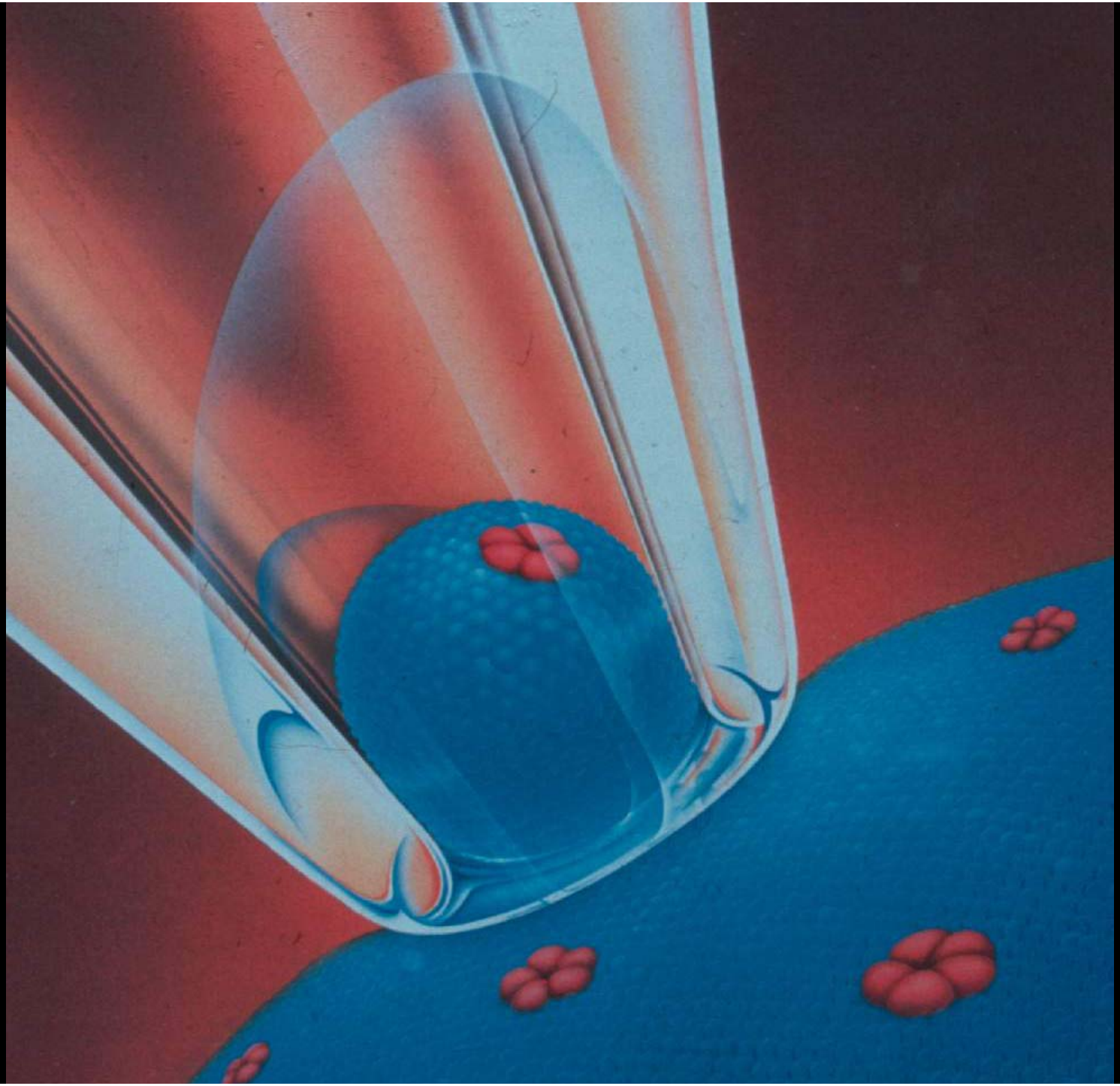


ION CHANNELS: Proteins with a Hole

Channels form a class of Biological Systems
that can be analyzed with

Physics as Usual

Engineering-Physics-Mathematics
are the proper language
for Ion Channels
in my opinion

ION CHANNELS: Proteins with a Hole

Physics as Usual

requires

Standards as Usual

so we can be sure

Calculations are Consistent

with each other and known physical laws

ION CHANNELS as Physical Objects

Channels control flow of Charged Spheres

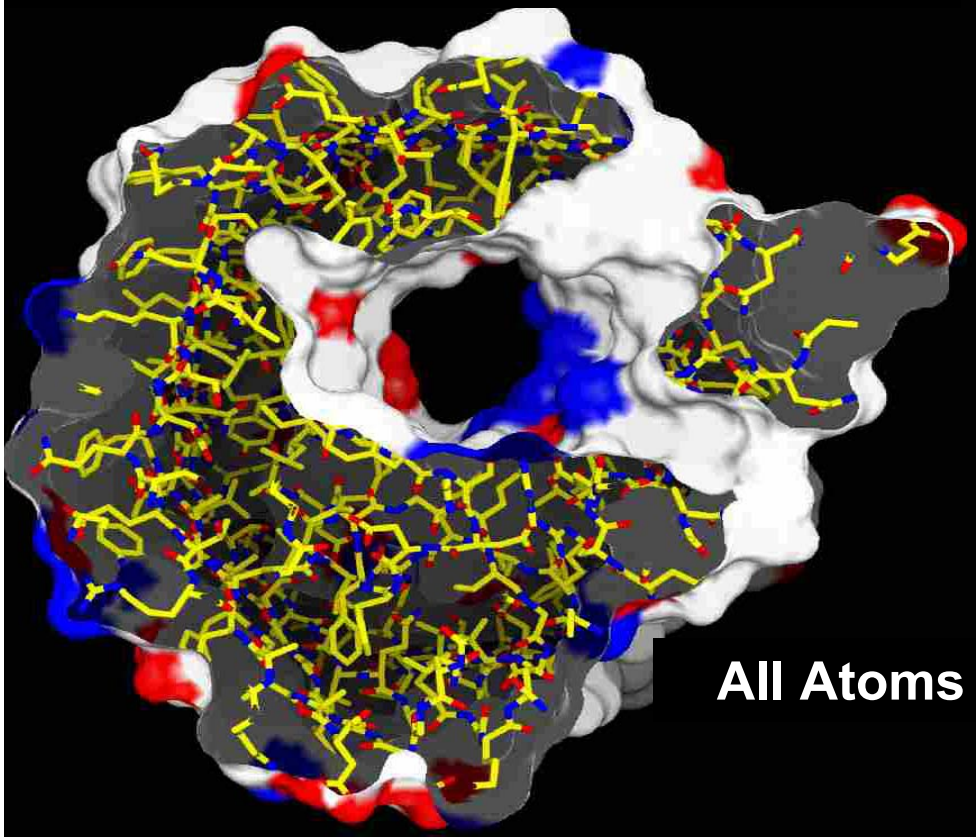
Channels have Simple Invariant Structure on the biological time scale.

Why can't physicists predict the movement of Charged Spheres through a Hole?

in 2003

Channels = Proteins with a Hole

Chemist's View

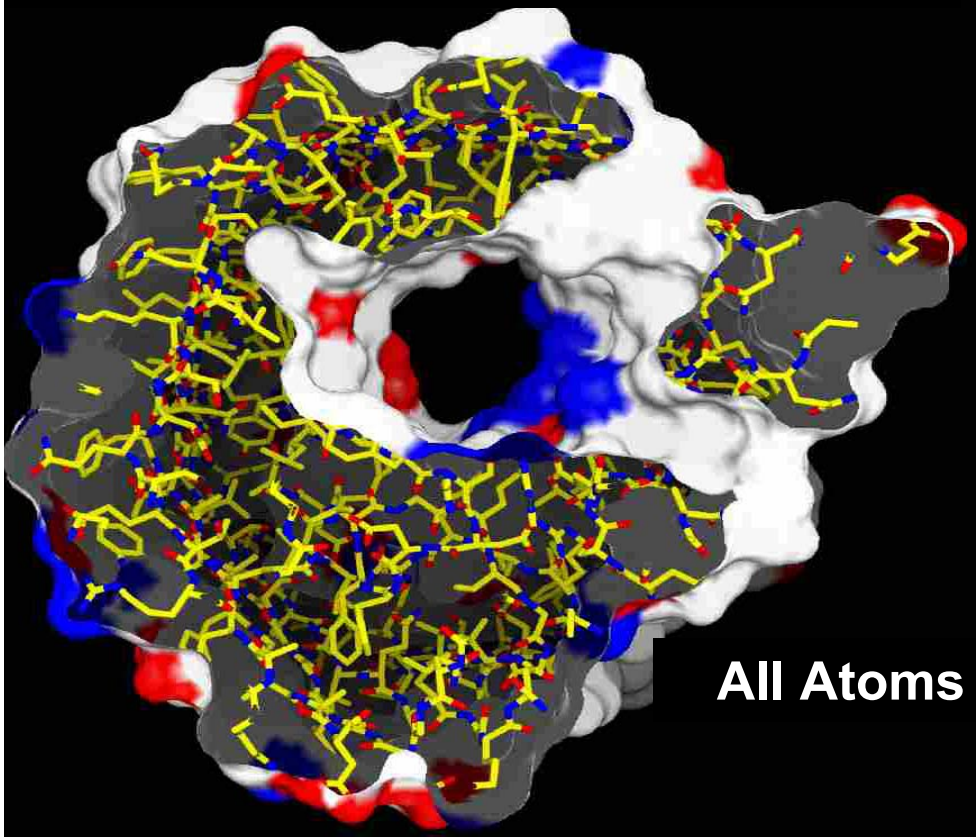


All Atoms View

Chemical Bonds are lines
Surface is Electrical Potential
Red is positive
Blue is negative

Channels = Proteins with a Hole

Chemist's View



All Atoms View

Chemical Bonds are lines
Surface is Electrical Potential
Red is positive
Blue is negative

Why can't we predict movement of <u>Charged Spheres through a Hole?</u>

Lack of Standards for Simulation

How do we know if a simulation is correct?

Physical Chemists have Standards:

Compute Pair Correlation Function
Compute Activity of Ionic Solutions

Computational Physicists have Standards:

Compute energy of macroscopic electric field
Compute Ohm's and Fick's Law

What are the

Standards for Computations

of Proteins and Channels??

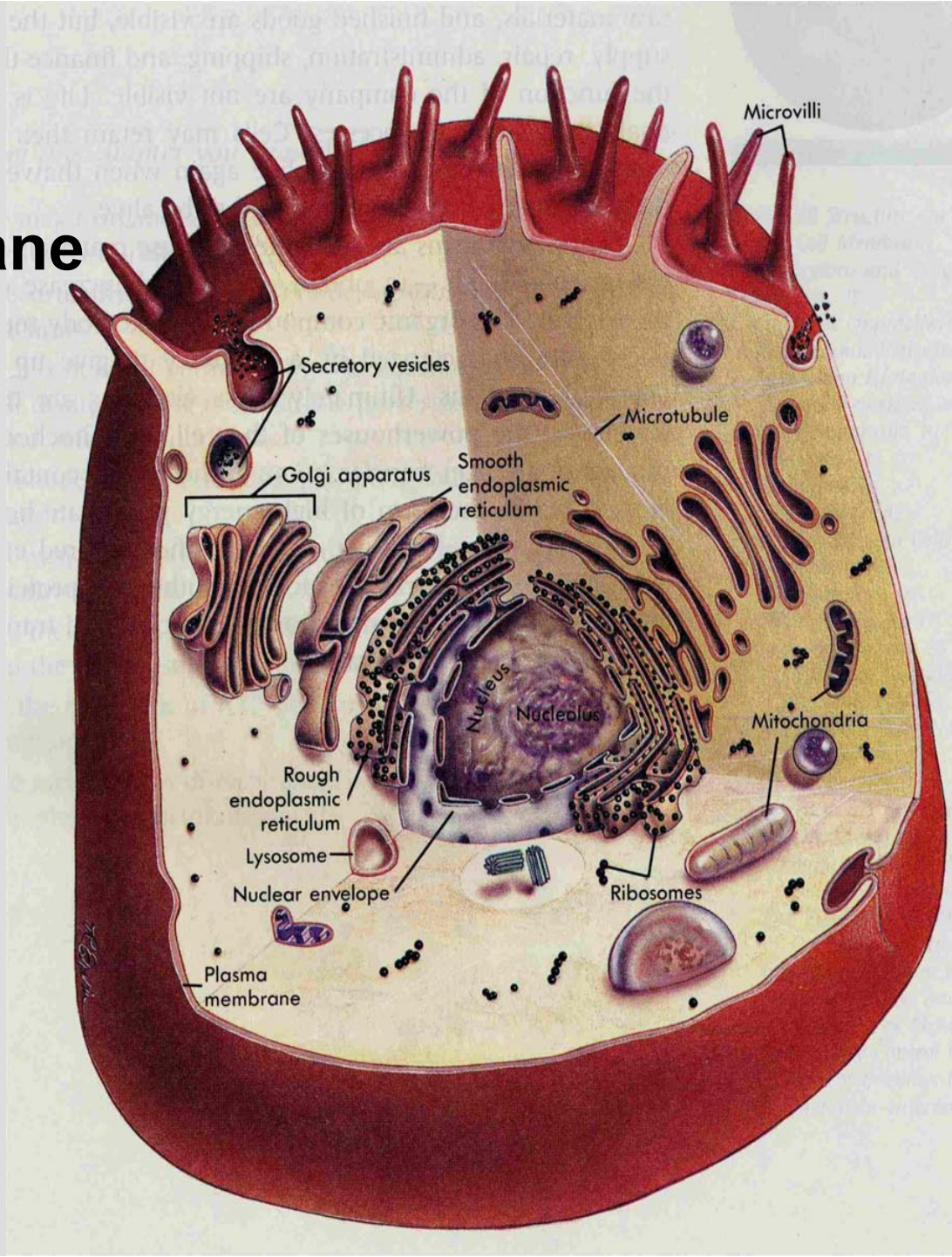
We might have been too early, a decade ago;

Now, we do not want to be too late!

