Poisson Fermi Approach to Ion Channels

Bob Eisenberg

IMA Institute of Mathematics and its Applications

University of Minnesota

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Ion Channels: Biological Devices, Diodes*

Natural nano-valves** for atomic control of biological function

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

Coordinate contraction in skeletal muscle

Control all electrical activity in cells

Produce signals of the nervous system

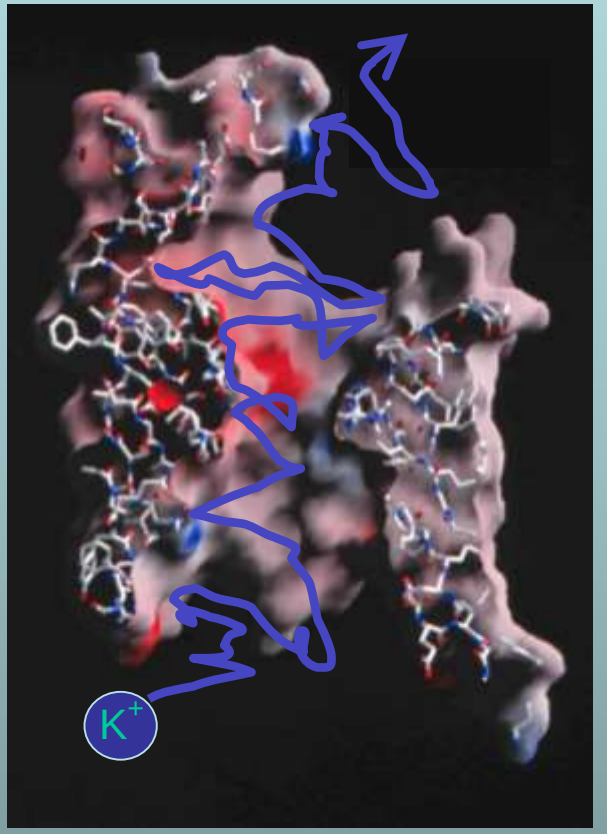
Are involved in secretion and absorption in all cells: kidney, intestine, liver, adrenal glands, etc.

Are involved in thousands of diseases and many drugs act on channels

Are proteins whose genes (blueprints) can be manipulated by molecular genetics

Have structures shown by x-ray crystallography in favorable cases

Can be described by mathematics in some cases

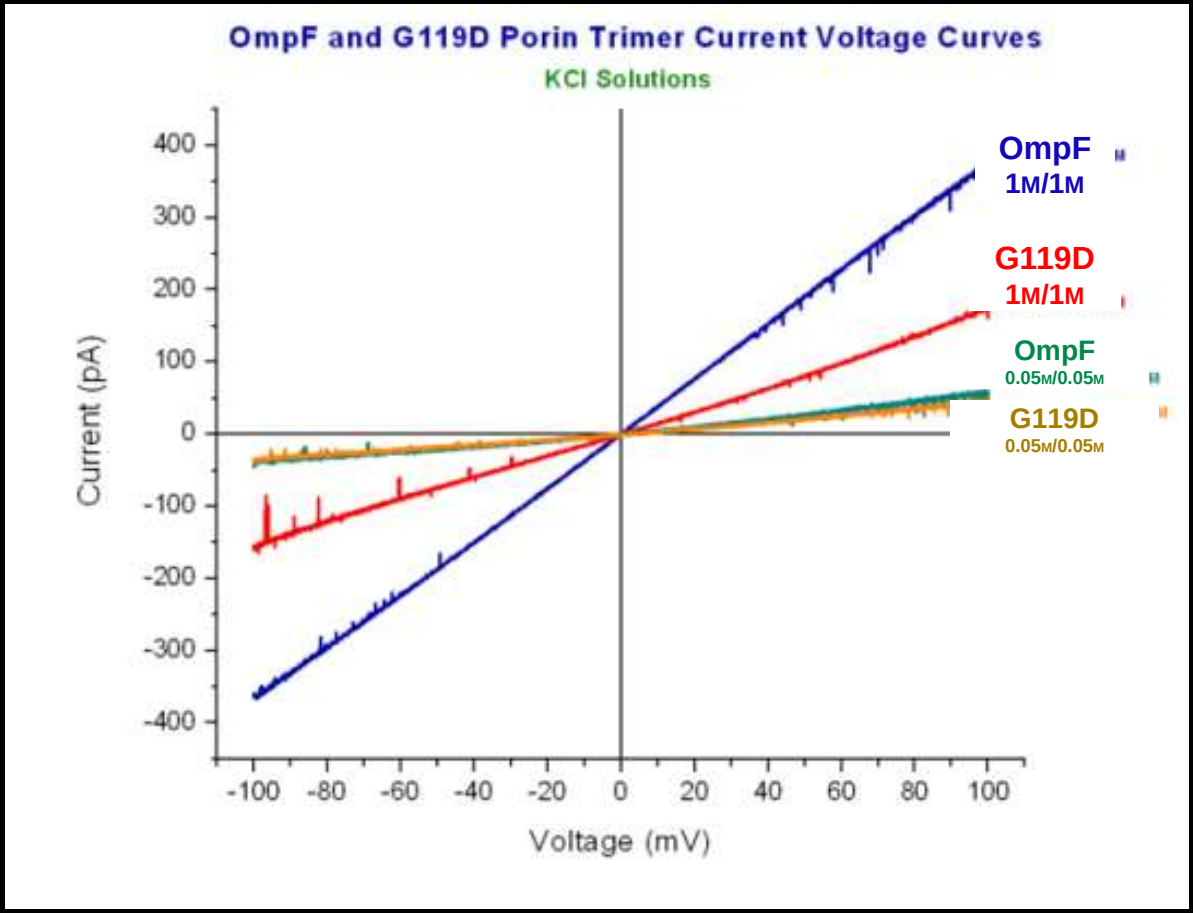


~3 x 10^{-9} meter

***Device is a Specific Word, that exploits specific mathematics & science**

***nearly pico-valves: diameter is 400 – 900 x 10^{-12} meter; diameter of atom is ~200 x 10^{-12} meter**

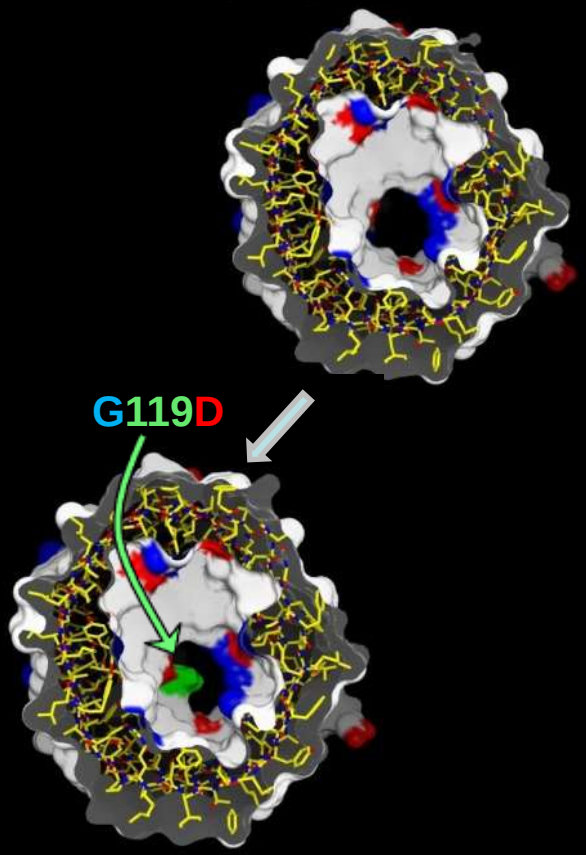
A few atoms make a BIG Difference



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

How do a few atoms control

(macroscopic)

Device Function ?

Mathematics of Molecular Biology
is about
How does the device work?

Multiscale Analysis is Inevitable

because a

Few Atoms

Ångstroms

control

Macroscopic Function

centimeters

Mathematics must be accurate

There is no engineering without numbers

and the numbers must be accurate!

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

Scientists

must Grasp

and not just reach

Calibrations are necessary

or nothing works

Channels are (nano) valves

Valves Control Flow

Classical Theory & Simulations

NOT designed for flow

Thermodynamics, Statistical Mechanics do not allow flow

Rate Models do not Conserve Current

if rate constants are constant

or even if

rates are functions of local potential

Uncalibrated Simulations will make devices that do not work

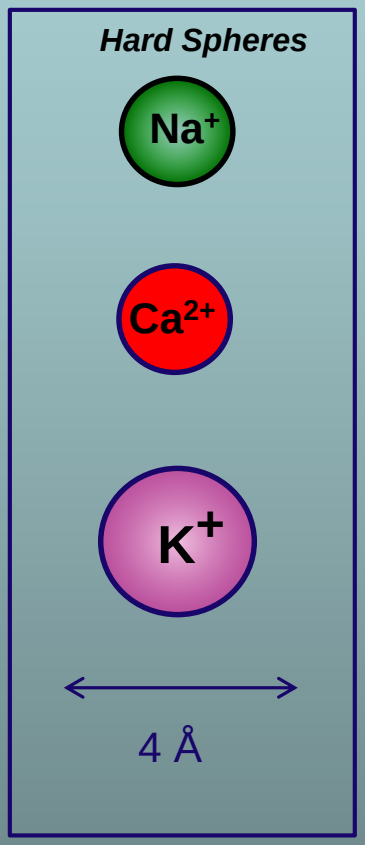
Details matter in devices

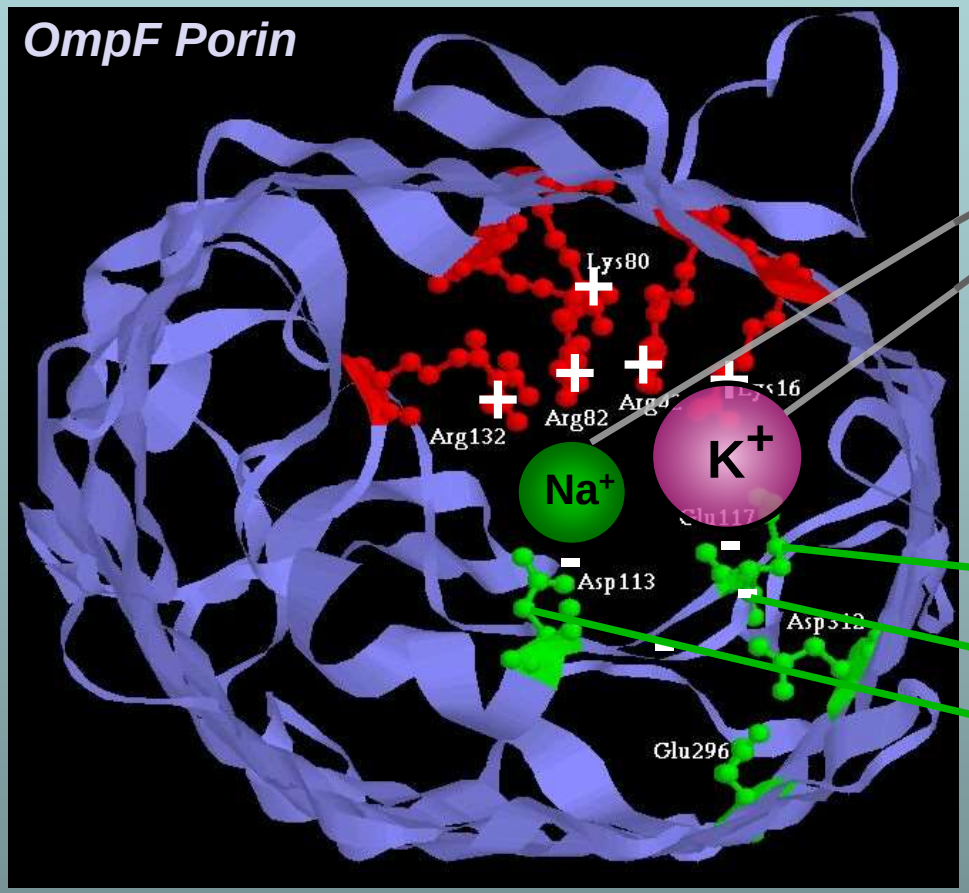
Physical basis of function

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**

Wise to use the Biological Adaptation
to make the reduced model!

