Saturation of Ions in Channels and Solutions:
a Fermi-Poisson Treatment

November 19, 2015
with corrections pointed out by Dexuan Xue November 20, 2015

Bob Eisenberg

Jinn Liang Liu

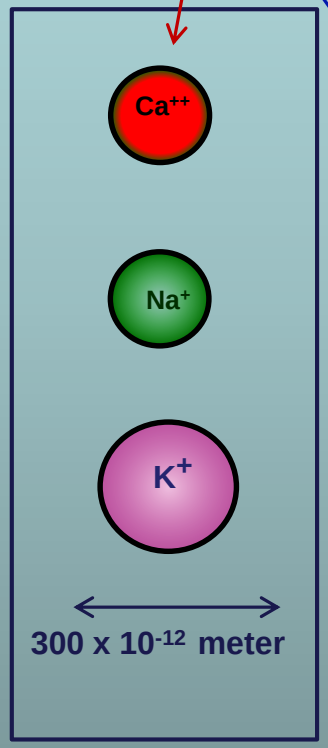
劉晉良

Jinn-Liang is first author on our papers

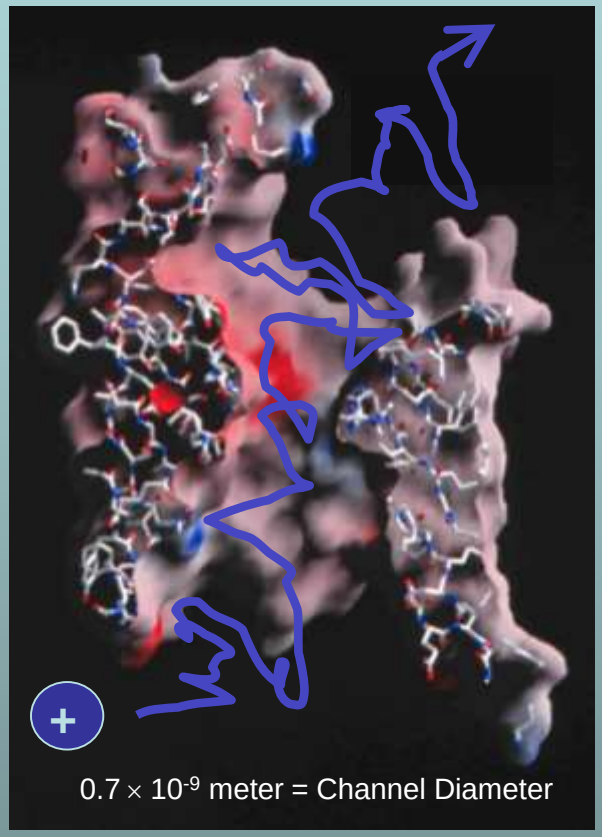
Channels are Devices

Valves and Diodes

Different Ions Carry Different Signals through Different Channels



ompF porin



Diameter matters

Ionic solutions are NOT ideal

Classical Biochemistry assumes ideal solutions.
K^+ & Na^+ are identical only in Ideal Solutions.

Flow time scale is 10^{-4} sec to 1 min

Figure of ompF porin by Raimund Dutzler

Channels are (nano) valves

Valves Control Flow

Classical Theory & Simulations

NOT designed for flow

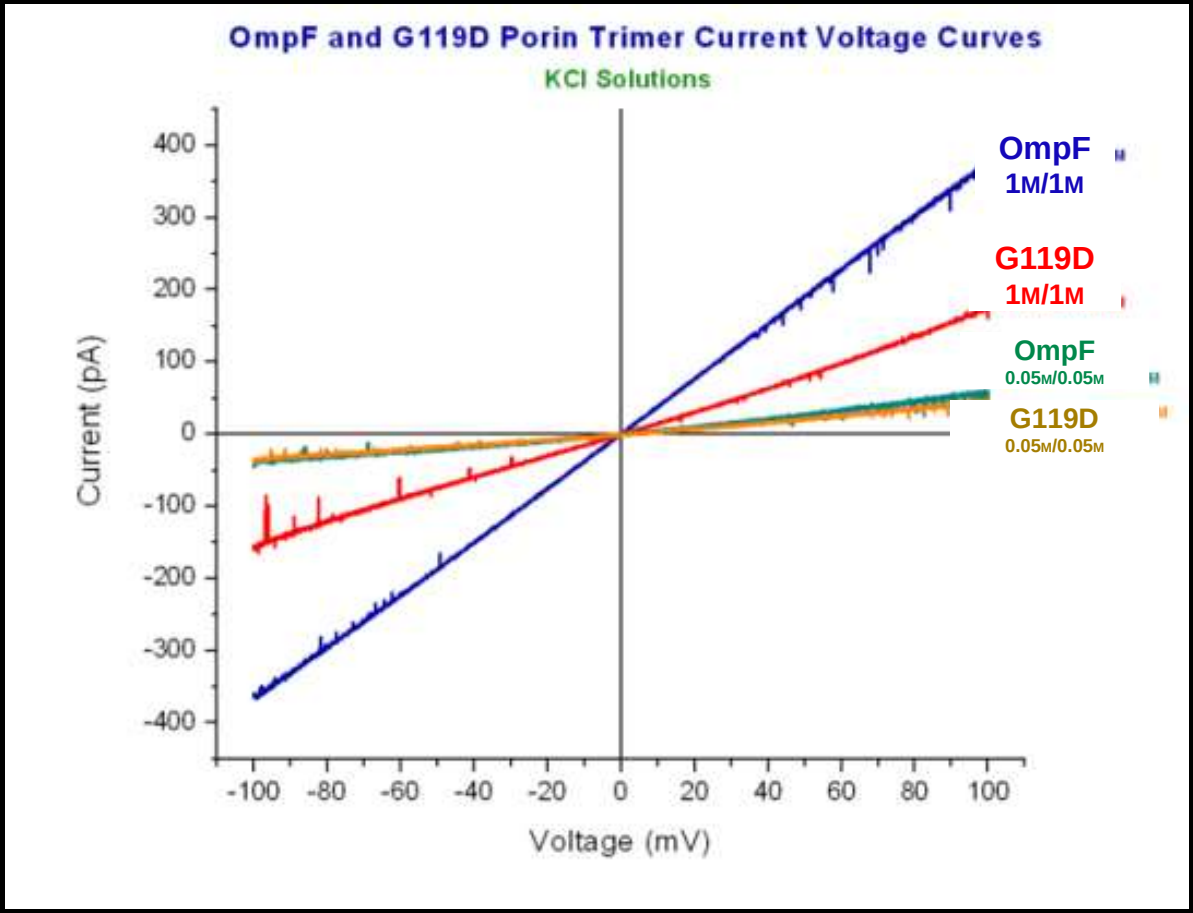
Thermodynamics, Statistical Mechanics do not allow flow

Rate and Markov Models do not Conserve Current

$$I_{AB} - I_{BA} \neq I_{BC} - I_{CB}$$

I_{AB} is a unidirectional current,
into an absorbing boundary condition

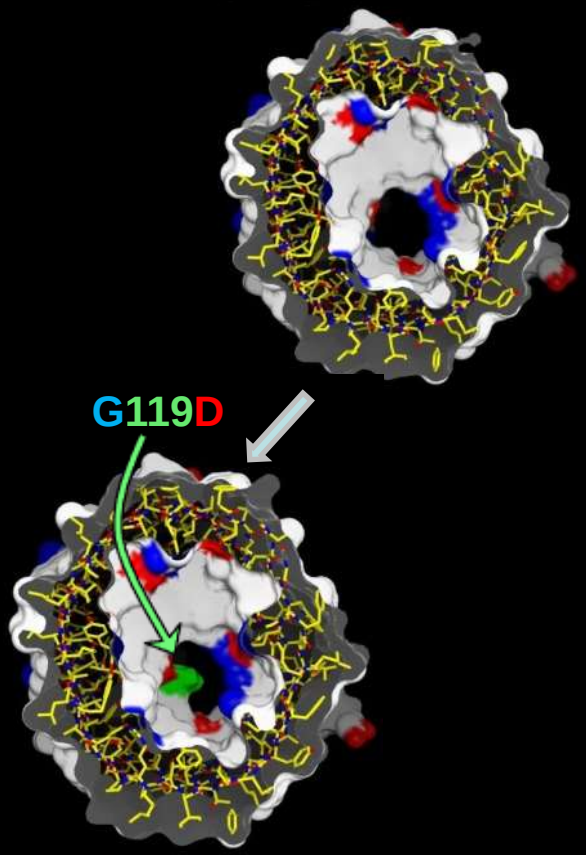
A few atoms make a BIG Difference



Current Voltage relation determined by
John Tang
in Bob Eisenberg's Lab

Glycine G
replaced by
Aspartate D

Ompf

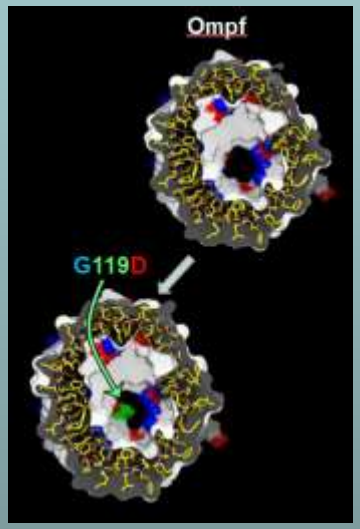


Structure determined by
Raimund Dutzler
in Tilman Schirmer's lab

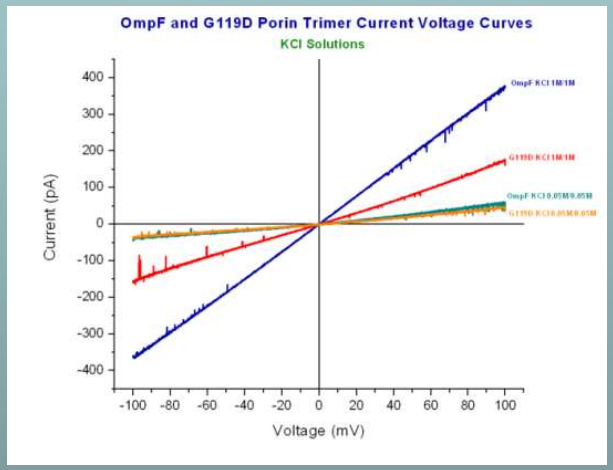
Mathematics of Devices must be accurate

There is no engineering without accurate numbers

Structure is Important



A few atoms make a BIG Difference



Details matter in devices!

Think of the clearances as a piston moves in a cylinder of an automobile motor

Mathematical Issues of Devices are fascinating and nontrivial

(1) Multi-scale in their essence

(2) Non-equilibrium in their essence

but of a special simple type,
power supplies = spatially non-uniform potentials

Mathematical Issues of Devices are fascinating and nontrivial

(3) Flows driven by Spatial Variation of macroscopic boundary conditions

usually inhomogeneous Dirichlet in electrical and chemical potentials

Physical, Chemical Issues of Devices are fascinating and nontrivial

(4) Everything involves non-ideal ionic mixtures, divalents

Ionic Solutions are the 'Liquid of Life'
Pure water is lethal

Where to start?

Compute all atoms in a device?

Calibrated
all-atom simulations
are
Barely Feasible
if they must accurately compute biological function
Macroscopic Time & Distance Scales
Macroscopic Electric Fields & Gradients
Power Supplies
i.e., inhomogeneous Dirichlet Boundary Conditions,
Flows,
Non-ideal mixtures ***including Ca^{2+}***

Scientists

must Grasp

and not just reach

Calibrations are necessary

or the Device does not Work

Poets

hope we will never learn the difference between dreams and realities

“Ah, … a man's reach should exceed his grasp,
Or what's a heaven for?”
Robert Browning
"Andrea del Sarto", line 98

Details matter in Devices

Uncalibrated Simulations will make Devices that do not work

Where to start?

