Ions in Solutions

Liquid Plasma
of
Chemistry & Biology

Bob Eisenberg

Colloquium
Department of Chemistry
Illinois Institute of Technology

February 27, 2019

Thanks to David Minh
For inviting me!

Much of Chemistry
All of Biology
occurs in
Ionic Solutions

‘Seawater’ is the liquid of life

Seawater and liquids of life
are
Concentrated Mixtures
of
sodium, potassium, calcium ions

Physical Chemists are Frustrated by Real Solutions

Classical Debye-Hückel,
Poisson Boltzmann
(even nonlinear) are
Inadequate Approximations

Fundamental Property of Solutions is Screening

(= shielding)

Charges on Ions move

because

Ions are in a liquid

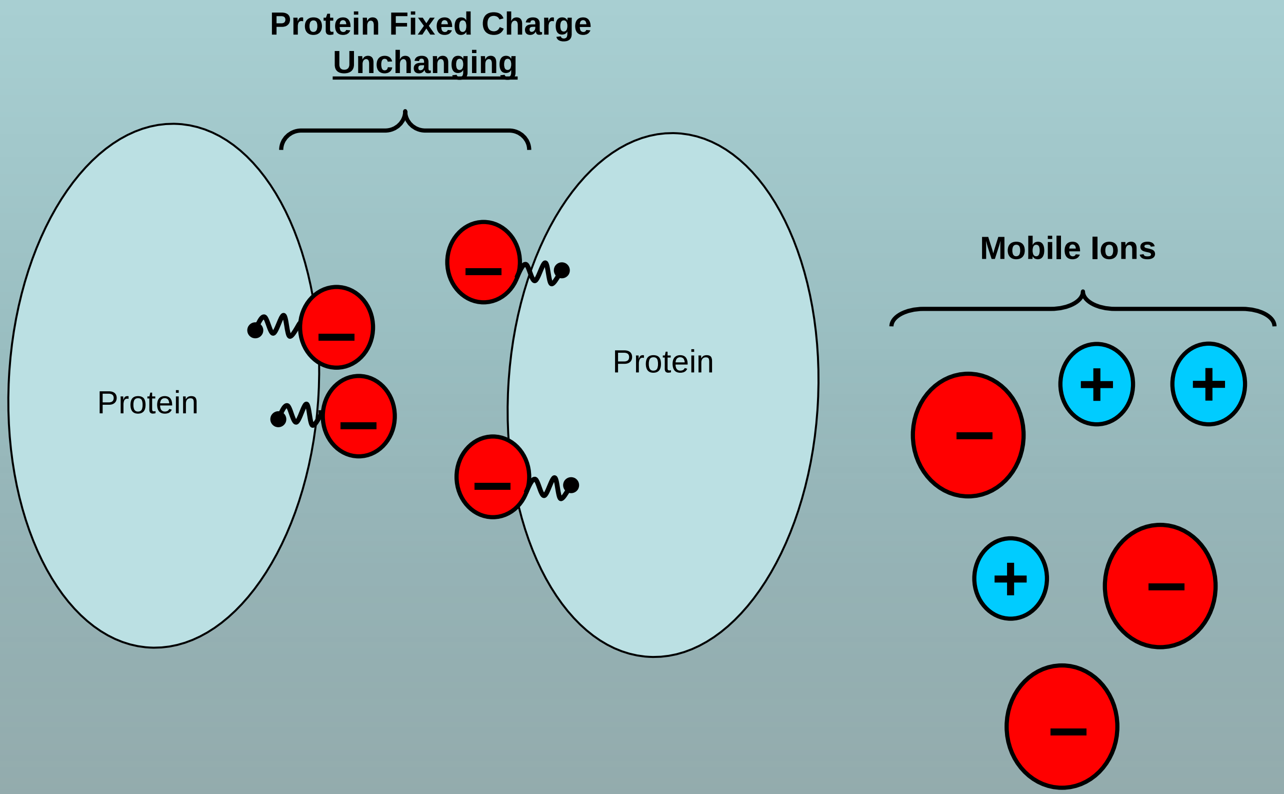
When a charge is added
to an ionic solution,

the other charge rearrange to form an
Ionic Atmosphere

Rearrangement is called
Screening

Chemists' frustration is that
Debye-Hückel Poisson Boltzmann are
inadequate theories of screening

Fixed and Mobile Charges



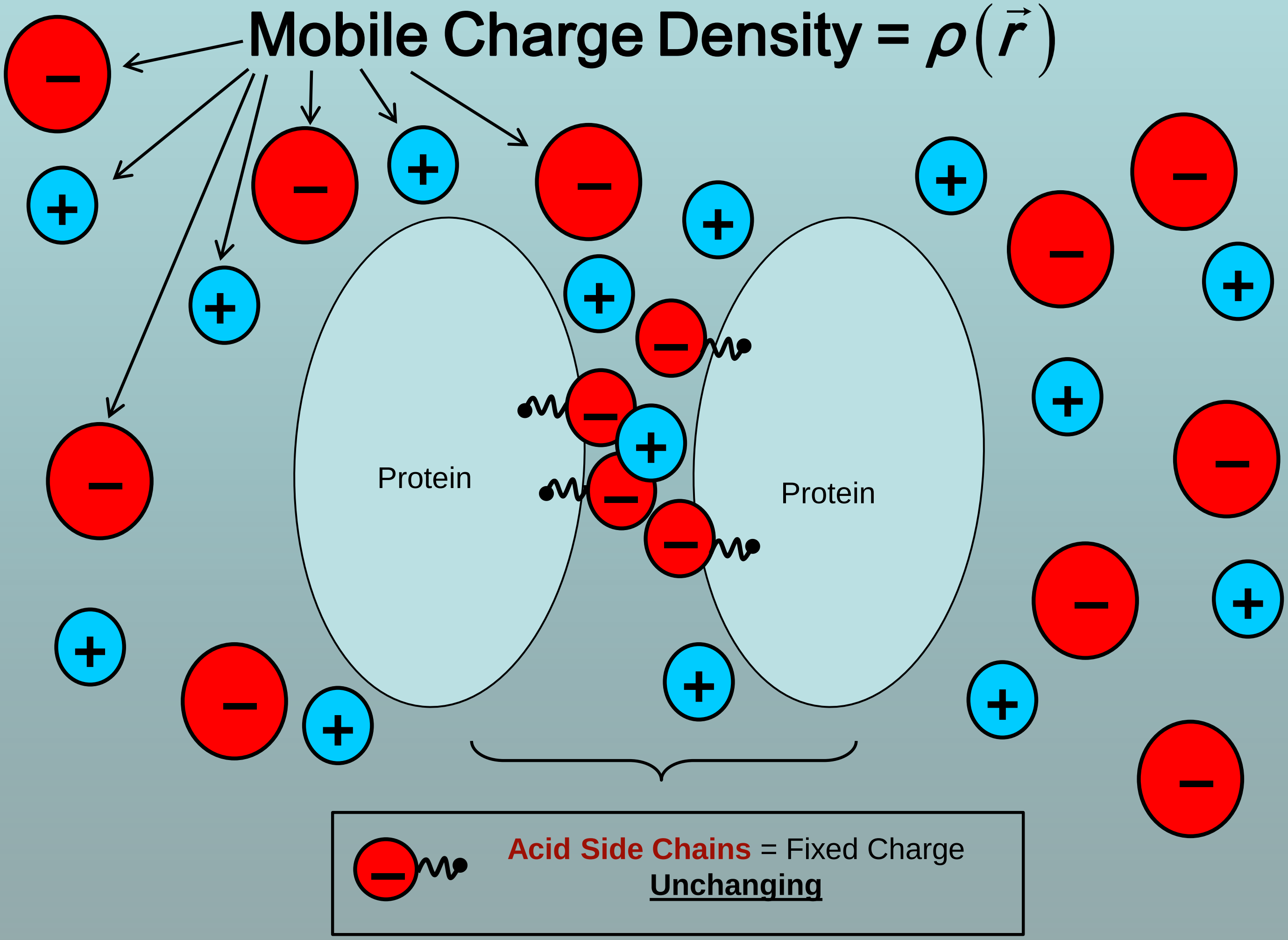
Protein Fixed Charge
<u>Unchanging</u>

Mobile Ions

Protein

Protein

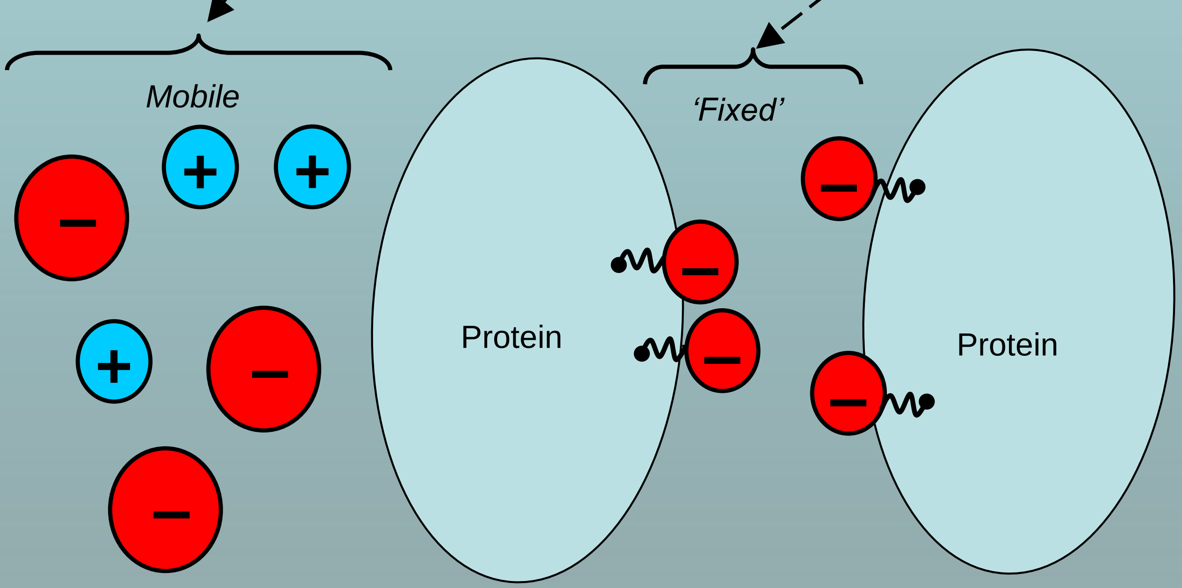
Mobile Charge Density = $\rho(\vec{r})$



Acid Side Chains = Fixed Charge
Unchanging

Coulomb's Law

$$U\left(\vec{r}_{obs}\right) = \int \frac{\overbrace{\rho_{mobile}\left(\vec{r}_{mobile}\right) d\vec{r}_{mobile}}^{\text{Mobile Ions...Screening}}}{4\pi\left|\vec{r}_{obs} - \vec{r}_{mobile}\right|} + \sum_{i} \frac{\overbrace{\rho_{i,\,fixed}\left(\vec{r}_{fixed}\right)}^{\text{Protein Fixed Charge } \underline{\text{Unchanging}}}}{4\pi\left|\vec{r}_{obs} - \vec{r}_{fixed}\right|}$$