Reduced Models allow much easier Atomic Scale Engineering

Crowded Active Sites

in 573 Enzymes

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

Working Hypothesis
math-speak:

Crowded Charge

enables

Dimensional Reduction

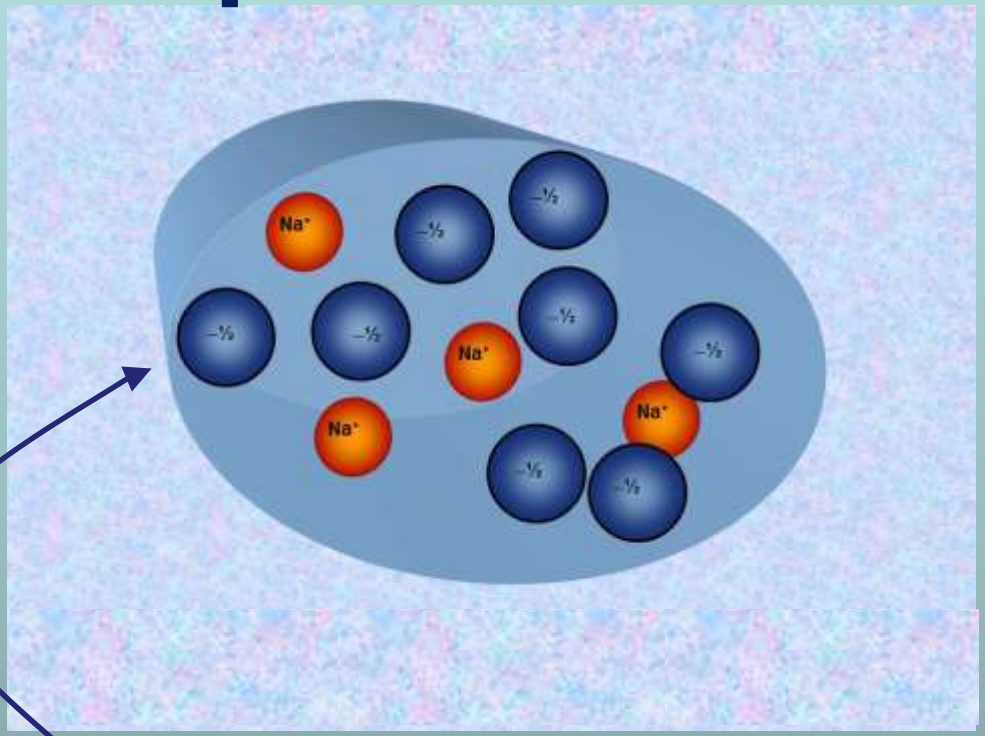
to a

Device Equation

which is

How it Works

‘All Spheres’ Model



Side Chains are Spheres

Channel is a Cylinder

Side Chains are free to move within Cylinder

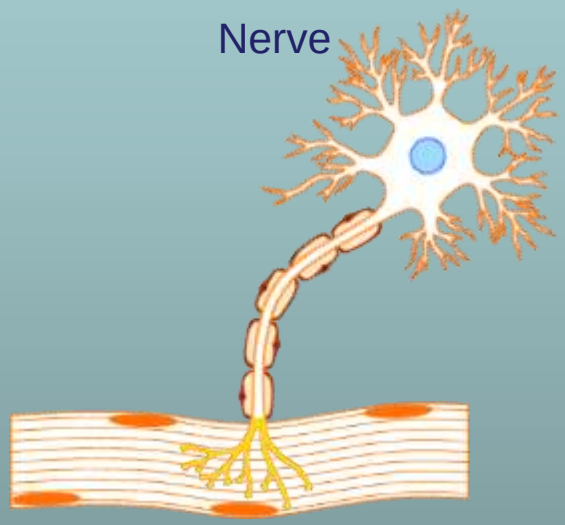
Ions and Side Chains are at free energy minimum

i.e., **ions and side chains are ‘self organized’,**

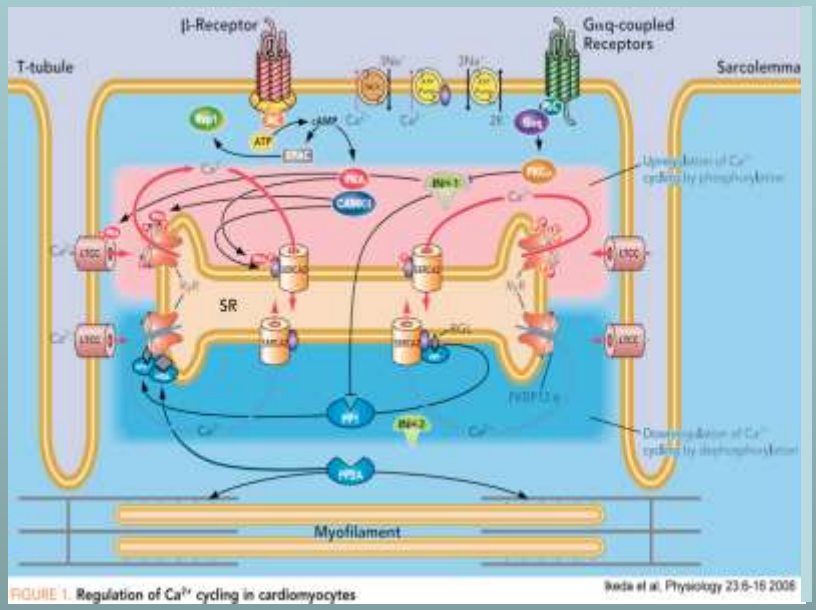
‘Binding Site” is induced by substrate ions

Nonner & Eisenberg

All Spheres Models
work well for Bulk Solutions
Calcium and Sodium Channels*



Skeletal muscle



Heart Muscle Cell

***Not yet for Potassium Channels**

Motivation

Fermi Description

of

Crowded Spheres & Saturation of Concentration

Largest effect of finite size is saturation

*Saturation cannot be described at all by classical Poisson Boltzmann approach and is described in a (wildly) uncalibrated way by **present day** Molecular Dynamics*

Biology occurs in concentrated >0.3 M mixtures of spherical charges

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)

Simulating saturation by interatomic repulsion (Lennard Jones) is a significant mathematical challenge
to be side-stepped if possible

Fermi Description
of
Crowded Charge
gives a
Saturating Distribution
for Concentration of Spherical Ions

Fermi (like) **Distribution**

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

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

$\Gamma(bath) =$ bulk void concentration

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

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

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

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.

5) We require exact consistency with electrodynamics of flow because

All life requires flow

Death is the only Equilibrium of Life

Gibbs-Fermi 'Grand' Free Energy Functional*

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

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

voids

$$\mu_i^B = k_B T \ln\left(\nu_i C_i^B / \Gamma^B \right), \text{ spatially constant}$$

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

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

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 add in, 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**

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

$=$ combinations for N_1 species in all vacant sites N.

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

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

W_{k+2} = combinations of **voids** to fill space and compute robustly & efficiently

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**

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

劉晉良

Jinn-Liang Liu made this clever analysis
Bob Eisenberg helped with the applications

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 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

is a

Quantitative Statement of Charge-Space Competition

Simulated and compared to experiments in
> 30 papers of *Boda, Henderson, 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 else

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] & **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 2nd order PDE's and
Appropriate boundary conditions
that are **consistent** and allow
Robust and Efficient Numerical Evaluation

4) PNPF couples force equation to 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

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

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

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 the dielectric properties of entire bulk solution including correlated motions of ions, following Kornyshev[1] using a corrected and consistent Fermi treatment of spheres

We introduce[2,3] **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. Ltrs. 106 046102 (2011) [2] J Comp Phys (2013) 247:88 [3] J Phys Chem B (2013) 117:12051

Nonequilibrium Force Equation

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

Cahn-Hilliard Type Fourth Order 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

$\varepsilon_{water}(l_c\nabla^2 - 1)$ approximates the dielectric properties of entire bulk solution including correlated motions of ions, following Kornyshev[1] using a corrected and consistent Fermi treatment of spheres

We introduce[2,3] **two second order equations** and **boundary conditions**

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

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

3D computation is facilitated by using 2nd order equations

[1] PhysRev. Ltrs. 106 046102 (2011) [2] J Comp Phys (2013) 247:88 [3] J Phys Chem B (2013) 117:12051

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

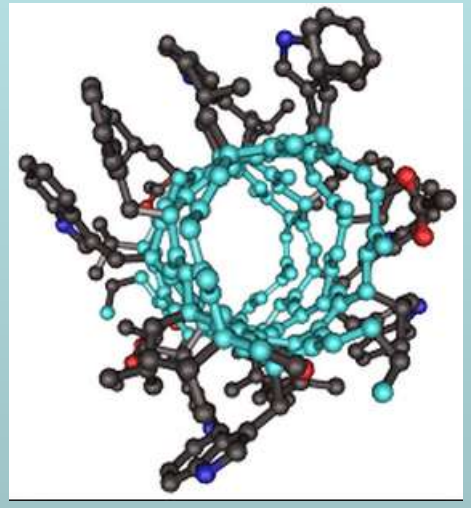
- **Gramicidin** *(tested with real structure, including nonequilibrium)*
  Physical Review E, 2015. 92:012711