Biological Adaptation

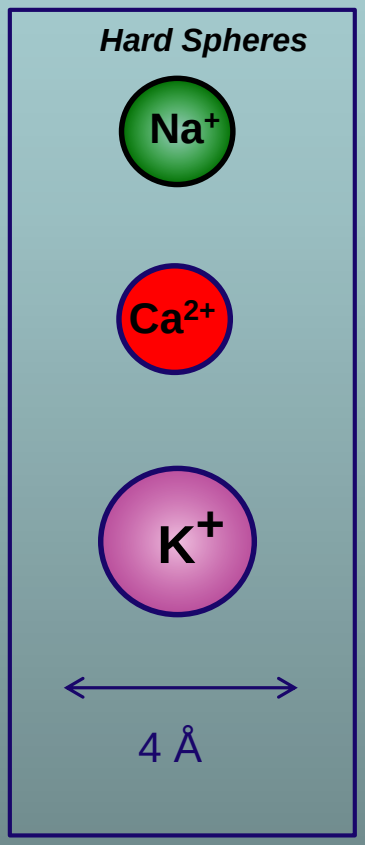
Crowded Charge

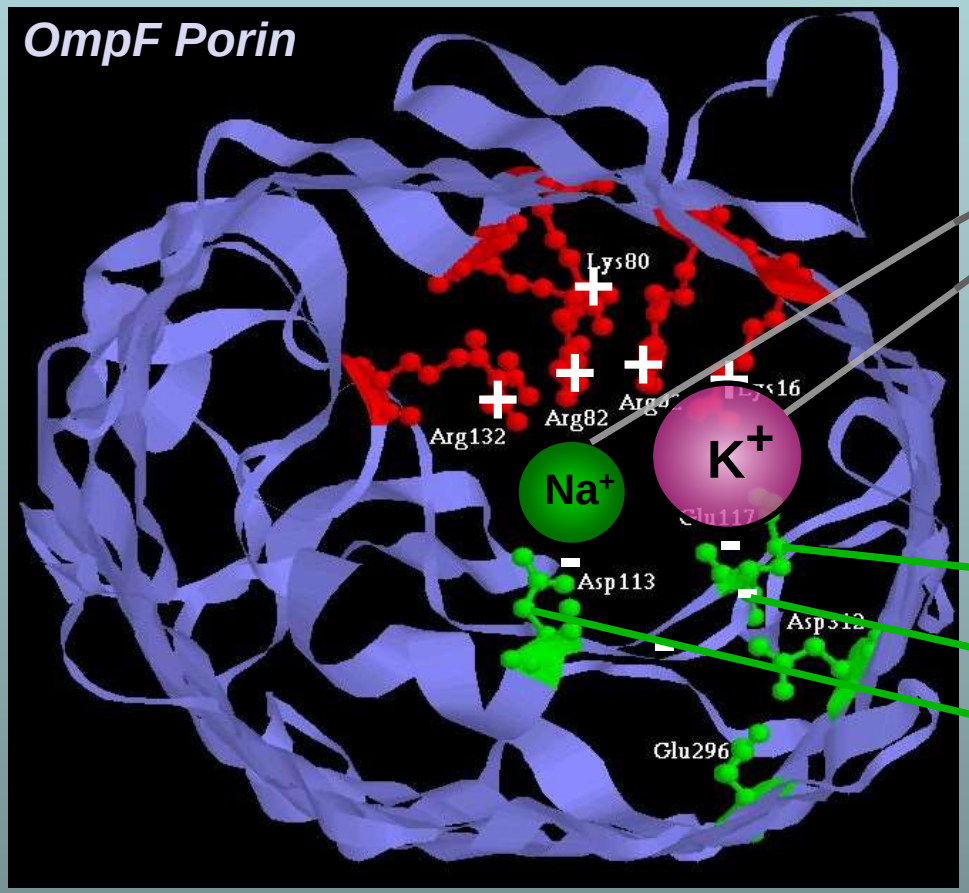
Physical basis of function

Active Sites of Proteins are ***Very*** **Charged**

7 charges ~ **20 M net charge** = 1.2×10^{22} cm^{-3}

liquid **Water** is **55 M**
solid **NaCl** is **37 M**





Ions are Crowded

Induced Fit of Side Chains

Selectivity Filters and Gates of Ion Channels are **Active Sites**

Figure adapted from Tilman Schirmer

Working Hypothesis
bio-speak:

Crucial Biological Adaptation is

Crowded Ions *and* Side Chains

Biology occurs in concentrated >0.3 M mixtures of spherical charges

NOT IDEAL AT ALL

Solutions are extraordinarily concentrated >10M where they are most important, near DNA, enzyme active sites, and channels and electrodes of batteries and electrochemical cells.

(Solid NaCl is 37M)

Poisson Boltzmann does NOT fit data!!

Crowded Active Sites

in 573 Enzymes

Enzyme Type		Catalytic Active Site Density (Molar)		
		Acid (positive)	*Basic* (negative)	*Total*
	Total (n = 573)	**10.6**	**8.3**	**18.9**
EC1	Oxidoreductases (n = 98)	7.5	4.6	12.1
EC2	Transferases (n = 126)	9.5	7.2	16.6
EC3	Hydrolases (n = 214)	12.1	10.7	22.8
EC4	Lyases (n = 72)	11.2	7.3	18.5
EC5	Isomerases (n = 43)	12.6	9.5	22.1
EC6	Ligases (n = 20)	9.7	8.3	18.0

Jimenez-Morales, Liang, Eisenberg

Electrolytes are Complex Fluids

Treating a
Complex Fluid
as if it were a
Simple Fluid
will produce
Elusive Results

"**Single-Ion Solvation**
… **Elusive*** Quantities"
690 pages 2604 references
Hünenberger & Reif, 2011

Idealized Theories

like Debye Hückel and Poisson Boltzmann

Do not fit data at all

in any biological solution

I do not exaggerate as quotations will show

Biological solutions are always <u>mixtures</u>
with total concentrations >100 mM
and involve Ca^{2+} and other <u>multi-valent ions</u>

Debye Hückel and Poisson Boltzmann are usable
ONLY
for pure NaCl <50 mM

Robinson and Stokes

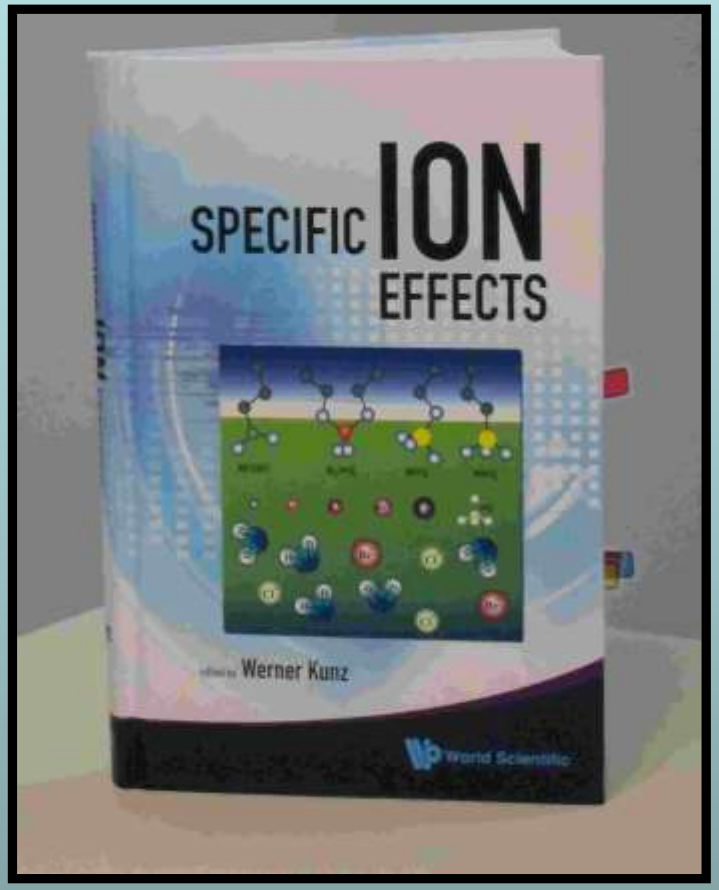
Austere Classic text in print since 1955

(not otherwise noted for its emotional content)

gives a glimpse of frustration of physical chemists

“In regard to concentrated solutions, many workers adopt a counsel of despair, confining their interest to concentrations below about 0.02 M, ... ”

p. 302 *Electrolyte Solutions* (1959) Butterworths, also Dover (2002), emphasis added



Kunz, W. "**Specific Ion Effects**"
World Scientific Singapore, 2009; p 11.

Werner Kunz
Evidence of Frustration

"It is still a fact that over the last decades,

it was easier to fly to the moon

than to describe the

free energy

of even the simplest salt solutions

beyond a concentration of 0.1M or so."

“Poisson Boltzmann theories are restricted to such low concentrations that the solutions cannot be studied in the laboratory”

slight paraphrase of p. 125 of Barthel, Krienke, and Kunz , Springer, 1998

Original text “… experimental verification often proves to be an unsolvable task”

Evidence of Frustration

“ …. it is almost never valid to use Debye-Hückel theory

… it is important to take proper account of ion size”

Stell, G. and C.G. Joslin *Biophys J, 1986.* ***50(5): p. 855-859.***

Cause of Frustration

Biochemistry Texts

Treatises on Enzymes

Reviews of Allostery

Do not mention activity at all

Don't worry!

Crowded Charge
is GOOD
for mathematicians

It enables
SIMPLIFICATION

by exploiting a biological fact
(an adaptation)

Charges are Crowded where they are important!

Working Hypothesis
in language of mathematics

Crowded Charge
enables
Dimensional Reduction
to a
Device Equation

Working Hypothesis in language of Engineering and Biology

Device Equation

is

How it Works!

Motivation

Natural Description of Crowded Charge

is a

Fermi Distribution

because it describes Saturation
in a simple way and is used throughout physics

Simulating saturation by interatomic repulsion (Lennard Jones)
is a significant mathematical challenge
to be side-stepped if possible
Eisenberg, Hyon and Liu (2010). JChemPhys 133: 104104

Motivation

Largest Effect
of
Crowded Charge
is
Saturation

*Saturation cannot be described at all by classical Poisson Boltzmann approach and is described in a uncalibrated way by **present day** Molecular Dynamics when Mixtures and Divalents are Biologically Important in Concentrations of 10^{-8} to 10^{1} M*

Motivation

Fermi Description

is designed to deal with

Saturation of Concentration

Simulating saturation by interatomic repulsion (Lennard Jones)
is a <u>significant mathematical challenge</u>
to be side-stepped if possible
Eisenberg, Hyon and Liu (2010). JChemPhys 133: 104104

Fermi Description
of
Saturation of Volume
by Spherical Ions

Fermi (like) **Distribution**

$$C_i(\mathbf{r}) = C_i^{bath} \exp\left(-\beta_i \phi(\mathbf{r}) + S^{teric}(\mathbf{r})\right)$$

$S^{teric}(\mathbf{r}) = \ln\left(\Gamma(\mathbf{r}) / \Gamma(bath)\right)$

$\Gamma(bath)$ = volume fraction of voids in bulk

$\Gamma(\mathbf{r})$ = volume fraction of voids in channel

J.-L. Liu J Comp Phys (2013) 247:88

Fermi (like) Distribution

depends on Steric Factor S^{teric} of System

Algebraic Model of Calcium Channel

works surprisingly well despite crudeness of molecular model

$$S^{teric}(\mathbf{r}) = \ln \frac{1 - \sum_{j=1}^{K+1} \nu_j C_j(\mathbf{r})}{1 - \sum_{j=1}^{K+1} \nu_j C_j(bath)}$$

$$C_{Na} = C_{Na}(\max) \frac{1}{1 + 3(1-\nu) e^{-\mathbf{e}/k_B T}}$$

J Comp Phys (2013) 247:88

$\nu_i = \text{volume} = 4\pi a_i^3/3; \quad a_i = \text{radius}$

Algebraic Model of Bulk Solution, *e.g. Calcium Chloride*

$$CaCl_2 : S^{teric} = \ln \frac{1 - \nu + \nu\left(z_+ e^{-z_+ \mathbf{e}\phi/k_B T} + z_- e^{-z_- \mathbf{e}\phi/k_B T}\right)}{z_+ + z_-}$$

Fermi Description of Crowded Charge and Saturation

4) We adopt the simplest treatment so we can deal with 3D structures

many chemical complexities are known to us and have been left out purposely for this reason

5) We require **exact consistency with electrodynamics** of flow because

Key to successful modelling of ions

Electric forces are so large
that deviations from consistency do not allow transferrable models and can easily wreck models all together

Flow is Essential
Death is the only Equilibrium of Life

Exact consistency with electrodynamics

of flow is

THE key to successful modelling of ions

in my opinion

Electric forces are so large

that deviations from consistency do not allow transferrable models

and can easily wreck models all together

Flow is Essential

Death is the only Equilibrium of Life

Challenge

Can Simplest Fermi Approach

- *Describe **ion channel selectivity** and permeation?*
- *Describe **non-ideal properties of bulk solutions?***

There are no shortage of chemical complexities to include, if needed!

Classical Treatments of Chemical Complexities

Fermi Description uses **Entropy of Mixture of Spheres** from Combinatoric Analysis

$$W = \prod_{j=1}^{K+1} W_j = \frac{N!}{\left(\prod_{j=1}^{K+1} N_j!\right) \cdot \left(N - \sum_{j=1}^{K+1} N_j\right)!}$$

***W* is the mixing entropy of UNEQUAL spheres with *N* available NON-UNIFORM sites**

$W_1 = N!/(N_1!(N - N_1)!)$

$= \text{combinations for } N_1 \text{ species in all vacant sites } N.$

$W_2 =$ combinations for N_2 species, and so on,…, through

$W_{k+1} =$ combinations for **water**

Connection to volumes of spheres and voids, and other details are published in 5 papers

Expressions in other literature are not consistent with this entropy

J Comp Phys (2013) 247:88 **J Phys Chem B (2013) 117:12051**
J Chem Phys (2014) 141: 075102 **J Chem Phys, (2014) 141: 22D532**
Physical Review E (2015) 92:012711

*(Electro)*Chemical Potential μ_i and Void Volume ν_i

$$\mu_i = \frac{\partial\,(\text{free energy})}{\partial\,(\text{mole}_i)} = \text{Electrostatic} + k_B T \ln \frac{\nu_i C_i(\mathbf{r})}{1 - \sum_{j=1}^{K=2} \nu_i C_i(\mathbf{r})}$$

Voids are Needed

It is impossible to treat all ions and water molecules
as
hard spheres
and
at the same time have
Zero Volume of interstitial Voids
between all particles.

Consistent Fermi Approach is Novel

Consistent Fermi approach has not been previously applied to ionic solutions
as far as we, colleagues, referees, and editors know

Previous treatments* have inconsistent treatment of particle size
They do not reduce to Boltzmann functionals in the appropriate limit
Previous treatments often do not include non-uniform particle size

Previous treatments* are inconsistent with electrodynamics and nonequilibrium flows including convection

Details
Previous treatments do not include discrete water or voids.
They cannot deal with volume changes of channels, or pressure/volume in general
Previous treatments do not include polarizable water
with polarization as an output

*Previous treatments

Bazant, Storey & Kornyshev,. *Physical Review Letters,* 2011. 106(4): p. 046102.
Borukhov, Andelman & Orland, *Physical Review Letters,* 1997. 79(3): p. 435.
Li, B. *SIAM Journal on Mathematical Analysis,* 2009. 40(6): p. 2536-2566.
Liu, J.-L., Journal of Computational Physics 2013. 247(0): p. 88-99.
Lu & Zhou, *Biophysical Journal,* 2011. 100(10): p. 2475-2485.
Qiao, Tu & Lu, *J Chem Phys,* 2014. 140(17):174102
Silalahi, Boschitsch, Harris & Fenley, JCCT 2010. 6(12): p. 3631-3639.
Zhou, Wang & Li *Physical Review E,* 2011. 84(2): p. 021901.

