zhao, 2006
J. Comput. Chem. 2008

Virus surfaces

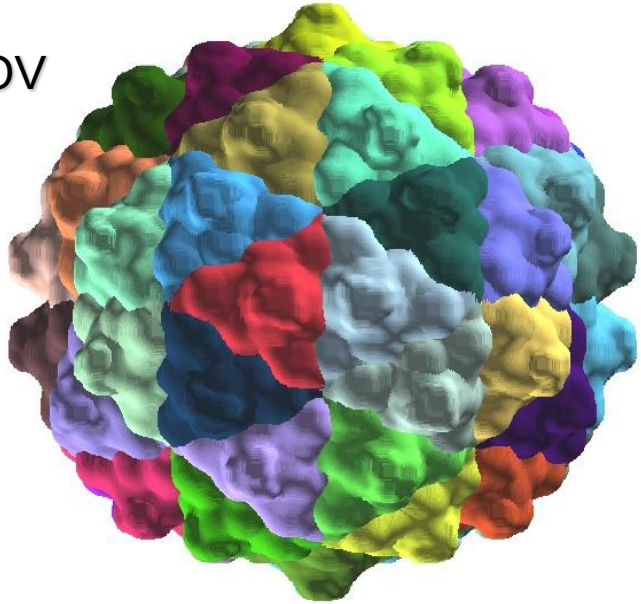
1CGM



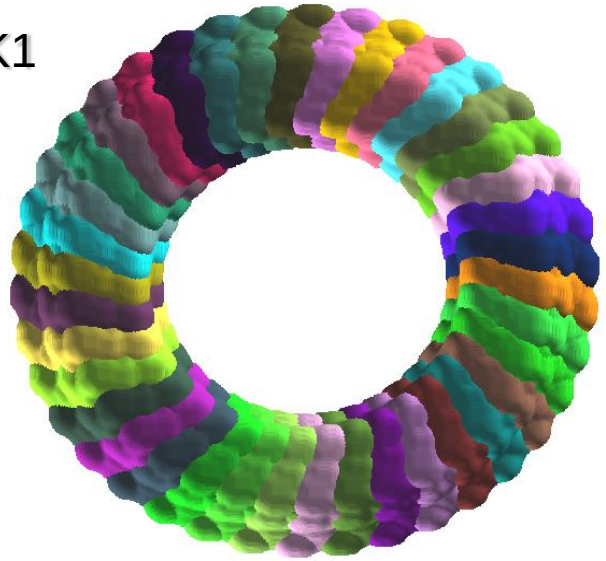
1EI7



1NOV



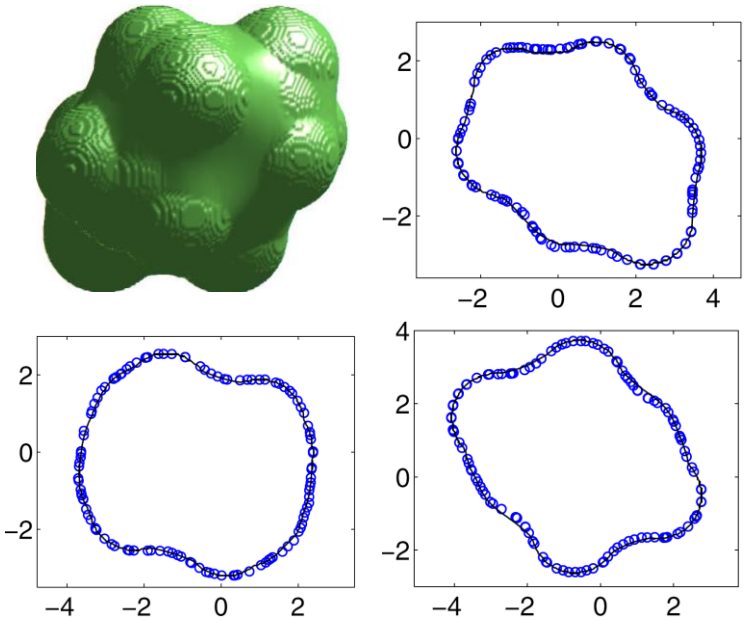
2BK1

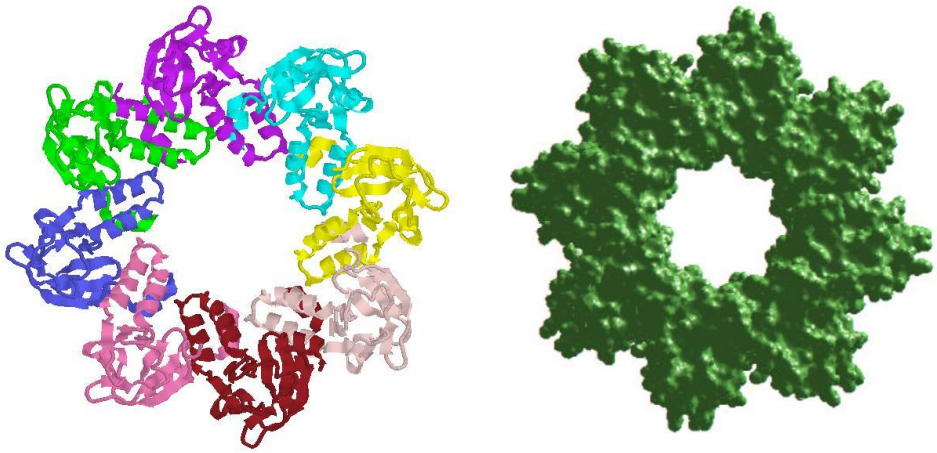


Chen, Saxena, Wei, IJBI, 2009

The first PDE based molecular surface model

$$\frac{\partial S}{\partial t} = \sum_{n=0} \nabla \bullet \left[d_n \left(|\nabla S| \right) \nabla \nabla^{2n} S \right] + P\left(|\nabla S| \right)$$





The cell division protein, PDB ID: 1N0E, 9245 atoms in 1328 residues

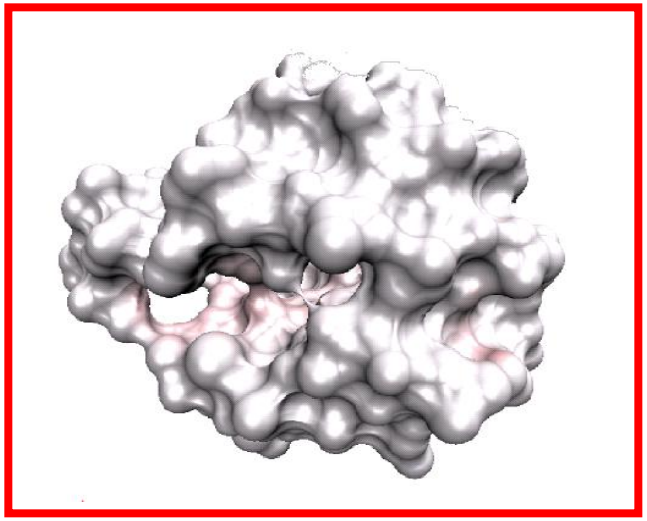
Major feature: Starting from atomic information, instead of a given surface

(Wei, Sun, Zhou and Feig, 2005)

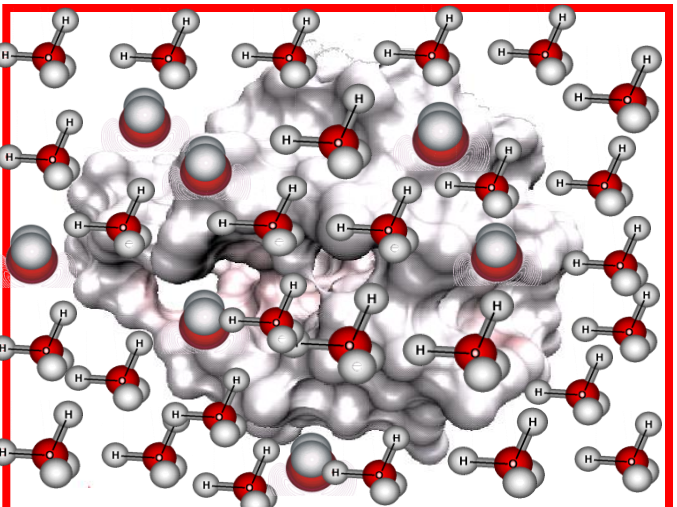
Solvation analysis

Physiological fact: 65-90% cell mass is water

Protein in vacuum:

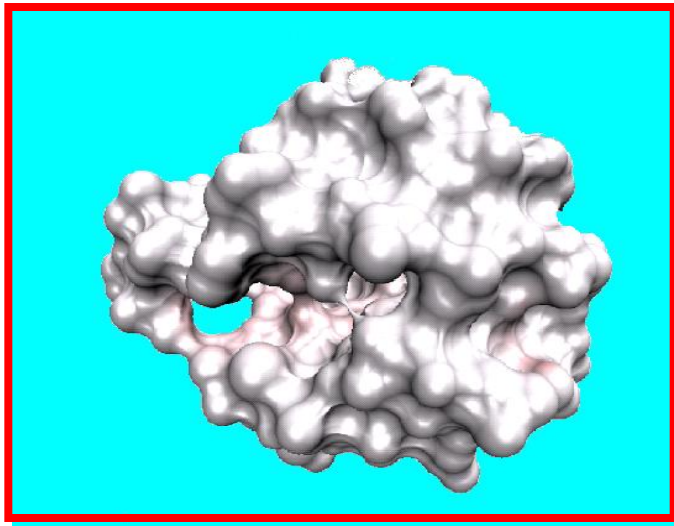


Protein in water:



Solvation

Implicit solvent model



Differential geometry based nonpolar solvation model

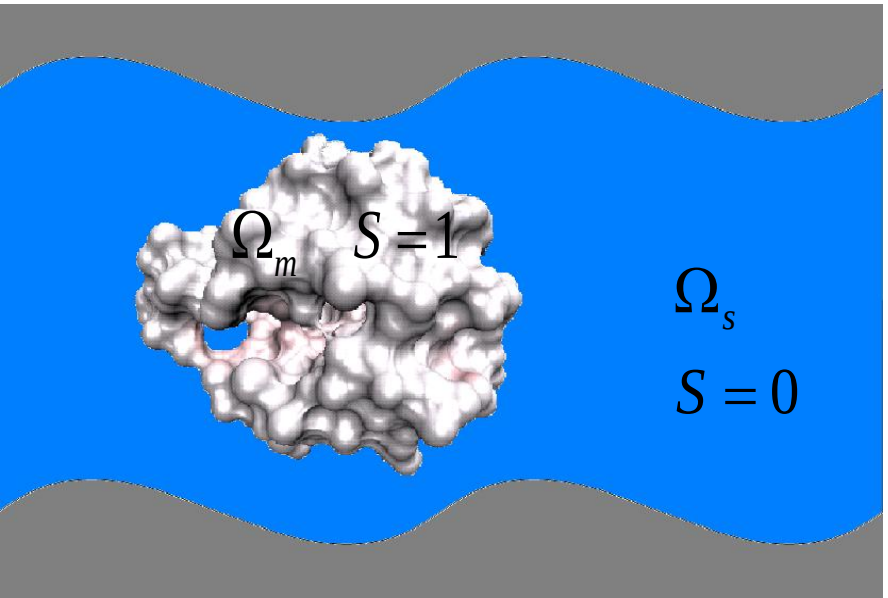
$$G = \int_{\Omega} \left[\gamma |\nabla S| + Sp + (1-S)U \right] dr$$

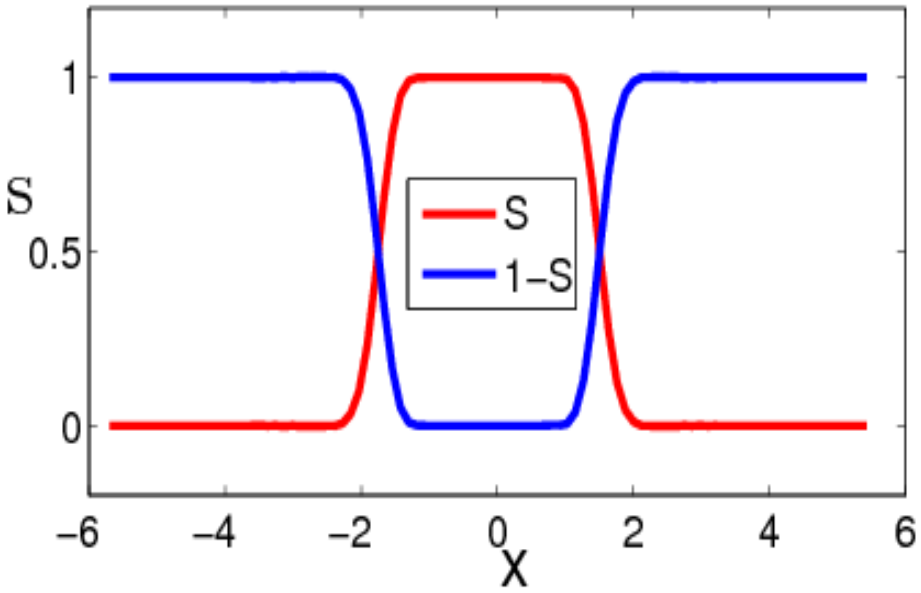
(Wei, BMB, 2010;
Chen, Zhao, Baker, Bates, Wei, 2011)

area + volume + van der Waals

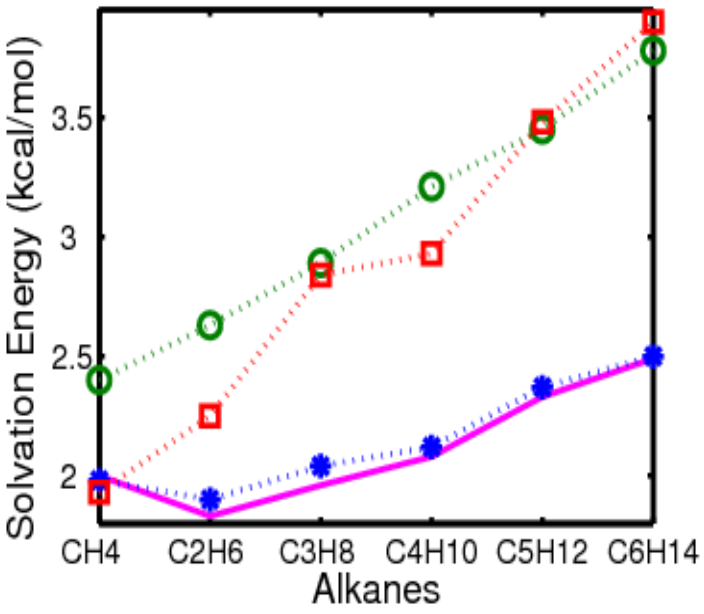
$$\frac{\partial S}{\partial t} = |\nabla S| \left[\nabla \bullet \frac{\gamma \nabla S}{|\nabla S|} - p + U \right]$$

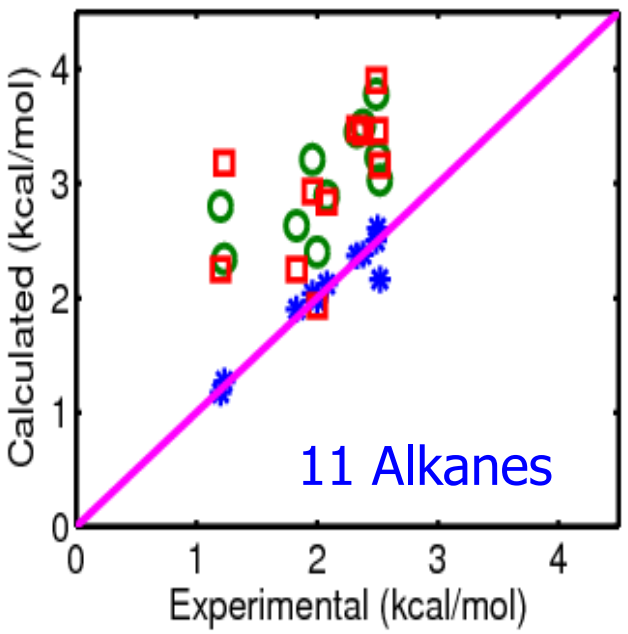
Laplace-Beltrami equation

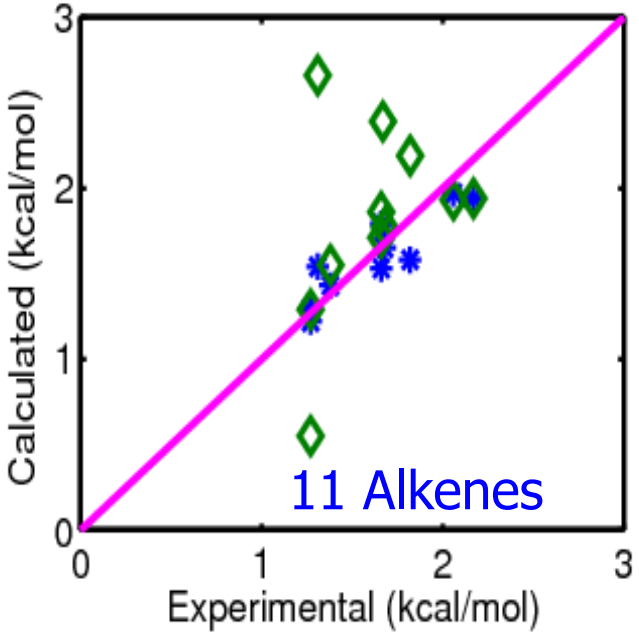




Comparison of nonpolar solvation free energies







- Variational multiscale (Chen, Zhao, Baker, Bates, Wei, 2011)
- Wagoner and Baker. PNAS,103, 8331, 2006.
- Gallicchio, Kubo, Levy, J. Phys. Chem. B, 104, 6271, 2000
- Ratkova et al, (integral eqn theory) J. Phys. Chem. B, 114, 12068, 2010.

