Thanks
to
PSU Math
particularly
Xiantao Li,
Chun Liu
Jinchao Xu, and
Yuxi Zheng

It is a privilege (and joy) to visit many times and work together.

Mathematics
describes only a tiny part of 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, …..***

Chemistry and Biology
occur in Salt Solutions
with
Multiple Components, Interactions, and Dissipation

Mathematics is now available

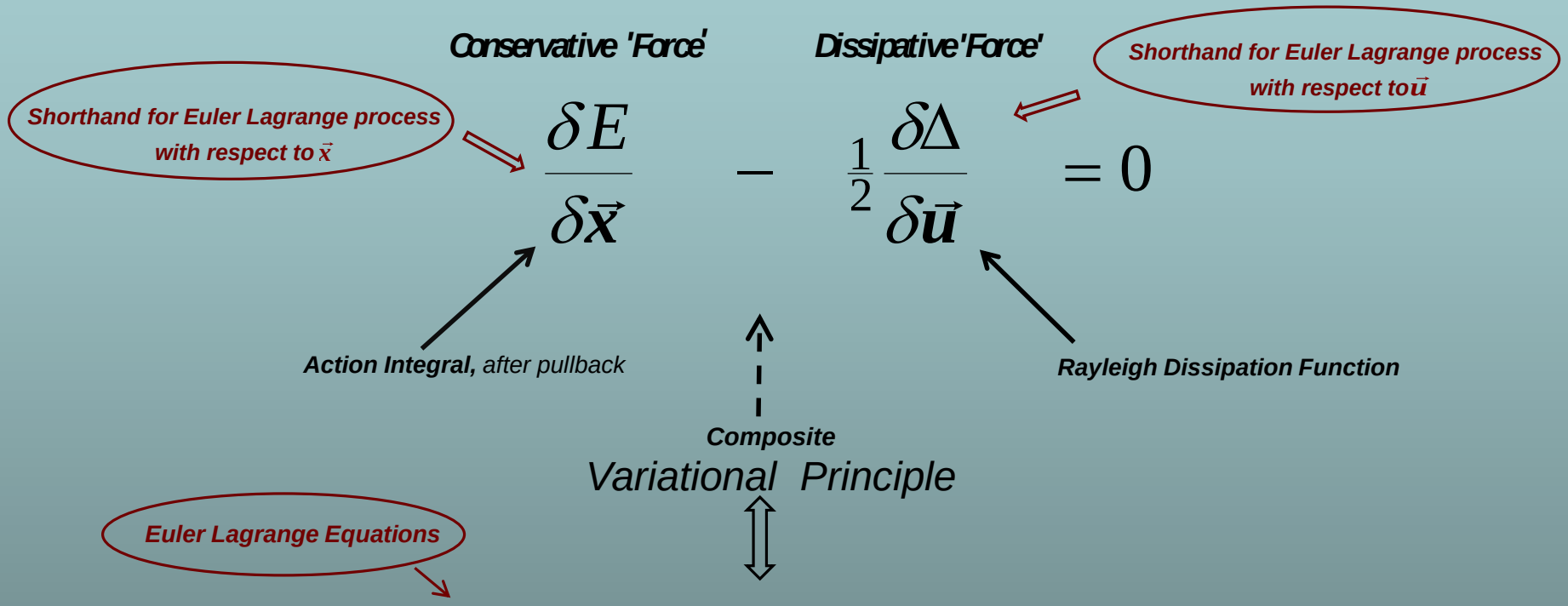
Energetic Variational Approach

Energetic Variational Approach

EnVarA

Chun Liu, Rolf Ryham, and Yunkyong Hyon

Mathematicians and Modelers: two different 'partial' variations written in one framework, using a 'pullback' of the action integral



Field Theory of Ionic Solutions: Liu, Ryham, Hyon, Eisenberg

Allows boundary conditions and flow
Deals Consistently with Interactions of Components

All of Biology occurs in Salt Solutions

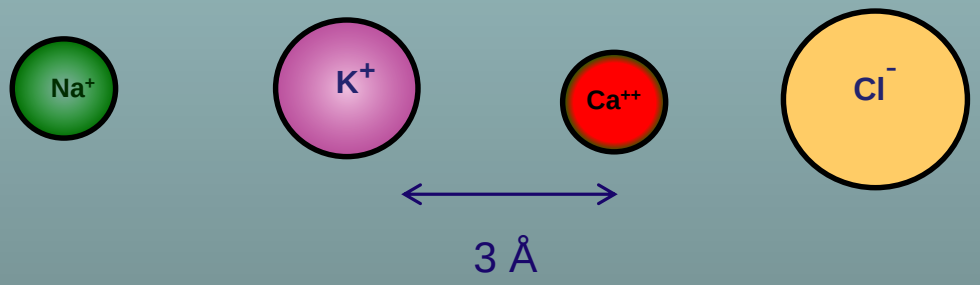
of definite composition and concentration
and that matters!

Salt Water is the Liquid of Life

Pure H_2O is toxic to cells and molecules!

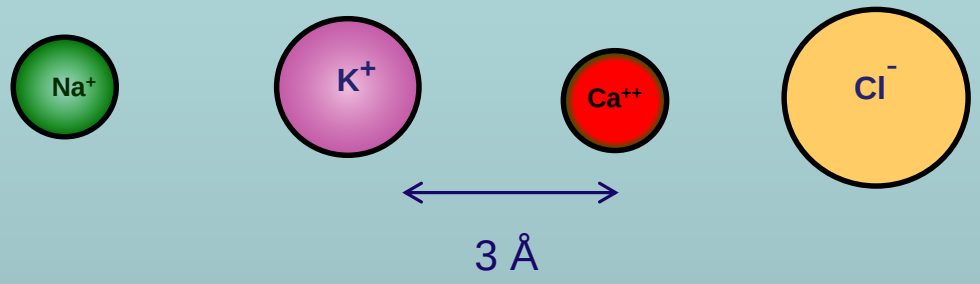
Main Ions are Hard Spheres, close enough

Sodium Na^+ Potassium K^+ Calcium Ca^{2+} Chloride Cl^-



Main Biological Ions are Hard Spheres, close enough

Sodium Na^+ Potassium K^+ Calcium Ca^{2+} Chloride Cl^-



General Theory of Hard Spheres is now available

Thanks to Chun Liu, more than anyone else

Took a long time, because dissipation, multiple fields, and multiple ion types had to be included

VARIATIONAL APPROACH IS NEEDED

Dissipation Principle

Conservative Energy dissipates into Friction

$$\overbrace{\frac{d}{dt}\int\left\{k_BT\sum_{i=n,p}c_i\log c_i+\frac{1}{2}\left(\rho_0+\sum_{i=n,p}z_iec_i\right)\phi+\sum_{i,j=n,p}\frac{c_i}{2}\int\tilde{\Psi}_{i,j}\;c_j\,d\vec{y}\right\}d\vec{x}}^{\textit{Conservative}}$$

time

Thermal Energy

Number Density

Permanent Charge of protein

Hard Sphere Terms

valence proton charge

$$=\;\underbrace{-\int\left\{\sum_{i=n,p}\frac{D_ic_i}{k_BT}\left|k_BT\frac{\nabla c_i}{c_i}+z_ie\nabla\phi-\sum_{j=n,p}\nabla\int\tilde{\Psi}_{i,j}\;c_j\,d\vec{y}\right|^2\right\}d\vec{x}}_{\textit{Dissipative}}$$

c_i number density; k_BT thermal energy; D_i diffusion coefficient; n negative; p positive; z_i valence; ε dielectric constant

Note that $\varepsilon\frac{|\nabla\phi|^2}{2}=\frac{1}{2}\left(\rho_0+\sum_{i=n,p}z_iec_i\right)\phi$ **with suitable boundary conditions**

Energetic Variational Approach

EnVarA

Conservative 'Force' *Dissipative 'Force'*

$$\frac{\delta E}{\delta \vec{x}} - \frac{1}{2}\frac{\delta \Delta}{\delta \vec{u}} = 0$$

is defined by the Euler Lagrange Process,

as I understand the pure math from Craig Evans

which gives

Equations like PNP

BUT

I leave it to you (all)

to argue/discuss with Craig

about the purity of the process

when two variations are involved

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

Non-equilibrium variational field theory *EnVarA*

Nernst Planck Diffusion Equation

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

Diffusion Coefficient

Thermal Energy

Coupling Parameters

Ion Radii

Number Densities

$$\frac{\partial c_n}{\partial t} = \nabla \cdot \left[D_n \left\{ \nabla c_n + \frac{c_n}{k_B T} \left(z_n e \nabla \phi - \int \frac{12 \varepsilon_{n,n} (a_n + a_n)^{12} (\vec{x} - \vec{y})}{|\vec{x} - \vec{y}|^{14}} c_n(\vec{y}) d\vec{y} - \int \frac{6 \varepsilon_{n,p} (a_n + a_p)^{12} (\vec{x} - \vec{y})}{|\vec{x} - \vec{y}|^{14}} c_p(\vec{y}) d\vec{y} \right) \right\} \right],$$

Poisson Equation

Dielectric Coefficient

valence proton charge

Permanent Charge of Protein

$$\nabla \cdot (\varepsilon \nabla \phi) = -\left(\rho_0 + \sum_{i=1}^{N} z_i e c_i \right) \qquad i = n \text{ or } p$$

Semiconductor *PNP* Equations

For Point Charges

Poisson's Equation

Dielectric Coefficient

Permanent Charge of Protein

$$-\frac{\varepsilon_0}{A(x)}\frac{d}{dx}\left(\varepsilon(x)A(x)\frac{d\phi}{dx}\right)=e\mathrm{P}(x)+e\sum_i z_i\rho_i(x)$$

Cross sectional Area

Valence Proton charge

Drift-diffusion & Continuity Equation

Number Densities

$$\frac{dJ_i}{dx}=0 \qquad -J_i=D_i(x)A(x)\rho_i(x)\frac{d\mu_i}{dx}$$

Flux

Diffusion Coefficient

Chemical Potential $\mu_i(x)$

$$\mu_i(\mathrm{x})=z_i e\phi(\mathrm{x})+kT\ln\left(\frac{\rho_i(\mathrm{x})}{\rho^*}\right)+\underbrace{\mu_i^{\mathrm{ex}}(\mathrm{x})}$$

valence proton charge

Thermal Energy

Finite Size Special Chemistry

All we have to do is

Solve it/them!

with boundary conditions

All we have to do is

Solve it / them!