When a charge is added
to an ionic solution,

the other charge rearrange to form an Ionic Atmosphere

Rearrangement is called
Screening

Screening depends on Concentration and Composition

$\mathbf{Na}^{+} \neq \mathbf{K}^{+}$

Debye-Hückel, Poisson Boltzmann

__Poor Approximations__

to pure NaCl > 25 mM concentration

Life occurs in ~ 135 mM NaCl

Concentrations reach 20 M near DNA

Solid NaCl is ~ 40 M

Debye-Hückel, Poisson Boltzmann

__Fail__

for

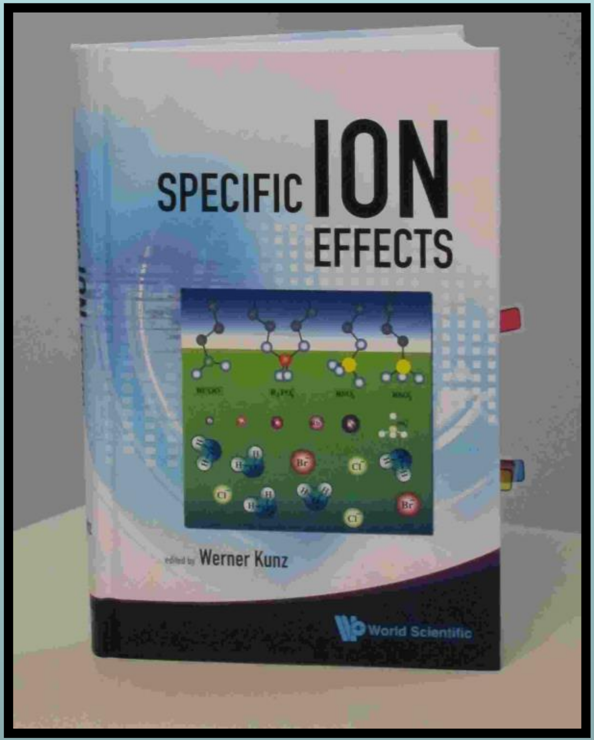
Asymmetrical electrolytes like calcium chloride $\mathrm{Ca_2Cl}$

Mixtures like all intra- and extra-cellular solutions in biology

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)



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

Werner Kurz

"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”

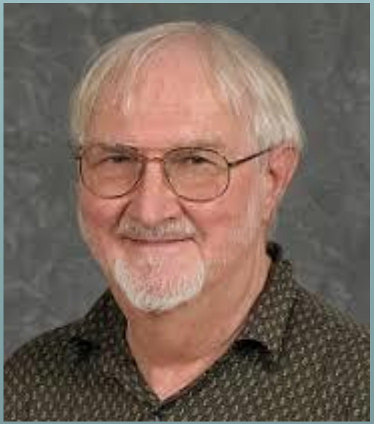
slight paraphrase of p. 125 of Barthel, Krienke, and Kunz, Springer, 1998

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

“ …. 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.***

Good Data


KONTOGEORGIS FOLAS
THERMODYNAMIC MODELS FOR INDUSTRIAL APPLICATIONS
WILEY
AQUEO
A. L. HORVATH
ELECTRO-CHEMICAL DATA
CONWAY
ACTIVITY COEFFICIENTS IN ELECTROLYTE SOLUTIONS
Activity Coefficients in
Thermodynamics Third Edition
Pitzer
McGRAW-HILL SERIES IN ADVANCED CHEMISTRY
The PHYSICAL CHEMISTRY of ELECTROLYTIC SOLUTIONS
HARNED OWEN
MONOGRAPH SERIES Nº 137
THIRD EDITION
REINHOLD
J. BARTHEL R. BUCHNER M. MÜNSTERER
ELECTROLYTE DATA COLLECTION
DIELECTRIC PROPERTIES OF WATER AND AQUEOUS SOLUTIONS
DECHEMA CHEMISTRY DATA SERIES
XII/2
KENNETH S. PITZER
ACTIVITY COEFFICIENTS IN ELECTROLYTE SOLUTIONS
HANDBOOK OF AQUEOUS ELECTROLYTE THERMODYNAMICS
JOSEPH F. ZEMAITIS, JR.
DIANE M. CLARK, MARSHALL RAFAL
NOEL C. SCRIVNER
A publication of the Design Institute for Physical Property Data (DIPPR)
Sponsored by the American Institute of Chemical Engineers (AIChE)
Zemaitis Clark Rafal Scrivner
AIChE DIPPR

Ions in Water are the Liquid of Life. They are not ideal solutions

Good Data

but

Poor Theories

and

Simulations!!

Chemically Specific Properties

of Ionic Solutions come from

Interactions

Determined Mostly by the

Finite Size of Ions

Good Data

Compilations of Specific Ion Effect

1. ***>139,175 Data Points*** *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.

Ions are Different

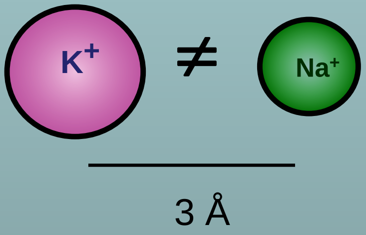
because

Diameter Matters

Ions are NOT Ideal Gases

Potassium K^+ and Na^+ Sodium are NOT the same

Potassium K^+ $\neq$ Na^+ Sodium



In solutions of point particles $K^+ = Na^+$

Ions in Water are the Liquid of Life. They are not ideal solutions

Chemically Specific Properties

of Ionic Solutions come from

Interactions

Determined Mostly by the

Finite Size of Ions

Good Data

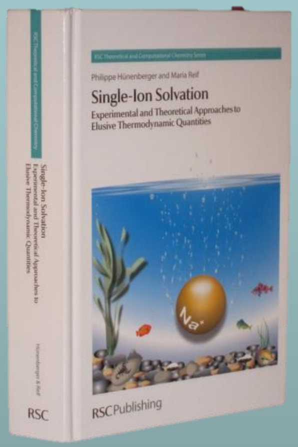
but

Poor Theories and Simulations!!

IONIC SOLUTIONS
are
COMPLEX FLUIDS
not ideal gases

Treating a
Complex Fluid
as if it were a
Simple Fluid
will produce
Elusive Results
because
Every Ion Interacts
with
Everything

After 690 pages and 2604 references,



“Single-Ion Solvation … Elusive* ”
Hünenberger & Reif, 2011
*** ‘elusive’ is in the title!**

It is not surprising that

Inconsistent Treatments

of ionic solutions

have been so

Unsuccessful

despite more than a century of work by fine scientists and mathematicians

Ions in Water are the Liquid of Life

They are not ideal solutions

Everything
Interacts
with
Everything

For Modelers and Mathematicians

Tremendous Opportunity for Applied Mathematics

Chun Liu's Energetic Variational Principle

EnVarA

Theory of Stochastic Processes
and
Thermodynamics

Do not deal easily with strong interactions

because

Interactions are not perturbations

Another Talk
for
mathematicians

**Usual Stochastic Processes and Law of Mass Action
are not good enough**

We start with Langevin equations of <u>charged</u> particles

Opportunity and Need

Simplest stochastic trajectories
are
Brownian Motion of <u>Charged</u> Particles

Einstein, Smoluchowski, and Langevin <u>ignored charge</u>
and therefore
do not describe Brownian motion of ions in solutions

We use

Theory of Stochastic Processes

to go

from Trajectories to Probabilities

Once we learn to count Trajectories of Brownian Motion of Charge,
we can count trajectories of <u>Molecular Dynamics</u>

Schuss, Nadler, Singer, Eisenberg

Langevin Equations

Positive ***cat*ion**,
e.g., p = Na$^+$

$$\ddot{x}_k^p - \frac{f_k^p(\tilde{x};q_k)}{m} = -\gamma\,\dot{x}_k^p + \sqrt{\frac{2\gamma kT}{m}}\,\dot{w}_k^p$$

Negative ***an*ion**,
e.g., n = Cl$^-$

$$\underbrace{\ddot{x}_k^n - \frac{f_k^n(\tilde{x};q_k)}{m}}_{\text{Newton's Law}} = \underbrace{-\gamma\,\dot{x}_k^n + \sqrt{\frac{2\gamma kT}{m}}\,\dot{w}_k^n}_{\text{Friction \& Noise}}$$

Electric Force

from **all charges** including
Permanent charge of **Protein,**
Dielectric Boundary charges,
Boundary condition charge

Schuss, Nadler, Singer, Eisenberg

Electric Force from **Poisson Equation**

not assumed

Excess
'Chemical'
Force

Electric Force
from **all charges** including
Permanent charge of **Protein,**
Dielectric Boundary charges,
Boundary condition charge,
MOBILE IONS

$$f_k^{p}(\vec{x}) - f_{xs} = \overbrace{q_k(\vec{x})\,\mathrm{div}\left(e\varepsilon_0\varepsilon(\vec{x})\,\vec{E}\right)} = \frac{e}{\varepsilon_0}\boldsymbol{P}(\vec{x}) + \frac{e}{\varepsilon_0}\sum_i z_i\boldsymbol{\rho}_i(\vec{x})$$

Total Force

Implicit Solvent
'Primitive' Model

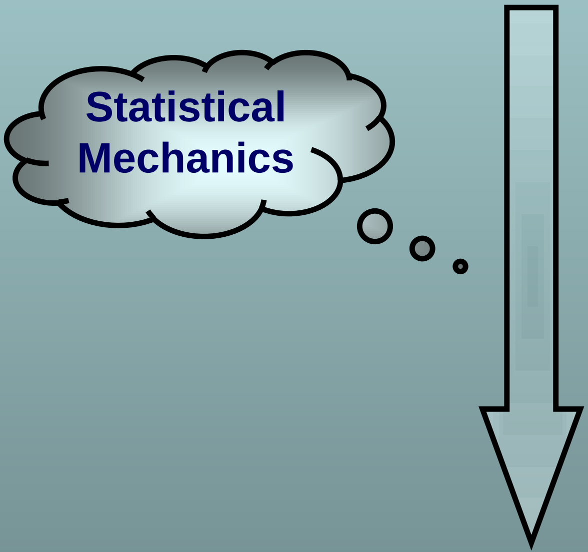
Schuss, Nadler, Singer, Eisenberg

Equilibrium Thermodynamics

Configurations

Boltzmann Distribution

$$\lim N, V \to \infty$$



Thermodynamics

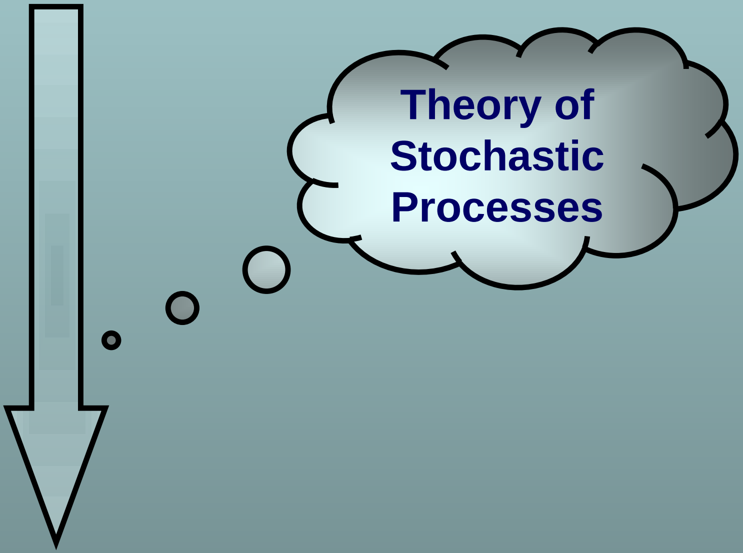
Nonequilibrium

Schuss, Nadler, Singer & Eisenberg

Trajectories

Fokker Planck Equation

Finite OPEN System



Device Equation

From Trajectories to Probabilities
in Diffusion Processes

‘Life Work’ of Ze’ev Schuss

Dept of Mathematics, Tel Aviv University

Eisenberg helped with some chemical and biological applications

1) Eisenberg, Kłosek, and **Schuss** J. Chem. Phys., 1995, 102, pp. 1767-1780
2) Barkai, Eisenberg, and **Schuss** Physical Review E, 1996, 54, (2), pp. 1161-1175
3) **Schuss**, Nadler, and Eisenberg Phys Rev E Stat Nonlin Soft, 2001, 64, pp. 036116
4) **Schuss**, Nadler, and Eisenberg Physical Review E, 2001, 64, pp. 036116
5) Nadler, **Schuss**, Singer and Eisenberg Nanotechnology, 2003, 3, pp. 439
6) Nadler, **Schuss**, Hollerbach, and Eisenberg Physical Review, 2004, 70, pp. 051912
7) Nadler, **Schuss**, Singer, Eisenberg, J Physics: Cond Matter, 2004, 16, pp. S2153
8) Singer, **Schuss**, Nadler and Eisenberg Phys Rev E 2004, 70 pp. 061106
9) Singer, **Schuss,** Nadler and Eisenberg in ‘Fluctuations and Noise in Biological, Biophysical, and Biomedical Systems II 5467’ (SPIE Proc., 2004), pp. 345-358
10) Singer, **Schuss,** and Eisenberg, J Statistical Physics, 2005, 119, (5/6), pp. 11
11) Singer, **Schuss**, Holcman, and Eisenberg, J Statistical Physics, 2006, 122, pp. 437