Differential geometry based solvation model

$$G = \int_{\Omega} [Nonpolar + Electro]\, dr$$

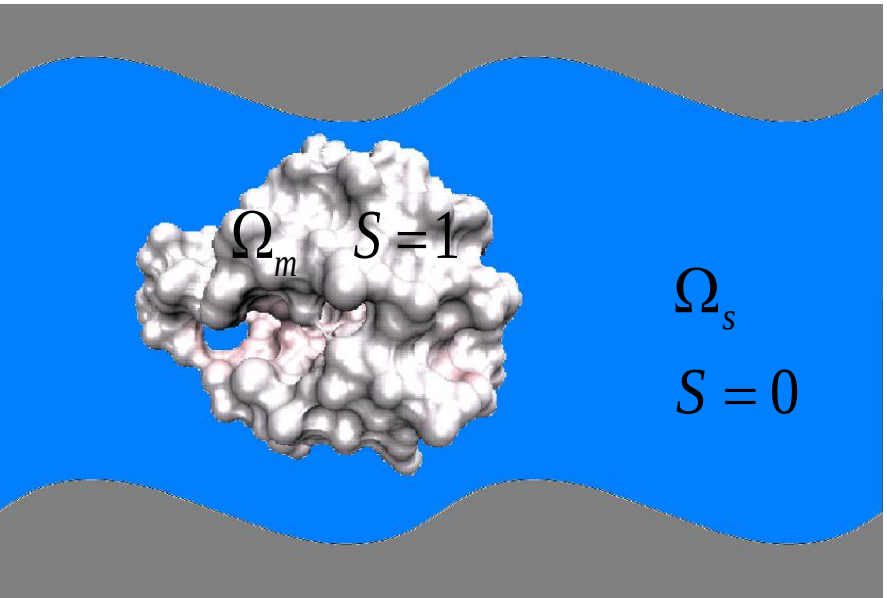
(Wei, BMB, 2010;
Chen, Baker, Wei, JCP,2010)

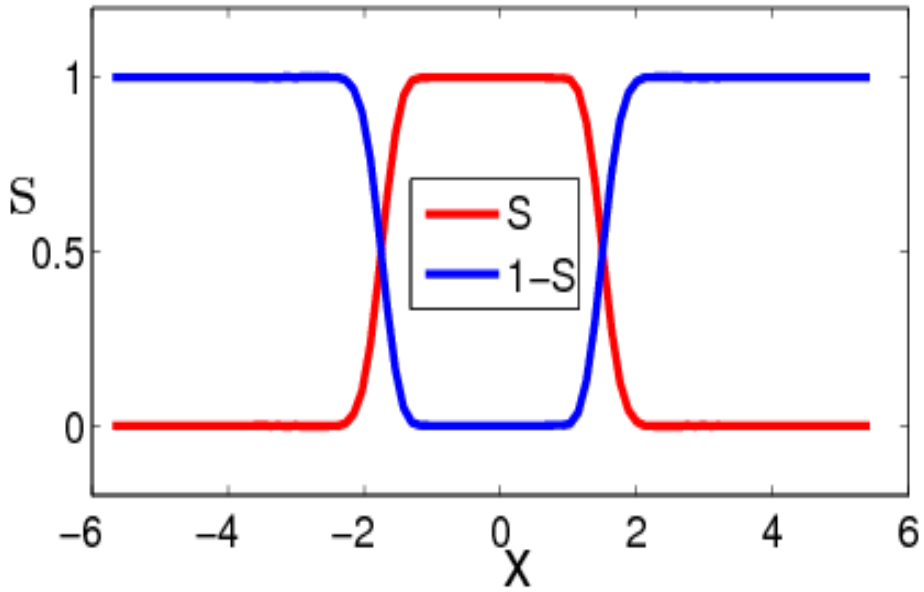
Geometric = area + volume + van der Waals:

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

Electro = electric field + solute charges + solvent ions:

$$Electro = S\left(\frac{\varepsilon_m}{2}|\nabla\phi|^2 - \phi n\right) + (1-S)\left[\frac{\varepsilon_s}{2}|\nabla\phi|^2 + kT\sum_i c_i\left(e^{-q_i\phi/kT} - 1\right)\right]$$





Variation of the total free energy functional

$$\frac{\partial S}{\partial t} = \nabla \bullet \left(\gamma \frac{\nabla S}{|\nabla S|} \right) - p + U - \frac{\varepsilon_m - \varepsilon_s}{2} |\nabla \phi|^2 + kT \sum_i c_i \left(e^{-q_i \phi / kT} - 1 \right) - \phi n$$

Generalized Laplace Beltrami equation

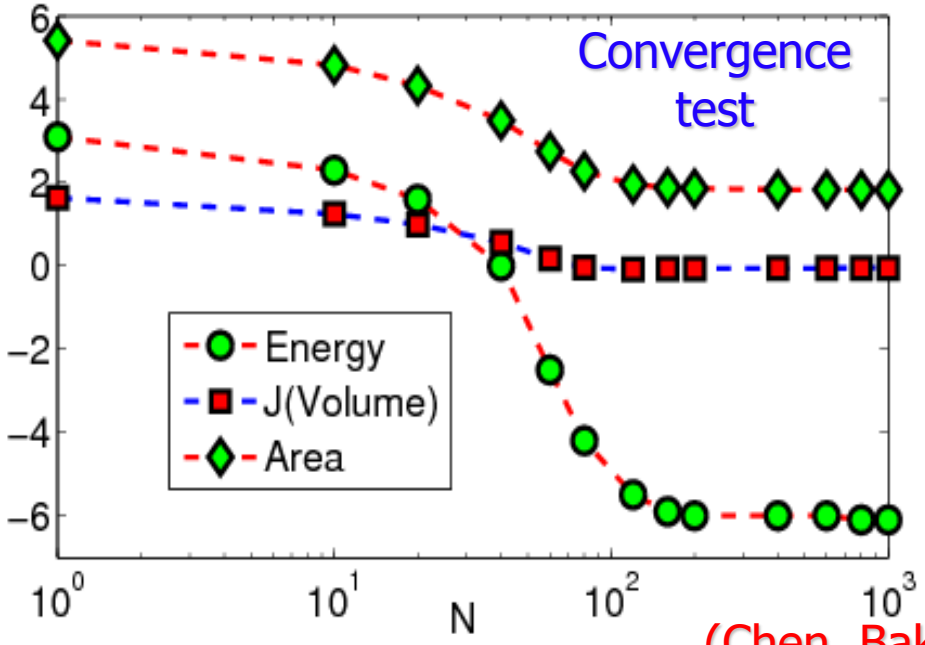
$$-\nabla \bullet \left(\varepsilon(S) \nabla \phi \right) = (1 - S) \sum_i q_i c_i e^{-q_i \phi / kT} + Sn$$

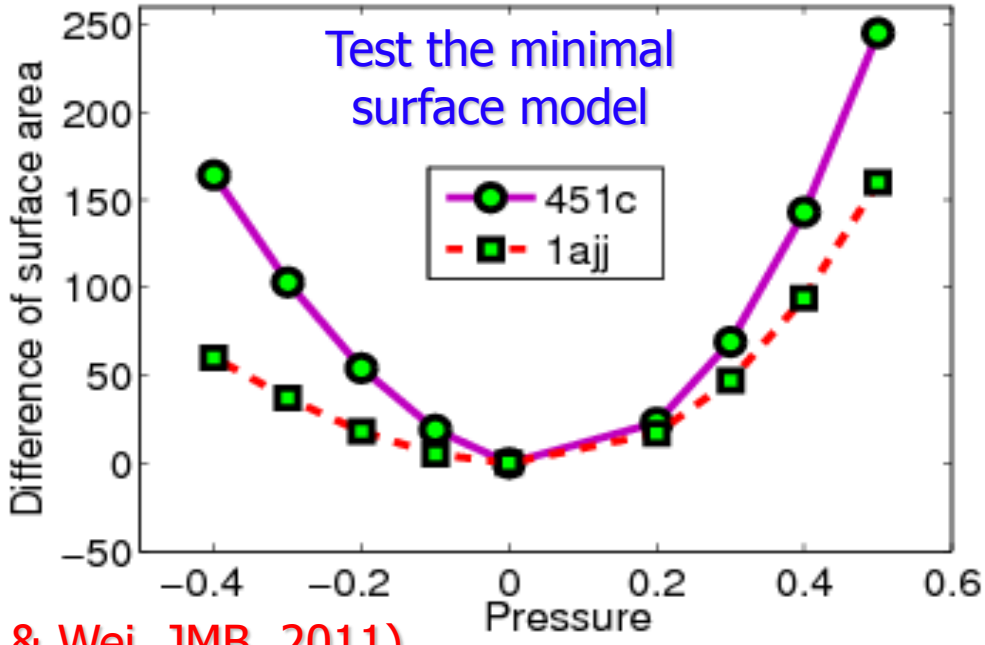
Generalized Poisson-Boltzmann equation

Applications

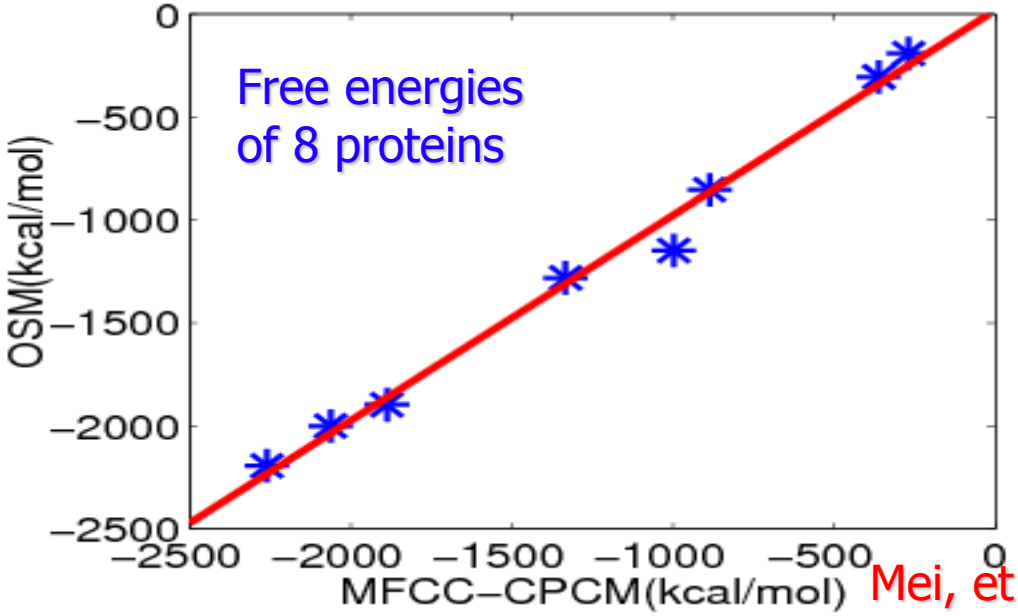
- Electrostatic binding and solvation energies
- pKa, pH values
- Electrostatic forces, ionic distributions
- Electrostatic matching between proteins and ligands
- Stability of protein folding
- Molecular dynamics
- A tool for rational drug design (interactions of receptor-inhibitor, protein-ligand, protein-protein, signal, enzyme, regulator, etc.)

Validation of the multiscale solvation model

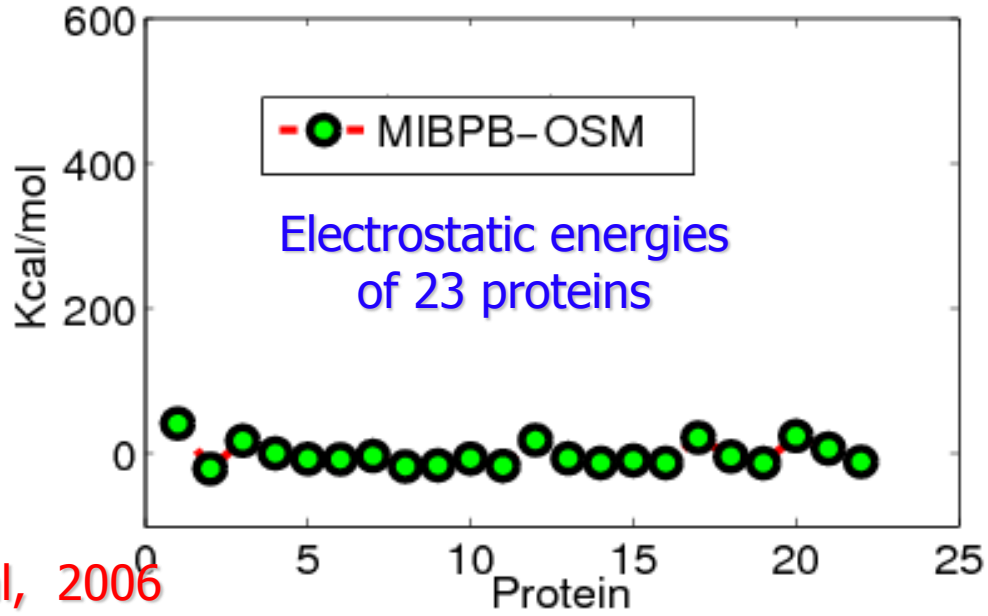




(Chen, Baker & Wei, JMB, 2011)



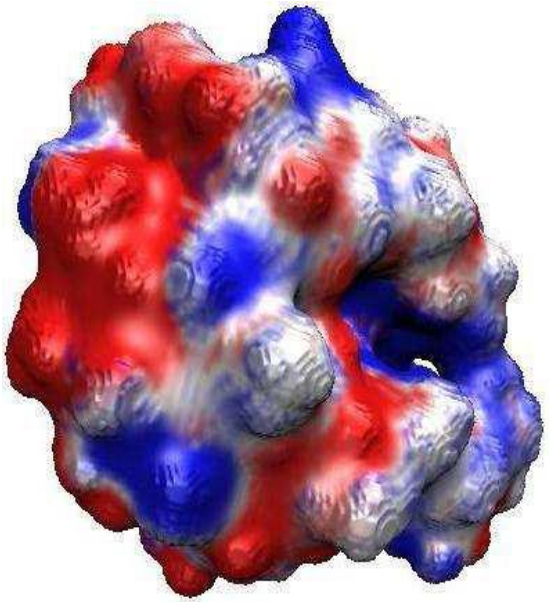
Mei, et al, 2006



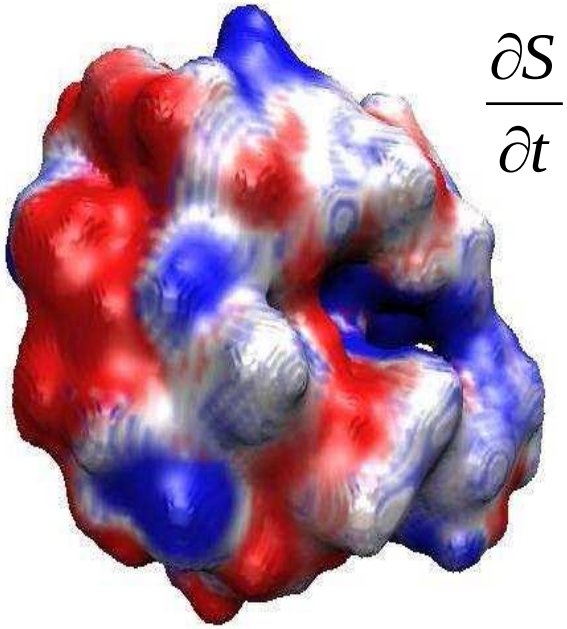
Effect of interaction potentials

(Chen, Baker & Wei, JCP, 2010)

$$\frac{\partial S}{\partial t} = \sqrt{g}\left[\nabla \cdot \left(\frac{\nabla S}{\sqrt{g}}\right) - V\right]$$

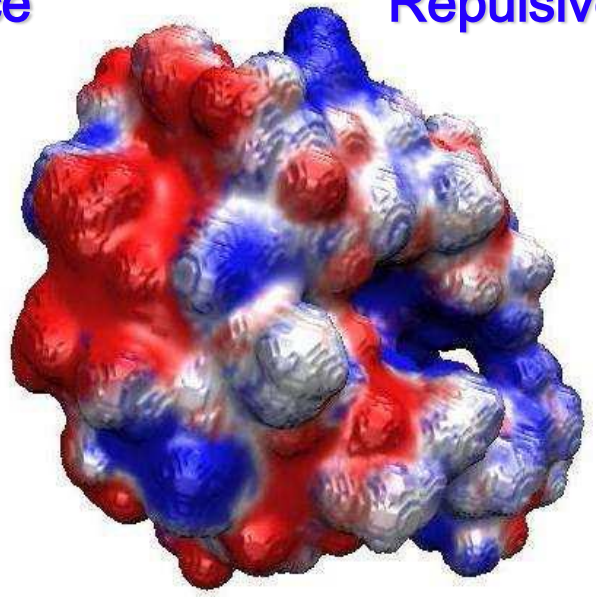


Minimal molecular surface

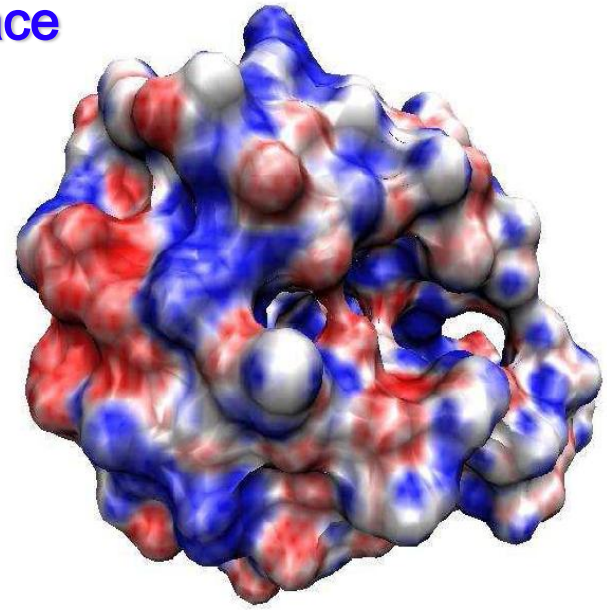


Repulsive surface

Protein 451c



Attractive surface



Connolly surface

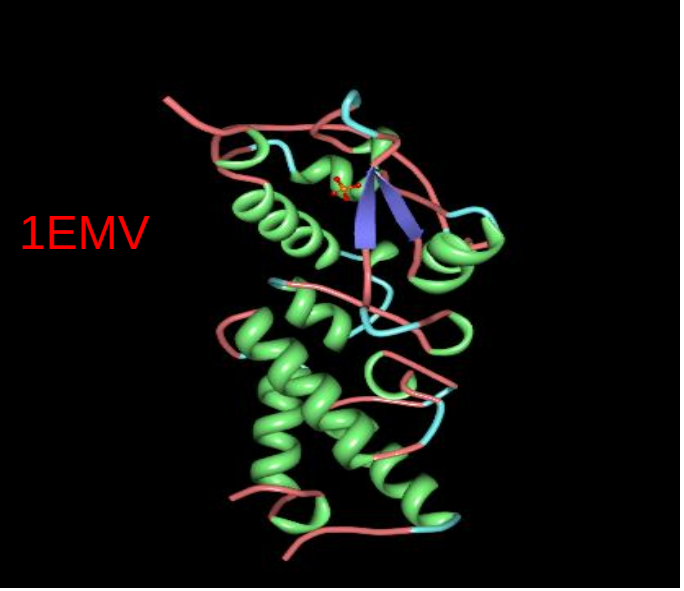
Blind test of 17 compounds: No parameter fitting!