Fermi (like) Distribution

$$C_i(\mathbf{r}) = C_i^{bath} \exp\left(-\beta_i \phi(\mathbf{r}) + S^{teric}(\mathbf{r})\right)$$

$$S^{teric}(\mathbf{r}) = \ln\left(\Gamma(\mathbf{r}) / \Gamma(bath)\right)$$

$\Gamma(bath)$ = bulk void concentration; $\Gamma(\mathbf{r})$ = channel void concentration

Fermi (like) Distribution

is a general

Quantitative Statement of Charge-Space Competition

Simulated and compared to experiments in
> 35 papers of *Boda, Henderson, et al,*
and >10 papers of Gillespie, et al,

also gives

Gibbs Fermi Functional

J Comp Phys, 2013 247:88; J Phys Chem B, 2013 117:12051

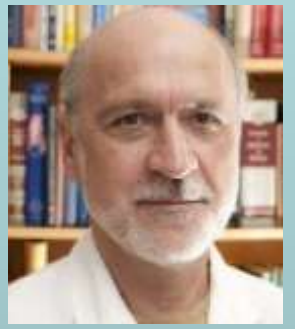
so the Fermi approach
Can be embedded in the ***E***nergy ***V***ariational ***F***ormulation
EnVarA developed by ***Chun Liu***, more than anyone
Eisenberg, Hyon and Liu (2010). JChemPhys 133: 104104

Charge-Space Competition

Monte Carlo Methods

Dezső Boda

Doug Henderson



Wolfgang Nonner

Nonner, W., D. P. Chen, and B. Eisenberg. 1998. Anomalous Mole Fraction Effect, Electrostatics, and Binding in Ionic Channels. Biophysical Journal 74:2327-2334.

Nonner, W., L. Catacuzzeno, and B. Eisenberg. 2000. Binding and Selectivity in L-type Ca Channels: a Mean Spherical Approximation. Biophysical Journal 79:1976-1992.

Nonner, W., D. Gillespie, D. Henderson, and B. Eisenberg. 2001. Ion accumulation in a biological calcium channel: effects of solvent and confining pressure. J Physical Chemistry B 105:6427-6436.

Boda, D., W. Nonner, D. Henderson, B. Eisenberg, and D. Gillespie. 2008. Volume exclusion in calcium selective channels. Biophys. J.:biophysj.107.122796.

Boda, D., M. Valisko, B. Eisenberg, W. Nonner, D. Henderson, and D. Gillespie. 2006. Effect of Protein Dielectric Coefficient on the Ionic Selectivity of a Calcium Channel. Journal of Chemical Physics 125:034901.

Boda, D., T. Varga, D. Henderson, D. Busath, W. Nonner, D. Gillespie, and B. Eisenberg. 2004. Monte Carlo simulation study of a system with a dielectric boundary: application to calcium channel selectivity. Molecular Simulation 30:89-96.

Boda, D., M. Valisko, B. Eisenberg, W. Nonner, D. Henderson, and D. Gillespie. 2007. The combined effect of pore radius and protein dielectric coefficient on the selectivity of a calcium channel. Physical Review Letters 98:168102.

More than 35 papers are available at

ftp://ftp.rush.edu/users/molebio/Bob_Eisenberg/reprints

Evidence

(start)

Best Evidence for All Spheres Charge Space Competition is from the

RyR Receptor

Dirk Gillespie

Dirk_Gillespie@rush.edu

Gerhard Meissner, Le Xu, et al,

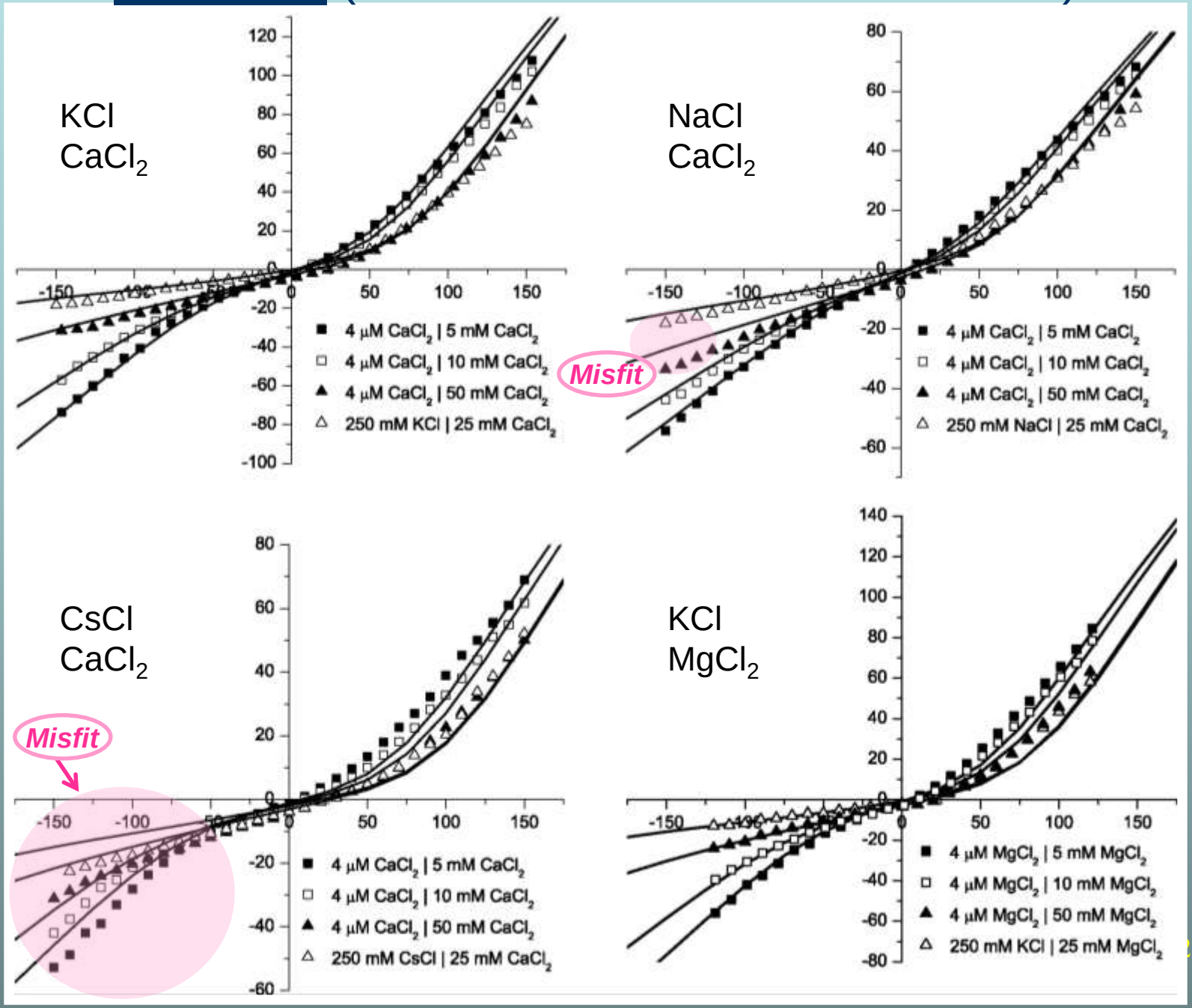
not *Bob Eisenberg*

- **More than 120 combinations of solutions & mutants**
- **7 mutants with significant effects fit successfully**
- **Errors in PREDICTIONS less than *0.2 $k_B T/e$***

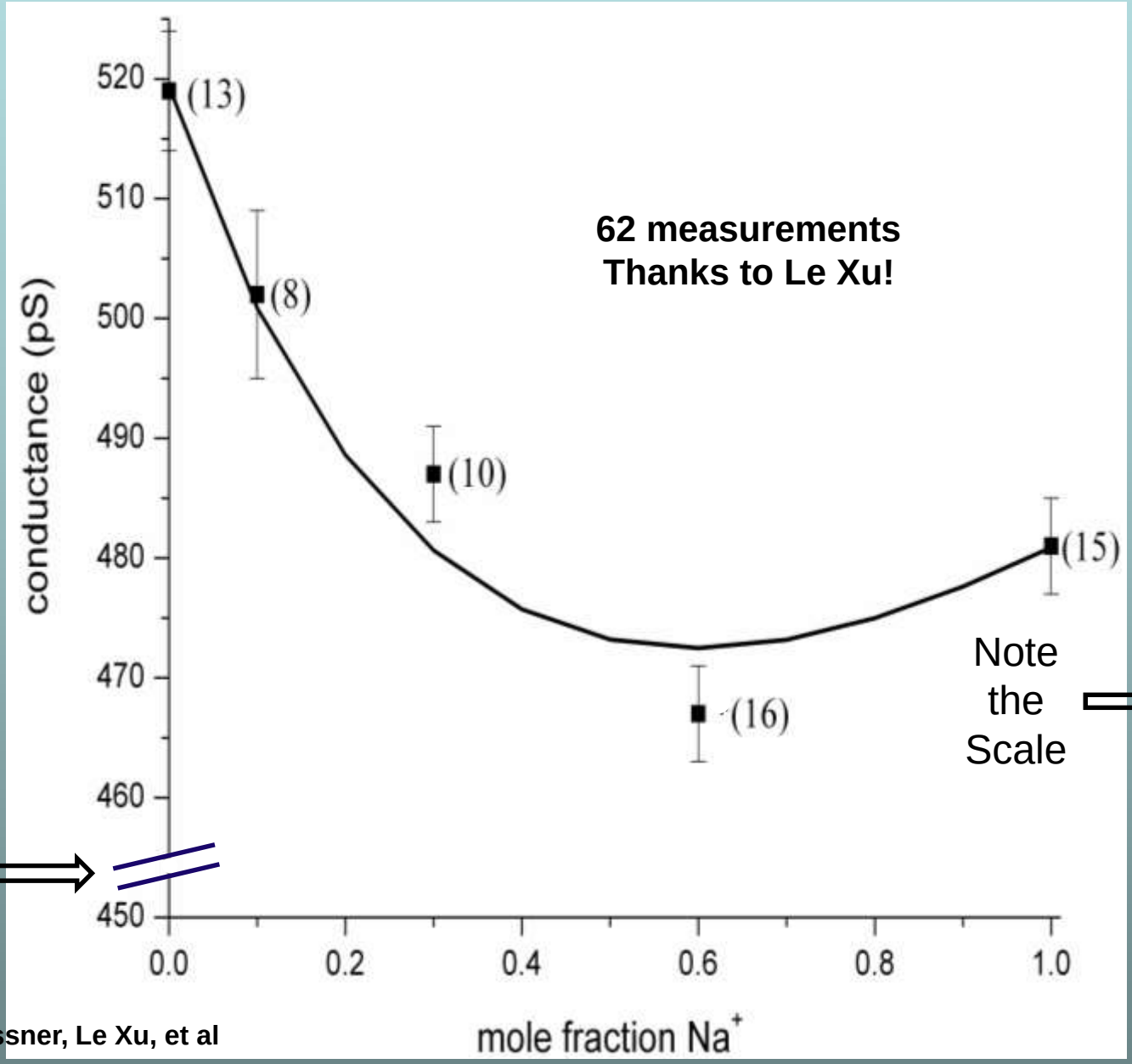
Gillespie (2008) "Energetics …. "Biophys J 94: 1169-84.

