Thanks to Pei and Arkadz for Inviting Me

Mathematics and Molecular Biology
GSMMA Webinar
May 20, 2020

Ions in Channels and Bulk

Mathematics and Molecular Biology
GSMMA Webinar
May 20, 2020

Bob Eisenberg
IIT and Rush University
Chicago

All biology occurs in Ionic Solutions

derived from seawater

Concentrated mixtures of sodium Na^+, potassium K^+, and chloride Cl^- ions

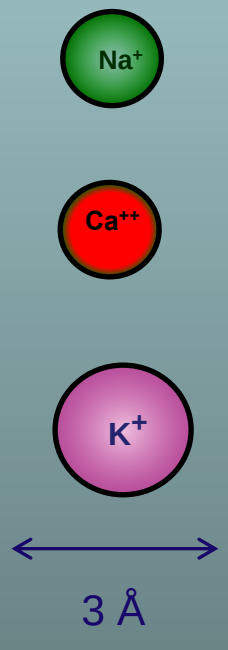
Ions in Water

~0.2 M

are the

Liquid of Life

Hard Spheres



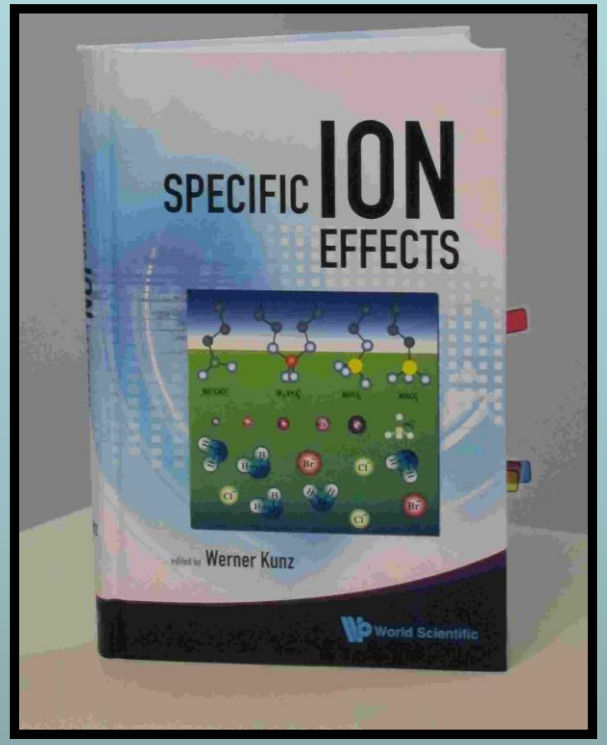
Physical Chemists

are

Frustrated

by

Ionic Solutions



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

Werner Kunz

"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."

The classical text of Robinson and Stokes
(not otherwise noted for its emotional content)
gives a glimpse of these feelings when it says

**“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)

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

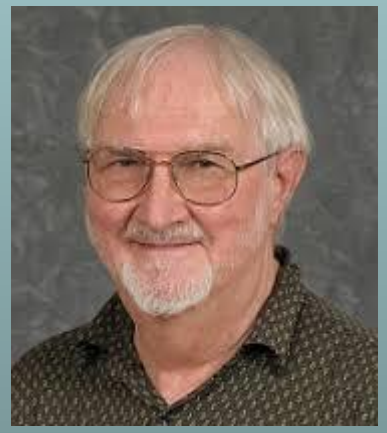
slight paraphrase of p. 125 of Barthel, Krienke, and Kunz, Springer, 1998

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

“ …. 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.***

Central Result of Physical Chemistry

Ions

in a solution are a

Highly Compressible Plasma

although the

Solution

itself is

Incompressible

Learned from Doug Henderson, Jean-Pierre Hansen, Steve Berry, and Stuart Rice, … Many Thanks!

Physical Chemists

are

Frustrated

by

Real Solutions

because

IONIC SOLUTIONS

are

COMPLEX FLUIDS

because of strong steric and electrodynamic interactions and substructure

not ideal gases

Ion Channels are the Valves of Cells

Ion Channels are Devices* that Control Biological Function

Selectivity

Different Ions carry Different Signals

Chemical Bonds are lines
Surface is Electrical Potential
***Red* is negative (acid)**
***Blue* is positive (basic)**

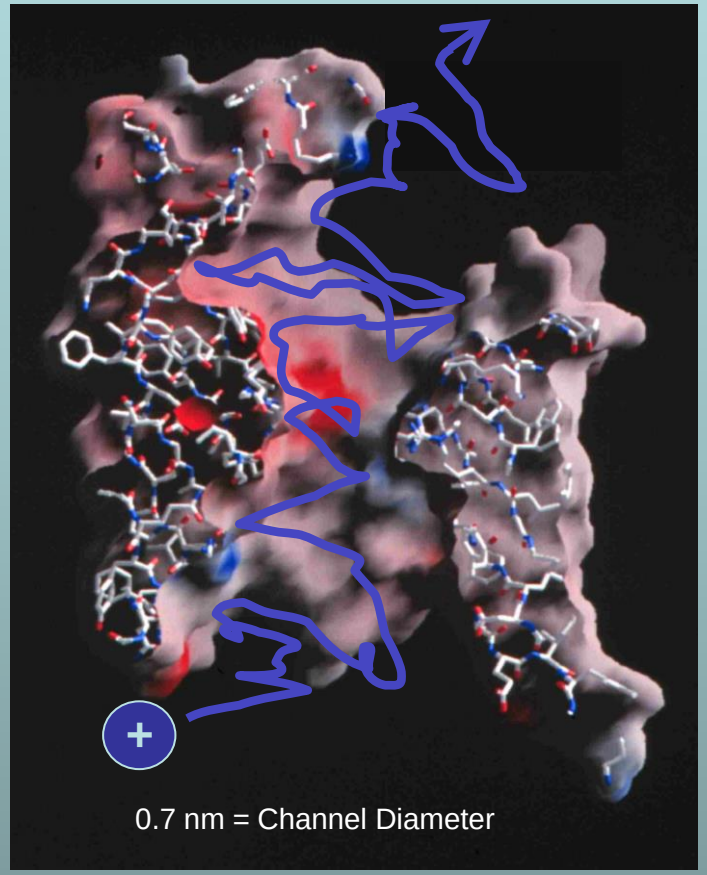


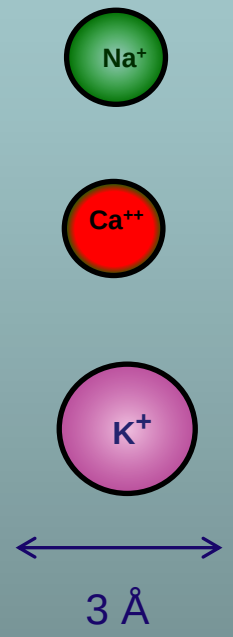
Figure of ompF porin by Raimund Dutzler

Ions in Water

are the

Liquid of Life

Hard Spheres



*Devices as defined in engineering , with inputs and outputs, and power supplies.

Central Result of Molecular Biology

Ions

Move through Protein Channels

as an atomic ionic plasma and

Control Many Processes of Life

Ion Channels are Biological Devices

Natural nano-valves* for atomic control of biological function

Ion channels coordinate contraction of cardiac muscle, allowing the heart to function as a pump

Ion channels coordinate contraction in skeletal muscle

Ion channels control all electrical activity in cells

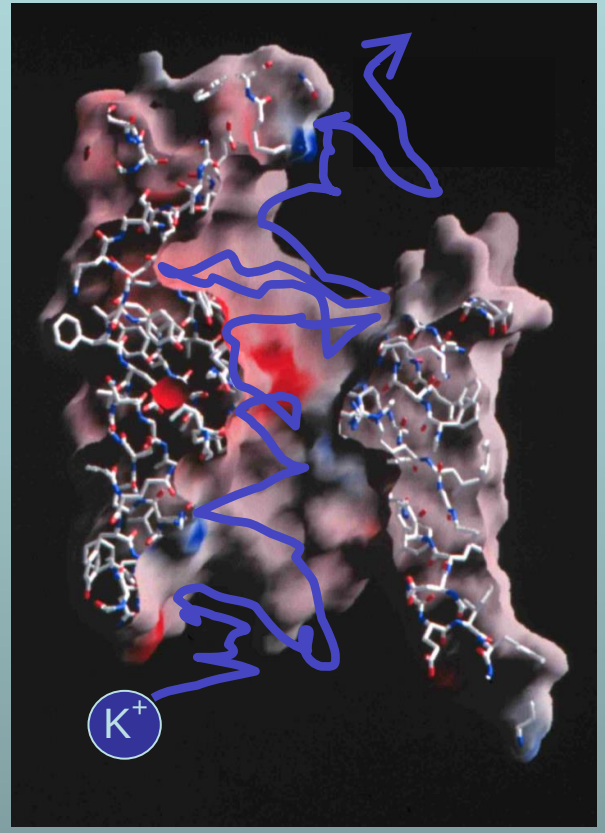
Ion channels produce signals of the nervous system

Ion channels are involved in secretion and absorption in all cells: kidney, intestine, liver, adrenal glands, etc.

Ion channels are involved in thousands of diseases and many drugs act on channels

Ion channels are proteins whose genes (blueprints) can be manipulated by molecular genetics

Ion channels have structures shown by x-ray crystallography in favorable cases



*nearly pico-valves: diameter is 400 – 900 picometers

Ion Channels

Series of DARPA projects
~2001-2010

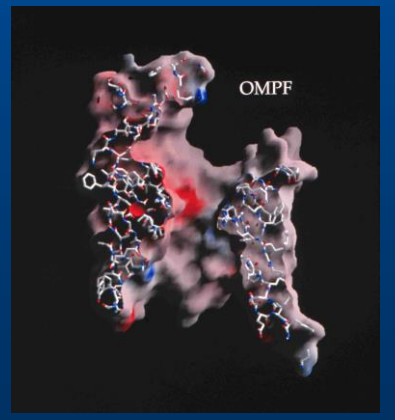
- **To design devices for useful purposes**

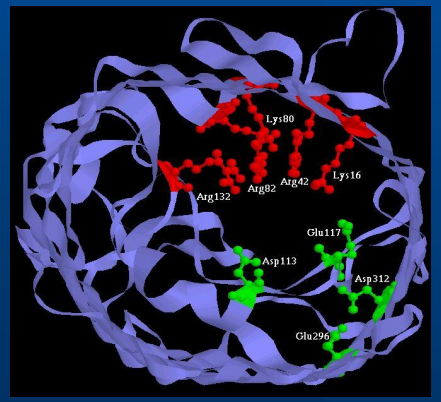
  using

- **Techniques & Knowledge of Molecular Biology**

  starting with existing

- **Biological Nanostructures**



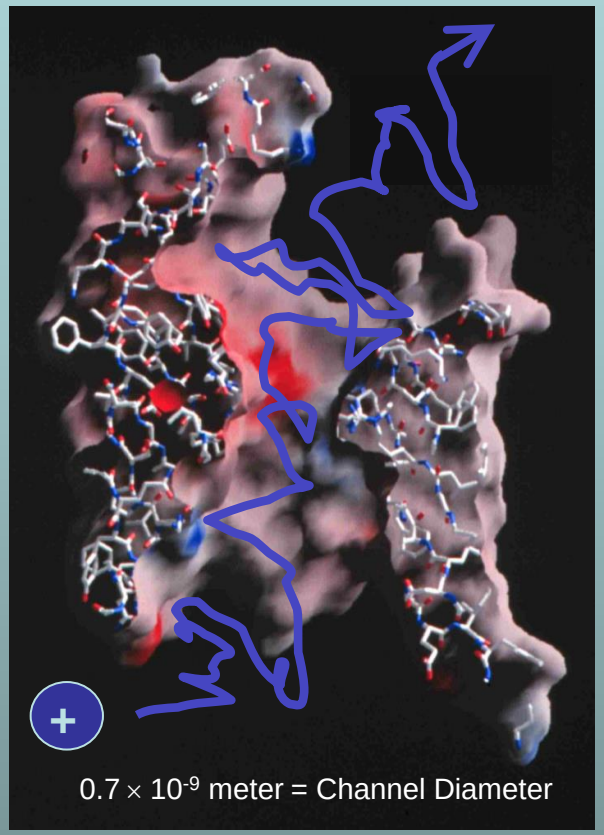


Channels are Devices

Valves and Diodes

Different Ions Carry Different Signals through Different Channels

ompF porin



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

Figure of ompF porin by Raimund Dutzler

Devices have	**INPUTS**
	OUTPUTS
connected by	**LAWS**
involving	**FLOW**
from	**POWER SUPPLIES**

so analysis of Devices must be NONEQUILIBRIUM with spatially non-uniform BOUNDARY CONDITIONS

Classical Thermodynamics, Statistical Mechanics, Molecular Dynamics have
No inputs, outputs, flows, or power supplies
Power supply=spatially nonuniform inhomogeneous Dirichlet conditions

Channels are Devices

Channels are (nano) valves

Valves Control Flow

Classical Theory & Simulations

NOT designed for valves or flow

Thermodynamics, Statistical Mechanics do not allow flow

Devices

have

INPUTS

OUTPUTS

connected by LAWS

involving FLOW

from POWER SUPPLIES

so

Analysis of Devices
must be
NONEQUILIBRIUM with spatially
non-uniform BOUNDARY CONDITIONS

Thermodynamics, Statistical Mechanics, Molecular Dynamics have
No inputs, outputs, flows, or power supplies
i.e., Power Supply = spatially nonuniform inhomogeneous Dirichlet conditions

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

Poisson Boltzmann does NOT fit data!!

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

Solutions are Extraordinarily Concentrated

>10M

Solid NaCl is 37M

where they are most important,

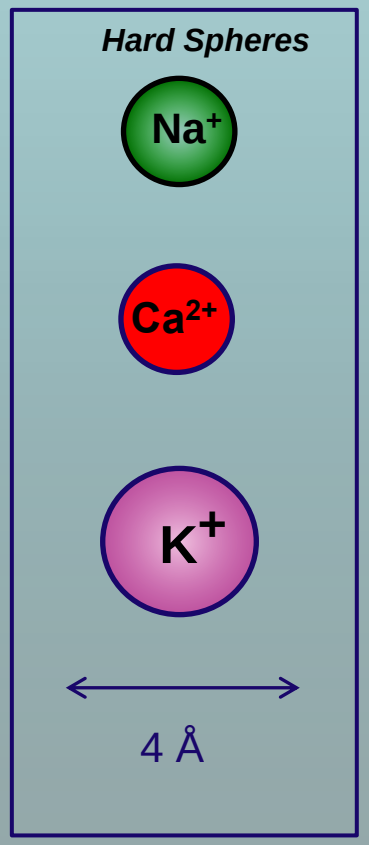
DNA,
enzyme active sites,
channels and
electrodes

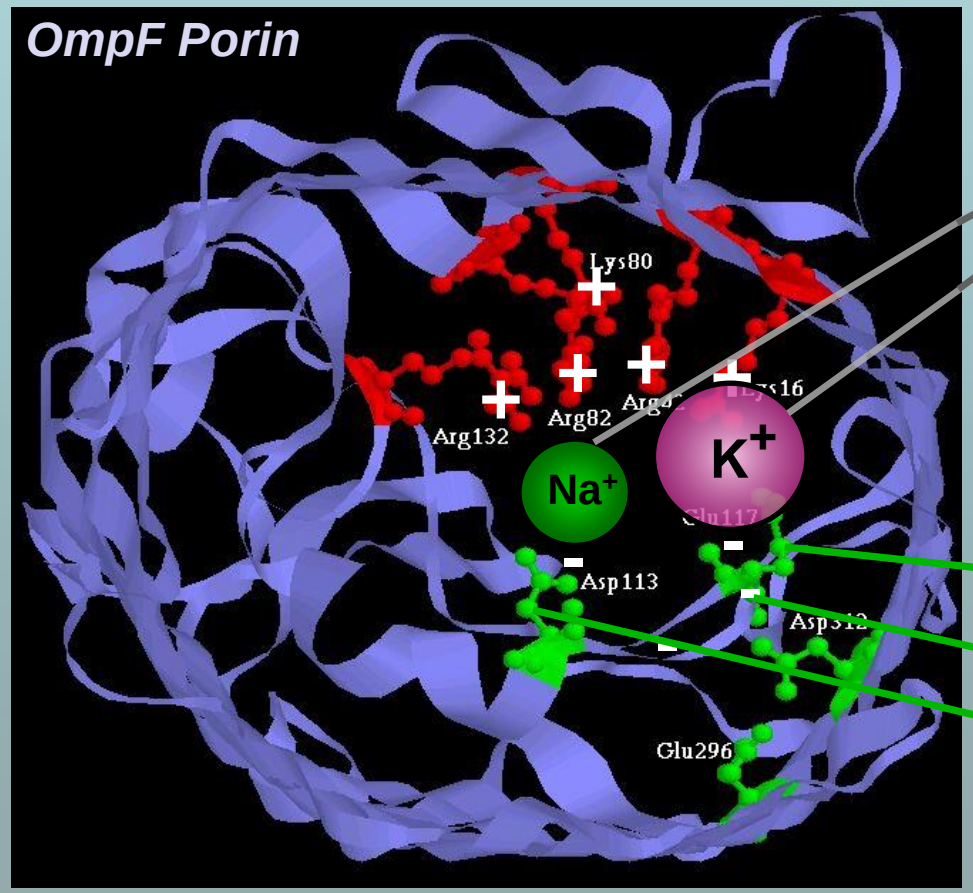
of batteries and electrochemical cells

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

Physical basis of function:
Charge Space Competition

Induced Fit of Side Chains

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

Figure adapted from Tilman Schirmer

Crowded Active Sites are 18.9 M

acid and base groups in 573 enzymes

assuming all are ionized fully

Enzyme Type		Catalytic Active Site Density (Molar)			Protein
		Acid *(positive)*	***Basic*** *(negative)*	***Total***	***Elsewhere***
	Total (n = 573)	**10.6**	**8.3**	**18.9**	**2.8**
EC1	Oxidoreductases (n = 98)	7.5	4.6	12.1	2.8
EC2	Transferases (n = 126)	9.5	7.2	16.6	3.1
EC3	Hydrolases (n = 214)	12.1	10.7	22.8	2.7
EC4	Lyases (n = 72)	11.2	7.3	18.5	2.8
EC5	Isomerases (n = 43)	12.6	9.5	22.1	2.9
EC6	Ligases (n = 20)	9.7	8.3	18.0	3.0

Jimenez-Morales, ***Liang****, Eisenberg*

European Biophysics Journal 2012 41 449-460.