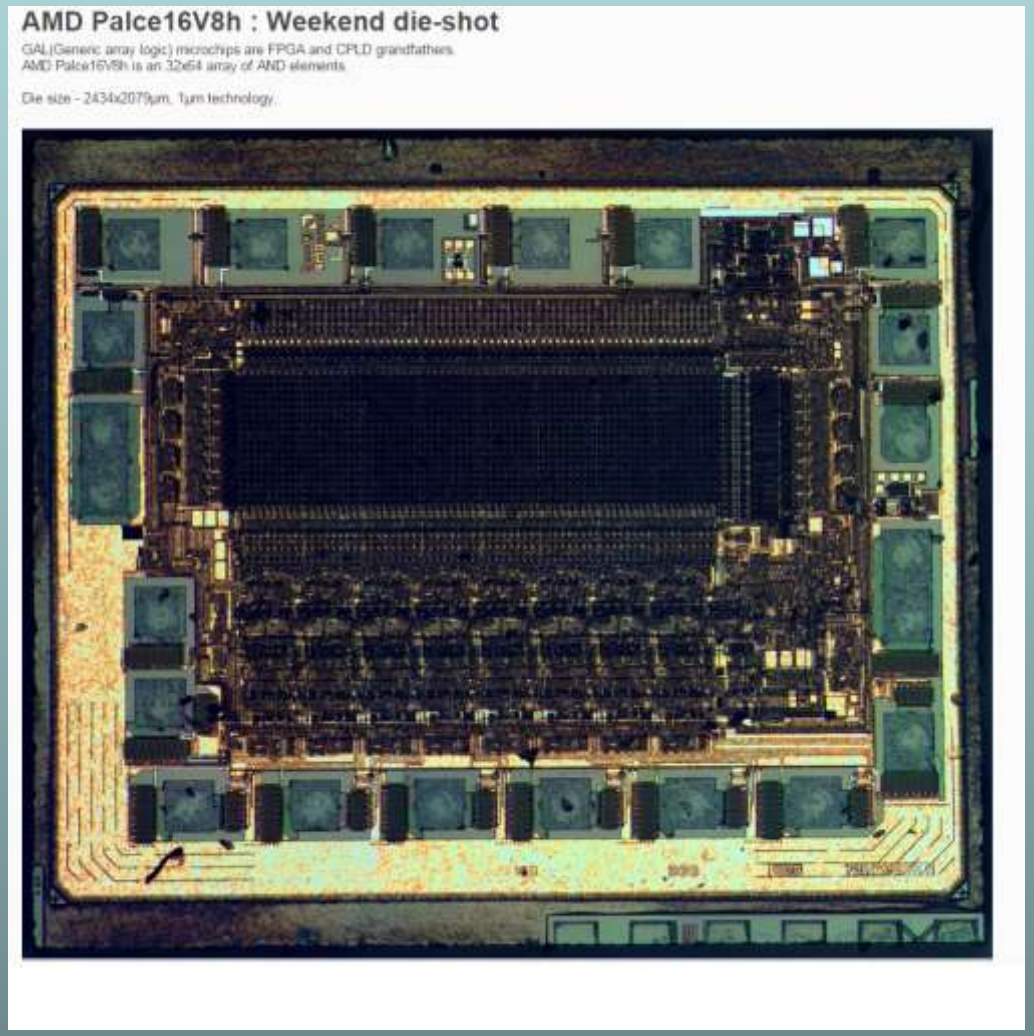
Boundary conditions:

STRUCTURES of Ion Channels

STRUCTURES of semiconductor devices and integrated circuits

Integrated Circuit

Technology as of ~2005



Semiconductor Devices

PNP equations describe many robust input output relations
Amplifier
Limiter
Switch
Multiplier
Logarithmic convertor
Exponential convertor

These are SOLUTIONS of PNP for different boundary conditions with ONE SET of CONSTITUTIVE PARAMETERS

PNP of POINTS IS TRANSFERRABLE

Analytical - Numerical Analysis should be attempted using techniques of

Weishi Liu University of Kansas
Tai-Chia Lin National Taiwan University & **Chun Liu** PSU

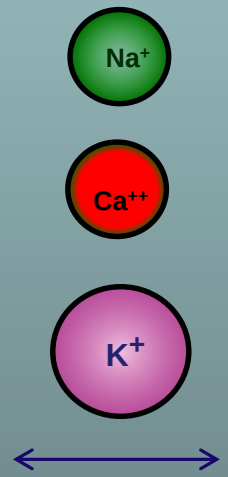
Ion Channels are Devices

Ion Channels are the Main Controllers of Biological Function

Biological Diodes

nonlinear current/voltage curves

Different Ions
Different Diameters
carry
Different Signals



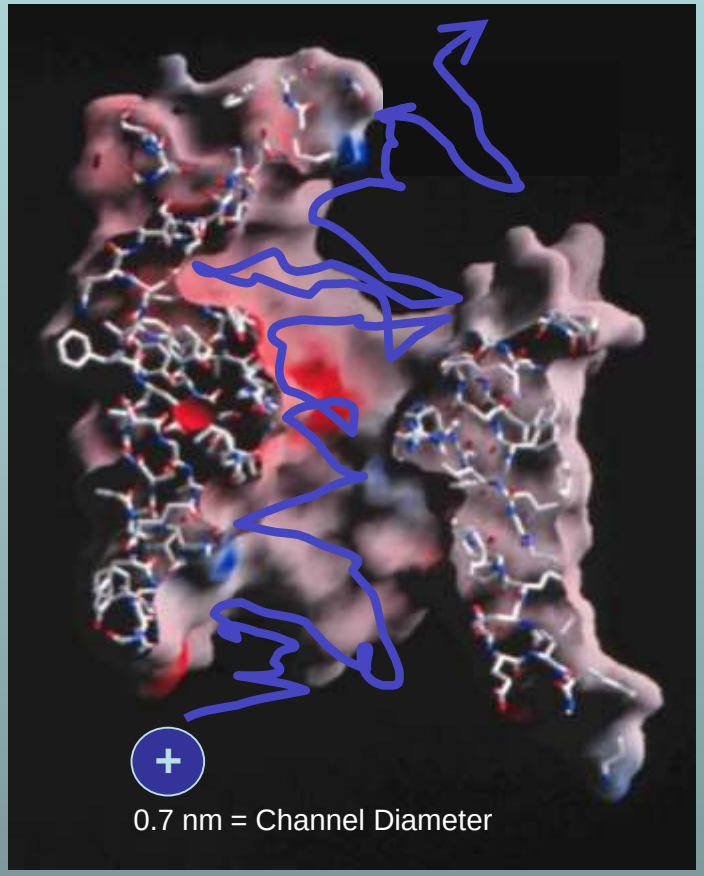


Figure of ompF porin by Raimund Dutzler

Ions in Water*

are the

Liquid of Life

***Pure H_2O is toxic to cells & proteins**

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

Mathematics of Molecular Biology Provides Great Opportunity

Biology Provides the Data

Engineering Provides the Approach

Mathematics Provides the Tools

particularly variational methods that allow
'everything' to interact with 'everything' else

Chemistry and Biology
Need a
TRANSFERRABLE Theory of

Salt Water

the liquid of life

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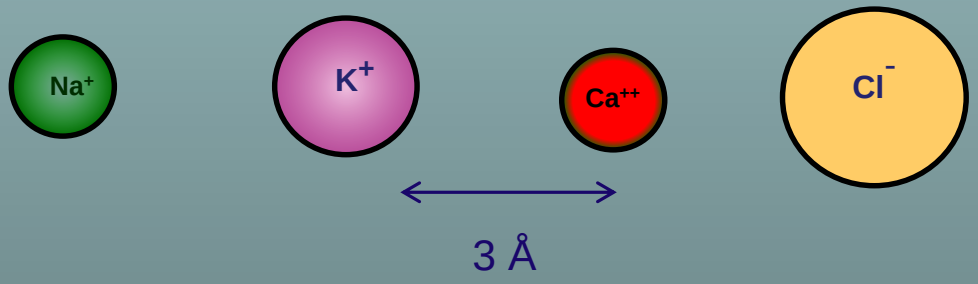


Classical text
Robinson and Stokes
still in print after sixty years

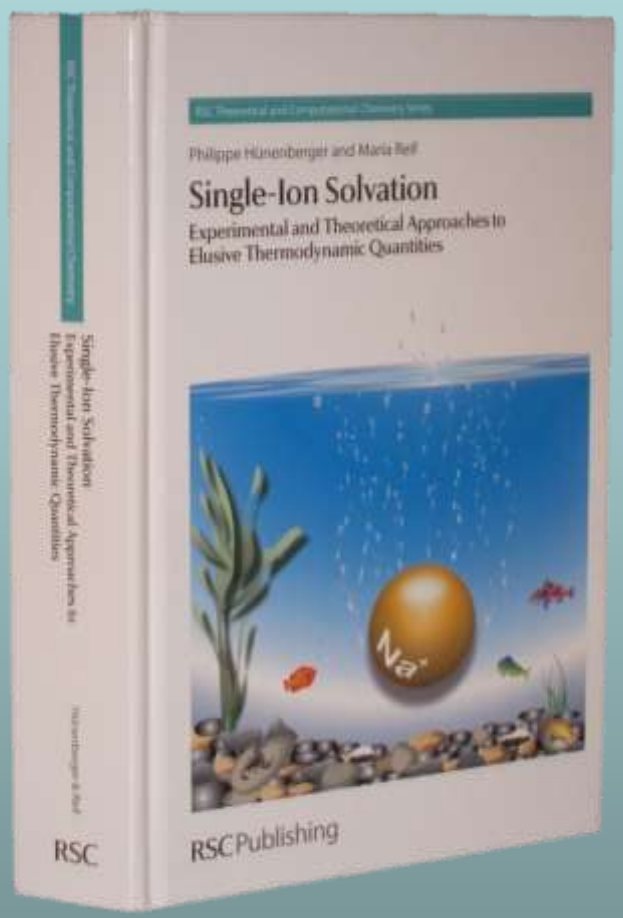
Not otherwise noted for its emotional content
gives a glimpse of these feelings when it says

“In regard to concentrated solutions, many workers adopt a counsel of despair,

confining their interest to concentrations below about 0.02 M, ... ”
Biology occurs in concentrations > 0.2 M

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

Ionic Solutions are Complex Fluids



Hünenberger & Reif (2011) Single-Ion Solvation Experimental and Theoretical Approaches to Elusive Thermodynamic Quantities
in infinitely dilute solutions!

After 664 pages and 2604 references, properties of

SINGLE Ions
are
Elusive

because

Every Ion Interacts
with
Everything

It is difficult to <u>even define</u>

in a unique way

Properties of One Ion

in infinitely dilute solution

when

Everything Interacts with Everything

Note Emotion IN TITLE

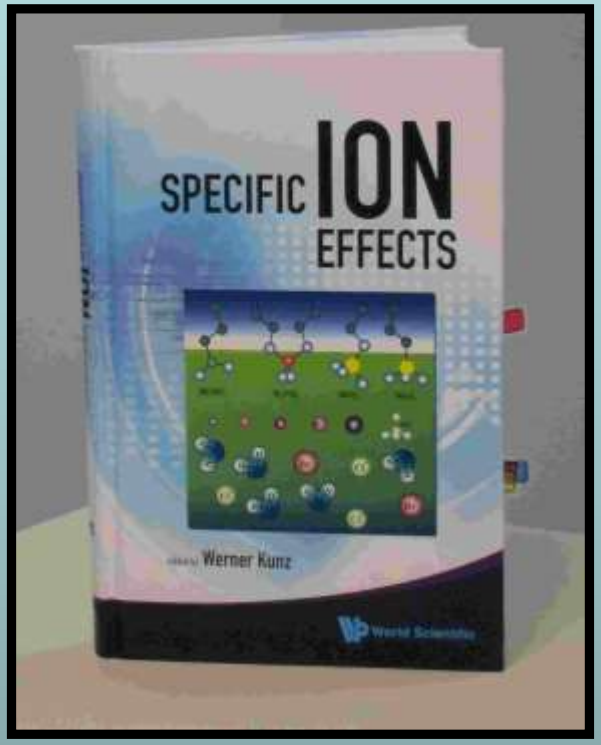
664 pages, 2604 references

Deals with infinitely dilute solutions

Hünenberger, P. and M. Reif, (2011) *Single-Io*
Solvation. Experimental and Theoretical
Approaches to
<u>Elusive</u> <u>Thermodynamic</u> <u>Quantities*</u>
Royal Society of Chemistry.

<u>*Emphasis Bob E.</u>

Tremendous Opportunity for Mathematics: Numerics and Variational Approach



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."