From Trajectories to Probabilities

Sum the trajectories

Sum satisfies Fokker-Planck equation

$$\boxed{0=\sum_j \mathrm{L}_j^p\, p(\tilde{x},\tilde{v})+\sum_j \mathrm{L}_j^n\, p(\tilde{x},\tilde{v})}$$

with Fokker Planck Operator

$$\boxed{\mathrm{L}_j^c\, p=-v_j^c\cdot\nabla_{x_j^c}\, p+\nabla v_j^c\cdot\left(\gamma v_j^c-f_j^c\big/m_j^c\right)p+\nabla\cdot\nabla_{v_j^c}\,\frac{\gamma kT}{m_j^c}\,p}$$

Coordinates are positions and velocities of N particles in 12N dimensional phase space

Main Result of Theory of Stochastic Processes

$p(\tilde{x},\tilde{v})=\Pr\left\{\{x,v\}_{j=1}^{2N}\right\}=$ ***Joint*** probability density of position and velocity

Schuss, Nadler, Singer, Eisenberg

Conditional PNP

Electric Force $\nabla\bar{\phi}$ depends on Conditional Density of Charge

$$\nabla_y \cdot \left[\frac{\varepsilon_0\varepsilon(y)}{e}\nabla_y\bar{\phi}(y|x)\right] = \boldsymbol{P}(y) + \overbrace{\rho_+(y|x) - \rho_-(y|x)}$$

Closure Needed
'Guess and Check'

Permittivity, Dielectric Coefficient,
Charge on Electron

Channel Protein

Nernst-Planck gives UNconditional Density of Charge

$$\nabla_y \cdot \left[\frac{1}{m\gamma(x)}\rho_+(x)\left[e\nabla_y\bar{\phi}(y|x)\Big|_{y=x} - (\text{Other Forces})\right]\right] = 0$$

Mass

Friction

Schuss, Nadler, Singer, Eisenberg

Here is where we guess!

Theory of Stochastic Processes
and
Thermodynamics
Do not deal easily with strong interactions
because
Interactions are not perturbations

Usual Stochastic Processes and Law of Mass Action
are not good enough

A Nonlocal Poisson-Fermi Model

for Electrolyte Solutions

Crucial Guess by

Jinn Liang Liu

劉晉良

1) J Comp Phys (2013) 247:88
2) J Phys Chem B (2013) 117:12051
3) J Chem Phys (2014) 141: 075102
4) J Chem Phys, (2014) 141: 22D532
5) Physical Review E (2015) 92: 012711
6) Chem Phys Letters (2015) 637: 1
7) J Phys Chem B (2016) 120: 2658
8) Physical Review E (2016), 94 012114
9) Molec Math Bio (2017) 5: 116
10) J Chem Phy (2018) 148: 054501
11) J Chem Phy (2018) 148: 054501

$\left.\right\}$ with Bob Eisenberg

Motivation

Largest Effect
of
Crowded Charge
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 when mixtures and divalents are present*

Motivation

Natural Description of Crowded Charge

is a

Fermi Distribution

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

because it describes

Saturation

in a simple way

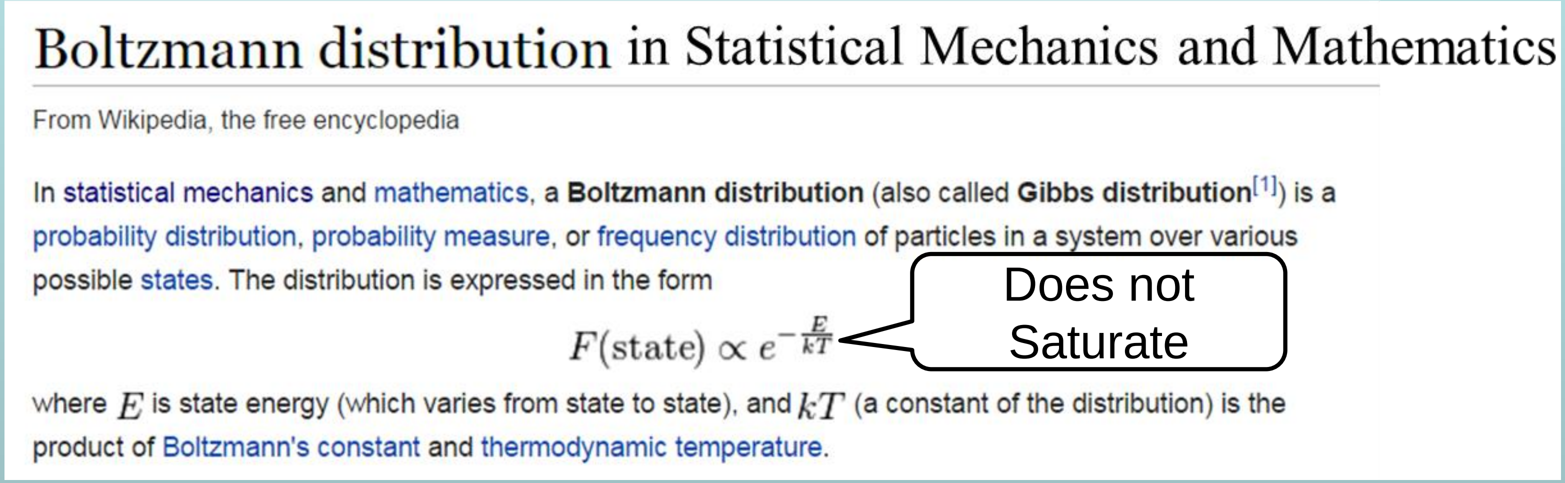
used throughout
Physics
and
Biophysics, ***where it has a different name!***

Simulating saturation by interatomic repulsion (Lennard Jones) is a significant mathematical challenge

to be side-stepped if possible

1) Eisenberg, Hyon and Liu (2010). J Chem Phys 133: 104104
2) Hyon, Fonseca, Eisenberg and Liu. (2012)
Discrete & Continuous Dynamical Systems Series B (DCDS-B) 17: 2725
3) Hyon, Eisenberg, and Liu
Communications in Mathematical Sciences (2011), 9: 459
4)) Hyon, Eisenberg, and Liu
Mathematical Methods in the Applied Sciences, 2014, 37: 952

Interdisciplinary Confusion



Boltzmann distribution in Statistical Mechanics and Mathematics

From Wikipedia, the free encyclopedia

In statistical mechanics and mathematics, a **Boltzmann distribution** (also called **Gibbs distribution**[1]) is a probability distribution, probability measure, or frequency distribution of particles in a system over various possible states. The distribution is expressed in the form

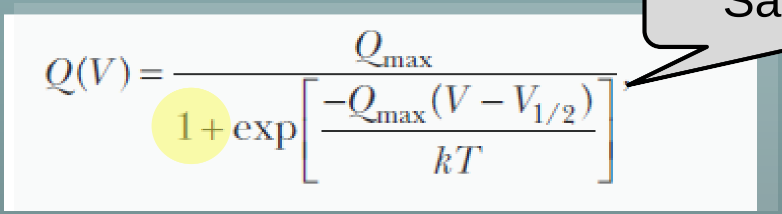
$$F(\text{state}) \propto e^{-\frac{E}{kT}}$$

where E is state energy (which varies from state to state), and kT (a constant of the distribution) is the product of Boltzmann's constant and thermodynamic temperature.

Does not Saturate

Boltzmann distribution in Physiology
Hodgkin & Huxley, 1948, 1953

Bezanilla and Villalba-Galea J. Gen. Physiol. (2013) 142: 575–578



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

Saturates!

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.

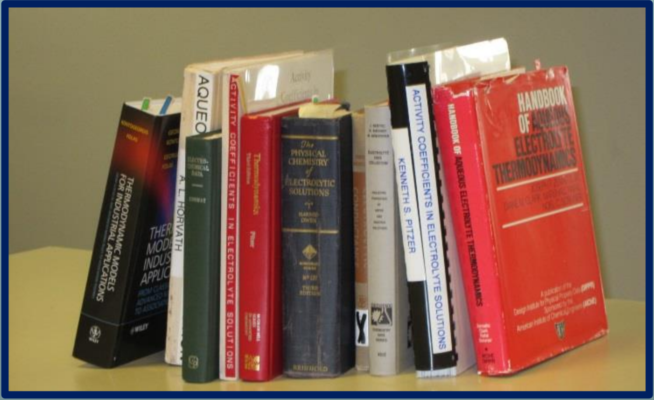
Challenge

Can Simplest Fermi Approach

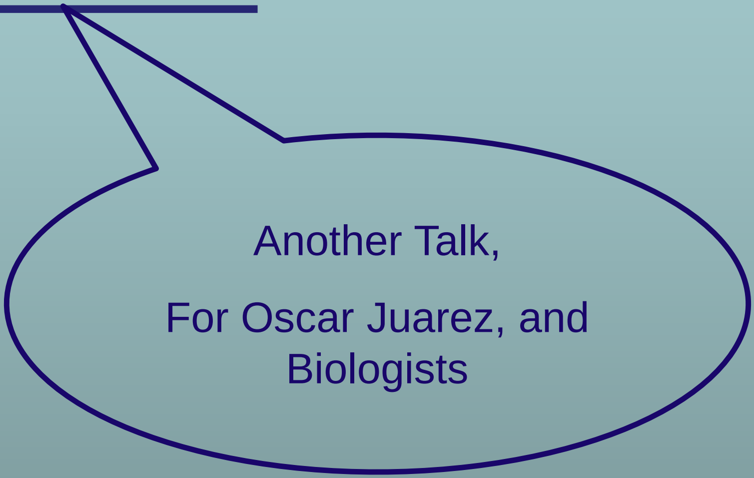
- **Describe ion channel <u>selectivity</u> and permeation?**
- **Describe non-ideal properties of <u>bulk solutions</u>?**