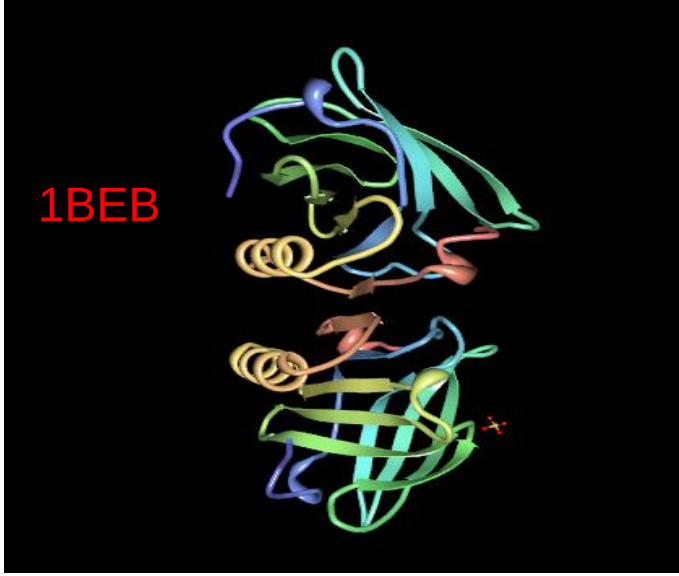
(Chen, Baker & Wei, JCP, 2010)

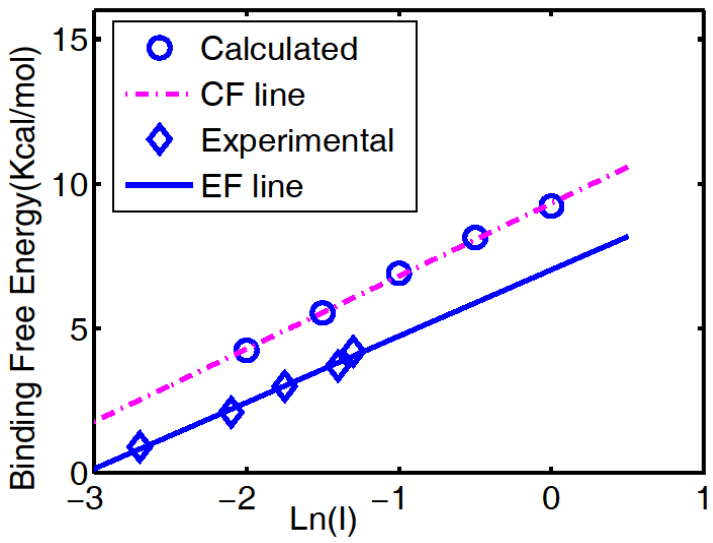
Compound	Area	Volume	G_{np}	ΔG_p	ΔG	Exptl	Error
glycerol triacetate	241.34	234.11	2.33	-12.36	-10.03	-8.84	-1.19
benzyl bromide	150.66	136.36	1.39	-4.87	-3.47	-2.38	-1.09
benzyl chloride	148.14	133.84	1.36	-5.06	-3.70	-1.93	-1.77
m-bis(trifluoromethyl)benzene	266.67	306.86	2.22	-3.30	-1.07	1.07	-2.14
N,N-dimethyl-p-methoxybenzamide	209.31	202.02	1.99	-9.22	-7.22	-11.01	3.79
N,N-4-trimethylbenzamide	200.27	193.25	1.91	-7.84	-5.93	-9.76	3.83
bis-2-chloroethyl ether	155.71	130.90	1.44	-4.16	-2.71	-4.23	1.52
1,1-diacetoxyethane	177.82	160.48	1.67	-8.21	-6.53	-4.97	-1.56
1,1-diethoxyethane	163.66	143.73	1.55	-4.63	-3.08	-3.28	0.20
1,4-dioxane	109.56	143.73	1.01	-5.64	-4.62	-5.05	0.43
diethyl propanedioate	195.06	182.22	1.87	-7.75	-5.88	-6.00	0.12
dimethoxymethane	109.17	88.36	1.02	-4.64	-3.62	-2.93	-0.69
ethylene glycol diacetate	168.19	160.95	1.62	-8.40	-6.78	-6.34	0.44
1,2-diethoxyethane	169.25	141.92	1.57	-4.40	-2.83	-3.54	0.71
diethyl sulfide	133.81	116.84	1.22	-2.40	-1.17	-1.43	0.26
phenyl formate	148.14	134.84	1.37	-7.82	-6.45	-4.08	-2.37
imidazole	89.05	68.59	0.80	-11.56	-10.76	-9.81	-0.95

RMS=1.78 compared with RMS=1.87 by Nicholls et al (2008)

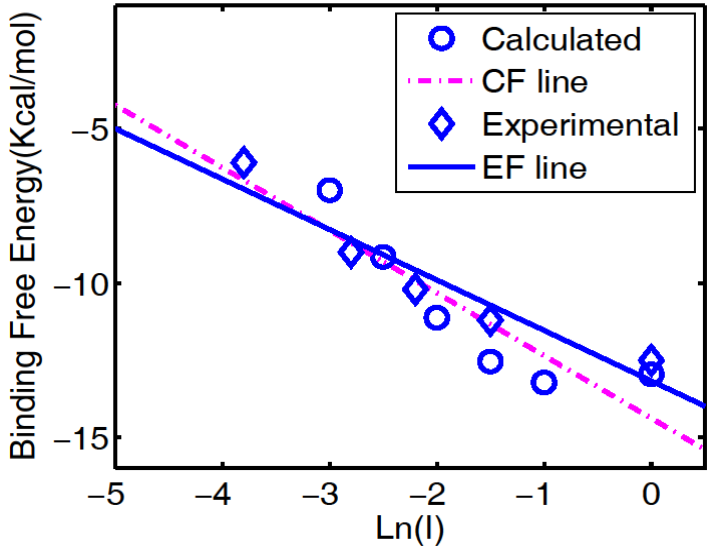
Binding free energies of protein-protein interactions





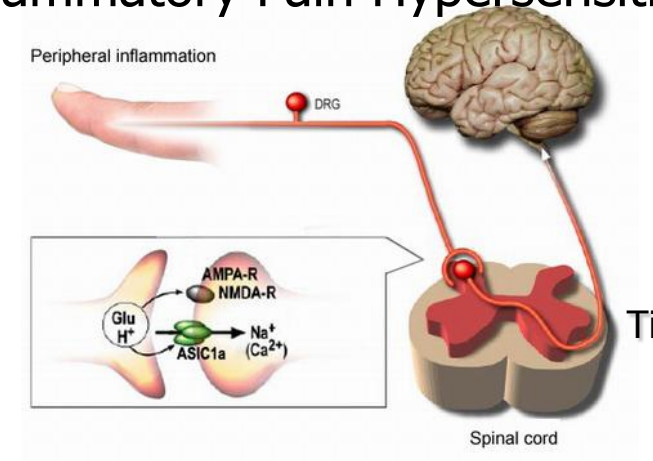


(Chen, Baker & Wei, JMB, 2011)



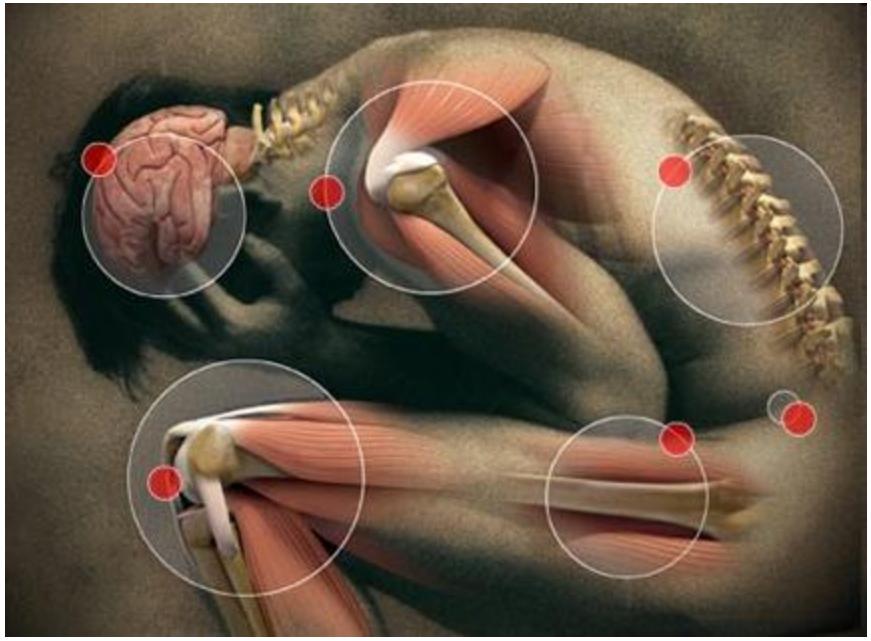
Complex	PDB code	Complex charge	Surface Area (Å²)	Charge of the free monomers	Experimental data	Calculated
E9Dnase-Im9 (10)	1emv	-3	1465	B=+5; A=-8	2.17	2.52
Lactoglobulin Dimer (57) (A-B)	1beb	+26	1167	A=B=+13	-1.62	-2.02

Acid-Sensing Ion Channel in Inflammatory Pain Hypersensitivity

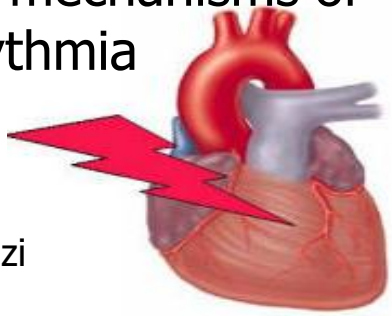


Tian-Le Xu

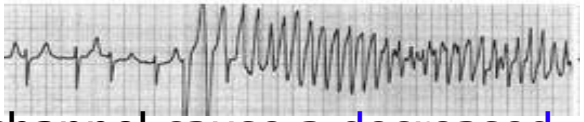
Increased ASIC ion channel activity in SDH neurons promotes pain by central sensitization



The molecular mechanisms of inherited arrhythmia

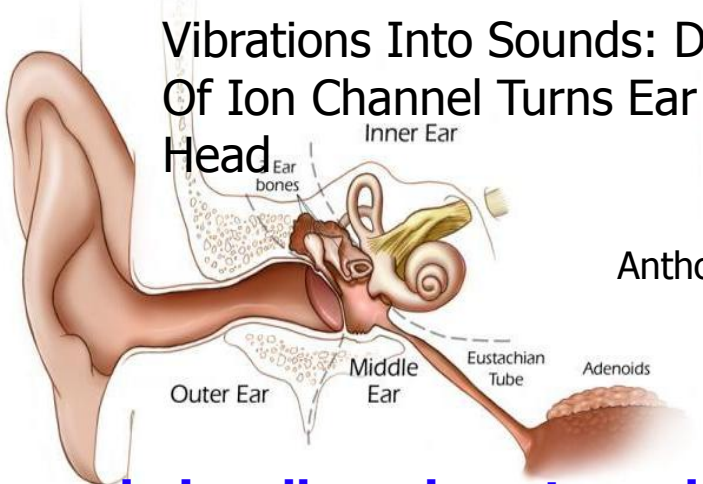


M. Tristani-Firouzi



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

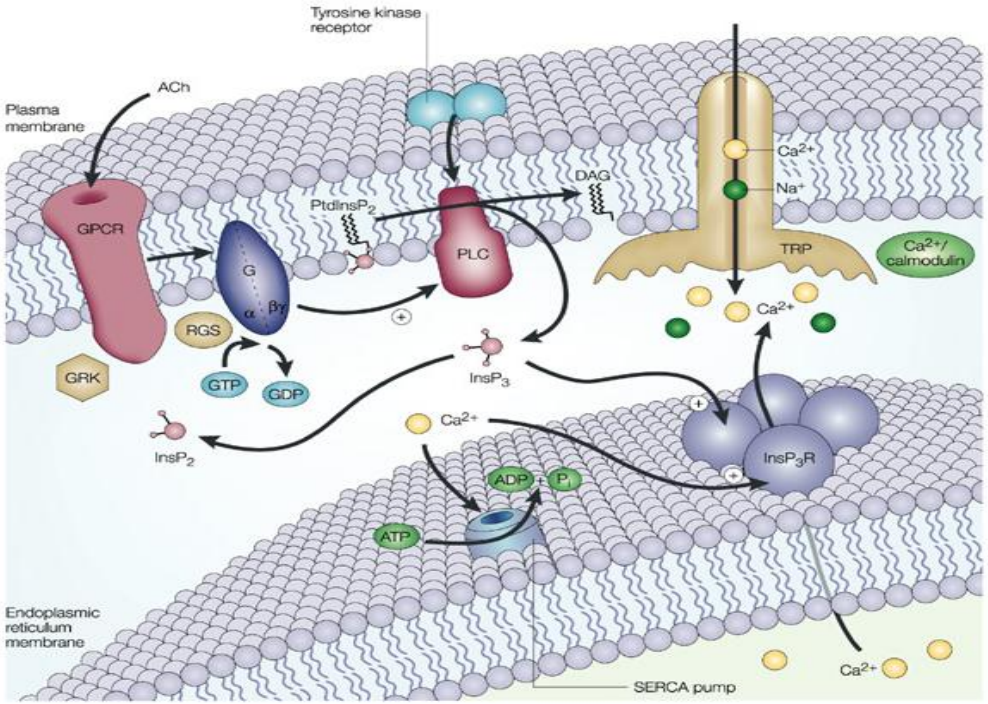


Anthony Ricci

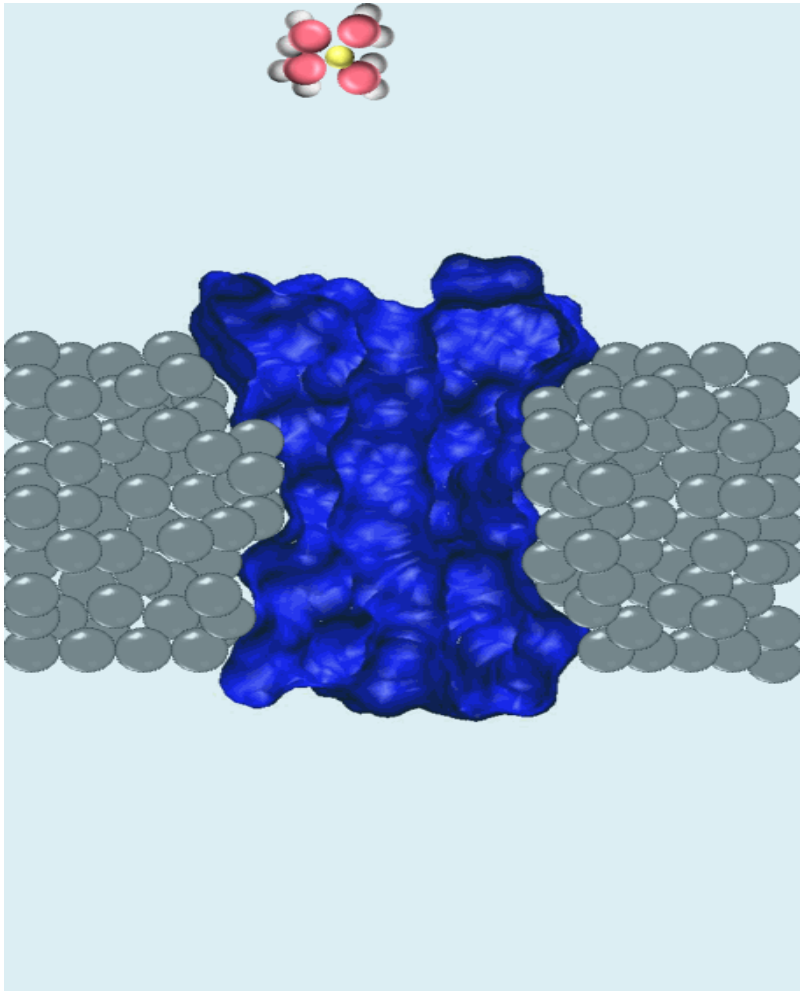
Inner hair cell mechanotransducer calcium channels turns sounds into electrical current