It is not surprising that

Inconsistent Treatments

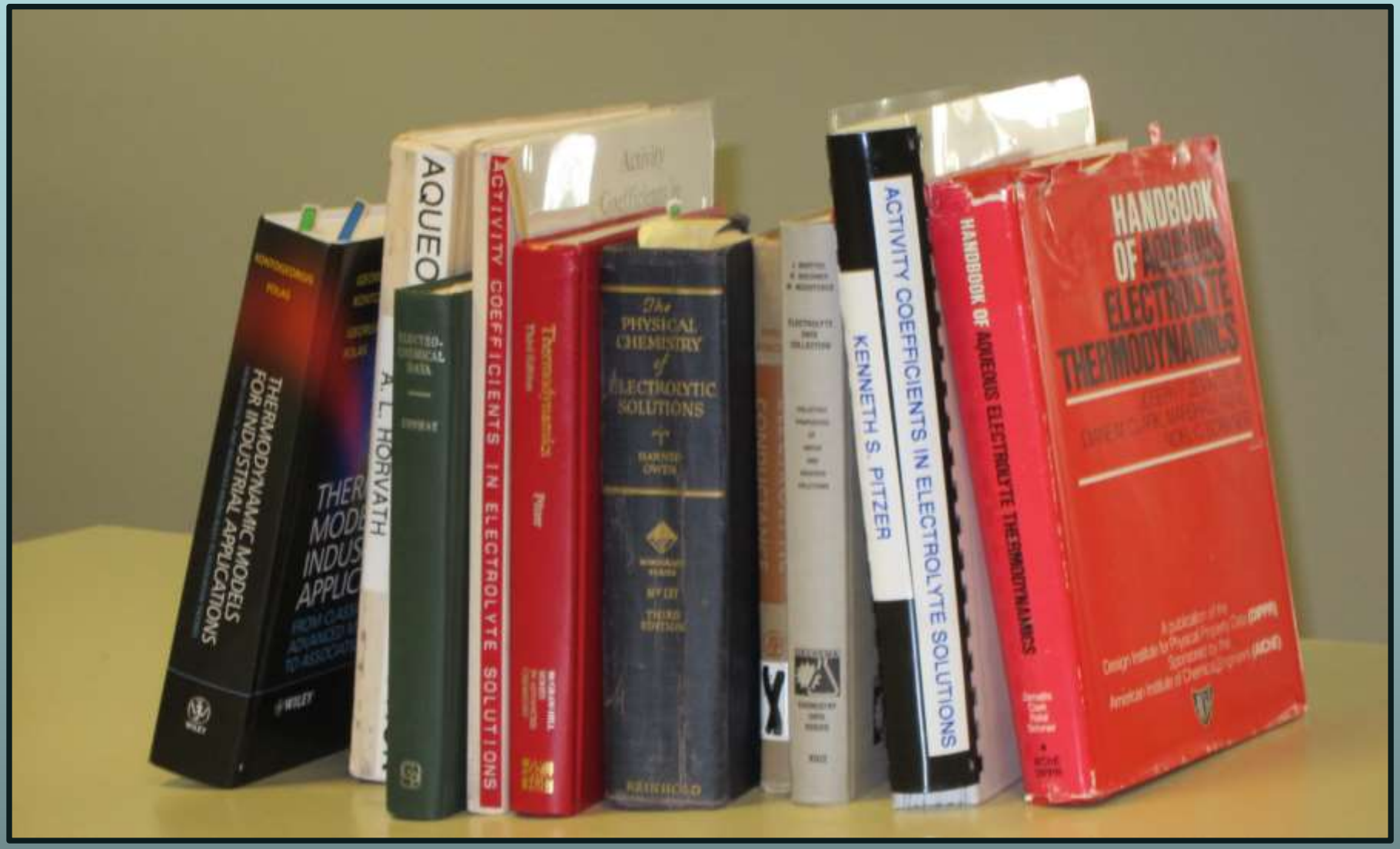
of ionic solutions

have been

Unsuccessful

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

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*** *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.

“Sometimes it is necessary to put a veil on the past, for the sake of the future”

Henry Clay

p. 375 of **Henry Clay, the Essential American**
David Heidler, Jeanne Heidler Random House

Mathematics can remove the veil!

Mathematics

is needed to replace

Trial and Error

Experiments and Simulations

with

Computations

and

Consistent Theories

Mathematics of Chemistry

must deal

Naturally

with

Interactions

'Law of Mass Action' assumes nothing interacts

So this is a great opportunity for new mathematics and applications!

Chemists have reliable quantitative date

but almost all their theory ignores interactions

Enormous opportunities
for
mathematics!

But you have to know which chemistry

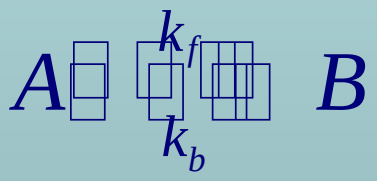
That is where I can help, ……. I hope!

Chemistry
is about
Chemicals

not signals

Law of Mass Action

is what how chemists describe chemicals



$$J_{AB} = -\frac{d}{dt}[A] = k_f\,[A]; \qquad J_{BA} = -\frac{d}{dt}[B] = k_b[B]$$

k is constant

[A] means the activity or approximately the concentration of species A, i.e., the number density of A

Law of Mass Action

is about

Conservation of Mass and Matter

It is not about conservation of charge

$$X \underset{k_{yx}}{\overset{k_{xy}}{\rightleftharpoons}} Y \underset{k_{zy}}{\overset{k_{yz}}{\rightleftharpoons}} Z$$

$$J_{xy}^{net} = J_{xy} - J_{yx}$$

$$= k_{xy}[X] - k_{yx}[Y]$$

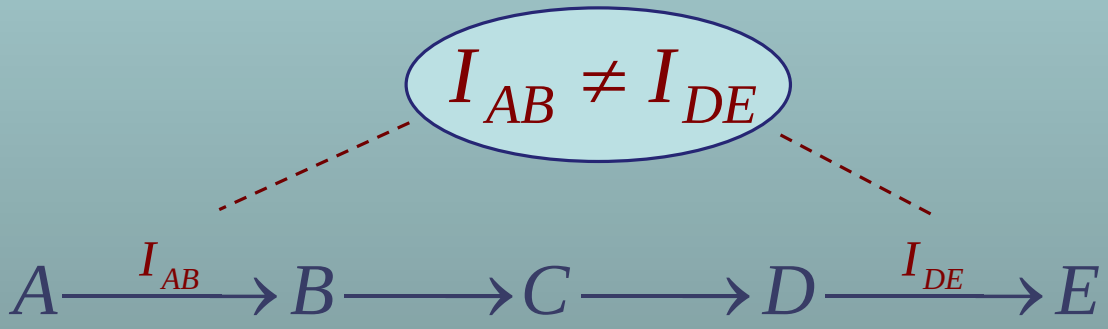
$$I_{xy}^{net} = z_x F k_{xy}[X] - z_y F k_{yx}[Y]$$

[X] means the concentration, really activity of species Z, i.e., concentration is the number density

F is Faraday constant 96,500 coulombs/mole=6.023×10^{23} particles

Units of current I_{xy} are (cou/sec)/liter

‘Current-in’
does not equal
‘Current-out’
in
Law of Mass Action



but **Kirchoff Current Law** *(i.e., Maxwell Eqns)*

requires

$$I_{AB} = I_{DE}$$

More specifically

$$X \underset{k_{yx}}{\overset{k_{xy}}{\rightleftharpoons}} Y \underset{k_{zy}}{\overset{k_{yz}}{\rightleftharpoons}} Z$$

$$I_{XY} - I_{YZ} = z_x F k_{xy}[X] - z_y F k_{yx}[Y]$$

$$- z_y F k_{yz}[Y] + z_z F k_{zy}[Z]$$

$$I_{XY} \neq I_{YZ}$$

Significance of Error

Asymmetry Determines Size of the Error

Special Case *A**: Set all **charges equal to one**, along with **concentrations equal to one**,

$$\frac{\hat{I}_{XY} - \hat{I}_{YZ}}{F \cdot 1 \frac{\text{mole}}{\text{liter}}} = k_{xy} - k_{yx} - k_{yz} + k_{zy};$$

$$\text{Concentrations} = 1 \frac{\text{mole}}{\text{liter}}; z_X = z_y = z_Z = 1$$

Special Case B: Alternatively, set all rate constants and all concentrations equal to one,

$$\frac{\widehat{I}_{XY} - \widehat{I}_{YZ}}{F \cdot 1 \frac{\text{mole}}{\text{liter}} \frac{1}{\text{sec}}} = z_X - z_Y - z_Y + z_Z;$$

$$\text{Concentrations} = 1 \frac{\text{mole}}{\text{liter}}; \text{rate constants} = 1 \frac{1}{\text{sec}}$$

Discontinuities in Current have Large Effects

$$I_{XY} - I_{YZ}$$

has large effects
exceeding breakdown voltages in
microseconds

Chemistry

is about

Isolated Substances

Engineering

is about

Signals

interactions with outside world,

not substances

Maxwell's Equations

Kirchoff's Current Law

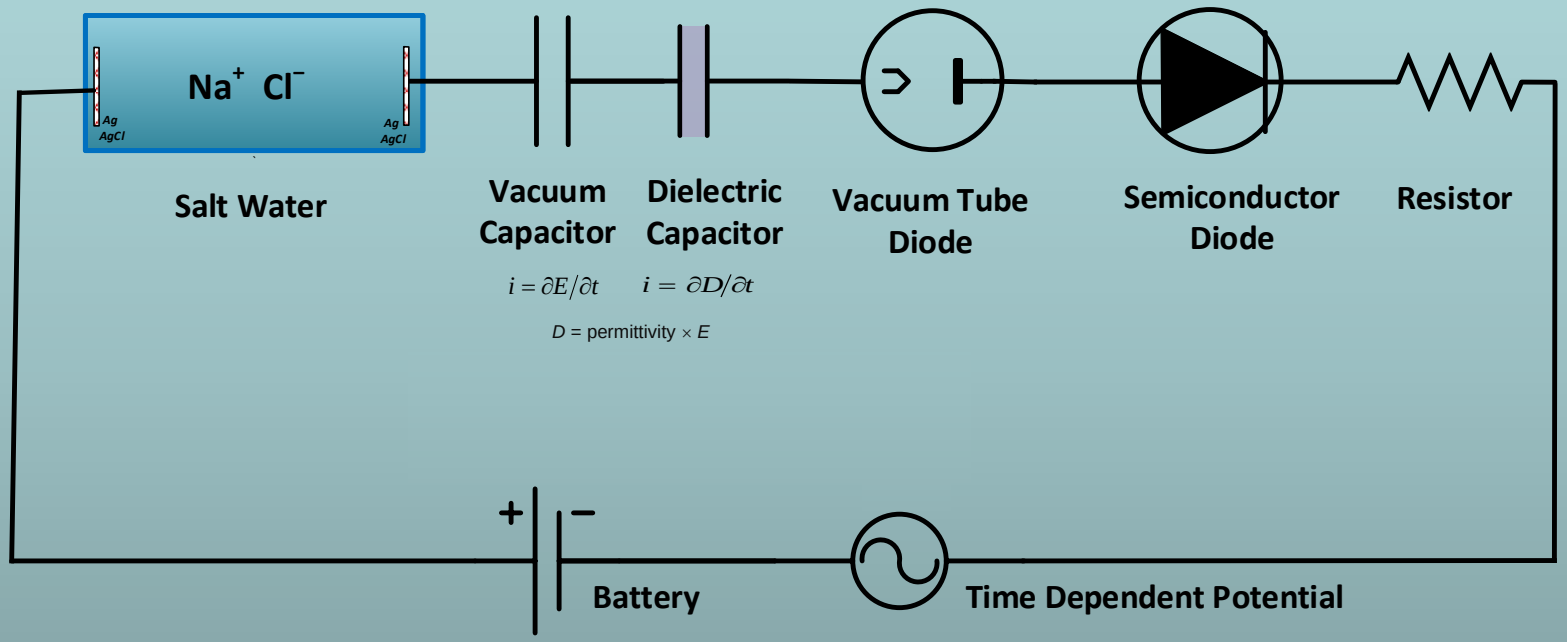
compute

Signals

from Conservation of Charge
and
Continuity of Current,
including displacement current

‘Charge’ is an Abstraction

with different physics in different systems



but **Continuity of Current is Exact**

No matter what carries the current!