Many Years of Experimental Work on Role of Electric Field in Enzymes

Stephen Boxer https://www.boxerlab.stanford.edu/electrostatics-in-enzyme-catalysis

Stanford

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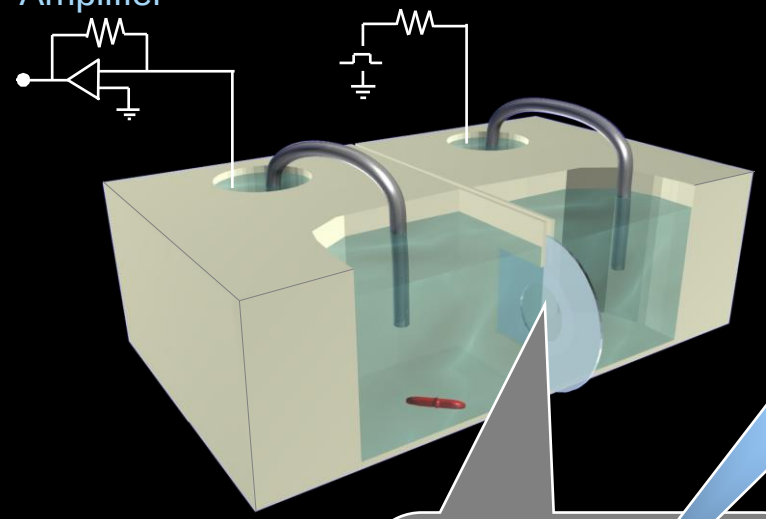
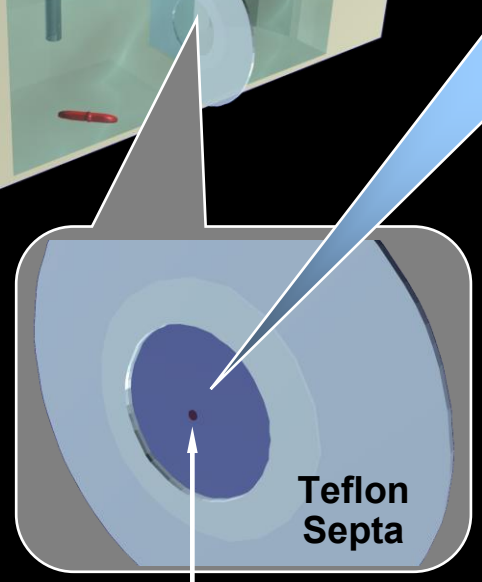
Single Calcium Channels
in Artificial Planar Lipid Bilayers

Conflict of Interest !

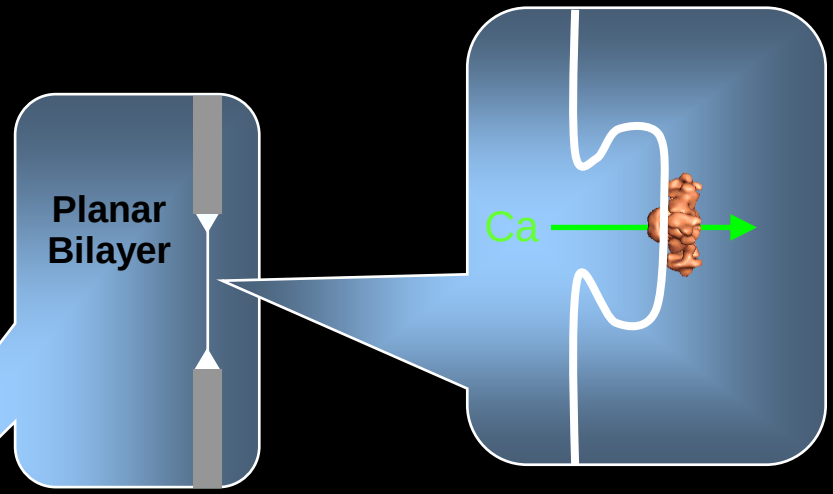
AxoPatch Clamp Amplifier



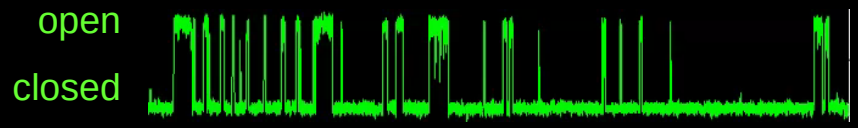
Experimental Chamber



80-100 µM Diameter



Single L-type Ca Channel: Sample Trace



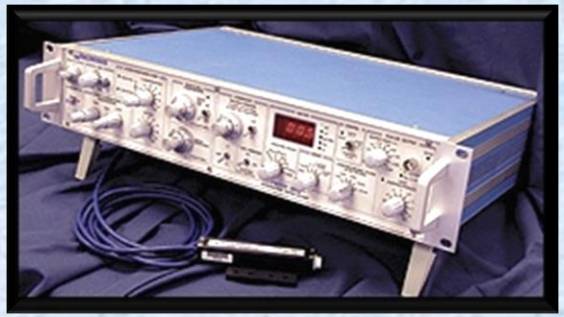
Thanks to Mike Fill !

Thousands of Molecular Biologists Study Channels every day,

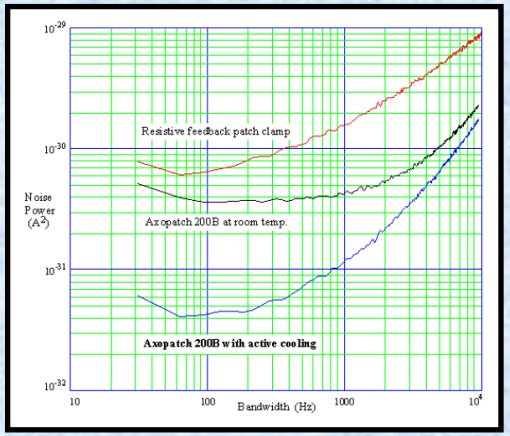
One protein molecule at a time

This number is not an exaggeration.

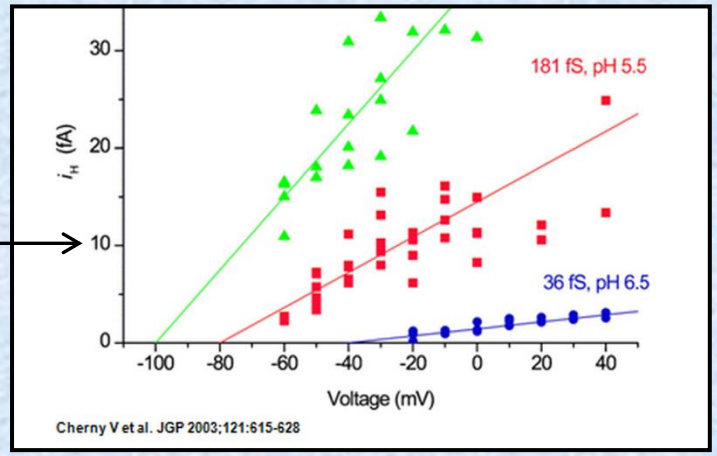
We have sold >10,000 AxoPatch amplifiers



AxoPatch 200B



Femto-amps
(10^{-15} A)



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Popular publications for March (view most recent)

1. Molecular basis of infrared detection by snakes. *Nature*
2. The Angelman Syndrome Protein Ube3A Regulates Synapse Development by Ubiquitinating Arc. *Cell*
3. AMPA receptors--another twist? *Science*
4. Molecular Basis of Calcium Signaling in Lymphocytes: STIM and ORAI. *Annu Rev Immunol*
5. Neurological Channelopathies. *Annu Rev Neurosci*
6. New antiarrhythmic drugs for treatment of atrial fibrillation. *Lancet*
7. A Glial Signal Consisting of Gliomedin and NrCAM Clusters Axonal Na(+) Channels during the Formation of Nodes of Ranvier. *Neuron*
8. Small Molecule Activators of TRPML3. *Chem Biol*
9. Truncated {beta}-amyloid peptide channels provide an alternative mechanism for Alzheimer's Disease and Down syndrome. *Proc Natl Acad Sci U S A*
10. Modelling the molecular mechanisms of synaptic plasticity using systems biology approaches. *Nat Rev Neurosci*

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- Nanion - Automated patch clamp
- Millipore - Ion channel cell lines

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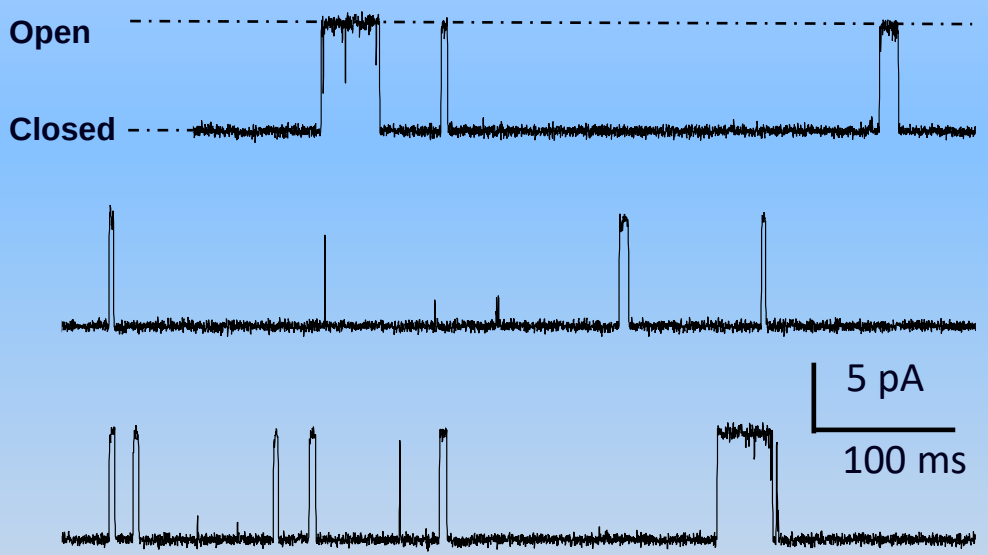
Channel Structure Does Not Change

once the channel is open

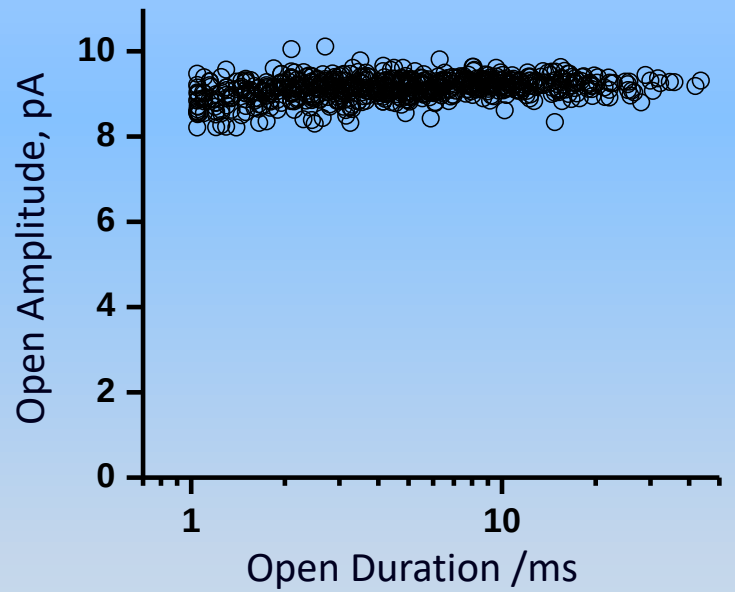
Current vs. time

Time dependence is called ‘gating’



Amplitude vs. Duration

Amplitude is Called Single or Open Channel Current

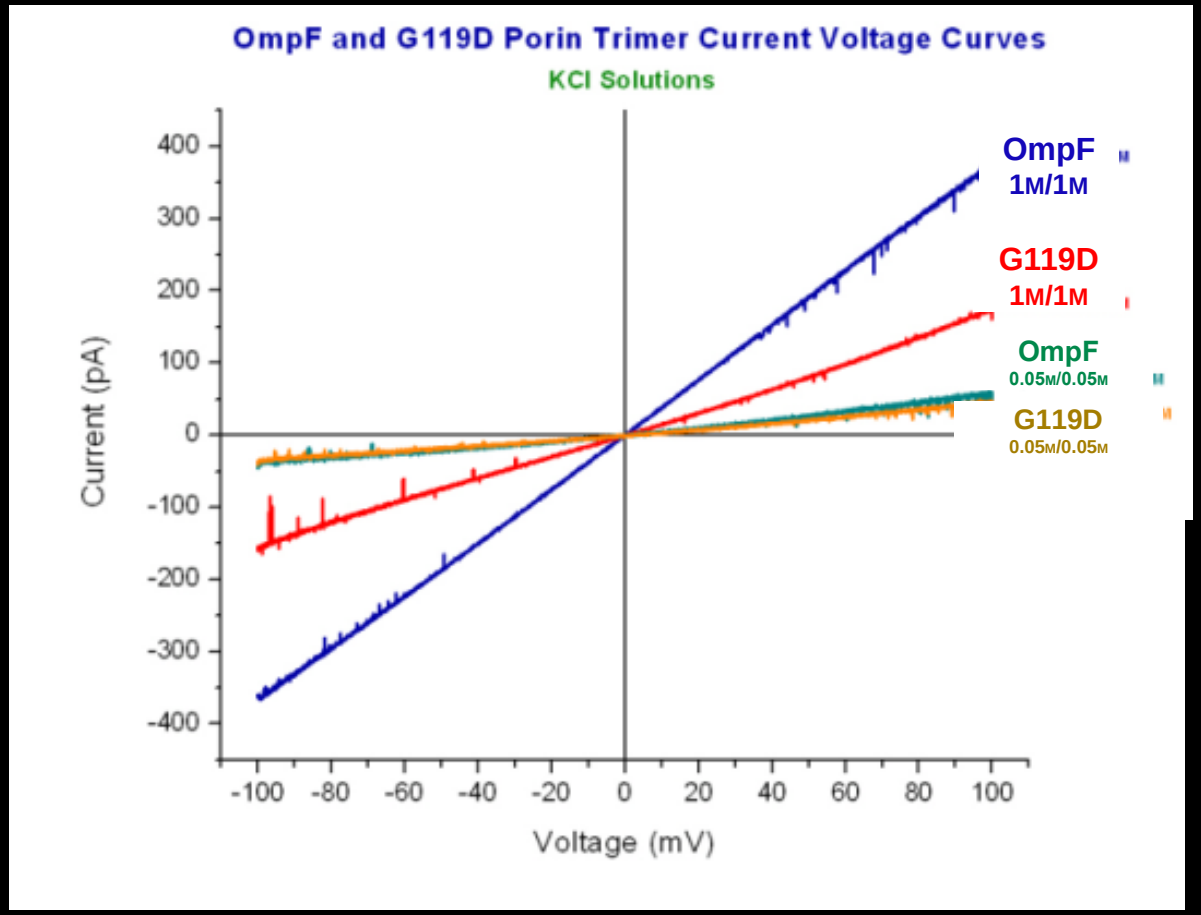


Lowpass Filter = 1 kHz Sample Rate = 20 kHz

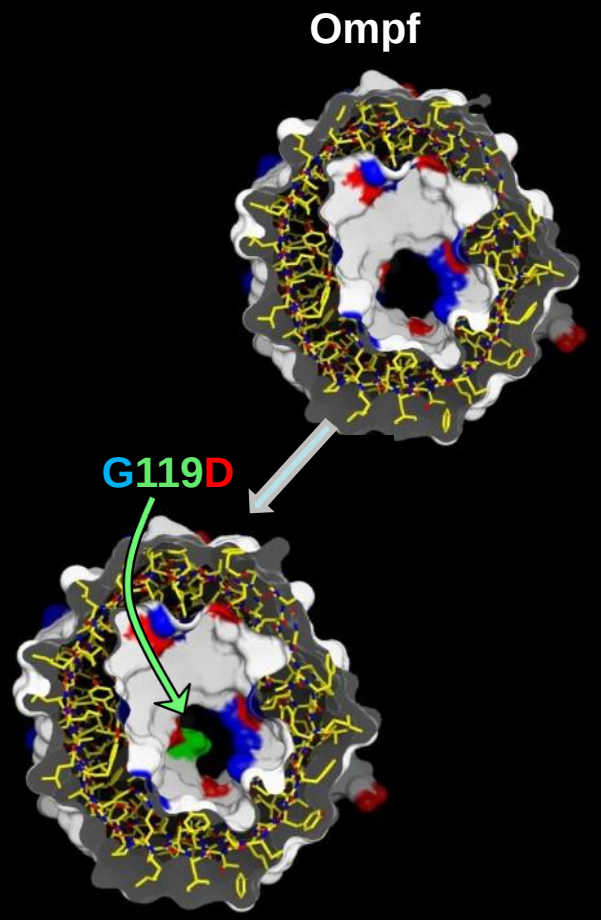
Typical Raw Single Channel Records

Ca^{2+} Release Channel of Inositol Trisphosphate Receptor: slide and data from Josefina Ramos-Franco. Thanks!