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

Classical Treatments of Chemical Complexities



Fermi Approach Fits Data from Bulk Solutions and Ion Channels



Another Talk,

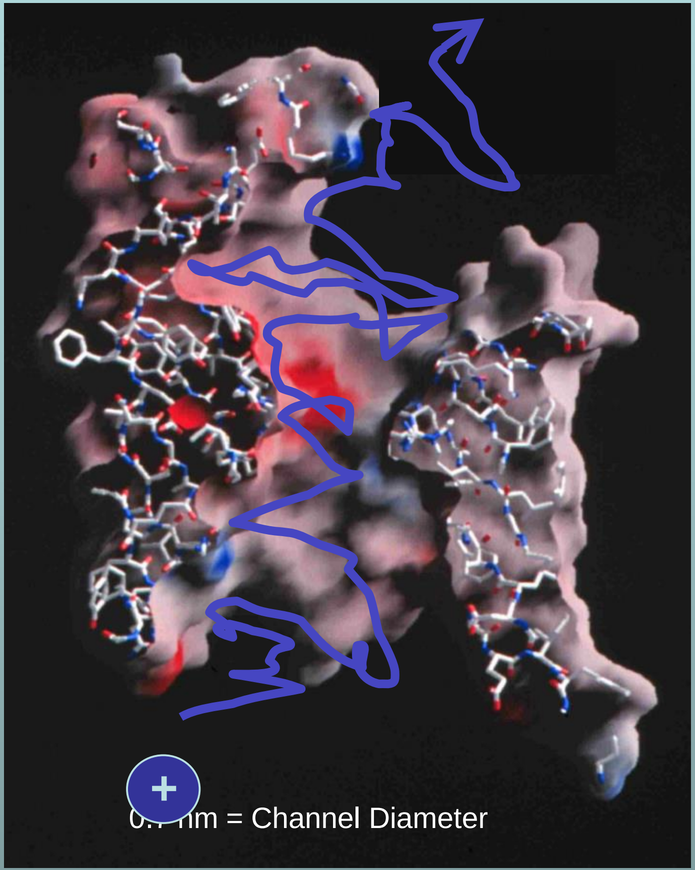
For Oscar Juarez, and Biologists

Ion Channels are the **Valves of Cells**

Ion Channels are Devices* that Control Biological Function

Selectivity

Different Ions carry Different Signals



~30 Å

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

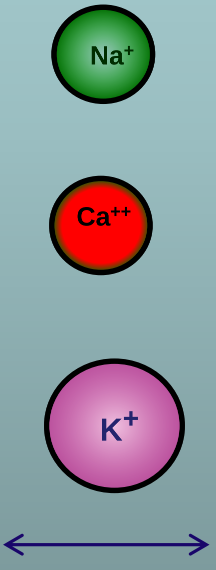
Figure of ompF porin
by Raimund Dutzler

Ions in Water

are the

Liquid of Life

Hard Spheres



3 Å

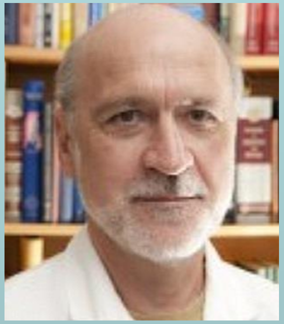
*Devices as defined in engineering , with inputs and outputs, and power supplies.

Calcium Channel of the Heart

JGP
The Journal of General Physiology
Vol 133 • No 5 • May 2009

www.jgp.org

Dezső Boda



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.

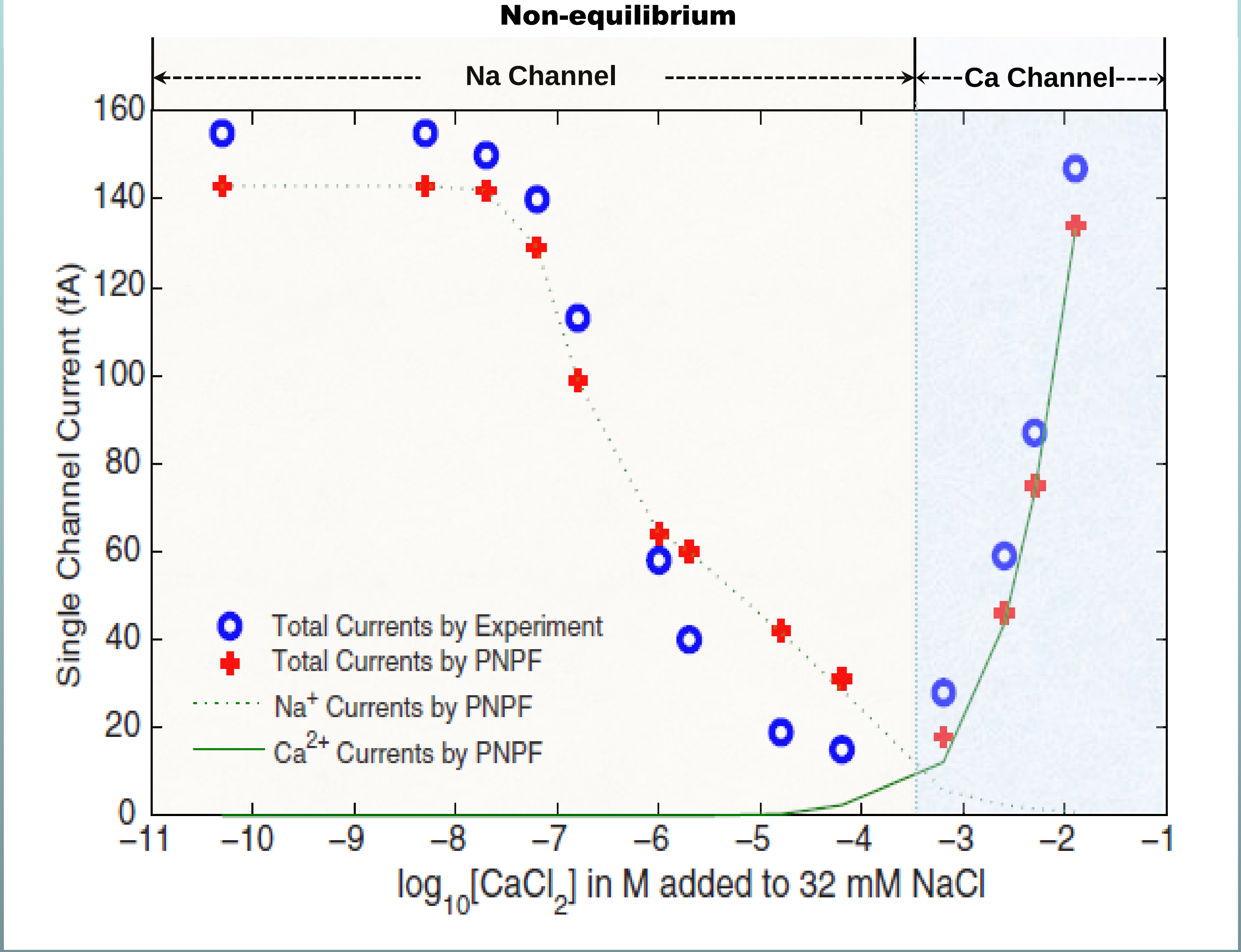
Boda, D., M. Valisko, B. Eisenberg, W. Nonner, D. Henderson, and D. Gillespie. 2007. The combined effect of pore radius and protein dielectric coefficient on the selectivity of a calcium channel. Physical Review Letters 98:168102.

More than 35 papers are available at

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

Cardiac Calcium Channel $Ca_V1.n$

Experimental Signature *Anomalous** Mole Fraction

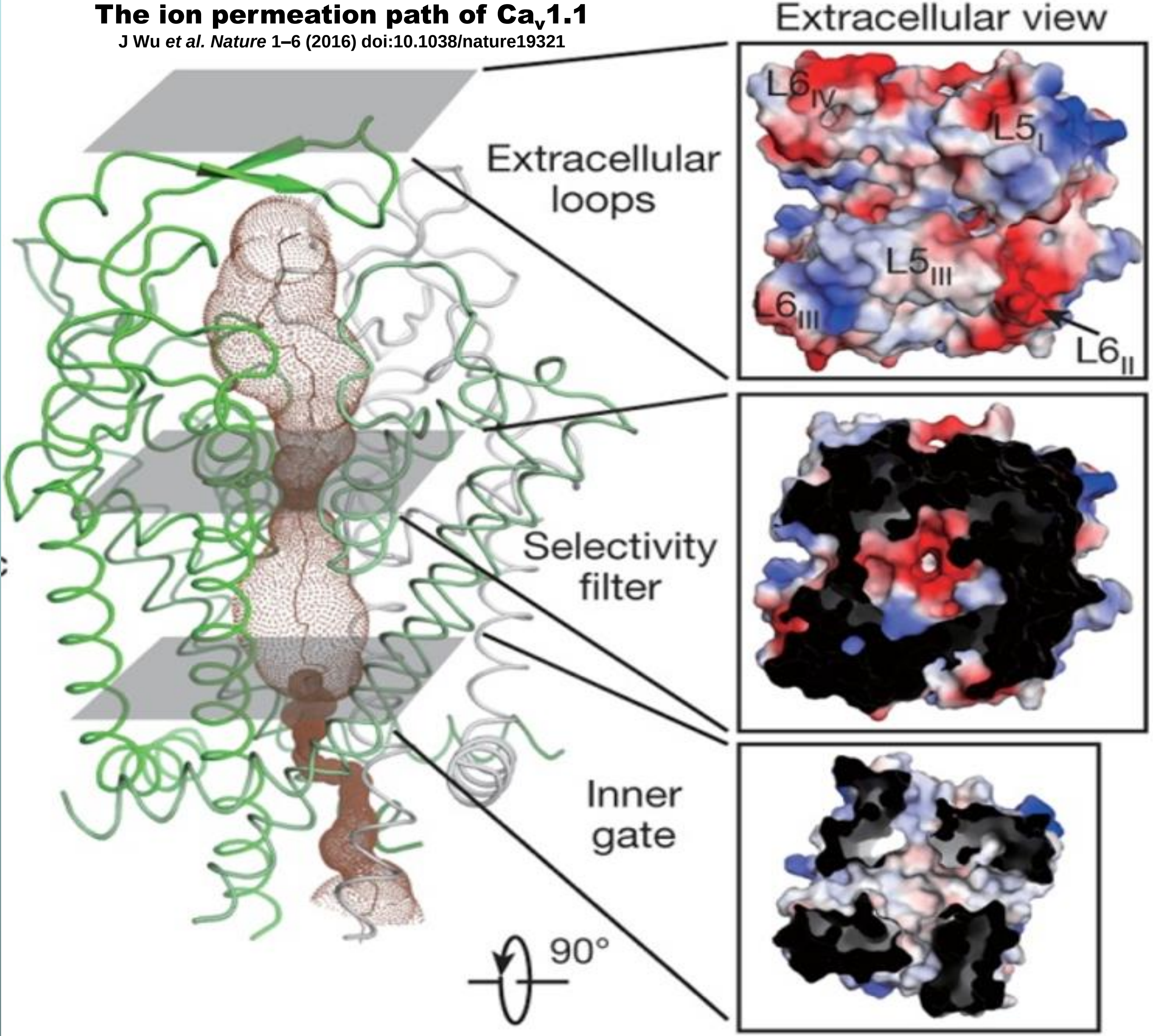


***Anomalous** because **CALCIUM CHANNEL IS A SODIUM CHANNEL** at $[CaCl_2] \cong 10^{-3.4}$
Ca^{2+} is conducted for $[Ca^{2+}] > 10^{-3.4}$, but Na^+ is conducted for $[Ca^{2+}] < 10^{-3.}$

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

The ion permeation path of Ca$_v$1.1

J Wu *et al.* *Nature* 1–6 (2016) doi:10.1038/nature19321



Other methods

give nearly identical results for calcium binding

Metropolis Monte Carlo
DFT (Density Functional Theory of fluids, *not electrons*)
DFT-PNP (Poisson Nernst Planck)
MSA (Mean Spherical Approximation)
SPM (Primitive Solvent Model)
EnVarA (Energy Variational Approach)
Non-equil MMC (Boda, Gillespie) *several forms*
Steric PNP (simplified EnVarA)
Poisson Fermi

In the future, I hope
Finite nanopore
Juergen Fuhrmann
Manuel Landstorfer

Fermi Approach Fits Data to <u>Bulk Solutions</u>

Fermi Description uses
Entropy of Mixture of Spheres
from Combinatoric Analysis

$$W = \prod_{j=1}^{K+2} W_j = \frac{N!}{\left(\prod_{j=1}^{K+2} N_j\,!\right)\cdot\left(N - \sum_{j=1}^{K+2} N_j\right)!}$$

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

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

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

$W_2 \quad =$ 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

<u>Connection to volumes of spheres and voids, and other details are published in 5 papers</u>