Physiological Facts

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



Nature Reviews | Drug Discovery



- Ion channels are small highly selective pores in the cell membrane
- Move ions or water
- Fast rate of transport 10^6 ions/s
- Transport is always down the gradient
- Non-equilibrium process

Ion channels - natural nano-bio devices

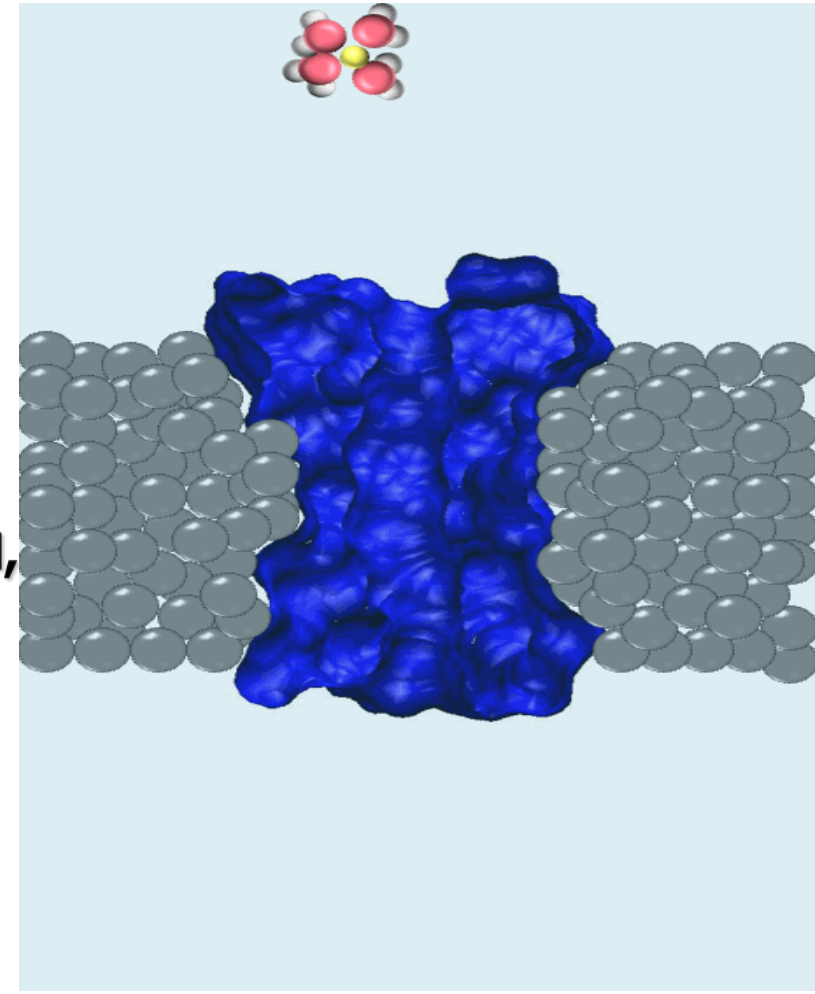
Ion channels are **Device Elements** that self-assemble into perfectly reproducible arrays.

Ion channels have **Selectivity**
K channel selects K+ over Na+ by ~104.

Ion channels **Gate/Switch** in response to chemical, thermal, acoustic, photonic, mechanical stimuli

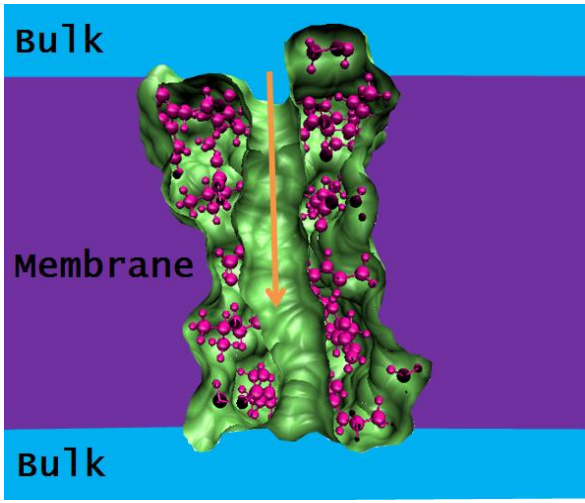
Ion channels allow **Mutations** and **Evolutions**

Ion channels give rise to **Templates** for design of nano-bio devices and sensors



Differential geometry based Poisson-Nernst-Planck

(Zheng, Chen, & Wei, 2011)



$$G = \int \{Nonpolar + Electro + Chemical\} dx$$

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

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

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

Nonpolar: Surface energy, mechanical work and general interactions
Electro: Electrostatic energies in protein and in solvent
Chemical: Chemical potentials and concentration effect

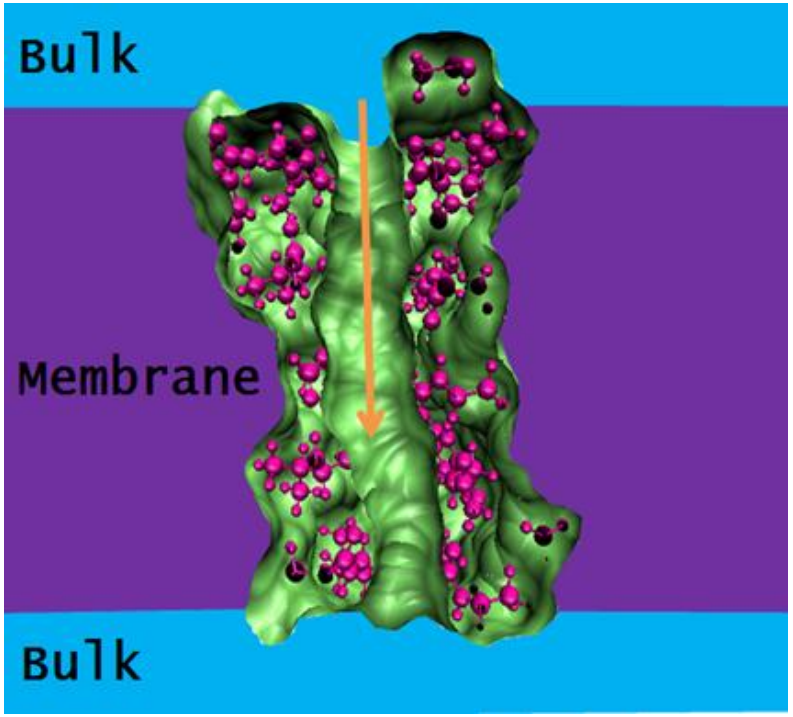
Generalized Poisson equation

$$\frac{\delta G}{\delta \phi} \quad \Rightarrow \quad -\nabla \bullet \varepsilon(S)\nabla\phi = S\sum_j Q_j \delta(r - r_j) + (1-S)\sum q_\alpha n_\alpha$$

$$\varepsilon(S) = S\varepsilon_m + (1-S)\varepsilon_s$$

Electrochemical potential

$$\frac{\delta G}{\delta n_\alpha} \Rightarrow \qquad \mu_\alpha = \mu_{0\alpha} + kT \ln \frac{n_\alpha}{n_{\alpha 0}} + q_\alpha \phi + U_\alpha$$



Nernst-Planck equation

$$J_\alpha = -D_\alpha n_\alpha \nabla \frac{\mu_\alpha}{kT}, \qquad \frac{\partial n_\alpha}{\partial t} = -\nabla \bullet J_\alpha$$

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

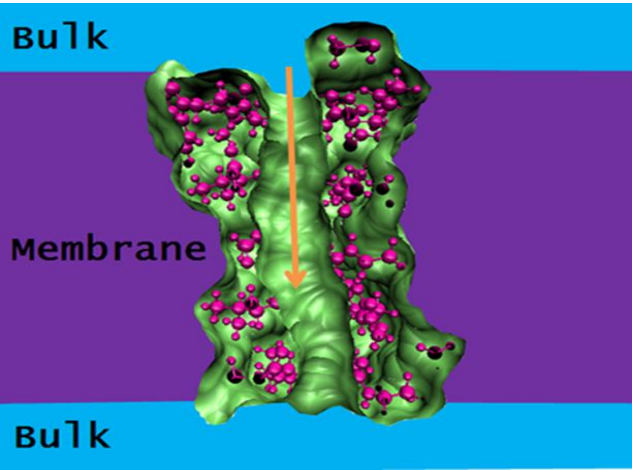
Generalized Laplace-Beltrami equation

$$\frac{\delta G}{\delta S} \Rightarrow \frac{\partial S}{\partial t} = |\nabla S| \left[\nabla \bullet \frac{\gamma \nabla S}{|\nabla S|} + V_{LB} \right]$$

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

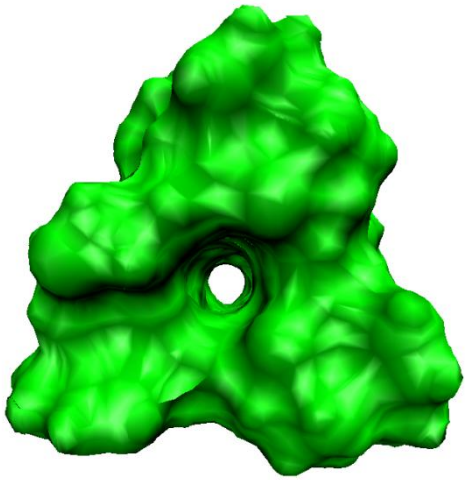
$$-\phi \sum_{j} Q_j \delta(r - r_j) + \frac{\varepsilon_m}{2} |\nabla \phi|^2 + \sum_{\alpha} n_{\alpha} q_{\alpha} \phi - \frac{\varepsilon_s}{2} |\nabla \phi|^2$$

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

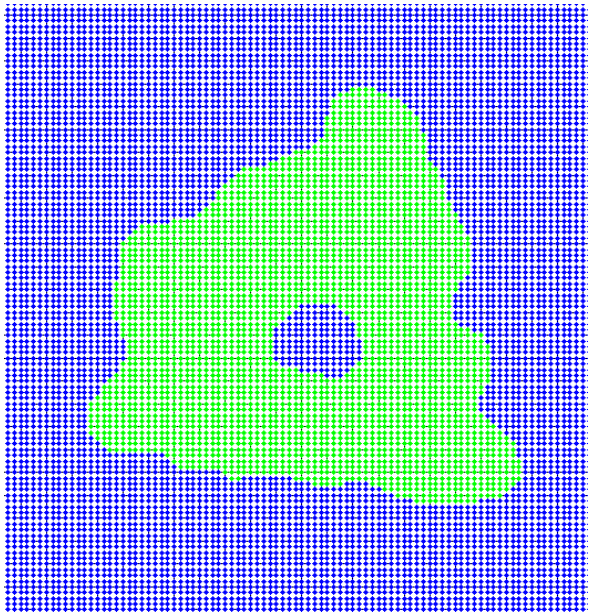


Computational issues

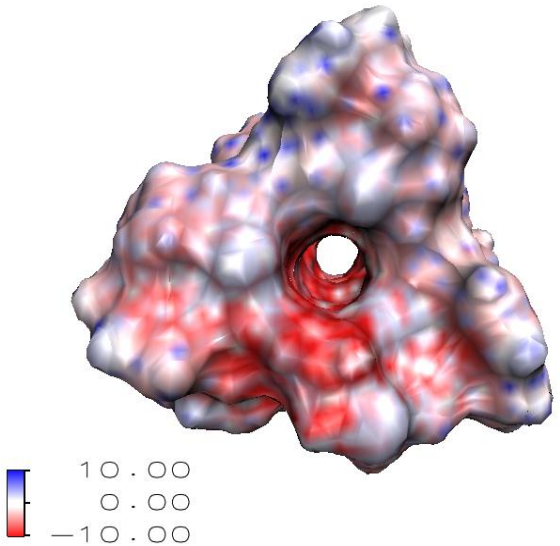
Channel surface



Computational domain



Electrostatic potential



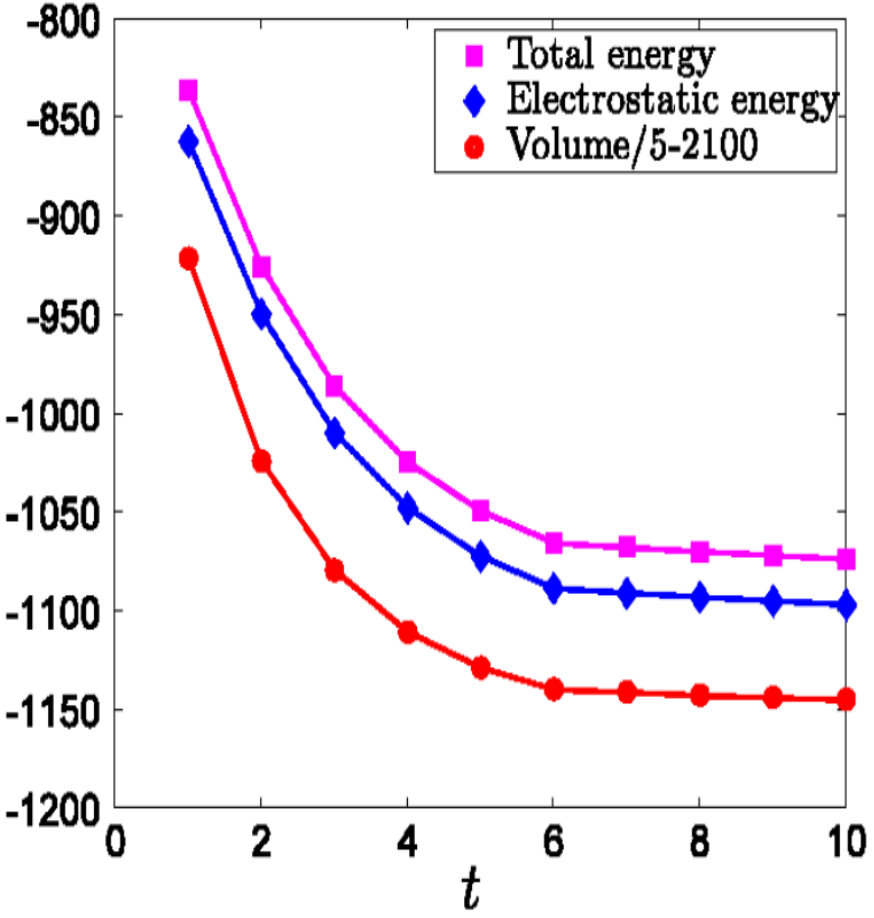
Boundary conditions:

Poisson equation: Dirichlet and Neumann
Nernst-Planck equation: Non-flux at the interface and Dirichlet
Laplace-Beltrami equation: Dirichlet