A few atoms make a BIG Difference



Glycine G
replaced by
Aspartate D



Structure determined by ***Raimund Dutzler***
in Tilman Schirmer's lab

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

Another Talk

How do a few atoms control (macroscopic) Device Function

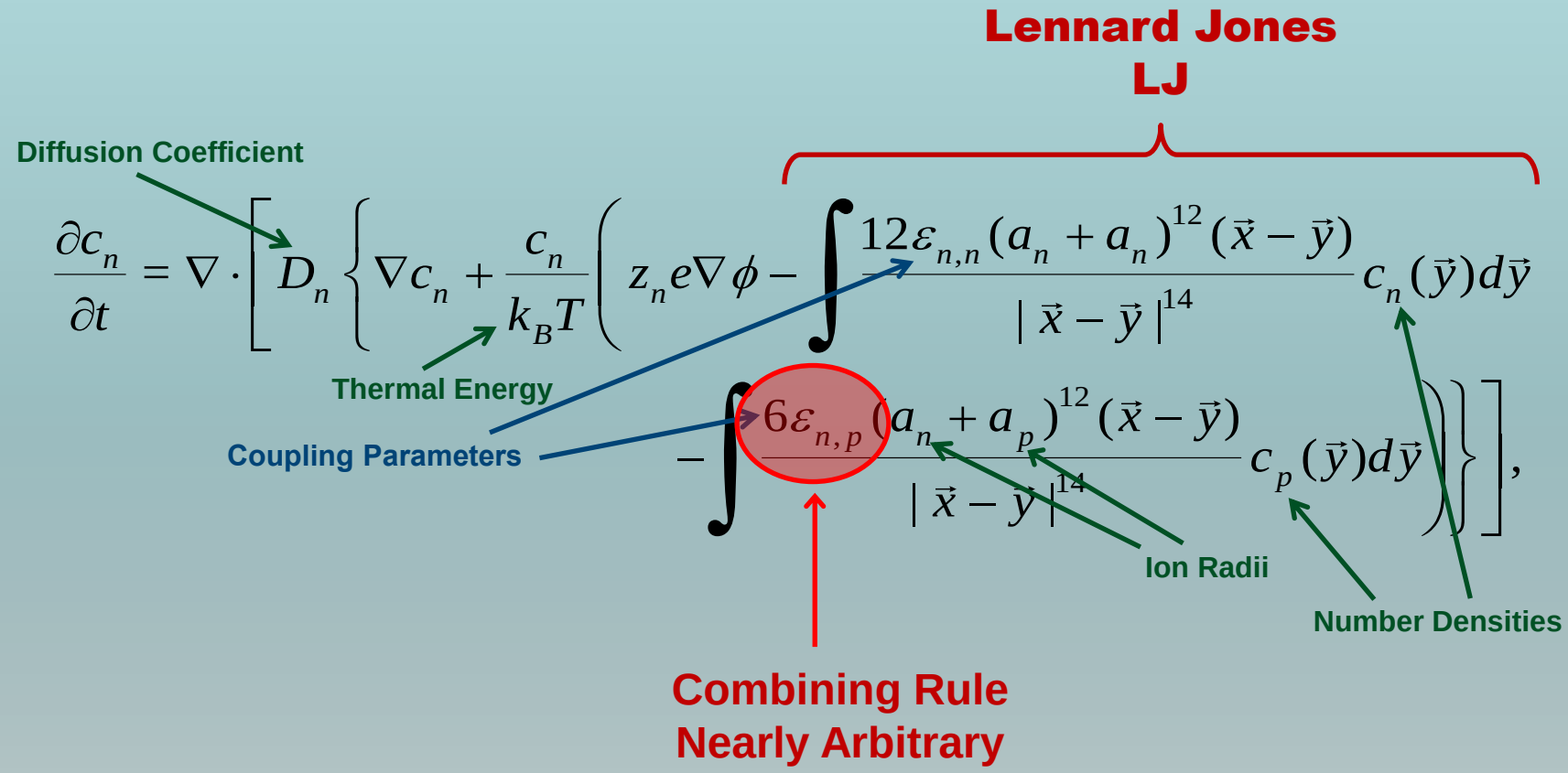
Mathematics of Molecular Biology is about

How does the device work?

Solving Specific Inverse Problems

PNP (Poisson **Nernst Planck**) for Spheres

*for **number density c_n** of negative n ions; positive ions are analogous*



Non-equilibrium variational field theory *EnVarA*

Motivation: Improve PNP

Replace Lennard Jones LJ forces

because

1) LJ forces are oscillatory and large, very hard to compute reliably

**2) combining rules are ill defined in experiments,
whether Lorentz-Berthelot or Kong**
as first pointed out to me by Prof. Allen Tzyy-Leng Horng

**3) Combining parameters are likely to depend on ionic species,
concentration and perhaps other variables.**

**4) It is difficult for a model to be reliable
that depends sensitively on parameters
poorly established by experiments.**

Motivation

Replace Lennard Jones LJ Force Calculations

with Saturating Distribution

analogous to Fermi distribution replacing electron-electron forces

Capture the important property
SATURATION
without calculating forces at all!

Molecular Mean Field Theory
PNPB

***Poisson Nernst Planck Bikerman, formerly called PNP-Fermi**

Bob Eisenberg

Jinn-Liang Liu

劉晉良 ***is first author on our papers***

Liu and Eisenberg. 2020. Entropy 22:550 Preprint available at https://arxiv.org/abs/2004.10300.

PNPB

Molecular Mean Field Theory

is the only theory

as far as we know

that

1. **Includes water as a molecule**
2. **Deals with unequal size ions with correct Boltzman limit***
3. **Deals correctly with voids (note: spheres do not fill space)***
4. **Fits properties of bulk solutions**
5. **Fits properties of Channels and a Transporter**
6. **Avoids <u>arbitrary</u> combining rules in Lennard-Jones forces**

***<u>Details are Important</u>**

Liu, J. and B. Eisenberg. 2020. Entropy 22:550 and https://arxiv.org/abs/2004.10300.

PNPB = Molecular Mean Field Theory

will surely be replaced by more successful theories.
It is just a step along the path

But it may be a productive new path
Molecular Mean Field treatment of Correlations

Evaluation of PNPB

1) Does the model include correlations produced by finite size of ions AND WATER?
   PNPB yes

2) Does model predict crucial properties of bulk solution, free energy per mole, i.e., activity, using only physical parameters? PNPB yes, but would rather derive parameters (3 per ion)

3) Does model predict properties of spatially complicated systems like electrodes and PHYSICAL models of ionic channels: gramicidin, potassium, and calcium channels
   PNPB yes

4) Is the model consistent with conservation of mass, charge, and current? PNPB yes

5) Is the model consistent with sum rules of thermodynamics? PNPB not quite: modification needed of Maxwell stress tensor at highly charged surface Misra, et al Langmuir 2019, 35, 11550

6) Does the model deal with differential capacitance of metal solution interfaces? PNPB well, but not perfectly

7) Does the model deal with chemical reactions at electrodes? PNPB not yet

Motivation

Natural Description of Crowded Charge

is a

Bikerman Distribution

of the Fermi class of distributions

designed to describe saturation

Bikerman 1942 Philosophical Magazine (Series 7) 33(220): 384-397

DETOUR

Physiologists§ give the following
Saturating Distribution
the name
'Boltzmann'

Interdisciplinary Confusion

Interdisciplinary Confusion

$$Q(V) = \frac{Q_{max}}{1+exp\left(-Q_{max}\left(V-V_{1/2}\right)/k_BT\right)}$$

§ p.503 of Hodgkin and Huxley. 1952.
'Quantitative description ...' J. Physiol. 117:500-544.
more recently
§ Bezanilla, Villalba-Galea J. Gen. Physiol (2013) 142: 575
'Gating charge … '

Boltzmann Distribution*
of Physicists
$exp(-Q_{max}(V)/k_BT)$
does NOT Saturate

Fermi Distribution Saturates

* Boltzmann. Berkeley 'Lectures on Gas Theory', 1904 (!)

Motivation

Largest Effect
of
Crowded Charge
is
Saturation

*Saturation cannot be described at all by classical Poisson Boltzmann approach and is described in an uncalibrated way by **present day** Molecular Dynamics when mixtures and divalents are present*

Motivation

Bikerman (Fermi) **Description**

is designed to deal with

Saturation of Concentration

without computing forces*

motivated by the Pauli Exclusion Principle
that avoids the calculation of inter-electron forces and correlations!

Eisenberg 1996. Journal of Membrane Biology 150:1–25. Preprint available on physics arXiv as document 1009.2857
Eisenberg 1996. Atomic Biology, Electrostatics and Ionic Channels.. R. Elber, editor World Scientific, Philadelphia, pp. 269-357 arXiv:0807.0715.

Bikerman Description
of
Saturation of Volume
by Spherical Ions

Uses a STERIC POTENTIAL

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

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

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

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

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

Voids are Needed

Computations without voids are ill posed and in that sense impossible.

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.

Details are Important

Formal Proof in Liu, J. and B. Eisenberg. 2020. Entropy 22:550 and https://arxiv.org/abs/2004.10300

STERIC POTENTIAL

introduced by Jinn Liang Liu

Journal of Computational Physics 2013 247(0):88-99.

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

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

Voids are NOT novel

Voids = 1 − volume fraction of [IONS + WATER] molecules

$$\Phi$$

Voids are NOT novel

STERIC POTENTIAL

depends on

Φ = Volume Fraction of all molecules, ions plus water

$$S^{teric}(\mathbf{r}) = \ln \frac{1-\Phi(\mathbf{r})}{1-\Phi(bath)}$$

Φ = Volume Fraction of [Ions plus water]

Liu, J. L., and B. Eisenberg. 2020. Entropy 22:550
Preprint available at https://arxiv.org/abs/2004.10300.

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

Bikerman 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,

Different Talk!

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 else

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!

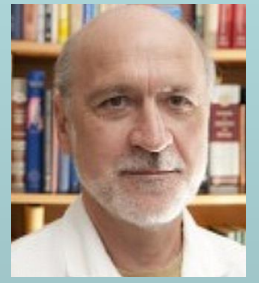
Classical Treatments of Chemical Complexities

Charge-Space Competition

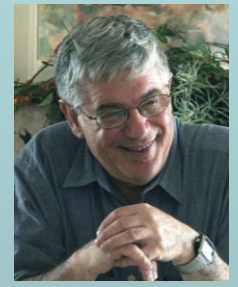
Monte Carlo Methods

Dezső Boda

Doug Henderson



Wolfgang Nonner



Bob Eisenberg

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

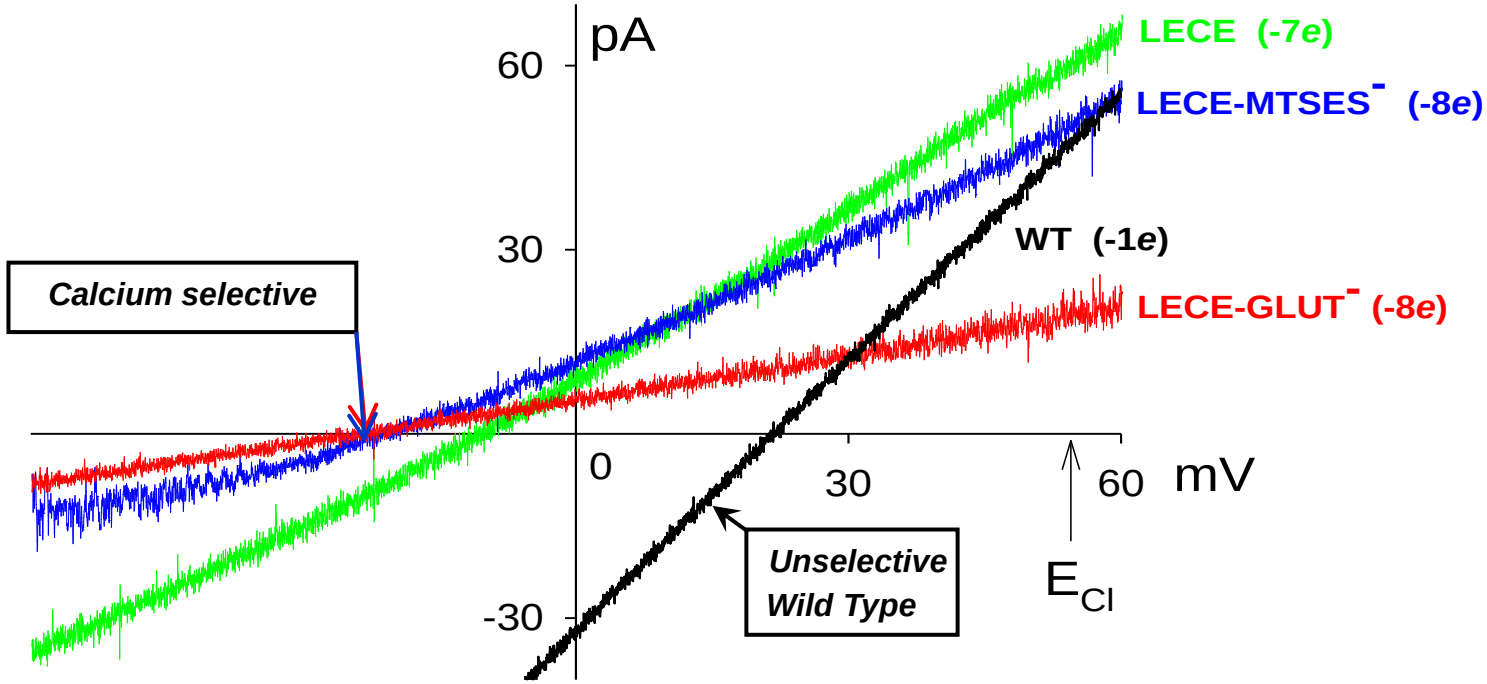
ftp://ftp.rush.edu/users/molebio/Bob_Eisenberg/reprints

Another 30 or so at websites of Dezso Boda and Dirk Gillespie

Synthetic Calcium Channels

Designed by Theory of Charge Space Competition

built by ***Henk Miedema, Wim Meijberg,*** ***George Robillard***
of BioMade Corp.,Groningen, Netherlands



As charge density increases, channel becomes calcium selective

$E_{rev} \rightarrow E_{Ca}$

Biophys J 2004 87(5): 3137-3147; Eur Biophys J 2006 36(1): 13-22.
Biophys J 2006 91(12): 4392-4400; Nano Lett. 2007 7(9): 2886-2891.
Biophys J 2006 90(4): 1202-1211.

Algebraic Model of Calcium Channel

works surprisingly well despite crudeness of molecular model

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

ν_i = volume $= 4\pi a_i^3/3$; a_i = radius

J Comp Phys (2013) 247:88

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

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

We believe satisfactory theory should contain

1) **Water as Molecules**
2) **Ions with unequal finite size**
3) **Steric potential to deal with correlations**
4) **MUST have explicit voids to allow stable computation**
5) **Must fit data from bulk and channels**
6) **Should not use LJ combining rules**
7) **Should have correct Boltzmann limit**

We couple the

Screened Coulomb (Yukawa) Potential*

and

Far Field Poisson Electrostatics

using our version of NON-local electrostatics

Other forms of nonlocal electrodynamics may be better!!