- **$Ca_V1.n$** **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.
  First physical analysis of a transporter using consistent mathematics
  Tested by comparison to superb physiological data, mostly complete



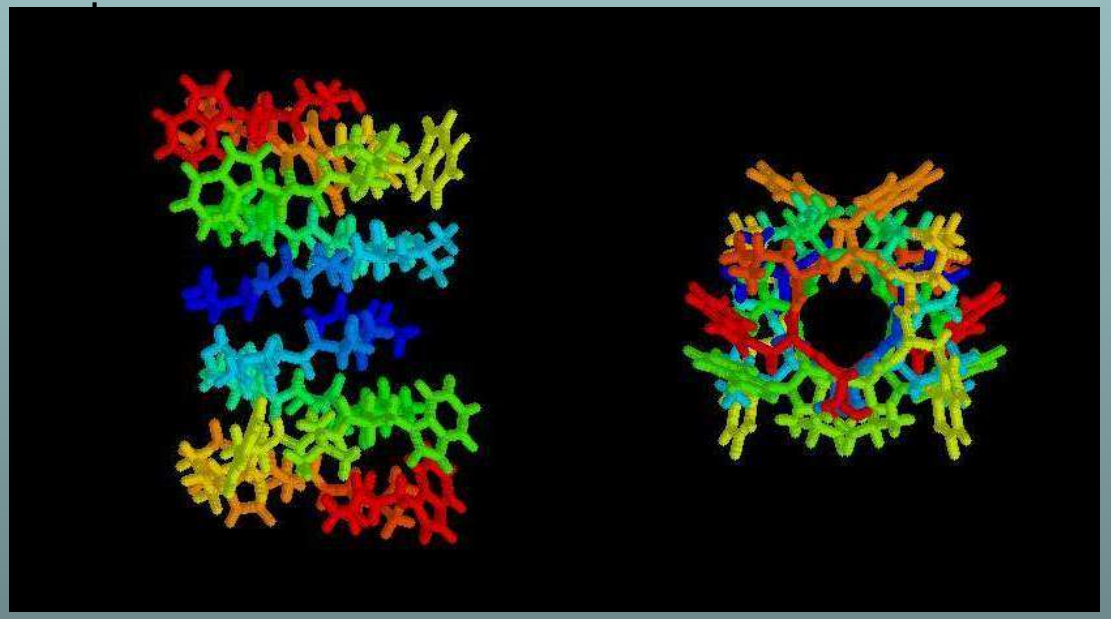
Gramicidin A
Unusual SMALL Bacterial Channel

often simulated and studied

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

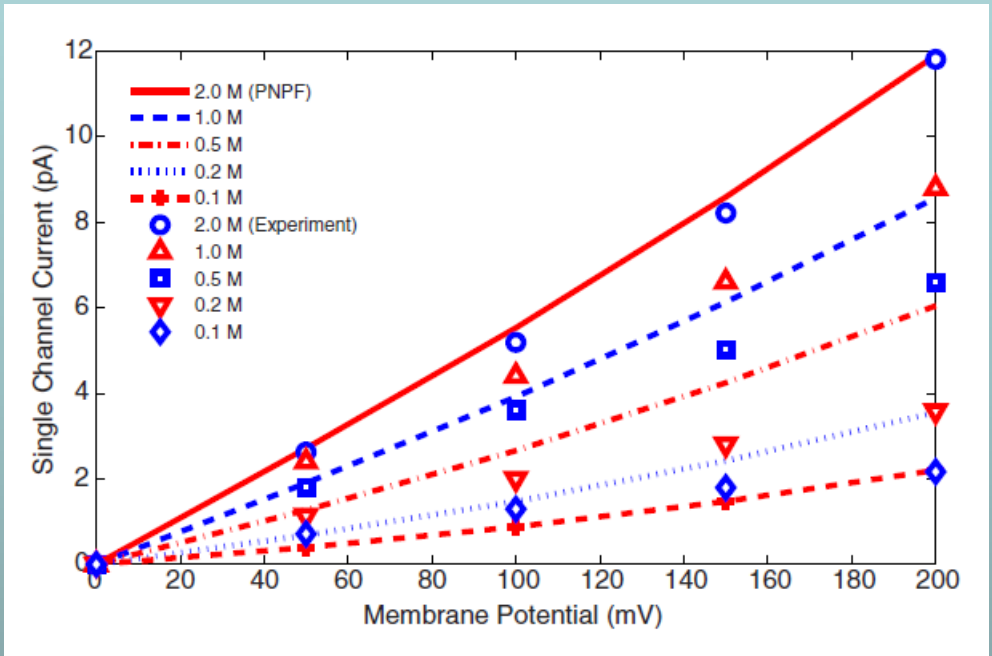
Validation of PNP Solvers
with Exact Solution

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



Comparison with Experiments

Gramicidin A



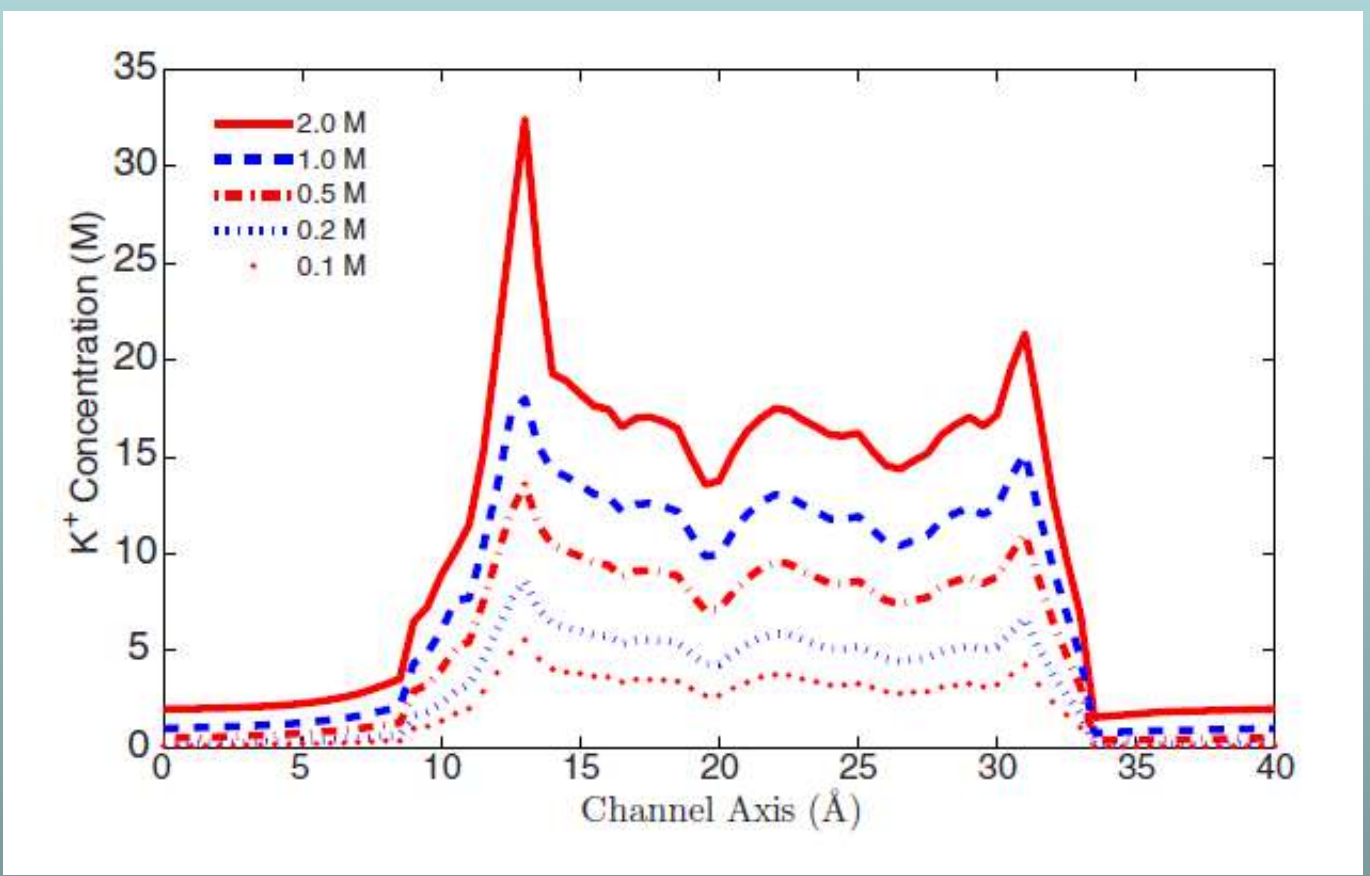
Data from

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

Two K^+ Binding Sites
in Gramicidin
OUTPUTS of our calculations

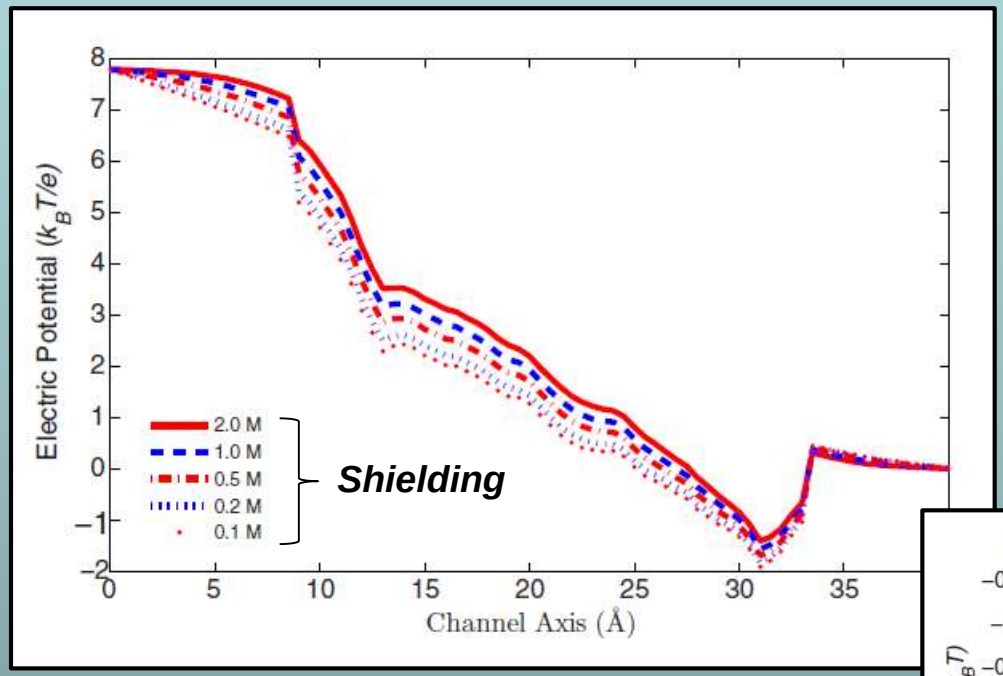


Binding sites are prominent in NMR measurements & MD calculations
BUT they VARY
with conditions in <u>any consistent model</u> and so
<u>cannot be assumed</u> to be of fixed size or location

