Ions in Channels
Natural Nanovalves

Workshop

Mathematical Models of Electrolytes in Molecular Biology

National Taiwan University

organized by

Prof. Tai Chia Lin, Chun Liu

Stochastic Derivation of PNP

done previously in some detail, starting with

Langevin Stochastic Differential Equation

using theory of Stochastic Processes,

all the way to Law of Mass Action

analytically, with evaluation of all integrals etc

Today,

Experimental Evidence for all spheres model

This is the best available test of different mathematical models,
in my opinion

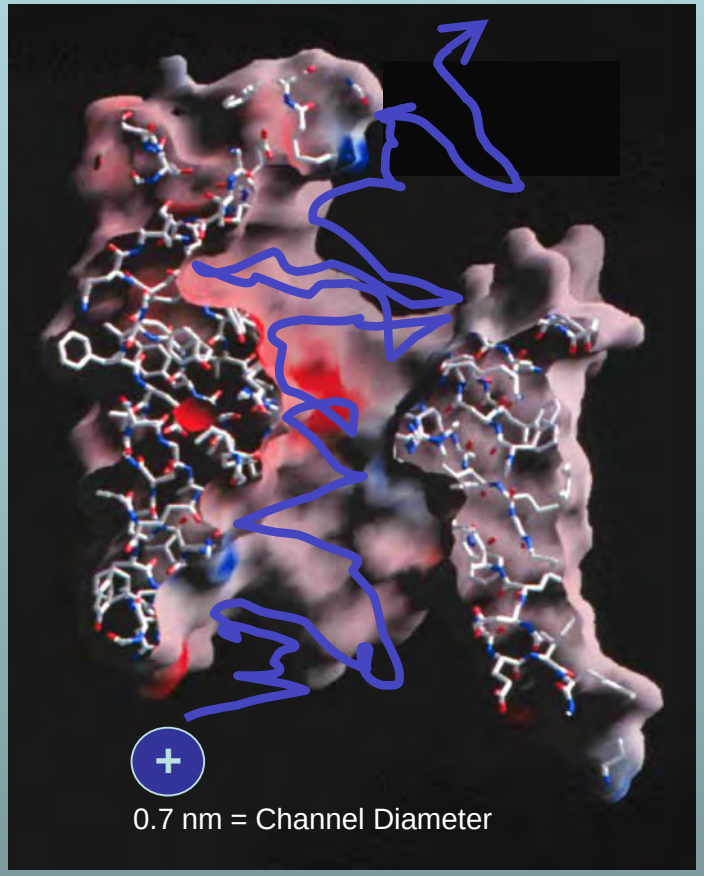
Ion Channels are the Valves of Cells

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

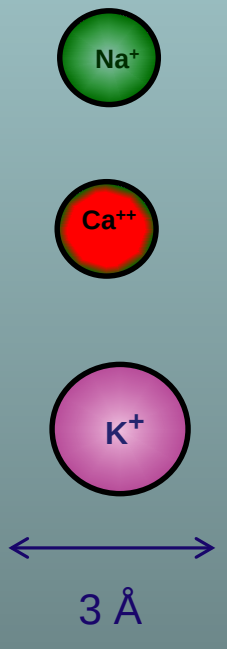
Ions in Water*

are the

Liquid of Life

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

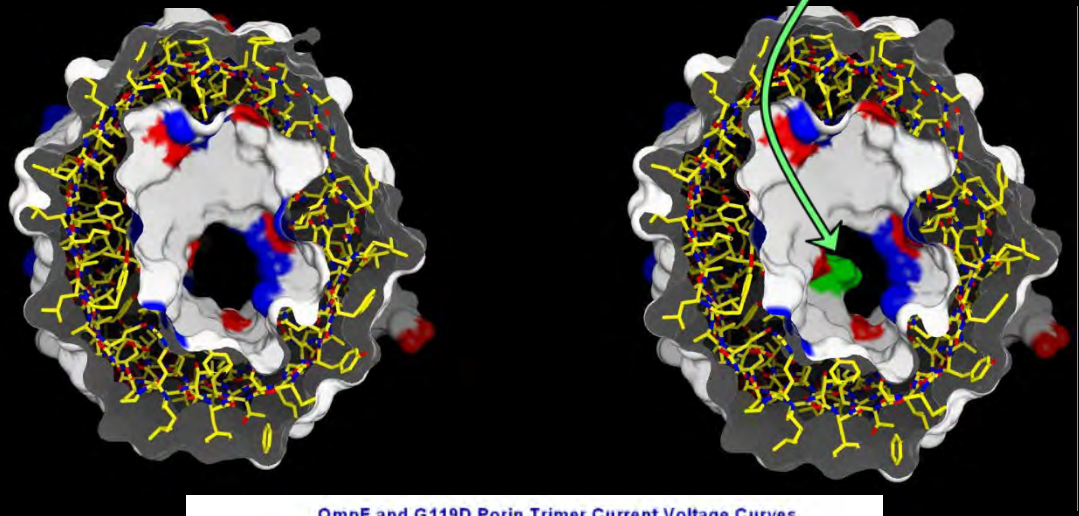
Hard Spheres

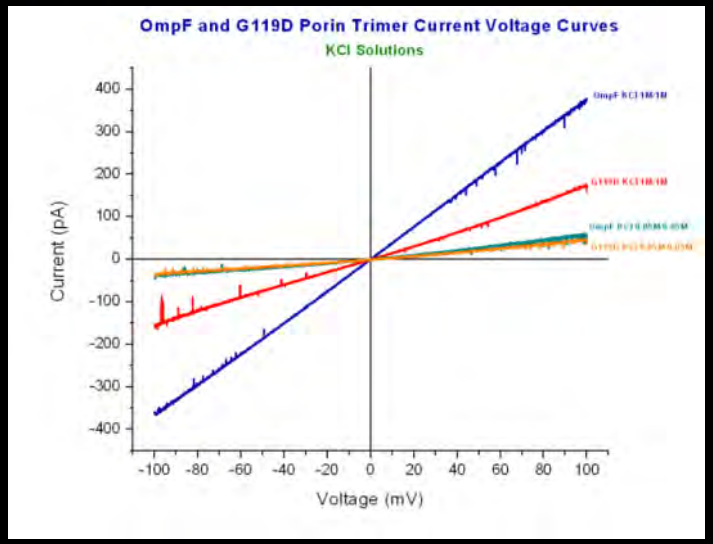


A few atoms make a BIG Difference

Ompf

G119D





Glycine replaced by Aspartate

Structure determined by Raimund Dutzler in Tilman Schirmer's lab

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

General Theme

Mathematics of Molecular Biology

is (mostly)

Reverse Engineering

i.e., solving specific

Inverse Problems

How does it work?
How do a few atoms control
(macroscopic) Biological Function

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

Coordinate contraction in skeletal muscle

Control all electrical activity in cells

Produce signals of the nervous system

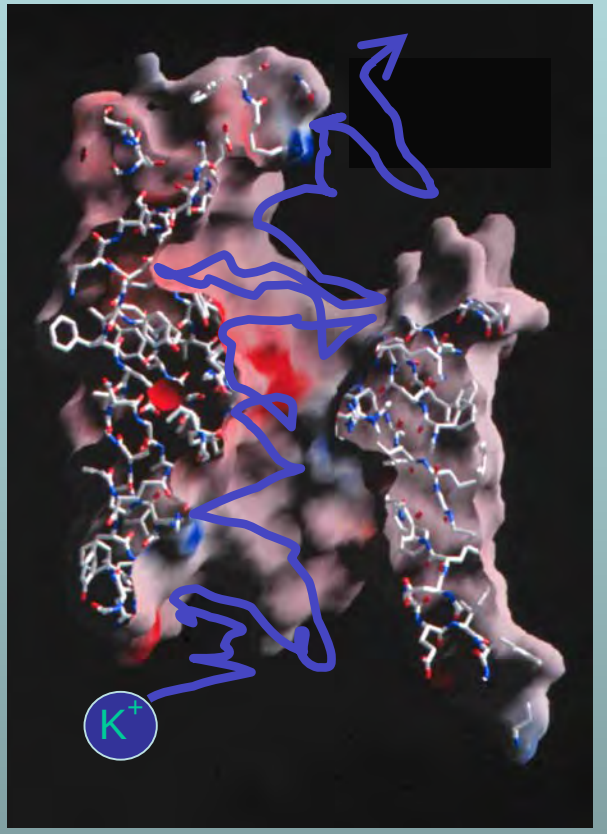
Are involved in secretion and absorption in all cells: kidney, intestine, liver, adrenal glands, etc.

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

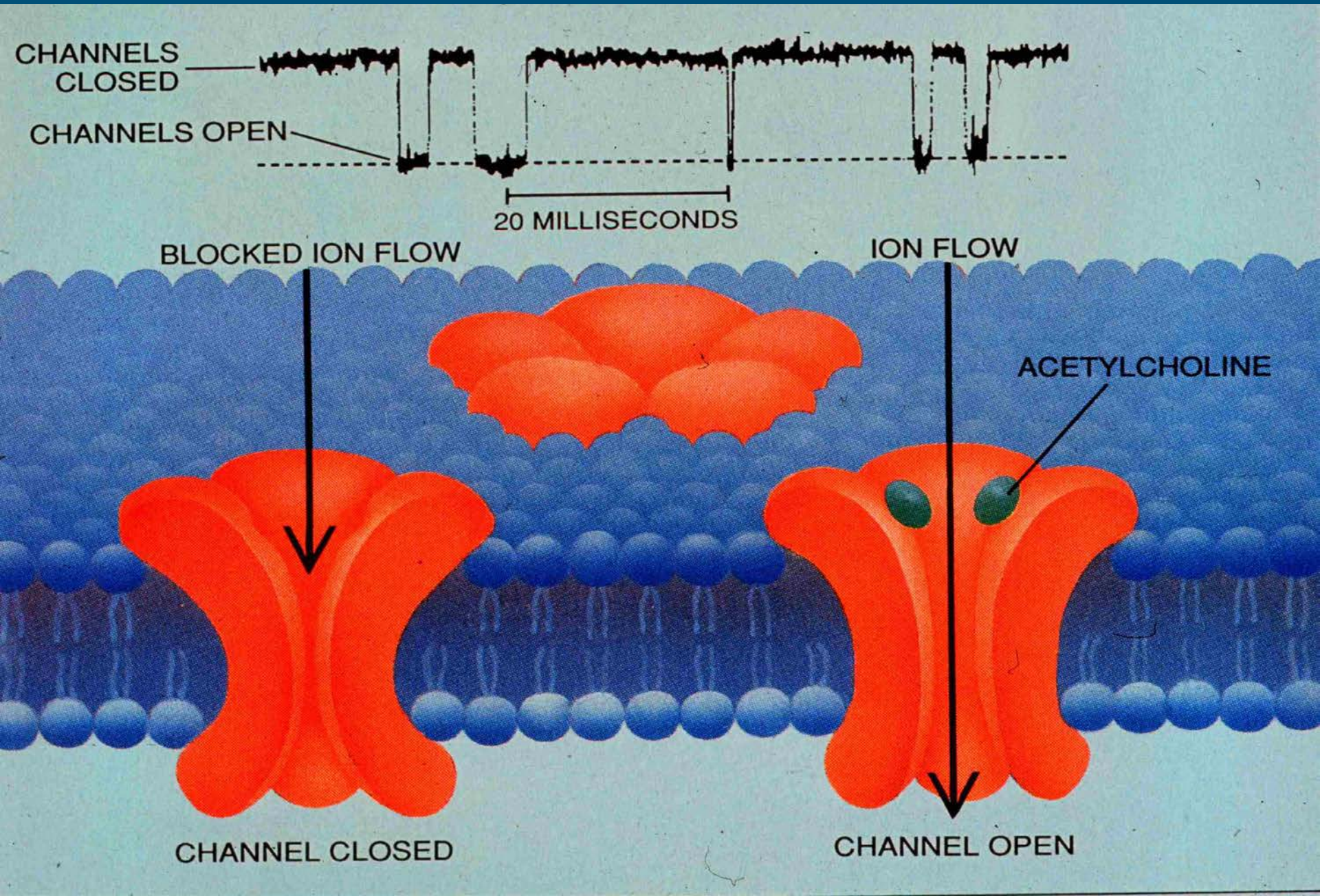


~30 x 10^{-9} meter

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

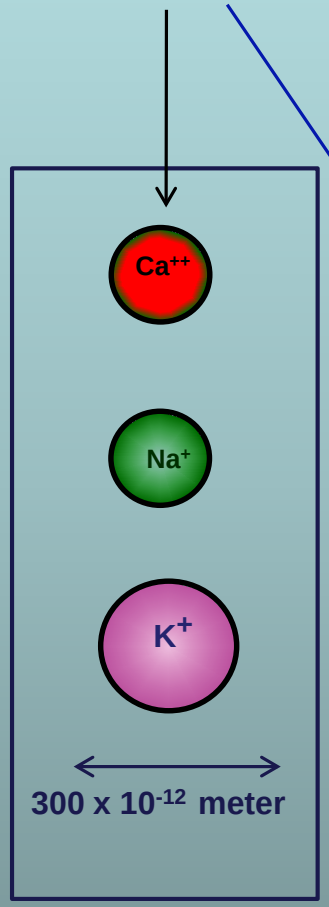
***nearly pico-valves: diameter is 400 – 900 x 10^{-12} meter; diameter of atom is ~200 x 10^{-12} meter**