NON-local electrostatics
deals
with shielding of charges
And needs the attention of fine young mathematicians
in my opinion

A few important References on Nonlocal Electrostatics

1. Liu, J.-L., and C.-L. Li. 2019. A generalized Debye-Hückel theory of electrolyte solutions. AIP Advances 9(1):015214.
2. Li, C.-L., and J.-L. Liu. 2018. Analysis of Generalized Debye-Huckel Equation from Poisson-Fermi Theory. arXiv preprint arXiv:1808.02757.
3. Blossey, R., A. C. Maggs, and R. Podgornik. 2017. Structural interactions in ionic liquids linked to higher-order Poisson-Boltzmann equations. Physical Review E 95(6):060602.
4. Ivaništšev, V., K. Kirchner, T. Kirchner, and M. V. Fedorov. 2015. Restructuring of the electrical double layer in ionic liquids upon charging. Journal of Physics: Condensed Matter 27(10):102101.
5. Kornyshev, A. A., and R. Qiao. 2014. Three-dimensional double layers. ACS Publications.
6. Kamrin, K., and G. Koval. 2012. Nonlocal constitutive relation for steady granular flow. Physical Review Letters 108(17):178301.
7. Fedorov, M. V., N. Georgi, and A. A. Kornyshev. 2010. Double layer in ionic liquids: The nature of the camel shape of capacitance. Electrochemistry communications 12(2):296-299.
8. Fedorov, M. V., and A. A. Kornyshev. 2008. Towards understanding the structure and capacitance of electrical double layer in ionic liquids. Electrochimica Acta 53(23):6835-6840.
9. Fedorov, M. V., and A. A. Kornyshev. 2008. Ionic liquid near a charged wall: Structure and capacitance of electrical double layer. The Journal of Physical Chemistry B 112(38):11868-11872.
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11. Hildebrandt, A., O. Kohlbacher, R. Blossey, and H.-P. Lenhof. 2002. Using nonlocal electrostatics for solvation free energy computations: ions and small molecules. arXiv preprint physics/0212074.
12. Foiles, S. M., and N. W. Ashcroft. 1981. Variational theory of phase separation in binary liquid mixtures. The Journal of chemical physics 75(7):3594-3598.
13. Mihara, N., and R. Puff. 1968. Liquid Structure Factor of Ground-State He 4. Physical Review 174(1):221.
14. Rayleigh, L., previously John Strutt. 1871. Some General Theorems Relating to Vibrations. Proceedings of the London Mathematical Society IV:357-368.

We use
van der Waals *vdW Yukawa* Screened Coulomb Potential

We use *vdW Yukawa* potential $\mathbf{Y}(\mathbf{r}-\mathbf{r}')$ to describe Bjerrum/Debye Screening

$$\mathbf{Y}(\mathbf{r}-\mathbf{r}') = \frac{\exp\left(-|\mathbf{r}-\mathbf{r}'|/\lambda\right)}{4\pi|\mathbf{r}-\mathbf{r}'|} \qquad (1)$$

VDw* potential $\mathbf{Y}(\mathbf{r}-\mathbf{r}')$ satisfies the differential equation

$$-\nabla^2\mathbf{Y}(\mathbf{r}-\mathbf{r}') + \frac{1}{\lambda^2}\mathbf{Y}(\mathbf{r}-\mathbf{r}') = \delta(\mathbf{r}-\mathbf{r}') \qquad (2)$$

$\mathbf{Y}(\cdot)$ is the lowest order amplitude term in a general expansion of interaction of a pair of fermions**
The effective dielectric function of $\mathbf{Y}(\boldsymbol{\rho})$ is $\exp(-\boldsymbol{\rho}/\boldsymbol{\lambda})$
$\boldsymbol{\lambda}$ is the Fermi-Thomas screening wave vector.

*Rowlinson, J. S. 1989. The Yukawa potential. Physica A: Stat Mech 156(1):15-34
**Muller-Kirsten, H. J. W. 2012. Intro to Quantum Mechanics: Schrodinger Equation and Path Integral World Scientific
Hildebrandt et al 2002 arXiv 0212074; Hildebrandt et al 2004. Phys Rev Ltrs 93(10):108104.

Other forms of nonlocal electrodynamics may be better!!

Definition

LOCAL POTENTIAL

$\tilde{\phi}(\mathbf{r})$ is defined by Poisson equation as

$$-\varepsilon_s \varepsilon_0 \nabla^2 \tilde{\phi}(\mathbf{r}) = \rho_I(\mathbf{r}) \stackrel{\text{def}}{=} \sum_{1}^{K} q_i C_i(\mathbf{r}) \qquad (4)$$

Local Potential and Yukawa interaction must be joined to create a long range global potential to deal with correlations in high field or crowded conditions in which the size and valence of ions and the polarization of water play significant roles.

We introduce a

GLOBAL POTENTIAL

$$\boldsymbol{\phi}(\mathbf{r})$$

Convolution of Yukawa and Poisson potential $\widetilde{\boldsymbol{\phi}}$

$$\boldsymbol{\phi}(\mathbf{r}) = \int \frac{\mathbf{1}}{\boldsymbol{\lambda}^{\mathbf{2}}} \mathbf{Y}(\mathbf{r} - \mathbf{r}')\widetilde{\boldsymbol{\phi}}(\mathbf{r}')\mathrm{d}\mathbf{r}' \qquad (5)$$

Multiply the Yukawa potential $\mathbf{Y}(\mathbf{r} - \mathbf{r}')$ in its defining differential equation (2) by the local Poisson potential $\widetilde{\phi}(\mathbf{r})$ and integrate to smooth the product, reducing the detail (and resolution) of the result.

The smoothed global potential $\boldsymbol{\phi}(\mathbf{r})$ allows easier computation in a differential equation we will now use.

GLOBAL POTENTIAL

$$\boldsymbol{\phi}(\mathbf{r})$$

is a convolution of the Yukawa screened Coulomb potential and the local Poisson potential

$$\boldsymbol{\phi}(\mathbf{r})=\int \frac{1}{\lambda^2}\mathbf{Y}(\mathbf{r}-\mathbf{r}')\tilde{\boldsymbol{\phi}}(\mathbf{r}')\mathrm{d}\mathbf{r}' \qquad (5)$$

The global potential is a convolution eq. (5) and also a solution of the differential equation

$$\lambda^2\nabla^2\phi(\mathbf{r})+\phi(\mathbf{r})=\tilde{\phi}(\mathbf{r}) \qquad (6)$$

ϕ becomes approximate when we impose a finite domain for computation

See Xie and Volkmer (2015) Comm Computational Physics 13:174-194.

also Hildebrandt et al (2004) Phys. Rev. Lett. **93**, 108104;
Xie, Liu, and Eisenberg, Phys. Rev. E (2016) **94**, 012114;
using numerical methods in Xie, et al, (2012) 34:B107-B126.

GLOBAL POTENTIAL $\phi(\mathbf{r})$

combines eq. (4) for local potential and Poisson Far Field

$$-\varepsilon_s\varepsilon_0\,\nabla^2\tilde{\phi}(\mathbf{r}) = \rho_I(\mathbf{r}) \stackrel{\text{def}}{=} \sum_{\mathbf{1}}^{\boldsymbol{K}} \boldsymbol{q_i}\,\boldsymbol{C_i}(\mathbf{r}) \qquad (4)$$

$$\lambda^2\nabla^2\phi(\mathbf{r})+\phi(\mathbf{r}) = \tilde{\phi}(\mathbf{r}) \qquad (6)$$

Eq. (4) and (6) give the fourth order equation

$$\lambda^2\varepsilon_s\varepsilon_0\nabla^4\phi(\mathbf{r}) + \varepsilon_s\varepsilon_0\nabla^2\phi(\mathbf{r}) = \rho_I(\mathbf{r}) \qquad (7)$$

which is best solved as a pair of second order differential equations, *we think*

Liu and Eisenberg (2015) Phys Rev E 92: 012711, also https://arxiv.org/pdf/011506.005953

Liu and Eisenberg (2018) J Chem Phys 148:054501, also https://arxiv.org/abs/1801.03470

PNPF

Poisson-Nernst-Planck-Fermi

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

We introduce[3,4] and use[5] **two second order equations** and **boundary conditions**

2nd order equations make computation of 3D proteins feasible

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

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

$-\varepsilon_{water}(l_c\nabla^2 - 1)$ approximates dielectric of entire bulk solution including correlated motions of ions, following **Santangelo** 2006[1] used by Kornyshev 2011[2], etc.

$-\varepsilon_{water}\psi = \rho_{pol}$ is Polarization Charge density an **OUTPUT** of our analysis

<u>Details are Important</u>

See p. 13-14 of Liu, J. and B. Eisenberg. 2020. Entropy 22:550 and https://arxiv.org/abs/2004.10300.

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

[5]Li, C.-L., and J.-L. Liu. 2018. arXiv:1808.02757.

Boundary Conditions are Important

The boundary and interface conditions for $\phi(\mathbf{r})$ and $\psi(\mathbf{r})$ in are

$$\phi(\mathbf{r}) = \psi(\mathbf{r}) = 0 \text{ on } \partial\Omega_s \backslash \partial\Omega_{sh}, \quad (35)$$

$$\psi(\mathbf{r}) = -\rho_s(\mathbf{r}) \text{ on } \partial\Omega_{sh} \cap \partial\Omega_s, \quad (36)$$

$$[\phi(\mathbf{r})] = 0 \text{ on } \partial\Omega_i \cup (\partial\Omega_{sh} \cap \partial\Omega_s), \quad (37)$$

$$[\nabla\phi(\mathbf{r}) \cdot \mathbf{n}] = 0 \text{ on } \partial\Omega_{sh} \cap \partial\Omega_s, \quad (38)$$

$$[\epsilon(\mathbf{r})\nabla\phi(\mathbf{r}) \cdot \mathbf{n}] = \epsilon_i \nabla\phi^*(\mathbf{r}) \cdot \mathbf{n} \text{on} \partial\Omega_i, \quad (39)$$

Details are Important

Symbols defined details discussed on p. 13-14 of Liu and Eisenberg. 2020. Entropy 22:550; https://arxiv.org/abs/2004.10300.

Many Numerical Problems Arise ONLY* when Dealing with Real Data

Challenges have been overcome using methods developed over many decades by the large community that works on the computational electronics of semiconductors.

***Models that have not been implemented to actually fit data are too vague to evaluate or compare with PNPB = Molecular Mean Field Theory**

Numerical Analysis Faces Challenges when dealing with Real Data

(1) Geometric singularities of molecular surfaces and delta function sources.
(2) Strong electric fields (100 mV/nm) and resulting exponential nonlinearities
(3) Enormous concentrations (> 10 M) often found where ions are important, for example, near electrodes in batteries, in ion channels, and in active sites of proteins.
(4) Wide ranging concentrations of Ca^{2+} in (10 M) and near (10^{-2} to 10^{-8}M) almost every protein in biological cells.

Challenges have been overcome using methods developed over many decades by the large community that works on the computational electronics of semiconductors. It is foolhardy, in my opinion, to ignore the existing literature.

It is dangerous

to avoid the checks found necessary in the literature of computational electronics of semiconductors.