The Cell

Defined by a Membrane

Note: intra-cellular compartments are defined by their membranes



ION CHANNELS – Biological Role

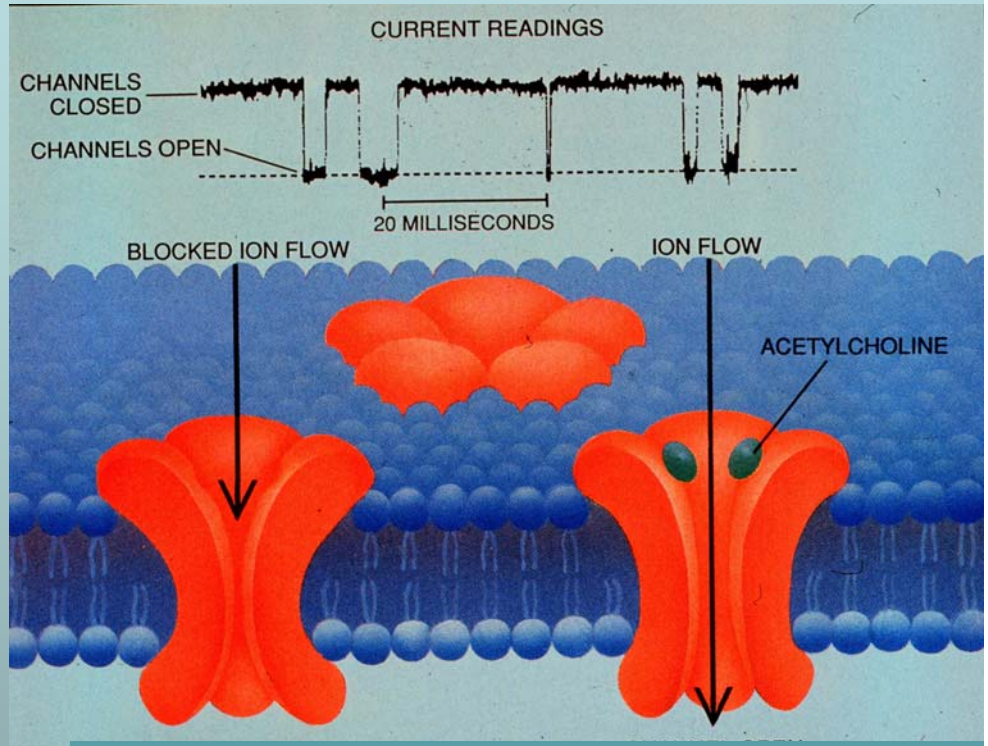
➔ **Channels are Proteins that form Nanoscale Tunnels through membranes of (nearly) all cells and subcellular organelles.**

➔ **Channels control electrical signaling in the nervous system, contraction of heart and muscle, and many other functions.**

➔ **Channels are the targets of many many drugs used in clinical medicine.**

➔ **Channels are involved in diseases. Viruses attach to channels to enter cells**

➔ **Channels control flow of ions into cells. and maintain intracellular ion concentration and electrical potential essential for cell life and function.**



Closed Channel **Open Channel**

ION CHANNELS – Experimental Data

Channels are studied in literally thousands of laboratories every day, one channel molecule at a time because of medical and biological interest:

~1/3 of all human proteins are Channels or Transporters.

ION CHANNELS – Natural Nanodevices

Ion channels are **Device Elements**
that self-assemble into perfectly reproducible arrays.

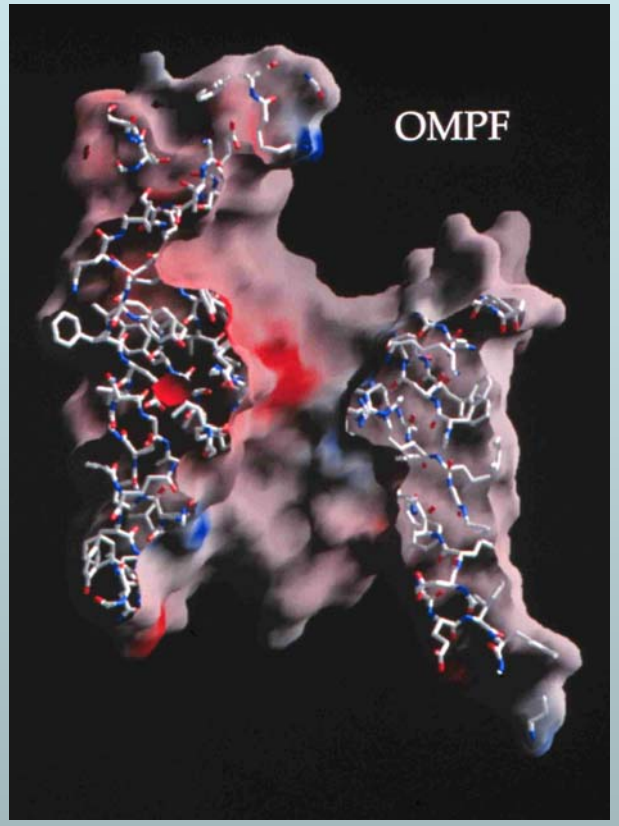
Ion channels have **Selectivity.**
K channel selects K^+ over Na^+ by ~10^4.

Ion channels **Gate/Switch** in response
to pH, voltage, chemical species and mechanical force
from conducting to nonconducting state.

Ion channels have
VERY Large Charge Densities
critical to I-V characteristics and selectivity (and gating?)

Ion channels allow
Mutations that modify conductance, selectivity, and
function.

Ion channels form
Templates for design of bio-devices and biosensors.



~30Å

Ion Channels

are simple enough to allow

Physical Analysis of Important Biological Function

using

Physics and Mathematics as Usual

Goal:

Predict Function

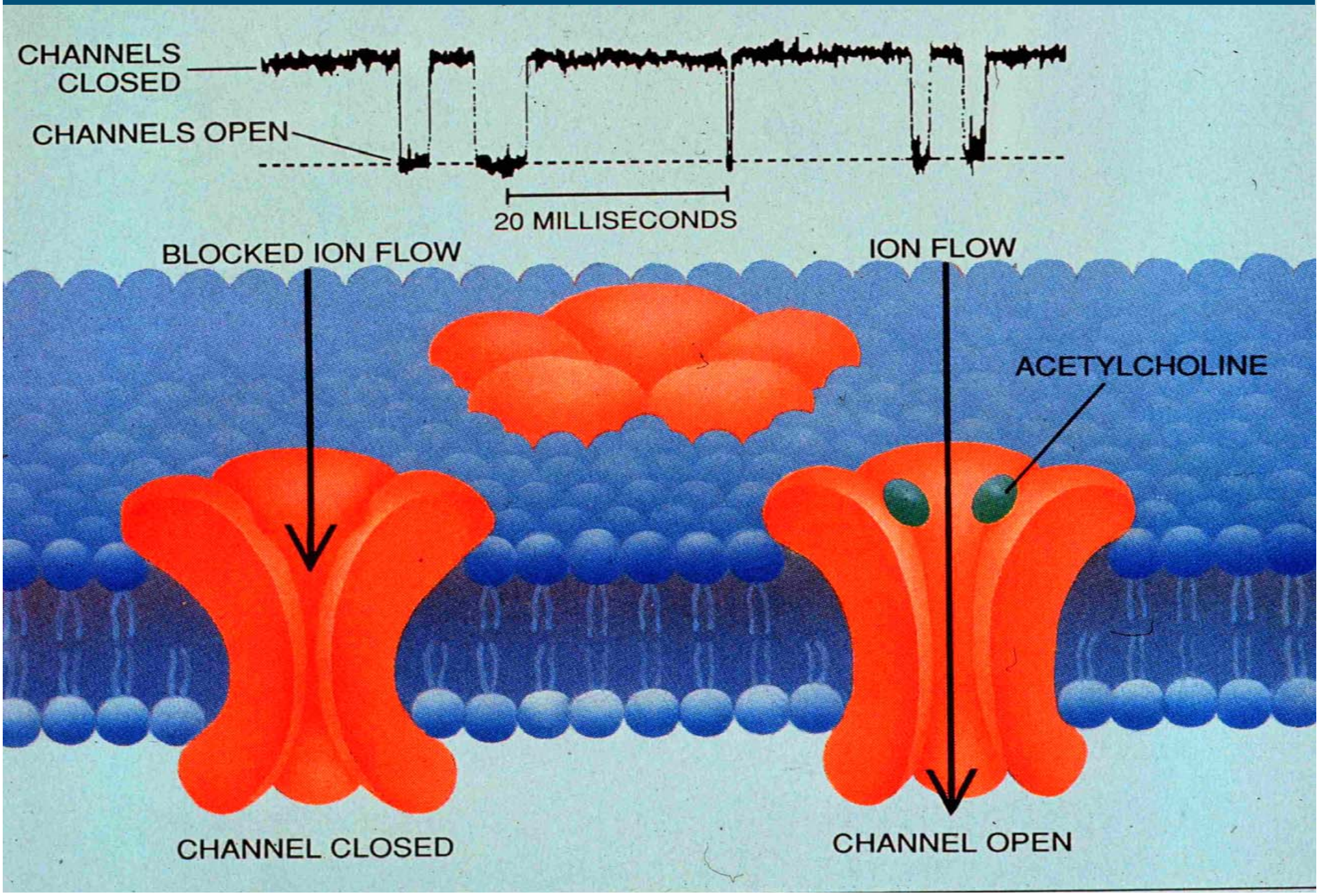
From Structure

given

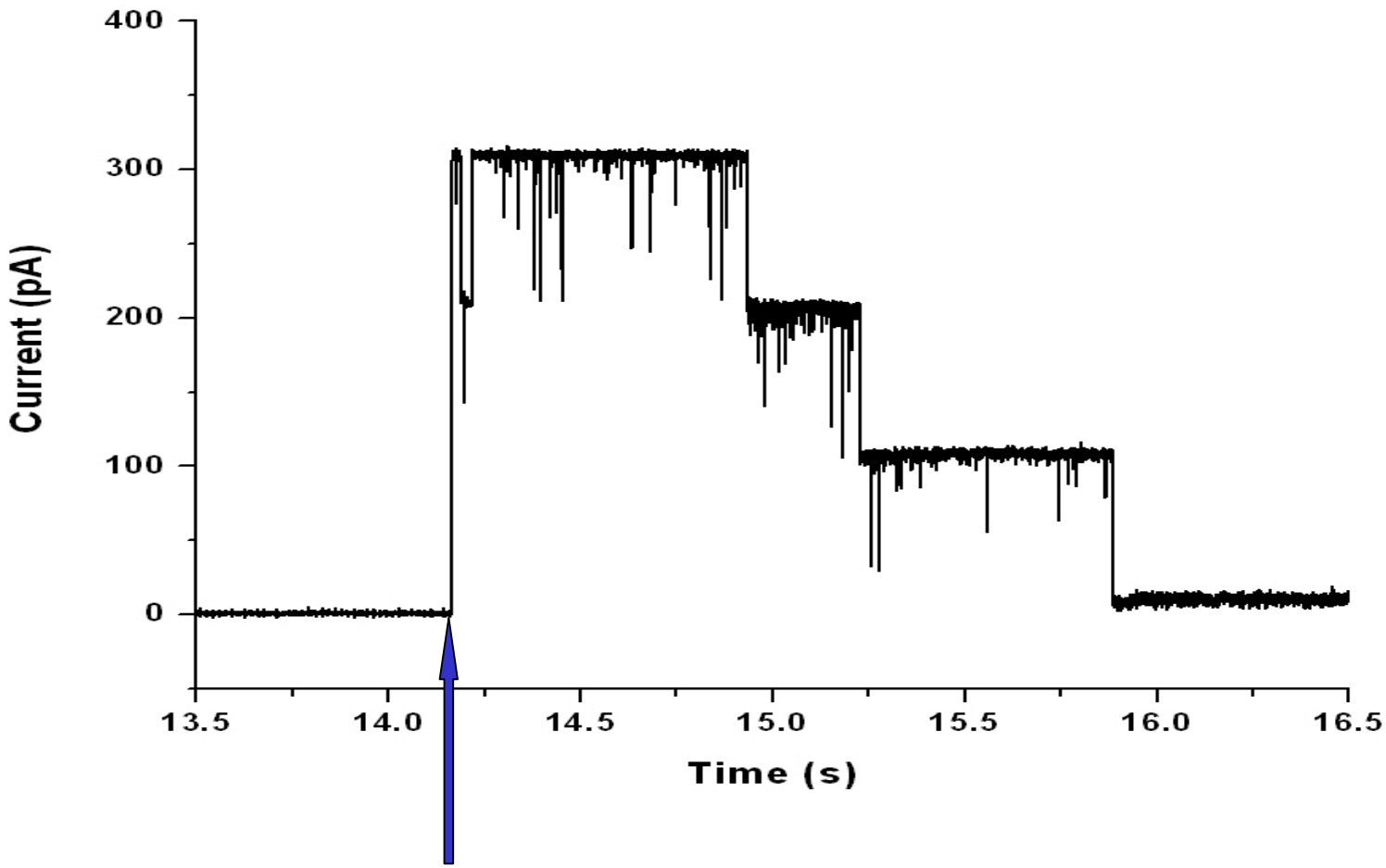
Fundamental

Physical Laws

Current in One Channel Molecule is a Random Telegraph Signal



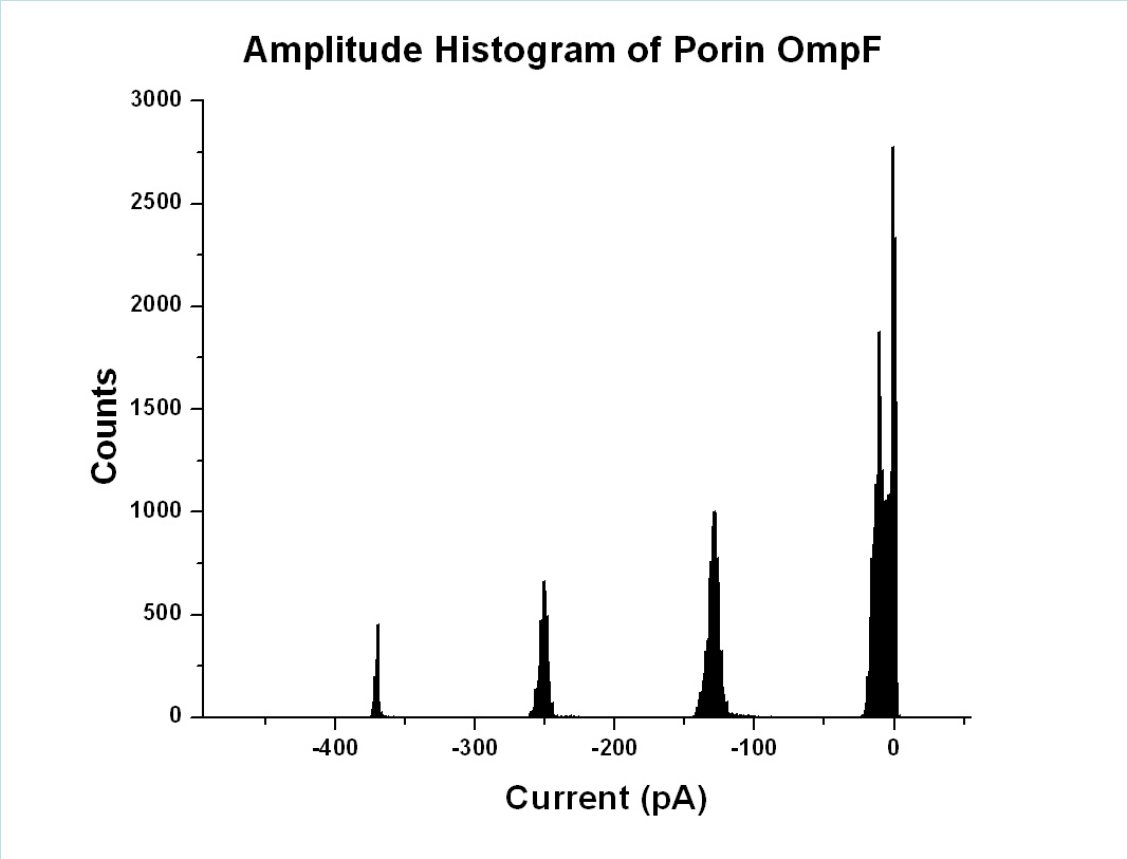
Gating: Opening of Porin Trimer



Voltage Step Applied Here (+ 80 mV; 1M KCl)