Current in One Channel Molecule is a Random Telegraph Signal

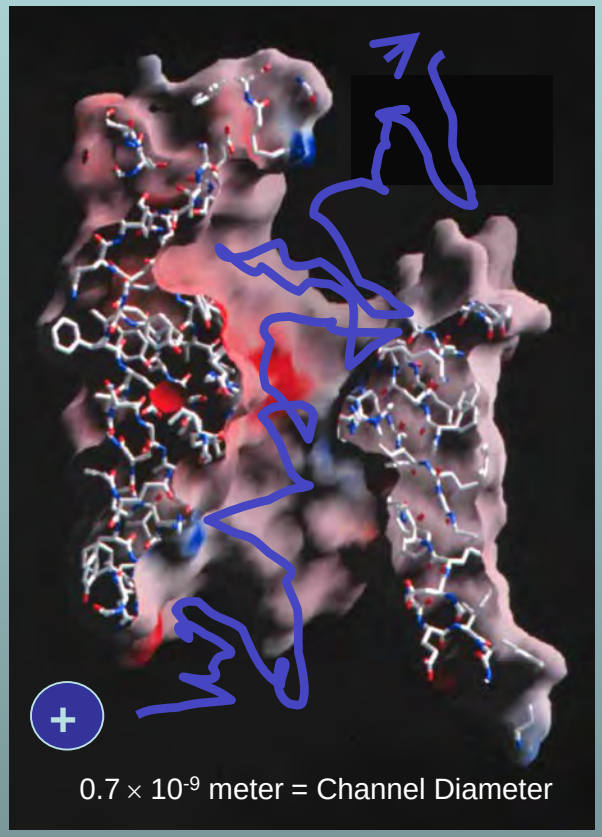


Channels are Selective Molecular Devices

Different Ions Carry Different Signals through Different Channels



ompF porin



Diameter matters

Ionic solutions are NOT ideal

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

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

Figure of ompF porin by Raimund Dutzler

Engineering of Channels
by evolution makes them
Selective Devices

Different Types of Channels

use

Different Types of Ions

for

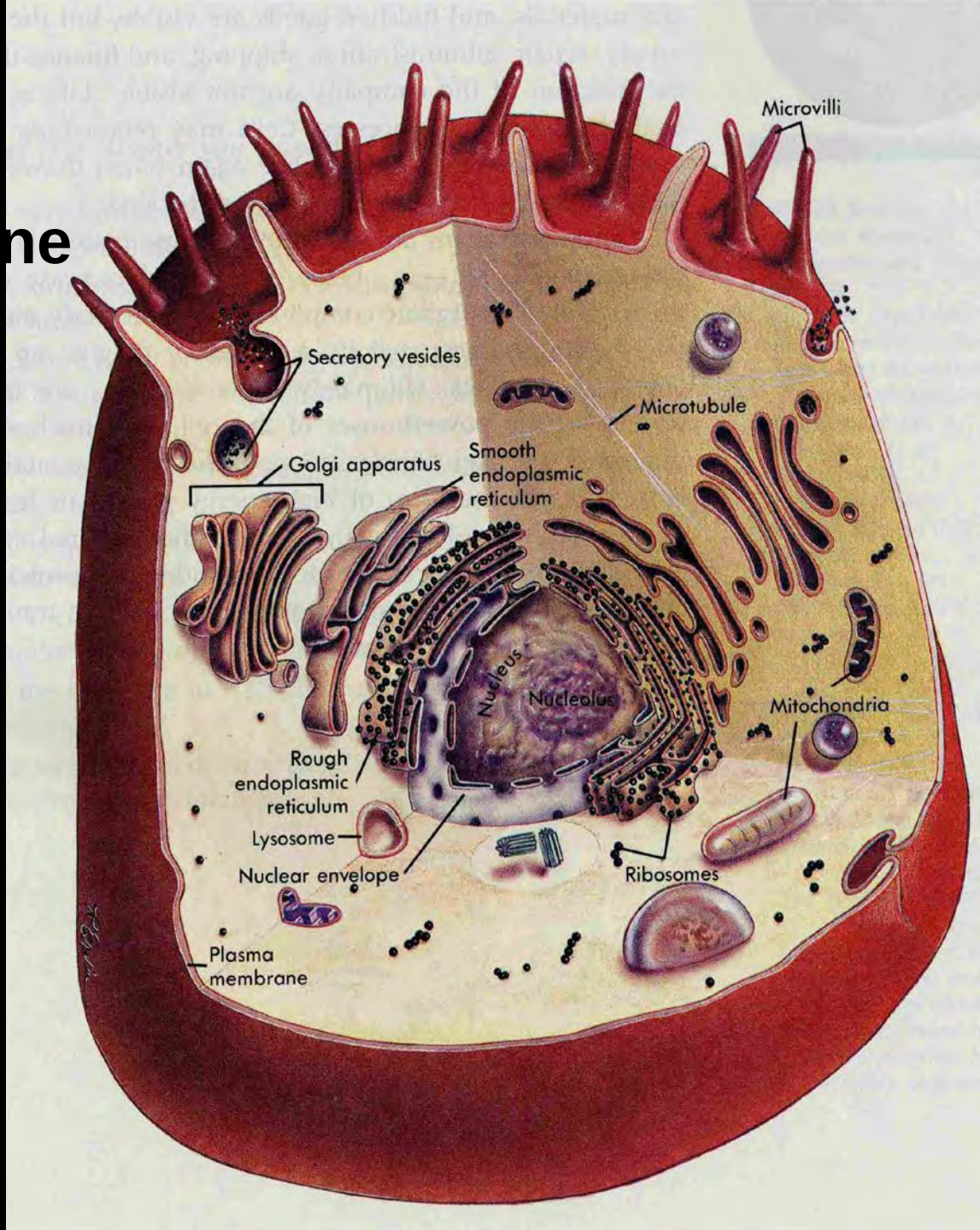
Different Information

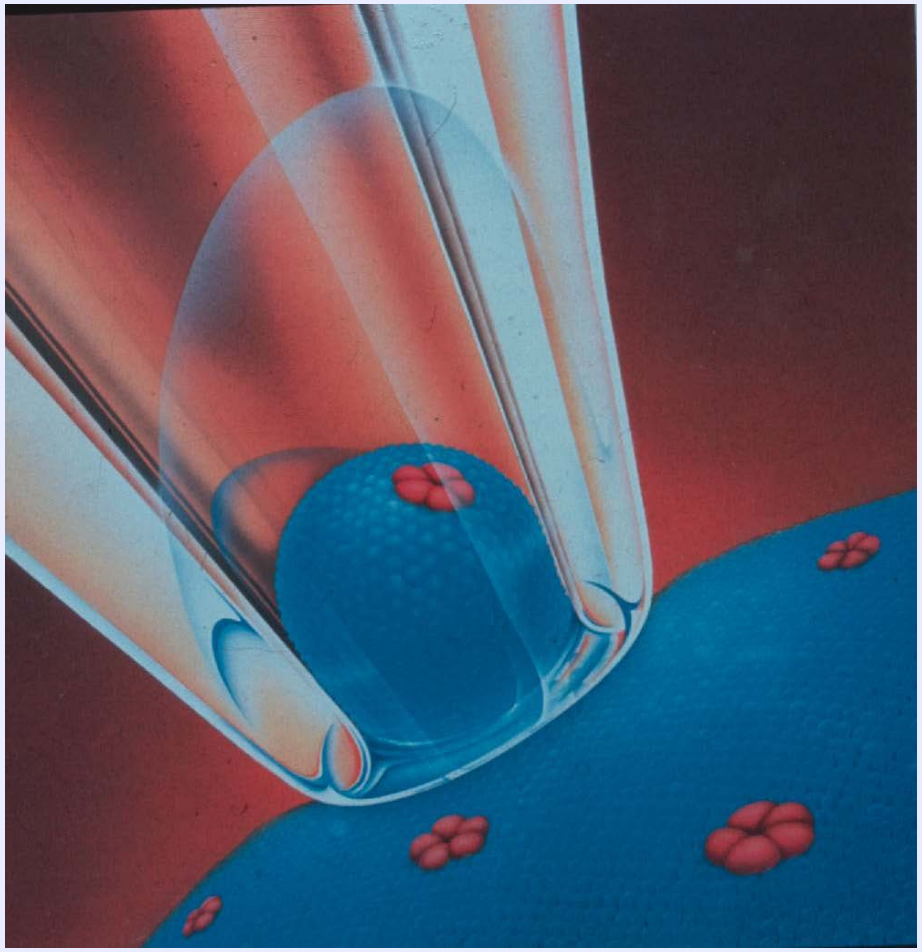
All of life depends on the differences between salts of potassium K^+ and sodium Na^+.

If cells cannot distinguish K^+ from Na^+, they swell, burst and die.

The Cell

Note: intra-cellular compartments are defined by their membranes



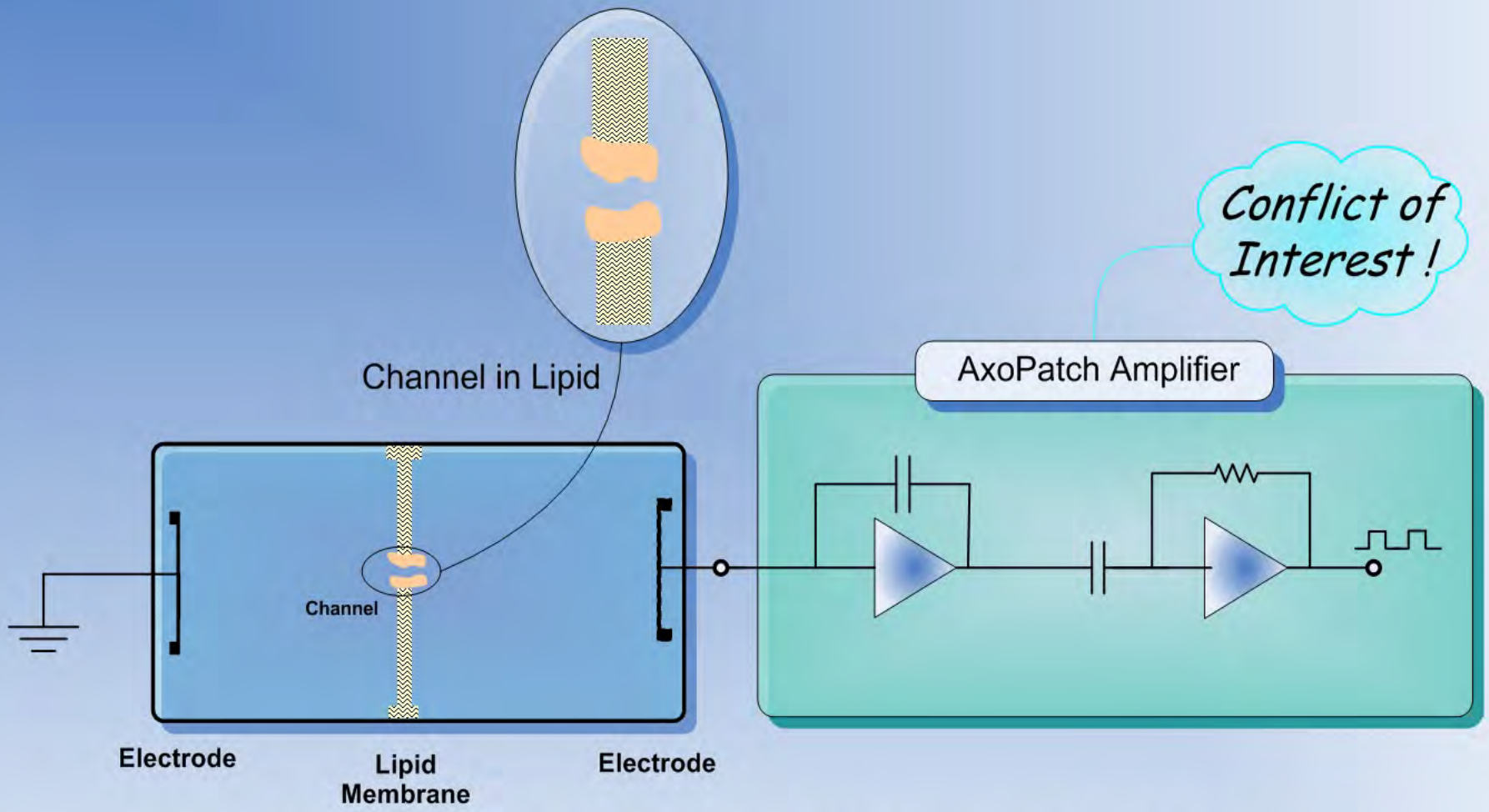


Patch clamp and
Bilayer apparatus clamp
ion concentrations
in the baths and the
voltage across membranes.