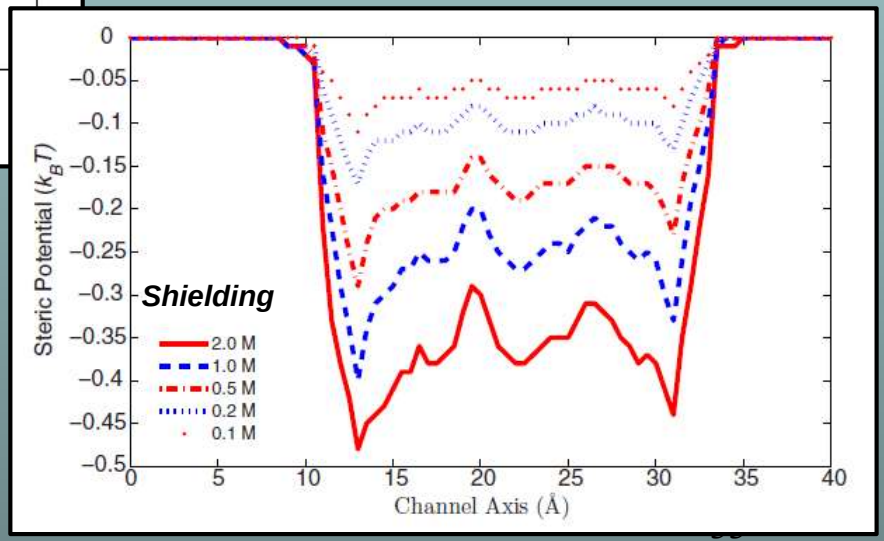
Steric Effect is Significant

Gramicidin is Crowded

Shielding is Substantial



Steric Potential

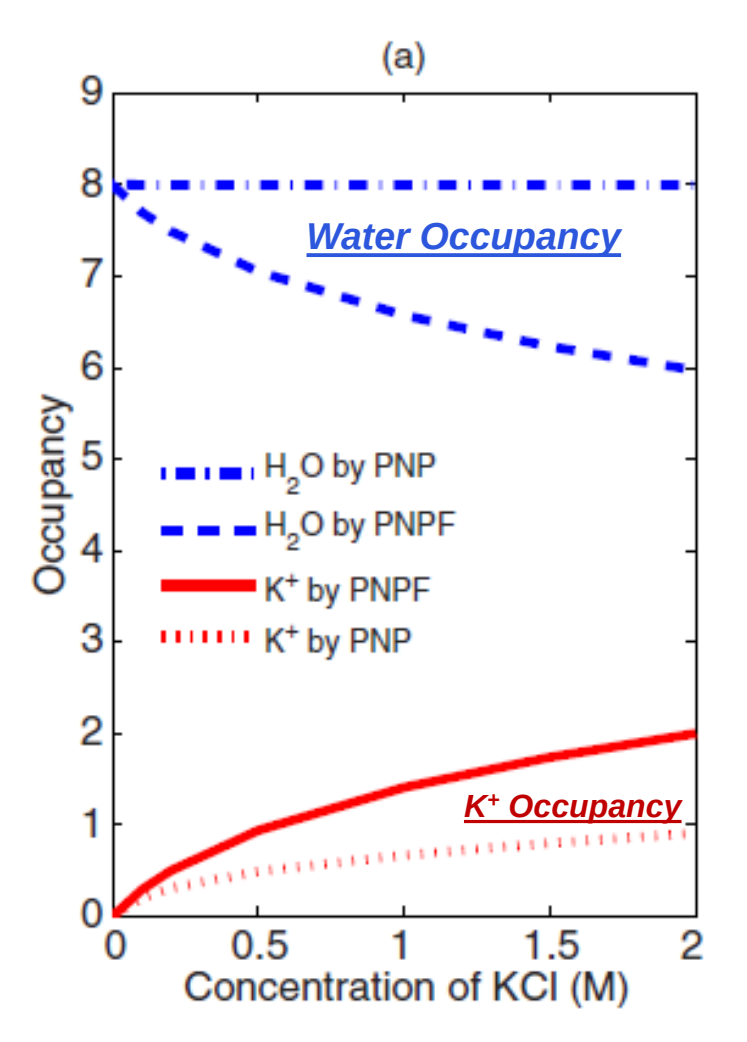


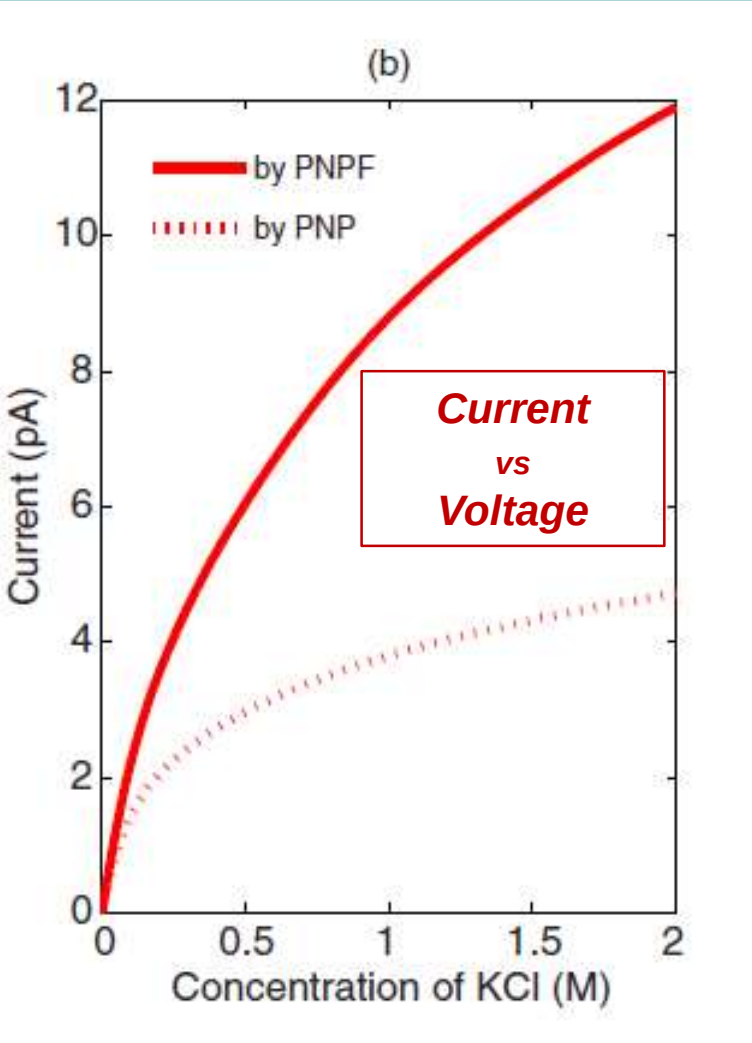
<u>Shielding has been ignored</u> in many papers
Results are often at one concentration or unspecified concentration,
as in most molecular dynamics

Channel is often described as a potential profile inconsistent with electrodynamics
as in classical rate models