PNPB = Molecular Mean Field

Results

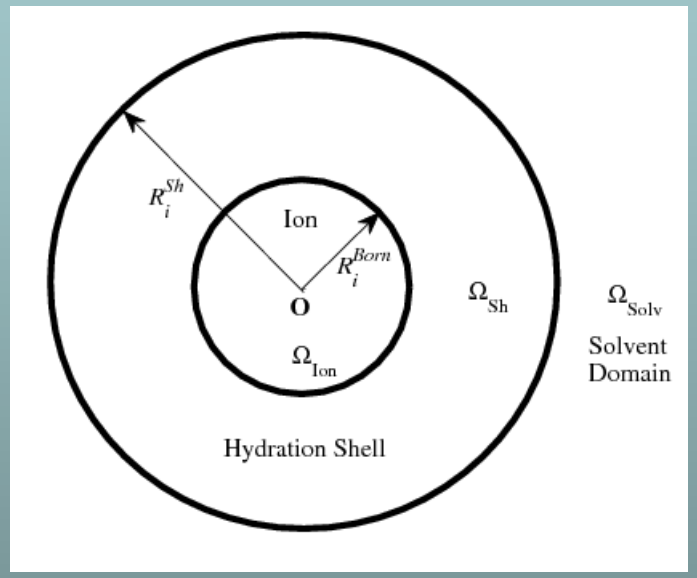
Bulk Solutions

Ion Channels
Transporter

Poisson Fermi Approach to

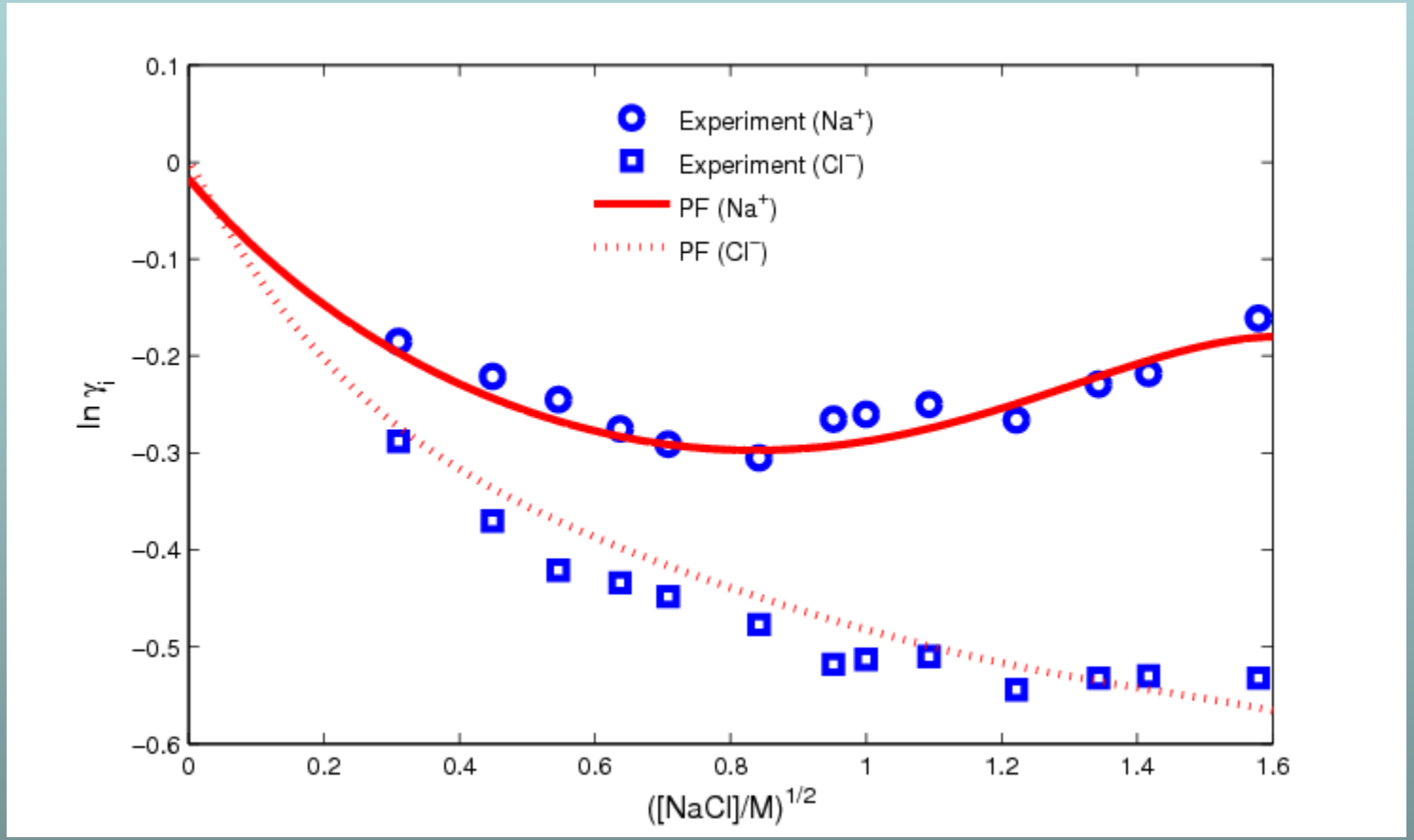
Bulk Solutions

Same equations, different model of nearby atoms

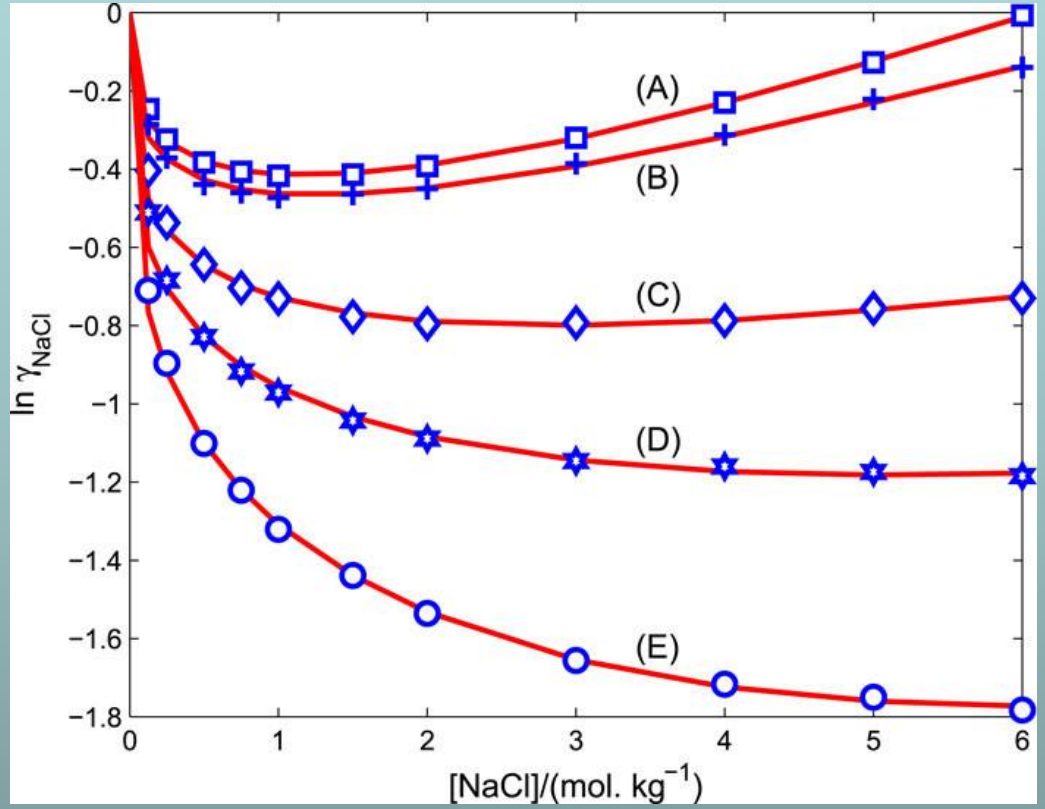


Activity Coefficients
Na^+ Cl^-

‘normalized’ free energy per mole



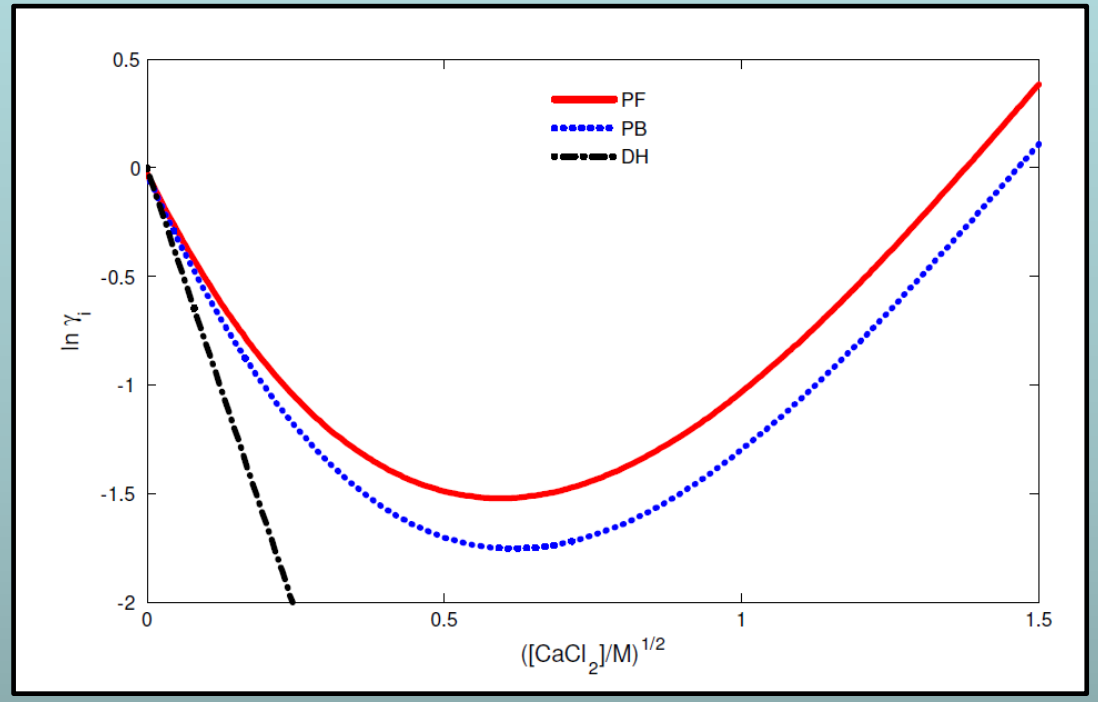
Activity Coefficients vs. Temperature
Na^+ Cl^-



Mean activity coefficients of 1:1 electrolyte at various temperatures. Comparison of PF results (curves) with experimental data (symbols) compiled in Ref. 13 from Refs. 27–29 on mean activity coefficients γ of NaCl in [NaCl] from 0 to 6 mol Kg^{-1} at T = (a) 298.15, (b) 373.15, (c) 473.15, (d) 523.15, (e) 573.15 K.

Published in: Jinn-Liang Liu; Bob Eisenberg; *J. Chem. Phys.* **148,** 054501 (2018)
DOI: 10.1063/1.5021508

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

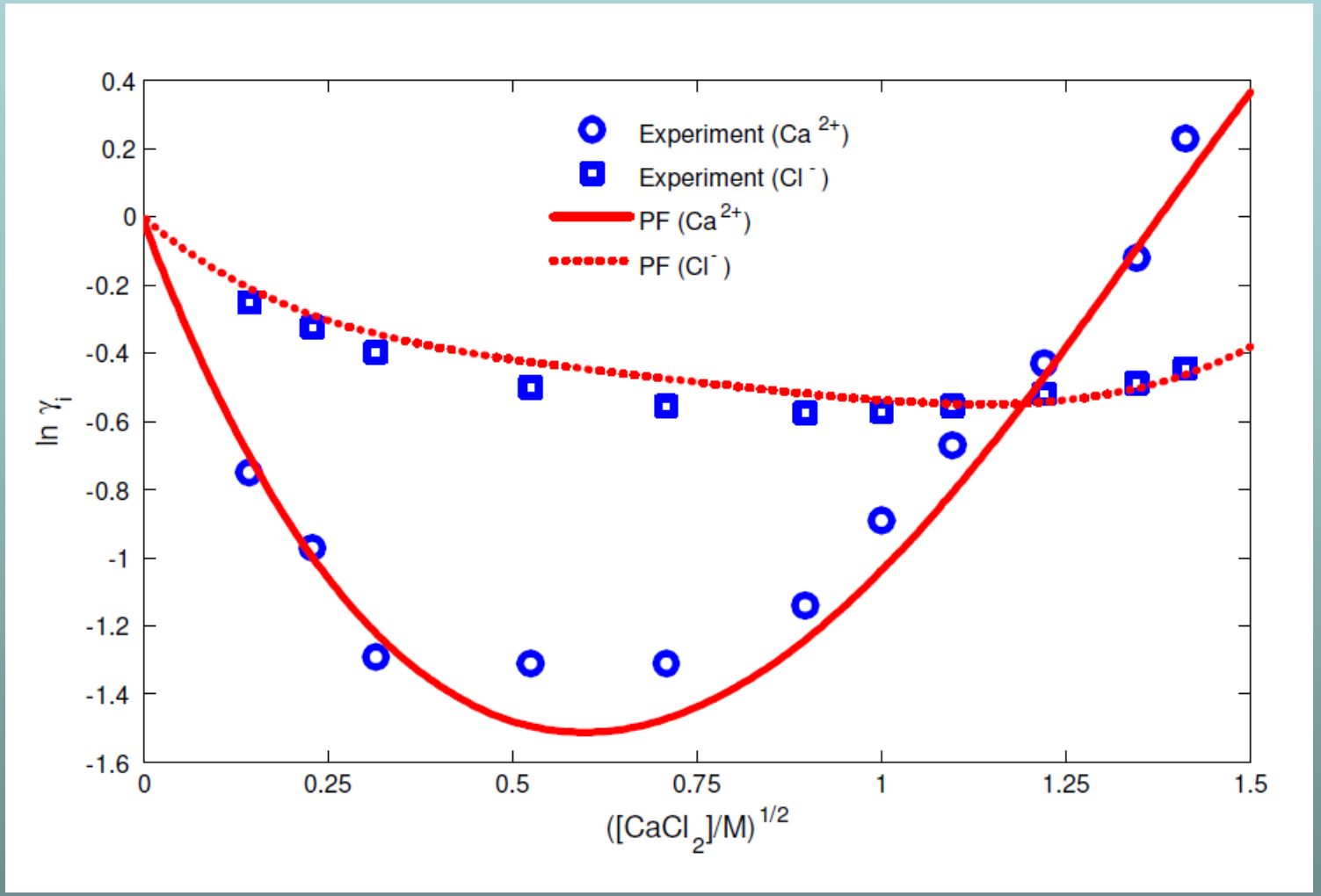
Parameters, NOT further adjusted

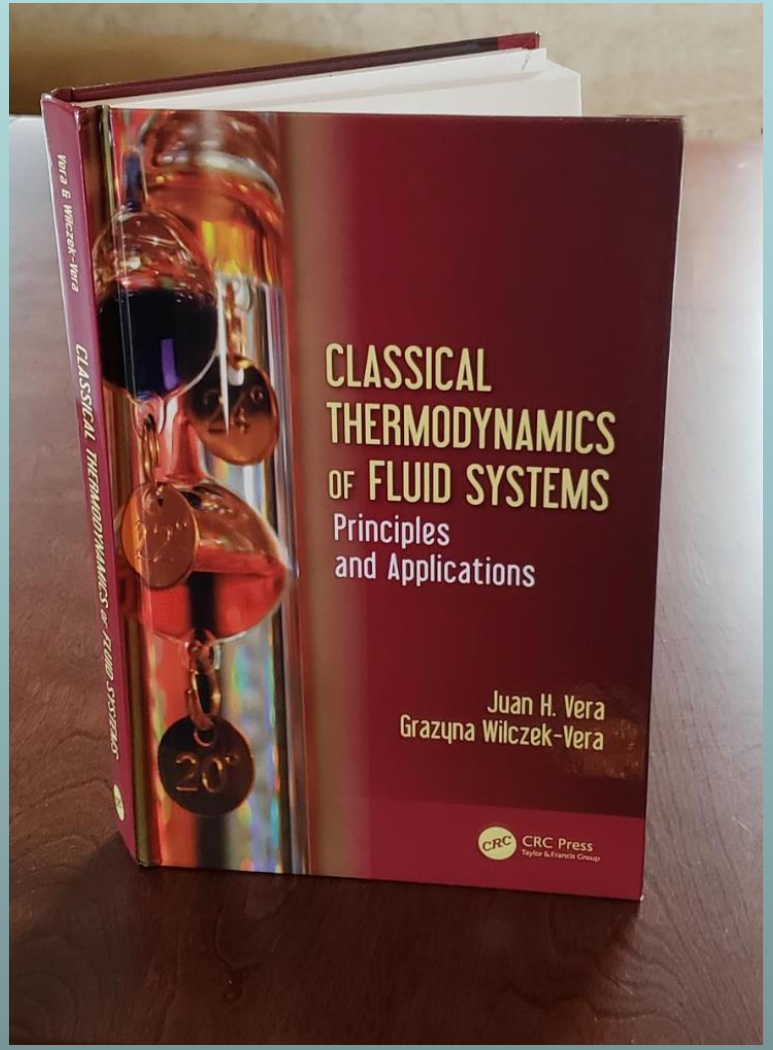
$l_c = 2a_i$	correlation length	$i = Na^+, Ca^{2+}, Cl^-$	Å
a_{Na^+}, $a_{Ca^{2+}}$	radii	0.95, 0.99	Å
a_{Cl^-}, a_{H_2O}	radii	1.81, 1.4	Å
$R^0_{Na^+}$, $R^0_{Ca^{2+}}$, $R^0_{Cl^-}$	Born radii in Eq. (12)	1.617, 1.706, 2.263	Å
δ_{Na^+}, $\delta_{Ca^{2+}}$, δ_{Cl^-}	in Eq. (11)	4.2, 5.1, 3.8	
O_i^w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

Activity Coefficients

$Ca^{2+}Cl_2^-$

'normalized' free energy per mole





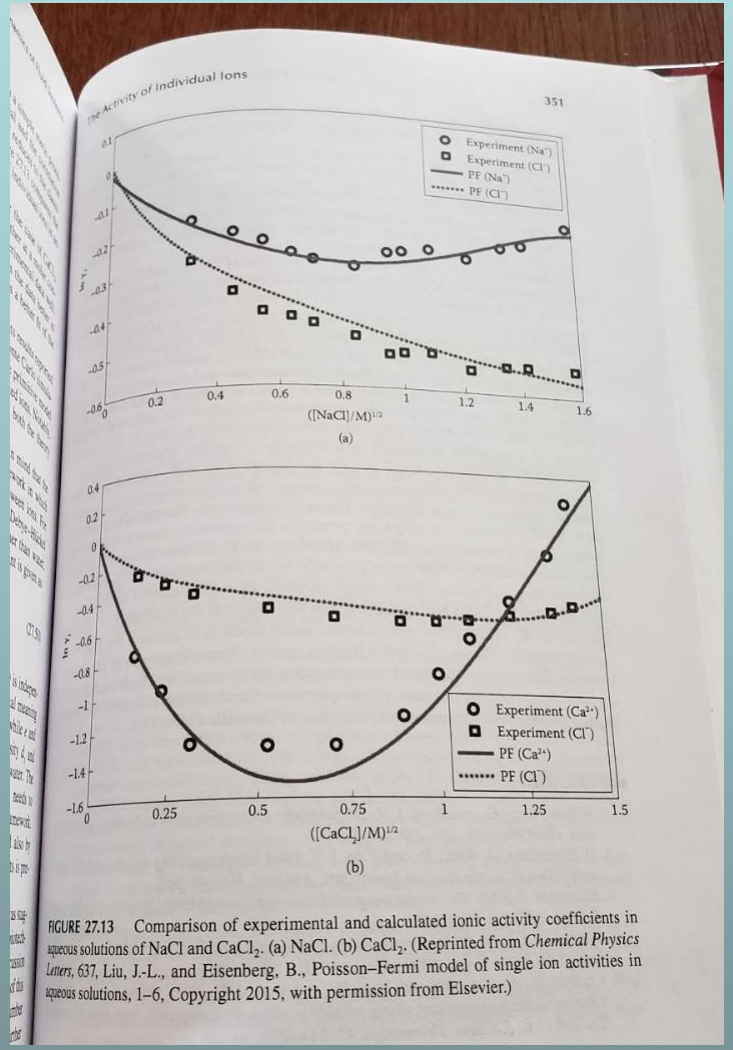
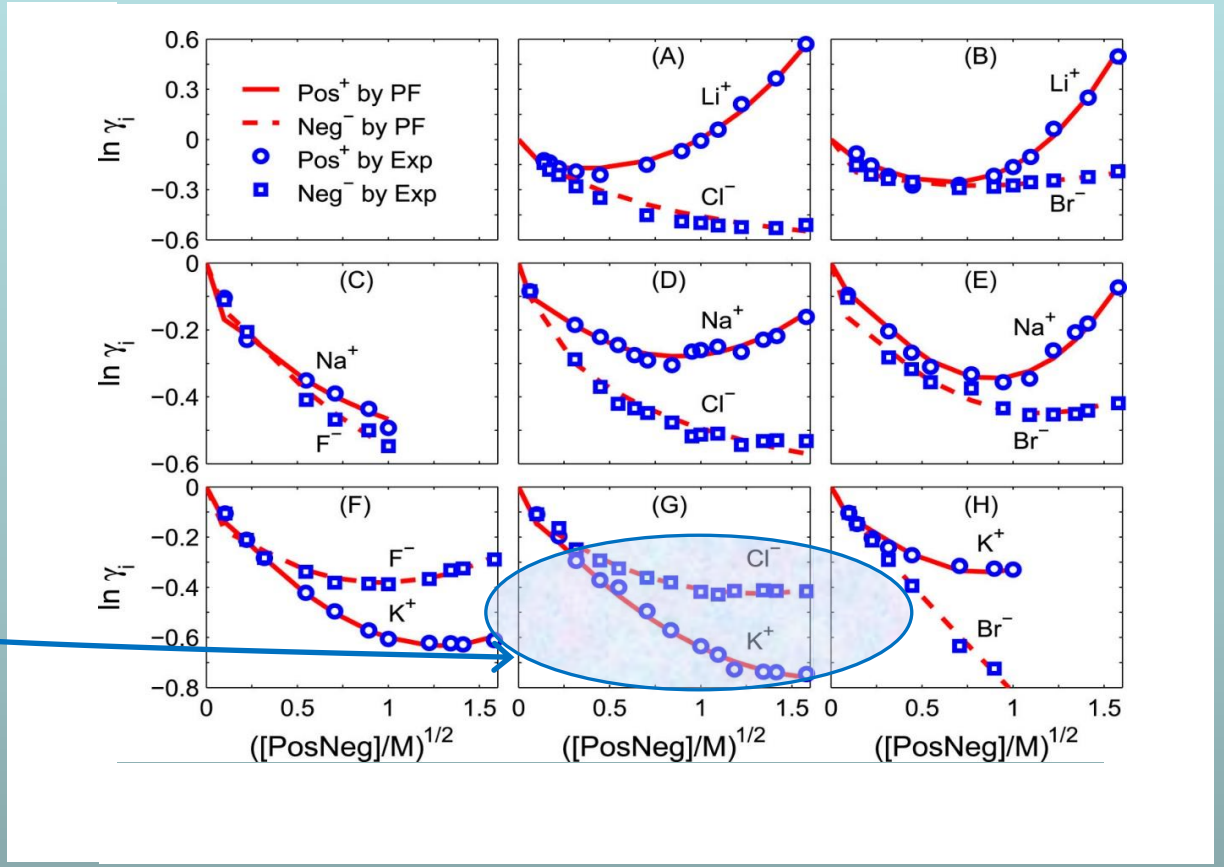


FIGURE 27.13 Comparison of experimental and calculated ionic activity coefficients in aqueous solutions of NaCl and $CaCl_2$. (a) NaCl. (b) $CaCl_2$. (Reprinted from *Chemical Physics Letters*, 637, Liu, J.-L., and Eisenberg, B., Poisson–Fermi model of single ion activities in aqueous solutions, 1–6, Copyright 2015, with permission from Elsevier.)