Currents are
NOT
just the sum of
Currents of Particles

Current is Abstract

it includes

Displacement Current

and

Current of quasi-particles

for example

Currents are NOT just the sum of fluxes of Charged particles

Current is Abstract

it includes

Displacement Current

$$i_{displacement} = C(\partial V/\partial t) = i_{\Sigma} = \text{ sum of fluxes of charges}$$

$\partial V/\partial t$ adjusts itself so generalized current has no discontinuities

Generalized Current $i_{displacement} + i_{\Sigma}$ is continuous

C is capacitance “to ground”, i. e. to infinity
Capacitance is charge divided by “self-energy”

Electricity is Different

it has a life of its own,
beyond mass

Mass accumulates

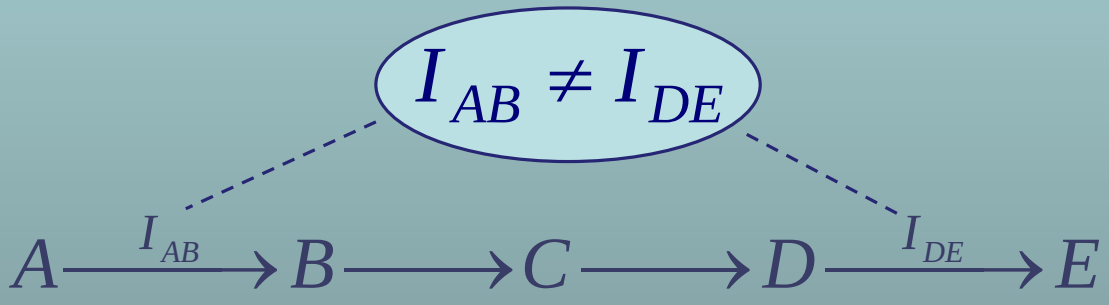
but voltage always changes so

GENERALIZED CURRENT

$$i_{displacement} + i_{\Sigma}$$

NEVER ACCUMULATES

‘Current-in’
does not equal
‘Current-out’
in
Law of Mass Action



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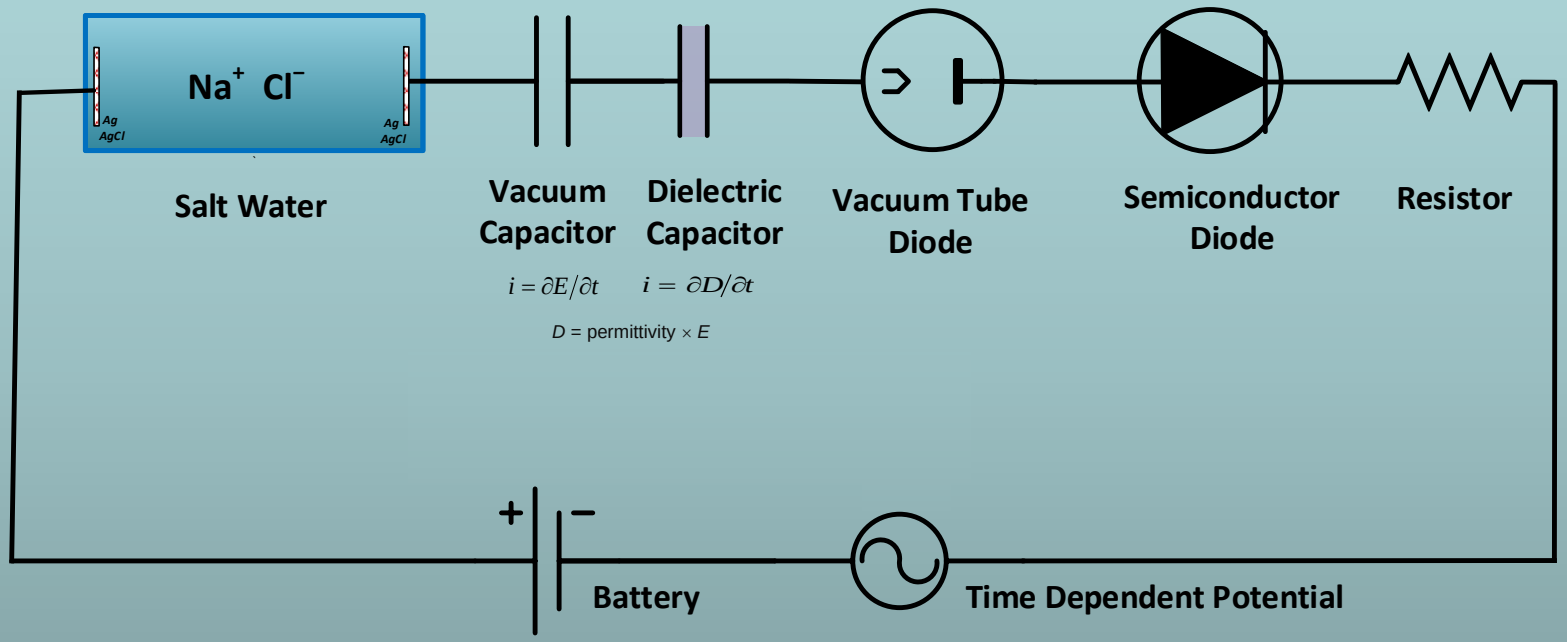

but **Continuity of Current is Exact**

No matter what carries the current!

Transferrable Models are not Possible

Rate constants chosen at one boundary charge or one potential cannot work for different charges or potentials.

Currents in Rate Models

are

Independent of Charge and Potential

but

in the real world

Currents depend on Charge and Potential

Correlation between Currents
0.999 999 999 999 999 999
because
Conservation of Charge is exact

Kirchoff Continuity of Current Law

Classical Chemical Reactions Assume
INDEPENDENT
uncorrelated
Rate Constants

Transferrable Models are not Possible with this assumption

Reconciling

Mass Action

and

Maxwell-Kirchoff

will no doubt be a

Long Journey

“Journey
of a thousand miles
starts
with a single step”

in the right direction,

I beg to add to this Chinese saying

Let's do Channels!
They are easier than bulk solution!!!

Biology is Easier than Physics
because reduced models exist!

Biology is Easier than Physics

Reduced Models Exist*

for important biological functions

or the

Animal would not survive

to reproduce

***Evolution provides the existence theorems and uniqueness conditions so hard to find in theory of inverse problems.**

(Some biological systems – the human shoulder – are not robust,
probably because they are incompletely evolved,
i.e they are in a local minimum 'in fitness landscape' .
I do not know how to analyze these.
I can only describe them in the classical biological tradition.)

Mathematics of Molecular Biology Provides Great Opportunity

Biology Provides the Data

Engineering Provides the Approach

Mathematics Provides the Tools

particularly variational methods that allow
'everything' to interact with 'everything' else

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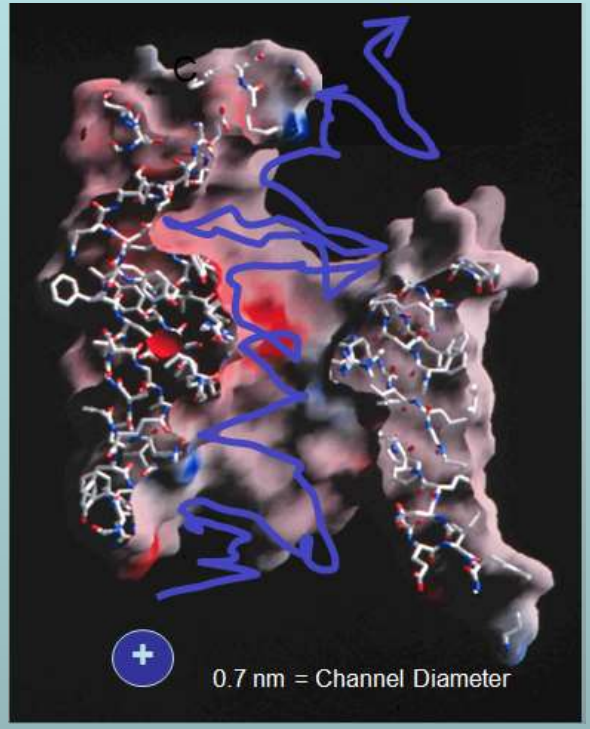


Thousands of Molecular Biologists Study Ion Channels Everyday,
One protein molecule at a time using amplifiers like the AxoPatch