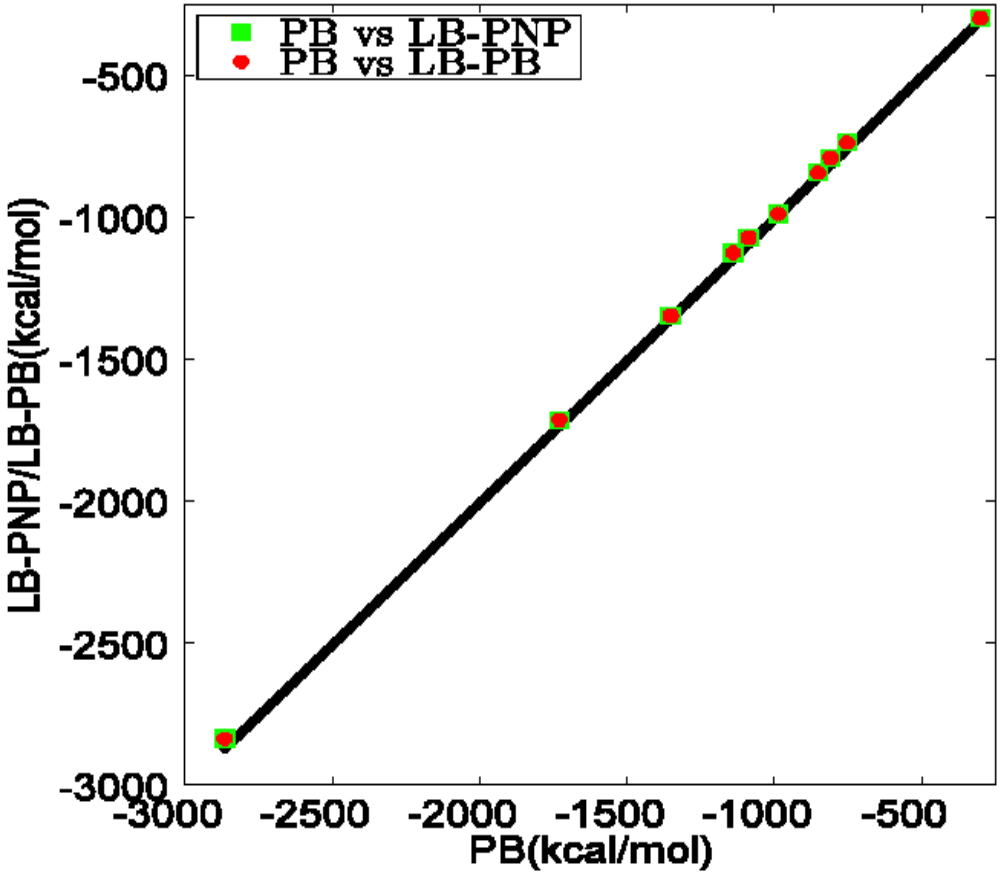
Numerical methods

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

Model validation at equilibrium



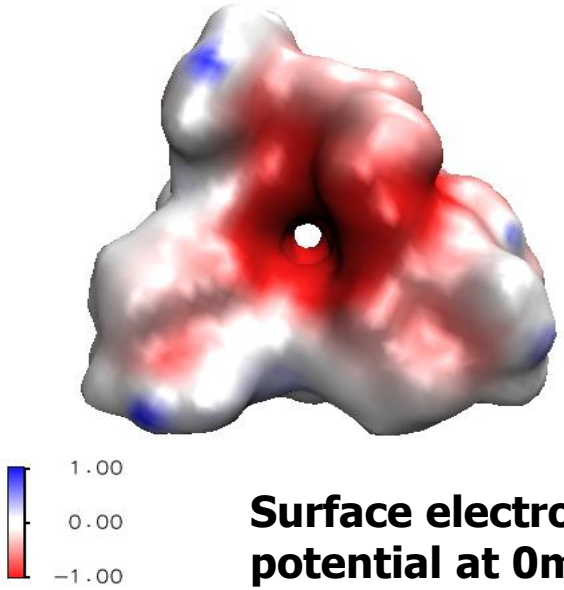
Convergence of the total energy



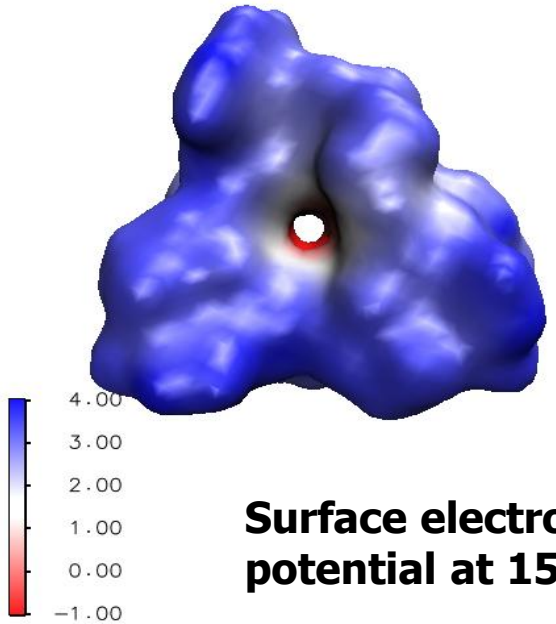
Consistency of three models at equilibrium with 10 proteins

Simulation of Gramicidin A

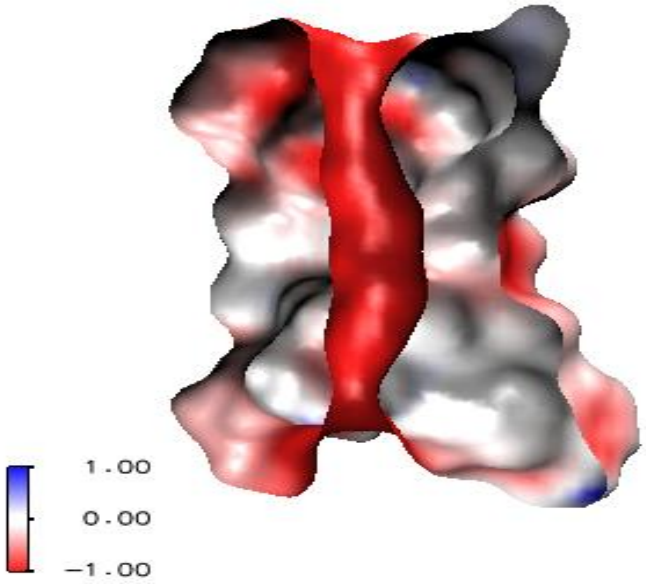
Laplace-Beltrami and Poisson-Nernst-Planck equations

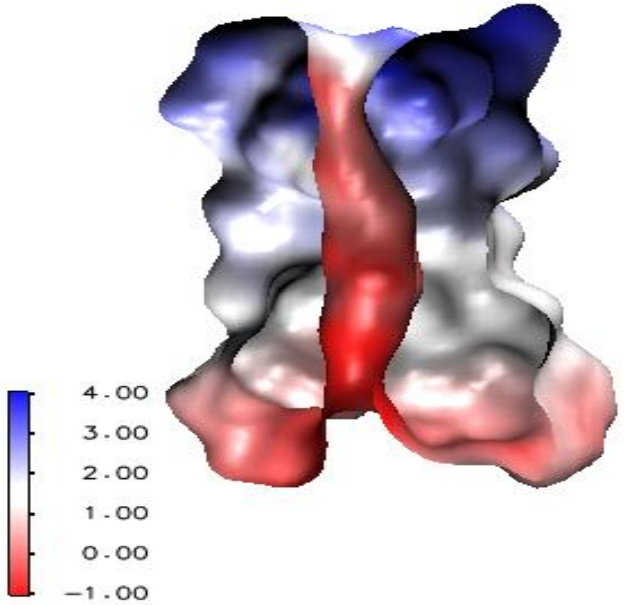


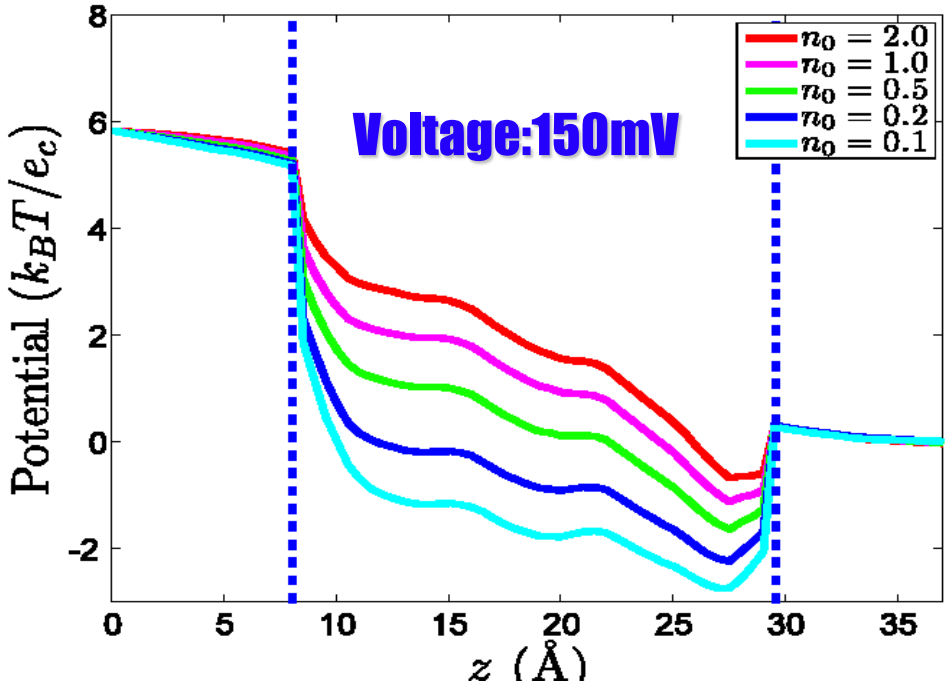
Surface electrostatic potential at 0mV

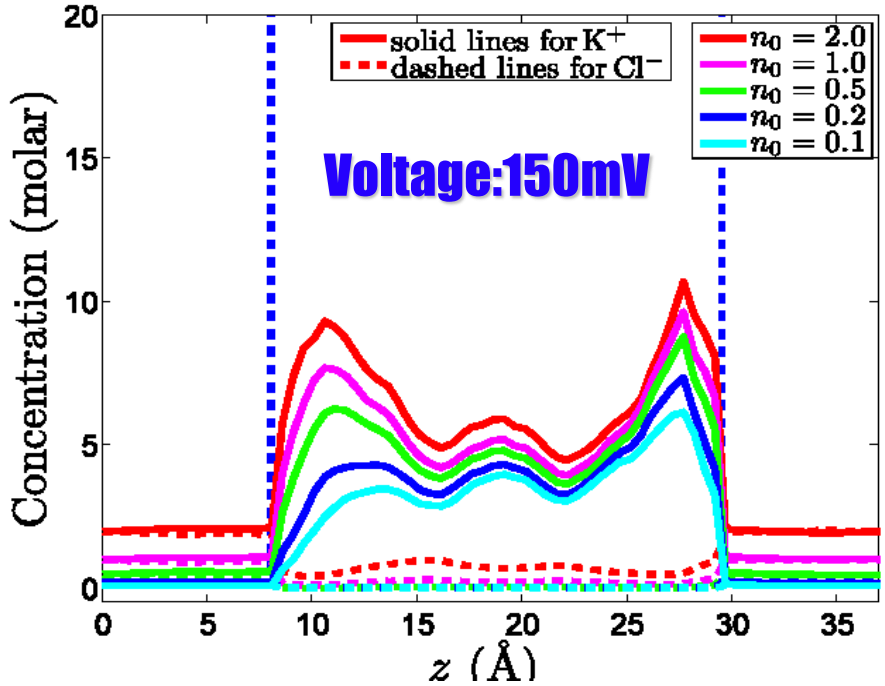


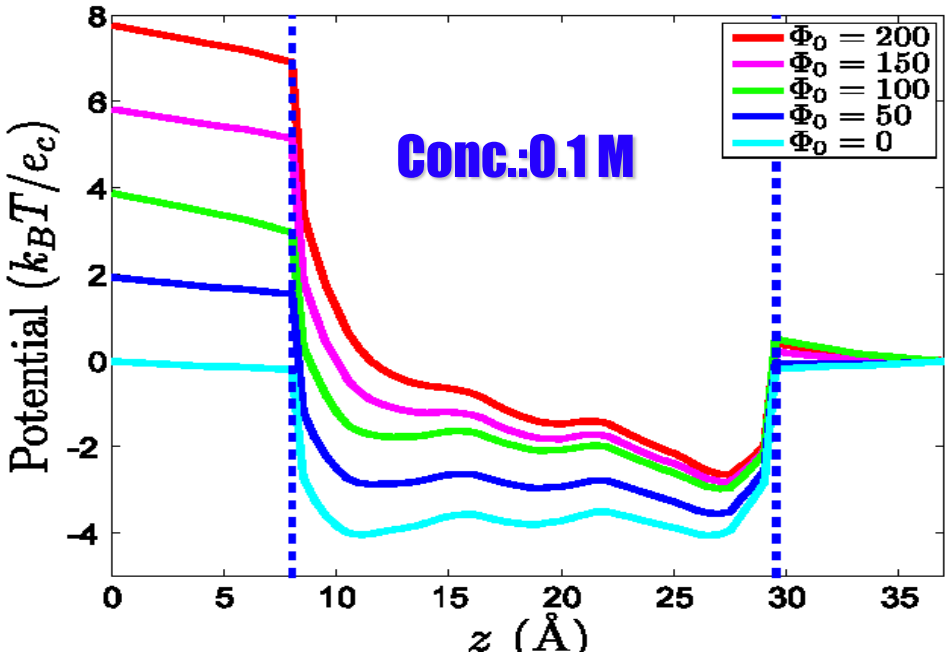
Surface electrostatic potential at 150mV

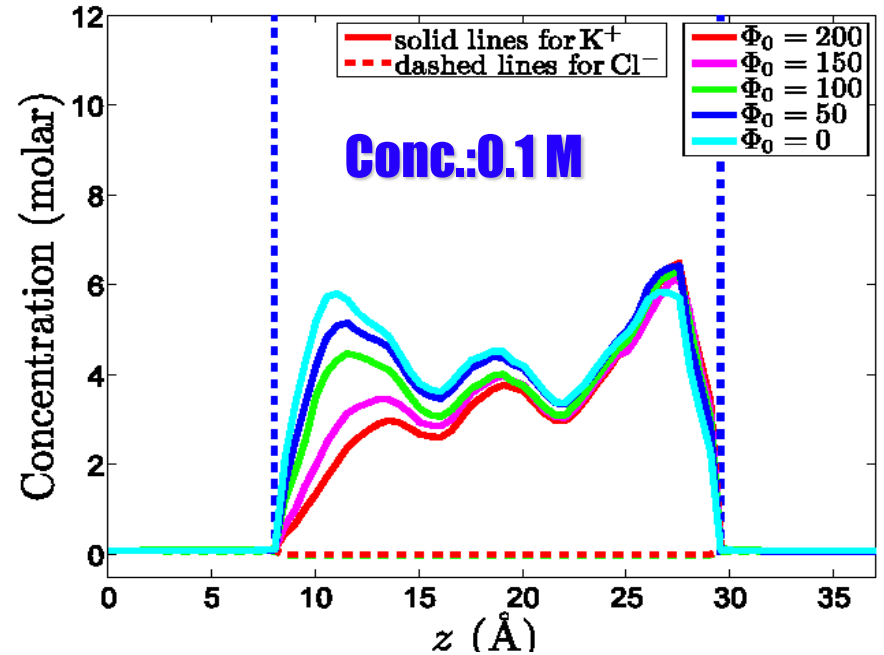





Voltage:150mV
$n_0 = 2.0$
$n_0 = 1.0$
$n_0 = 0.5$
$n_0 = 0.2$
$n_0 = 0.1$
Potential (k_BT/e_c)
z (Å)


solid lines for K^+
dashed lines for Cl^-
Voltage:150mV
$n_0 = 2.0$
$n_0 = 1.0$
$n_0 = 0.5$
$n_0 = 0.2$
$n_0 = 0.1$
Concentration (molar)
z (Å)


Conc.:0.1 M
$\Phi_0 = 200$
$\Phi_0 = 150$
$\Phi_0 = 100$
$\Phi_0 = 50$
$\Phi_0 = 0$
Potential (k_BT/e_c)
z (Å)


solid lines for K^+
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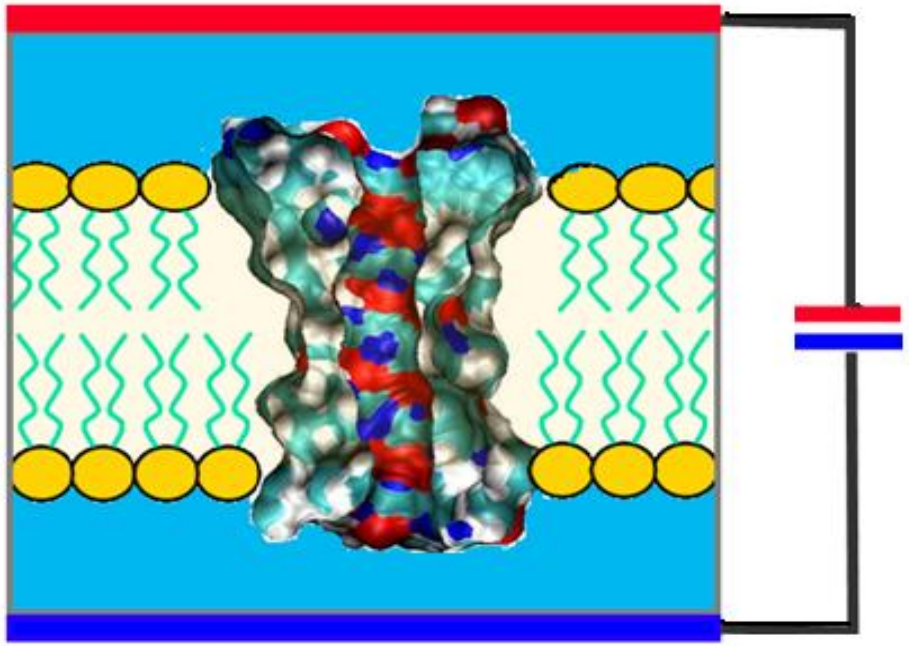
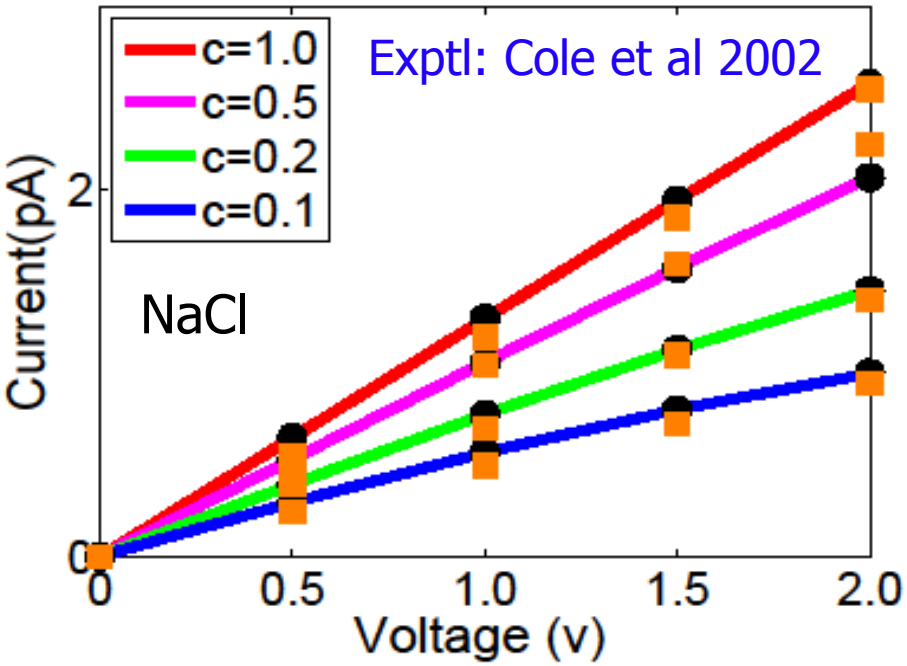
Conc.:0.1 M
$\Phi_0 = 200$
$\Phi_0 = 150$
$\Phi_0 = 100$
$\Phi_0 = 50$
$\Phi_0 = 0$
Concentration (molar)
z (Å)