1. Gillespie, D., Energetics of divalent selectivity in a calcium channel: the ryanodine receptor case study. *Biophys J, 2008. 94(4): p. 1169-1184.*
2. Gillespie, D. and D. Boda, Anomalous Mole Fraction Effect in Calcium Channels: A Measure of Preferential Selectivity. *Biophys. J., 2008. 95(6): p. 2658-2672.*
3. Gillespie, D. and M. Fill, Intracellular Calcium Release Channels Mediate Their Own Countercurrent: Ryanodine Receptor. *Biophys. J., 2008. 95(8): p. 3706-3714.*
4. Gillespie, D., W. Nonner, and R.S. Eisenberg, Coupling Poisson-Nernst-Planck and Density Functional Theory to Calculate Ion Flux. *Journal of Physics (Condensed Matter), 2002. 14: p. 12129-12145.*
5. Gillespie, D., W. Nonner, and R.S. Eisenberg, Density functional theory of charged, hard-sphere fluids. Physical Review E, 2003. 68: p. 0313503.
6. Gillespie, D., Valisko, and Boda, Density functional theory of electrical double layer: the RFD functional. *Journal of Physics: Condensed Matter, 2005. 17: p. 6609-6626.*
7. Gillespie, D., J. Giri, and M. Fill, Reinterpreting the Anomalous Mole Fraction Effect. The ryanodine receptor case study. Biophysical Journal, 2009. 97: p. pp. 2212 - 2221
8. Gillespie, D., L. Xu, Y. Wang, and G. Meissner, (De)constructing the Ryanodine Receptor: modeling ion permeation and selectivity of the calcium release channel. *Journal of Physical Chemistry, 2005. 109: p. 15598-15610.*
9. Gillespie, D., D. Boda, Y. He, P. Apel, and Z.S. Siwy, Synthetic Nanopores as a Test Case for Ion Channel Theories: The Anomalous Mole Fraction Effect without Single Filing. *Biophys. J., 2008. 95(2): p. 609-619.*
10. Malasics, A., D. Boda, M. Valisko, D. Henderson, and D. Gillespie, Simulations of calcium channel block by trivalent cations: Gd(3+) competes with permeant ions for the selectivity filter. *Biochim Biophys Acta, 2010. 1798(11): p. 2013-2021.*
11. Roth, R. and D. Gillespie, Physics of Size Selectivity. *Physical Review Letters, 2005. 95: p. 247801.*
12. Valisko, M., D. Boda, and D. Gillespie, Selective Adsorption of Ions with Different Diameter and Valence at Highly Charged Interfaces. *Journal of Physical Chemistry C, 2007. 111: p. 15575-15585.*
13. Wang, Y., L. Xu, D. Pasek, D. Gillespie, and G. Meissner, Probing the Role of Negatively Charged Amino Acid Residues in Ion Permeation of Skeletal Muscle Ryanodine Receptor. *Biophysical Journal, 2005. 89: p. 256-265.*
14. Xu, L., Y. Wang, D. Gillespie, and G. Meissner, Two Rings of Negative Charges in the Cytosolic Vestibule of T Ryanodine Receptor Modulate Ion Fluxes. *Biophysical Journal, 2006. 90: p. 443-453.*

Divalents (WORST fit of some 120 solutions)



The model predicted an AMFE for Na^+/Cs^+ mixtures before it had been measured



Gillespie, Meissner, Le Xu, et al

Evidence

(end)

Poisson-Fermi Analysis is NON-Equilibrium

Flows are Essential in Devices & Biology
Structure is Essential in Devices & Biology
Implemented fully in 3D Code to accommodate 3D Protein Structures

Flows cease only at death

1) PNPF uses treatment by **Santangelo** 2006[1] used by Kornyshev 2011[2]
of near/far fields crudely separated by fixed correlation length l_c

2) PNPF introduces steric potential[3,4] so unequal spheres are dealt with consistently

3) PNPF force equation reduces[3,4] to pair of 2*nd* order PDE's and
Appropriate boundary conditions
that are **consistent** and allow
Robust and Efficient Numerical Evaluation

4) PNPF combines force equation and Nernst-Planck Description of Flow

[1]PhysRev E (2006) 73:041512 [2]PhysRev Ltrs (2011) 106:046102 [3]JCompPhys (2013) 247:88 [4]J PhysChem B (2013) 117:12051

PNPF

Poisson-Nernst-Planck-Fermi

Implemented fully in 3D Code to accommodate 3D Protein Structures

Flow

$$\nabla \cdot \mathbf{J} = 0$$

$$\mathbf{J}_i = -D_i \left[\nabla C_i + (z_i \boldsymbol{e} / k_b T)\, \nabla \phi - C_i \nabla S^{teric} \right]$$

Force

$$\nabla^2 \phi = \psi$$

$$\varepsilon_{water} \left(l_c \nabla^2 - 1 \right) \nabla^2 \phi(\mathbf{r}) \psi = \rho(\mathbf{r})$$

$\varepsilon_{water}(l_c \nabla^2 - 1)$ approximates dielectric of entire bulk solution including correlated motions of ions, following **Santangelo** 2006[1] used by Kornyshev 2011[2] with Liu's corrected and consistent Fermi treatment of spheres

We introduce[3,4] **two second order equations** and **boundary conditions**

That give the polarization charge density $-\varepsilon_{water} \psi = \rho_{pol}$

3D computation is facilitated by using 2nd order equations

[1]PhysRev E (2006) 73:041512 [2]PhysRev Ltrs (2011) 106:046102 [3]JCompPhys (2013) 247:88 [4]J PhysChem B (2013) 117:12051

Nonequilibrium Force Equation

Implemented fully in 3D Code to accommodate 3D Protein Structures

Fourth Order Santangelo[1] PDE

$$\varepsilon_{water}\left(l_c\nabla^2-1\right)\nabla^2\phi(\mathbf{r})=\sum_i^K q_i C_i(\mathbf{r})=\rho(\mathbf{r})$$

with $C_i(\mathbf{r})=C_i^{bath}\exp\left(-\beta_i\phi(\mathbf{r})+S^{teric}(\mathbf{r})\right)$

l_c is introduced as a crude correlation length to separate near and far fields

$\varepsilon_{water}\left(l_c\nabla^2-1\right)$ approximates dielectric properties of entire bulk solution including correlated motions of ions, **Santangelo** (2006)[1] followed by **Kornyshev** (2011)[2] using J.-L. Liu's[3] (2013) consistent Fermi treatment of spheres that corrects previous oversimplifications[2]

We introduce[3,4] **two second order equations** and **boundary conditions**

$$\varepsilon_{water}\left(l_c\nabla^2-1\right)\nabla^2\psi=\rho(\mathbf{r});\quad \nabla^2\phi=\psi$$

That give the polarization charge density $\eta=-\varepsilon_{water}\psi=\rho$

3D computation is facilitated by using 2nd order equations

[1]PhysRev E (2006) 73:041512 [2]J Chem Phys 141: 22D532; Phys Rev Ltrs (2011) 106:046102
[3]JCompPhys (2013) 247:88 [4]J Phys Chem B (2013) 117:12051

Gibbs-Fermi 'Grand' Free Energy Functional*

$$G^{Fermi} = \int_{\Omega} d\mathbf{r} \left\{ -\tfrac{1}{2}\varepsilon_{H_2O} l_c^2 \left[\nabla^2 \phi(\mathbf{r}) \right]^2 - \tfrac{1}{2}\varepsilon_{H_2O} \left| \nabla \phi(\mathbf{r}) \right|^2 + \rho(\mathbf{r})\phi(\mathbf{r}) + g \right\}$$

$$g = k_B T \sum_{j=1}^{K+2} \left\{ C_j(\mathbf{r}) \ln\left[\nu_j C_j(\mathbf{r}) \right] - C_j(\mathbf{r}) - \ln\left[\nu_{K+2} C_{K+2}(\mathbf{r}) \right] - \mu_i^B C_j(\mathbf{r}) / k_B T \right\}$$

voids

$$\mu_i^B = k_B T \ln\left(\nu_i C_i^B / \Gamma^B \right)$$

$$\nu_i = \text{ ion volume } = \tfrac{4}{3}\pi a_i^3$$

*Liu & Eisenberg, JChemPhys (2014) **141**:22D532).
N.B. *Dissipation to be determined*

Computational Problems Abound and are Limiting

if goal is to fit real data

It is very easy to get results that only ***seem to converge***, and are in fact ***Not Adequate*** approximations to the converged solutions

Jerome, J. (1995) Analysis of Charge Transport. Mathematical Theory and Approximation of Semiconductor Models. New York, Springer-Verlag.

Markowich, P. A., C. A. Ringhofer and C. Schmeiser (1990). Semiconductor Equations. New York, Springer-Verlag.

Bank, R. E., D. J. Rose and W. Fichtner (1983). Numerical Methods for Semiconductor Device Simulation IEEE Trans. on Electron Devices ED-30(9): 1031-1041.

Bank, R, J Burgler, W Coughran, Jr., W Fichtner, R Smith (1990) Recent Progress Algorithms for Semiconductor Device Simulation Intl Ser Num Math 93: 125-140.

Kerkhoven, T. (1988) On the effectiveness of Gummel's method SIAM J. Sci. & Stat. Comp. 9: 48-60.

Kerkhoven, T and J Jerome (1990). "L(infinity) stability of finite element approximations to elliptic gradient equations." Numer. Math. 57: 561-575.

Computing Flows is Difficult in Electric Field Problems

because the electric field is so strong

1% error in concentrations does little
1% error in charge "lifts the earth"

***One percent* more electrons than protons would**

Lift the Entire Earth!

paraphrase of third paragraph, p. 1-1 of
Feynman, R. P., R. B. Leighton, and M. Sands. 1963. *The Feynman: Lectures on Physics, Mainly Electromagnetism and Matter.* New York: Addison-Wesley Publishing Co.,
also at *http://www.feynmanlectures.caltech.edu/II_toc.html.*

Computational Electronics

has solved these problems over the last 40 years in thousands of papers used to design our digital devices

Vasileska, D, S Goodnick, G Klimeck (2010) Computational Electronics: Semiclassical and Quantum Device Modeling and Simulation. NY, CRC Press.

Selberherr, S. (1984). Analysis and Simulation of Semiconductor Devices. New York, Springer-Verlag.

Jacoboni, C. and P. Lugli (1989). The Monte Carlo Method for Semiconductor Device Simulation. New York, Springer Verlag.

Hess, K. (1991). Monte Carlo Device Simulation: Full Band and Beyond. Boston, MA USA, Kluwer.

Hess, K., J. Leburton, U.Ravaioli (1991). Computational Electronics: Semiconductor Transport and Device Simulation. Boston, Kluwer.

Ferry, D. K. (2000). Semiconductor Transport. New York, Taylor and Francis.

Hess, K. (2000). Advanced Theory of Semiconductor Devices. New York, IEEE Press.

Ferry, D. K., S. M. Goodnick and J. Bird (2009). Transport in Nanostructures. New York, Cambridge University Press.

It is very easy to get results that only seem to converge, and are in fact not adequate approximations to the converged solutions.

Jerome, J. W. (1995). Analysis of Charge Transport. Mathematical Theory and Approximation of Semiconductor Models. New York, Springer-Verlag.

Keys to Successful Computation

1) Avoid errors by checking against analytical solutions of Guowei and collaborators

2) Avoid singularities on boundaries of protein (that wreck convergence)

3) Use a simplified Matched Interface Boundary sMIB method of Guowei and collaborators modified to embed **Scharfetter Gummel** SG criteria of computational electronics (extended to include steric effects).

Scharfetter Gummel is REQUIRED
to ENSURE CONTINUITY OF CURRENT
Charge Conservation is not enough

Scharfetter and Gummel, IEEE Trans. Elec. Dev.**16**, 64 (1969)
P. Markowich, et al, IEEE Trans. Elec. Dev. **30**, 1165 (1983).
Zheng, Chen, and G.-W. Wei, J. Comp. Phys. **230**, 5239 (2011).
Geng, S. Yu, and G.-W. Wei, J. Chem. Phys. **127**, 114106 (2007).
S. M. Hou and X.-D. Liu, J. Comput. Phys. **202**, 411 (2005).
J.-L. Liu, J. Comp. Phys. **247**, 88 (2013).

4) Modified Successive Over-relaxation SOR for fourth order PNPF

Poisson Fermi Analysis

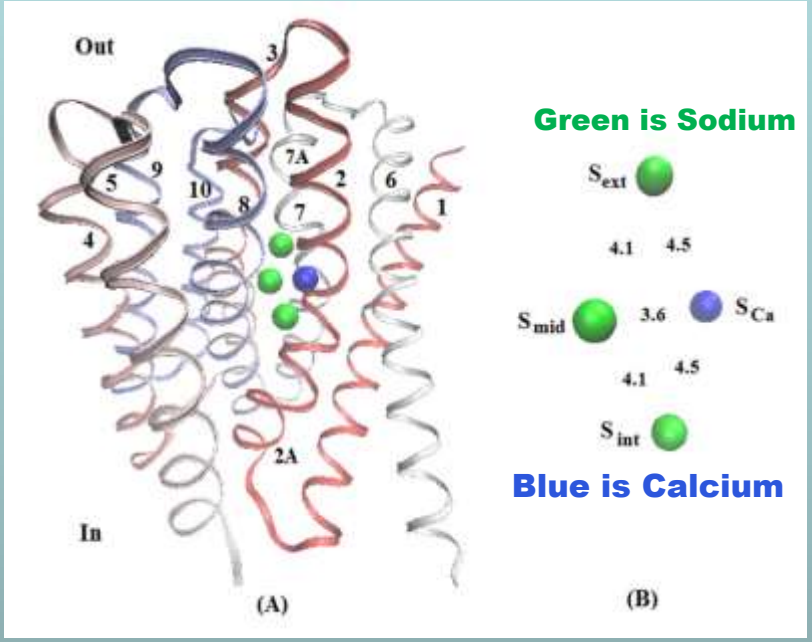
Status Report

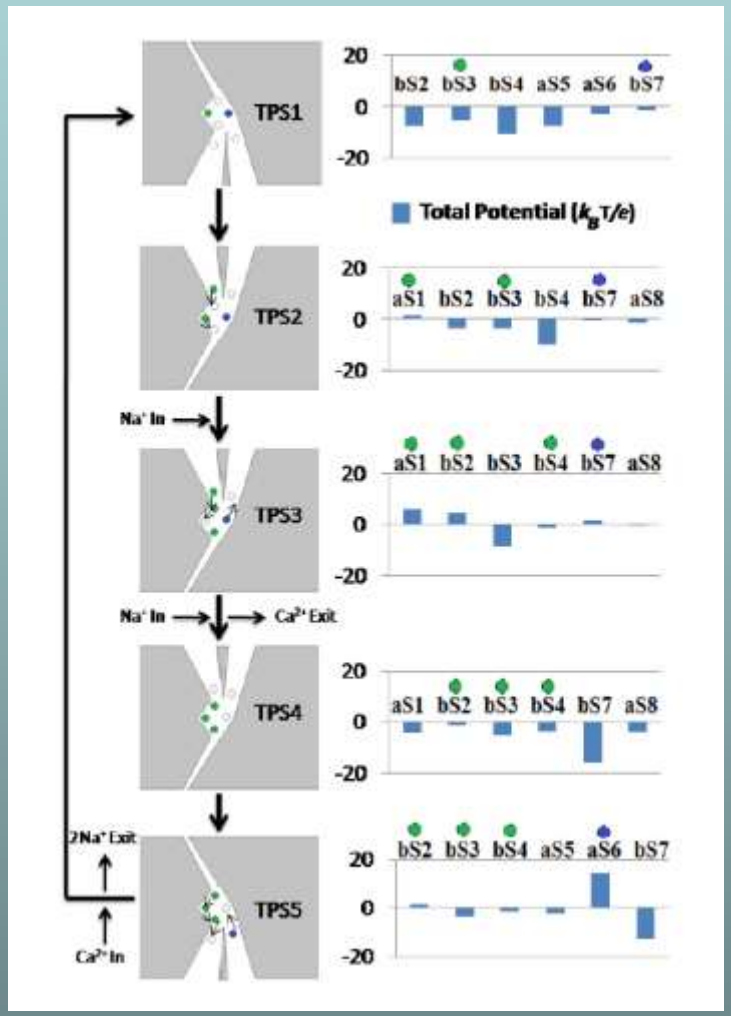
Nonequilibrium implemented fully in 3D Code to accommodate 3D Protein Structures
But only partially compared to experiments
In Bulk or Channels, so far.