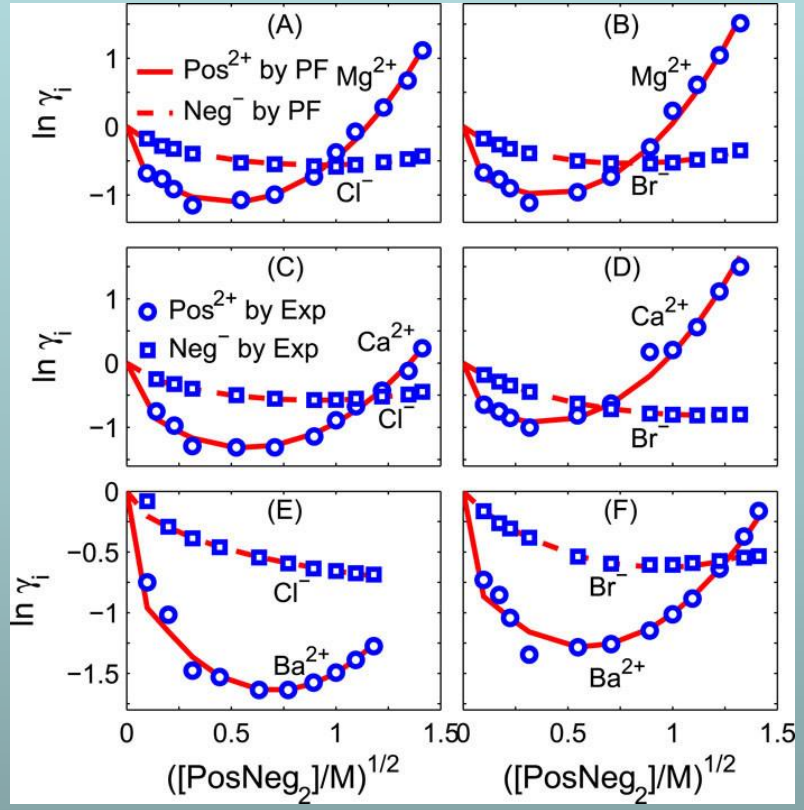
KCl



Individual activity coefficients of 1:1 electrolytes. Comparison of PF results with experimental data[26] on i = Pos$^+$ (cation) and Neg$^-$ (anion) activity coefficients γ_i in various [PosNeg] from 0 to 1.6M.

Published in: Jinn-Liang Liu; Bob Eisenberg; *J. Chem. Phys.* **148,** 054501 (2018)
DOI: 10.1063/1.5021508

Activity Coefficients of 2:1 Electrolytes



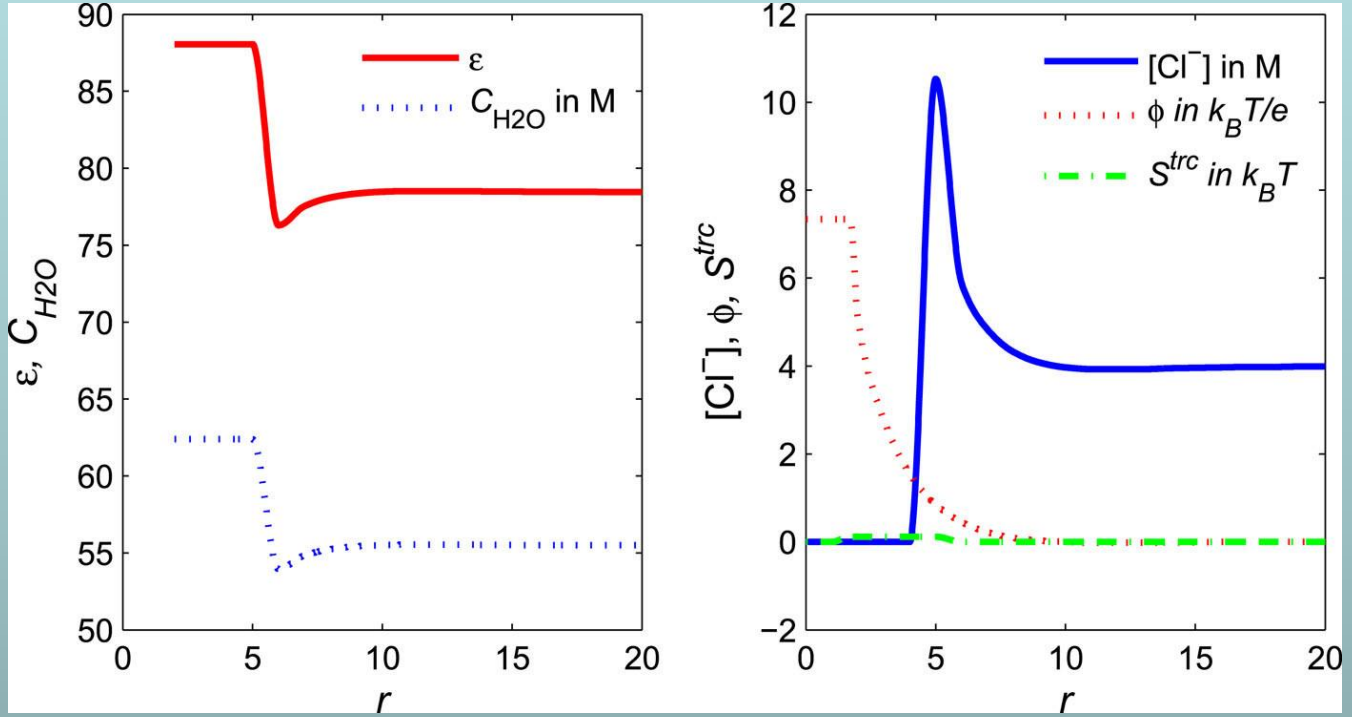
Published in: Jinn-Liang Liu; Bob Eisenberg; *J. Chem. Phys.* **148,** 054501 (2018)
DOI: 10.1063/1.5021508

Why are the fits so good?

Not sure,
Probably the composite Dielectric Function
joining atomic near field to electrodynamic far field

Stay tuned for new work

dielectric function $\varepsilon_{water}\left(l_c^{\,2}\nabla^2 - 1\right)$



Dielectric function $\tilde{\epsilon}(r)$ (denoted by ε in the figure), water density CH2O(r) (CH2O), Cl^- concentration CCl−(r) ([Cl^-]), electric potential $\phi^{PF}(\mathbf{r})$ (ϕ), and steric potential $S^{trc}(\mathbf{r})$ (S^{trc}) profiles near the solvated ion Ca^{2+} at [$CaCl_2$] = 2M, where r is the distance from the center of Ca^{2+} in angstrom.

Published in: Jinn-Liang Liu; Bob Eisenberg; *J. Chem. Phys.* **148,** 054501 (2018)
DOI: 10.1063/1.5021508

Approximate Composite Potential[1,2,3,4]
Convolution of Yukawa and Poisson

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

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

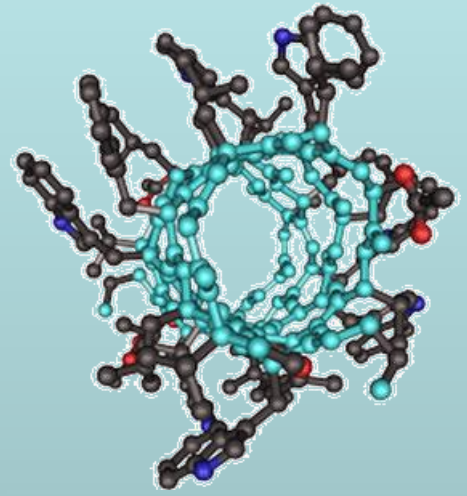
$\varepsilon_{water}\left(l_c{}^2\nabla^2 - 1\right)$ is a **dielectric function** that includes the correlated motions of ions

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

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

More Detail

CHANNELS



Gramicidin A

Unusual SMALL Bacterial Channel

often simulated and studied

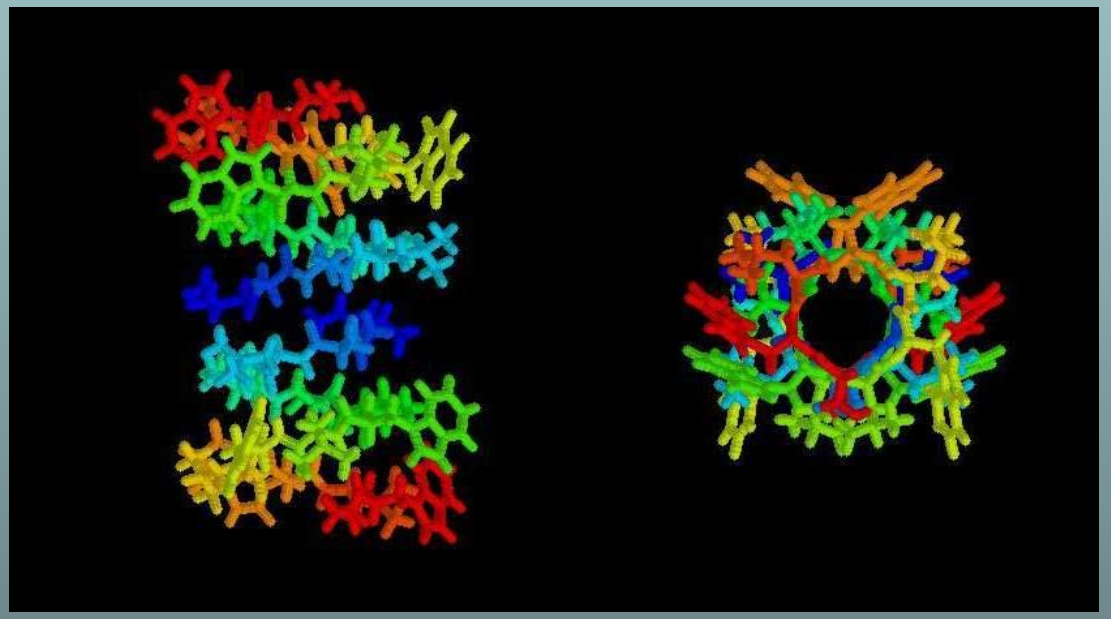
Margaret Thatcher,
student of Nobelist Dorothy Hodgkin
Bonnie Wallace leading worker

Validation of PNP Solvers with Exact Solution

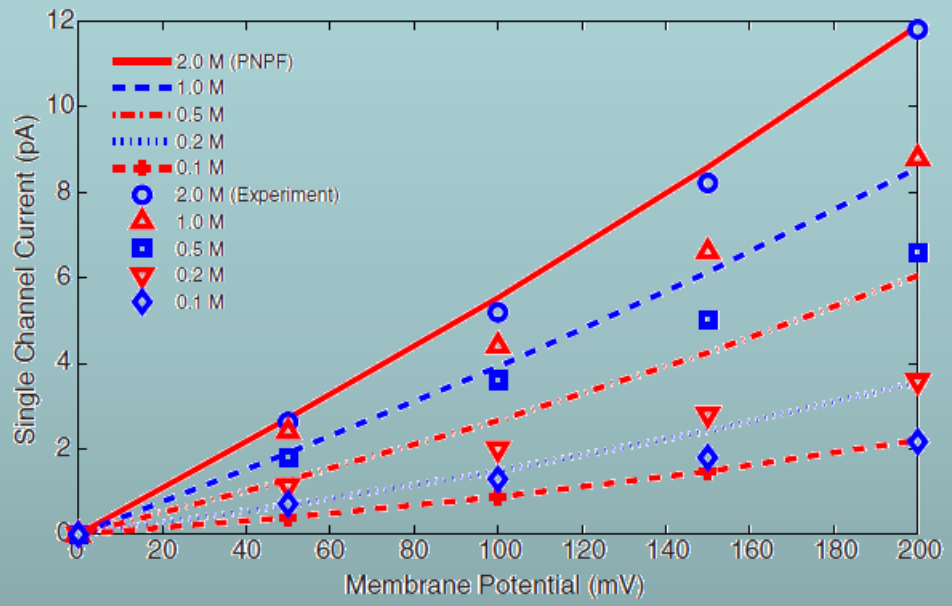
following the lead of

Zheng, Chen & Wei

J. Comp. Phys. (2011) **230**: 5239



Three Dimensional Theory
Comparison with Experiments
Gramicidin A

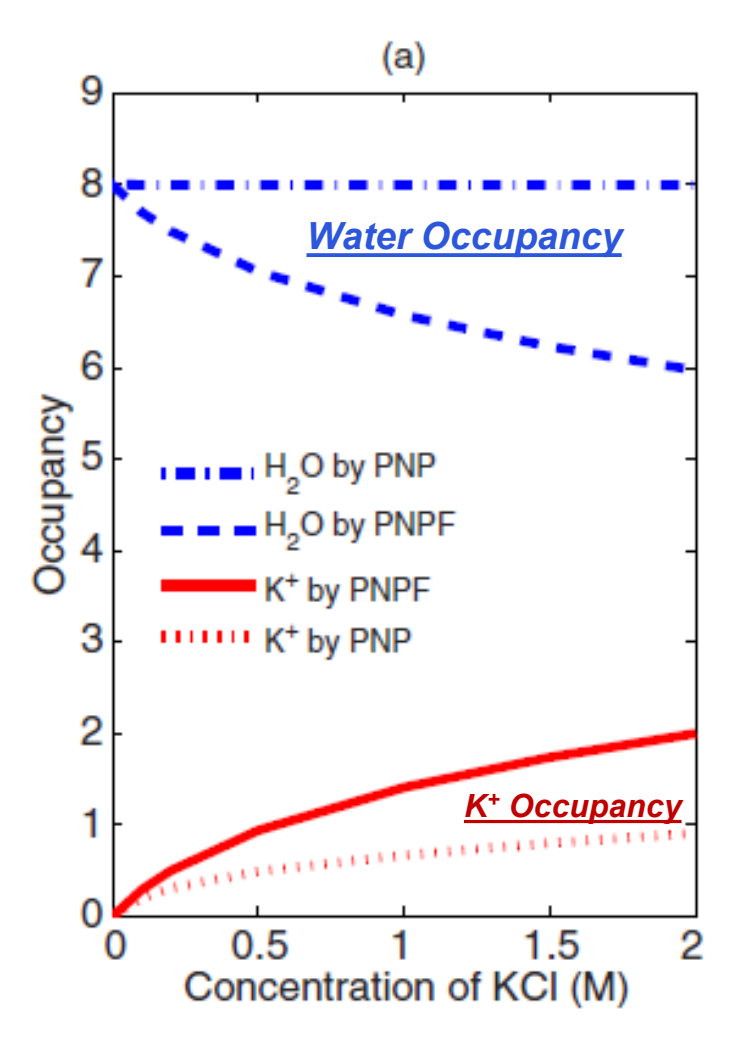


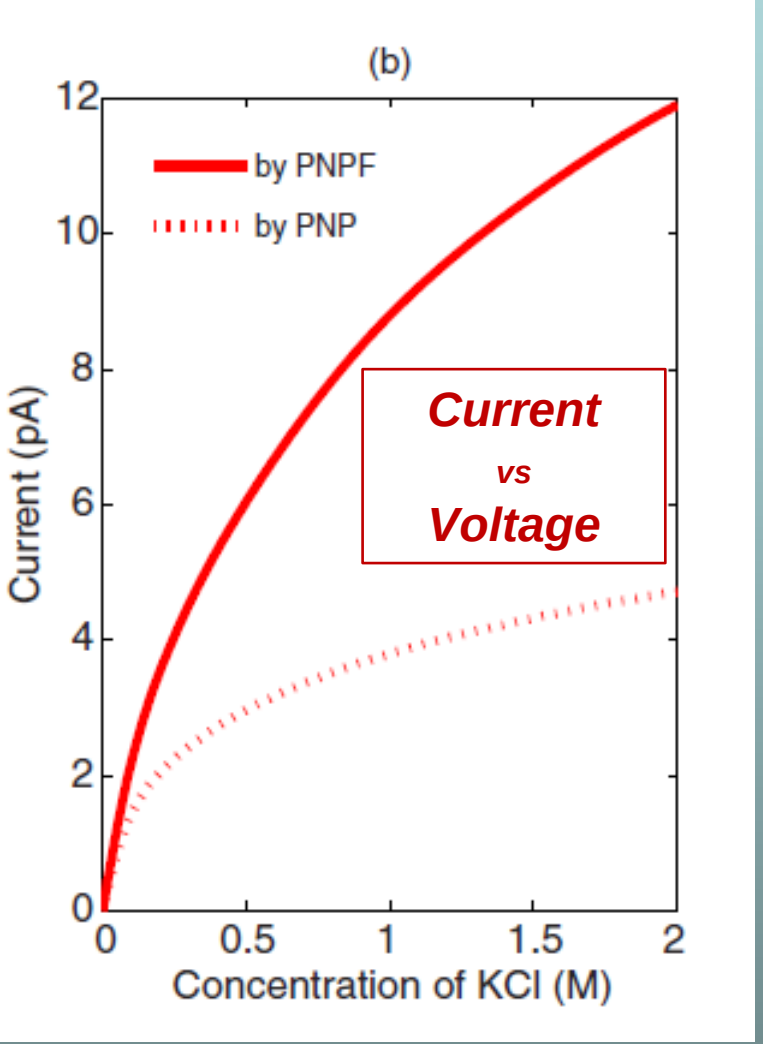
Data from
Cole, Frost, Thompson, Cotten, ***Cross****, &* ***Busath****, Biophys J (2002)* ***83****:1974*