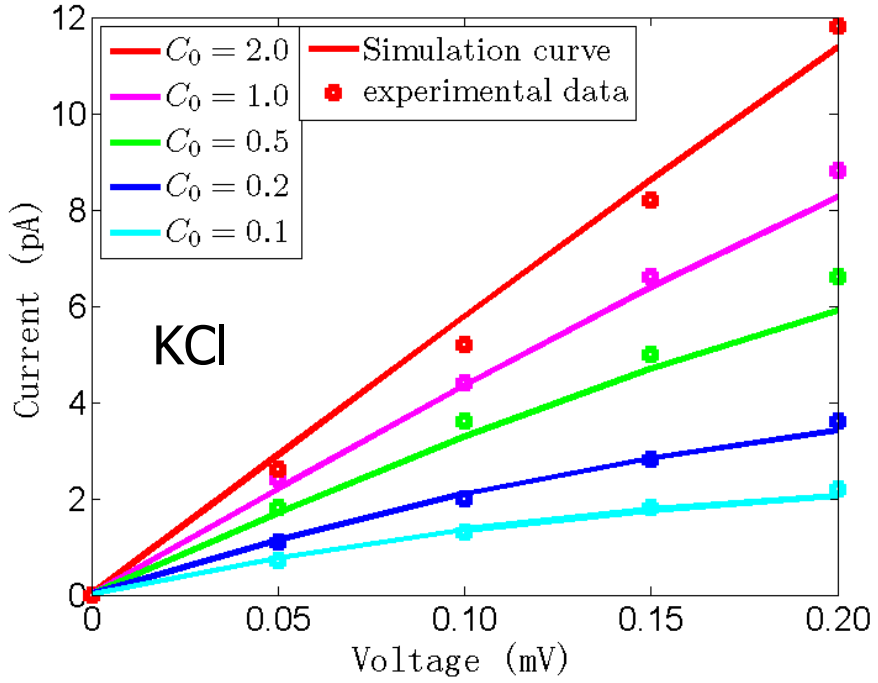


Simulation of Gramicidin A

Laplace-Beltrami and Poisson-Nernst-Planck equations

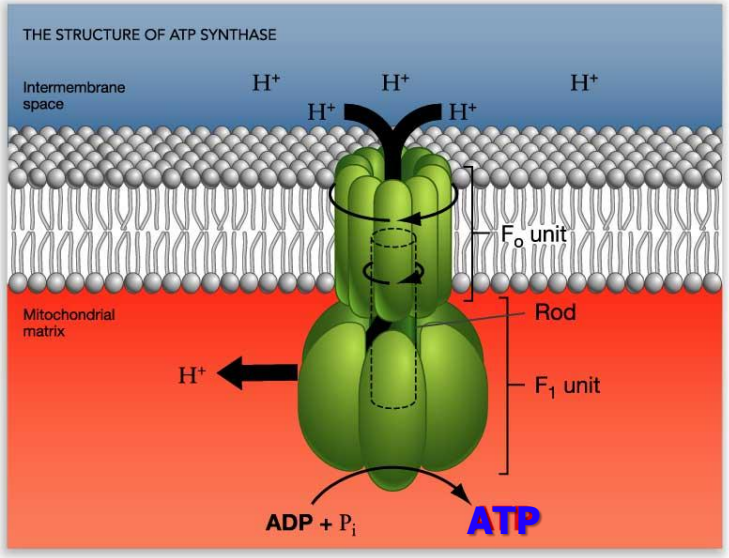
(Zheng, Chen, Wei, JBM, 2011)

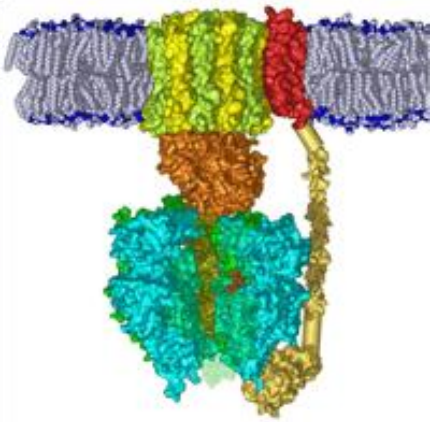


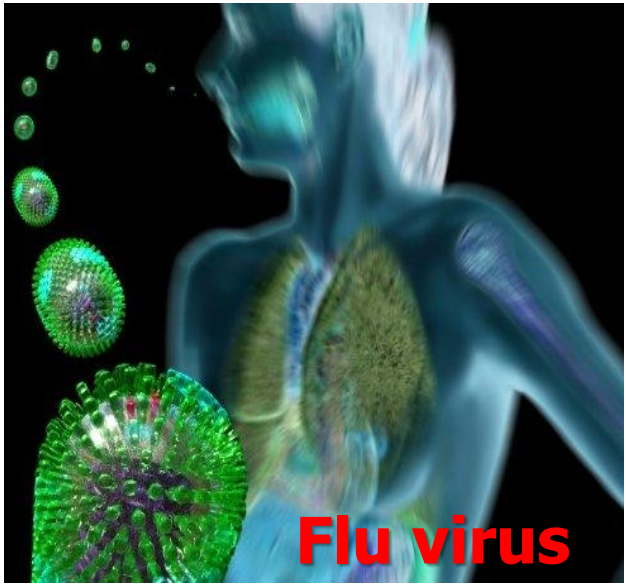


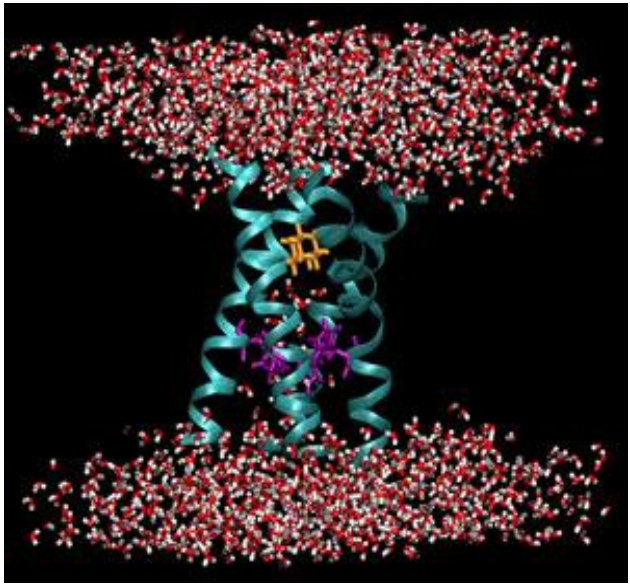
Proton transport

ATP production





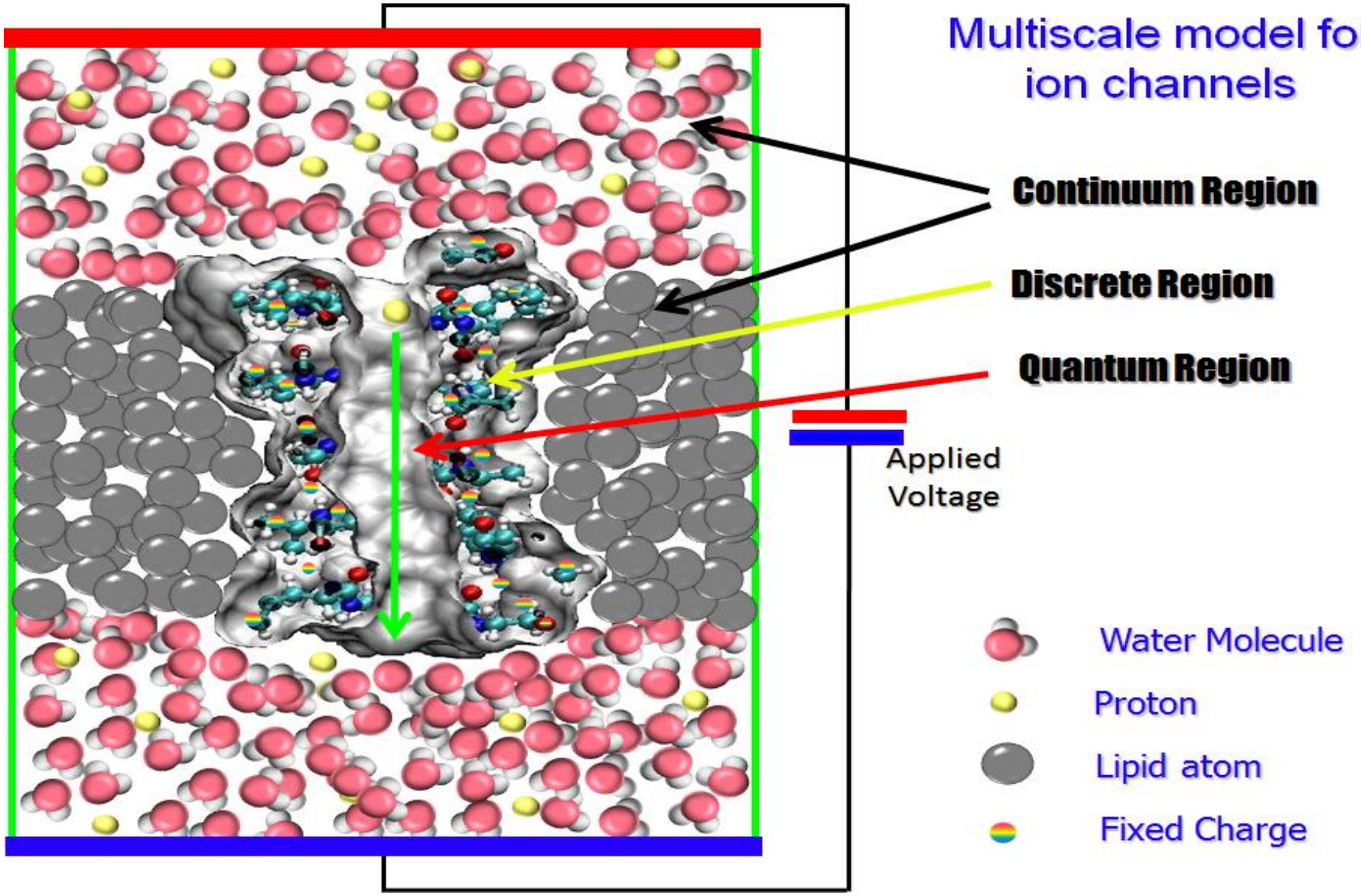




ATP is the energy currency in human body

Influenza M2 proton channel regulates viral replication process in a host cell.

Multiscale model for proton transport



Total energy functional for proton transport

$$G = \int_\Omega G_f d\Omega = \int_\Omega \left[Nonpolar + Electro + QM \right] dr$$

Geometric = area + volume + van der Waals:

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

Electro = electric field + point charges + proton charges:

$$Electro = \frac{1}{2} \varepsilon(S) \left| \nabla \phi \right|^2 - S \sum_i q_i \delta\left(r - r_i \right) - (1 - S) \phi n$$

QM = kinetic + potential + Lagrange multiplier :

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

Proton density: $n = \int \left| \psi_E \right|^2 f dE \qquad f = e^{-(E-\mu)/kT}$

(Chen & Wei, IJNMBE,2011)

Variation of the total free energy functional

$$\frac{\partial S}{\partial t} = \nabla \bullet \left(\frac{\gamma}{|\nabla S|} \nabla S \right) - p + U - \frac{1}{2}\left(\varepsilon_p - \varepsilon_s\right)|\nabla \phi|^2 + \sum_i q_i \delta(r - r_i) - \phi n - QM / S = 0$$

Generalized Laplace Beltrami equation

$$-\nabla \bullet \left(\varepsilon(S) \nabla \phi\right) = S \sum_i q_i \delta(r - r_i) + (1 - S) n$$

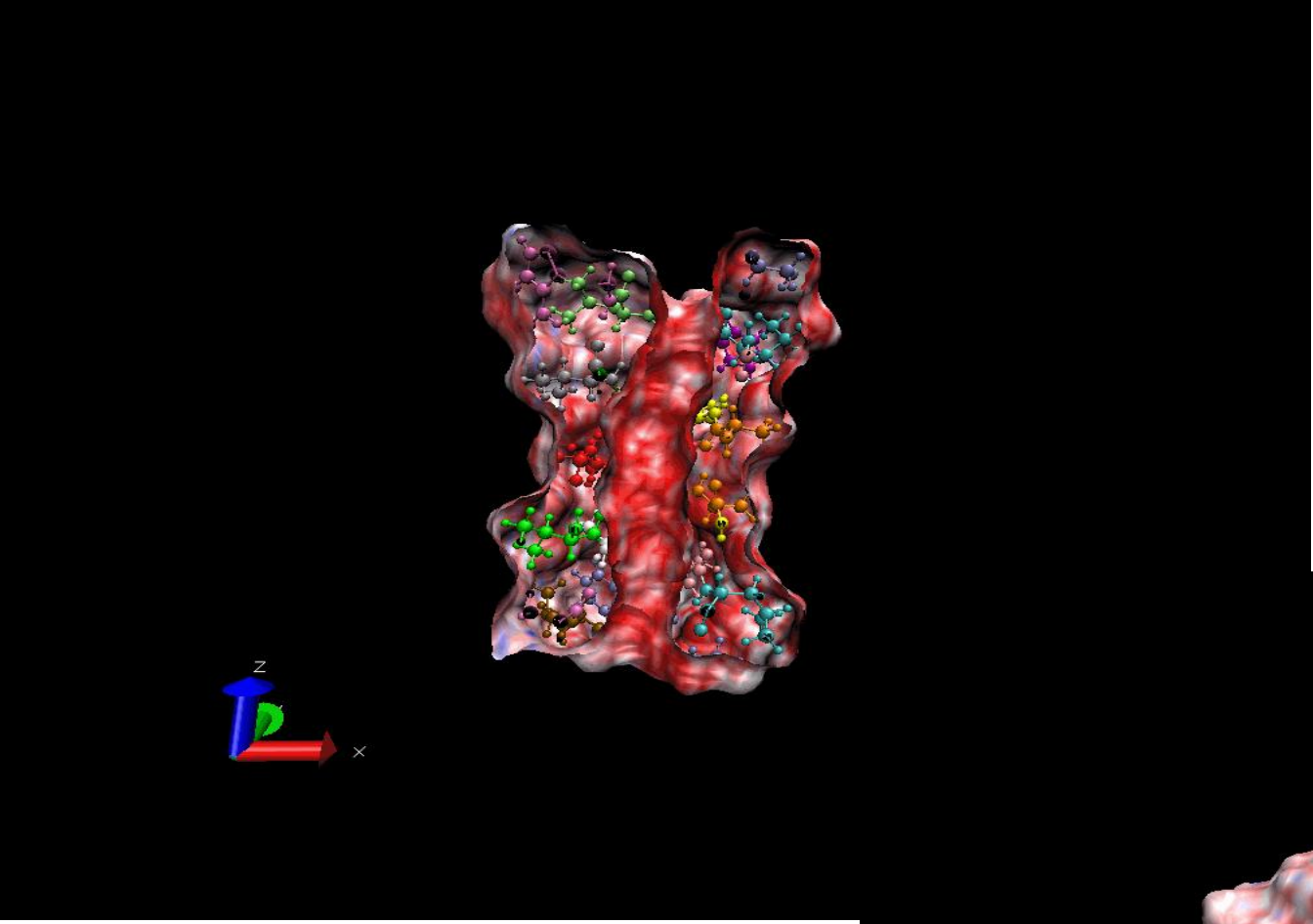
Generalized Poisson-Boltzmann equation

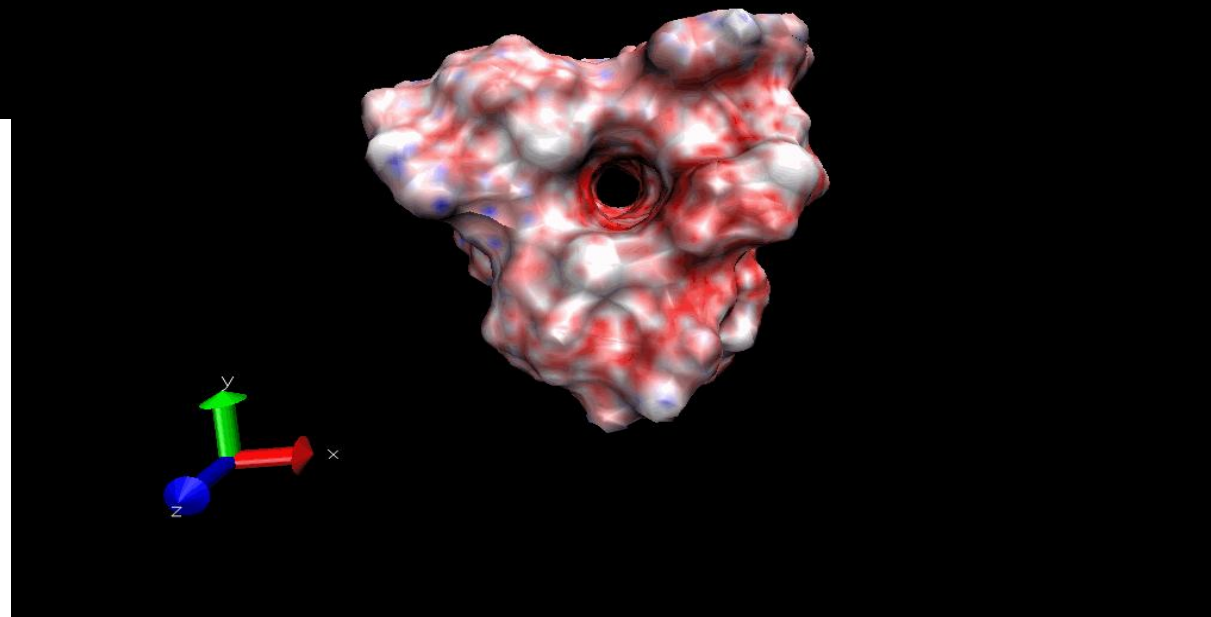
$$-\frac{\hbar^2}{2m} \nabla^2 \psi_E + \left(U_{GC}[n] - q\phi\right)\psi_E = E_E \psi_E$$