- **Gramicidin** *(tested with **real three dimensional structure**, including flow)*
  Physical Review E, 2015. 92:012711
- **$Ca_V1.n$** **EEEE**, i.e., **L-type Calcium Channel**, *tested with homology model*
  J Phys Chem B, 2013 117:12051 (nonequilibrium data is scarce)
- **PNPF** **Poisson-Nernst-Planck-Fermi** for systems with volume saturation
  General PDE, Cahn-Hilliard Type, Four Order, Pair of 2nd order PDE's
  Not yet tested by comparison to bulk data
  J Chem Phys, 2014. 141:075102; J Chem Phys,141:22D532
- **Numerical Procedures** tailored to PNPF have been implemented *(tested)*
  J Comp Phys, 2013 247:88; Phys Rev E, 2015. 92:012711
- **NCX** **Cardiac Ca^{2+}/Na^{+} exchanger** branched **Y** shape **KNOWN** structure.
  Physical analysis of a transporter using consistent mathematics
  using crystallographic structure
  *This is an **ALL ATOM CALCULATION with POLARIZABLE WATER MOLECULES***
  and is feasible and has actually been done
  Liu & Eisenberg, Neurosciences 2015 :450.09

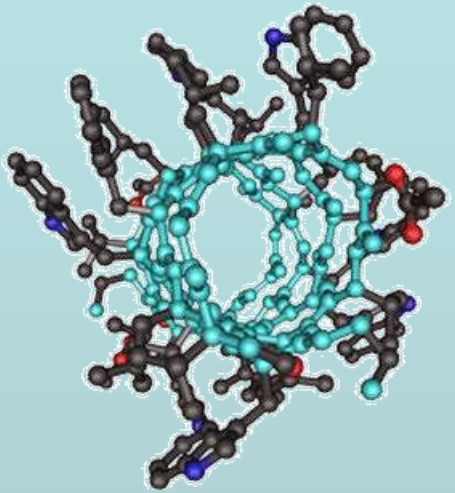
NCX Sodium Calcium Transporter Crucial* to Cardiac Function

strongly implicated in short term memory and learning





*More than 1,000 experimental references
in Blaustein & Lederer Physiological Reviews,1999.



Gramicidin A

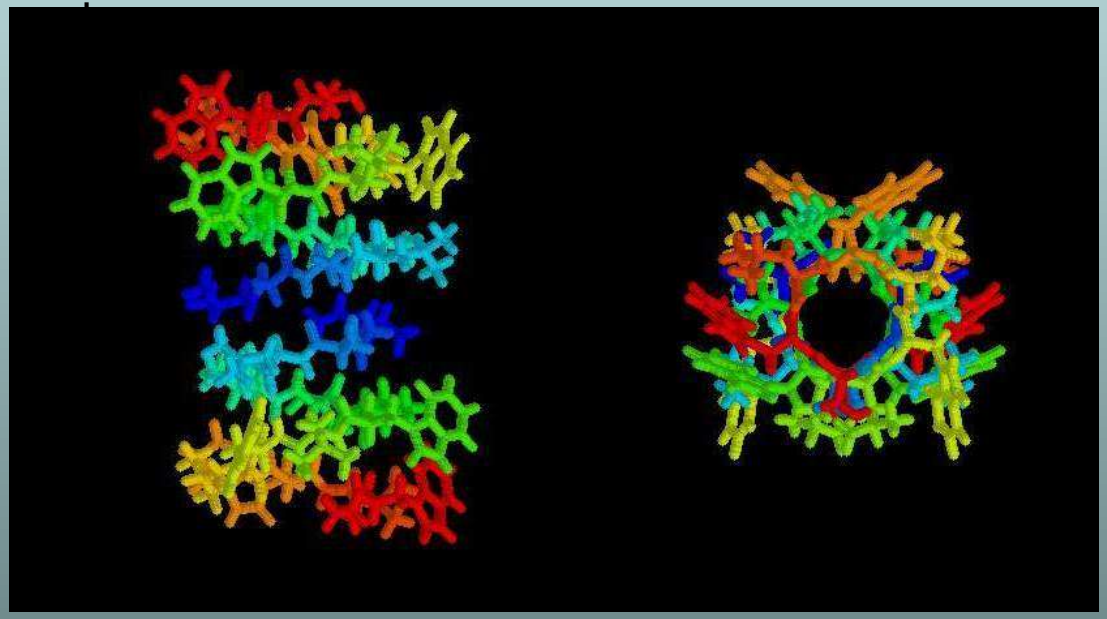
Unusual SMALL Bacterial Channel

often simulated and studied

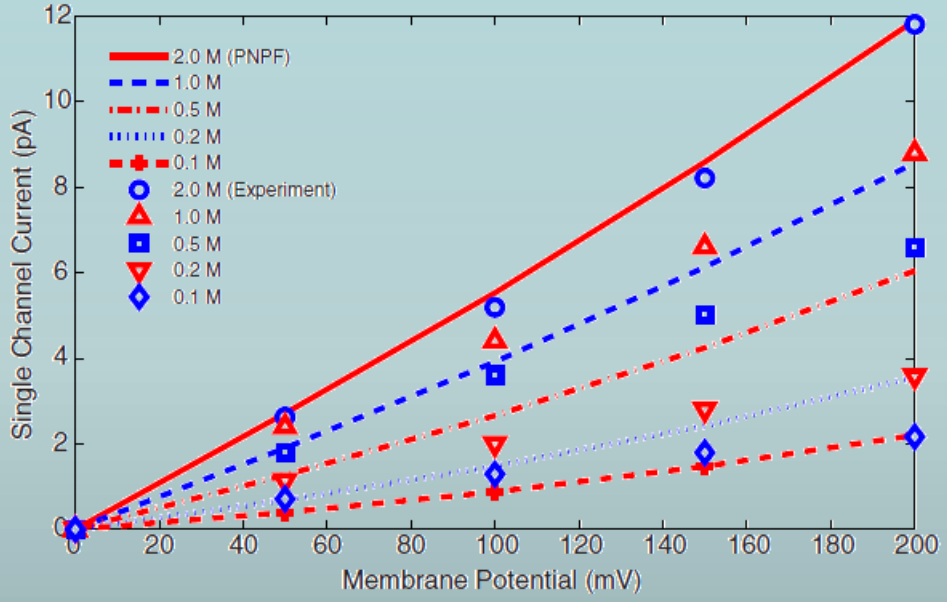
Margaret Thatcher,
student of Nobelist Dorothy Hodgkin
Bonnie Wallace leading worker

Validation of PNP Solvers with Exact Solution

following the lead of
Zheng, Chen & Wei
J. Comp. Phys. (2011) **230**: 5239



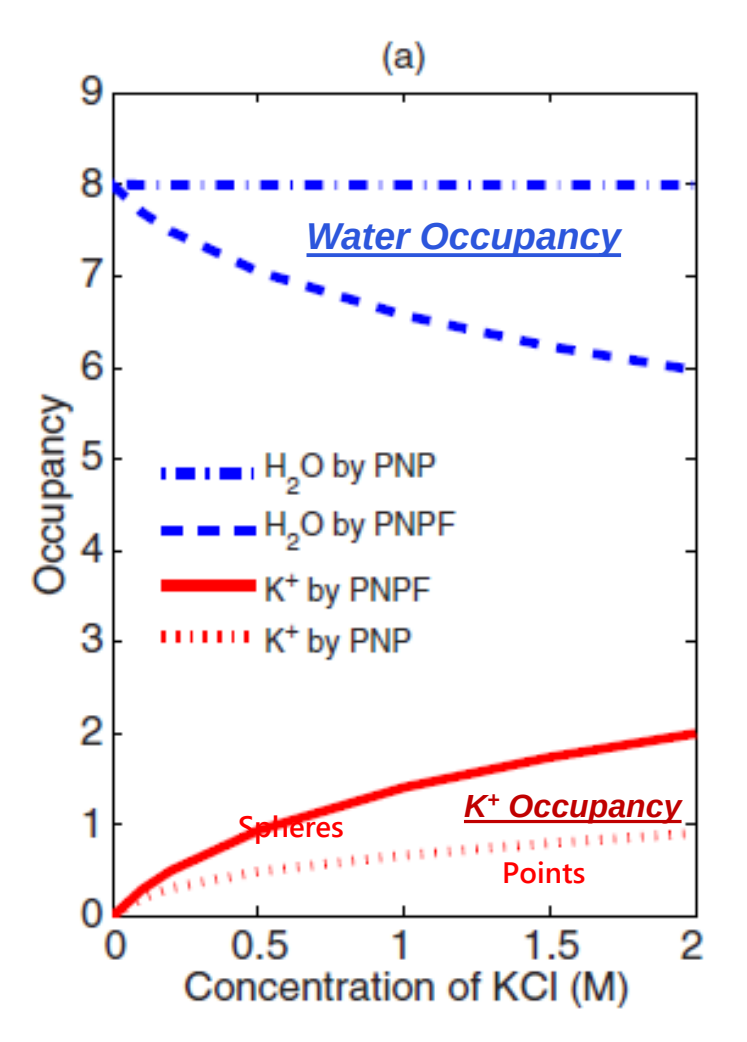
Three Dimensional Theory
Comparison with Experiments
Gramicidin A

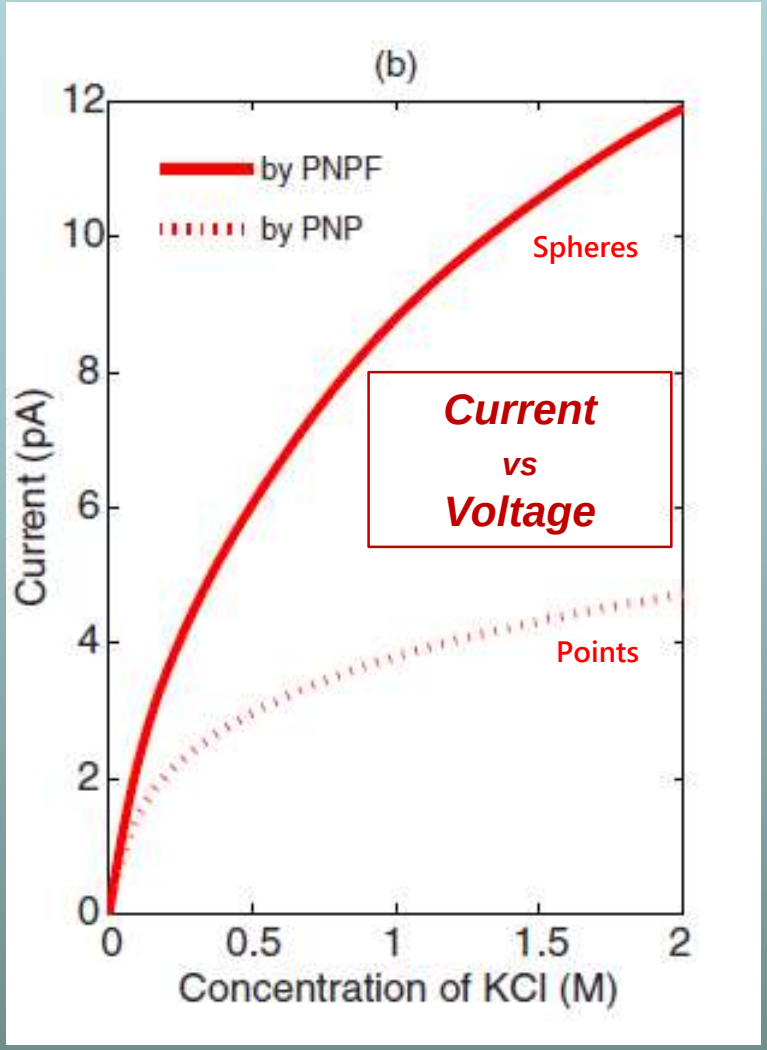


Data from
*Cole, Frost, Thompson, Cotten, **Cross**, & **Busath**, Biophys J (2002) **83**:1974*

Theory from *Liu & Eisenberg J ChemPhys 141: 22D532*
with one adjustable parameter never changed