Steric Effect is Large in *(crowded)* Gramicidin

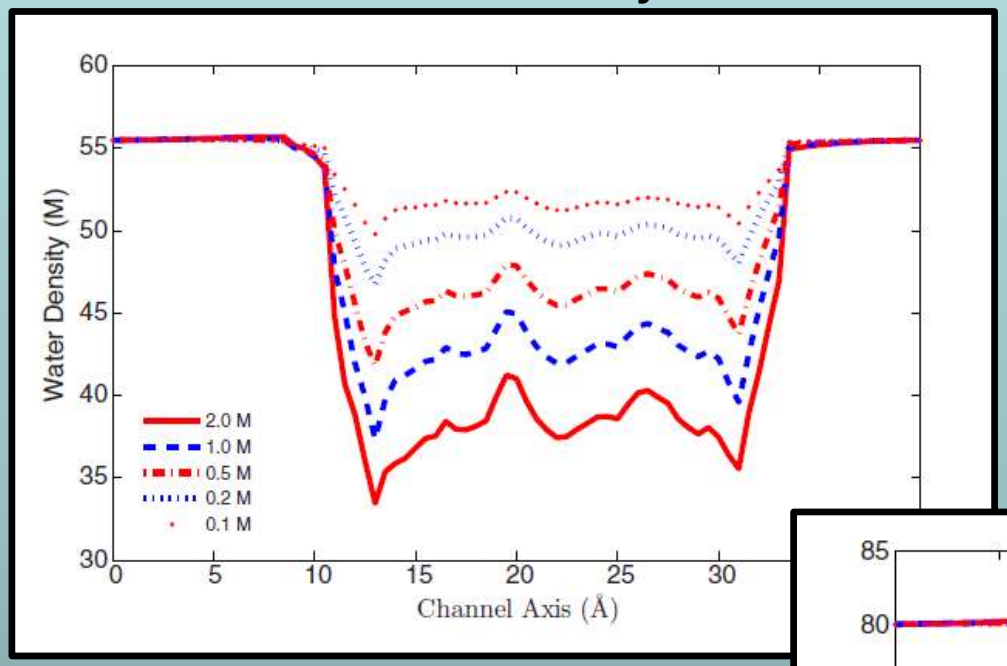
PNPF *vs* PNP



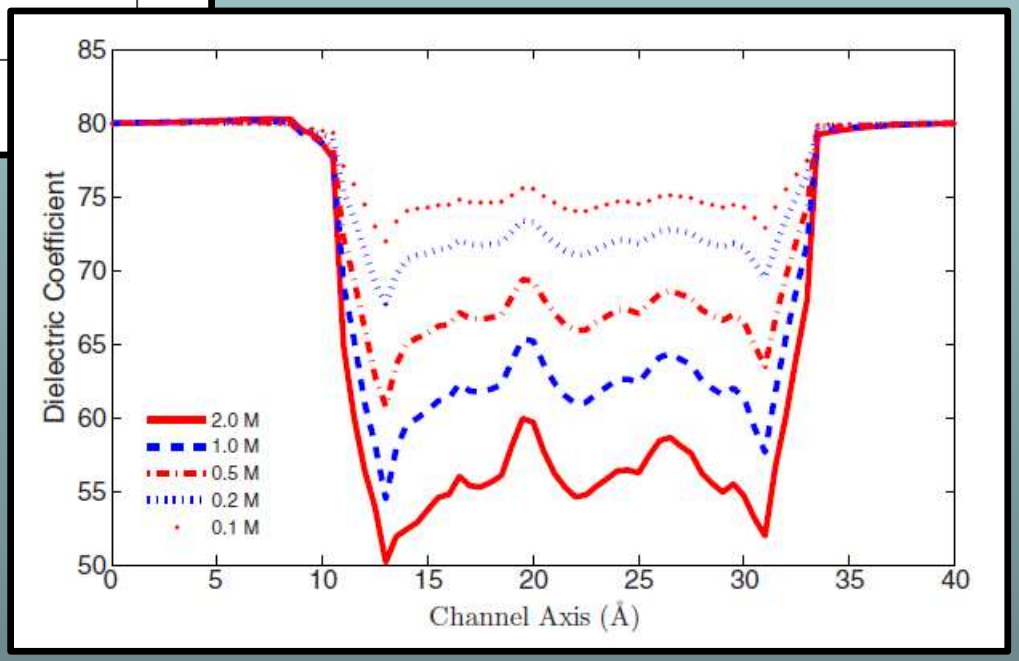


Inside Gramicidin

Water Density



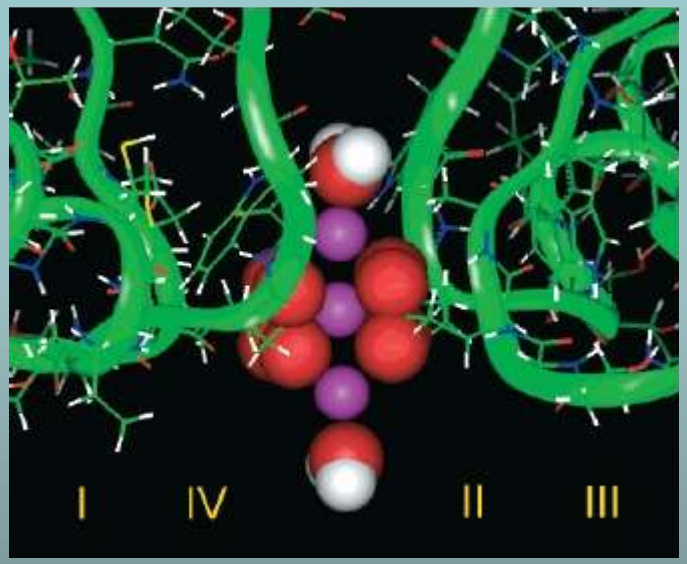
Dielectric Function an OUTPUT of model



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

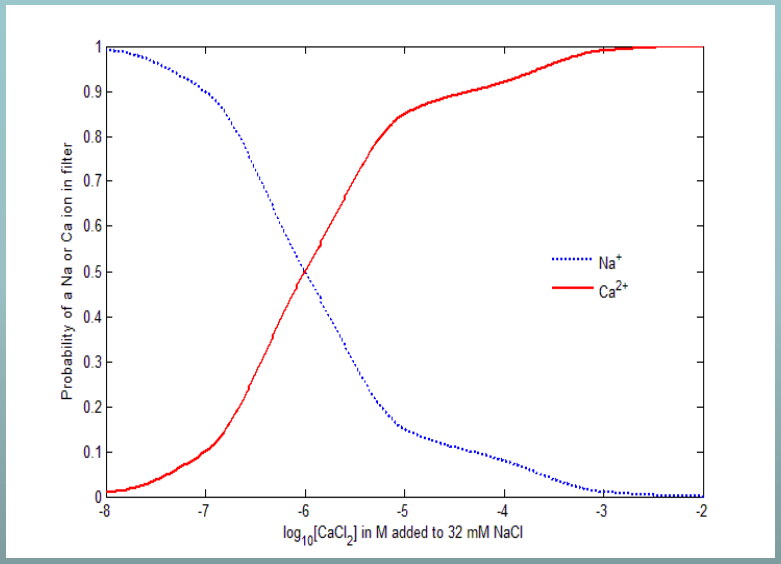
Cardiac Calcium Channel $Ca_V.n$

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

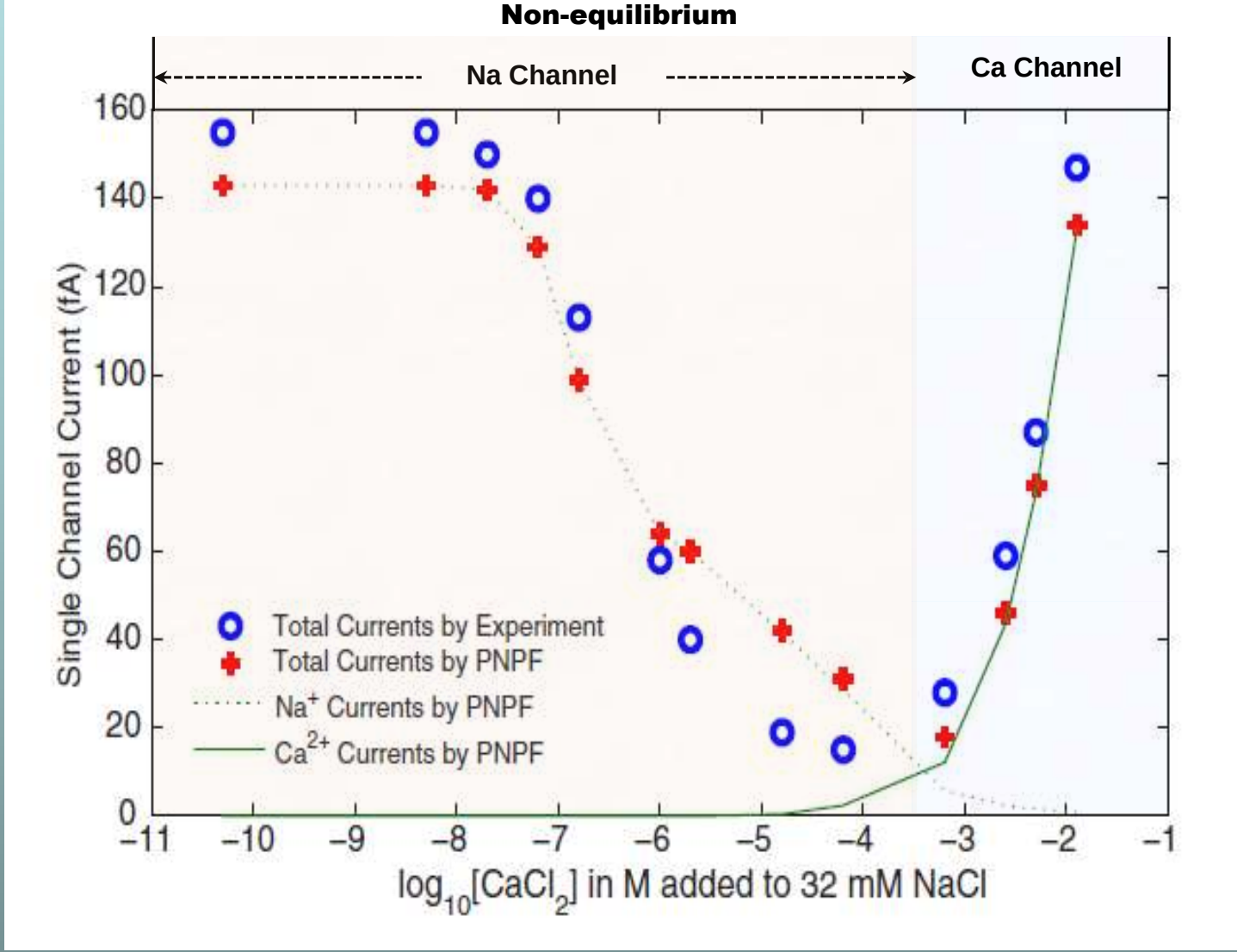
Binding Curve



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

Cardiac Calcium Channel $Ca_V1.n$

Experimental Signature *Anomalous** Mole Fraction

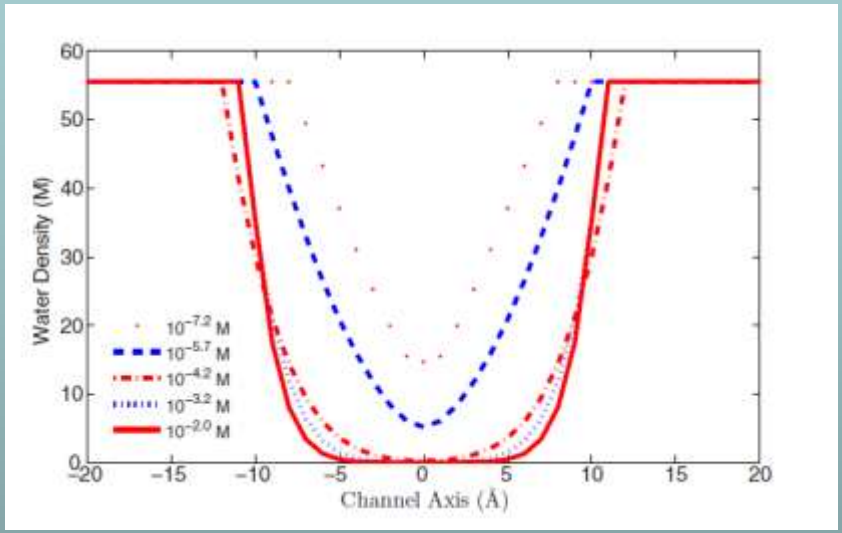


***Anomalous* because CALCIUM CHANNEL IS A SODIUM CHANNEL at $[CaCl_2] \cong 10^{-3.4}$**
Ca^{2+} is conducted for $[Ca^{2+}] > 10^{-3.4}$, but Na^+ is conducted for $[Ca^{2+}] < 10^{-3.}$

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

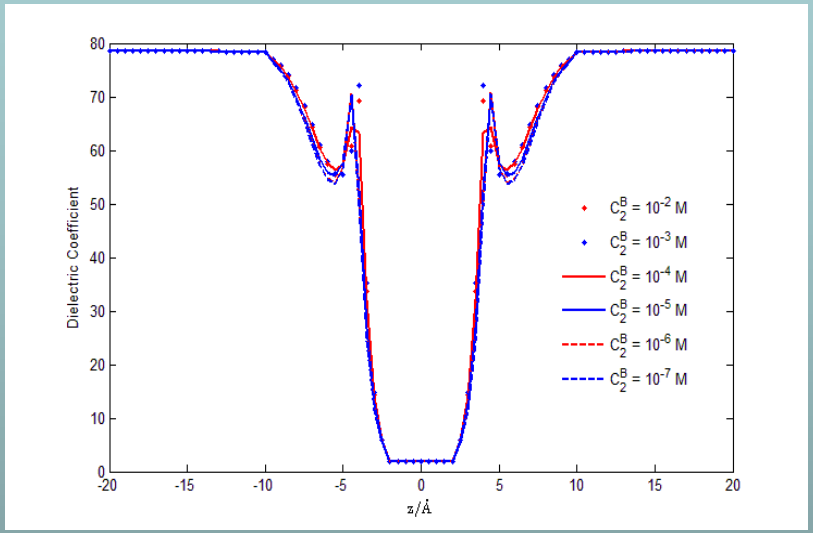
Inside the
Cardiac Calcium Channel
$Ca_V1.n$