Patch Clamp Setup

Recordings from One Molecule

Single Channel Recording

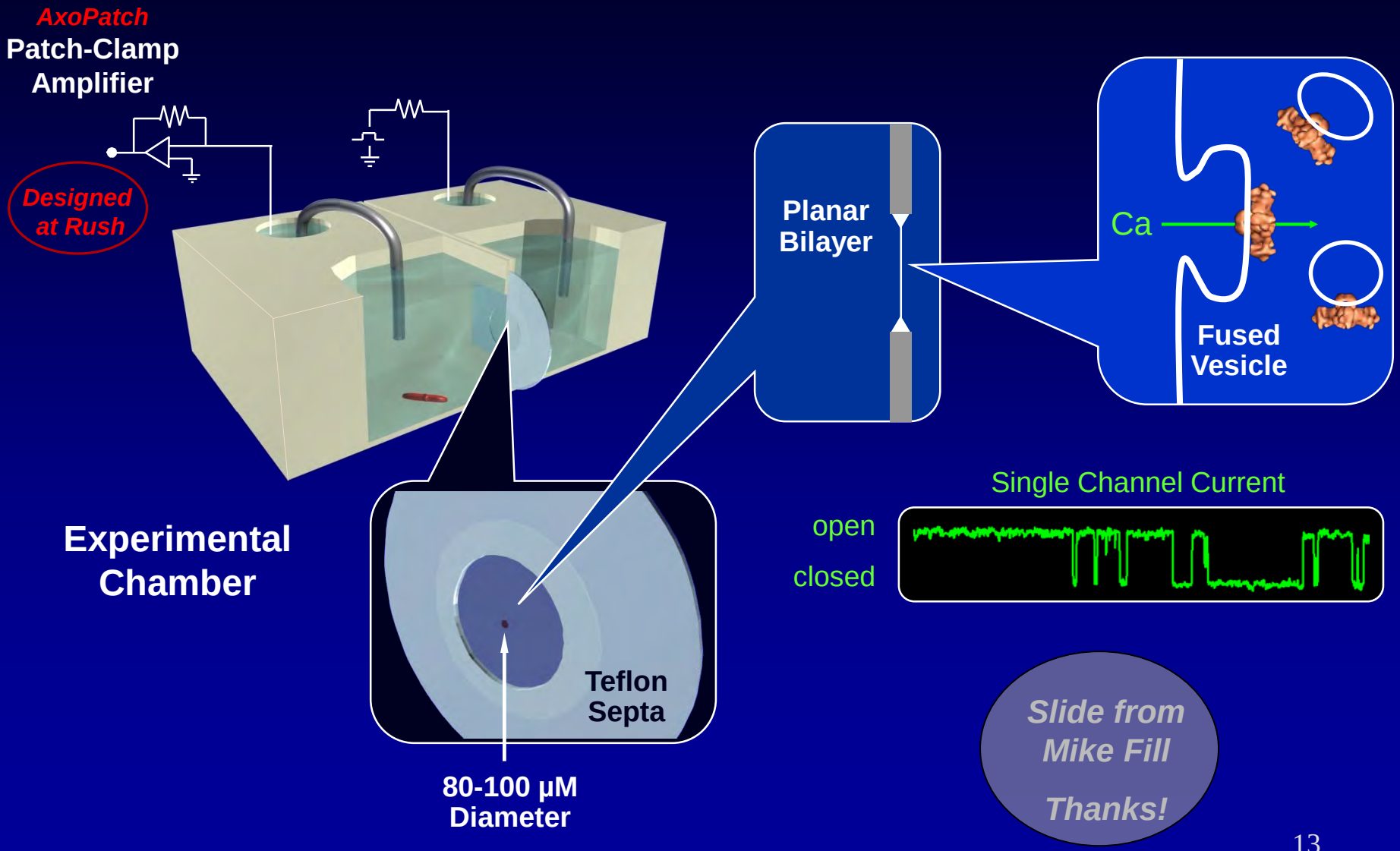


Channel in Lipid Bilayer Set-up

Recording Current from One Protein Molecule

SINGLE isolated RyR Channels

in Artificial Planar Lipid Bilayers

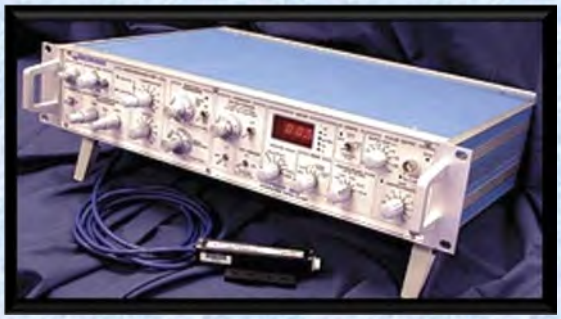


Thousands of Molecular Biologists Study Channels as Devices every day,

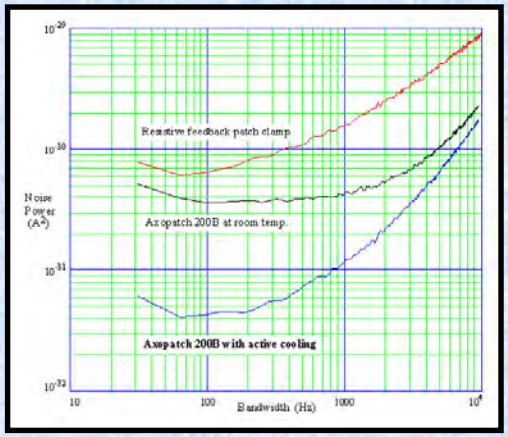
One protein molecule at a time

This number is not an exaggeration.
We have sold >10,000 AxoPatch amplifiers

AxoPatch 200B

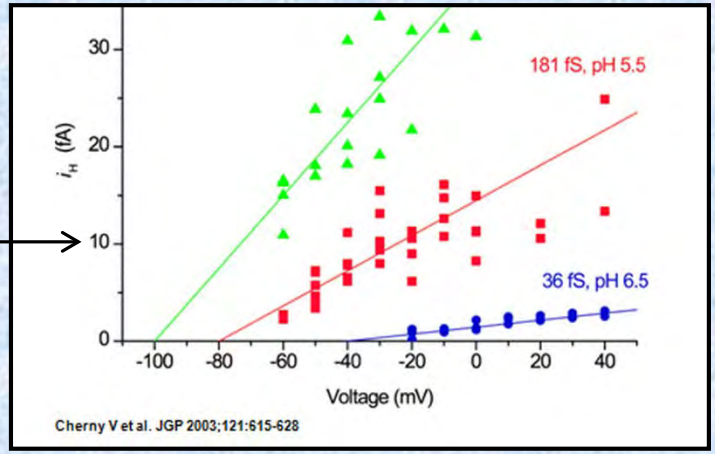


Designed at Rush
Current Noise



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

Current Noise



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Popular publications for March (view most recent)

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

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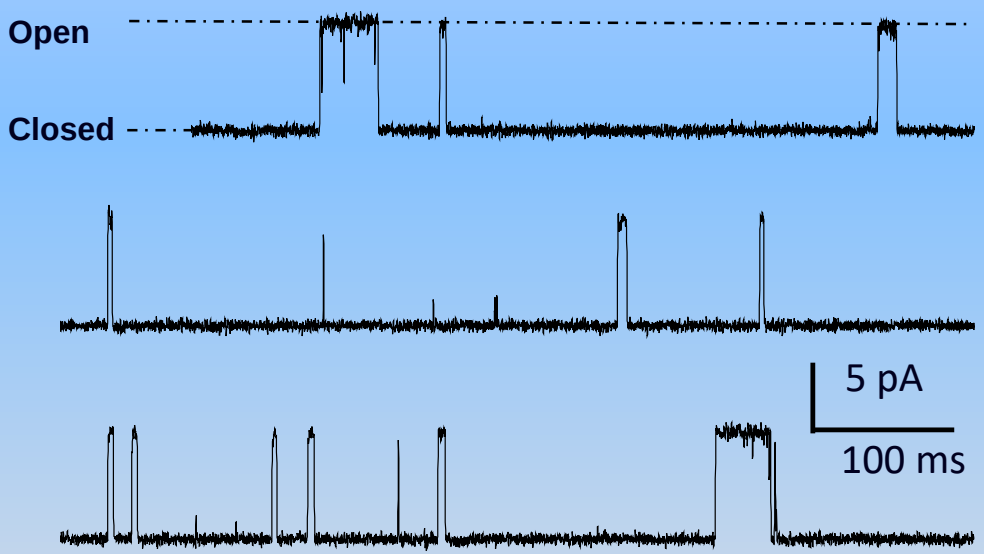
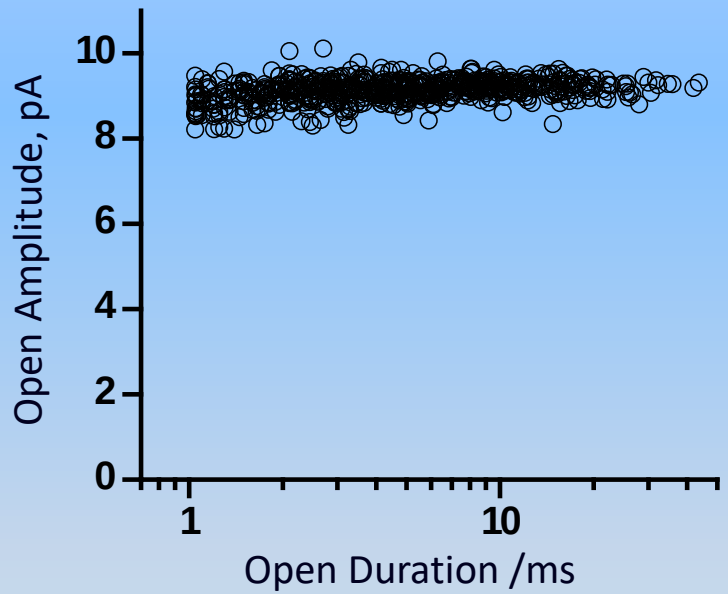
Channel Structure Does Not Change

once the channel is open

Current vs. time



Amplitude vs. Duration



Lowpass Filter = 1 kHz Sample Rate = 20 kHz

<u>Typical</u> Raw Single Channel Records

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

Where to start?

Why not compute all the atoms?

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}**
Spatial Resolution	***Three Dimensional*** **$(10^{4})^{3}$**	**10^{12}**
Volume 10^{-30} m^3	$(10^{-4}$ m$)^3$ = 10^{-12} m^3	**10^{18}**
Solute Concentration *including Ca^{2+}mixtures*	10^{-11} to 10^{1} M	**10^{12}**

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 are Always Present

in

Atomic Scale Engineering

Atomic & Macro Scales are
<u>both</u> used by channels
just because
<u>Channels are Nanovalves</u>

By definition: all valves use small structures to control large flows

Atomic Scale Engineering

uses a

Few Atoms

to

Control

Macroscopic Flows

so **Atomic and Macro Scales** must be

Computed

and

CALIBRATED

together

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

Uncalibrated Simulations will make devices that do not work

Details matter in devices

Where to start?

Mathematically ?

Physically ?

.

Reduced Models are Needed

Reduced Models are Device Equations

like Input Output Relations of Engineering Systems

The device equation is the mathematical statement of how the system works

Device Equations describe 'Slow Variables'

found in some complicated systems

How find a Reduced Model?

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.)

Multi-scale Engineering

is

MUCH easier when robust

Reduced Models Exist

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

Bioengineers: **this is reverse engineering**

Inverse Problems

Given the Output
Determine the Reduced Model

For example,

Find Charge Distribution
in Channel
from
Current Voltage Relations

Problem (with noise and systematic error) has
actually been solved byTikhonov Regularization
Burger, Eisenberg, Engl (2007) SIAM J Applied Math 67: 960-989

using procedures developed by Engl to study Blast Furnaces and their Explosions

Inverse Problems

Find the Model, given the Output

*Many answers are possible: 'ill posed' **

Central Issue

Which answer is right?

***Ill posed problems with too little data seem complex, even if they are not. Some of biology seems complex for that reason. The question is which 'some'?

Inverse Problems: many answers possible

Central Issue

Which answer is right?

Key is

ALWAYS

Large Amount of Data

from

Many Different Conditions

Almost too much data was available for reduced model:

Burger, Eisenberg and Engl (2007) SIAM J Applied Math 67:960-989

Inverse Problems: many answers possible

Which answer is right?

Key is

Large Amount of Data from **Many Different Conditions**

Otherwise problem is 'ill-posed' and has no answer or even set of answers

Molecular Dynamics

usually yields

ONE data point

at one concentration

MD is not yet well calibrated

(i.e., for activity = free energy per mole)

for Ca^{2+} or ionic mixtures like seawater or biological solutions

Working Hypothesis:

Crucial Biological Adaptation is

Crowded Ions *and* Side Chains

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

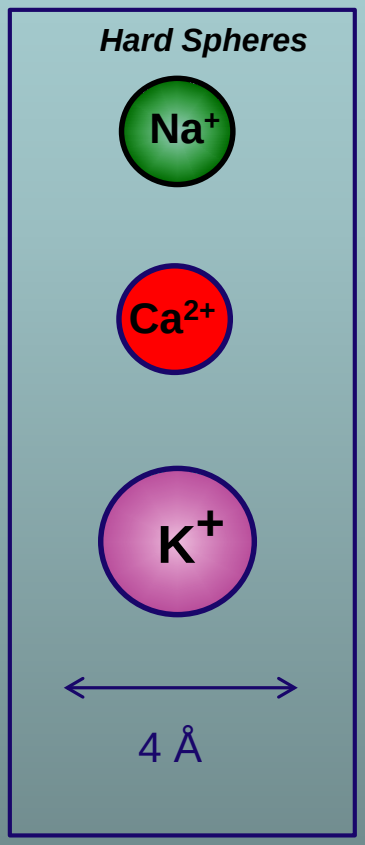
Reduced Models allow much easier Atomic Scale Engineering