Expressions in <u>other literature are not consistent with this entropy</u>

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

Fermi (like) **Distribution**
depends on Steric Factor S^{teric} of System

Algebraic Model of Calcium Channel

works surprisingly well despite crudeness of molecular model

$$S^{teric}(\mathbf{r}) = \ln \frac{1-\sum_{j=1}^{K+2} v_j C_j(\mathbf{r})}{1-\sum_{j=1}^{K+2} v_j C_j(bath)}$$

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

J Comp Phys (2013) 247:88

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

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

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

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

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

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

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

Different Talk!
For physical chemists

also gives

Gibbs Fermi Functional

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

so the Fermi approach

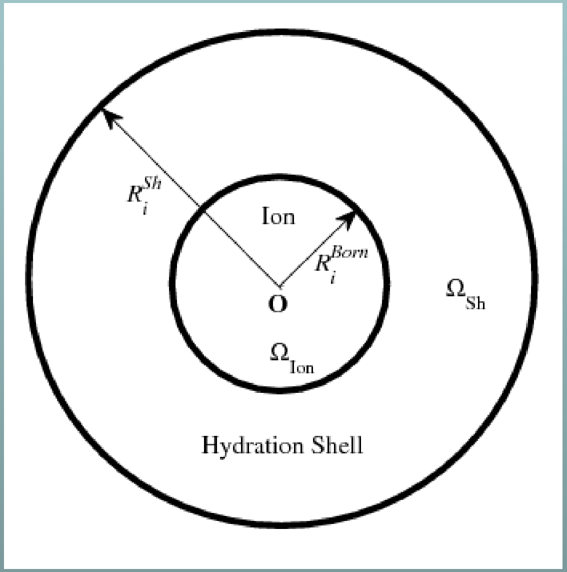
Can be embedded in the ***E***nergy ***V***ariational ***F***ormulation

EnVarA developed by ***Chun Liu***, more than anyone else

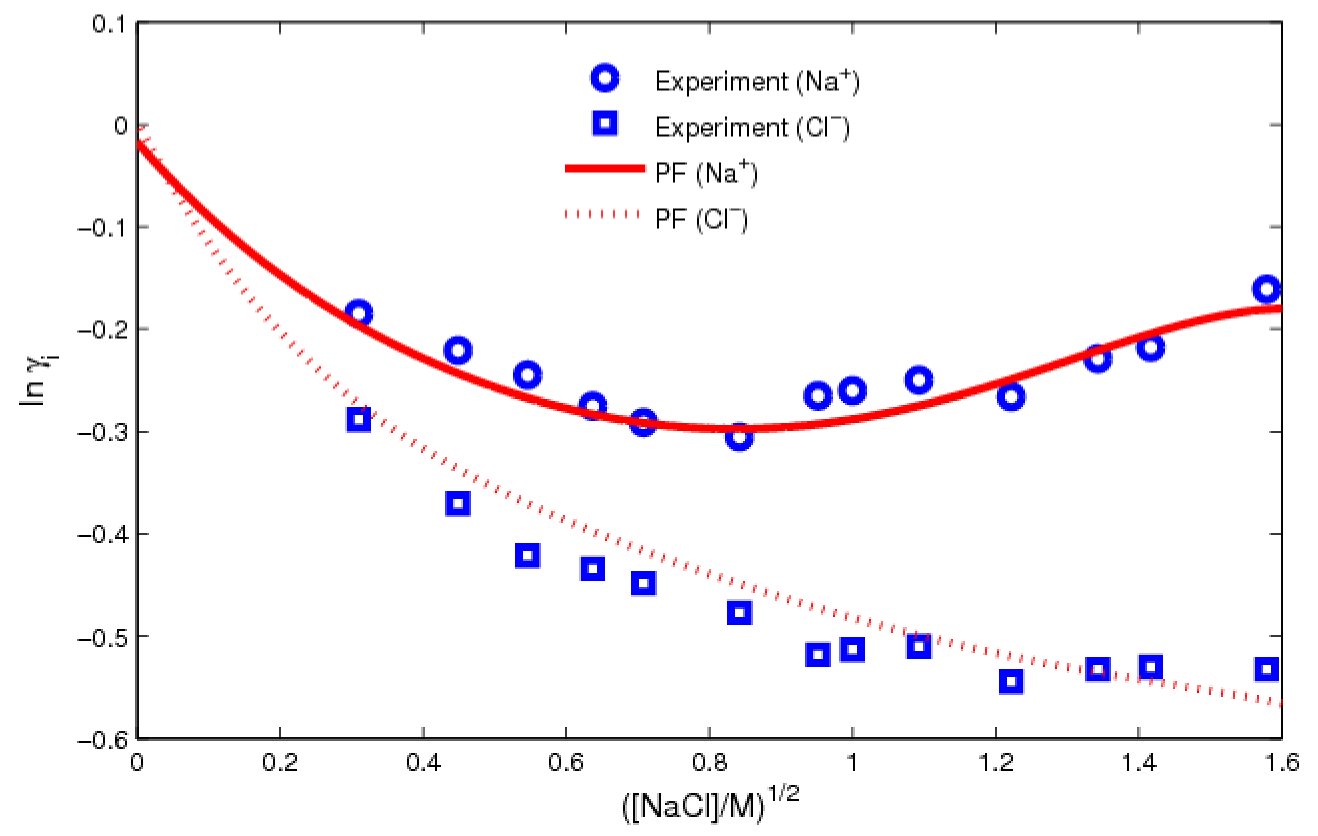
Poisson Fermi Approach to

Bulk Solutions

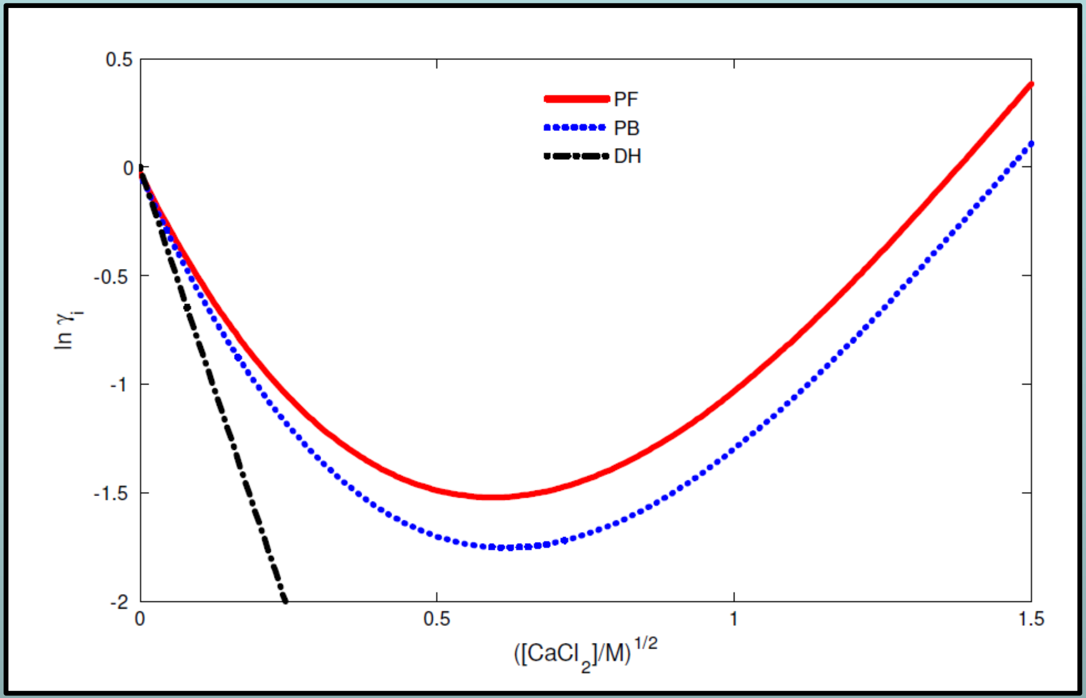
Same equations, different model of nearby atoms



Activity Coefficients
Na^+ Cl^-
'normalized' free energy per mole

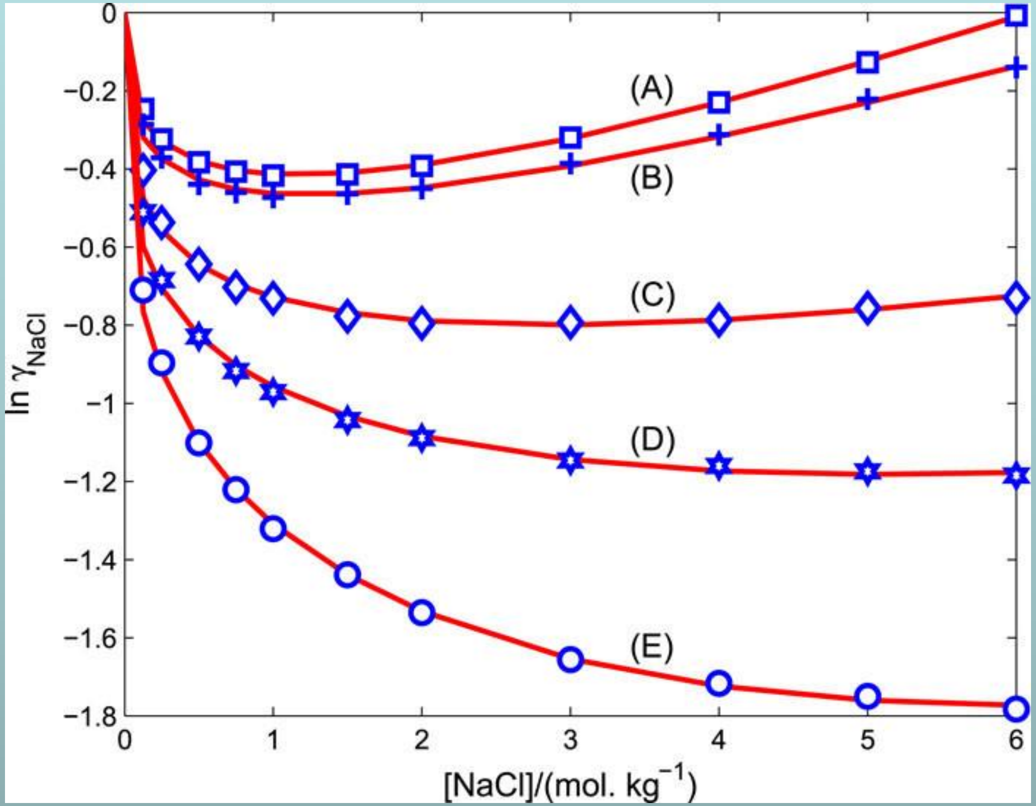


Debye-Hückel Fails Disastrously
Poisson Boltzmann is quite inaccurate
Poisson Fermi does Surprisingly Well