John Tang
Rush Medical Center

Single Channel Currents have little variance



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Rush Medical Center

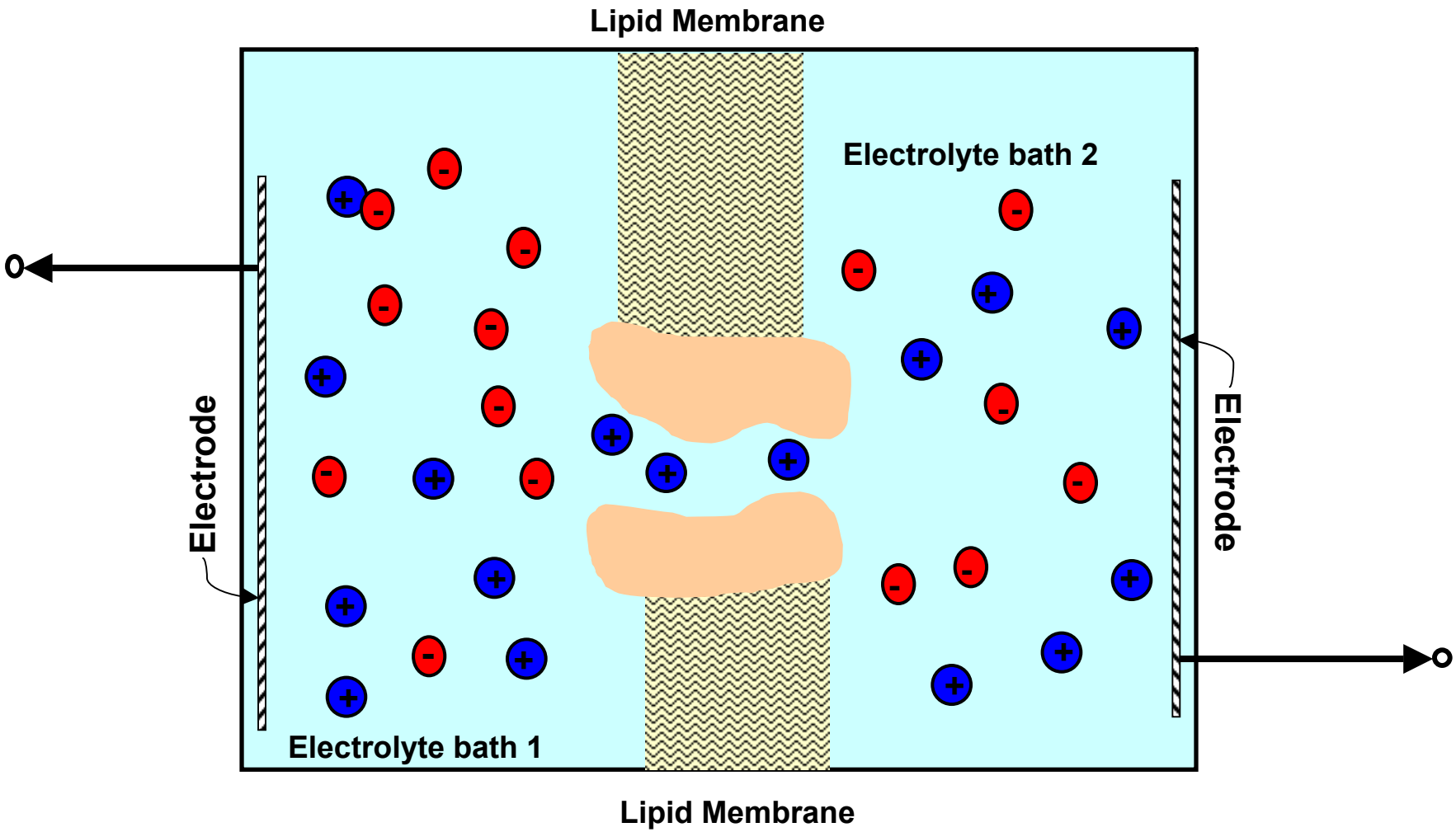
Ion Channels

are usually studied in a

Classical Electrochemical Cell

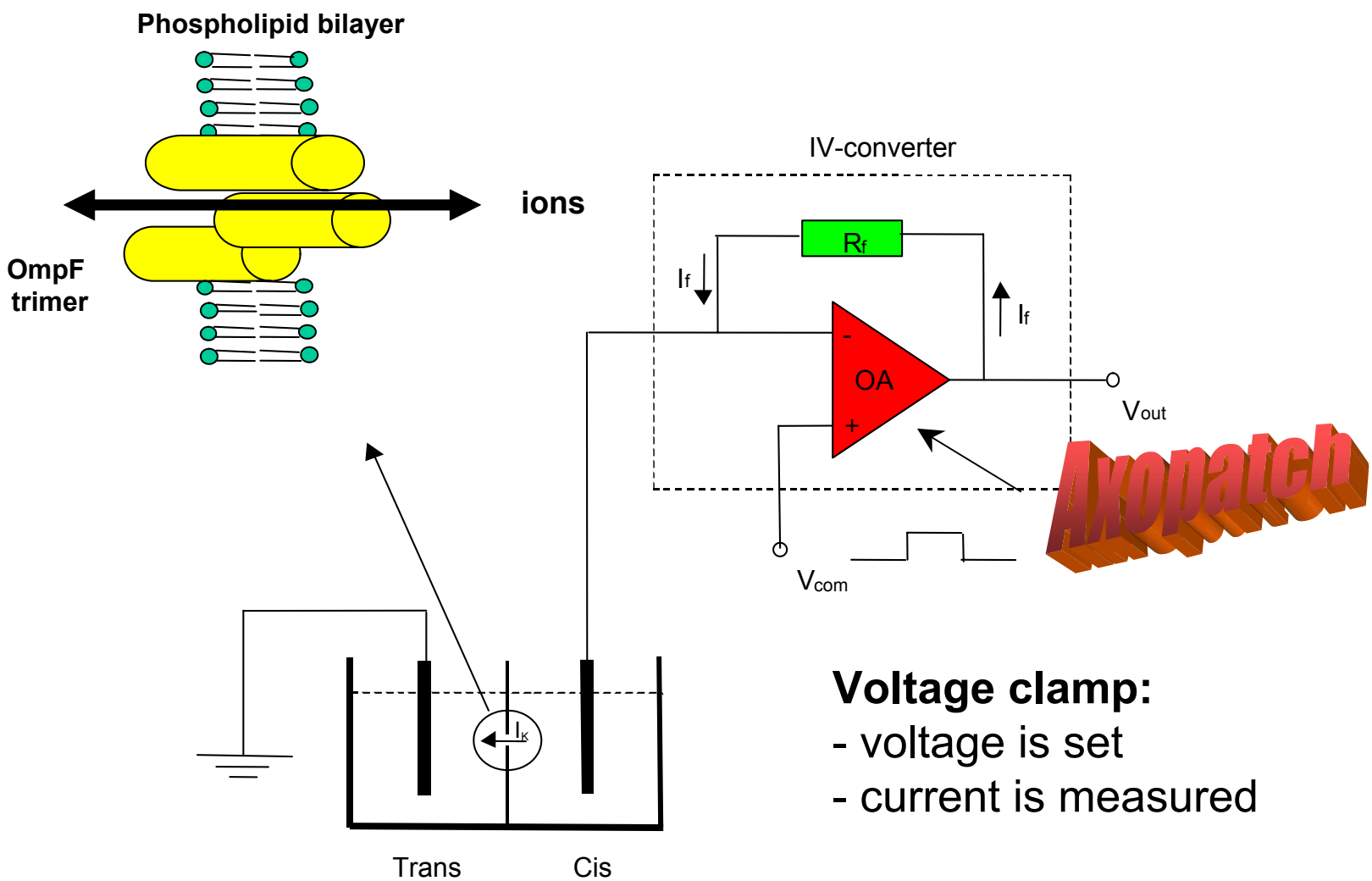
which mimics the Biological Cell

Ions in Channel and Baths

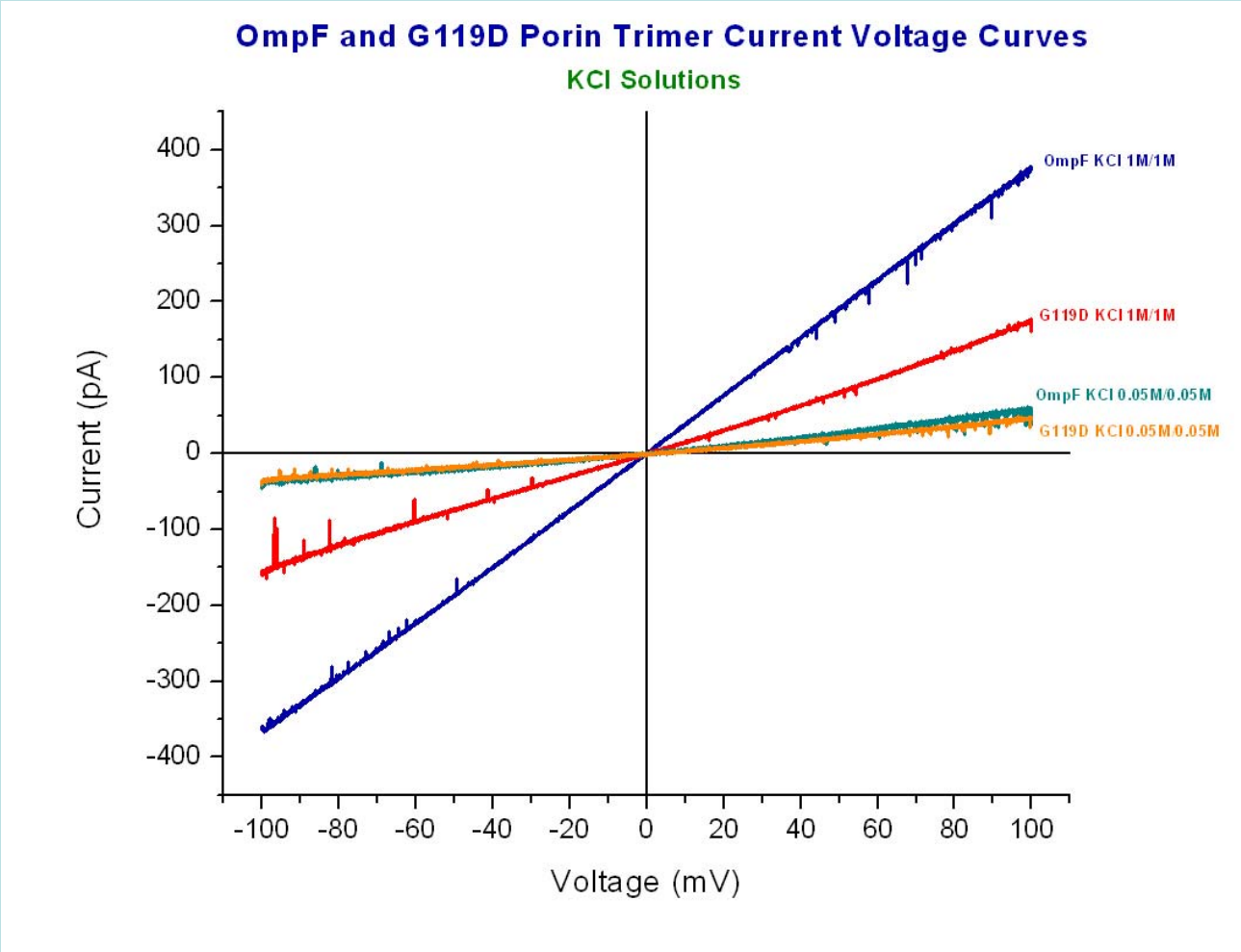


Ionic concentrations and electrostatic potential held constant far from channel

Lipid Bilayer Setup
Recordings from a Single Molecule



Voltage clamp:
- voltage is set
- current is measured



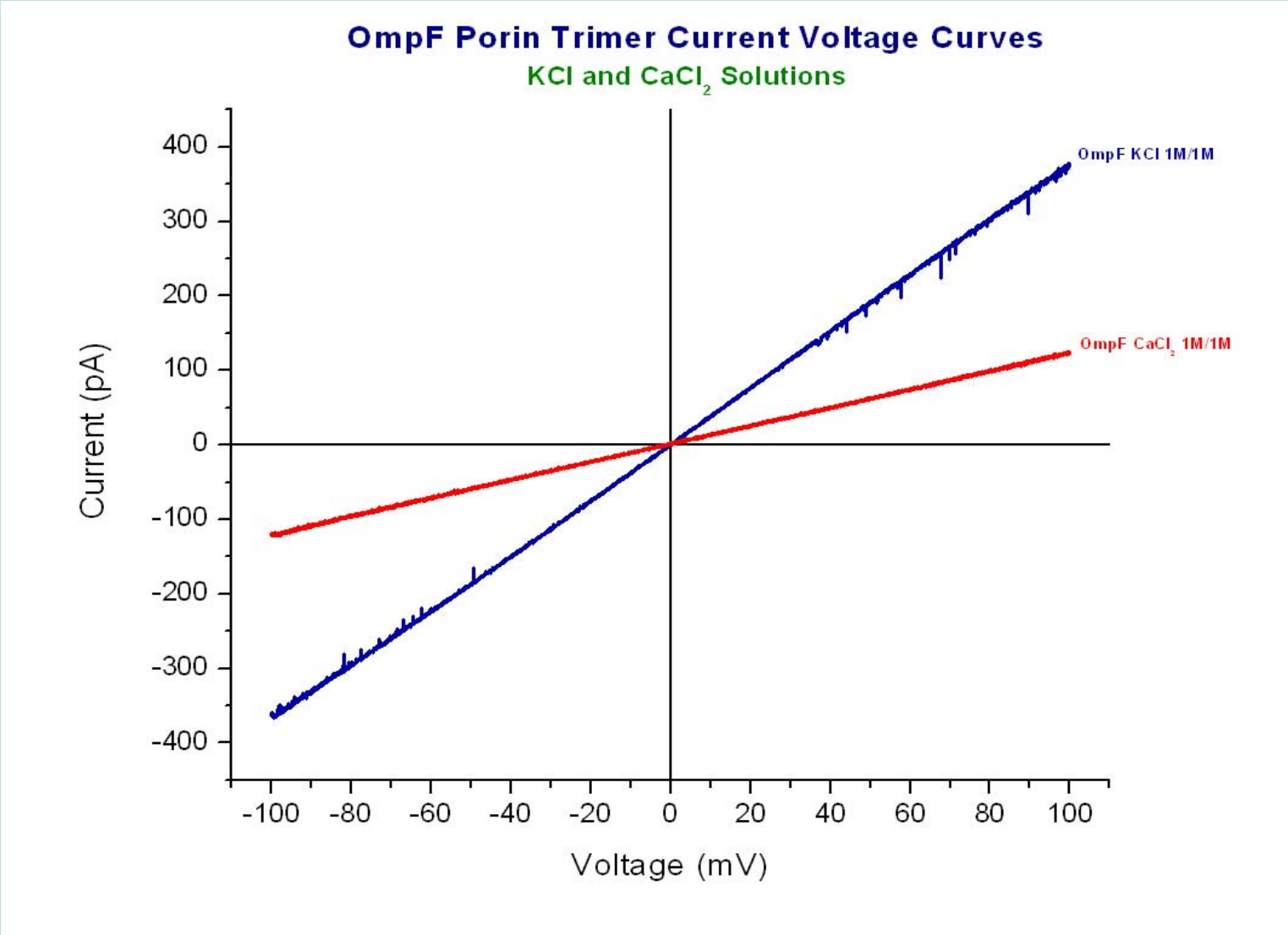
Current depends on

Voltage

Concentration

Fixed Charge **on channel protein**

John Tang
Rush Medical Center



Current depends on type of ion

Selectivity

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Rush Medical Center