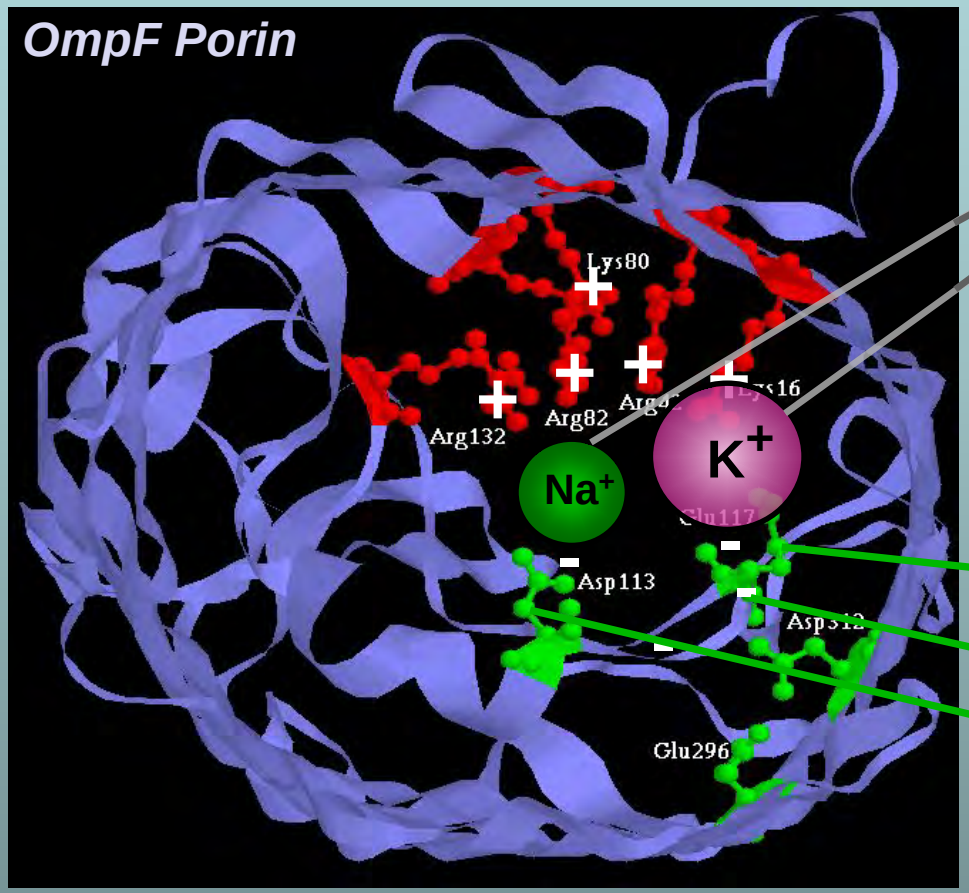
Physical basis of function

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

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

EC2: TRANSFERASES

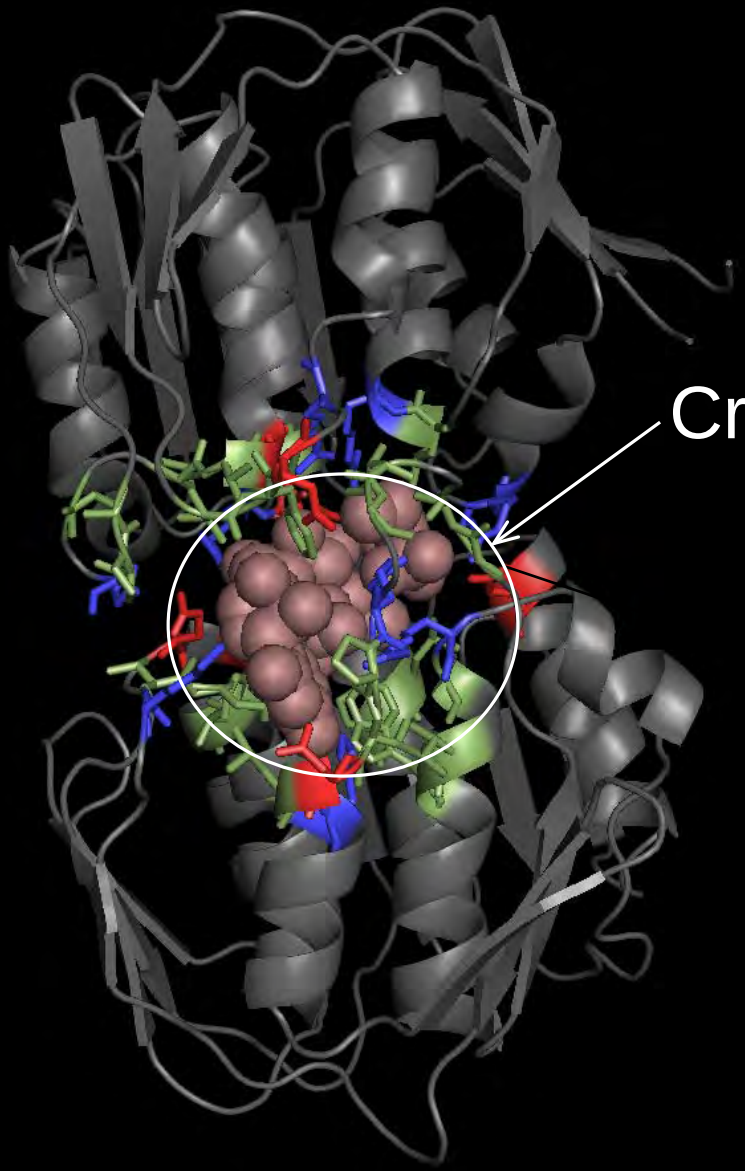
Average Ionizable Density: 19.8 Molar

Example

UDP-N-ACETYLGLUCOSAMINE ENOLPYRUVYL TRANSFERASE (PDB:1UAE)

Functional Pocket Volume: 1462.40 $Å^3$

Density : 19.3 Molar (11.3 M+. 8 M-)



Green: Functional pocket residues
Blue: Basic = Probably Positive = R+K+H
Red: Acid = Probably Negative = E + Q
Brown Uridine-Diphosphate-N-acetylclucosamine

Jimenez-Morales, Liang, Eisenberg

Everything Interacts
with
Everything Else

by steric exclusion
inside crowded active sites

Everything interacts with macroscopic Boundary Conditions
(and much else)
through long range electric field

‘Law’ of mass action needs to be generalized

Three Channel Types

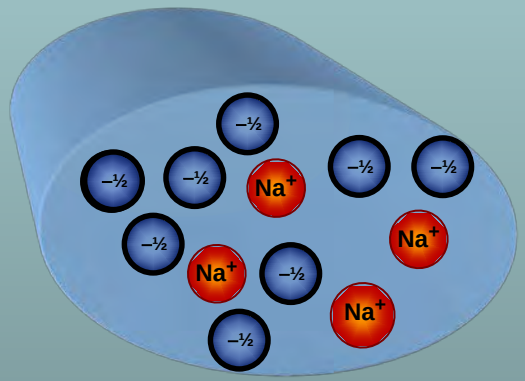
RyR, Ca_V = EEEE, and **Na_V** = DEKA

analyzed <u>successfully</u>*

in a wide range of solutions by the

‘All Spheres’ Primitive Model

Implicit solvent model of open channel



ions and protein side chains are hard spheres in this model

* Many methods have been used in more than 30 papers since Nonner and Eisenberg, 1998

Best Evidence is from the

RyR Receptor

Dirk Gillespie

Dirk_Gillespie@rush.edu

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

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

1. Gillespie, D., Energetics of divalent selectivity in a calcium channel: the ryanodine receptor case study. *Biophys J, 2008. 94(4): p. 1169-1184.*
2. Gillespie, D. and D. Boda, Anomalous Mole Fraction Effect in Calcium Channels: A Measure of Preferential Selectivity. *Biophys. J., 2008. 95(6): p. 2658-2672.*
3. Gillespie, D. and M. Fill, Intracellular Calcium Release Channels Mediate Their Own Countercurrent: Ryanodine Receptor. *Biophys. J., 2008. 95(8): p. 3706-3714.*
4. Gillespie, D., W. Nonner, and R.S. Eisenberg, Coupling Poisson-Nernst-Planck and Density Functional Theory to Calculate Ion Flux. *Journal of Physics (Condensed Matter), 2002. 14: p. 12129-12145.*
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7. Gillespie, D., J. Giri, and M. Fill, Reinterpreting the Anomalous Mole Fraction Effect. The ryanodine receptor case study. Biophysical Journal, 2009. 97: p. pp. 2212 - 2221
8. Gillespie, D., L. Xu, Y. Wang, and G. Meissner, (De)constructing the Ryanodine Receptor: modeling ion permeation and selectivity of the calcium release channel. *Journal of Physical Chemistry, 2005. 109: p. 15598-15610.*
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11. Roth, R. and D. Gillespie, Physics of Size Selectivity. *Physical Review Letters, 2005. 95: p. 247801.*
12. Valisko, M., D. Boda, and D. Gillespie, Selective Adsorption of Ions with Different Diameter and Valence at Highly Charged Interfaces. *Journal of Physical Chemistry C, 2007. 111: p. 15575-15585.*
13. Wang, Y., L. Xu, D. Pasek, D. Gillespie, and G. Meissner, Probing the Role of Negatively Charged Amino Acid Residues in Ion Permeation of Skeletal Muscle Ryanodine Receptor. *Biophysical Journal, 2005. 89: p. 256-265.*
14. Xu, L., Y. Wang, D. Gillespie, and G. Meissner, Two Rings of Negative Charges in the Cytosolic Vestibule of T Ryanodine Receptor Modulate Ion Fluxes. *Biophysical Journal, 2006. 90: p. 443-453.*

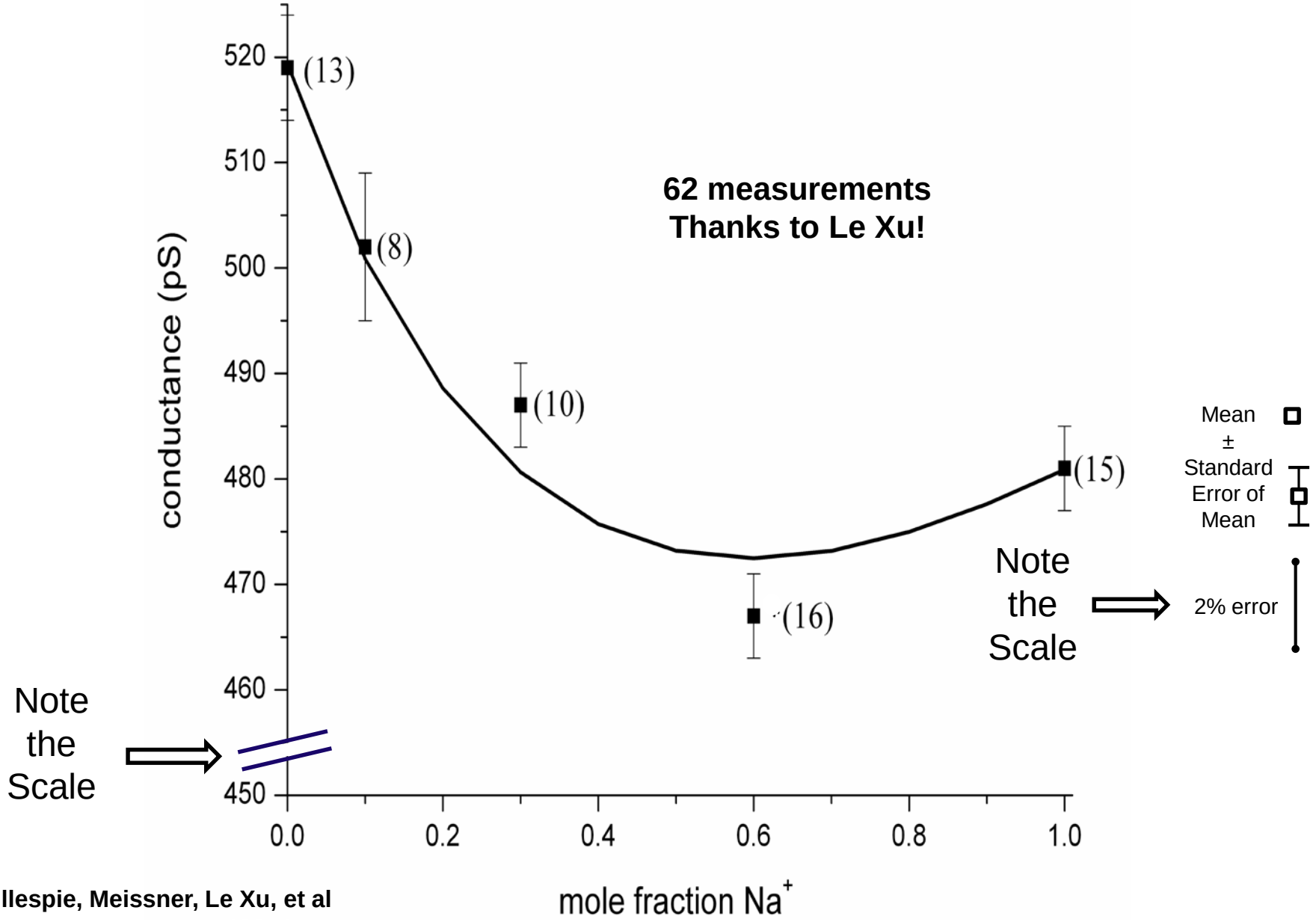
Solved bY DFT-PNP (Poisson Nernst Planck)

DFT-PNP
gives location
of Ions and ‘Side Chains’
as OUTPUT

Other methods
give nearly identical results

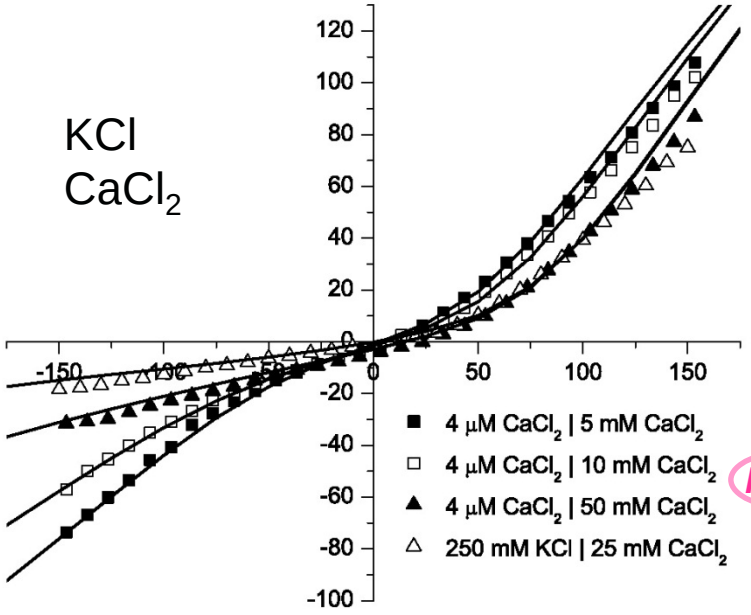
DFT (Density Functional Theory of fluids, *not electrons*)
MMC (Metropolis Monte Carlo))
SPM (Primitive Solvent Model)
EnVarA (Energy Variational Approach)
Non-equil MMC (Boda, Gillespie) several forms
Steric PNP (simplified EnVarA)
Poisson Fermi

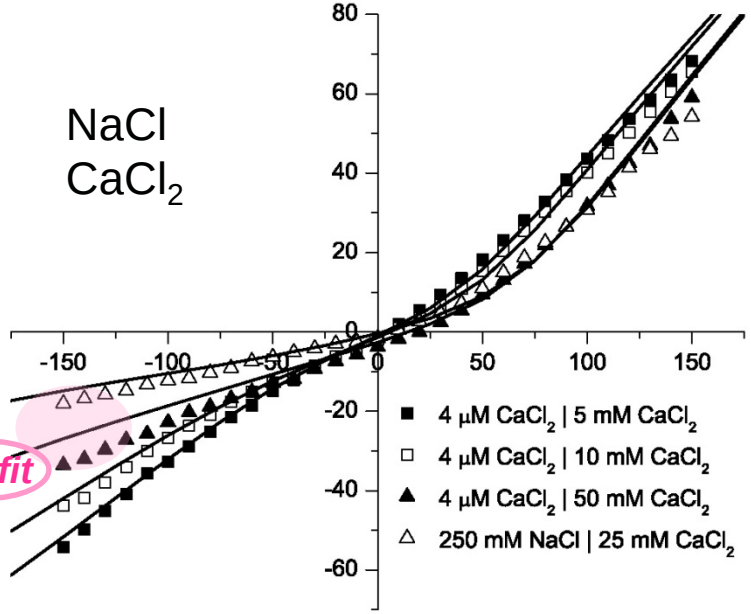
The model predicted an AMFE for Na^+/Cs^+ mixtures before it had been measured