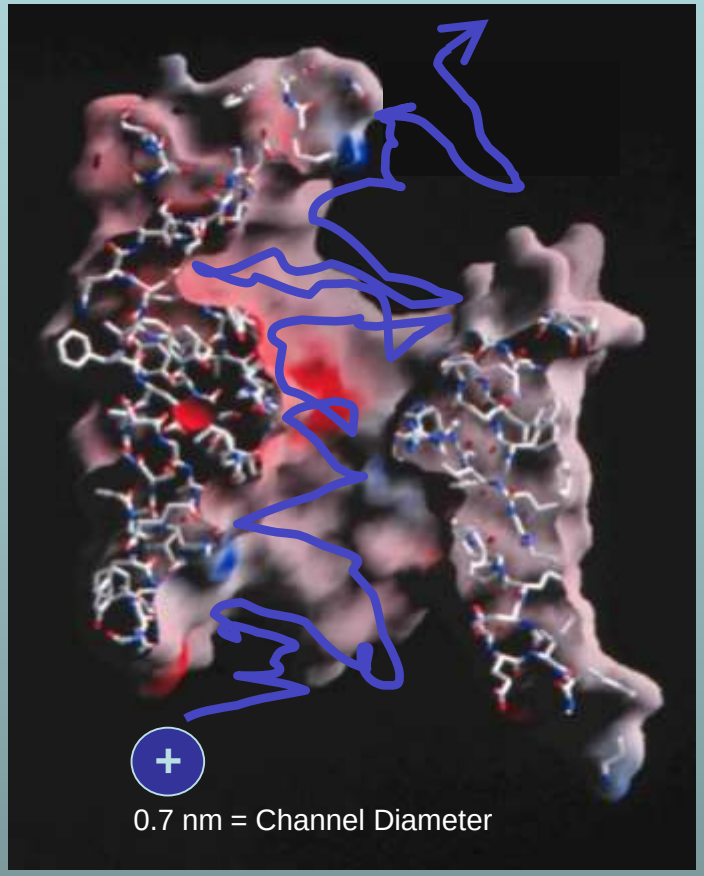
Ion Channels are the Valves of Cells

Ion Channels are the Main Controllers of Biological Function

Selectivity

Different Ions carry Different Signals

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



~30 Å

Figure of ompF porin by Raimund Dutzler

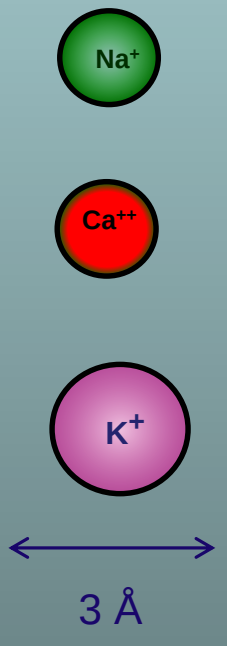
Ions in Water*

are the

Liquid of Life

***Pure H_2O is toxic to cells & proteins**

Hard Spheres



3 Å

ION CHANNELS – Biological Role

Ion channels coordinate contraction of cardiac muscle making the heart a pump

Ion channels coordinate contraction in skeletal muscle

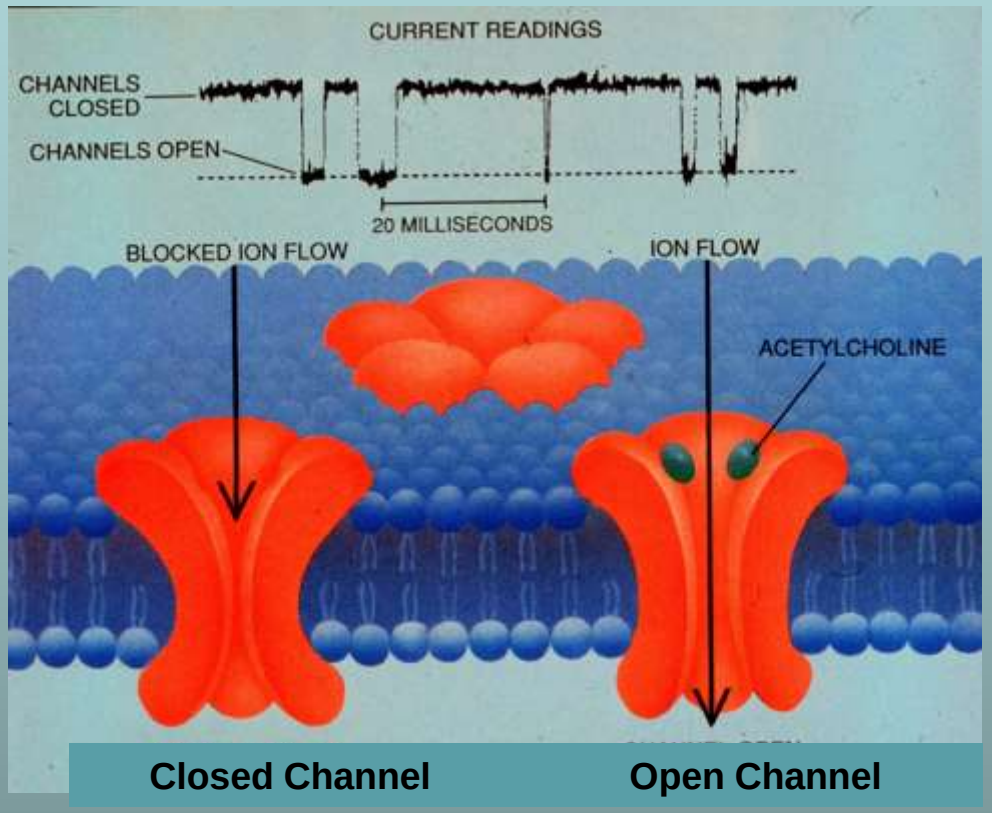
Ion channels control all electrical activity and produce nerve signals

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 with genes (blueprints) manipulated by molecular genetics

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



Reduced models exist

because

they are the adaptation

created by evolution

to perform a biological function

like selectivity

Reduced Models

and its parameters

are found by

Inverse Methods

of Reverse Engineering

I have presented evidence for a satisfactory reduced model of Calcium Channels in many previous talks so I did not want to bore you with again.

Just send an email!!

bob.eisenberg@gmail.com
or
beisenbe@rush.edu

The End

Any Questions?

Evidence

Best Evidence is from the

RyR Receptor

Dirk Gillespie

Gerhard Meissner, Le Xu, et al,
not *Bob Eisenberg*

- **More than 120 combinations of solutions & mutants**
- **7 mutants with significant effects fit successfully**

1. Gillespie, D., Energetics of divalent selectivity in a calcium channel: the ryanodine receptor case study. *Biophys J, 2008. 94(4): p. 1169-1184.*
2. Gillespie, D. and D. Boda, Anomalous Mole Fraction Effect in Calcium Channels: A Measure of Preferential Selectivity. *Biophys. J., 2008. 95(6): p. 2658-2672.*
3. Gillespie, D. and M. Fill, Intracellular Calcium Release Channels Mediate Their Own Countercurrent: Ryanodine Receptor. *Biophys. J., 2008. 95(8): p. 3706-3714.*
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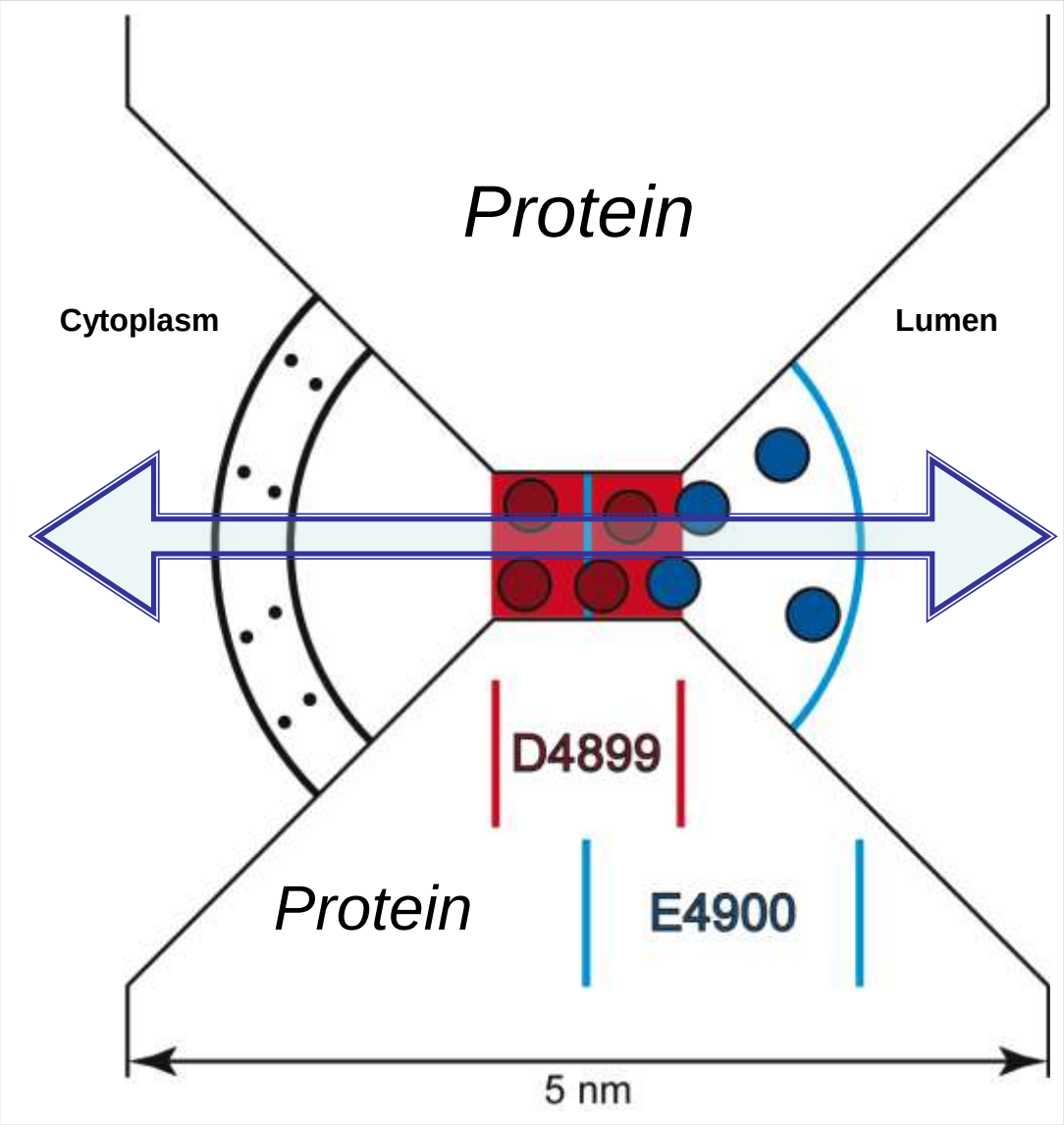
14. Xu, L., Y. Wang, D. Gillespie, and G. Meissner, Two Rings of Negative Charges in the Cytosolic Vestibule of T Ryanodine Receptor Modulate Ion Fluxes. *Biophysical Journal, 2006. 90: p. 443-453.*

The Geometry



Selectivity Filter

- is 10 Å long and 8 Å in diameter
- confines four **D4899** negative amino acids
- Four **E4900** positive amino acids are on lumenal side,overlapping D4899
- **Cytosolic distributed charge**

D. Gillespie *et al.*, *J. Phys. Chem.* 109, 15598 (2005).

Ryanodine Receptor Pore

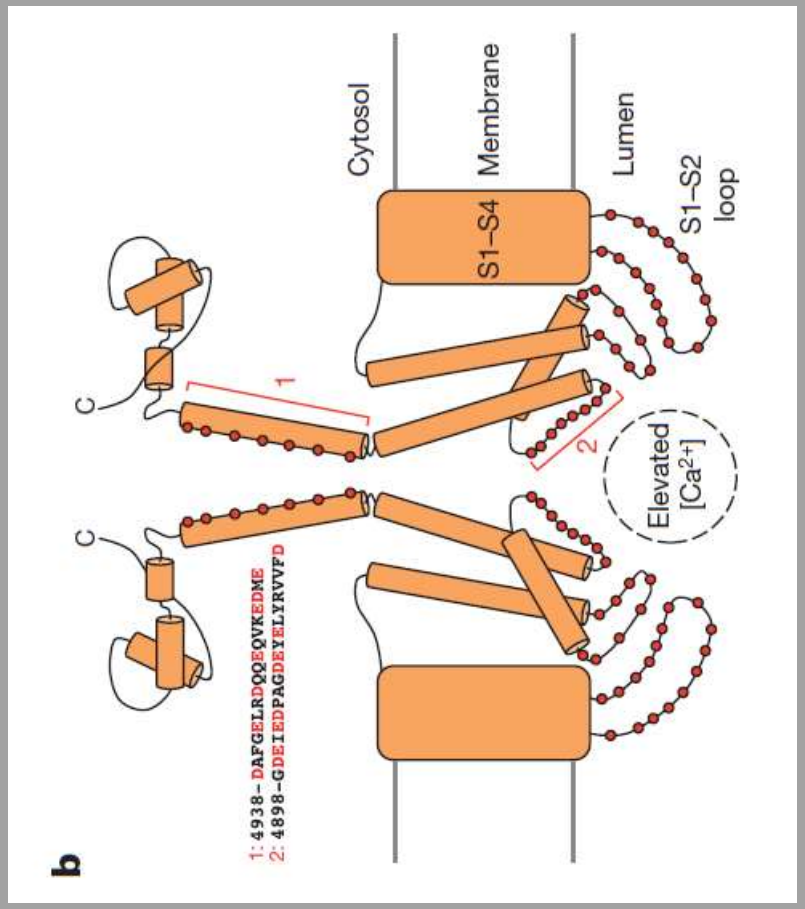
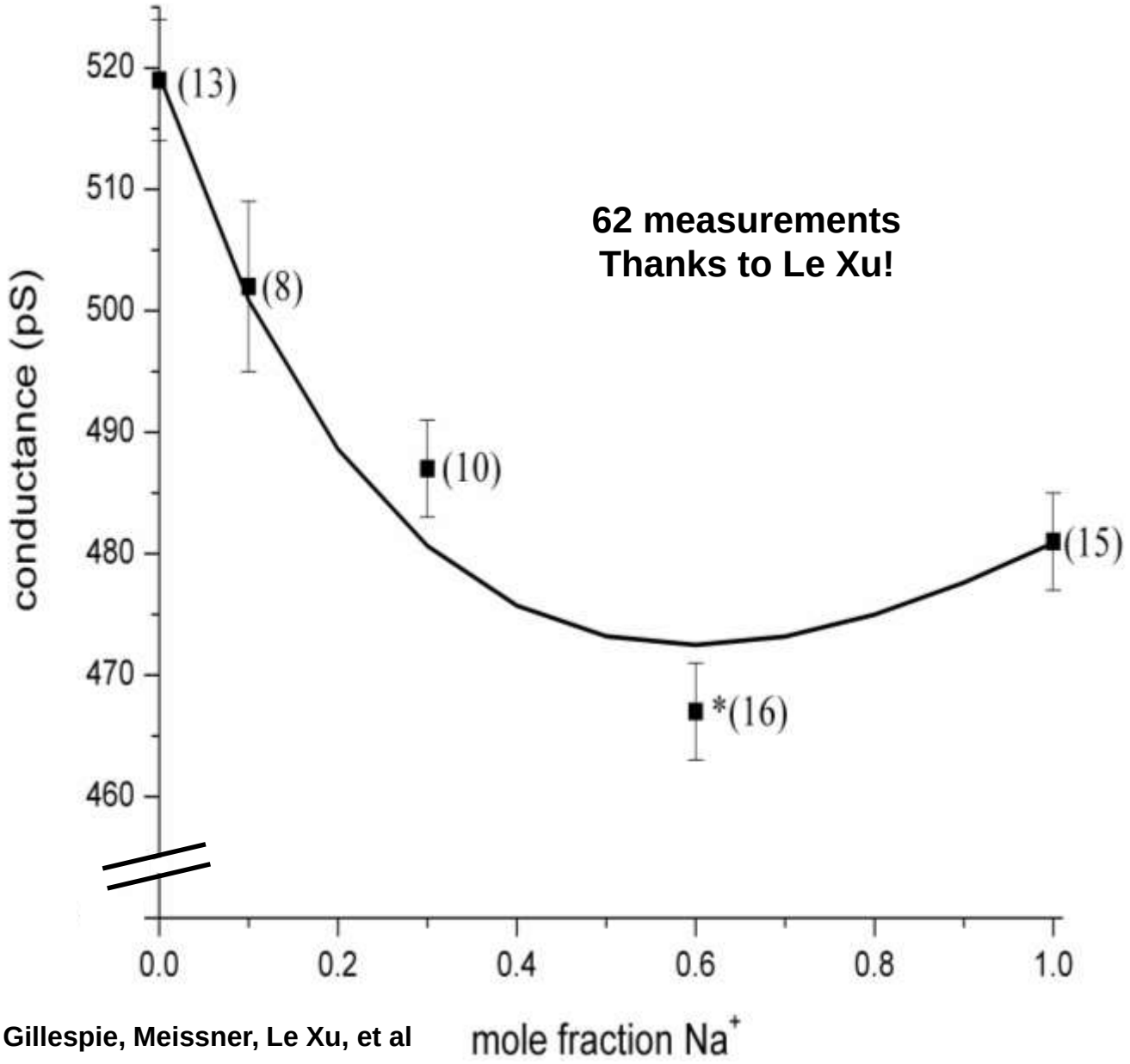