Goal:

Predict Function

From <u>Structure</u>

given

Fundamental

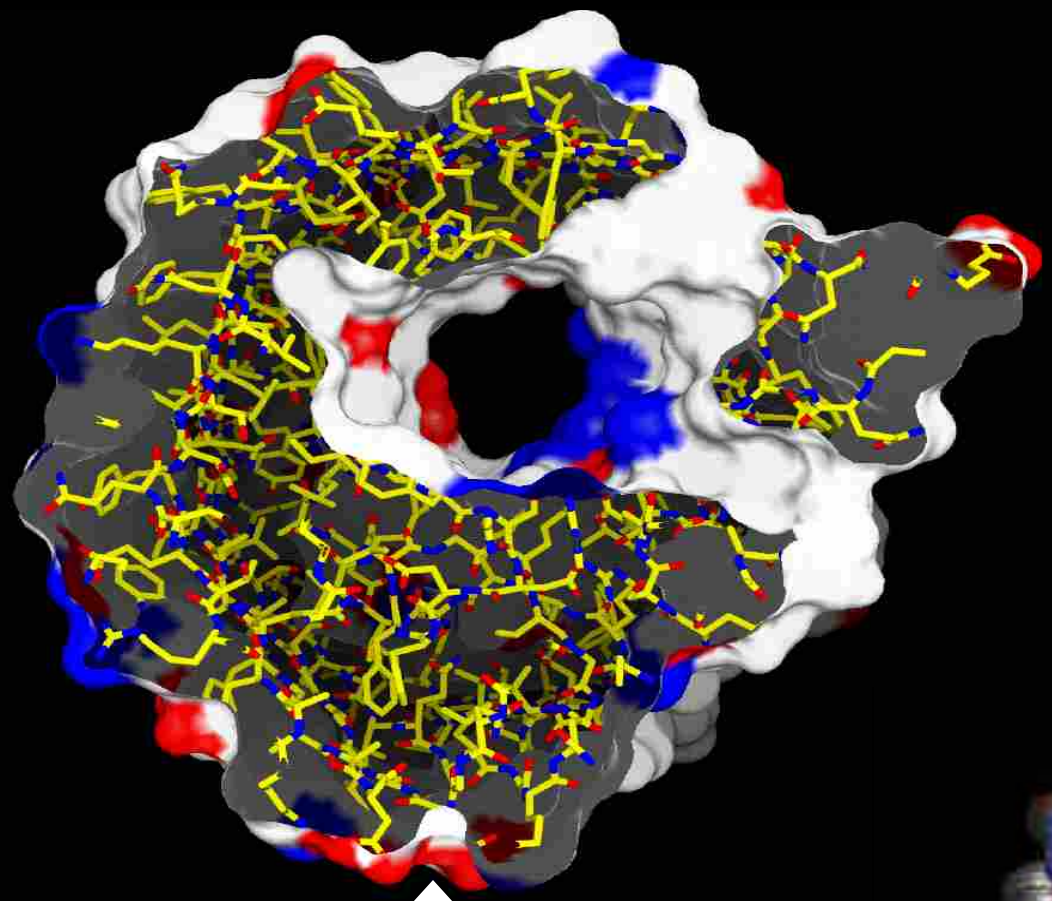
Physical Laws

Structures…

Location of charges are known with atomic precision (~0.1 Å) in favorable cases.

Structure

OmpF Biochemist's View

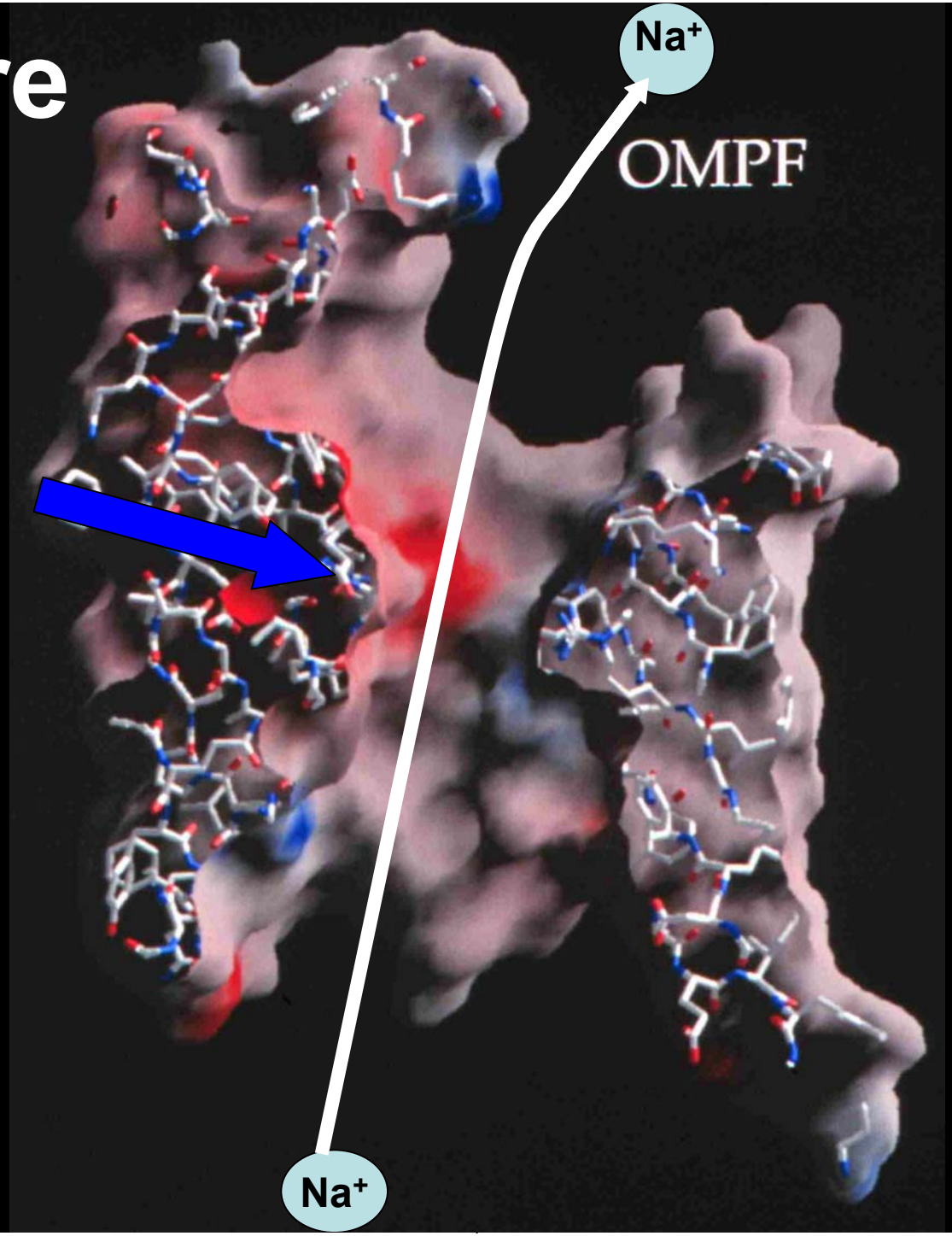


Chemical Bonds are lines
Surface is Electrical Potential
Red is positive
Blue is negative

All Atoms View

Structure

Specific Mutations
are made Every Day

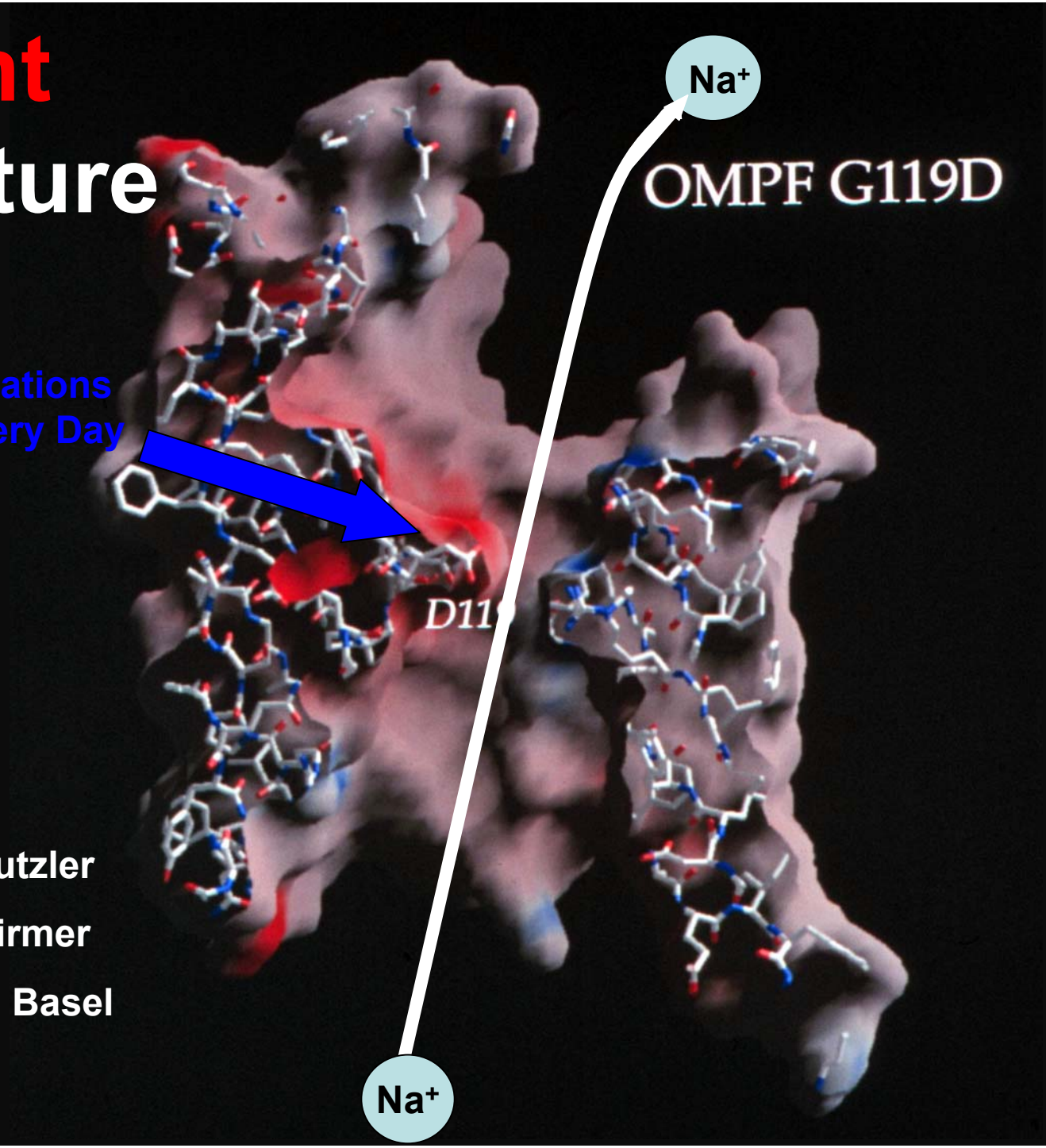


Raimund Dutzler

Tilman Schirmer

Biozentrum Basel

Mutant Structure



Specific Mutations are made Every Day

Raimund Dutzler

Tilman Schirmer

Biozentrum Basel

Goal:

Predict Function

From Structure

given

Fundamental

Physical Laws

But …

What **are the Fundamental Physical 'Laws'?**

Verbal Models Are Popular with Biologists

but

Inadequate

They are hardly physics at all!