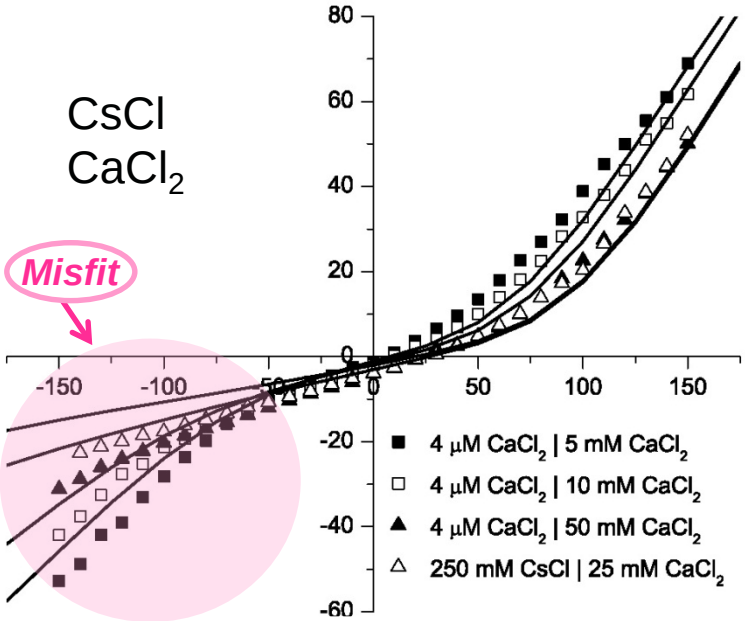


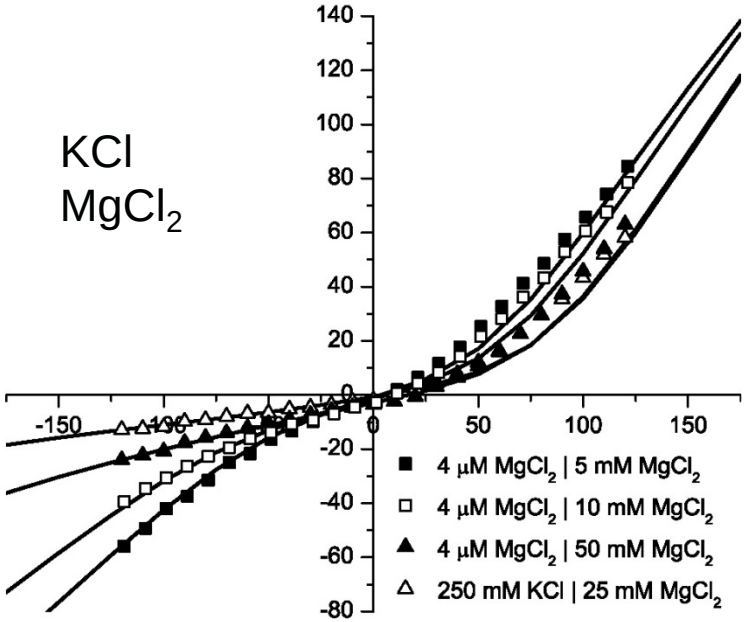
Gillespie, Meissner, Le Xu, et al

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

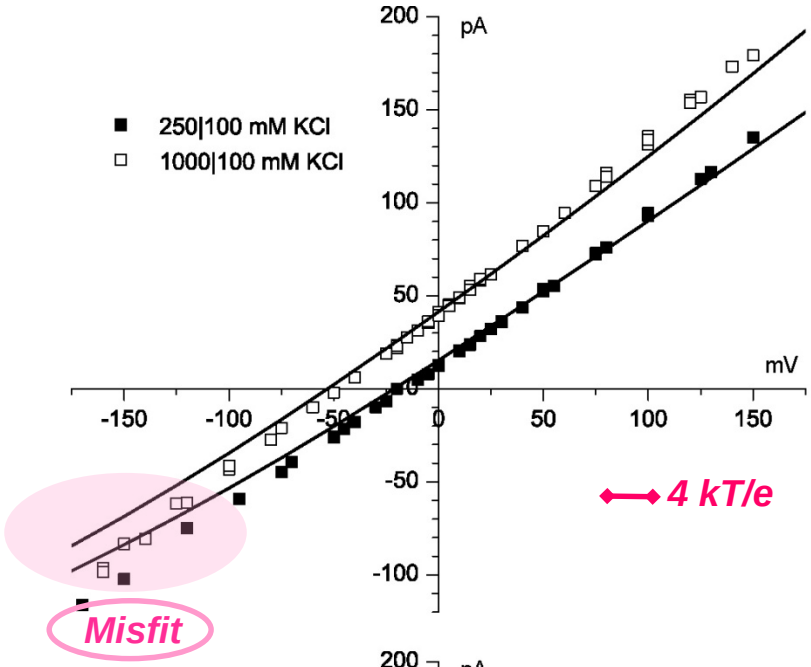

NaCl
CaCl2
Misfit
4 μM CaCl2 | 5 mM CaCl2
4 μM CaCl2 | 10 mM CaCl2
4 μM CaCl2 | 50 mM CaCl2
250 mM NaCl | 25 mM CaCl2

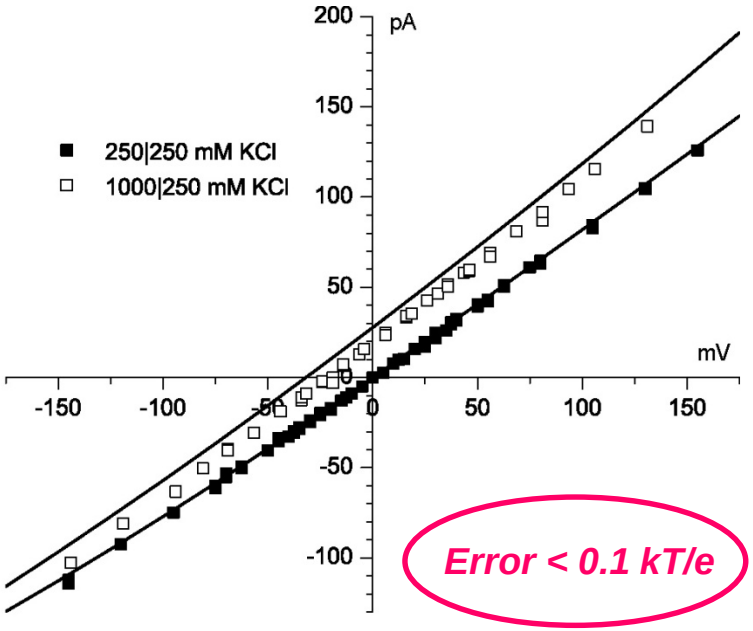

CsCl
CaCl2
Misfit
4 μM CaCl2 | 5 mM CaCl2
4 μM CaCl2 | 10 mM CaCl2
4 μM CaCl2 | 50 mM CaCl2
250 mM CsCl | 25 mM CaCl2

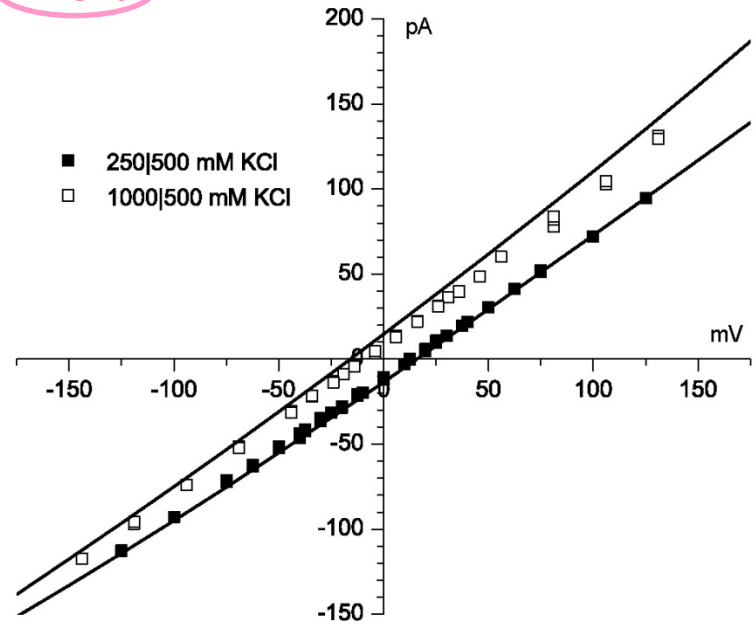

KCl
MgCl2
4 μM MgCl2 | 5 mM MgCl2
4 μM MgCl2 | 10 mM MgCl2
4 μM MgCl2 | 50 mM MgCl2
250 mM KCl | 25 mM MgCl2

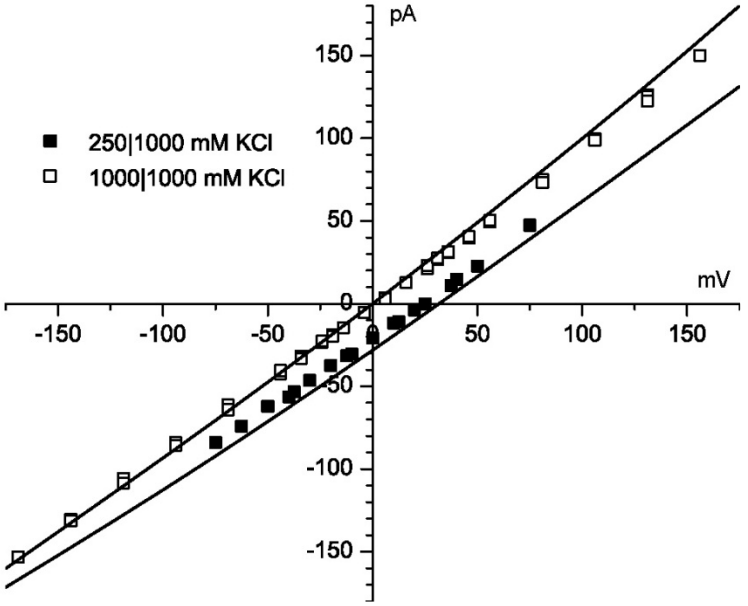
KCl

Gillespie, Meissner, Le Xu, et al



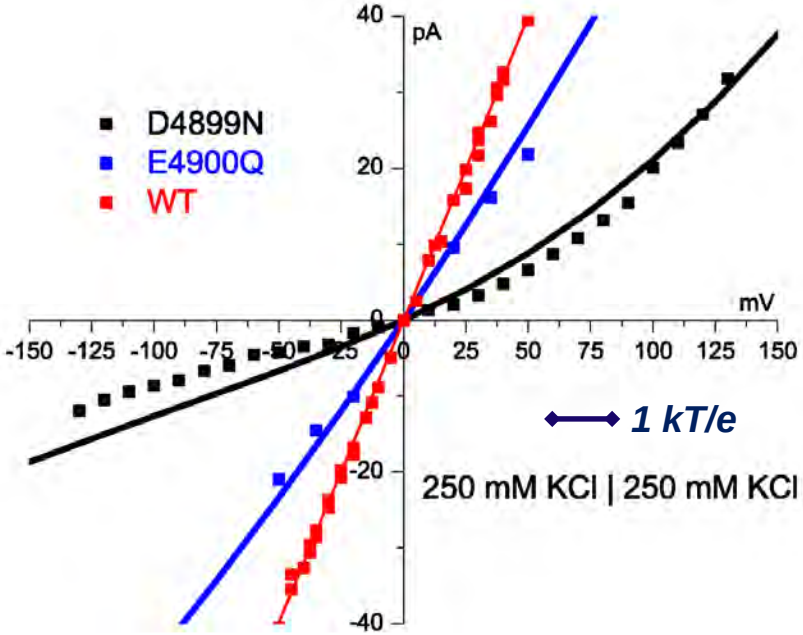




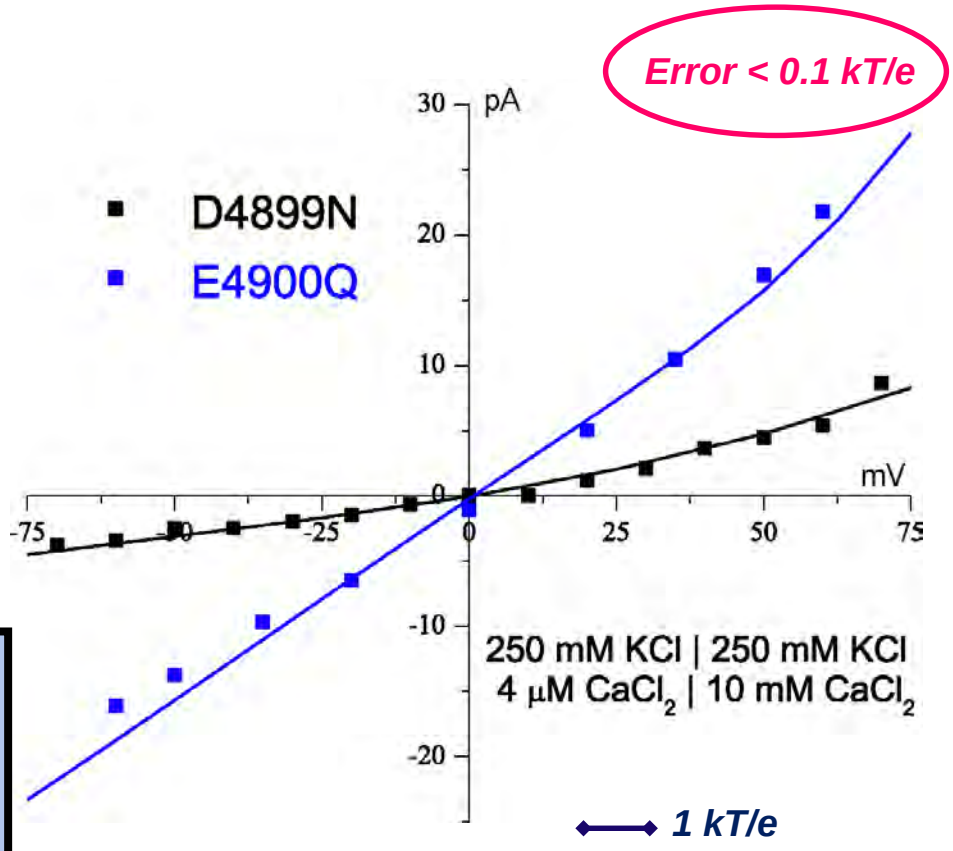


Theory fits Mutation with Zero Charge

Theory Fits Mutant in K



Theory Fits Mutant in K + Ca



Protein charge density

wild type* 13 M ⇨ 0 M *in* D4899

Solid Na^+Cl^- is 37 M

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

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

Calcium Channel

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

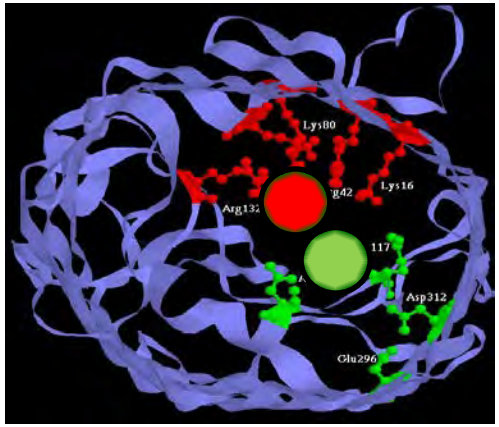
ftp://ftp.rush.edu/users/molebio/Bob_Eisenberg/reprints