Fig 3 The RyR1 conduction pathway

from Zalk et al, Nature, 2014, 10.1038/nature13950

"b, Scheme … of all the negatively charged residues in the ionic pathway (red dots) and the [other] negatively charged residues"

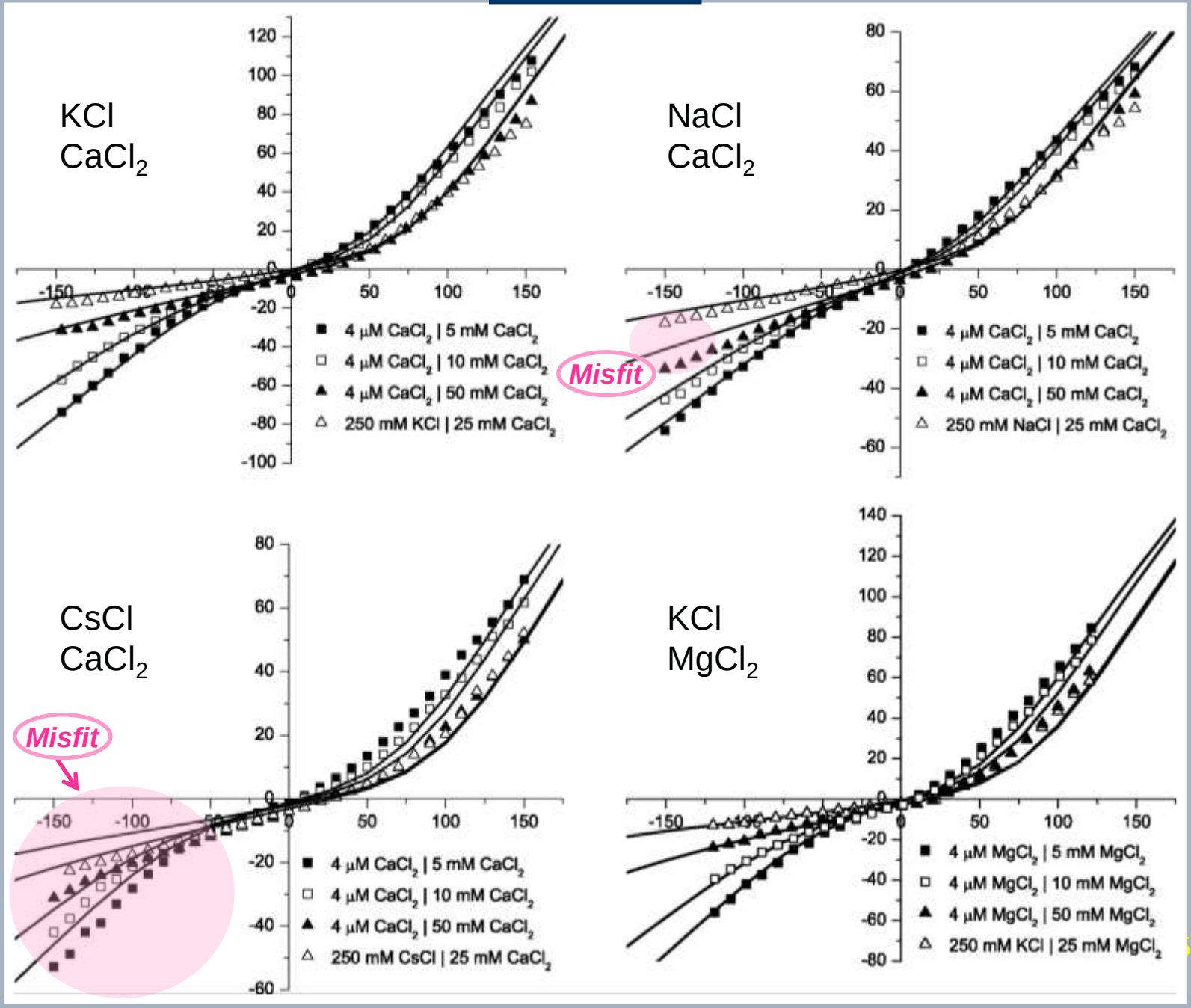
The model predicted an AMFE for Na^+/Cs^+ mixtures before it had been measured



62 measurements
Thanks to Le Xu!

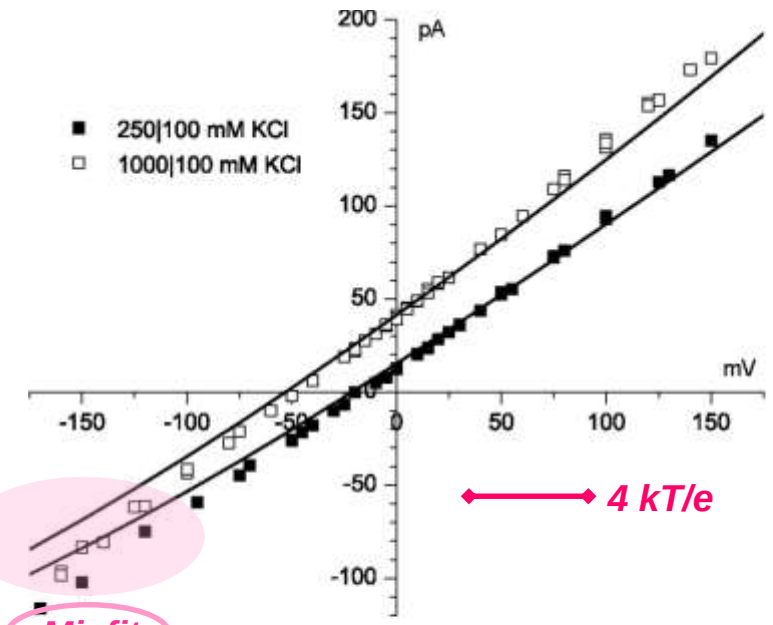
Gillespie, Meissner, Le Xu, et al

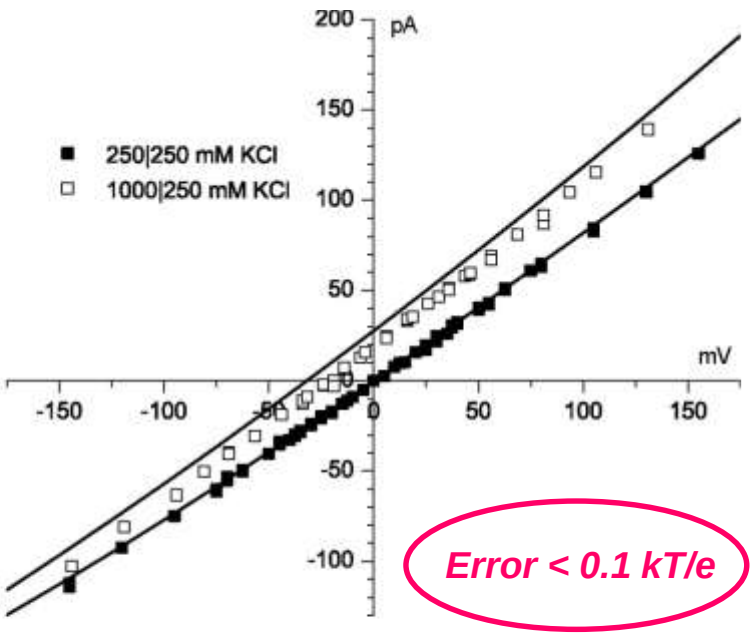
Divalents

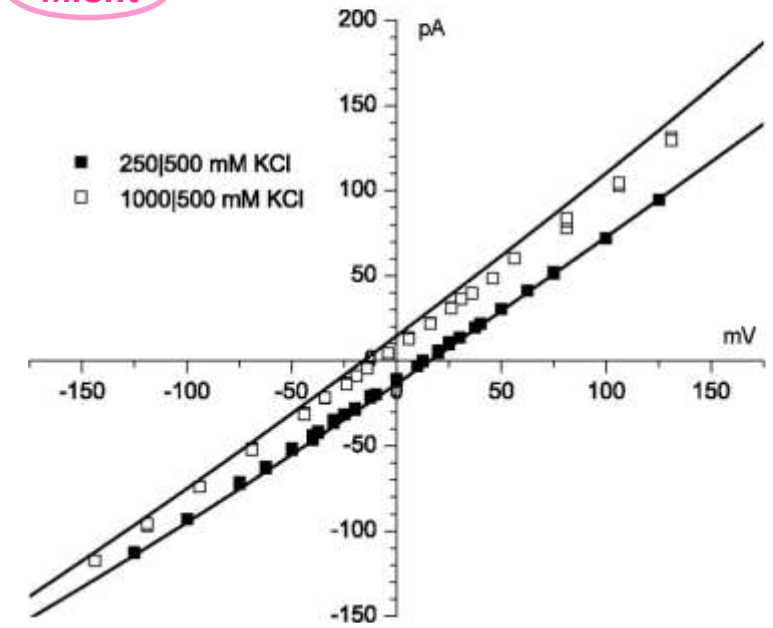

KCl
CaCl2
4 μM CaCl2 | 5 mM CaCl2
4 μM CaCl2 | 10 mM CaCl2
4 μM CaCl2 | 50 mM CaCl2
250 mM KCl | 25 mM CaCl2
NaCl
CaCl2
Misfit
4 μM CaCl2 | 5 mM CaCl2
4 μM CaCl2 | 10 mM CaCl2
4 μM CaCl2 | 50 mM CaCl2
250 mM NaCl | 25 mM CaCl2
CsCl
CaCl2
Misfit
4 μM CaCl2 | 5 mM CaCl2
4 μM CaCl2 | 10 mM CaCl2
4 μM CaCl2 | 50 mM CaCl2
250 mM CsCl | 25 mM CaCl2
KCl
MgCl2
4 μM MgCl2 | 5 mM MgCl2
4 μM MgCl2 | 10 mM MgCl2
4 μM MgCl2 | 50 mM MgCl2
250 mM KCl | 25 mM MgCl2