Verbal Models

are

Vague

and

Difficult to Test

Verbal Models

lead to

<u>Interminable</u> Argument

and

<u>Interminable</u> Investigation

thus,

to Interminable Funding

Verbal Models Are Popular

What are the Fundamental Physical ‘Laws’?

Why not simulate?

Simulations so far cannot reproduce macroscopic variables and phenomena known to dominate biology

Direct Simulations are Problematic
Even today

Meanwhile, I use an Engineering Approach

Indirect Simulations are Essential

to determine
validity
and parameters
of
low resolution models

Direct Simulations are problematic even today

Direct Simulations

so far often

do not reproduce

Conservation Laws

(e.g., of energy)

Concentration

(i.e., number density)

Activity coefficient

(i.e., free energy per mole)

Direct Simulations are Problematic

Even today

Direct Simulations

so far often

do not reproduce

Ohm's 'law'

(in simple situations)

Fick's 'law'

(in simple situations)

Direct Simulations are Problematic
Even today

Why not simulate?

First Principle of Numerical Integration

The larger the calculation,
the more work done,
the greater the error

First Principle of Experimentation

The more work done,
the less the error

Why not simulate?

Simulations produce too many numbers

10^6 trajectories each 10^{-6} sec long, with 10^9 samples in each trajectory,

in background of 10^{22} atoms

Simulations
need a theory that
Estimates
(e.g., averages)
or Ignores
Variables

Theories and Models are Unavoidable!

(in my opinion)

Central Unsolved Mathematical Issue

(in my opinion)

How do we include
Macroscopic Variables
in
Atomic Detail Calculations?

Meanwhile, I use an Engineering Approach

Hierarchy of Low Resolution Models

The
Essence of Engineering
is knowing
What Variables to Ignore!

WC Randels
quoted in Warner IEEE Trans CT 48:2457 (2001)

What variables should we ignore when we make low resolution models?

What are the Standards we should use when we decide what variables to ignore?

for Computations of Proteins and Channels.

We will ignore chemistry
(only at first)

Note: biologists, like engineers, **never** ignore structure, even to begin with.

We start
with
Electrostatics

Note: physicists rarely ignore the electric field, even to begin with.

Then we will add
Crowded Charge

Electrostatics are ignored

(more or less)

in traditional Structural Biology

Note: physicists rarely ignore the electric field, even to begin with.

I am covering an enormous range of material in a short time, sometimes with surprising results.

***So*,**

<u>It is appropriate to be skeptical</u>,

of Surprising Results

like our success

with so little chemistry.

But give me a chance, ask

beisenbe@rush.edu

for the papers.

Then, please
Climb on our shoulders,
Or push us aside,
And DO BETTER
than we have!
We need all the help we can get.

Poisson-Nernst-Planck (PNP)

starts

with

<u>Electrostatics</u>

Note: physicists rarely ignore the electric field, even to begin with.

Small Charge in Small Places

Large Potentials

One charge produces 1 volt
in a
Sphere of diameter 14 Å

Dielectric constant = 2

(psec time scale)

Large Potentials in Small Places

One charge travels 7Å

and changes the potential

1 Volt in 460 femtoseconds

because

Ions move at the speed of sound

(in water)

Proteins
Bristle with Charge

Cohn (1920's) & Edsall (1940's)

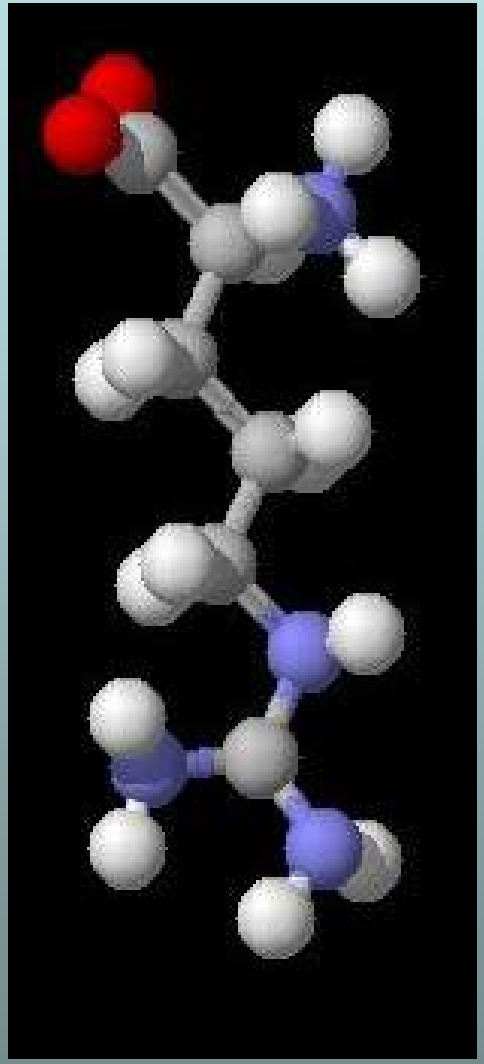
Ion Channels are no exception

Many atoms in a protein have Permanent Charge ~1e

Permanent charge is the (partial) charge on the atom when the local electric field is zero.

Atomic Charge in Arginine

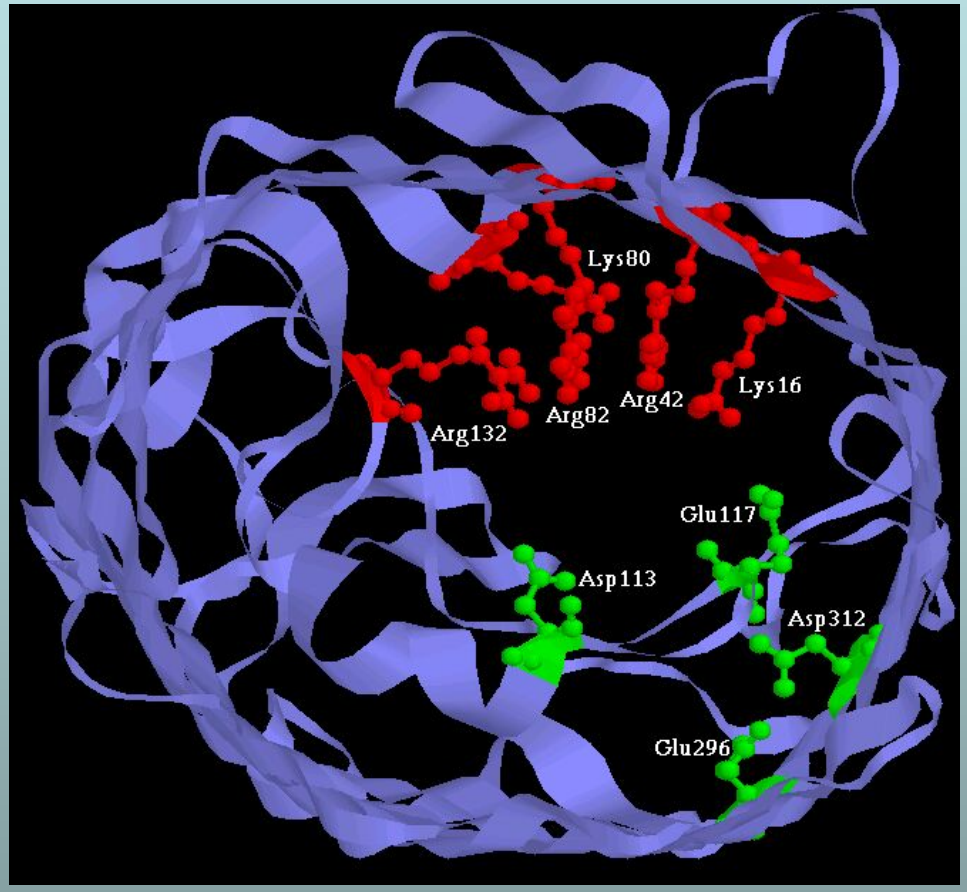
Atom	Charge (*units* /e)
N	−0.40
H	0.25
C_a	0.10
C_b	0.00
C_g	0.00
C_d	0.10
N_e	−0.40
H_e	0.30
C_z	0.50
NH_1	−0.45
HH_11	0.35
HH_12	0.35
NH_2	−0.45
HH_21	0.35
HH_22	0.35
C	0.60
O	−0.55
Average Magnitude	0.32



according to CHARMM

Active Sites of Proteins are ***Very* Charged**

e.g. **20 M = 1.2×10^{22} cm^{-3}**



Selectivity Filters and Gates of Ion Channels

are

Active Sites

ION CHANNEL SIMULATION – Continuum Models

Poisson's Equation

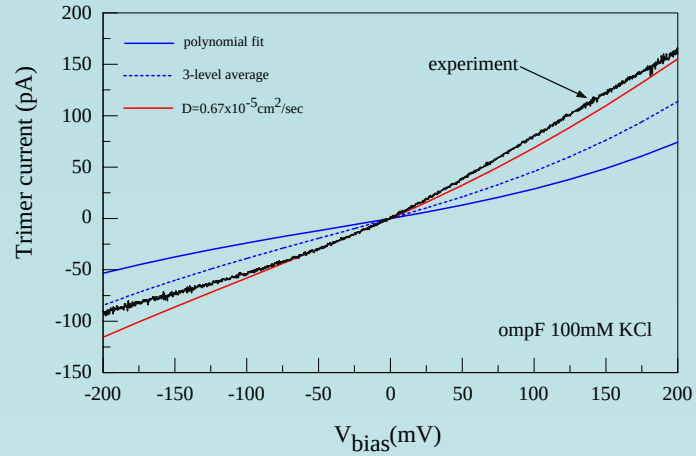
$$\nabla \cdot (\varepsilon \nabla \psi) = -(\rho_{fixed} + \rho_{+} + \rho_{-})$$

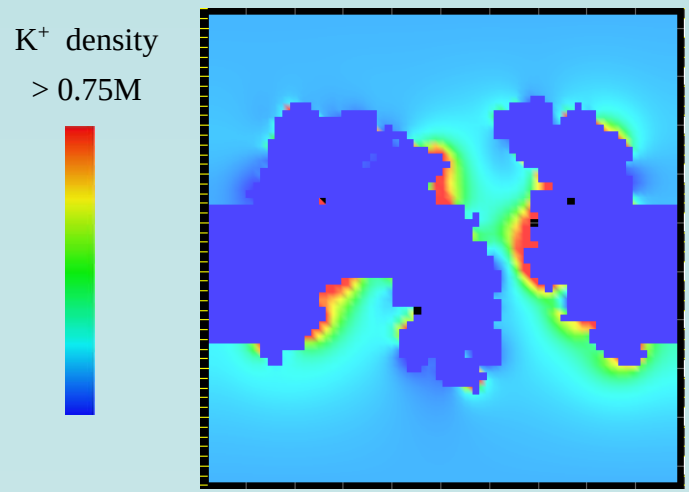
Drift-diffusion Equation

$$j_{\pm} = -(D_{\pm}/kT)\rho_{\pm}\nabla\psi_{\pm}$$

Continuity Equation

$$\nabla \cdot j_{\pm} + \frac{\partial \rho_{\pm}}{\partial t} = S_{\pm \text{Stored Charge}}$$





➔ **IV curves generated in minutes or hours**

➔ **Neglect of ion size leads to unreasonably high ion densities near fixed charges**