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

Experiments have 'engineered' channels (5 papers) including

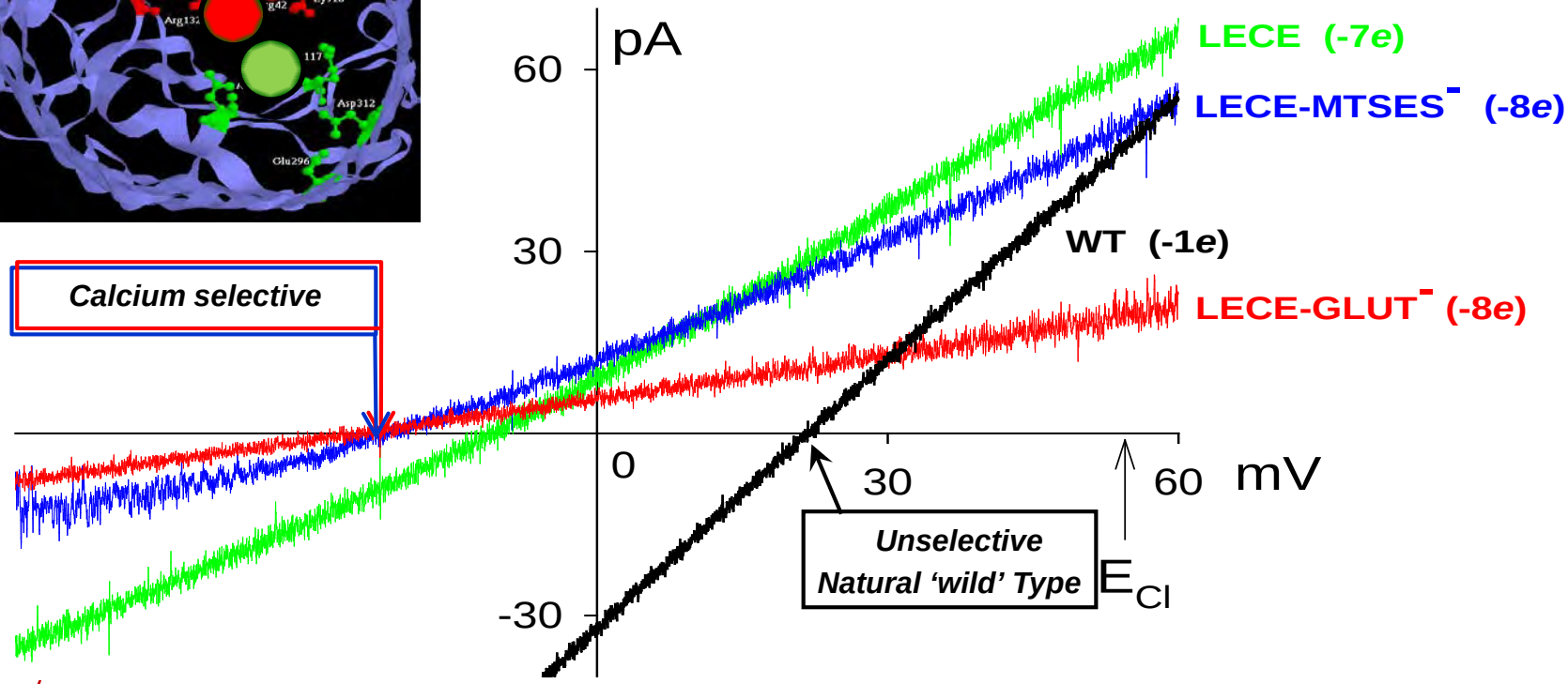
Two Synthetic Calcium Channels

Atomic Scale



Designed by Theory

Glutathione derivatives



As density of permanent charge increases, channel becomes calcium selective

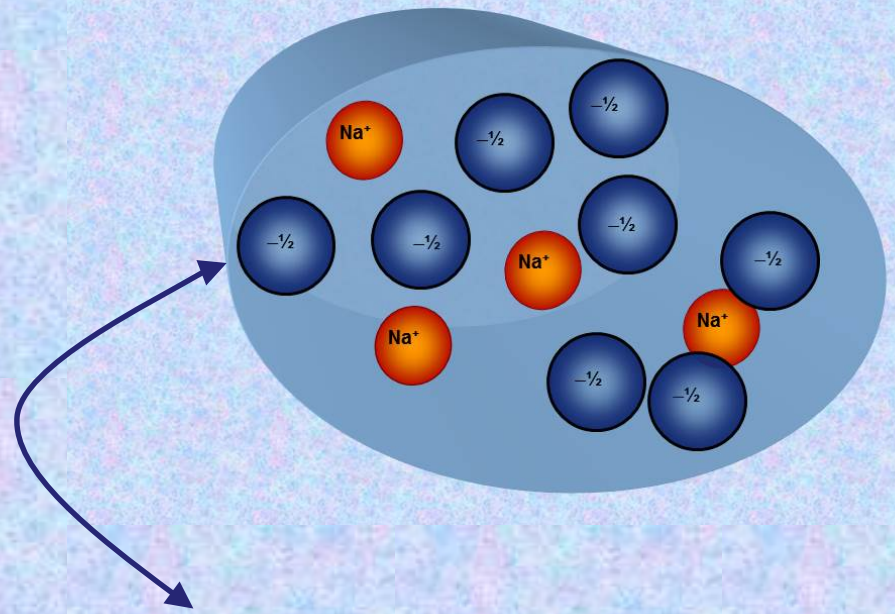
$E_{rev} \rightarrow E_{Ca}$ in 0.1M ||1.0 M $CaCl_2$; pH 8.0

Macro Scale

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

***Miedema** et al, Biophys J 87: 3137–3147 (2004); 90:1202-1211 (2006); 91:4392-4400 (2006)*

‘All Spheres’ Model



Side Chains are Spheres

Channel is a Cylinder

Side Chains are free to move within Cylinder

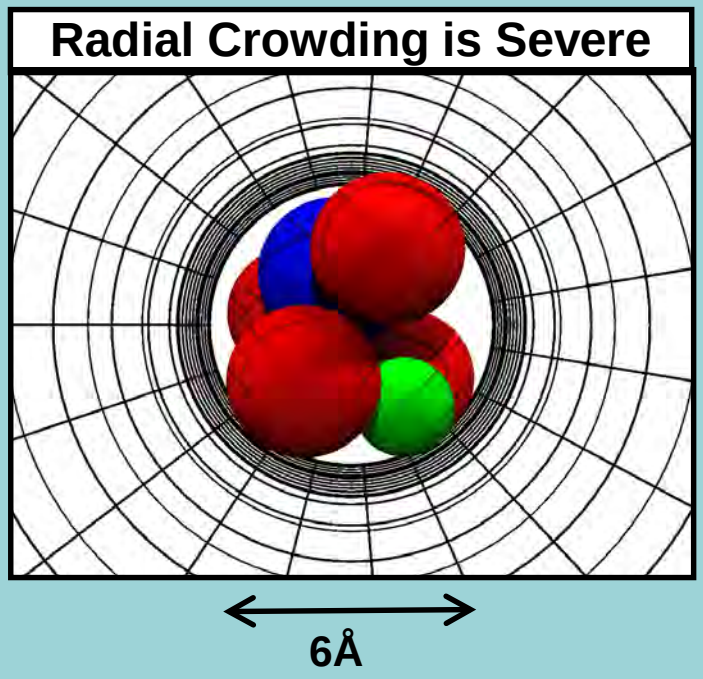
Ions and Side Chains are at free energy minimum

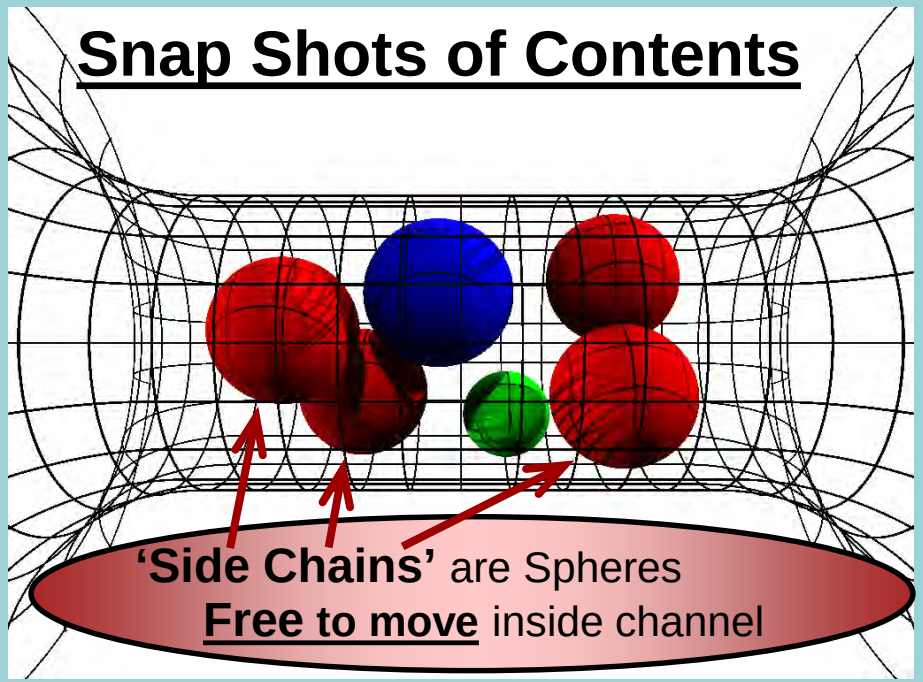
i.e., **ions and side chains are ‘self organized’,**

‘Binding Site” is induced by substrate ions

Nonner & Eisenberg

Crowded Ions





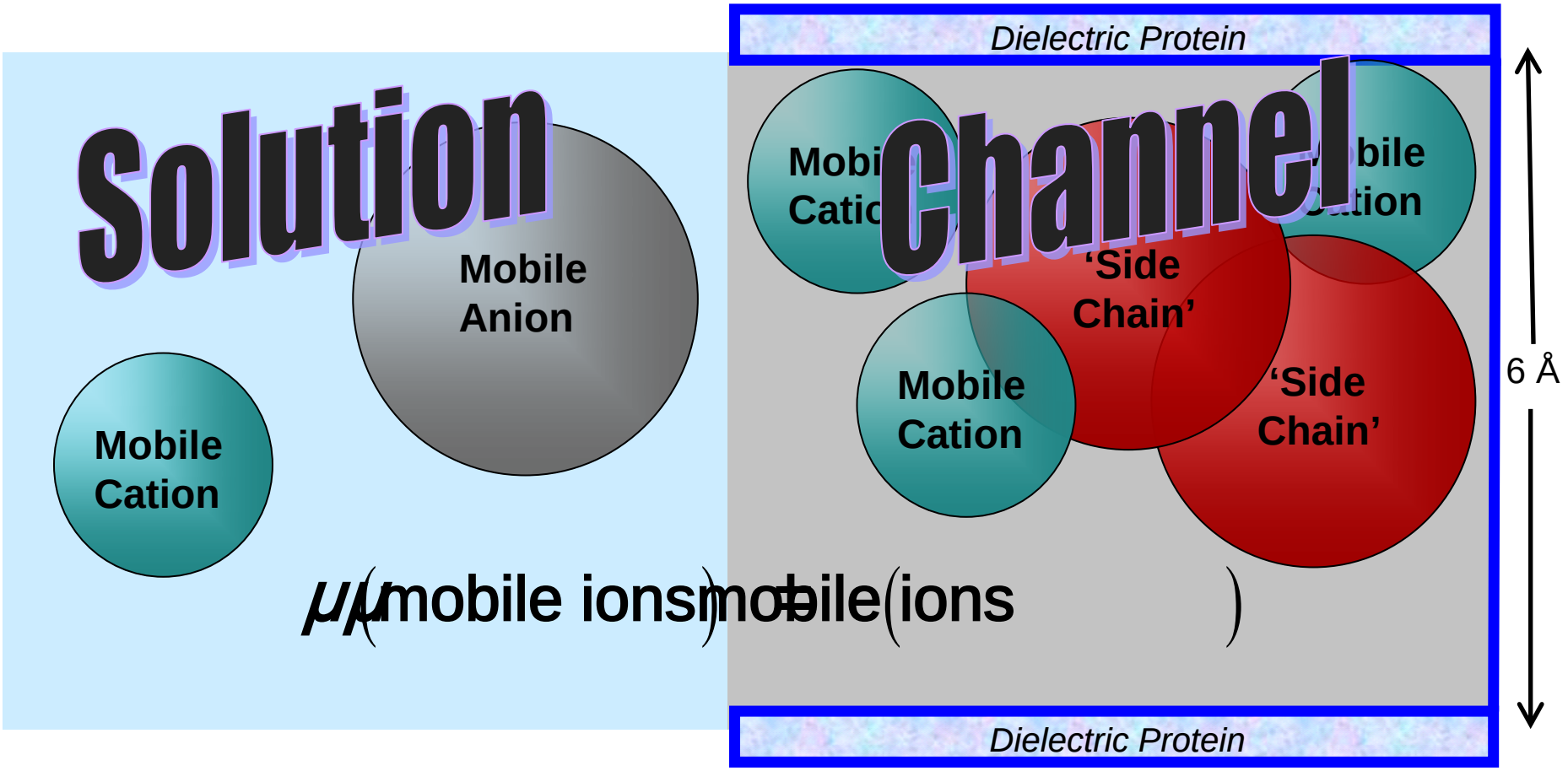
Ion Diameters *'Pauling' Diameters*	
Ca^{++}	1.98 Å
Na^{+}	2.00 Å
K^{+}	2.66 Å
'Side Chain' Diameter	
Lysine K	3.00 Å
D or E	2.80 Å
Channel Diameter 6 Å	

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

Ion 'Binding' in Crowded Channel



μ(mobile ions) = μ(mobile ions)

Classical Donnan Equilibrium of Ion Exchanger

large mechanical forces

Side chains move within channel to their equilibrium position of minimal free energy.

We compute the Tertiary Structure as the structure of minimal free energy.