Water Density



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

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



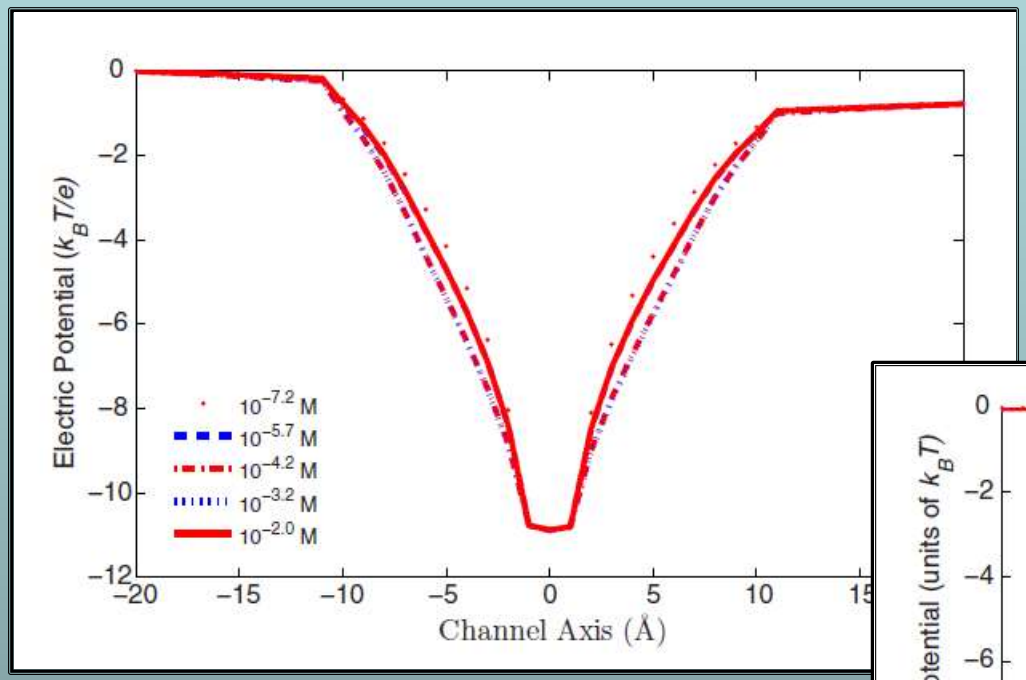
Liu & Eisenberg J Chem Phys 141(22): 22D532

Inside the

Cardiac Calcium Channel

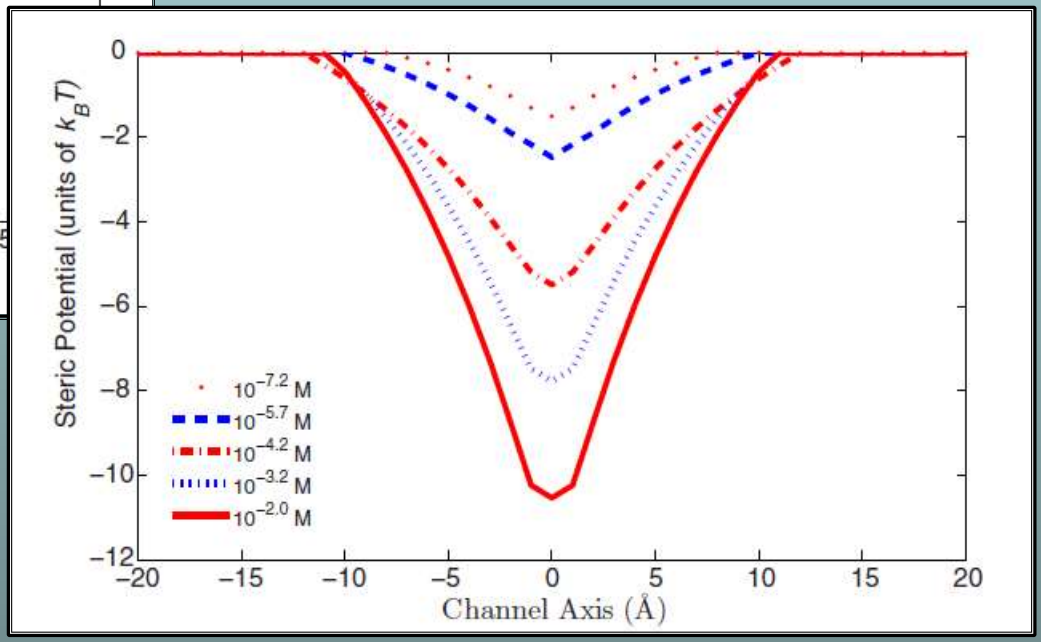
$Ca_V1.n$

Electric Potential



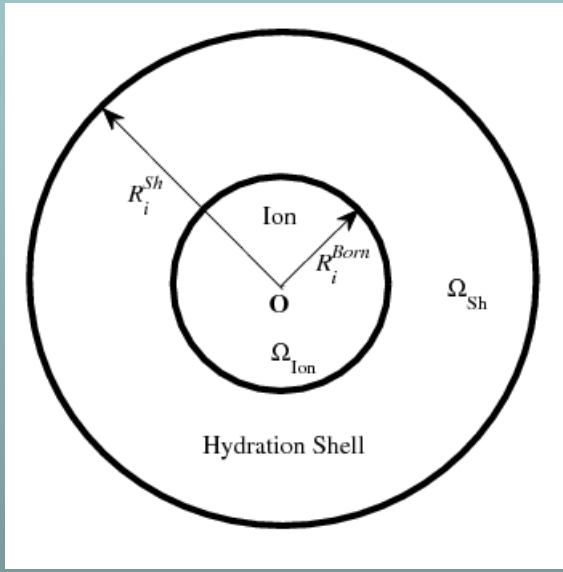
Steric Potential

Estimator of Crowding



Poisson Fermi Approach
to Bulk Solutions

Same equations, different model of nearby atoms



Bulk Solution

How well does the Poisson Fermi Approach for Bulk Solutions?