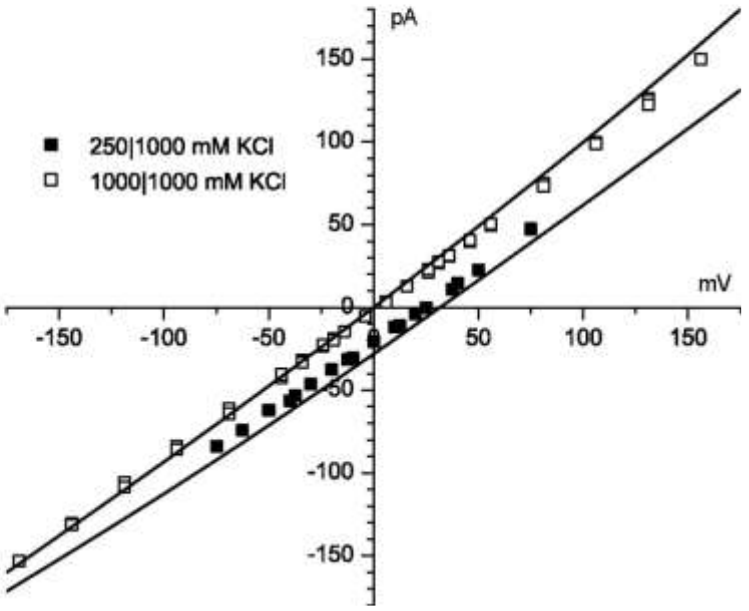
KCl

Gillespie, Meissner, Le Xu, et al



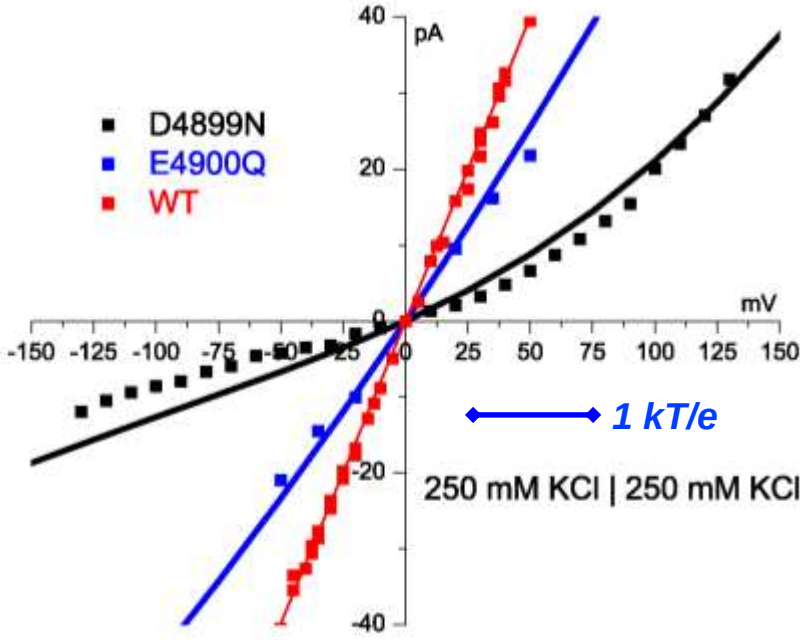




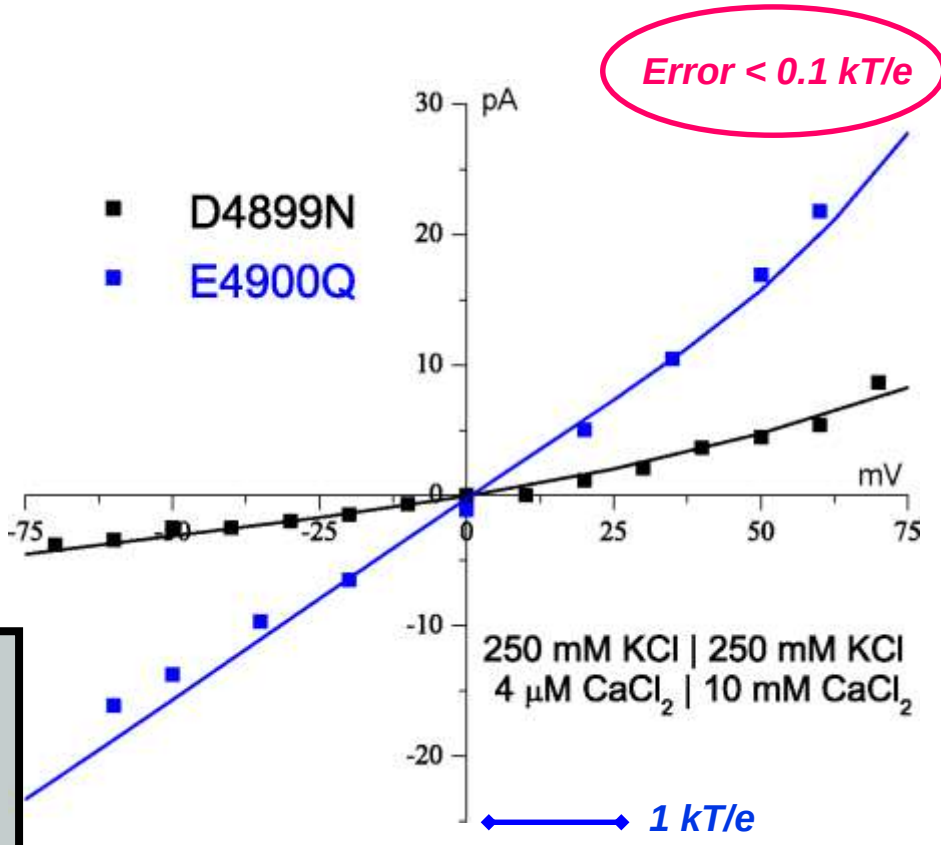


Theory fits Mutation with Zero Charge

Theory Fits Mutant in K



Theory Fits Mutant in K + Ca



Protein charge density

wild type* 13 M ⇨ 0 M *in* D4899

Water is 55 M

some wild type curves not shown, 'off the graph'

Gillespie *et al*
J Phys Chem 109 15598 (2005)

Calcium Channel

has been examined in ~35 papers, e.g.,

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.

Most of the papers are available at

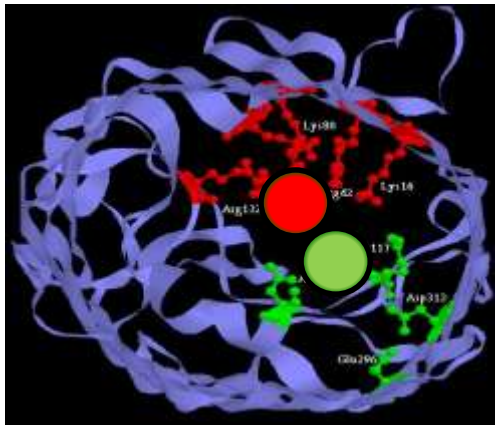
ftp://ftp.rush.edu/users/molebio/Bob_Eisenberg/Reprints