Boda, Nonner, Valisko, Henderson, Eisenberg & Gillespie

*M*etropolis *M*onte *C*arlo Simulates Location of Ions

both the mean and the variance

MMC *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, $E_B \neq 0$ and configuration may be accepted

(4.1) If $E_B < E_A$: accept new configuration.

(4.2) If $E_B > E_A$: accept new configuration with probability $\exp\left[-(E_A - E_B)/k_B T\right]$

Key idea

Instead of choosing configurations from uniform distribution, then weighting them with $\exp(-E/k_B T)$, ***MMC*** chooses them with a Boltzmann probability and weights them evenly.

Ca Channel

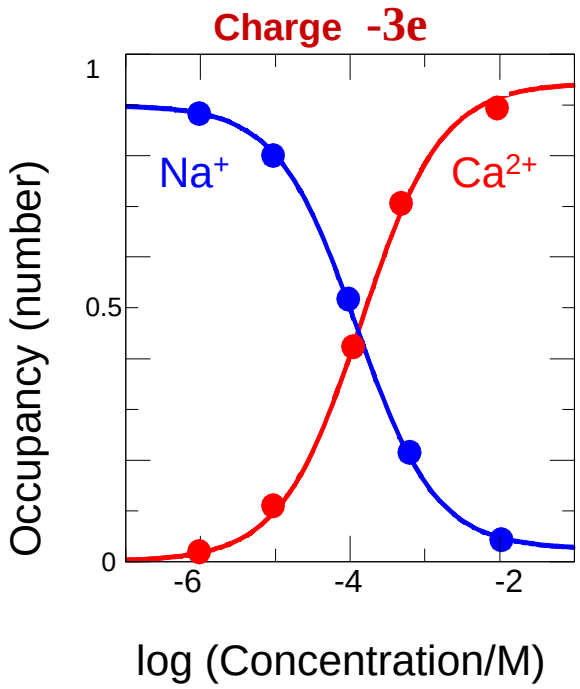
Mutation

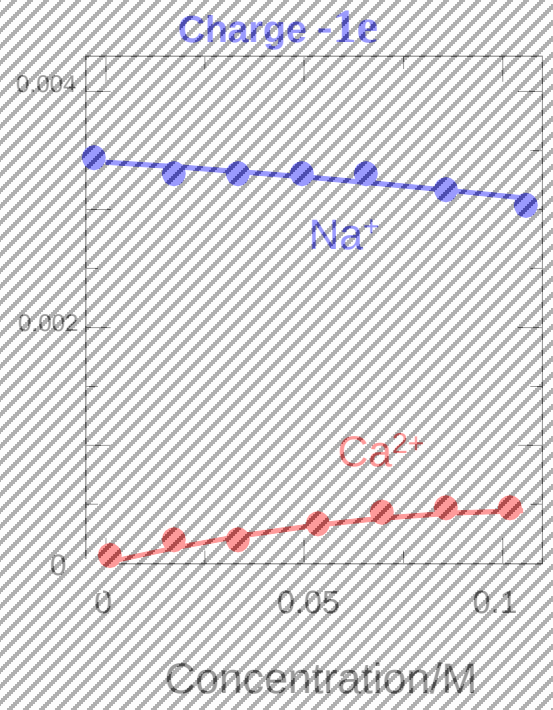
Na Channel

Same Parameters

E
E
E
A

D
E
K
A





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 channologists

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

Same Parameters

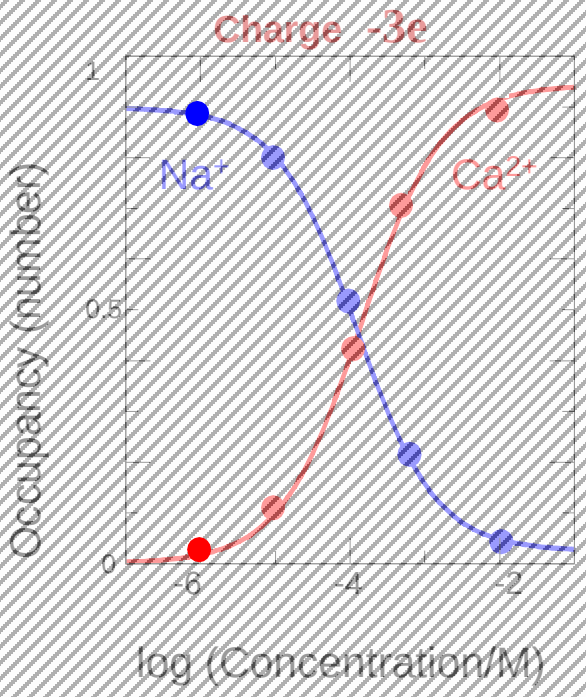
Na Channel

E → D

E → E

E → K

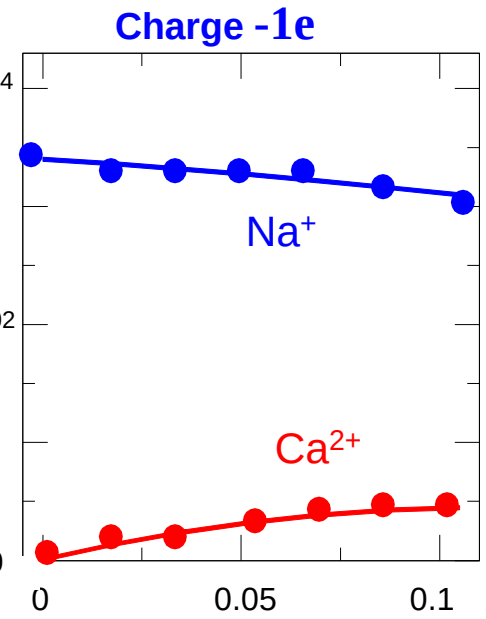
A → A



Mutation

Same Parameters

pH 8



EEEE has full biological selectivity in similar simulations

Monte Carlo simulations of Boda, et al

Nothing was Changed

from the

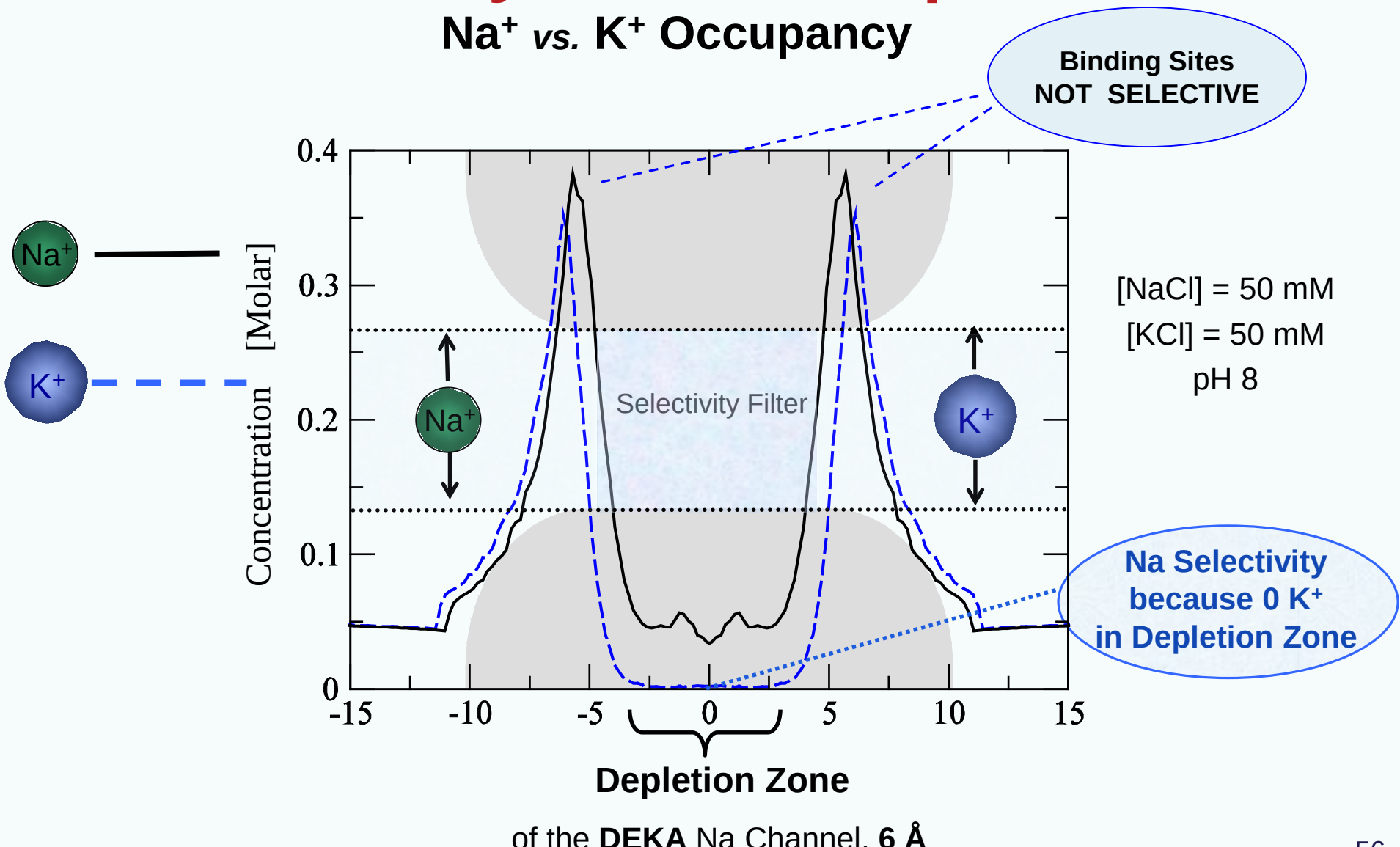
EEEA Ca channel

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

Size Selectivity is in the Depletion Zone



of the **DEKA** Na Channel, **6 Å**

Boda, et al

How?

Usually Complex Unsatisfying Answers*

How does a Channel Select Na^+ *vs.* K^+ ?

* Gillespie, D., Energetics of divalent selectivity in the ryanodine receptor. *Biophys J (2008). 94: p. 1169-1184*

* Boda, *et al,* Analyzing free-energy by Widom's particle insertion method. *J Chem Phys (2011) 134: p. 055102-14*

Calculations and experiments done at pH 8

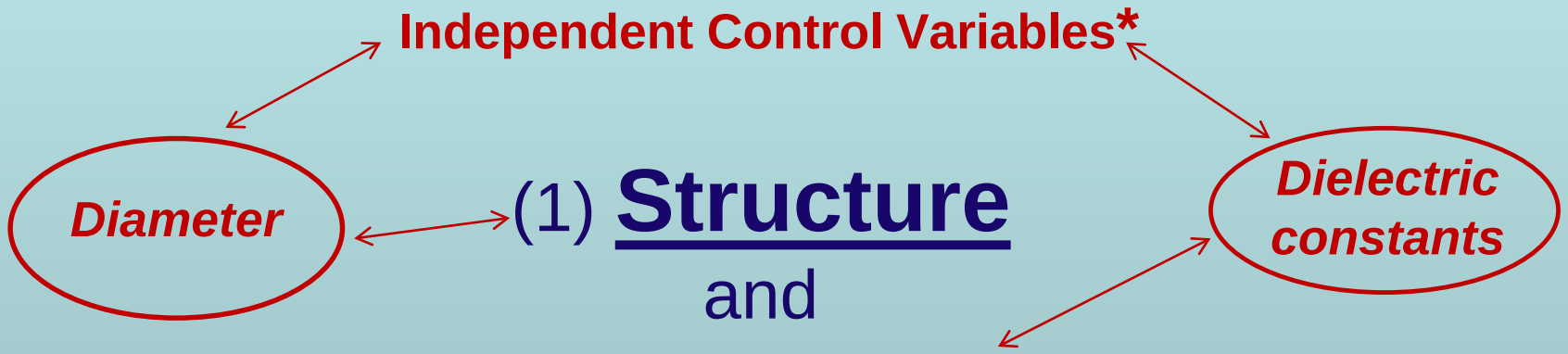
Simple

Independent[§] Control Variables*

DEKA Na^+ channel

Amazingly simple, not complex
for the most important selectivity property
of DEKA Na^+ channels

Control variab**le = position of **gas pedal** or dimmer on **light switch
[§] Gas pedal and **brake pedal are** (hopefully**) independent control variables**



(1) **Structure**

and

(2) **Dehydration/Re-solvation**

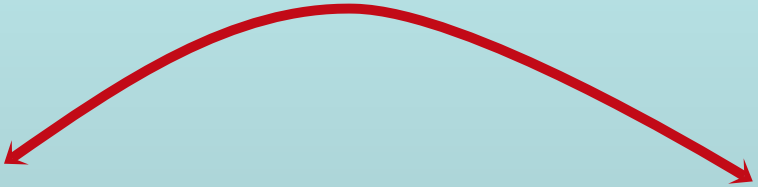
emerge from calculations

Structure (diameter) controls Selectivity

Solvation (dielectric) controls Contents

**Control variables emerge as outputs*

*Control variables are **not** inputs*



Structure (diameter) controls Selectivity

Solvation (dielectric) controls Contents

Control Variables emerge as <u>outputs</u>
Control Variables are <u>not</u> inputs

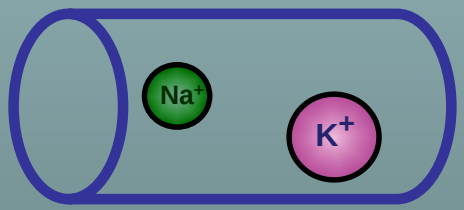
Monte Carlo calculations of the DEKA Na channel