Parameters, NOT further adjusted

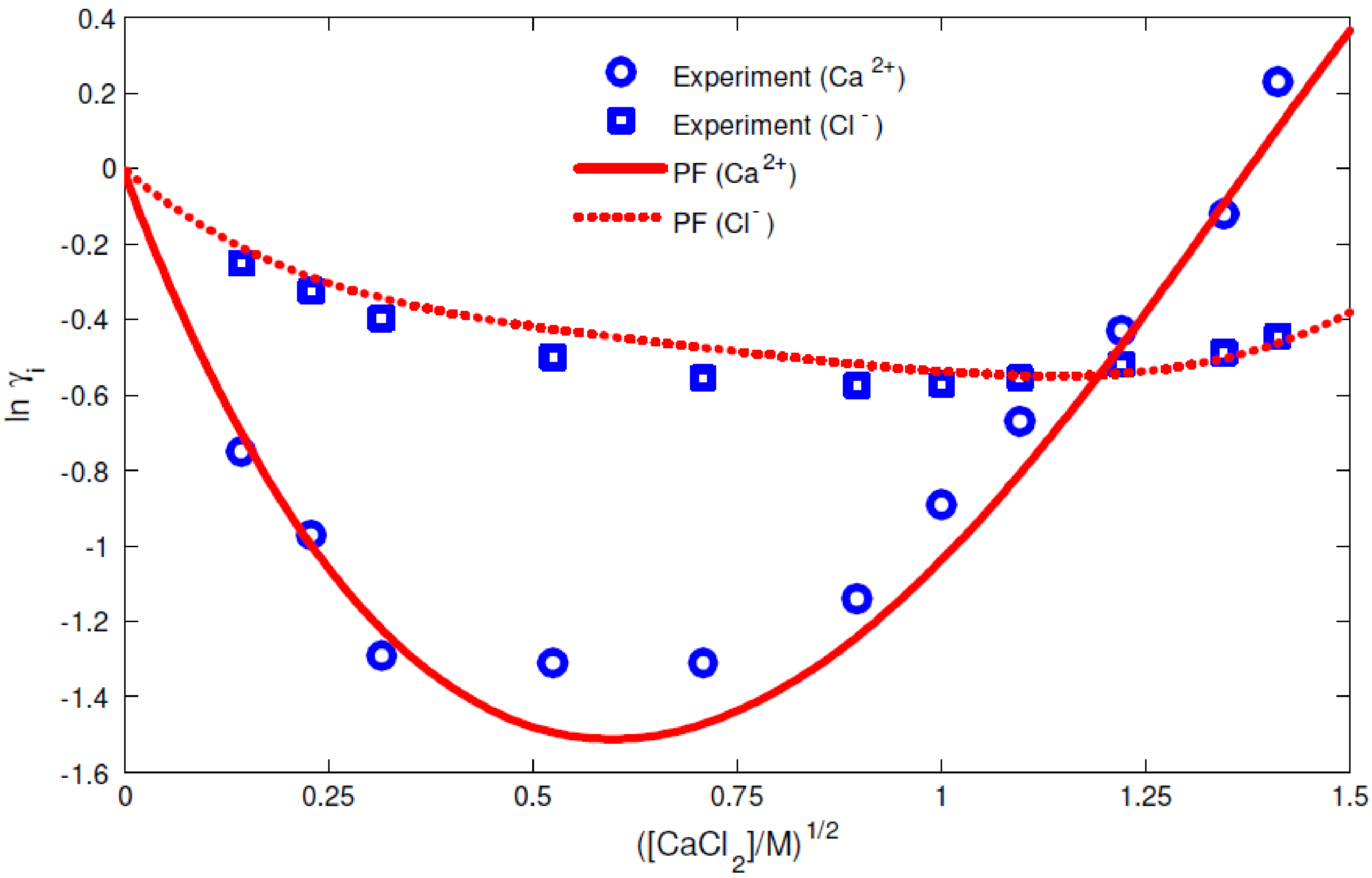
$l_c = 2a_i$	correlation length	$i = \mathrm{Na}^+, \mathrm{Ca}^{2+}, \mathrm{Cl}^-$	Å
$a_{\mathrm{Na}^+}, a_{\mathrm{Ca}^{2+}}$	radii	0.95, 0.99	Å
$a_{\mathrm{Cl}^-}, a_{\mathrm{H_2O}}$	radii	1.81, 1.4	Å
$R^0_{\mathrm{Na}^+}, R^0_{\mathrm{Ca}^{2+}}, R^0_{\mathrm{Cl}^-}$	Born radii in Eq. (12)	1.617,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



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

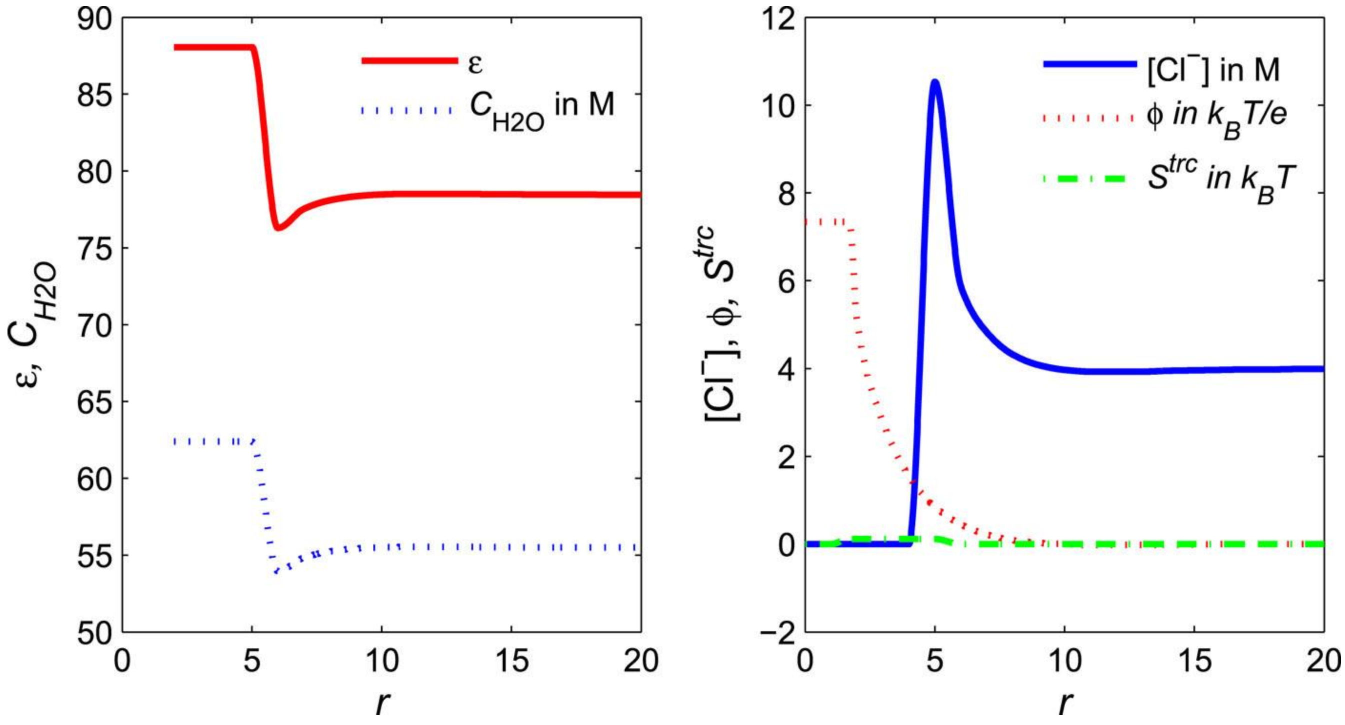


Why are the fits so good?

Different Talk
For physicists/physical chemists

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

Stay tuned for new work



Dielectric function $\tilde{\varepsilon}(r)$ (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

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

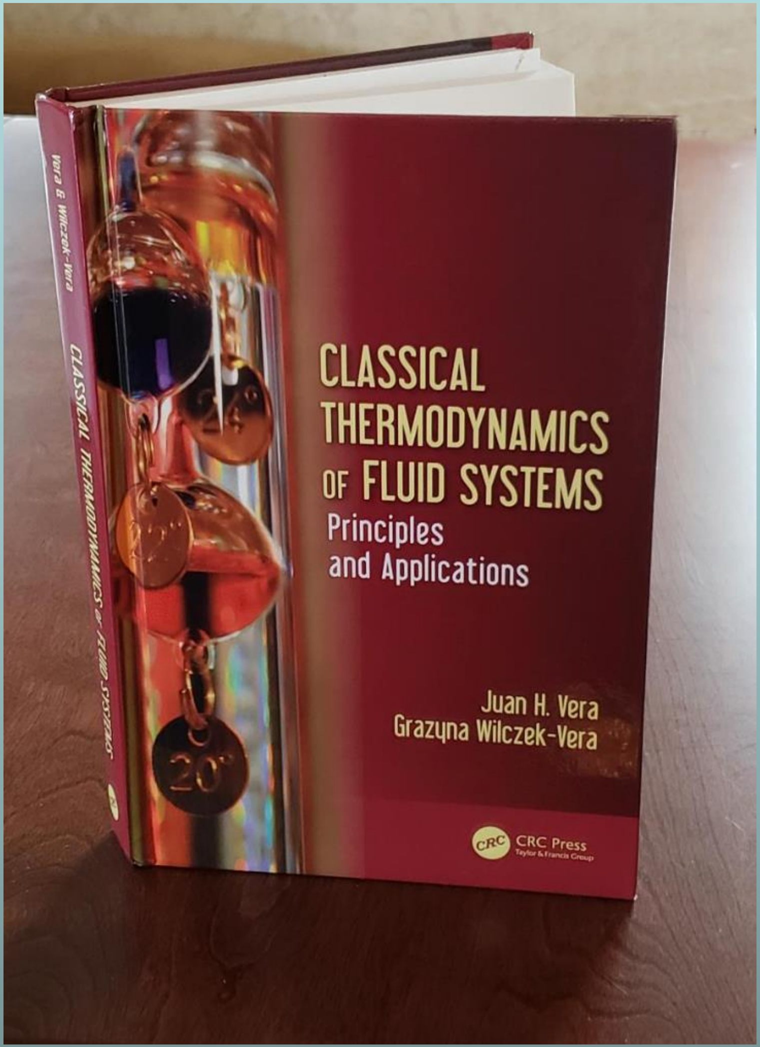
$$\varepsilon_{water}\left(l_c^{\,2}\nabla^2 - 1\right)\psi = \rho(\mathbf{r})$$