Stochastic Derivation is in progress Schuss, et al …

Trudy van der Straaten
Umberto Ravaioli
Univ Illinois Urbana Champaign

PNP Forward Problem

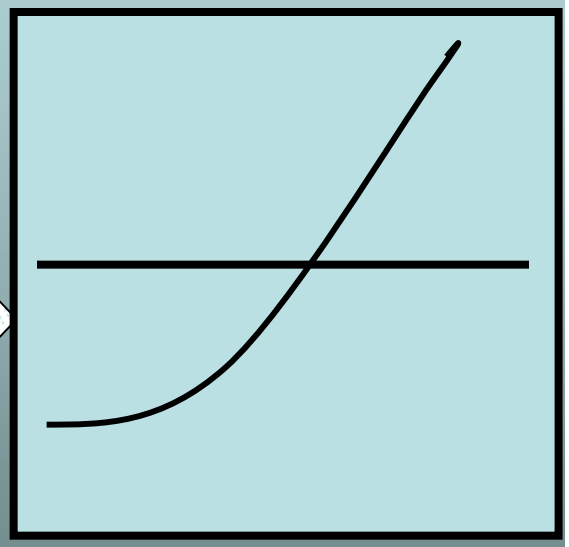
INPUT THEORY OUTPUT

EXPERIMENTAL CONDITIONS

Bath concentrations

Bath Potential Difference

PNP



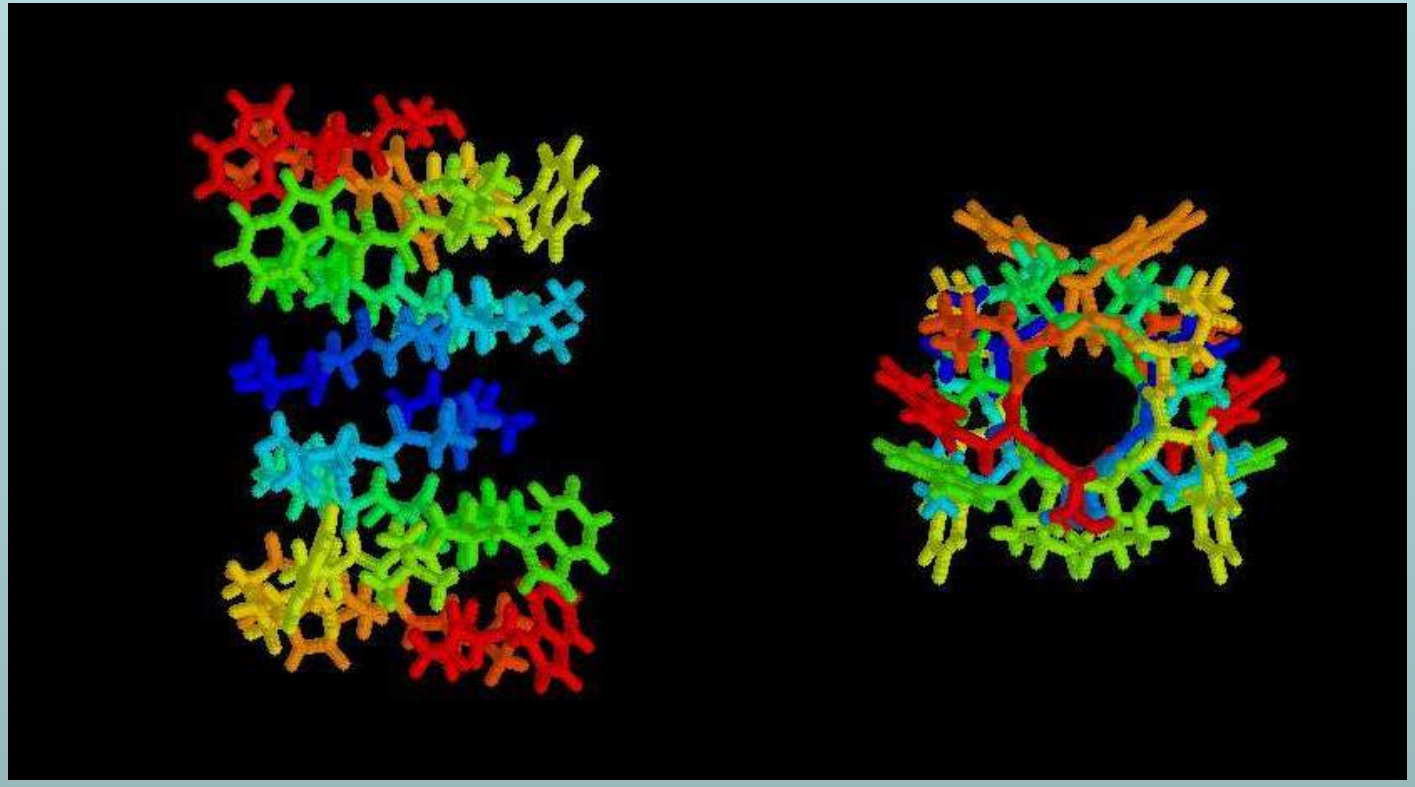
STRUCTURE

Length, diameter,

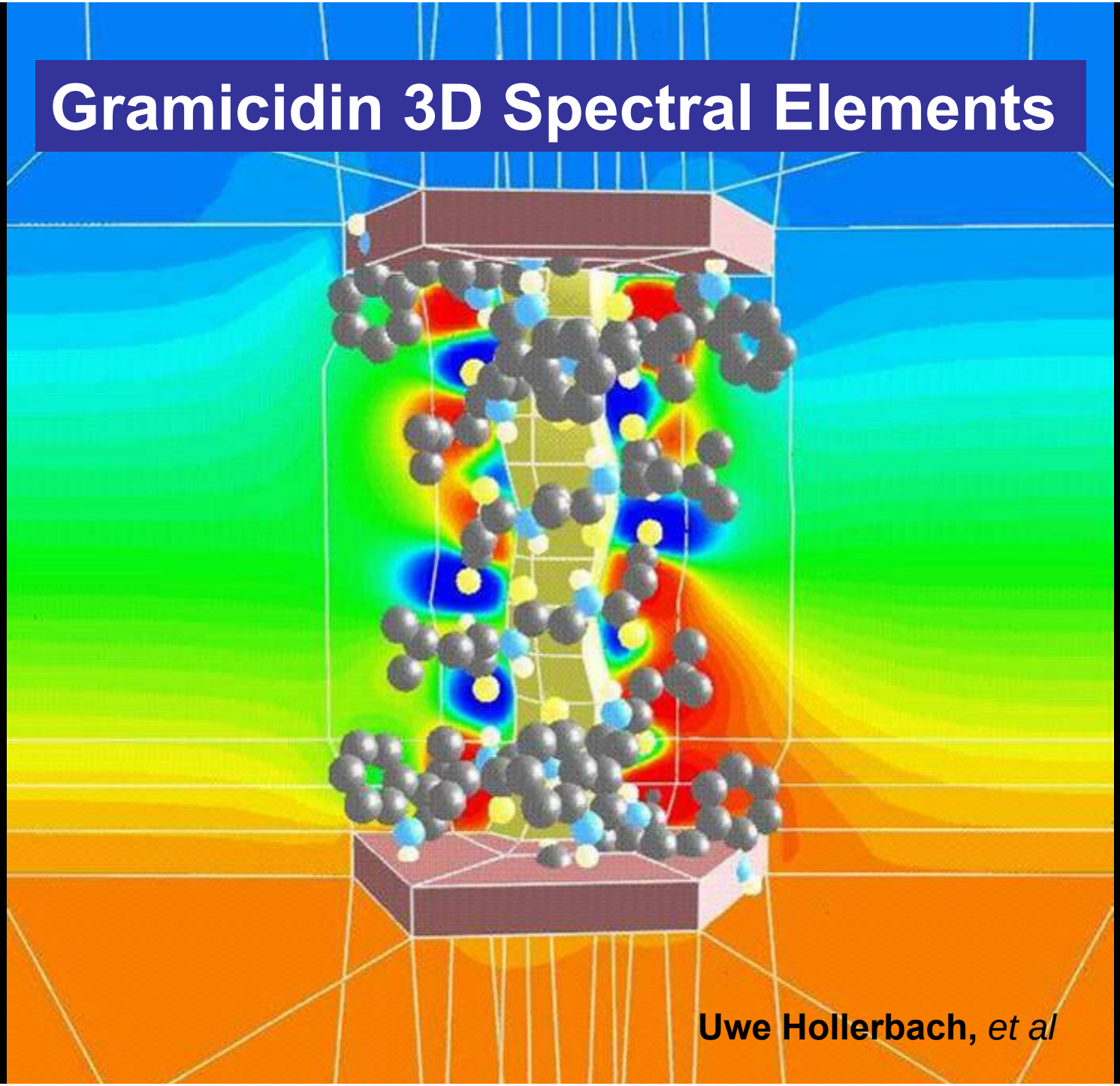
Permanent Charge

Dielectric Coefficient

Gramicidin Backbone



Gramicidin 3D Spectral Elements

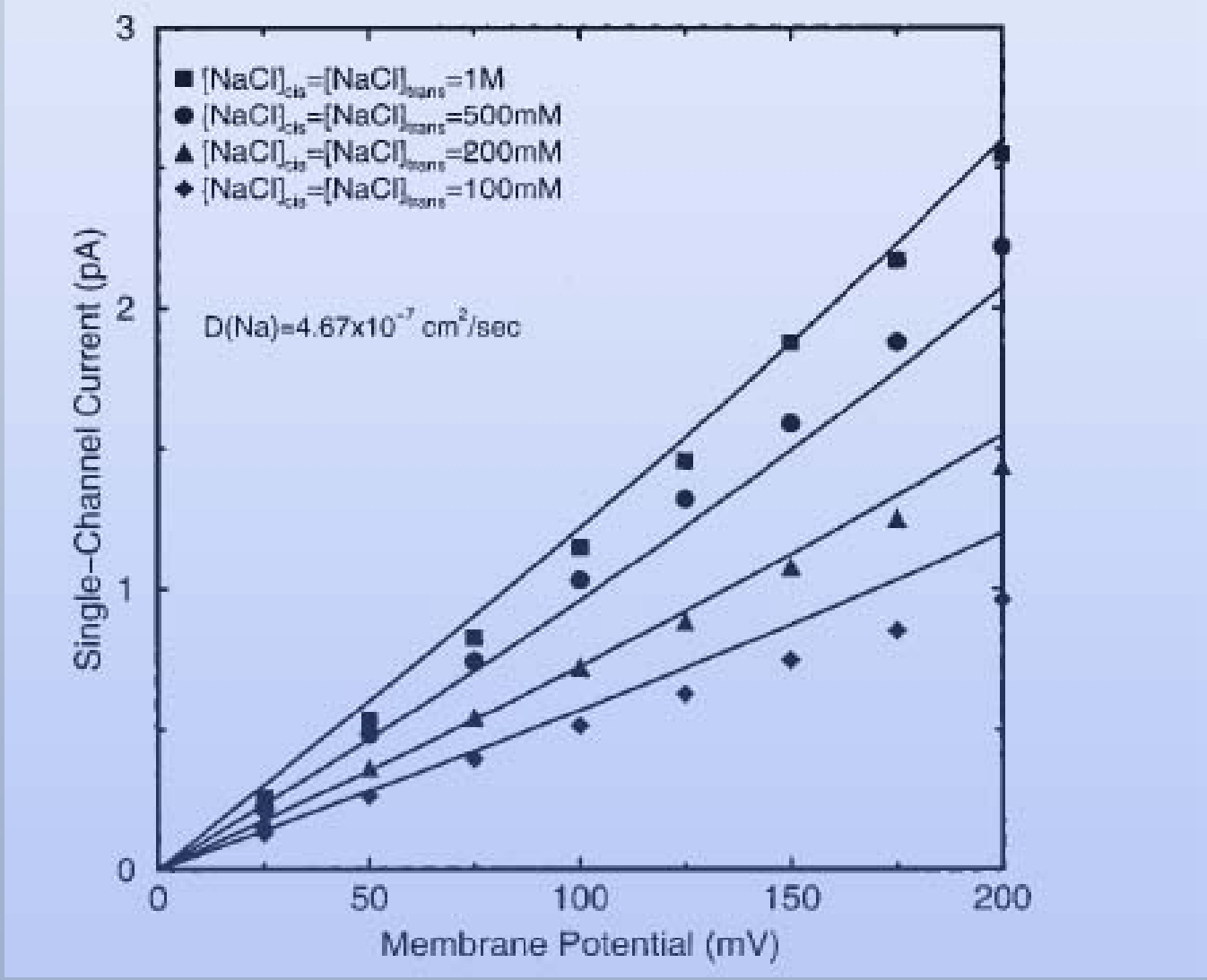


Uwe Hollerbach, *et al*

Current Voltage Relation Gramicidin

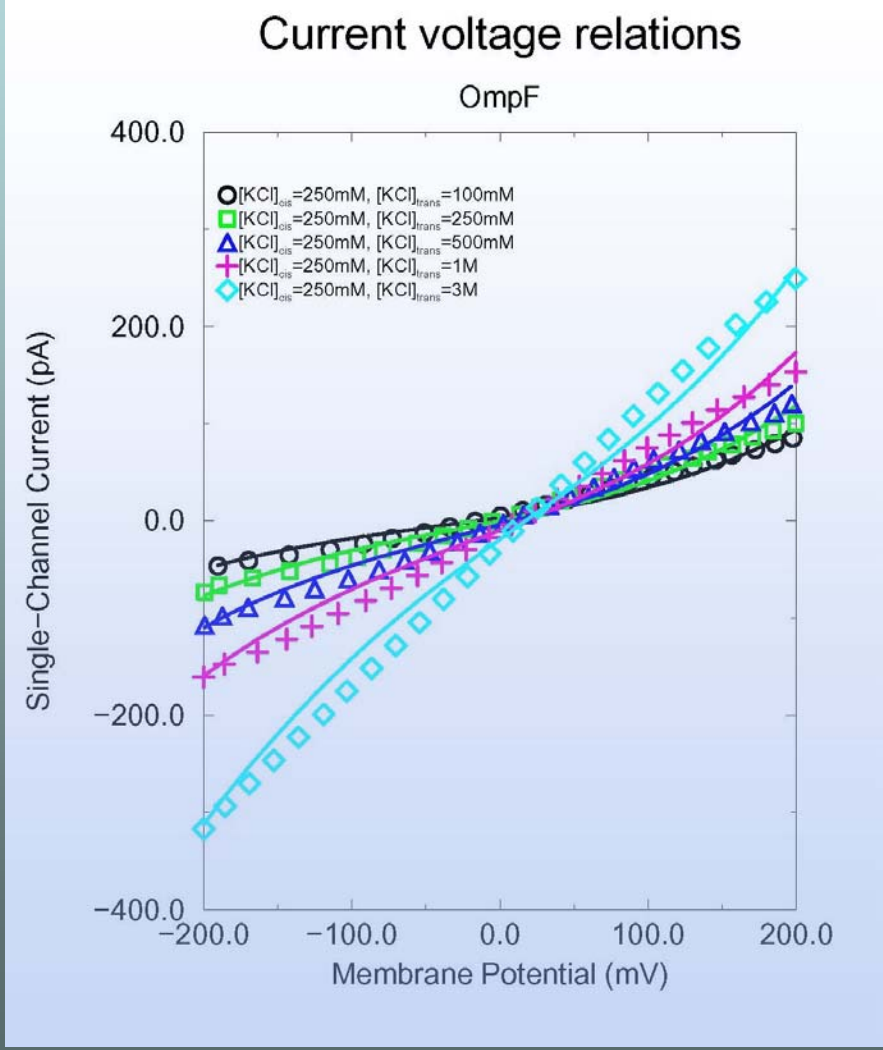
3D PNP

Uwe Hollerbach



Bad Fits of 1D PNP

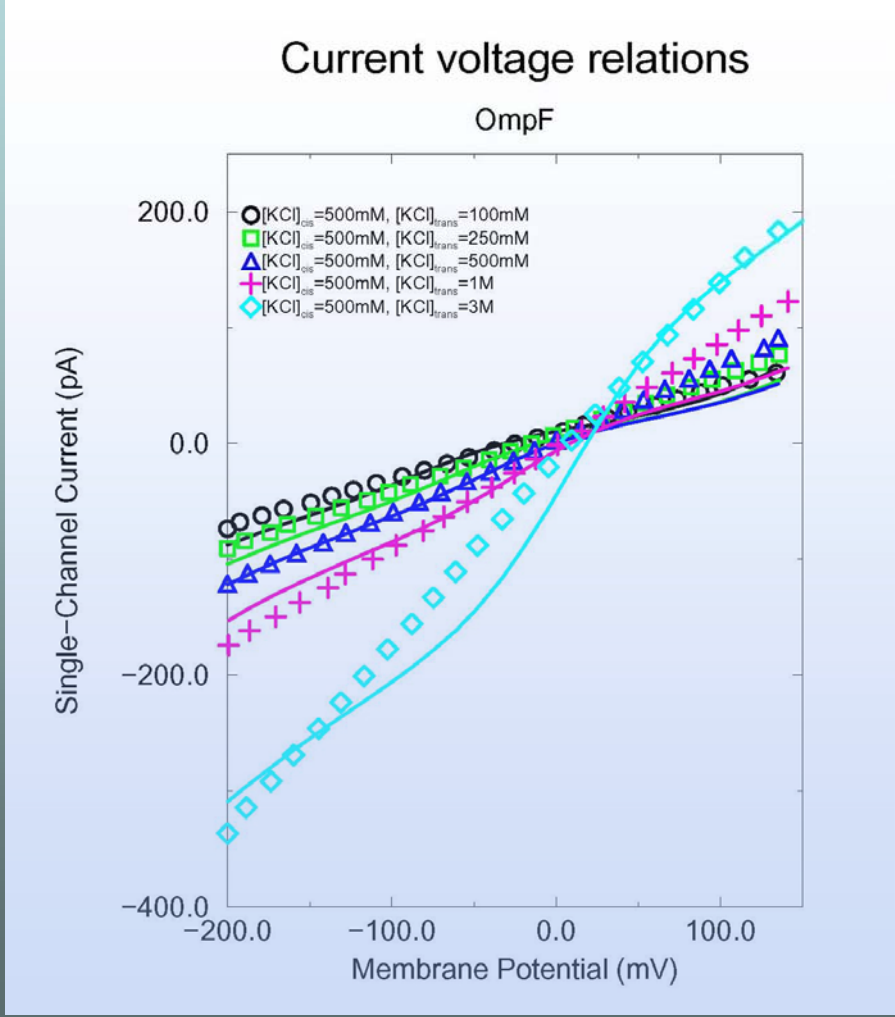
even with ‘optimal’ nonuniform D(x)



Duan Chen
John Tang
Rush Medical Center

Bad Fits of 1D PNP

even with ‘optimal’ nonuniform D(x)



Duan Chen
John Tang
Rush Medical Center

Dielectric Boundary Force

$$\mathbf{F}(\mathbf{r}) = -q\nabla\left(\Phi(\mathbf{r}) - \frac{q(\mathbf{r}_0)}{4\pi\varepsilon\varepsilon_0|\mathbf{r}-\mathbf{r}_0|}\right)_{\mathbf{r}-\mathbf{r}_0}$$

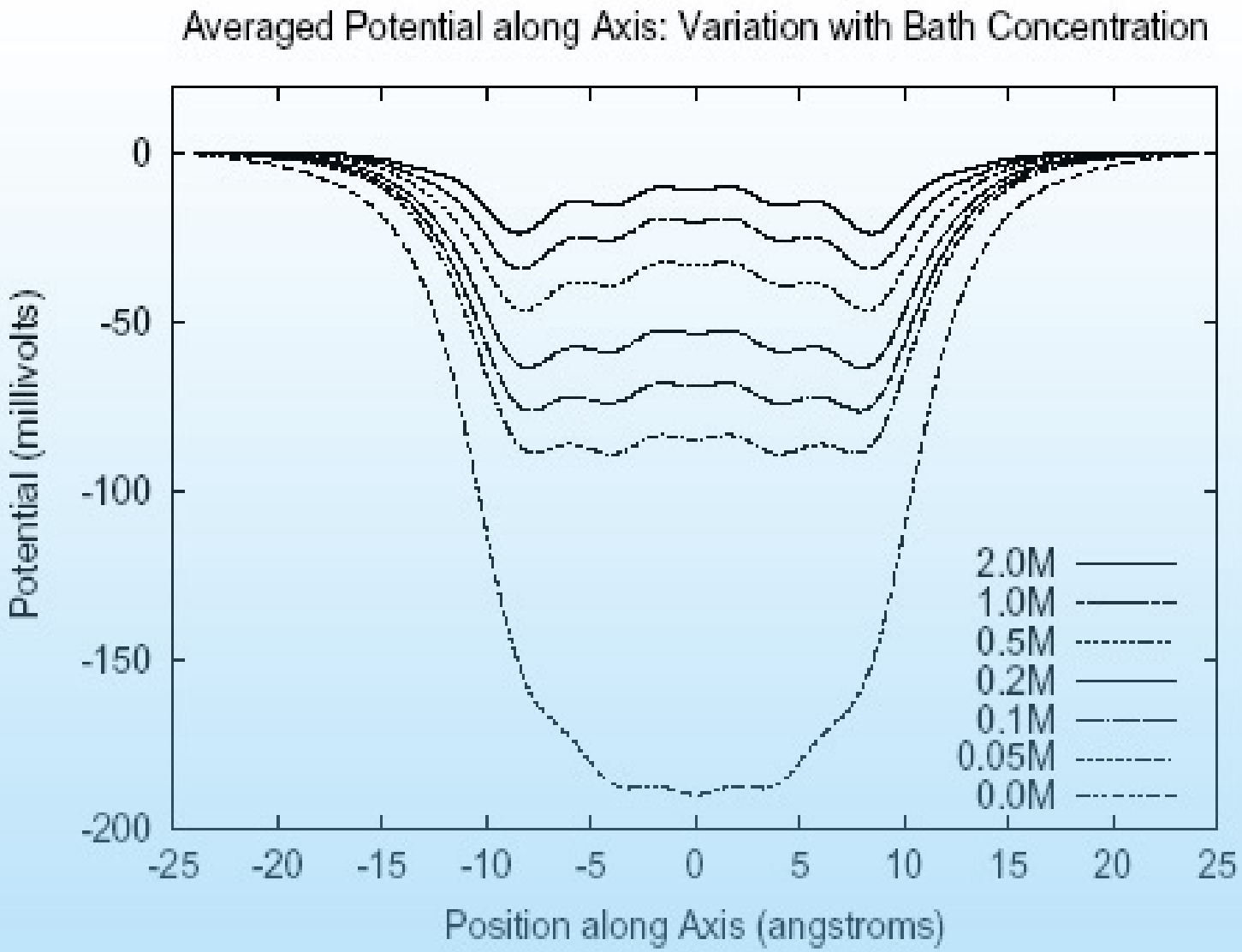
Dielectric Boundary Force $\mathbf{F}(\mathbf{r})$ for point charge $\mathbf{q}(\mathbf{r}_0)$

Boaz Nadler and Uwe Hollerbach

Yale University Dept of Mathematics

Rush Medical Center

Shielding in Gramicidin



Uwe Hollerbach
Rush Medical Center