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

Steric Effect is Large in *(crowded)* Gramicidin

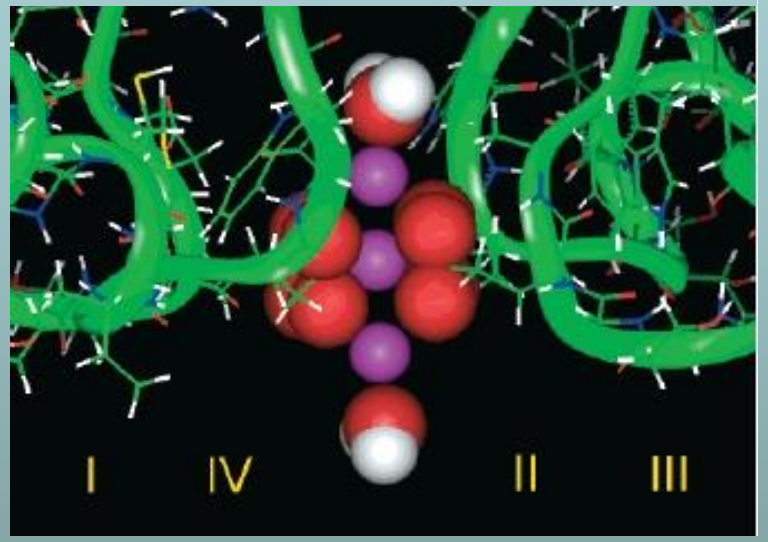
PNPF *vs* PNP





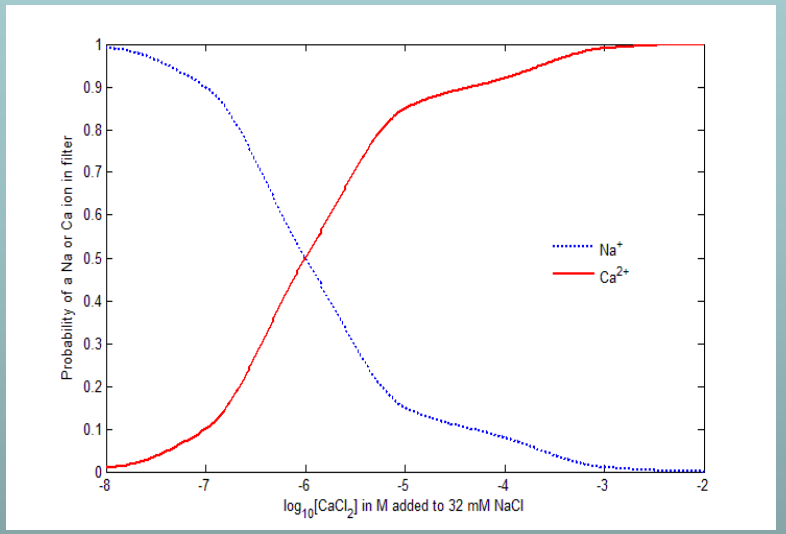
Cardiac Calcium Channel $Ca_V.n$

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

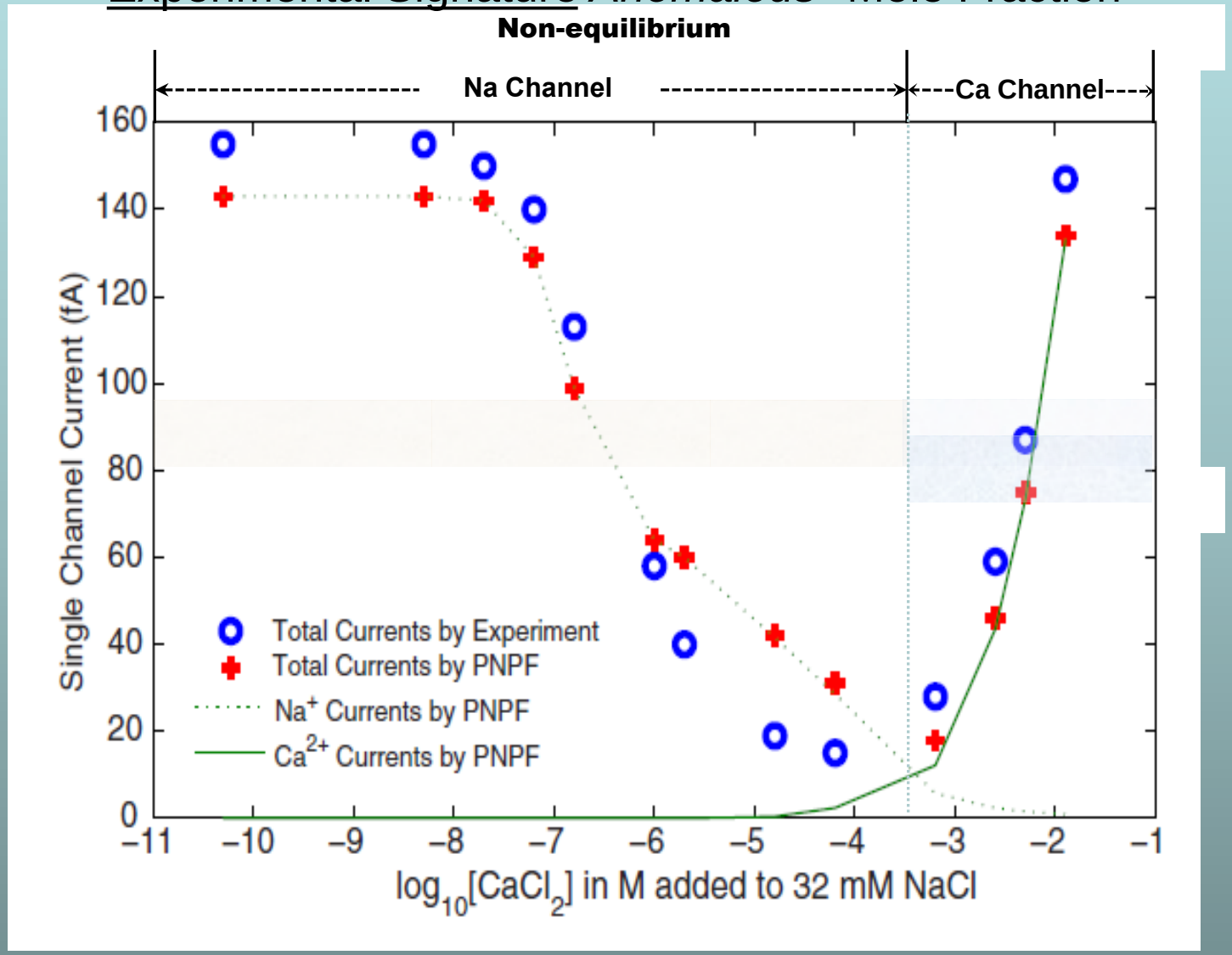
Binding Curve



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 $[Ca^{2+}] < 10^{-3.}$

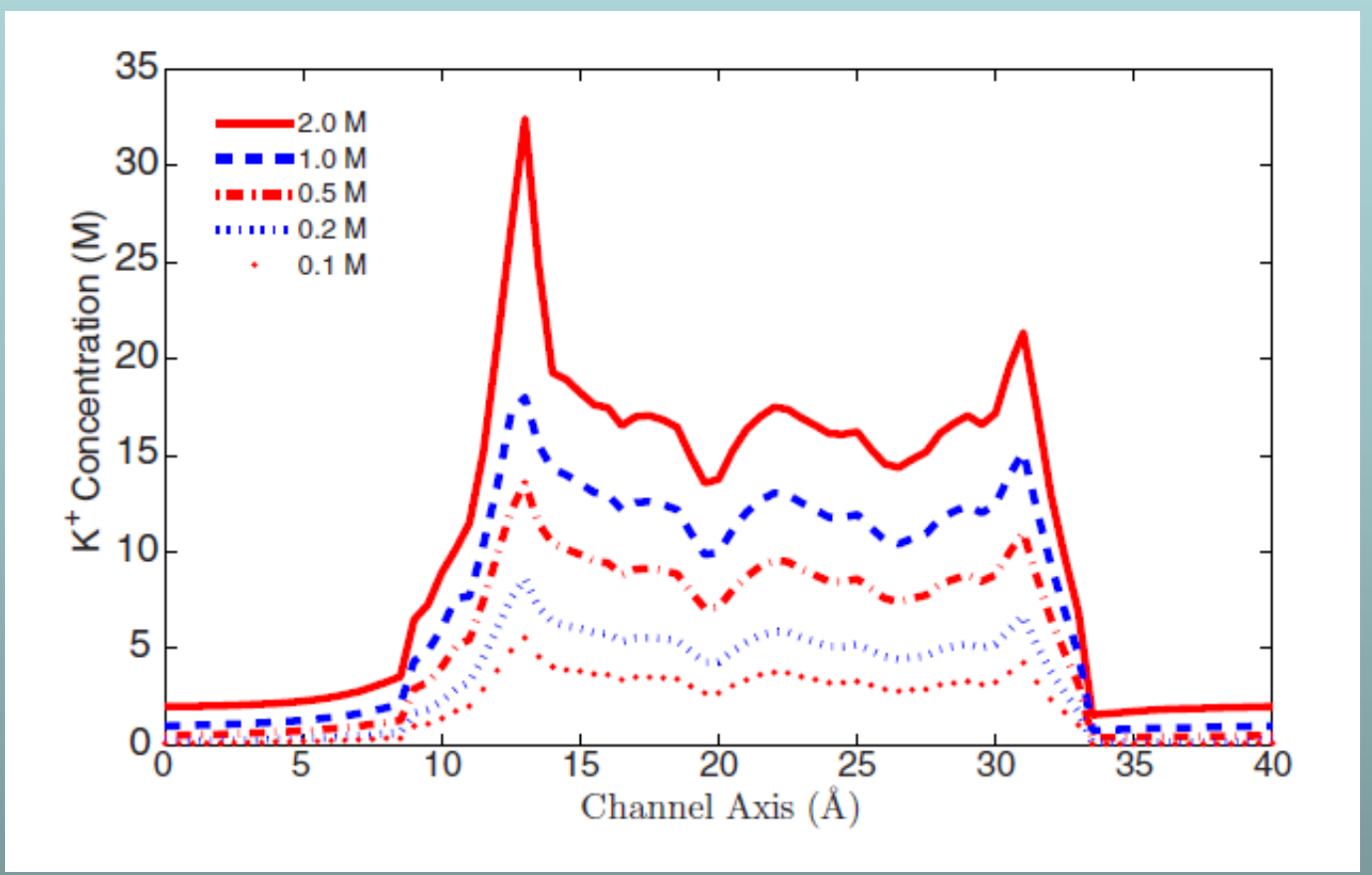
Liu & Eisenberg (2015) Physical Review E 92: 012711

More Detail

INSIDE CHANNELS

Gramicidin

Two K^+ Binding Sites
OUTPUTS of our calculations

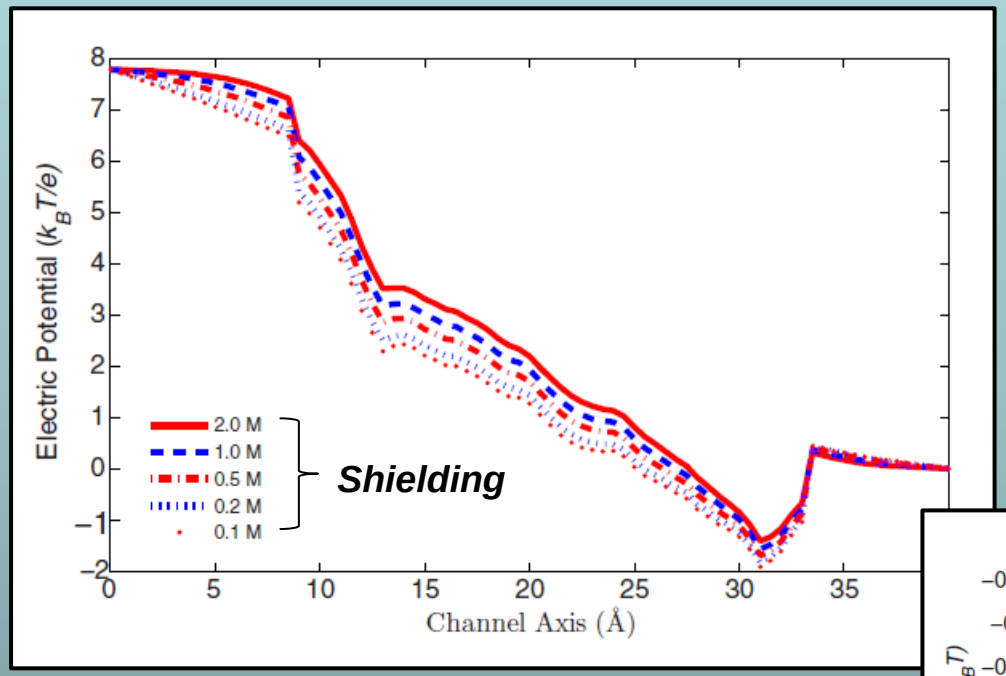


Binding sites are prominent in NMR measurements & MD calculations
BUT they VARY
with conditions in <u>any consistent model</u> and so
<u>cannot be assumed</u> to be of fixed size or location