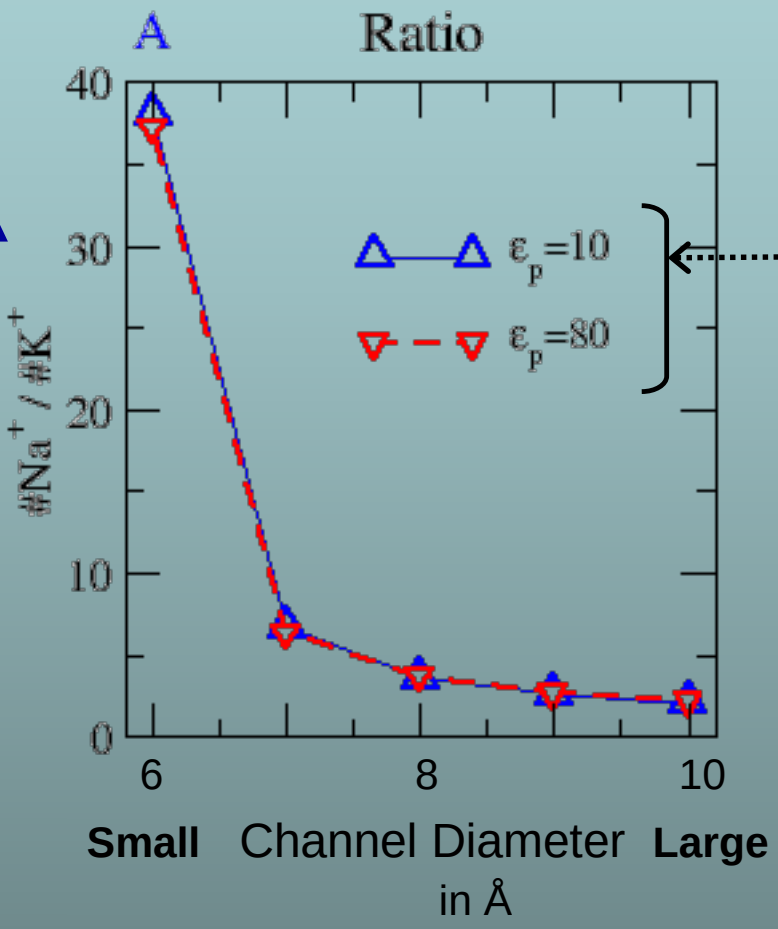
Na^+ vs K^+ (size) Selectivity (ratio)

Depends on Channel Size,

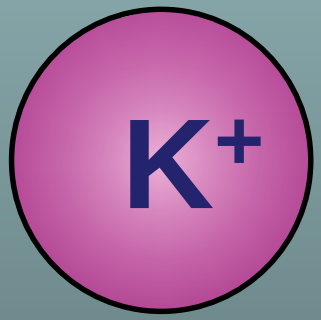
not dehydration (*not on* Protein Dielectric Coefficient)*

Selectivity
for small ion





2.00 Å



2.66 Å

Boda, et al

in* **DEKA Na channel

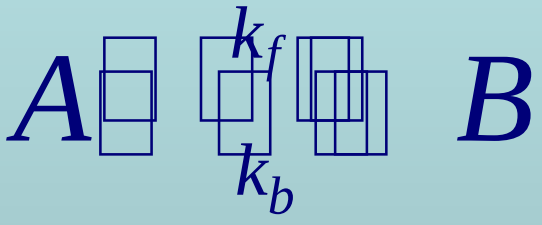
Generalization
of
‘Law’ of Mass Action
is needed because

the ‘law’ assumes

NO FLOW

and
NO INTERACTIONS

Law of Mass Action



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

$$K_{eq} = \frac{[B]}{[A]} = \frac{k_f}{k_b}$$

$$J_{A\to B} = k_f [A]; \qquad J_{B\to A} = k_b [B]$$

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

In the minds of most biochemists, many chemists, and textbook authors

A, B are assumed to be **ideal solutions of noninteracting particles**

k_f, k_b are assumed to be **constants independent of concentration** of any species

but

Everything interacts with Everything Else

in biology

and

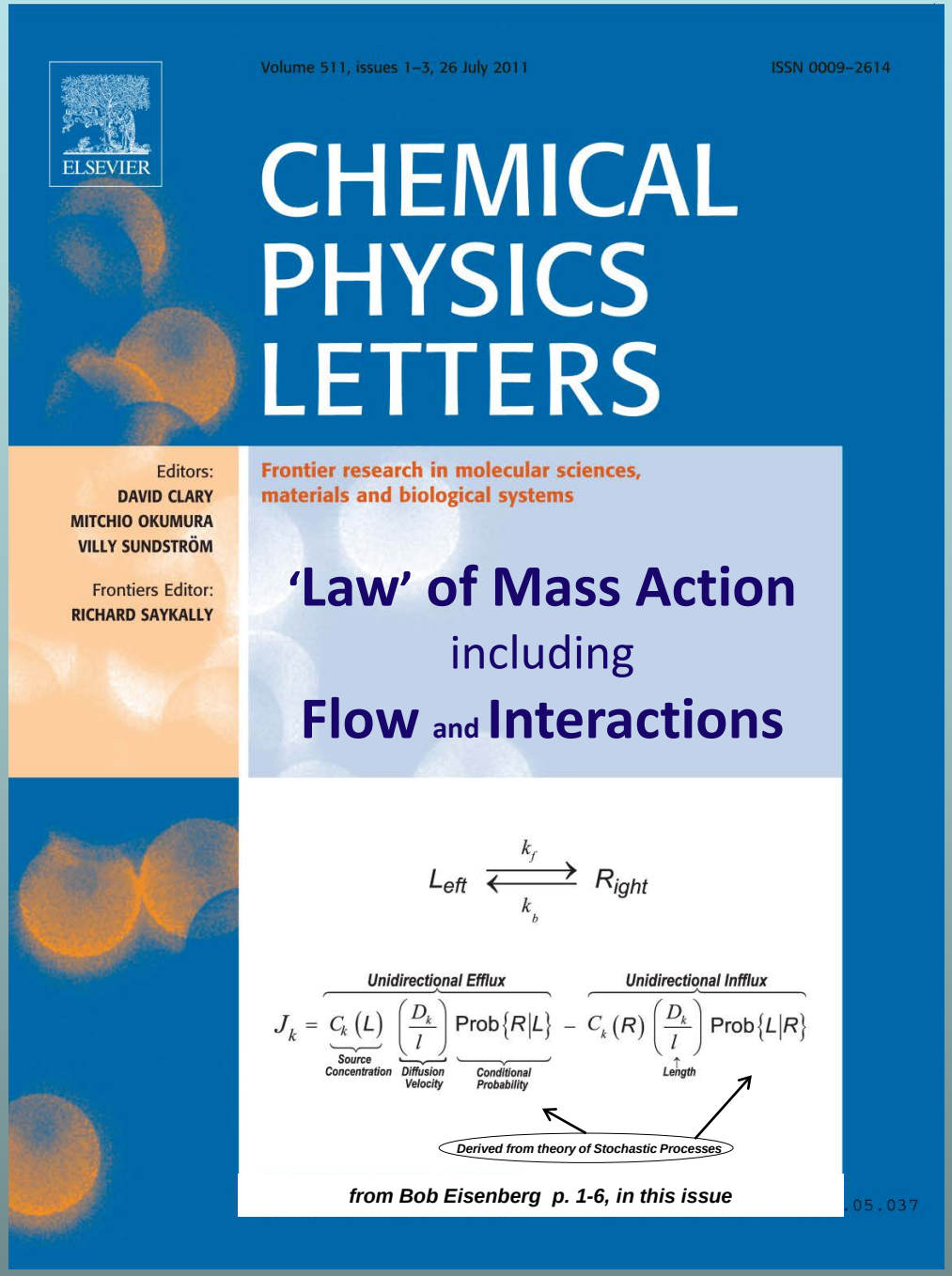
flows cease only at death

Everything is hidden

in K_{eq}, k_f and k_b

Interactions are significant in biological solutions (Ringer)
Interactions are large in and near channels

$k_{f,b}$ and K_{eq} are functions of 'everything'
They are not constants



Great Opportunity
for
New Science

Chemical Reactions
in
Complex Fluids

Variational Approach
EnVarA

Conservative ***Dissipative***

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

Energetic Variational Approach allows

accurate computation of

Flow and Interactions

in Complex Fluids like Liquid Crystals

Classical theories and Molecular Dynamics have difficulties with flow, interactions, and complex fluids

Engineering needs Calibrated Theories and Simulations

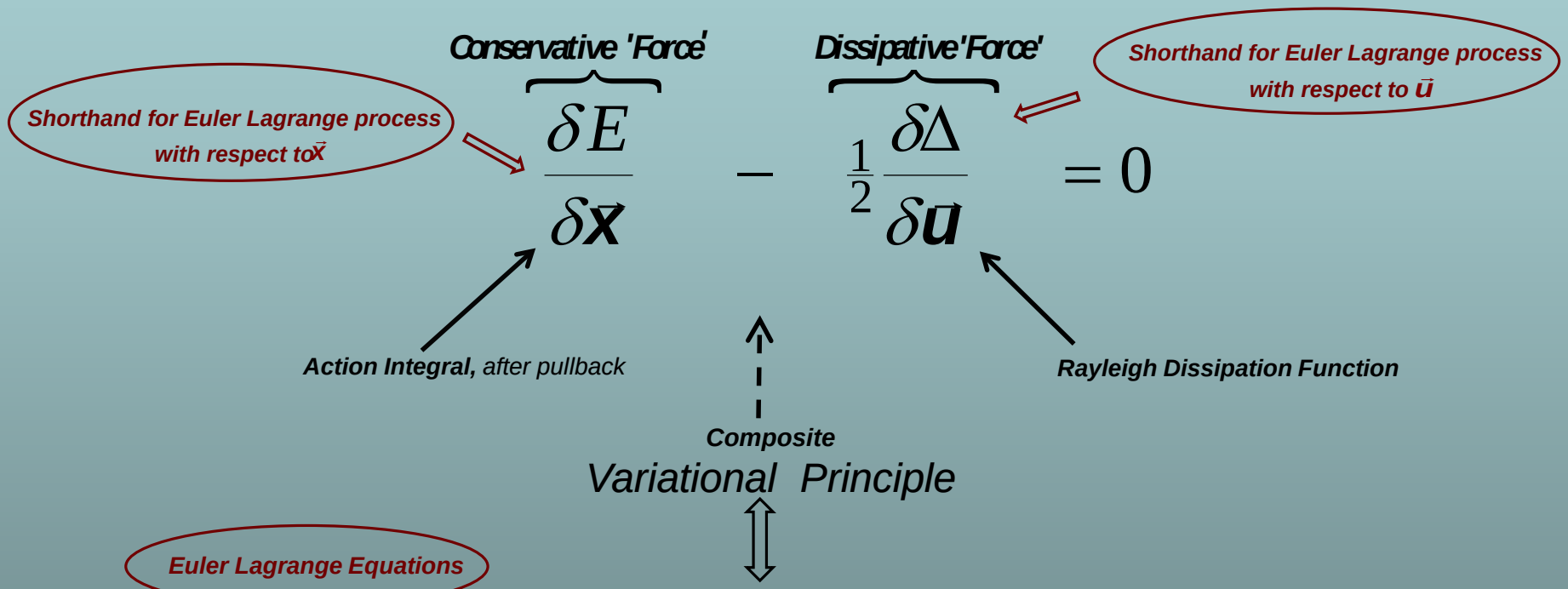
Engineering Devices almost always use flow

Energetic Variational Approach

EnVarA

Chun Liu, Rolf Ryham, Yunkyong Hyon, and Bob Eisenberg

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



that allows boundary conditions and flow and deals Consistently with Interactions of Components

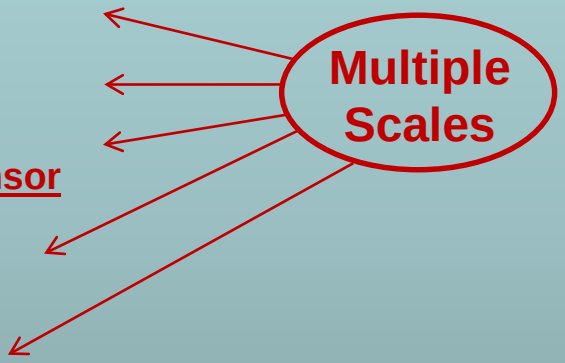
Energetic Variational Approach

EnVarA across biological scales: molecules, cells, tissues

Variational theory of complex fluids developed by Chun Liu

with

(1) Hyon, Eisenberg	Ions in →	Channels
(2) Horng, Lin, Liu, Eisenberg	Ions in →	Channels
(3) Bezanilla, Hyon, Eisenberg	Conformation Change of	Voltage Sensor
(4) Ryham, Cohen	Membrane flow →	Cells
(5) Mori, Eisenberg	Water flow in →	Tissues



creates a new

Multiscale Field Theory of Interacting Components

needed for Molecular Engineering in general

that allows boundary conditions and flow

and deals with

Ions in solutions self-consistently

Take Home Lessons

Take Home Lesson 1

Ionic Solutions

are

Complex Fluids

and

cannot be well analyzed by the theory of simple fluids

Take Home Lesson 2

Energetic Variational Approach allows

accurate computation of

Flow and Interactions

in

Complex Fluids like Liquid Crystals

Engineering needs Calibrated Theories and Simulations

Engineering Devices almost always use flow

Classical theories
and
Molecular Dynamics
have difficulties
with
Flow, Interactions,
and Complex Fluids

Engineering needs Calibrated Theories and Simulations

Engineering Devices almost always use flow

Take Home Lesson 3

Structure

is the

Computed Consequence

of Forces

in these models

Selectivity Depends on Structure

What does the protein do?

Channel and Contents
form a
Self-Organized Structure

with Side Chains at position of
Minimum Free Energy

Protein Fits the Substrate

‘Induced Fit Model of Selectivity’

Binding Sites* are **outputs**
of our Calculations

This is the
Self-organized
Induced fit model
of Koshland
and the founders of enzymology,

Made specific by
Mathematics and Computation

We can actually compute the Structures that determine Selectivity

New Miracle??

Can *EnVarA* actually compute the function of these systems?

Can *EnVarA* serve as a useful Mathematical Framework for Multi-scale Engineering?

The End

Any Questions?

Solved with Metropolis Monte Carlo

MMC Simulates Location of Ions

both the mean and the variance

Produces Equilibrium Distribution

of location

of Ions and 'Side Chains'

MMC yields Boltzmann Distribution with correct Energy, Entropy and Free Energy

Other methods

give nearly identical results

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

Crowded Channels,

Crowded Active Sites

are

Complex Fluids

like liquid crystals of LCD displays

All atom simulations of complex fluid are particularly challenging because ‘Everything’ interacts with ‘everything’ else on atomic & macroscopic scales

Generalization of "Law of Mass Action" is Feasible for Ionic Solutions

using the Implicit Solvent Model of ionic solutions*

*and perhaps the solvent primitive model or more sophisticated models and simulations that professional physical chemists know better than I

Energetic Variational Approach allows

accurate computation of

Flow and Interactions

in Complex Fluids like Liquid Crystals

Classical theories and Molecular Dynamics have difficulties with flow, interactions, and complex fluids

Engineering needs Calibrated Theories and Simulations

Engineering Devices almost always use flow