$$where: \qquad U_{GC}[n] = \frac{\delta E_{GC}[n]}{\delta n}$$

Generalized Kohn-Sham equation

with Boltzmann statistics and scattering boundary conditions

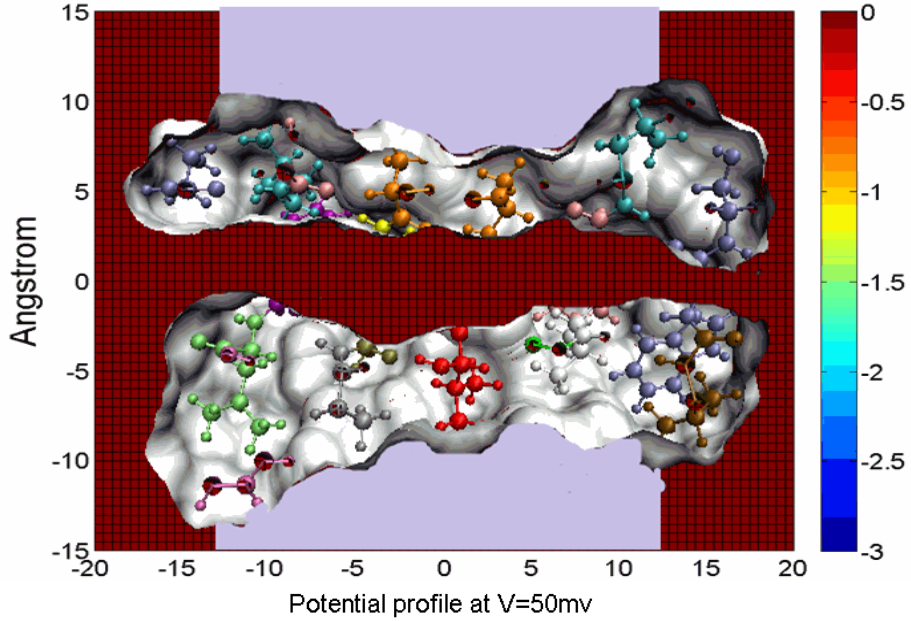

Z
X

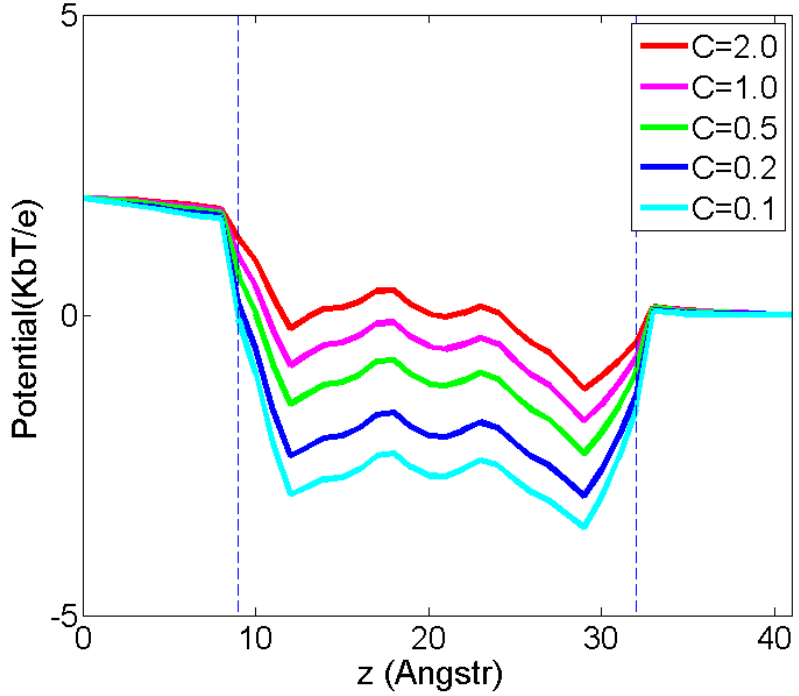

Y
X
Z

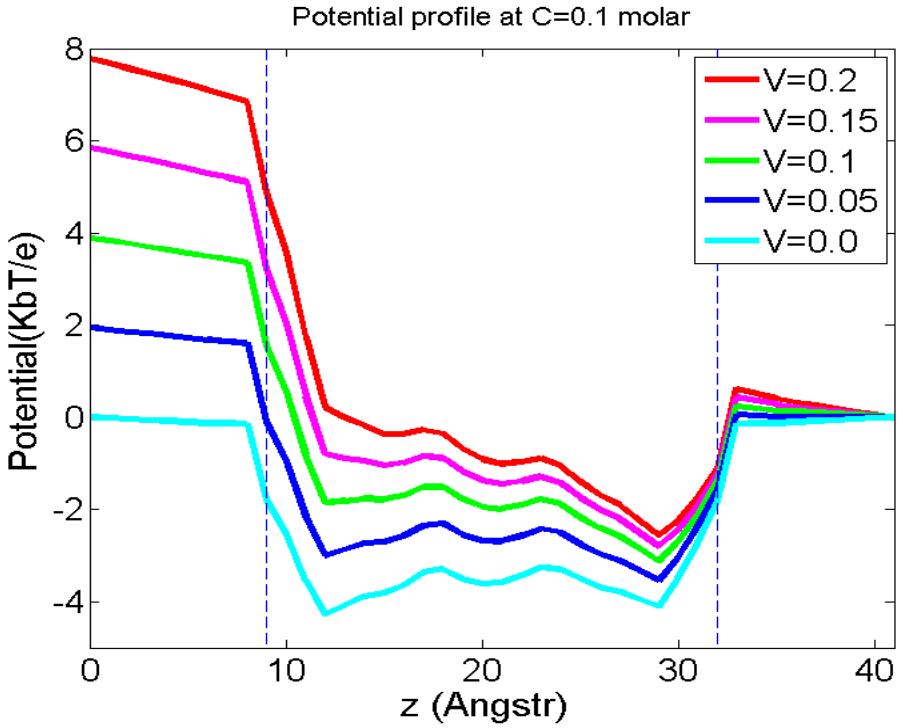
Simulation of Gramicidin A

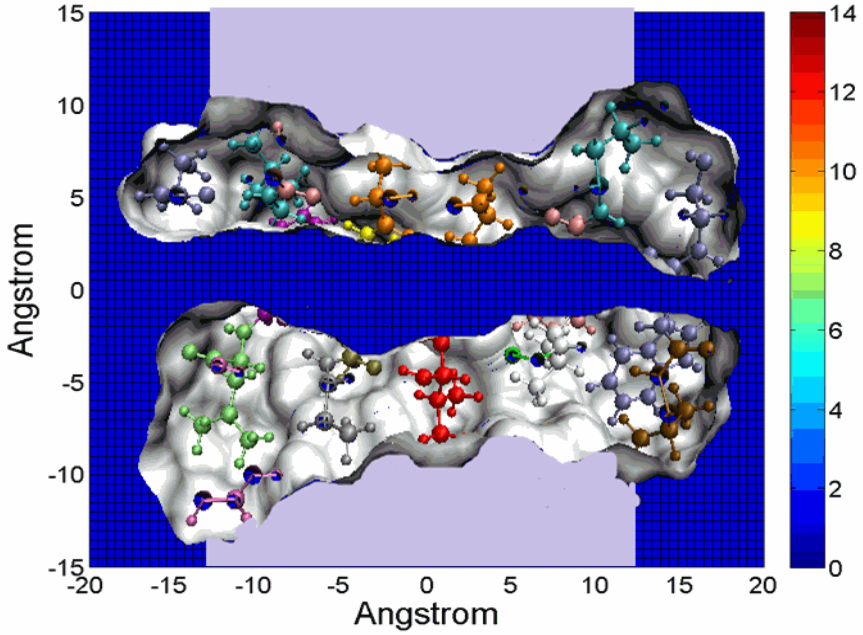
Laplace-Beltrami and Kohn-Sham equations

(Chen, Wei, CiCP, 2011)









Simulation of Gramicidin A

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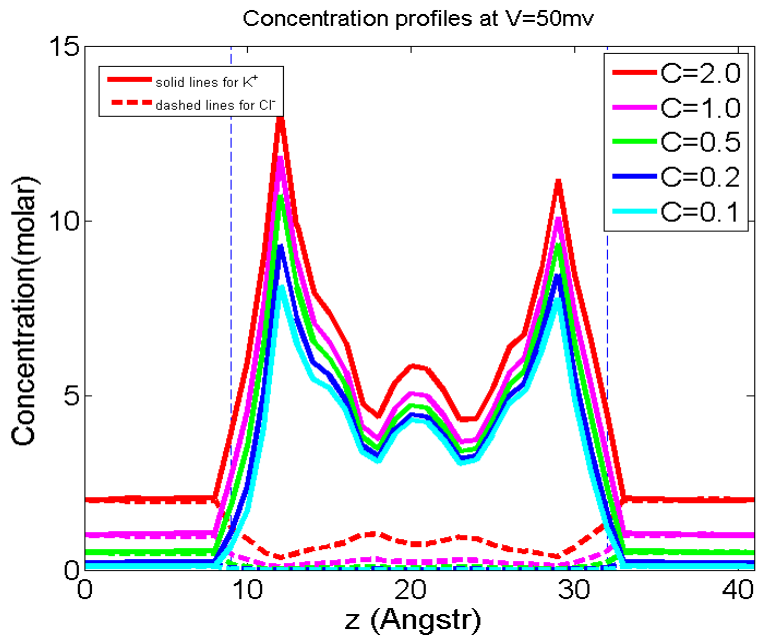
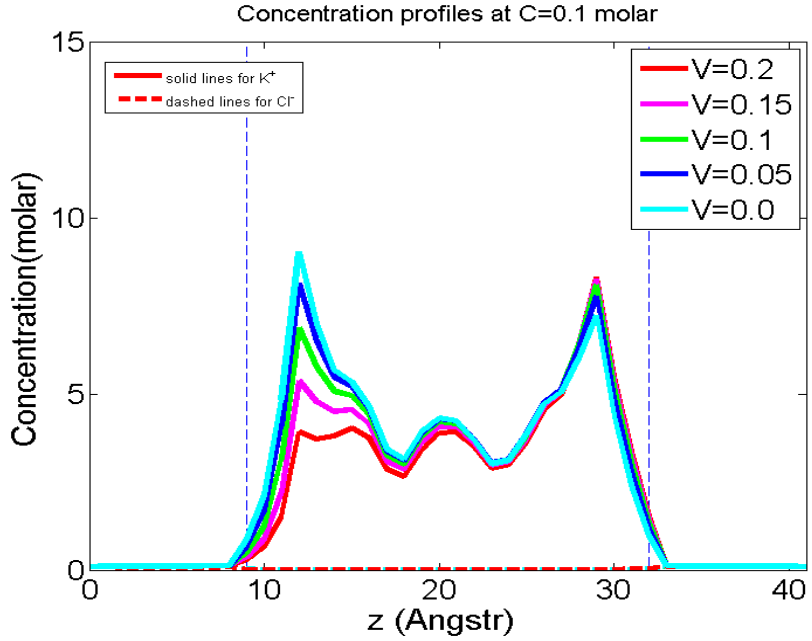
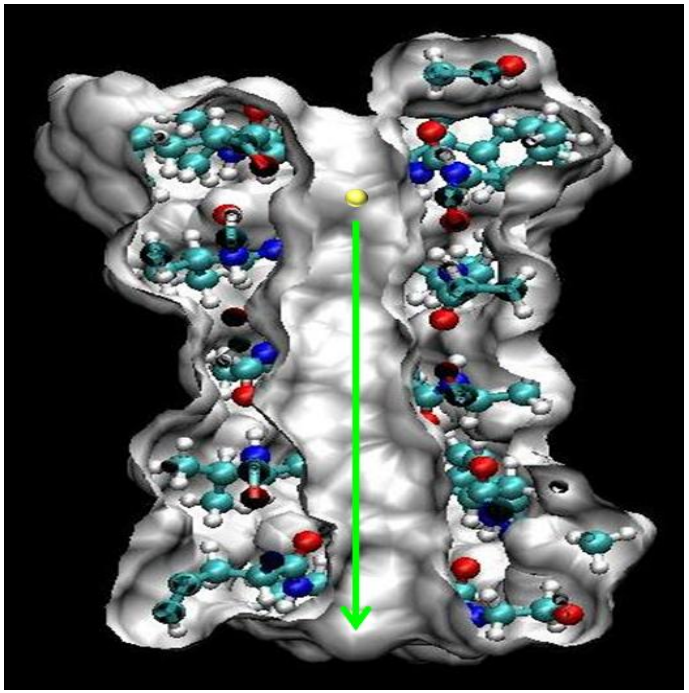
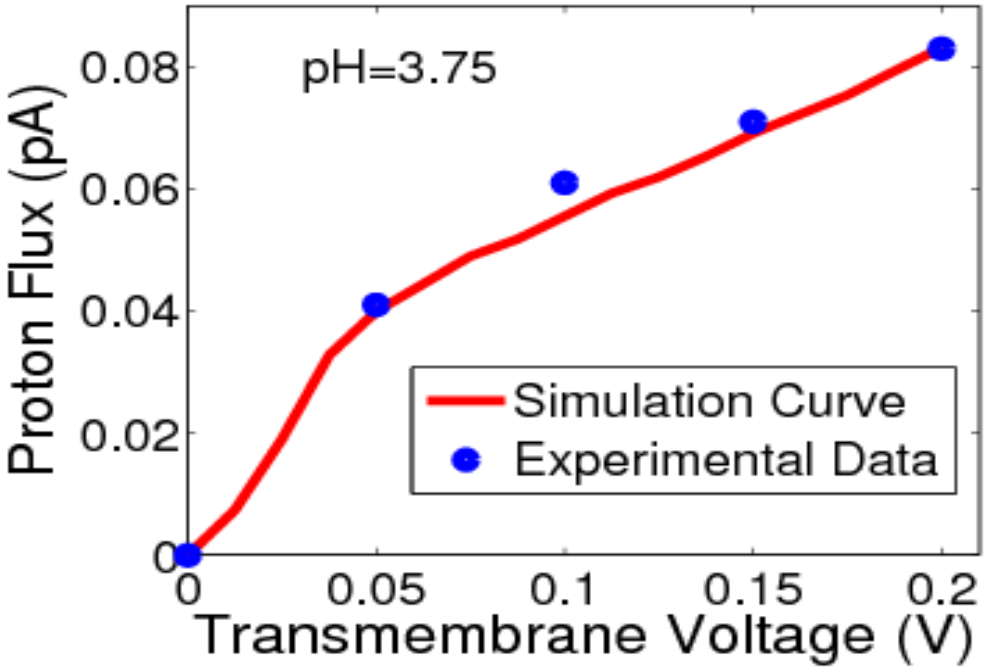
(Chen, Wei, CiCP, 2011)