Steric Effect is Large in *(crowded)* Gramicidin
PNPF spheres *vs* PNP points

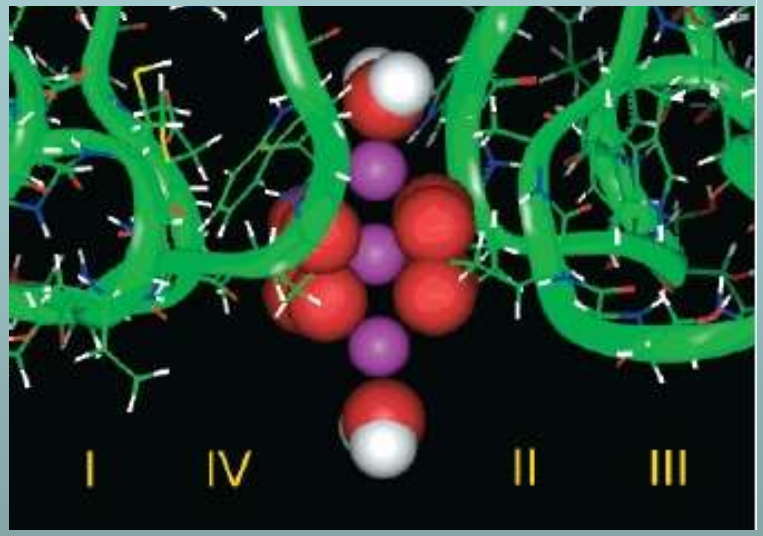




Three Dimensional Calculation Starting with Actual Structure

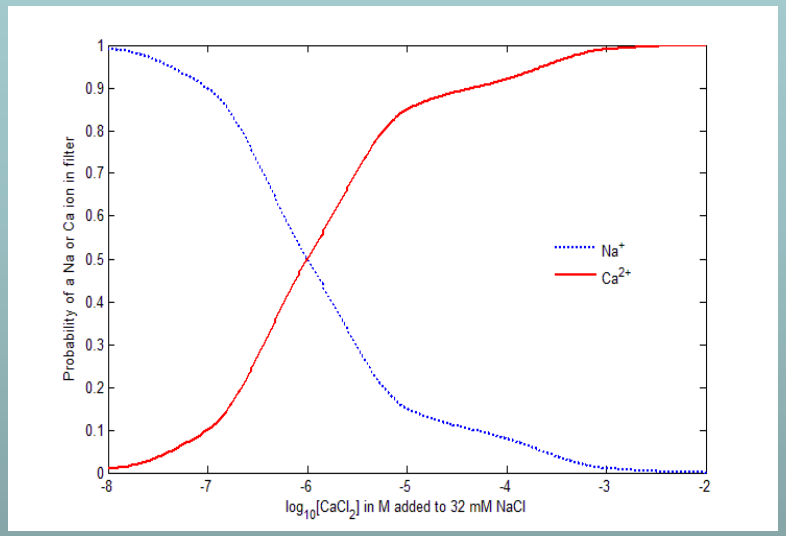
Cardiac Calcium Channel $Ca_V.n$

Lipkind-Fozzard Model



Ca^{2+} are shown in **violet**,
8 $O^{0.5-}$ in **red**, H_2O in **white** and **red**
Lipkind & Fozzard, Biochem (2001) **40** 6786

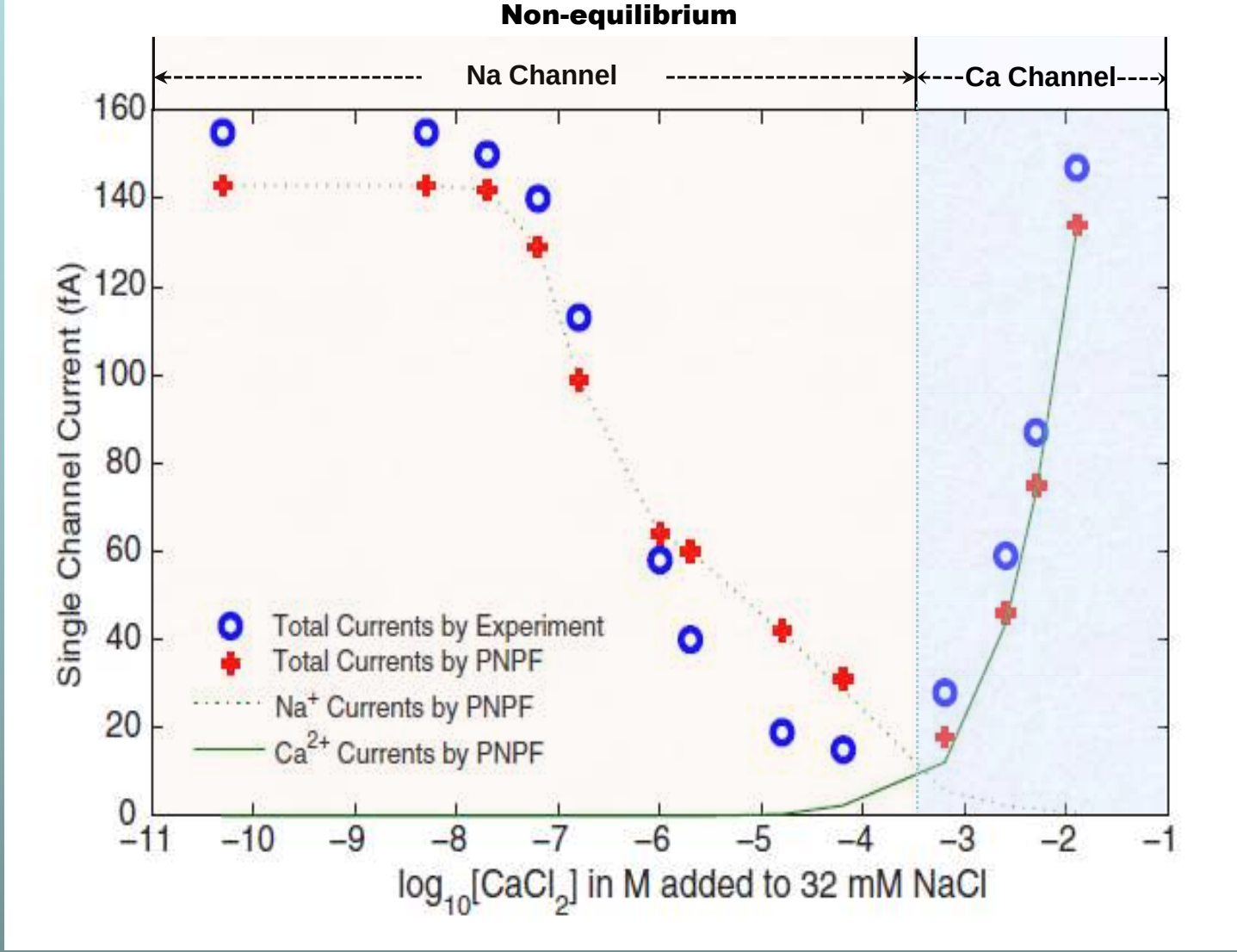
Binding Curve



Liu & Eisenberg J Chem Phys 141(22): 22D532

Cardiac Calcium Channel $Ca_V1.n$

Experimental Signature *Anomalous** Mole Fraction

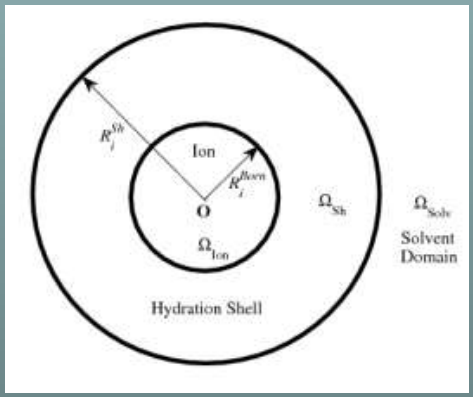


***Anomalous* because CALCIUM CHANNEL IS A SODIUM CHANNEL at $[CaCl_2] \cong 10^{-3.4}$**
Ca^{2+} is conducted for $[Ca^{2+}] > 10^{-3.4}$, but Na^+ is conducted for $[Ca^{2+}] < 10^{-3.}$

Liu & Eisenberg (2015) Physical Review E 92: 012711

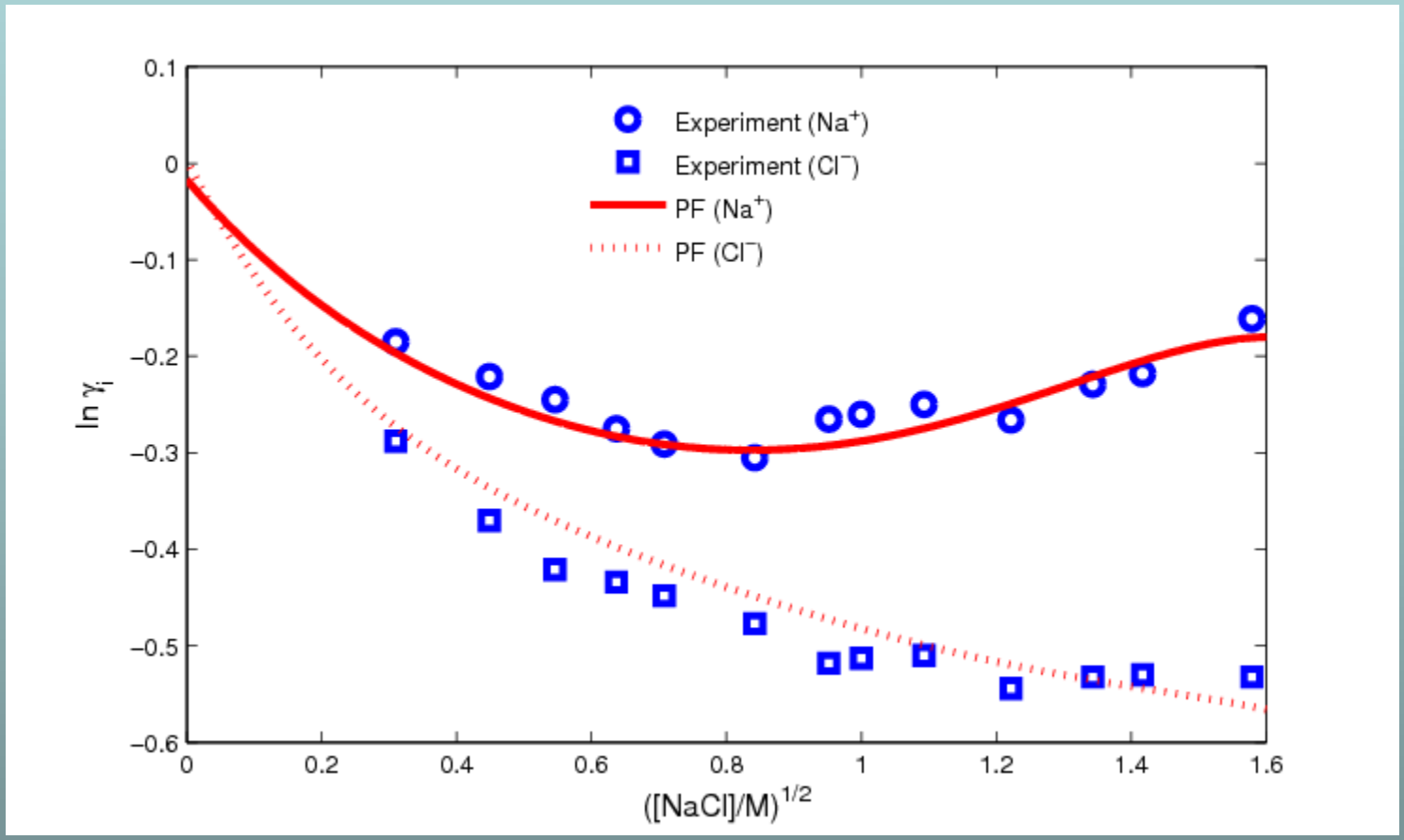
Poisson Fermi Approach to
Bulk Solutions

Same Fermi Poisson Equations,
different model of nearby atoms in
Hydration Shells