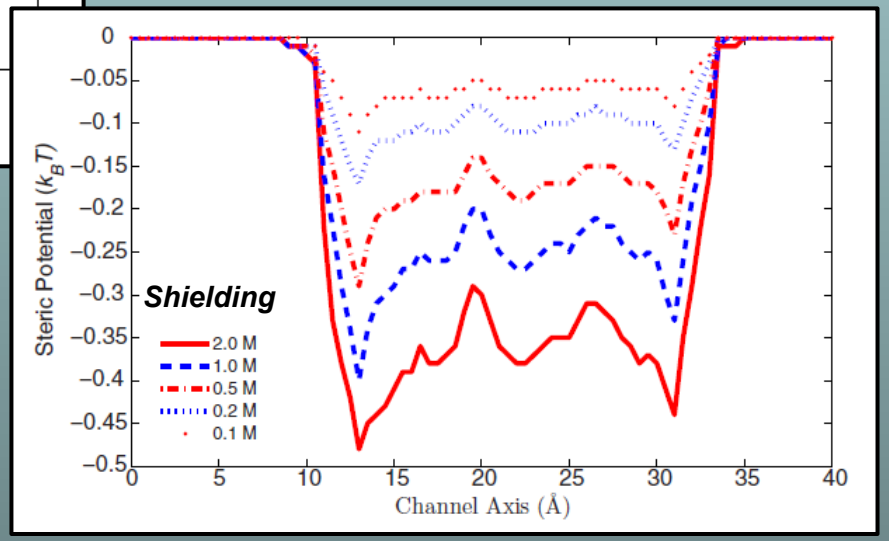
Steric Effect is Significant

Gramicidin is Crowded

Shielding is Substantial



Steric Potential

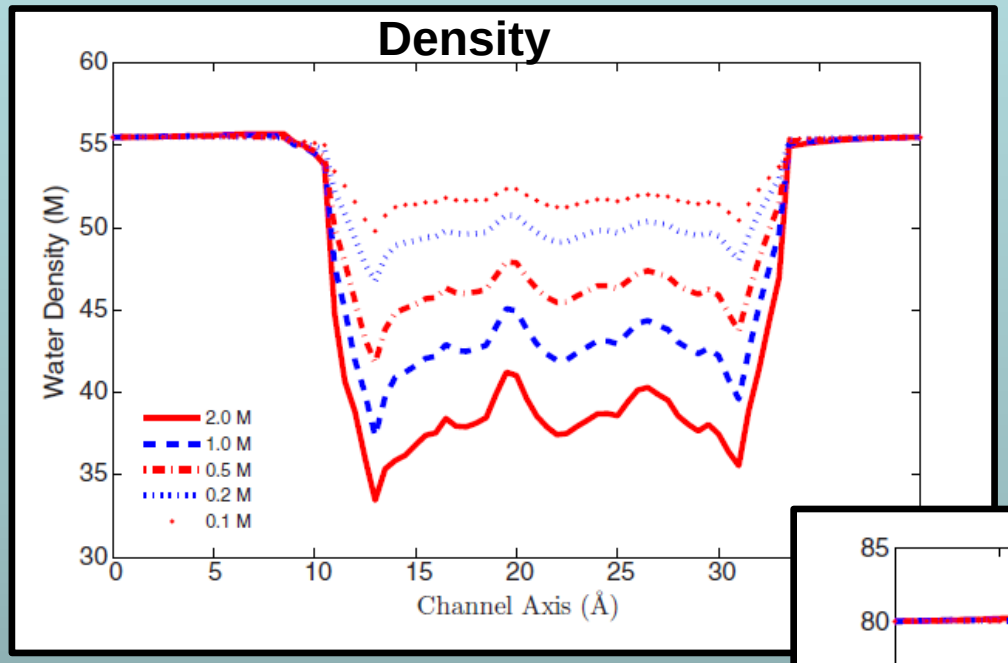


<u>Shielding has been ignored</u> in many papers
Results are often at one concentration or unspecified concentration,
as in most molecular dynamics

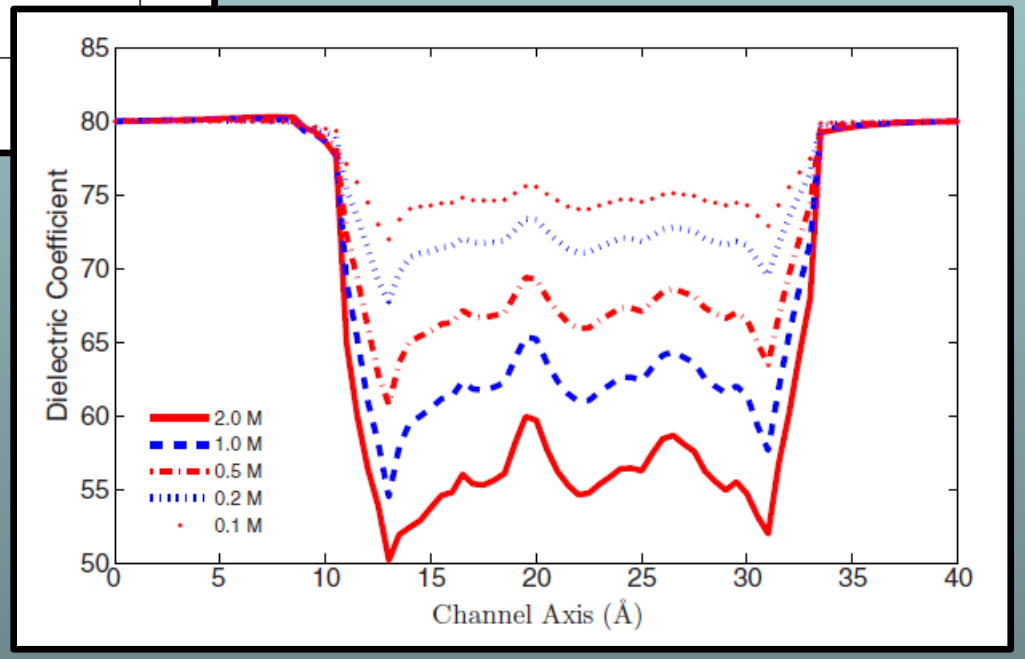
Channel is often described as a potential profile
<u>This is inconsistent with electrodynamics</u>
as in classical rate models

Inside Gramicidin

Water Density



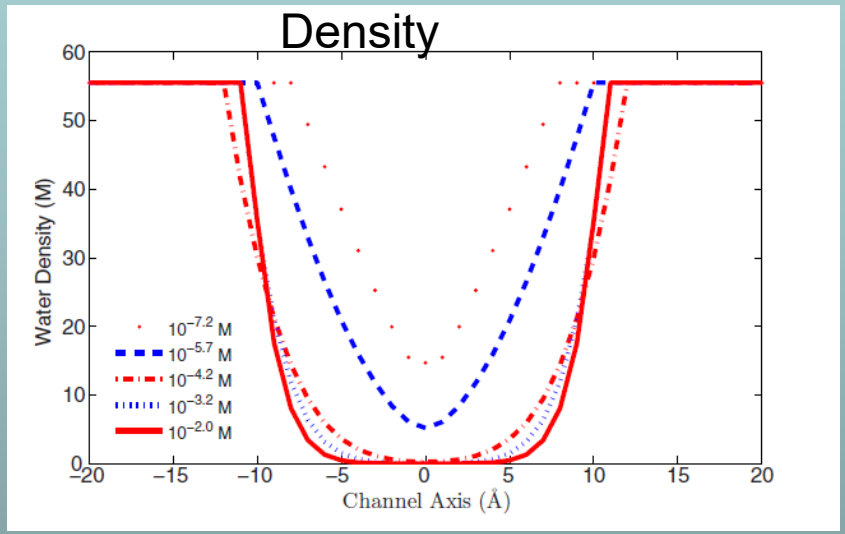
Dielectric Function an OUTPUT of model



Liu & Eisenberg
J Chem Phys 141: 22D532

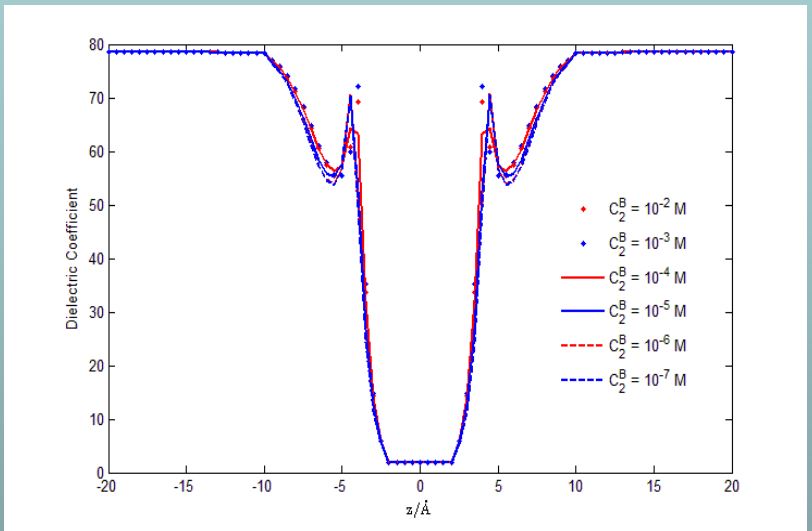
Inside the
Cardiac Calcium Channel
$Ca_V1.n$

Water Density



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

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



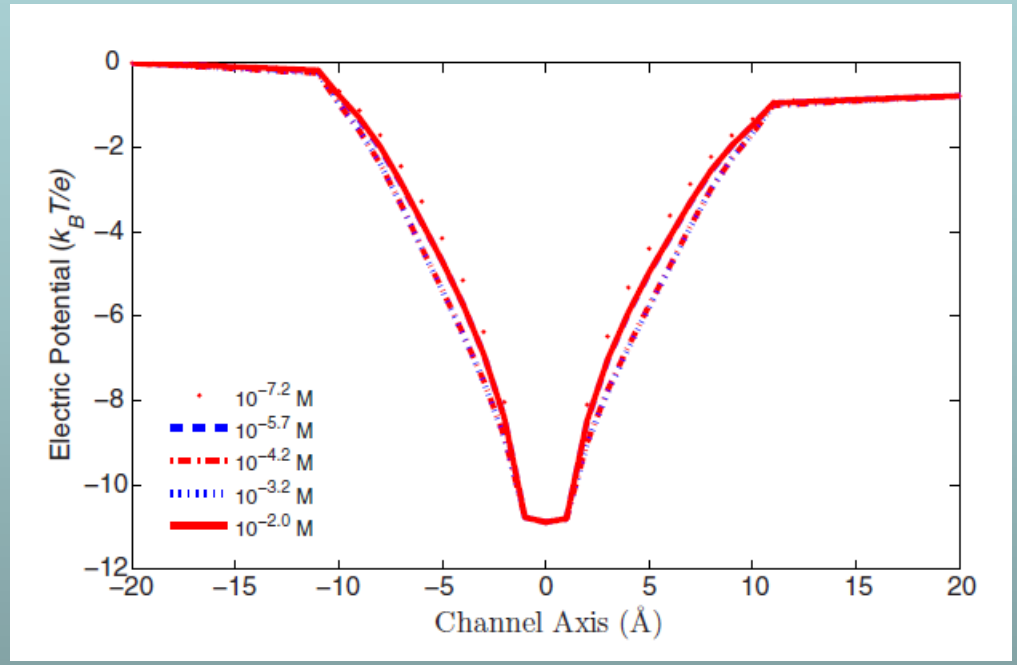
Liu & Eisenberg J Chem Phys 141(22): 22D532

Inside the

Cardiac Calcium Channel

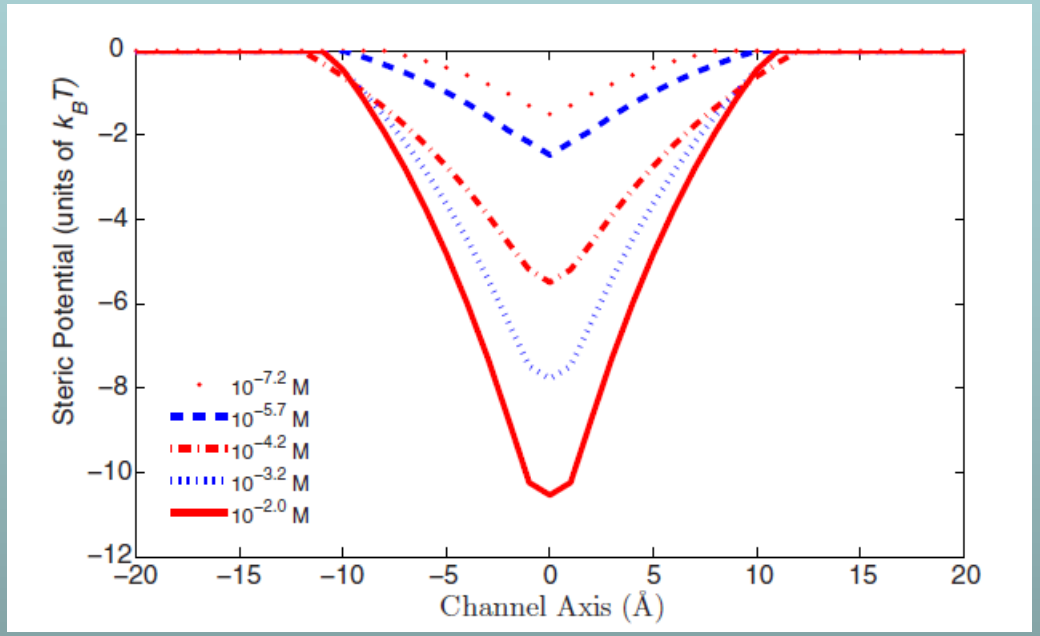
$Ca_V1.n$

Electric Potential



Steric Potential

Estimator of Crowding



The End

Any Questions?

Extra Slides

Proof: Voids are Needed

Proof: Voids are Needed

Bob Eisenberg

May 2019

Guided by Jinn-Liang Liu

Fermi Distribution ⇔ Saturation

$$\boldsymbol{C_i(\mathrm{r})=C_i^B \exp\left(-\beta_i \phi(\mathrm{r})+ \frac{\nu_i}{\nu_0} S^{trc}(\mathrm{r})\right)} \qquad \text{where} \quad \beta_i = q_i/k_B\mathrm{T}$$

All concentration functions $C_i(\mathbf{r}) < 1/\nu_i$

$C_i(\mathbf{r})$ cannot exceed the maximum value $1/\nu_i$
for any arbitrary (**or even infinite**) potential

Voids

Spheres cannot fill space

Treatments with water as spheres cannot be computed unless voids are included

Proof Follows

Proof: System Must Contain Voids

Consider a system without voids,

i.e., with $\boldsymbol{V_{K+2} = 0}$

Let's try to fill the volume

(1) with ions $\mathbf{1, 2, 3 \cdots K}$ at concentrations $\boldsymbol{C_i(\mathrm{r})}$
and
(2) with the single water species K+1

and then use a Fermi Distribution.

We will find a contradiction.

We can use a Fermi Distribution only if we include voids.

Proof: System Must Contain Voids

Consider a system without voids,
i.e., with $\boldsymbol{V_{K+2} = 0}$

We will find a contradiction.

Fermi Distribution for Spheres Requires Voids

Consider a system without voids,

i.e., with $\boldsymbol{V_{K+2} = \nu_{K+2} = 0}$

If the system is filled with spheres, with zero voids,
then the volume fraction of voids is zero: $\Gamma(\boldsymbol{voids};\ \mathbf{r}) = \mathbf{0}$

$$\Gamma(\boldsymbol{voids};\ \mathbf{r}) = \mathbf{0} = \mathbf{1} - \underbrace{\sum_{\mathbf{1}}^{\boldsymbol{K+1}} \boldsymbol{\nu_i}\, \boldsymbol{C_i}(\mathbf{r})}_{\text{Ions + Water}} \tag{22}$$

$$\mathbf{1} = \sum_{\mathbf{1}}^{\boldsymbol{K+1}} \boldsymbol{\nu_i}\, \boldsymbol{C_i}(\mathbf{r}) \tag{23}$$

Consider a system without voids,

i.e., with $\boldsymbol{V_{K+2}= \nu_{K+2} = 0}$

If the system is filled with spheres, with zero voids,
then the volume fraction of voids $\Gamma(\boldsymbol{voids};\ \mathbf{r}) = \mathbf{1}\ - \sum_{1}^{K+1} \boldsymbol{\nu_i C_i}(\mathbf{r}) = \mathbf{0}$

$$\textbf{Steric Potential} = S^{trc}(\underbrace{filled\ with\ spheres}_{Ions\ +\ Water};\mathbf{r}) = \ln\left(\boldsymbol{\Gamma(voids};\ \boldsymbol{r})/\boldsymbol{\Gamma}^{\mathrm{B}}\right) = \ln\left(0/\boldsymbol{\Gamma}^{\mathrm{B}}\right)$$

$$\textbf{Steric Potential} = S^{trc}(filled\ with\ spheres;\mathbf{r}) = -\infty \qquad (24)$$

Consider a system without voids,

i.e., with $V_{K+2} = \nu_{K+2} = 0$

If the system is filled with spheres, without voids,
then the volume fraction of voids $\Gamma(voids) = \Gamma(voids;\ \mathbf{r}) = 0$ is zero

$$\textbf{Steric Potential} = S^{trc}(filled\ with\ spheres; \mathbf{r}) \stackrel{?}{=} -\infty \qquad (25)$$

$$C_i(\mathbf{r}) = C_i^B\ exp\left(-(q_i/k_BT)\phi(\mathbf{r}) + \overbrace{\frac{\nu_i}{\nu_0} S^{trc}(\mathbf{r})}^{-\infty}\right) \Longrightarrow C_i(\mathbf{r}) \stackrel{?}{=} 0 \qquad (26)$$

$C_i(\mathbf{r}) \stackrel{?}{=} 0$ contradicts our original assumption of general $C_i(\mathbf{r})$

Proof

Consider a system without voids,

i.e., with $V_{K+2} = \nu_{K+2} = 0$

Conclusion:

We must have voids if we use a Fermi Distribution

But we only need the
Total Void Volume,

or Volume Fraction

No other details are needed about the voids

The End
Any Questions?

Extra Slides

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
Power Supply = spatially nonuniform 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

Devices are built to
Implement Equations
in Engineering

Devices evolve to
Provide Functions
in Biology

In engineering
we know the equation
and seek to improve the device.

In biology often
we have to discover the function, and
how molecules perform the function.

Thermodynamics, Statistical Mechanics, Molecular Dynamics are UNSUITED for DEVICES

Thermodynamics, Statistical Mechanics, Molecular Dynamics have

No inputs, outputs, flows, or power supplies

Power supply = spatially nonuniform inhomogeneous Dirichlet conditions

Analysis of Devices must be NONEQUILIBRIUM with spatially non-uniform BOUNDARY CONDITIONS