Same equations, different model of nearby atoms

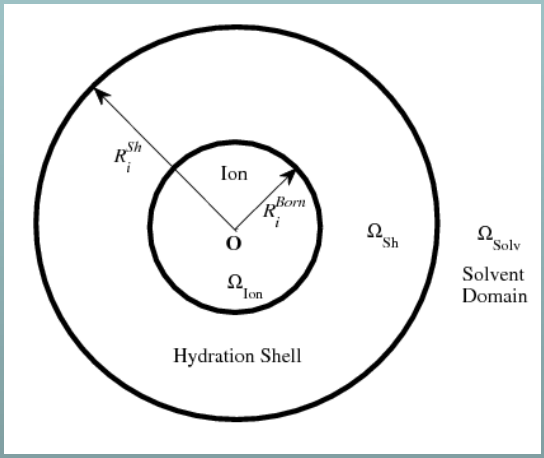
Occupancy is 18 Waters*

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



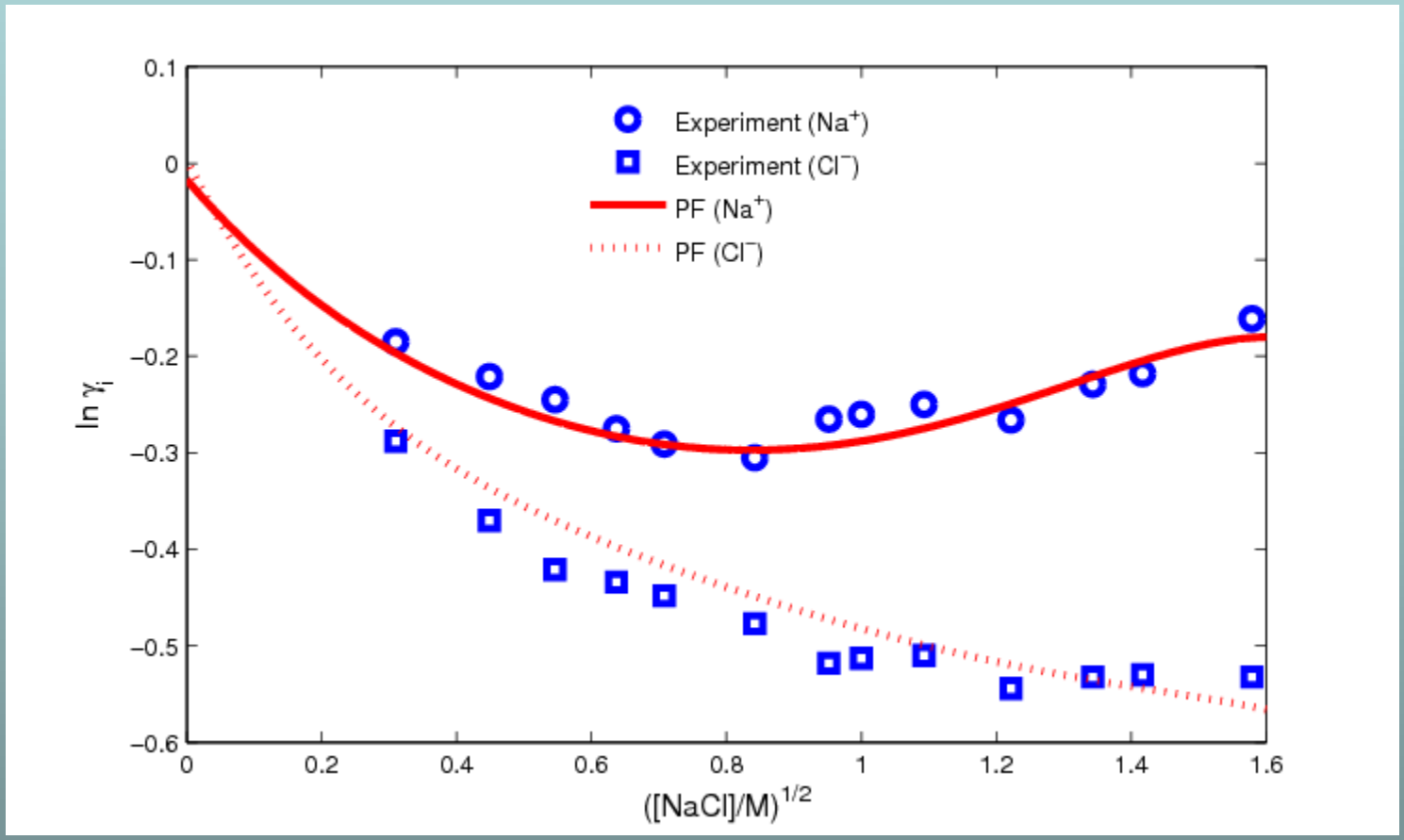
***Experimental Data on Occupancy**

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

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

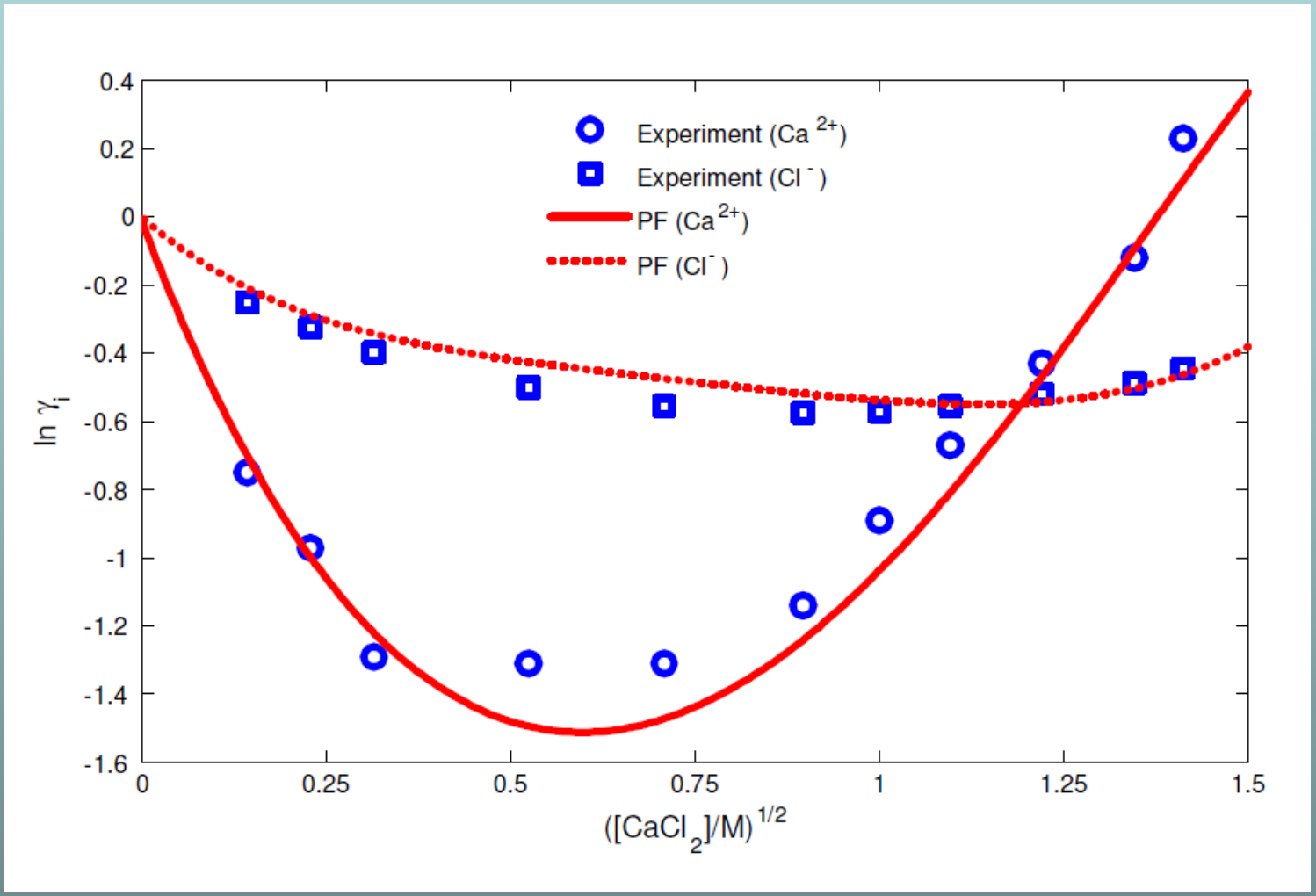
Activity Coefficients
Na^+ Cl^-

'normalized' free energy per mole



Activity Coefficients
Ca^{2+} Cl^-

'normalized' free energy per mole



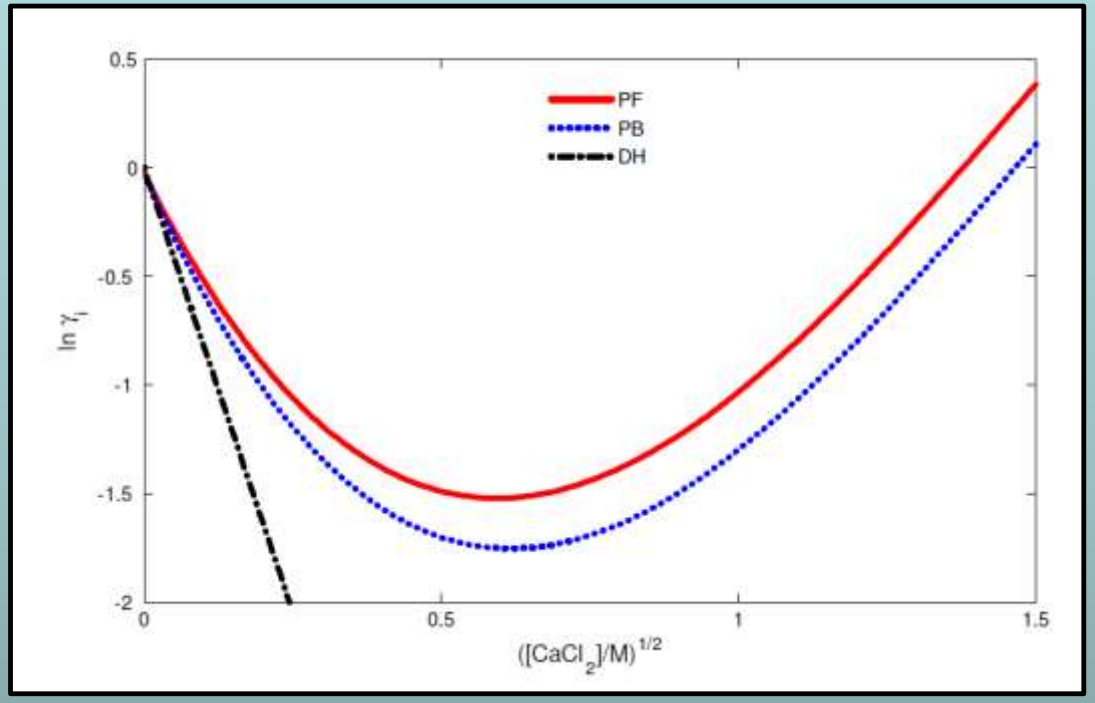
Activity Coefficients

have not done other ions or mixtures
yet

Conductance

*not **yet** done*
nor anomalous conductance
(uphill transport)

Debye-Huckel 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	

“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”

Physical Chemists

are

Frustrated

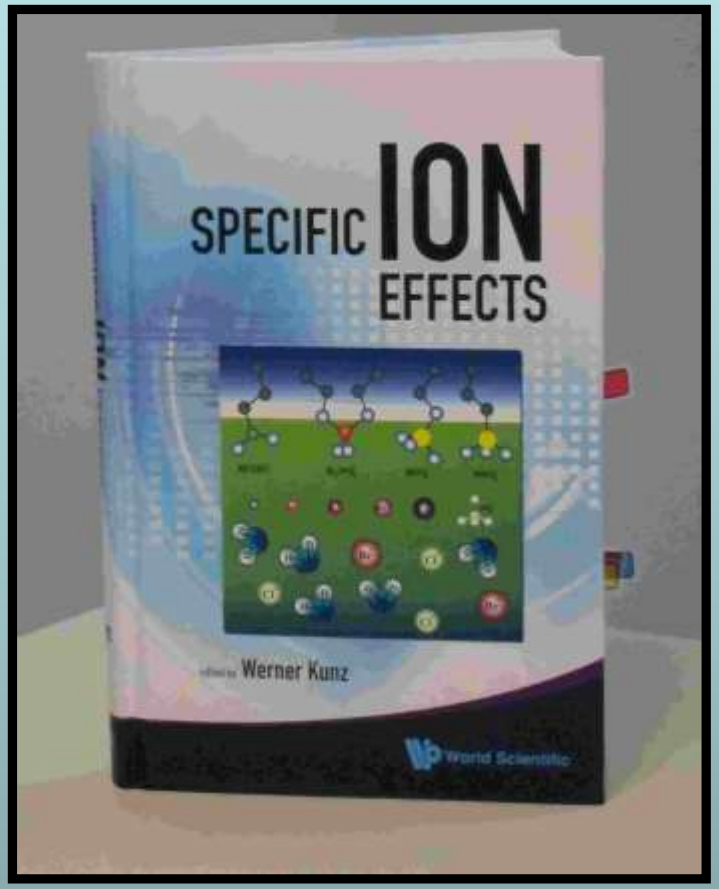
by

Real Solutions

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), emphasis added



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

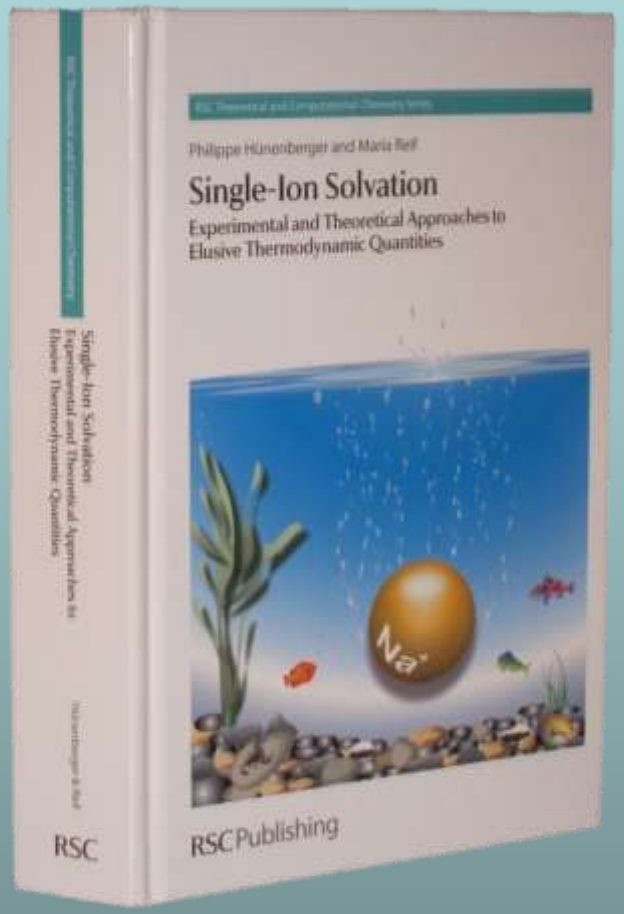
than to describe the

free energy

of even the simplest salt solutions

beyond a concentration of 0.1M or so."