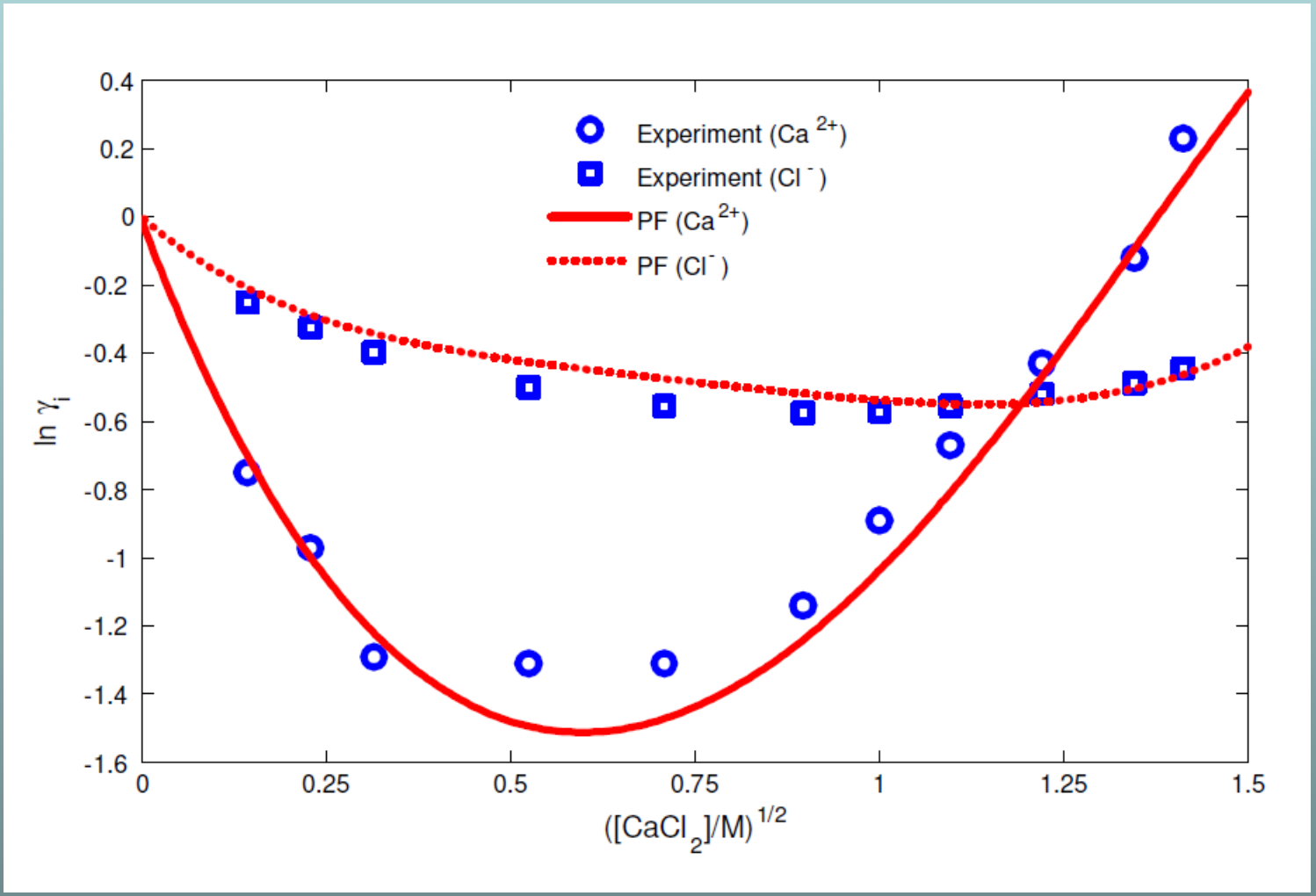


Activity Coefficients
Na^+ Cl^-

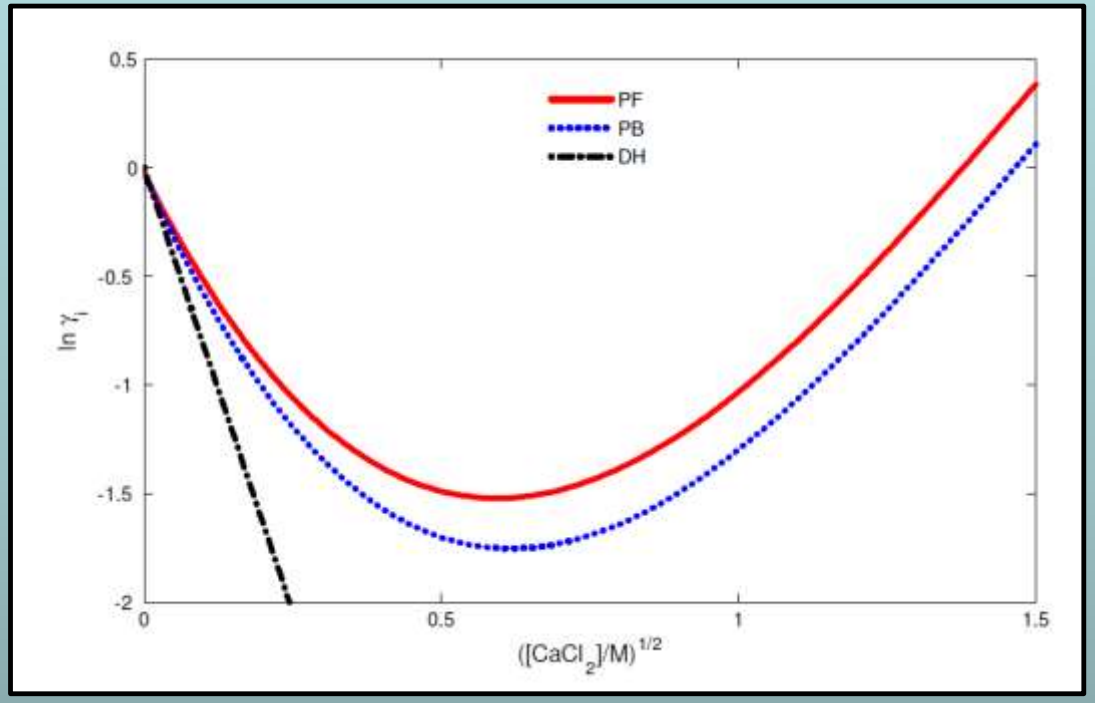
'normalized' free energy per mole



Activity Coefficients
$Ca^{2+}Cl_2^-$
'normalized' free energy per mole



Debye-Hückel Fails Disastrously
Poisson Boltzmann is quite inaccurate
Poisson Fermi does Surprisingly Well



Parameters, NOT further adjusted

$l_c = 2a_i$	correlation length	$i = Na^+, Ca^{2+}, Cl^-$	Å
a_{Na^+}, $a_{Ca^{2+}}$	radii	0.95, 0.99	Å
a_{Cl^-}, a_{H_2O}	radii	1.81, 1.4	Å
$R^0_{Na^+}$, $R^0_{Ca^{2+}}$, $R^0_{Cl^-}$	Born radii in Eq. (12)	1.617, 1.706, 2.263	Å
δ_{Na^+}, $\delta_{Ca^{2+}}$, δ_{Cl^-}	in Eq. (11)	4.2, 5.1, 3.8	
O_i^w	in Eq. (10)	18	

Bulk Solution

How well does the Poisson Fermi Approach for Bulk Solutions?

Same equations, different model of nearby atoms

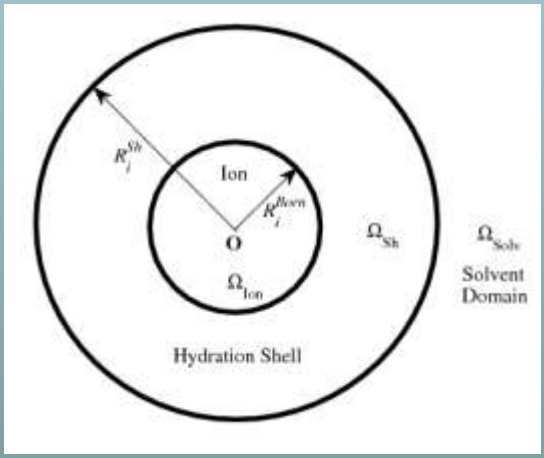
Occupancy is 6+12 Waters*

held Constant in

Model of Bulk Solution

in this oversimplified Poisson Fermi Model

Liu & Eisenberg (2015) Chem Phys Ltr 10.1016/j.cplett.2015.06.079



***in two shells: experimental Data on Occupancy**

Rudolph & Irmer, Dalton Trans. (2013) 42, 3919

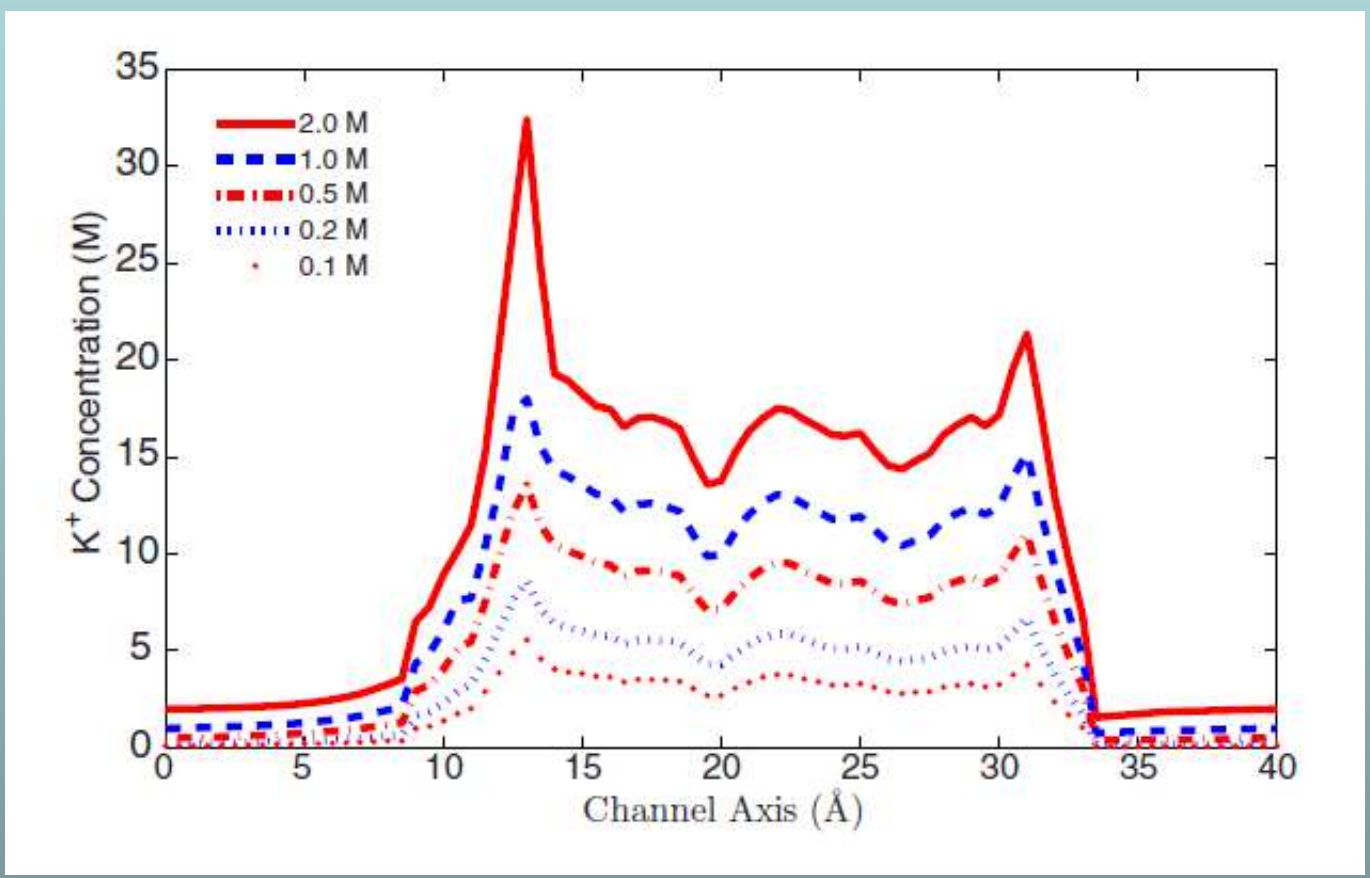
Mähler & Persson, Inorg. Chem. (2011) 51, 425

More Detail

INSIDE CHANNELS

Gramicidin

Two K^+ Binding Sites
OUTPUTS of our calculations

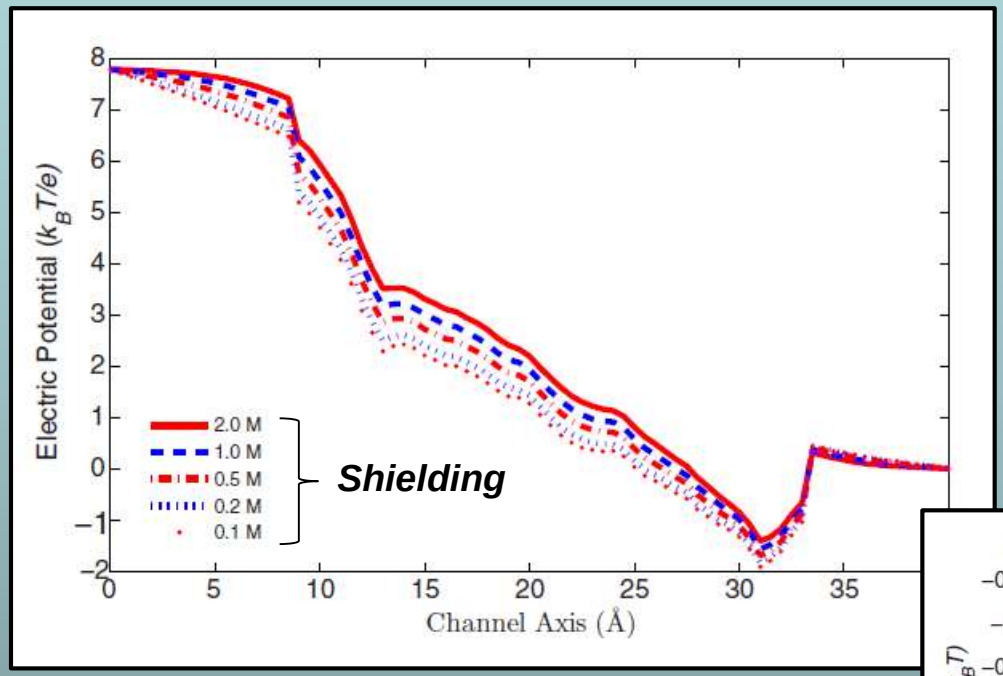


Binding sites are prominent in NMR measurements & MD calculations
BUT they VARY
with conditions in <u>any consistent model</u> and so
<u>cannot be assumed</u> to be of fixed size or location