Different Talk
For mathematicians

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



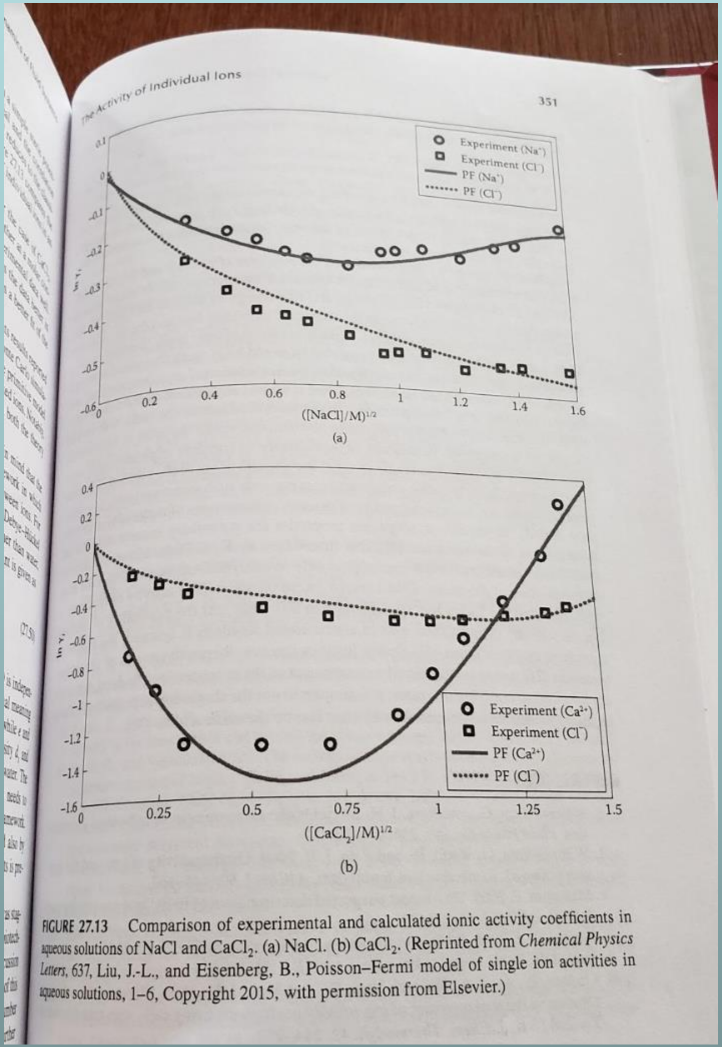
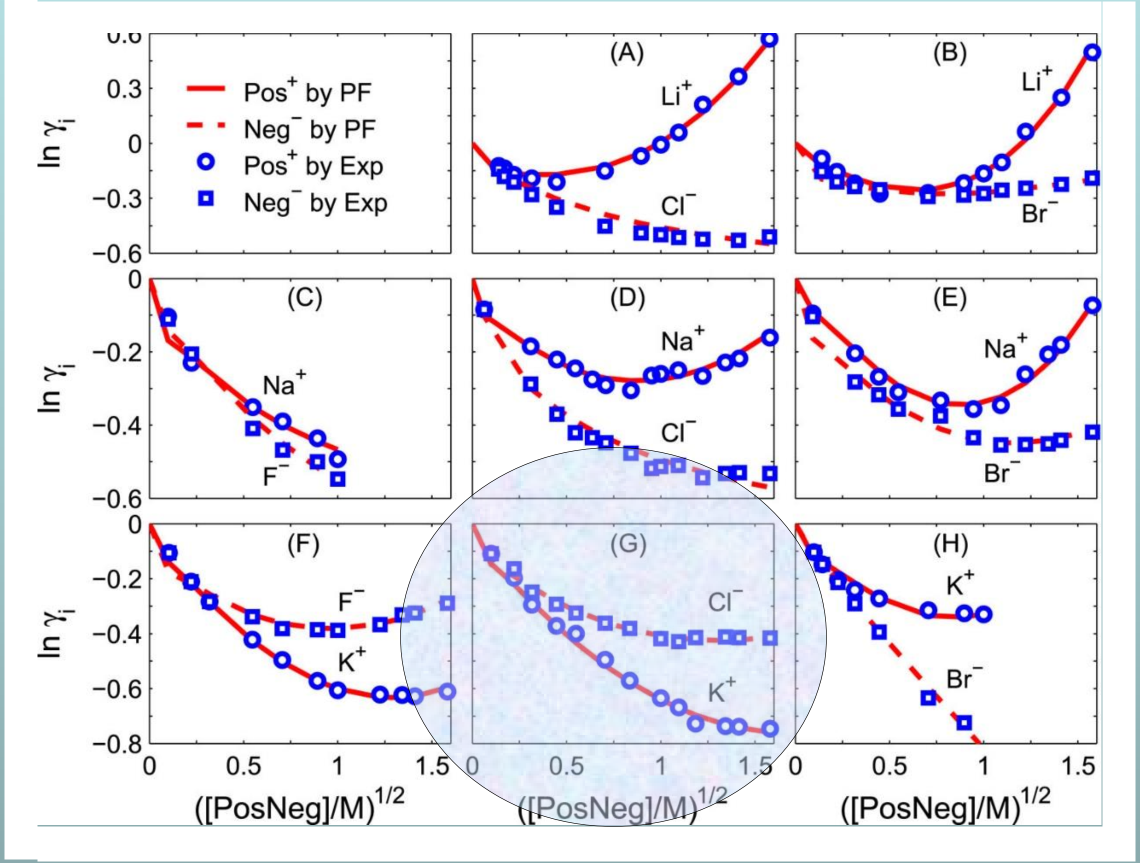
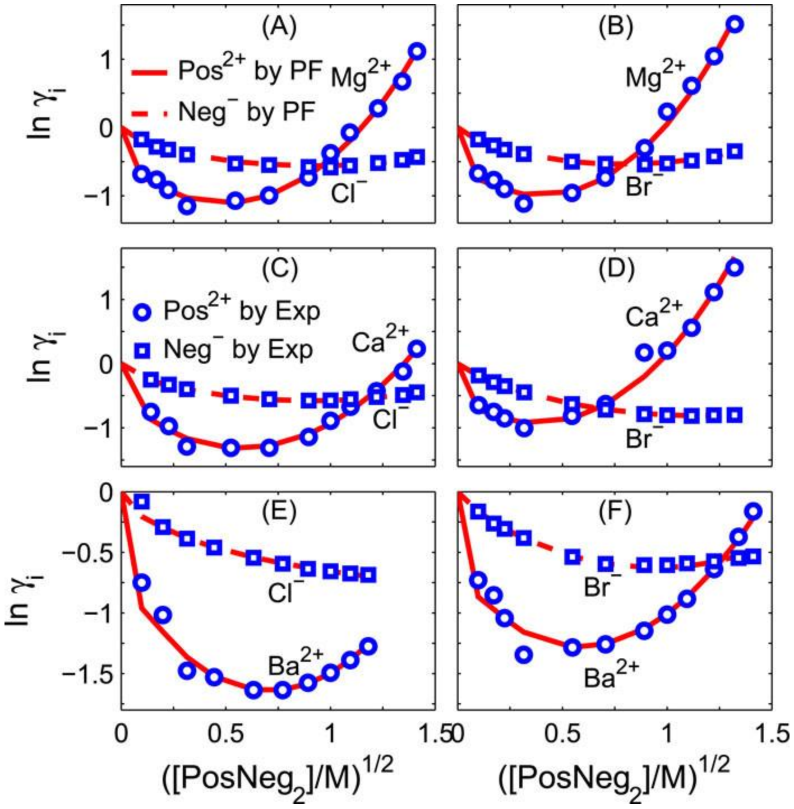

The Activity of Individual Ions 351

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.)



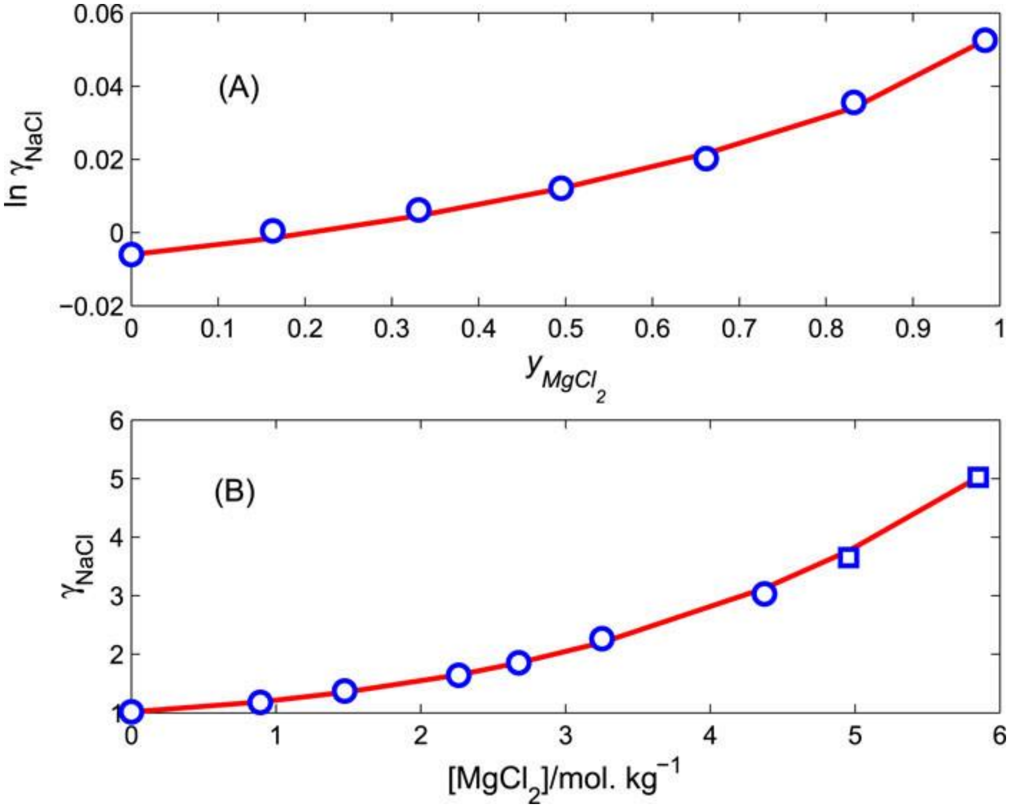
Individual activity coefficients of 1:1 electrolytes. Comparison of PF results with experimental data[26] on i = Pos$^+$ (cation) and Neg$^-$ (anion) activity coefficients γ_i in various [PosNeg] from 0 to 1.6M.

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



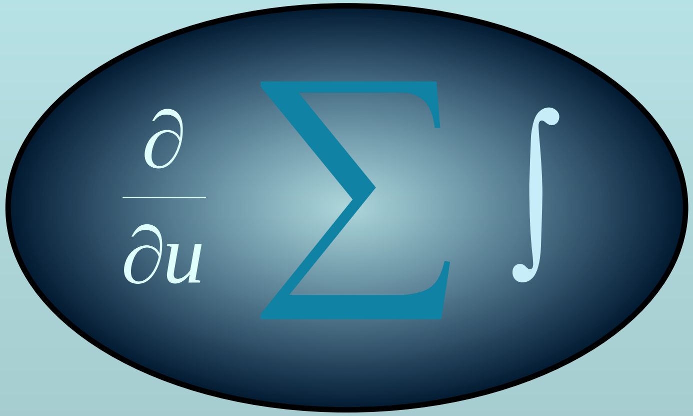
Individual activity coefficients of 2:1 electrolytes. Comparison of PF results with experimental data[26] *on i =* Pos^{2+} *(cation) and* Neg^{-} *(anion) activity coefficients* γ_i *in various* [PosNeg$_2$] *from 0 to 1.5M.*

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



Mean activity coefficients of mixed electrolytes. Comparison of PF results (curve) with experimental data (symbols) compiled in Ref. 13 (a) from Ref. 33 on mean activity coefficients γ of NaCl as a function of the ionic strength (I) fraction $yMgCl_2$ of $MgCl_2$ in NaCl + $MgCl_2$ mixtures at I = 6 mol Kg^{-1} and T = 298.15 K and (b) from Ref. 34 (circles) and Ref. 35 (squares) on γ of NaCl as a function of the $MgCl_2$ molality in NaCl + $MgCl_2$ mixtures at [NaCl] = 6 mol Kg^{-1} and T = 298.15 K.

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



Mathematics
describes only a little of
Daily Life

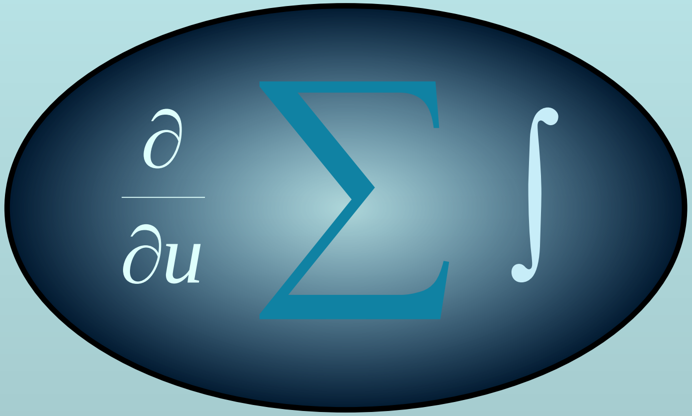
But

Mathematics* Creates

our

Standard of Living

**Electricity, Computers 10^9 in 50 years, Fluid Dynamics, Optics, Structural Mechanics, …..*



Mathematics Creates
our
Standard of Living

because

Mathematics replaces Trial and Error with Computation

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

$$\frac{\partial}{\partial u} \sum \int$$

Mathematics of Plasmas
can describe
Ionic Solutions

The End

Any Questions?