http://www.phys.rush.edu/RSEisenberg/physioeis.html

Experiments have built

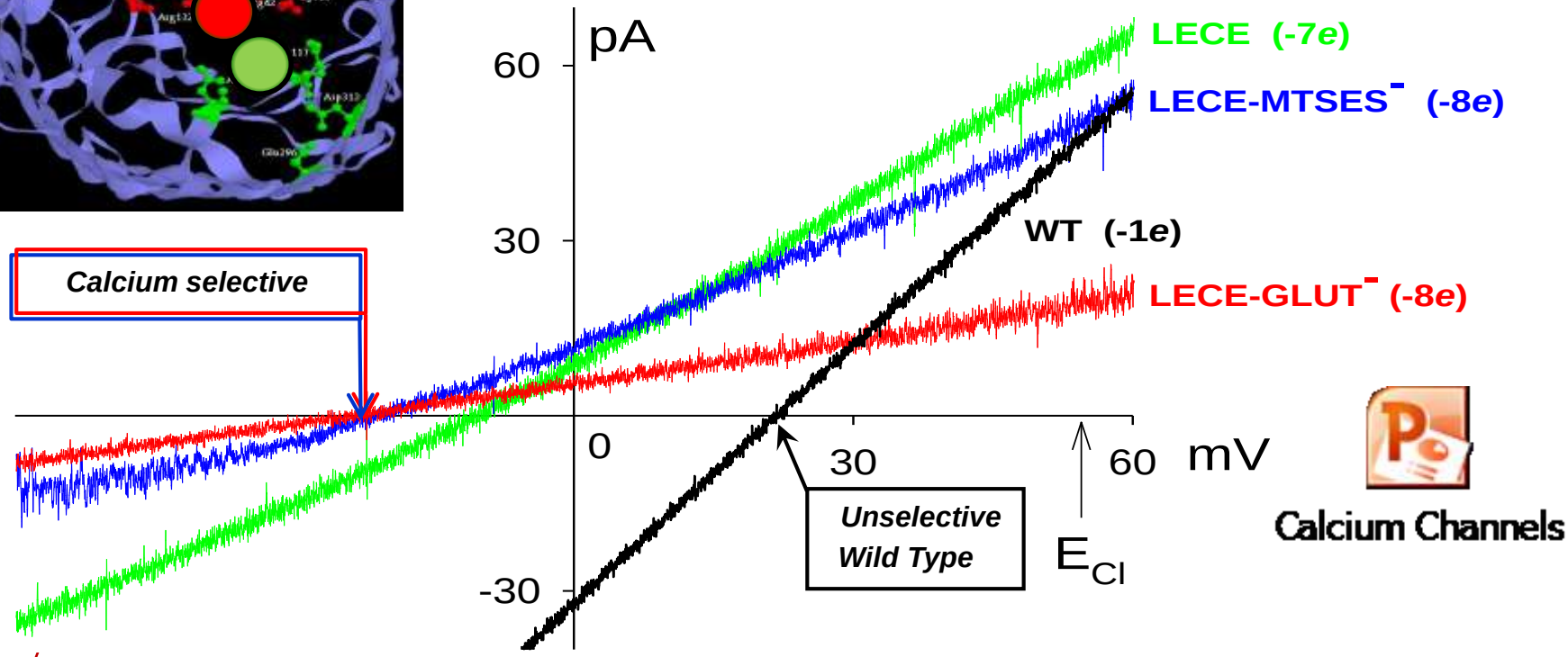
Two Synthetic Calcium Channels

Atomic Scale



Designed by Theory

Glutathione derivatives



As density of permanent charge increases, channel becomes calcium selective

$E_{rev} \rightarrow E_{Ca}$ in 0.1M || 1.0 M $CaCl_2$

Macro Scale

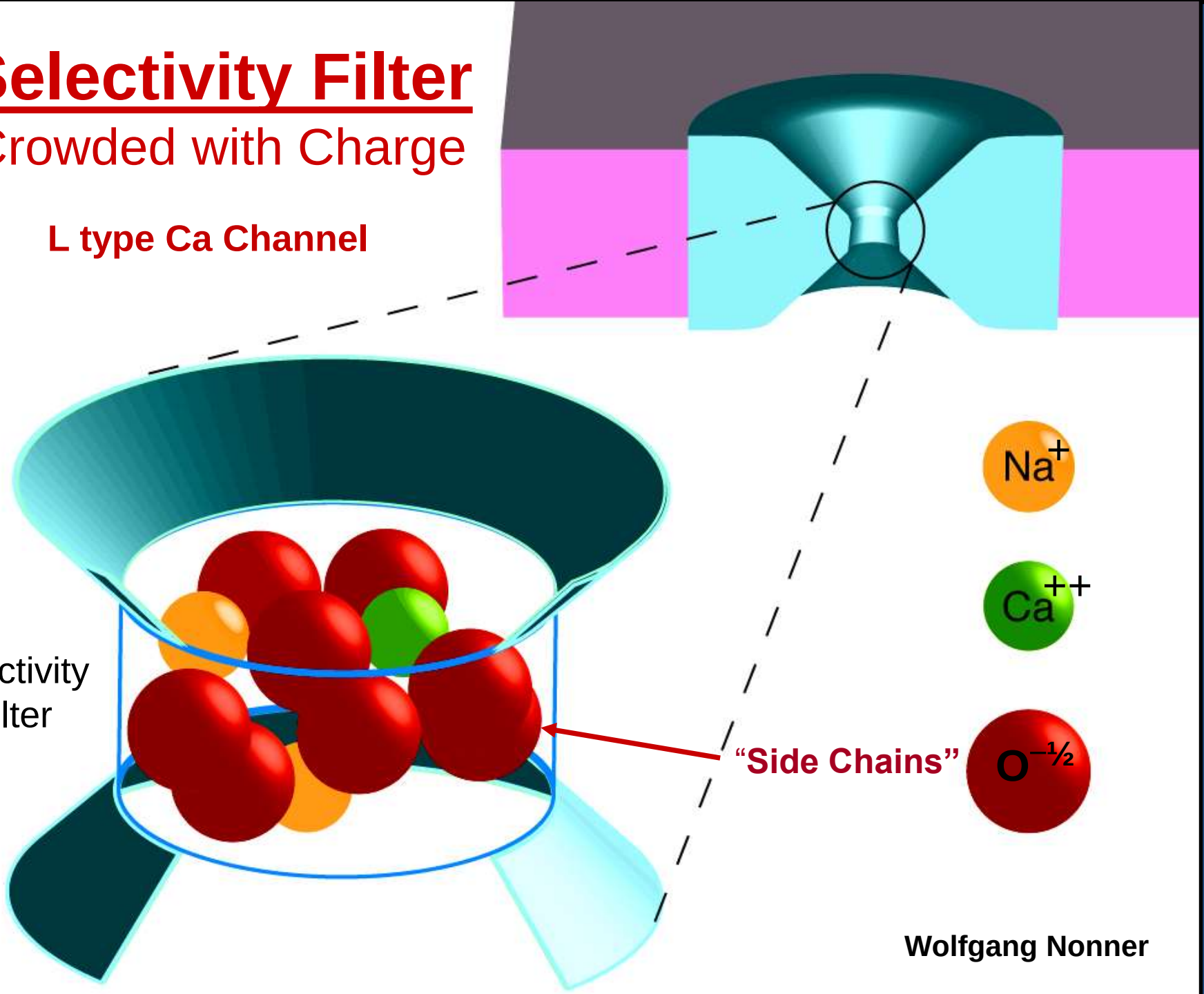
built by Henk Miedema, Wim Meijberg of BioMade Corp.,Groningen, Netherlands

Miedema** et al, **Biophys J 87: 3137–3147 (2004)

Selectivity Filter

Crowded with Charge

L type Ca Channel



Wolfgang Nonner

Ca Channel

Mutation

Na Channel

Same Parameters

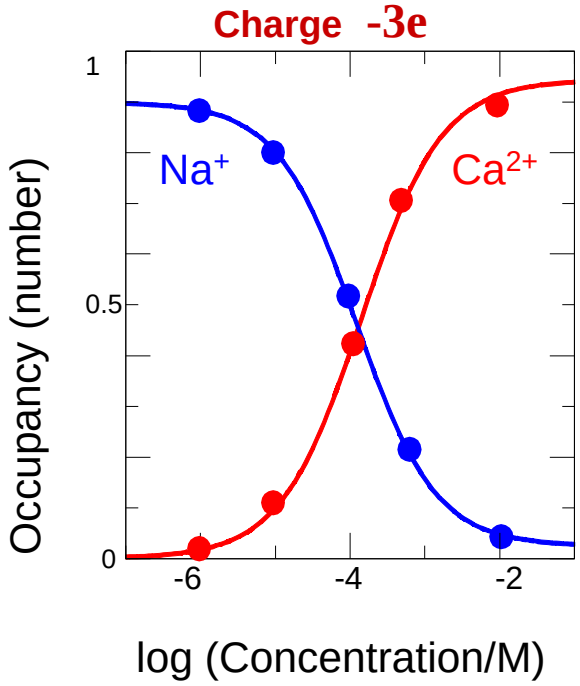
Calcium Channels

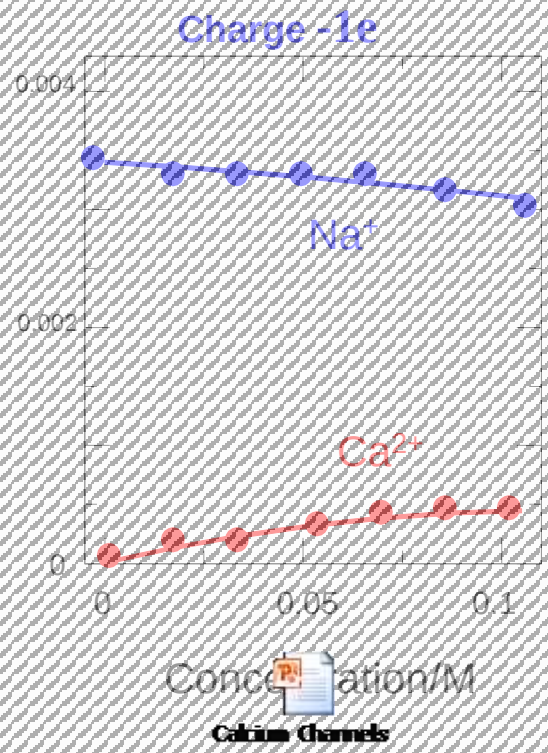
E → D

E → E

E → K

A → A





Calcium Channels

EEEE has full biological selectivity in similar simulations

Boda, et al

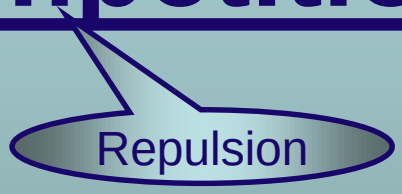
Selectivity

comes from

Electrostatic Interaction

and

Steric Competition for Space



Location and Strength of Binding Sites
Depend on Ionic Concentration and
Temperature, etc

Rate Constants are Variables

Sodium Channel

Voltage controlled channel responsible for signaling in nerve and coordination of muscle contraction

Challenge

from leading biophysicists

Walter Stühmer and Stefan Heinemann

Göttingen *Leipzig*

Max Planck Institutes

Can THEORY explain the MUTATION Calcium Channel into Sodium Channel?

DEEA ⟺ ***DEKA***

Calcium Channel ***Sodium Channel***

Ca Channel

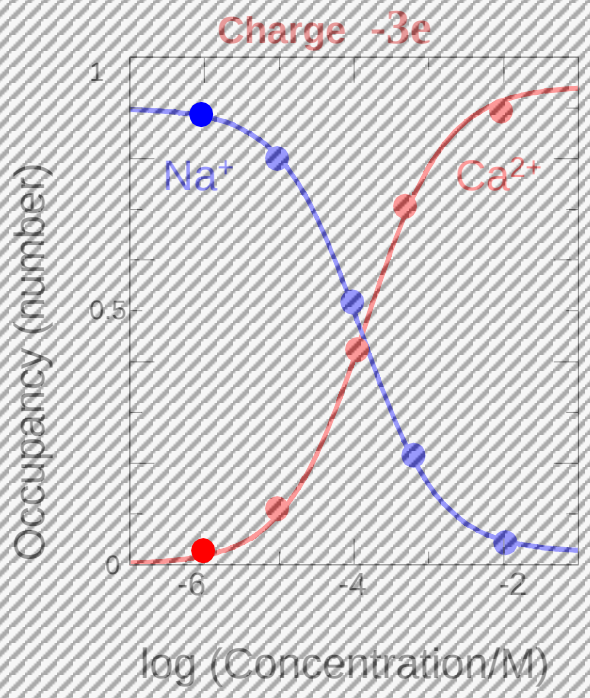
Mutation

Na Channel

Same Parameters

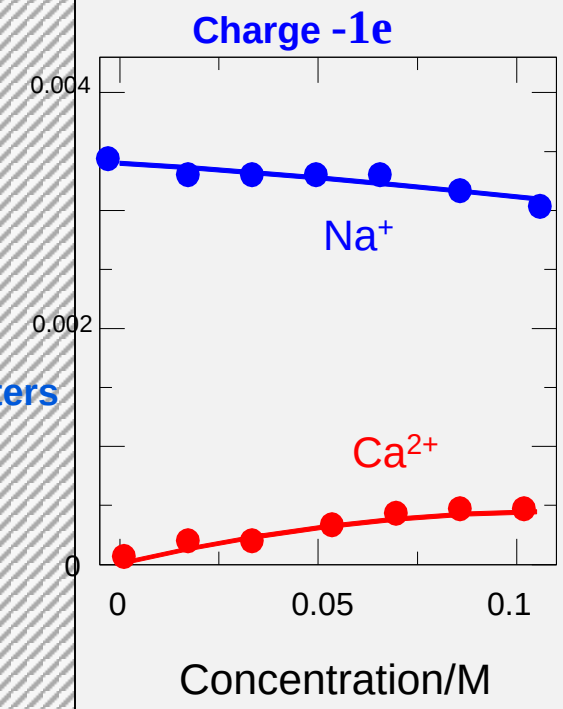
E
E
E
A

D
E
K
A



Mutation

Same Parameters



EEEE has full biological selectivity in similar simulations

Boda, et al

Nothing was changed

from the

EEEA Ca channel

except the amino acids

Calculated DEKA Na Channel
Selects
Ca^{2+} ***vs.*** **Na^{+}** *and also* **K^{+}** ***vs.*** **Na^{+}**

Calculations and experiments done at pH 8

Metropolis Monte Carlo Simulates Location of Ions

both the mean and the variance

Details:

1) Start with Configuration *A*, with computed energy E_A
2) Move an ion to location *B*, with computed energy E_B
3) If spheres overlap, $E_B \rightarrow \infty$ and configuration is rejected
4) If spheres do not overlap, $E_B \rightarrow 0$ and configuration is accepted
5) If $E_B < E_A$: accept new configuration.
6) If $E_B > E_A$: accept new configuration with probability $\exp\left[-\left(E_A - E_B\right)/k_B T\right]$

Key idea

MMC chooses configurations with a Boltzmann probability and weights them evenly

instead of

choosing them from uniform distribution and then weighting them with $\exp(-E/k_B T)$