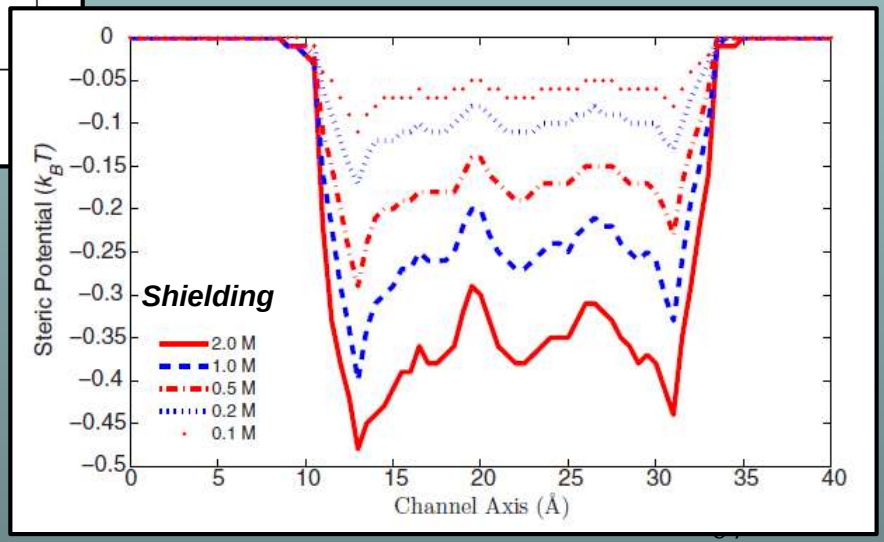
Steric Effect is Significant

Gramicidin is Crowded

Shielding is Substantial



Steric Potential

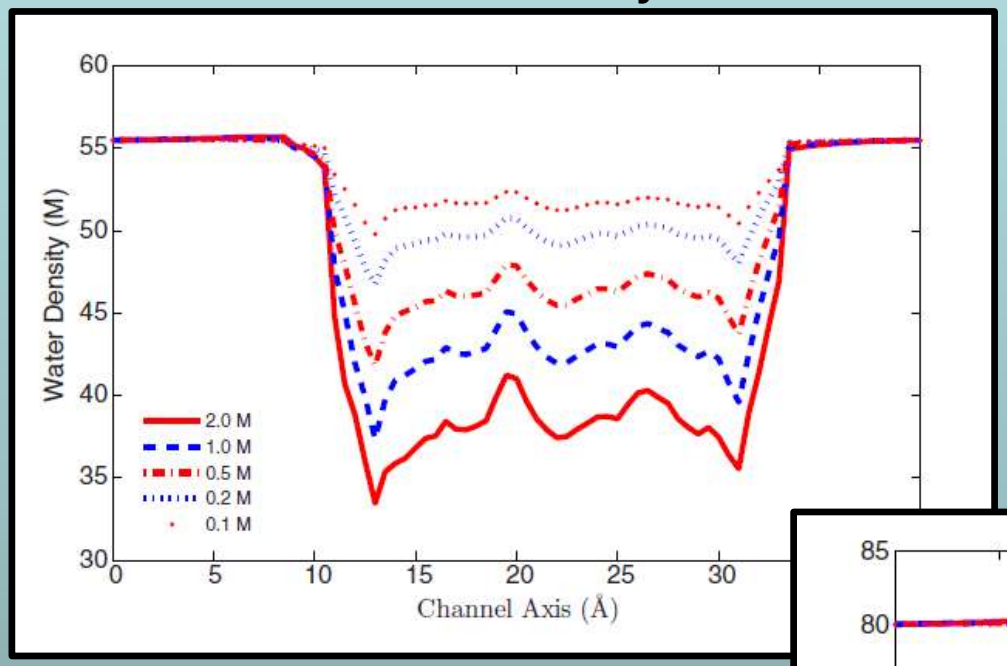


<u>Shielding has been ignored</u> in many papers
Results are often at one concentration or unspecified concentration,
as in most molecular dynamics

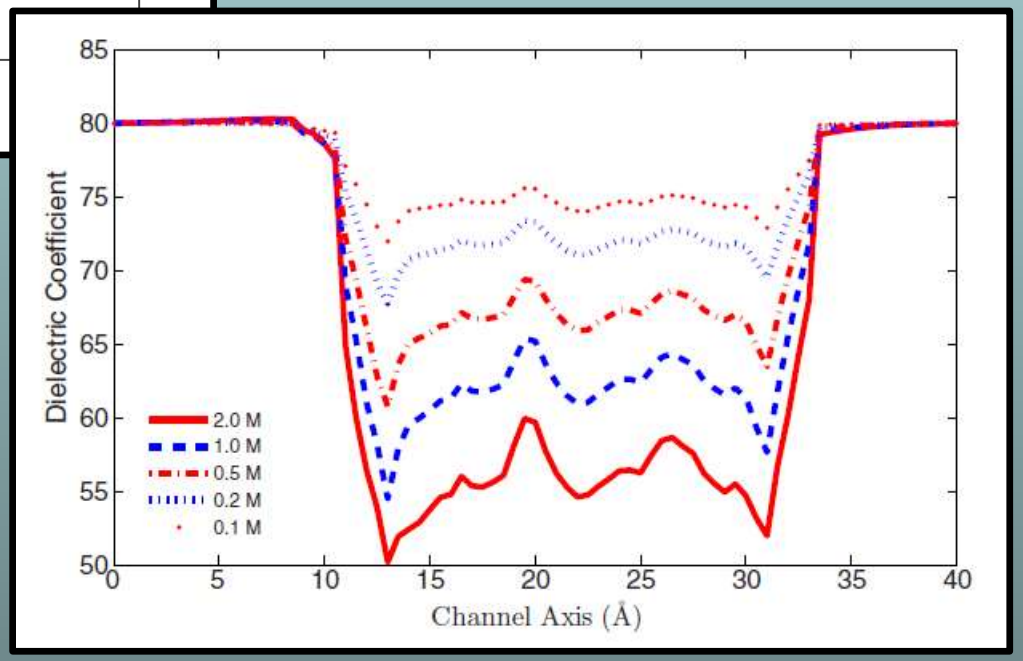
Channel is often described as a potential profile
<u>This is inconsistent with electrodynamics</u>
as in classical rate models

Inside Gramicidin

Water Density



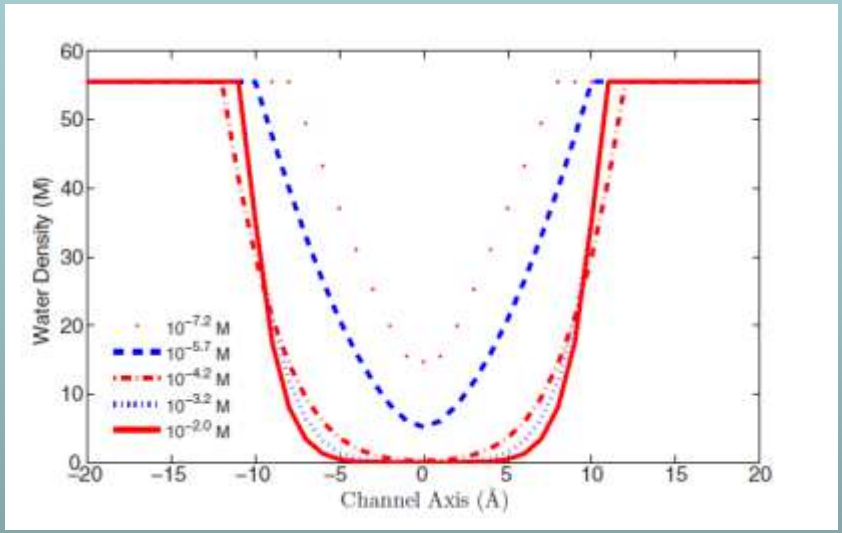
Dielectric Function an OUTPUT of model



Liu & Eisenberg
J Chem Phys 141: 22D532

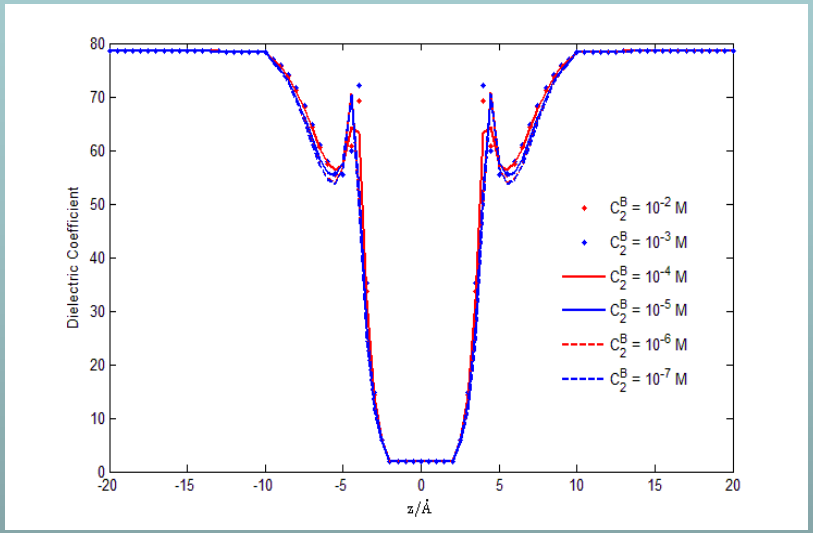
Inside the
Cardiac Calcium Channel
$Ca_V1.n$

Water Density



Liu & Eisenberg (2015) Phys Rev E 92: 012711

Dielectric Function
An ***Output*** of this Model



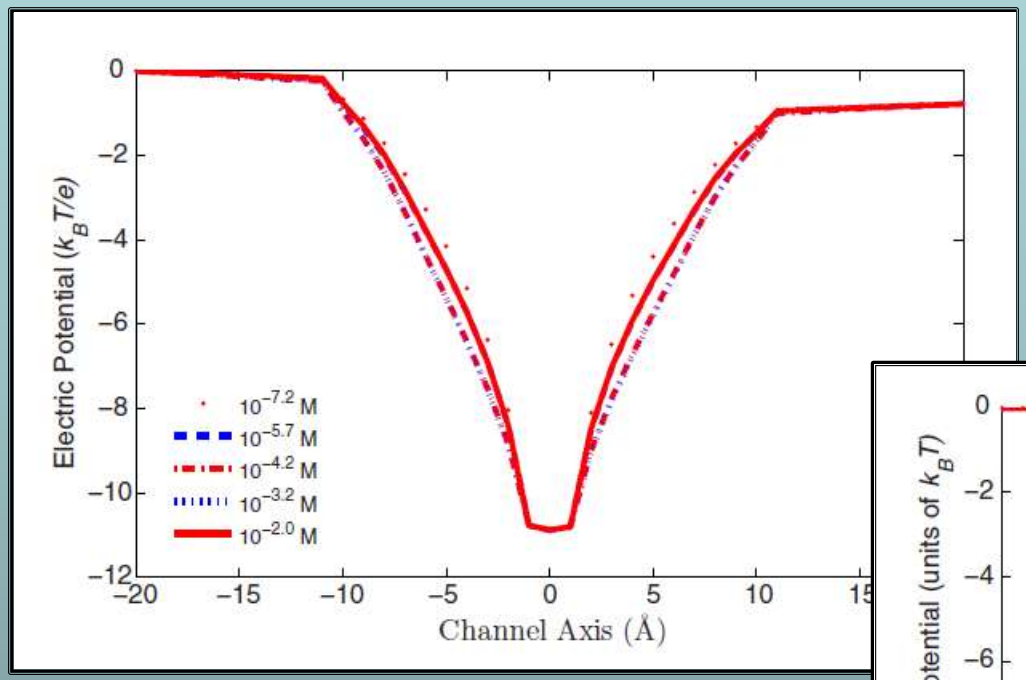
Liu & Eisenberg J Chem Phys 141(22): 22D532

Inside the

Cardiac Calcium Channel

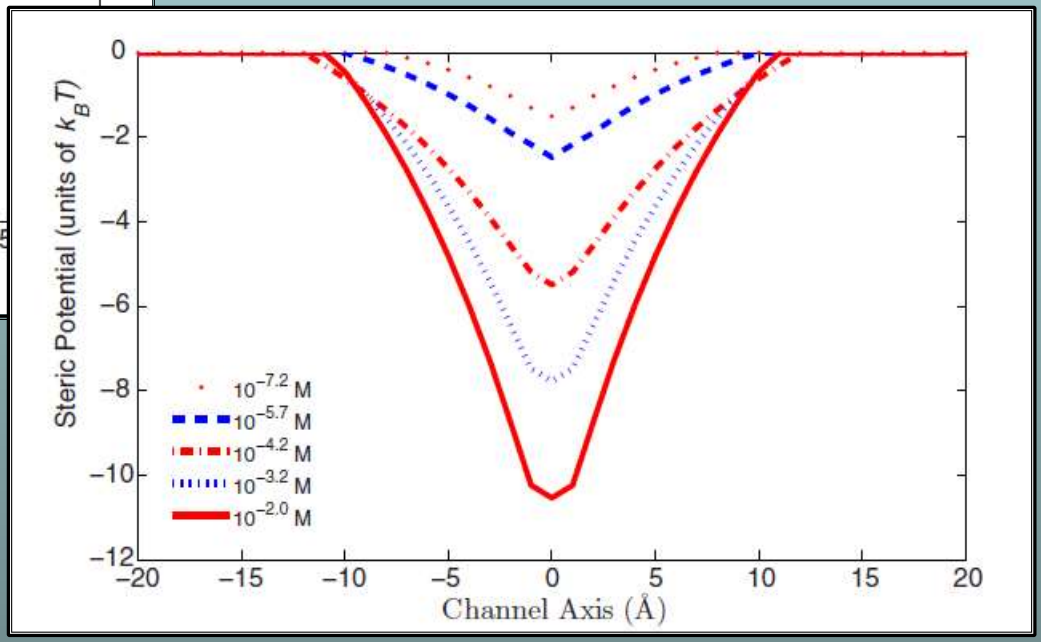
$Ca_V1.n$

Electric Potential



Steric Potential

Estimator of Crowding



The End

Any Questions?

Engineering and Physiology:

Essence of Engineering

is knowing

What Variables to Ignore!

WC Randels

quoted in Warner IEEE Trans CT 48:2457 (2001)

Take Home Lesson

Devices in Engineering are Defined

by their

Reduced Model

Physiology and Medicine

are all about

Reduced Models

in which

SOME atomic details Control Function