Next Steps

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

<u>Electric forces are so large</u>

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

PNPF

Poisson-Nernst-Planck-Fermi

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

$$\textit{Flow}\ \begin{cases} \nabla\cdot\mathbf{J}=0 \\ \mathbf{J}_i=-D_i\left[\nabla C_i+\left(k_bT/z_i\boldsymbol{e}\right)\nabla\phi-C_i\nabla S^{teric}\right] \end{cases}$$

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

$\varepsilon_{water}(l_c\nabla^2-1)$ 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**

$$-\varepsilon_{water}\psi=\rho_{pol}$$

That give the polarization charge density

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

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

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 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**

$$\eta=-\varepsilon_{water}\psi=\rho$$

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*

Computational Problems Abound and are limiting if you wish 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

Markowich, P. A., C. A. Ringhofer and C. Schmeiser (1990). Semiconductor Equations

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. E., J. Burgler, W. M. Coughran, Jr., W. Fichtner and R. K. Smith (1990). "Recent Progress in 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, and 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.*

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 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

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 Wei and collaborators modified to embed **Scharfetter Gummel** criteria of computational electronics (extended to include steric effects).
THIS IS REQUIRED TO ENSURE CONTINUITY OF CURRENT

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$_V$1**.*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

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
Markowich, P. A., C. A. Ringhofer and C. Schmeiser (1990). Semiconductor Equations
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.

Take Home Lessons

1) Ionic solutions are plasmas, not perfect gases.

2) Composition of ionic solutions has profound effects
on almost all chemical reactions that occur in them.

3) Interactions in ionic solutions are mostly the interactions of charged hard spheres.

4) Mathematical Theories of Ionic Solutions of Variable Composition are surprisingly successful,
even in the special geometries of ion channels

The End

Any Questions?

Supplementary Material

All biology occurs in Ionic Solutions

‘Seawater’ is the liquid of life

Seawater and liquids of life
are
Concentrated Mixtures
of
sodium, potassium, calcium ions

No gas phase models of traditional channel biochemistry

Liquids are not Gases

Rate Constants are Variables

No discussions of individual trajectories of Structural Biologists

Counting and Statistics are essential

James Clerk Maxwell

“I carefully abstain
from asking molecules
where they start…

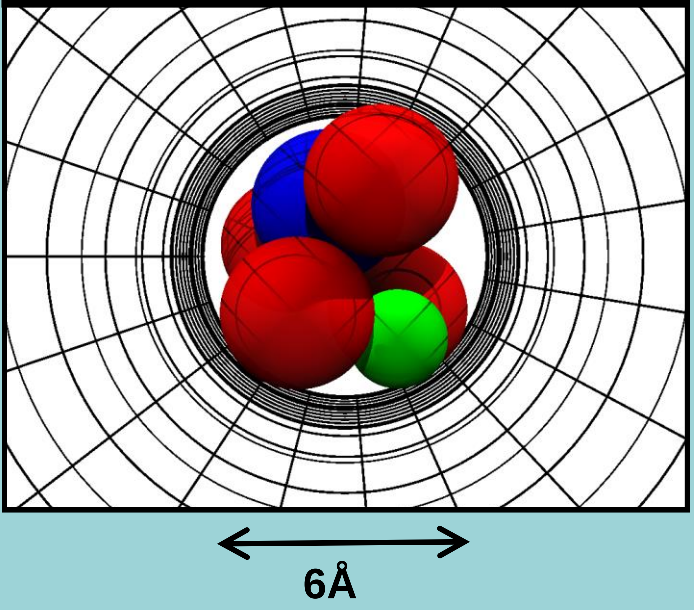
I only count them….,

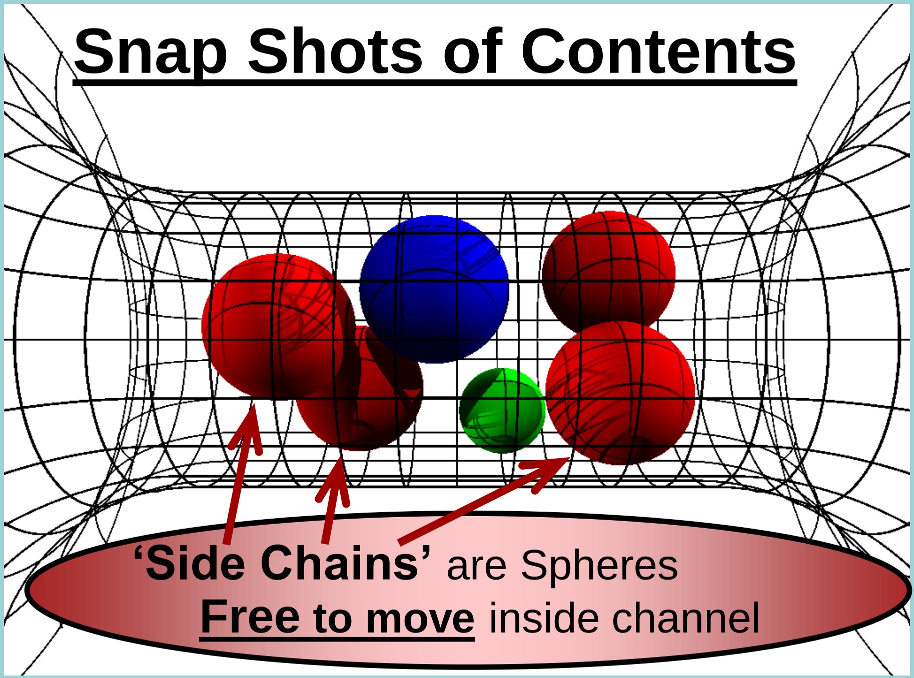
avoiding all personal enquiries
which would only get me into trouble.”

slightly reworded from Royal Society of London, 1879, Archives no. 188
In Maxwell on Heat and Statistical Mechanics, Garber, Brush and Everitt, 1995

Crowded Ions

Radial Crowding is Severe





Snap Shots of Contents

'Side Chains' are Spheres
<u>Free to move</u> inside channel

Ion Diameters *'Pauling' Diameters*	
Ca^{++}	**1.98 Å**
Na^{+}	**2.00 Å**
K^{+}	**2.66 Å**
'Side Chain' Diameter	
Lysine K	**3.00 Å**
D or E	**2.80 Å**
Channel Diameter 6 Å	

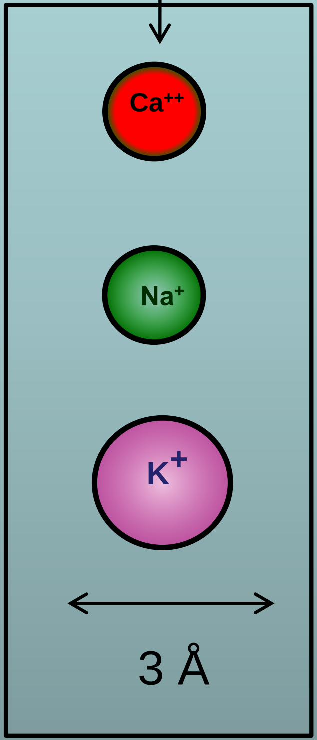
Parameters are Fixed in all calculations
in all solutions for all mutants

Experiments and Calculations done at pH 8

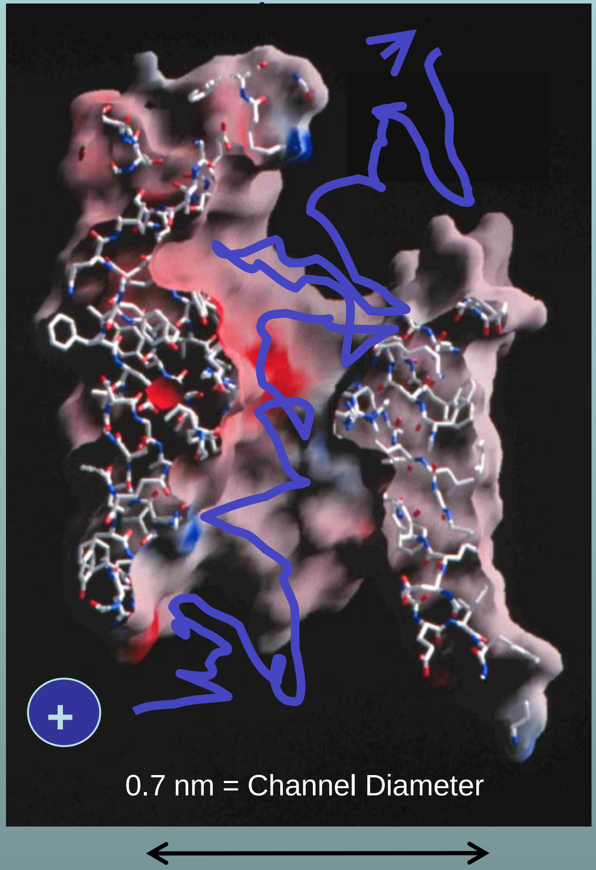
Boda, Nonner, Valisko, Henderson, Eisenberg & Gillespie

Channels are Selective

Different Ions Carry Different Signals through Different Channels



ompF



Diameter matters

In ideal solutions $K^+ = Na^+$

Flow time scale is 0.1 msec to 1 min

Figure of ompF porin by Raimund Dutzler

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

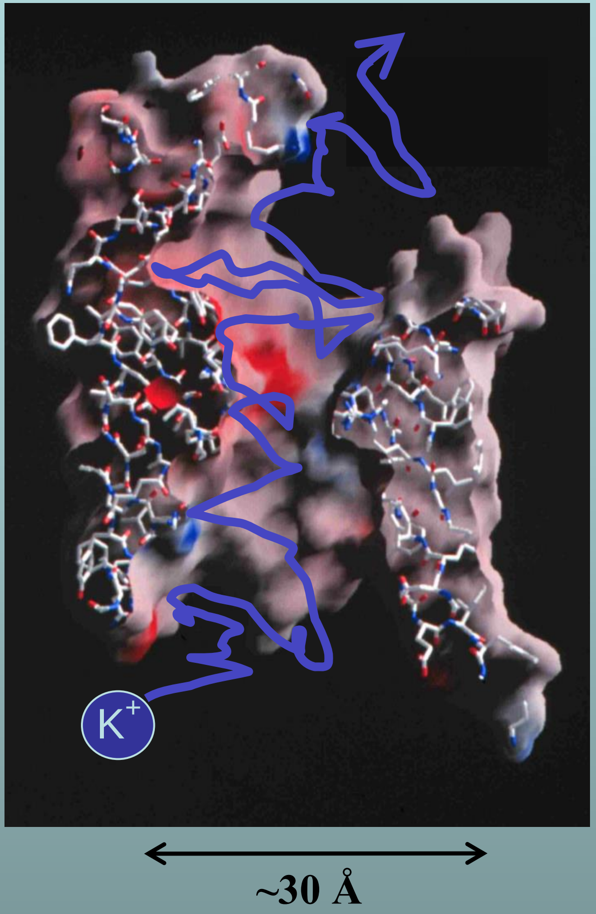
Ion channels produce signals of the nervous system

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

Central Result of Physical Chemistry

Ions

in a solution are a

Highly Compressible Plasma

although the

Solution

itself is

Incompressible

Learned from Henderson, J.-P. Hansen, Berry, Rice, and Ross…Thanks!

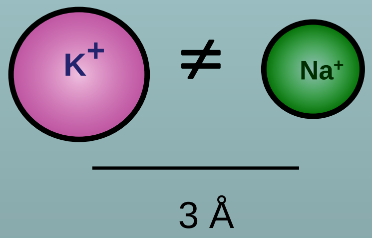
Channels are Selective

because

Diameter Matters

Ions are NOT Ideal

Potassium K^+ ≠ Na^+ Sodium



Ideal Ions are Identical

if they have the same charge

In ideal solutions $K^+ = Na^+$

Physical Chemists

are

Frustrated

by

Real Solutions

because

IONIC SOLUTIONS

are

COMPLEX FLUIDS

not ideal gases

The ion permeation path of Ca$_v$1.1

J Wu *et al.* *Nature* 1–6 (2016) doi:10.1038/nature19321