Electrolytes are Complex Fluids



Hünenberger & Reif (2011)
"**Single-Ion Solvation**
… Approaches to **Elusive*** Thermodynamic Quantities"

After 690 pages and 2604 references, properties of

SINGLE Ions
are
Elusive*

because

Every Ion Interacts
with
Everything

*'elusive' is in the authors' choice in the title
but **emphasis** is added

Electrolytes are Complex Fluids

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

Ions

in a solution are a

Highly Compressible Plasma

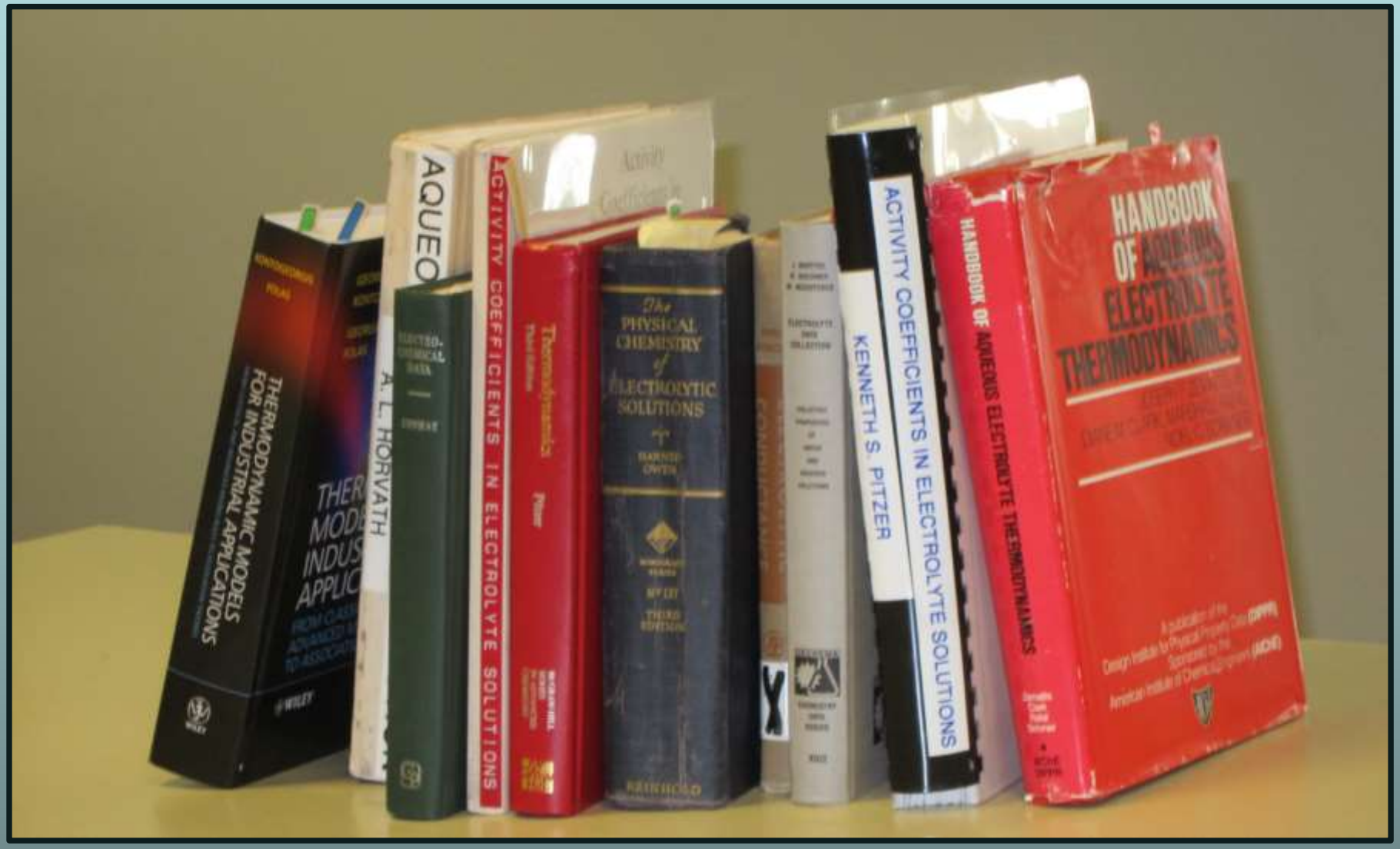
although the

Solution is Incompressible

Free energy of an ionic solution is mostly determined by the
Number density of the ions.
Density varies from 10^{-11} to 10^{1}M
in typical biological system of proteins, nucleic acids, and channels.

Learned from Doug Henderson, J.-P. Hansen, Stuart Rice, among others…Thanks!

Good Data


THERMODYNAMIC MODELS FOR INDUSTRIAL APPLICATIONS
A. L. HORVATH
ACTIVITY COEFFICIENTS IN ELECTROLYTE SOLUTIONS
The PHYSICAL CHEMISTRY of ELECTROLYTIC SOLUTIONS
KENNETH S. PITZER
ACTIVITY COEFFICIENTS IN ELECTROLYTE SOLUTIONS
HANDBOOK OF AQUEOUS ELECTROLYTE THERMODYNAMICS
HANDBOOK OF AQUEOUS ELECTROLYTE THERMODYNAMICS

Good Data
Compilations of Specific Ion Effect

1. ***>139,175 Data Points*** [Sept 2011] *on-line*
IVC-SEP Tech Univ of Denmark
http://www.cere.dtu.dk/Expertise/Data_Bank.aspx

2. Kontogeorgis, G. and G. Folas, *2009:*
Models for Electrolyte Systems. Thermodynamic
John Wiley & Sons, Ltd. 461-523.

3. Zemaitis, J.F., Jr., D.M. Clark, M. Rafal, and N.C. Scrivner, *1986,*
Handbook of Aqueous Electrolyte Thermodynamics.
American Institute of Chemical Engineers

4. Pytkowicz, R.M., *1979,*
Activity Coefficients in Electrolyte Solutions. Vol. 1.
Boca Raton FL USA: CRC. 288.

Where to start?

Why not
Compute all the atoms?

Computational Science Demands a New Paradigm

The field has reached a threshold at which better organization becomes crucial. New methods of verifying and validating complex codes are mandatory if computational science is to fulfill its promise for science and society.

Douglass E. Post and Lawrence G. Votta Physics Today 58:35

Calibration!*

AIChE Journal

Perspective

From discovery to data: What must happen for molecular simulation to become a mainstream chemical engineering tool

Edward J. Maginn

Volume 55, Issue 6
June 2009
Pages 1304–1310

First published: 7 May 2009 Full publication history

DOI: 10.1002/aic.11932 View/save citation

*not so new, really, just unpleasant

Mathematics Must Include Structure

and

Function

Variables of Function

are

Concentration

Flux

Membrane Potential

Current

Mathematics Must Include Structure

and

Function

Atomic Space = Ångstroms

Atomic Time = 10^{-15} sec

Cellular Space = 10^{-2} meters

Cellular Time = Milliseconds

Variables that are the function,

like

Concentration, Flux, Current

Multi-Scale Issues

Journal of Physical Chemistry C (2010)114:20719

Computational Scale	Biological Scale	**Ratio**
Time 10^{-15} sec	10^{-4} sec	**10^{11}**
Length 10^{-11} m	10^{-5} m	**10^{6}**

DEVICES DEPEND ON FINE TOLERANCES
parts must fit

Atomic and Macro Scales are BOTH used by channels because they are nanovalves
so atomic and macro scales must be
Computed and CALIBRATED Together

This may be impossible in all-atom simulations

Multi-Scale Issues

Journal of Physical Chemistry C (2010)114:20719

Computational Scale	Biological Scale	**Ratio**
Spatial Resolution	***Three Dimensional*** $(10^4)^3$	10^{12}
Volume 10^{-30} m^3	$(10^{-4}\ m)^3 = 10^{-12}\ m^3$	10^{18}

DEVICES DEPEND ON FINE TOLERANCES
parts must fit

Atomic and Macro Scales are BOTH used by channels because they are nanovalves
so atomic and macro scales must be
Computed and CALIBRATED Together

This may be impossible in all-atom simulations

Multi-Scale Issues

Journal of Physical Chemistry C (2010)114:20719

Computational Scale	Biological Scale	**Ratio**
Solute Concentration *including Ca^{2+} mixtures*	10^{-11} to 10^{1} M	**10^{12}**

DEVICES DEPEND ON FINE TOLERANCES
parts must fit

so atomic and macro scales must be
Computed and CALIBRATED Together

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Multi-Scale Issues

Journal of Physical Chemistry C (2010)114:20719

DEVICES DEPEND ON FINE TOLERANCES
parts must fit

Atomic and Macro Scales are BOTH used by channels because they are nanovalves
so atomic and macro scales must be

Computed and CALIBRATED Together

This may be impossible in all-atom simulations

All Life Occurs in Ionic Mixtures

in which $[Ca^{2+}]$ is important* as a control signal

Simulations must deal with

Multiple Components

as well as
Multiple Scales

This may be nearly impossible for ionic mixtures

because

'everything' interacts with 'everything else'
on both atomic and macroscopic scales
particularly when mixtures flow

*$[Ca^{2+}]$ ranges from 1×10^{-8} M inside cells to 10 M inside channels

FACTS

(1) Atomistic Simulations of Mixtures are extraordinarily difficult

because all interactions must be computed correctly

(2) All of life occurs in ionic mixtures like Ringer solution

(3) No <u>calibrated</u> simulations of Ca^{2+} are available.

because almost all the atoms present are water, not ions.

No one knows how to do them.

(4) Most channels, proteins, enzymes, and nucleic acids change significantly when $[Ca^{2+}]$ changes from its background concentration 10^{-8}M ion.

Uncalibrated Simulations
Vague
and
Difficult to Test

Uncalibrated Simulations

lead to

Interminable Argument

and

Interminable Investigation

thus,

to Interminable Funding

and so

Uncalibrated Simulations Are Popular

The End

Any Questions?

Mathematics describes only a little of Daily Life

But

Mathematics* Creates

our

Standard of Living

**e.g., Electricity, Computers, Fluid Dynamics, Optics, Structural Mechanics, …..*

Mathematics Creates

our

Standard of Living

Mathematics replaces Trial and Error with Computation

**e.g., Electricity, Computers, Fluid Dynamics, Optics, Structural Mechanics, …..*

Mathematics is Needed

to

Describe and Understand

Devices

of

Biology and Technology

How can we use mathematics to describe biological systems?

I believe some biology is

Physics ‘as usual’

‘Guess and **Check’**

But you have to know which biology!

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