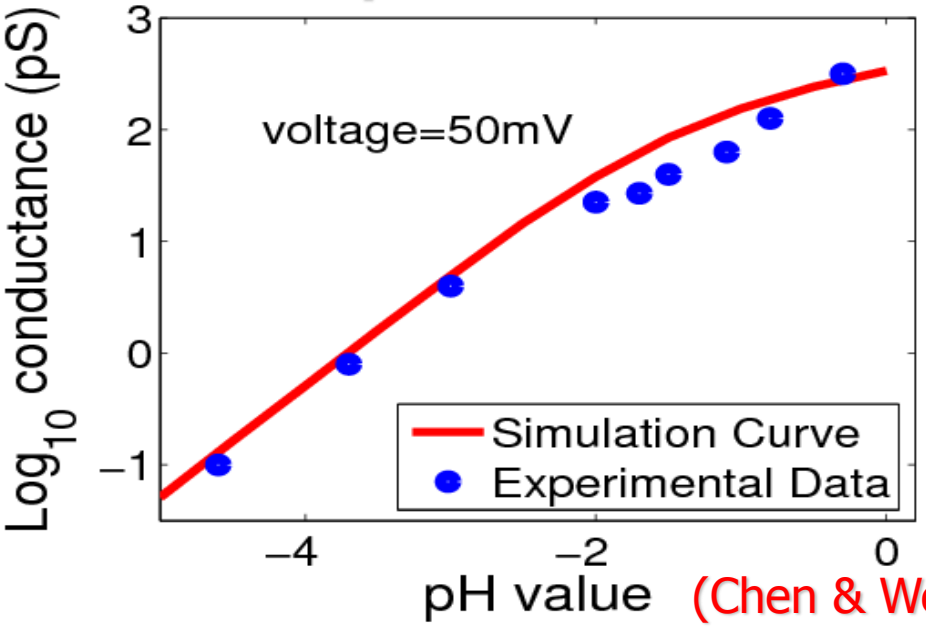


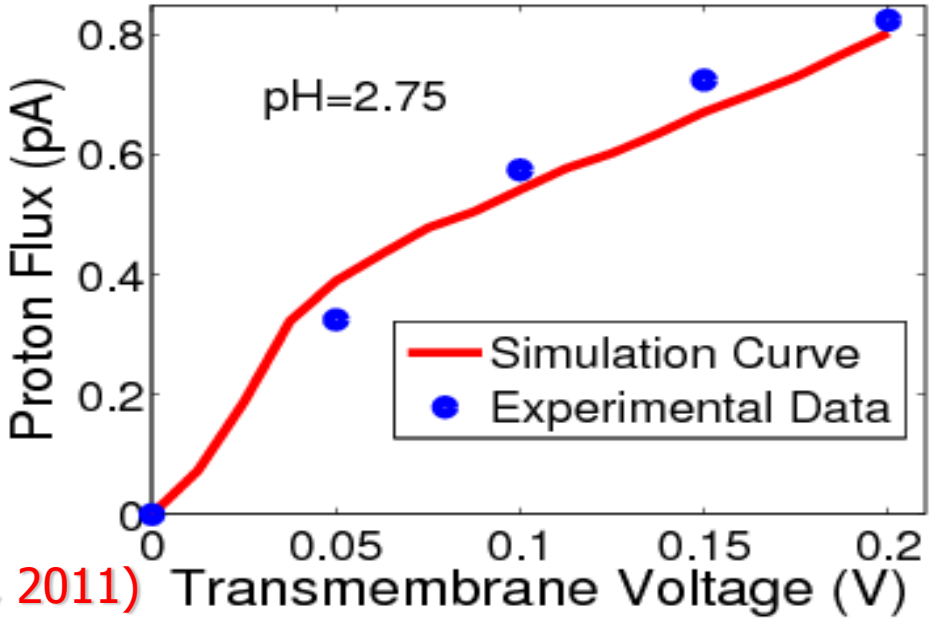




Proton transport of Gramicidin A

(Expl: Eisenman et al., 1980)





(Chen & Wei, CiCP, 2011)

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

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

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

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

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

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

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

(Wei, BMB, 2010)

Generalized Navier-Stokes Equation

$$\rho_s\left(\frac{\partial v}{\partial t}+v\cdot\nabla v\right)=-\nabla p+\frac{1}{1-S}\nabla\bullet(1-S)T+F$$

$$F=\frac{S}{1-S}\left(-\nabla p-\frac{1-S}{S}\nabla\left(\rho_s U_s+\sum_\alpha n_\alpha q_\alpha\phi\right)+\frac{\rho_m}{S}\nabla(S\phi)\right)$$

$$\nabla\cdot v=0$$

Generalized Newton equation for molecular dynamics

$$\rho_j\frac{d^2z_j}{dt^2}=f_{SSI}^j+f_{RF}^j+f_{PI}^j$$

$$f_{SSI}^j=-\frac{1-S}{S}\nabla_j(\rho_s U_s)$$

$$f_{RF}^j=\frac{\rho_m}{S}\nabla_j(S\phi)-\frac{1-S}{S}\nabla_j n_\alpha q_\alpha\phi$$

$$f_{PI}^j=-\nabla_j U(z)$$

Generalized Poisson-Boltzmann Equation

$$-\nabla \bullet \varepsilon(S)\nabla\phi = S\rho_m + (1-S)\sum n_\alpha q_\alpha$$

$$\varepsilon(S) = S\varepsilon_m + (1-S)\varepsilon_s$$

Electrochemical potential

$$\frac{\delta G}{\delta n_\alpha} \Rightarrow \qquad \mu_\alpha = \mu_{0\alpha} + kT\ln\frac{n_\alpha}{n_{\alpha 0}} + q_\alpha\phi + U_\alpha$$

Nernst-Planck equation

$$J_\alpha = -D_\alpha n_\alpha \nabla\frac{\mu_\alpha}{kT}, \qquad \frac{\partial n_\alpha}{\partial t} + v \bullet \nabla n_\alpha = -\nabla \bullet J_\alpha$$

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

Generalized Laplace-Beltrami equation

$$\frac{\partial S}{\partial t} = |\nabla S| \left[\nabla \bullet \frac{\gamma \nabla S}{|\nabla S|} + V_{LB} \right]$$

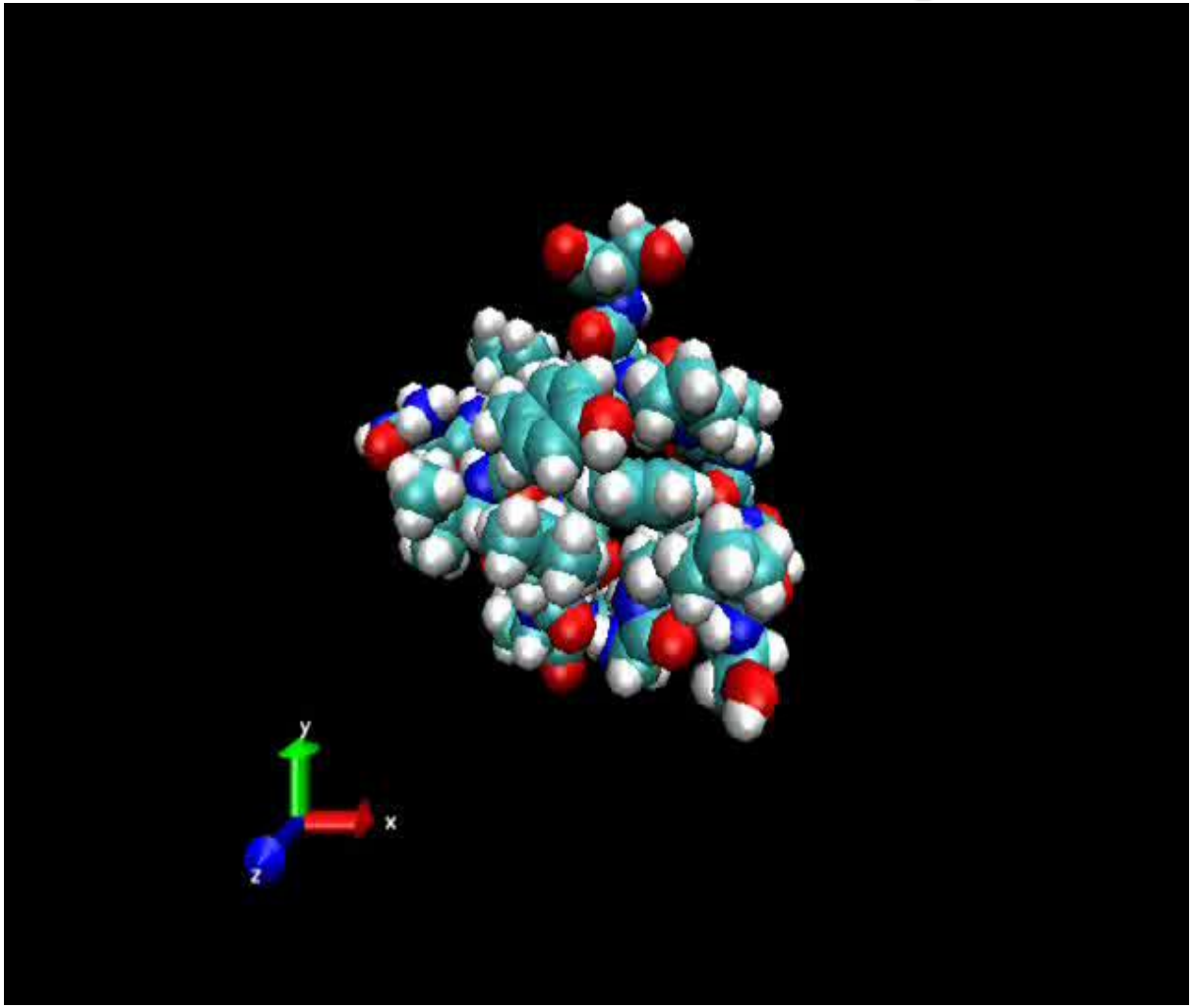
$$V_{LB} = -p + \sum_{\alpha} n_{\alpha} U_{\alpha} - \rho_m \phi + \frac{\varepsilon_m}{2} |\nabla \phi|^2 + \sum_{\alpha} n_{\alpha} q_{\alpha} \phi - \frac{\varepsilon_s}{2} |\nabla \phi|^2$$

$$+ \sum_{\alpha} n_{\alpha} \left[\mu_0 + kT \ln \left(\frac{n_{\alpha}}{n_{\alpha 0}} - 1 \right) \right]$$

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

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

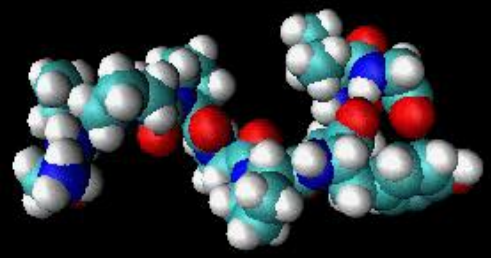
Multiscale Molecular dynamics

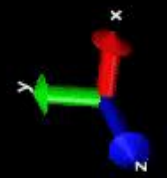


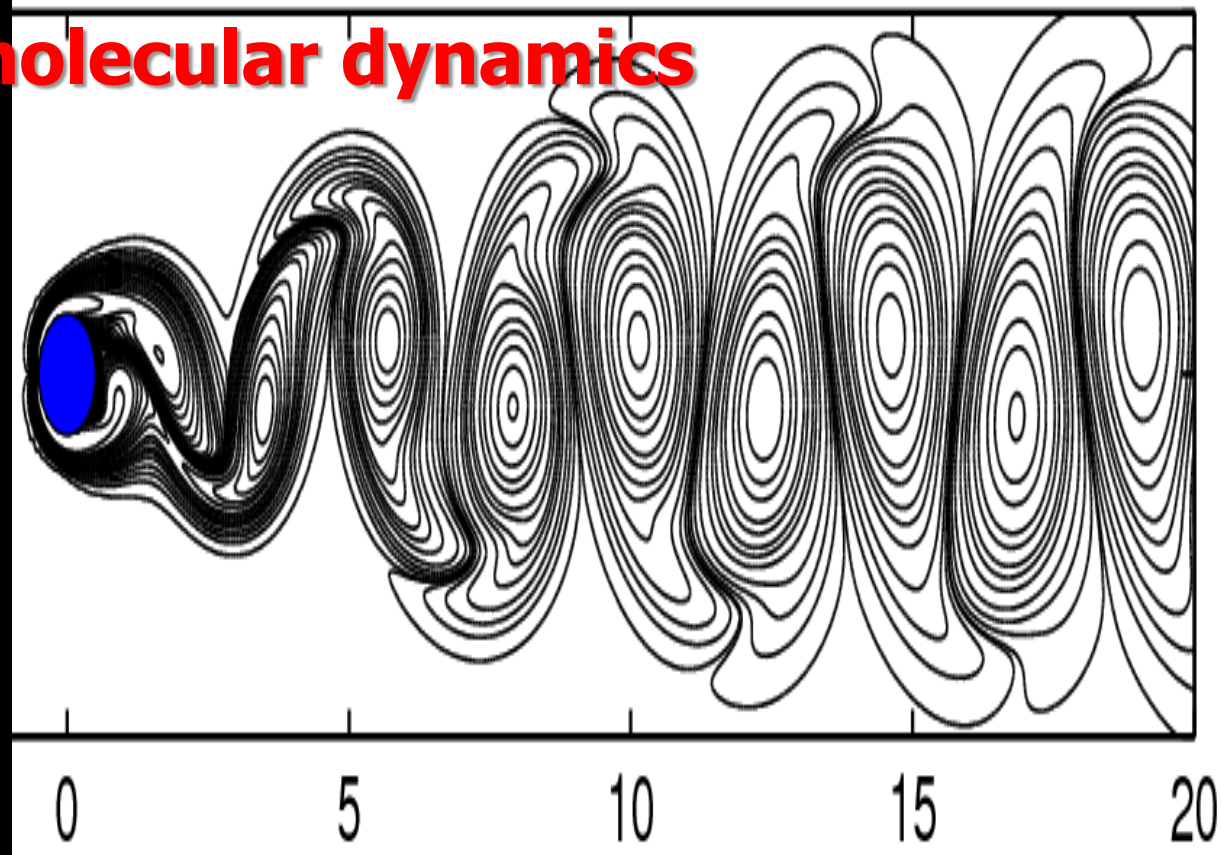
Multiscale MD of Trp-cage miniprotein (1L2Y)

(Geng & Wei, JCP, 2011)

Coupling of fluid & molecular dynamics



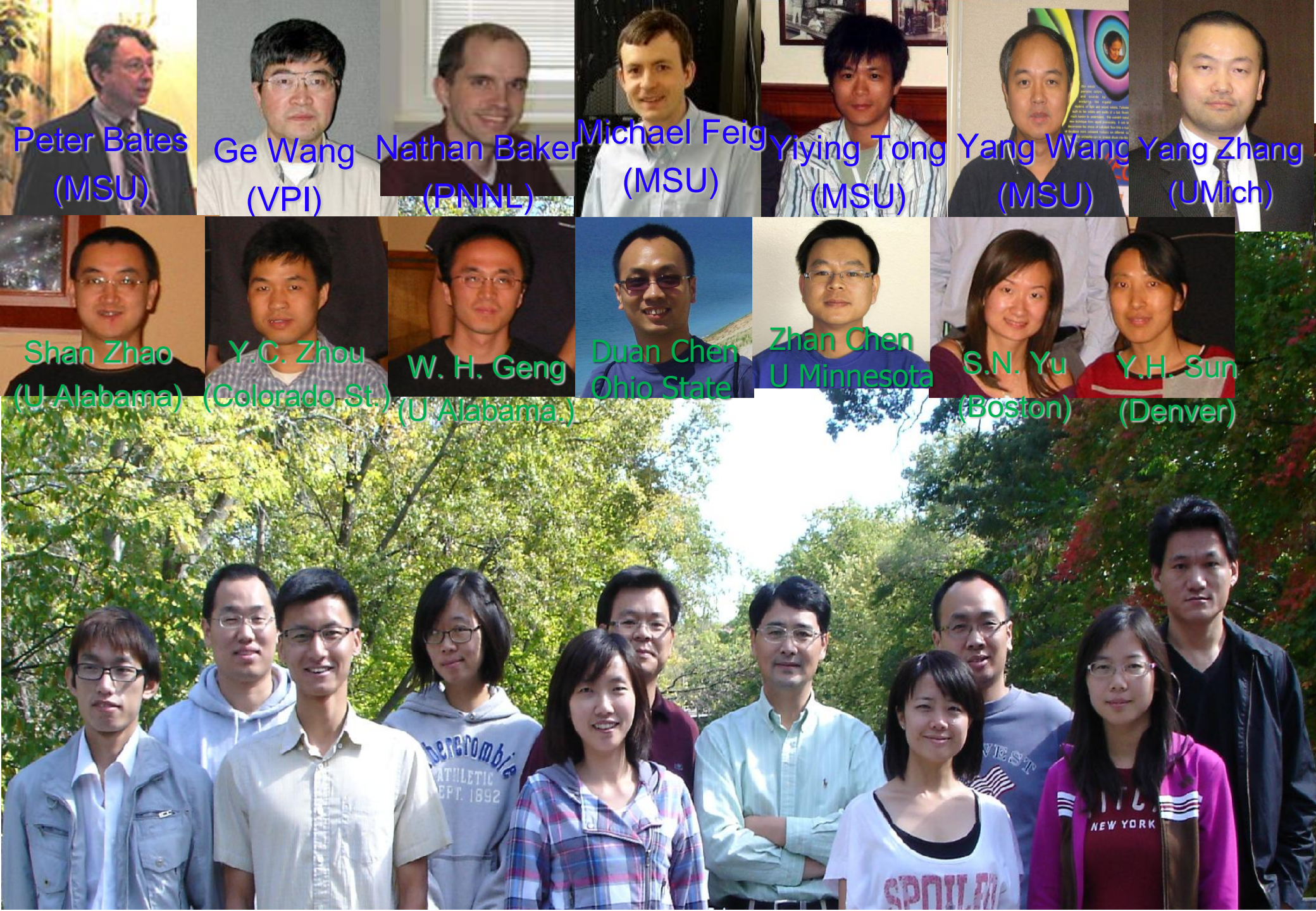




Work in progress

Concluding remarks

- **Integration of multiscales/multiphysics/multidisciplines**
- **Fundamental laws of physics**
- **Total energy functional paradigm for multiscale and multiphysics**
- **Validation with experimental data**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