Neither

Field Theory nor Statistical Mechanics

easily accommodates

Finite Size

of Ions and Protein Side-chains

How can that be Changed?

Learn from the

Physical Chemists!

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

In particular,

Details of Hydration Shells,

Orbital Delocalization, *etc.*

are

NOT important

in determining the

Activity

(free energy per mole)

of ionic solutions

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

Central Result of Physical Chemistry

Physical Properties of the

Highly Compressible Plasma

determine the

Key Properties of Ionic Solutions

NOT details of
Hydration and Orbital delocalization

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

Selectivity
of bulk solutions comes from
Diameter and Charge

which, in turn, determine the compressibility

N.B., selectivity of concentrated salt solutions is quite substantial

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

Selectivity

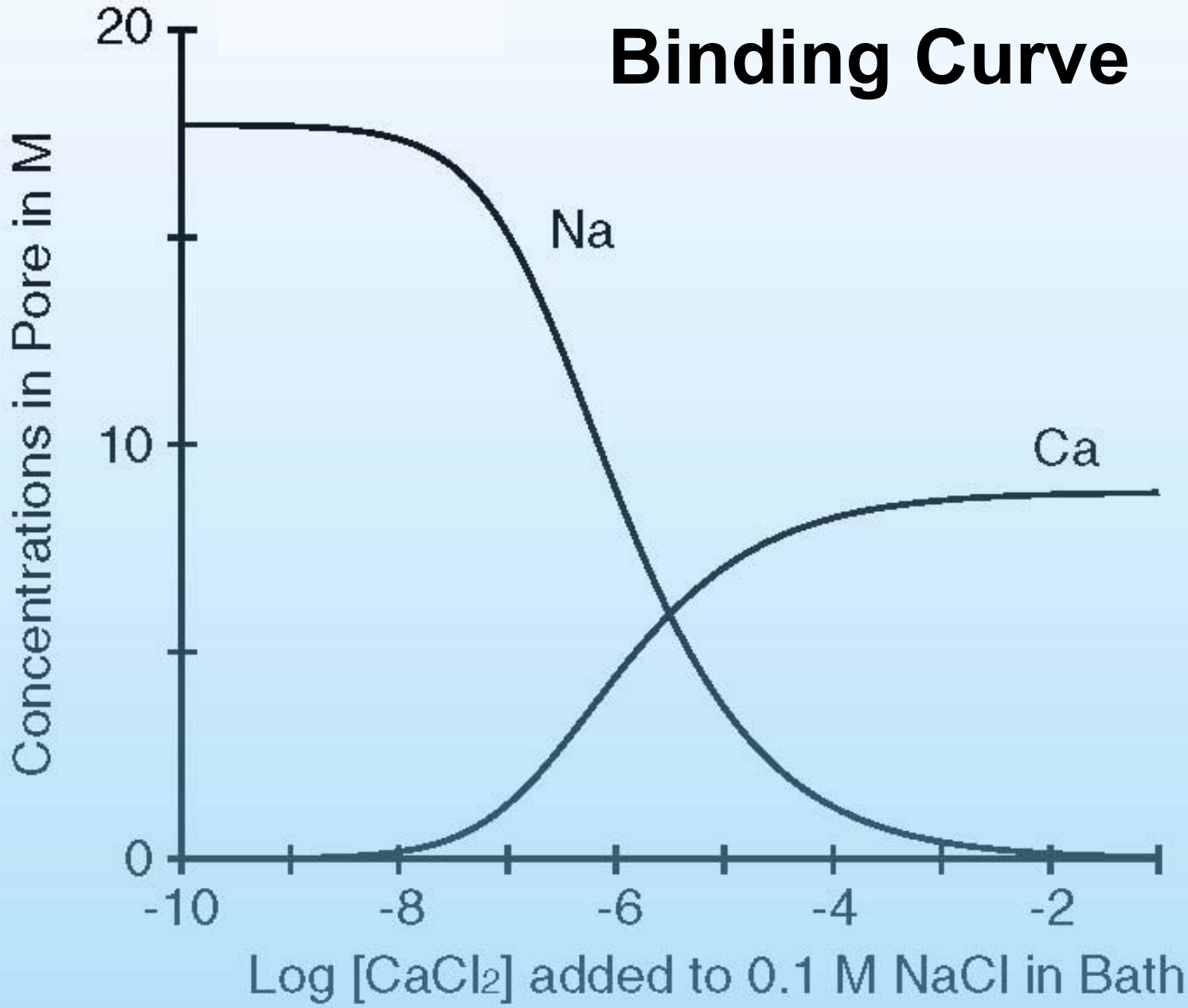
Channels and Enzymes
Distinguish between very similar ions

Cation$^+$ *vs.* **Anion$^-$**
Na^+ *vs.* **Ca^{++}**
Na^+ *vs.* **K^+**

in very unfavorable conditions

Wolfgang Nonner, Dirk Gillespie
University of Miami and Rush Medical Center

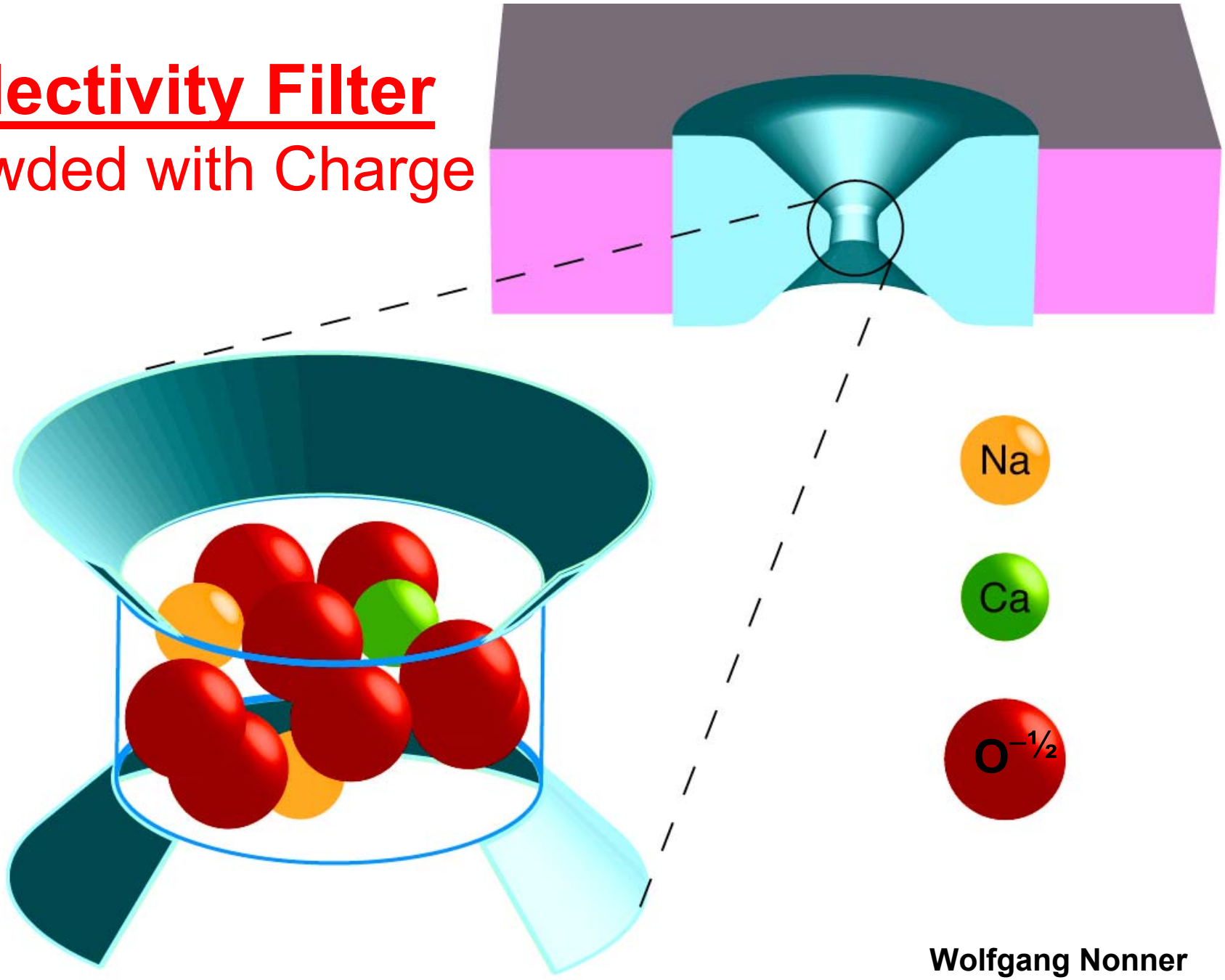
Binding Curve



Wolfgang Nonner

Selectivity Filter

Crowded with Charge



Wolfgang Nonner

Goal:

Understand Selectivity

well enough to

Make a Calcium Channel

using techniques of molecular genetics, site-directed Mutagenesis

George Robillard, Henk Mediema, Wim Meijberg

Central Result of Physical Chemistry

Properties of Highly Compressible Plasma

are computed with similar results by many different theories and types of simulation

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

Three Independent Computations of Compressible Plasmas

Bulk Liquid Approximation (equilibrium)

assume that the channel contents can be described as a bulk liquid that is in equilibrium with a bath of electrolyte solution

Monte Carlo simulations (equilibrium)

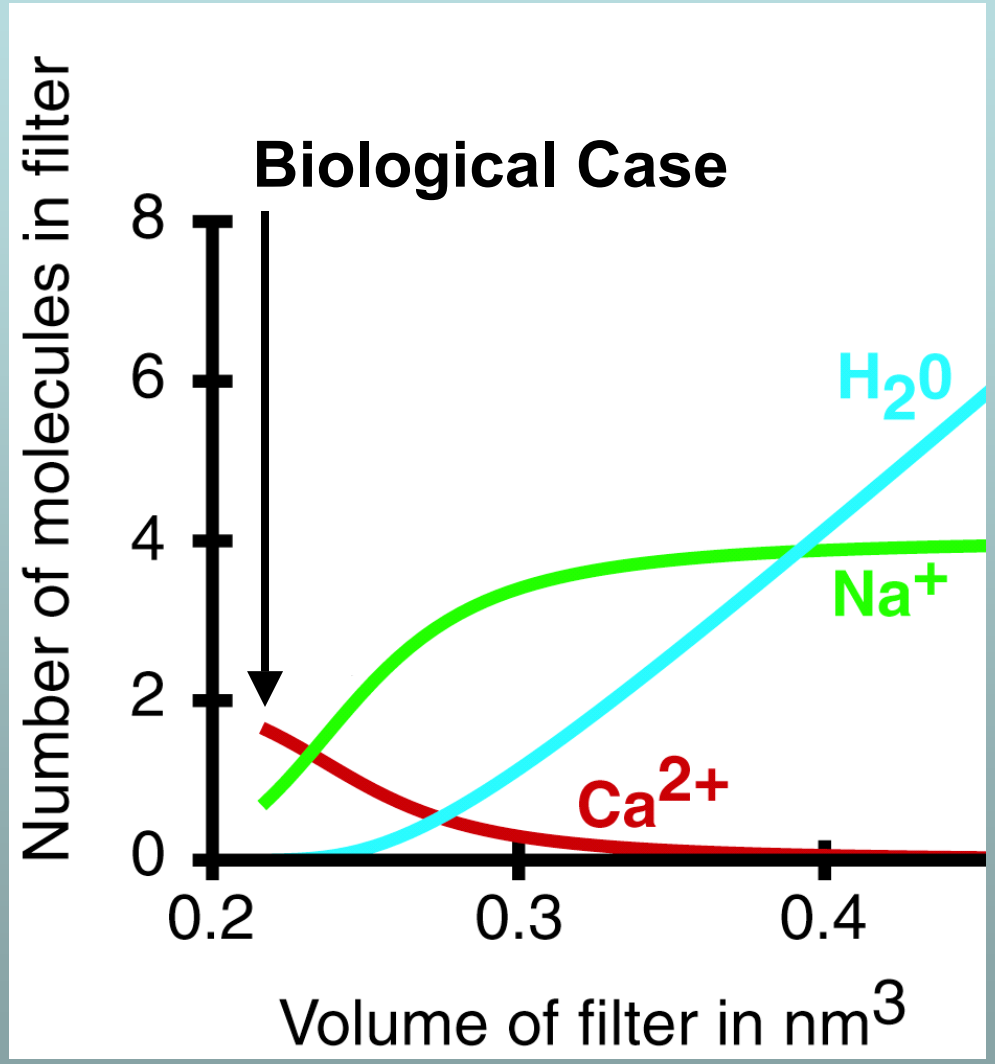
determine equilibrium ion densities by minimizing the energy of the system

DFT/PNP (non-equilibrium)

Density Functional Theory to model ions of finite size coupled to Poisson-Nernst-Planck (drift-diffusion) theory to model ion flux through the channel

Wolfgang Nonner
Dirk Gillespie

Selectivity Arises in a Crowded Space



Biological case:
0.1 M NaCl and 1 μM $CaCl_2$ in the baths

As the volume is decreased, water is excluded from the filter by hard-sphere effects Ca^{2+} enters the filter and displaces Na^{+}

Wolfgang Nonner
Dirk Gillespie

Ionic Selectivity in Protein Channels
Crowded Charge Mechanism
Simplest Version: MSA

4 Negative Charges
of glutamates of protein

DEMAND
4 Positive Charges
nearby

Wolfgang Nonner
Dirk Gillespie

Ionic Selectivity in Protein Channels
Crowded Charge Mechanism
Simplest Version: MSA

2 Ca^{++} are **LESS CROWDED** than 4 Na^{+}, so

Ca^{++} **SHIELDS BETTER** than Na^{+}, so

Protein Prefers Calcium

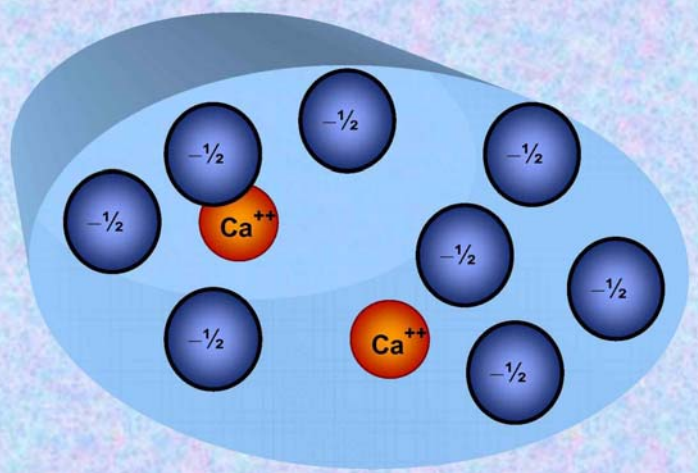
Wolfgang Nonner
Dirk Gillespie

L type Ca Channel Filled with Ca^{++}

(not to scale)

Channel Protein is only

1) Glutamate Oxygens = 4e
   8 of –½ charge each
2) Volume 0.38 nm^3
3) Dielectric Constant 64



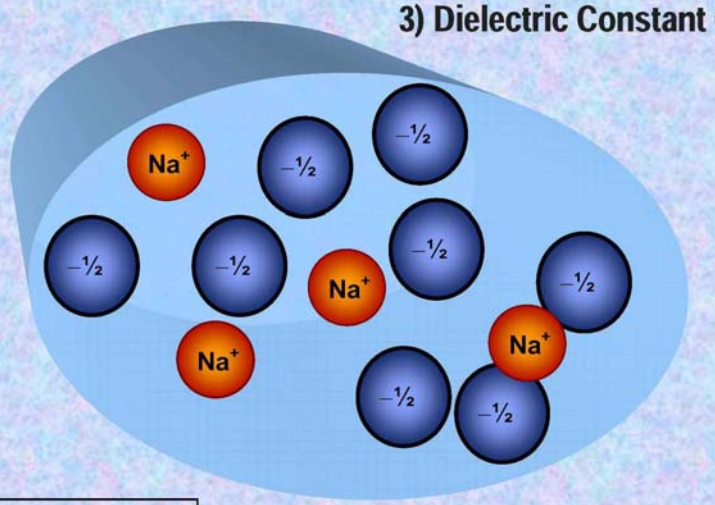
Outside the Filter
Bulk Solution
NaCl and $CaCl_2$

L type Ca Channel Filled with Na^{+}

(not to scale)

Channel Protein is only

1) Glutamate Oxygens = 4e
   8 of –½ charge each
2) Volume 0.38 nm^3
3) Dielectric Constant 64



Outside the Filter
Bulk Solution
NaCl and $CaCl_2$

Wolfgang Nonner
Dirk Gillespie

Conclusion about Selectivity

Selectivity arises from
Electrostatics and Crowding of Charge

Precise Arrangement of Atoms is not involved in the model.

but

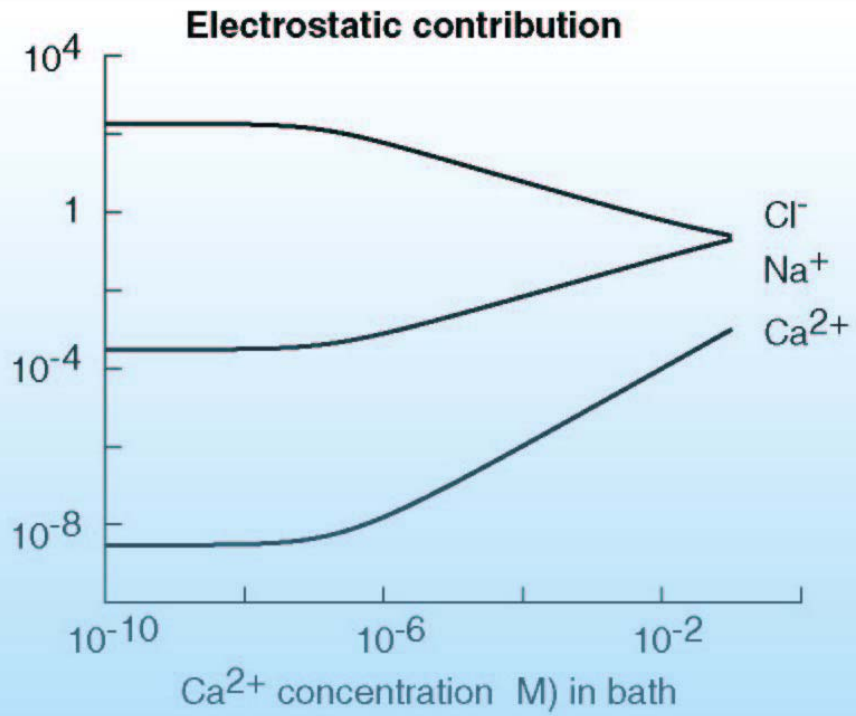
Certain MEASURES of structure are
Powerful DETERMINANTS of Function
e.g., Volume, Dielectric Coefficient, etc.

Implications for Traditional Biochemistry

Traditional Biochemistry more or less ignores the electric field

and assumes

Rate Constants independent of Concentration



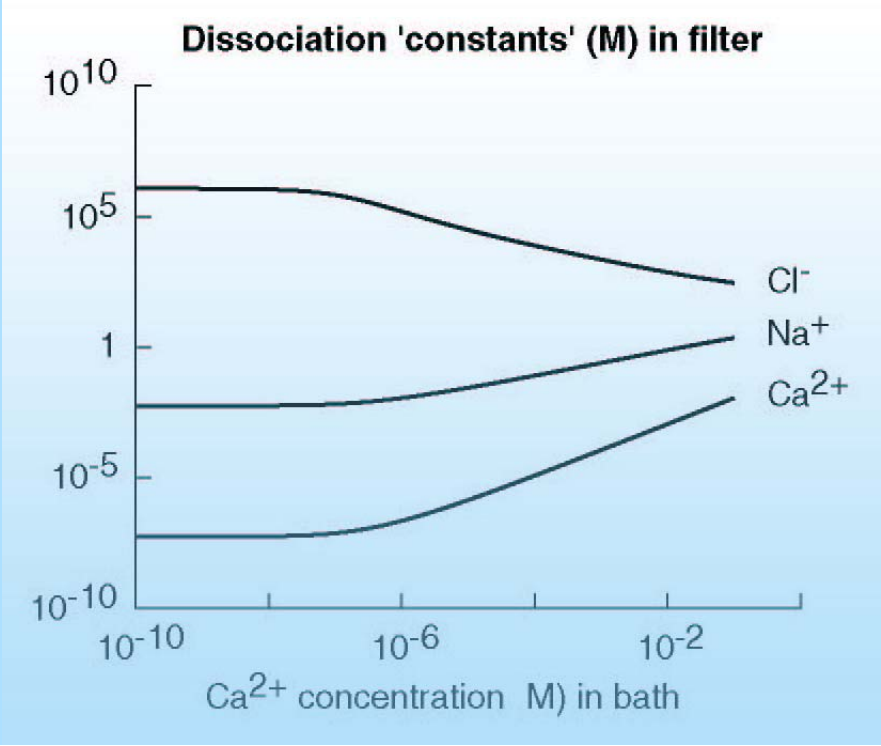
Electrostatic Contribution
to 'Dissiociation Constant' is large

and is an

Important Determinant of Biological Properties

Change of Dissociation 'Constant'
with concentration is large and is an

Important Determinant of Biological Properties



Shielding and Crowded Charge
are ignored

in traditional treatments

of Ion Channels and of

Active Sites of proteins
although

Shielding Dominates
Properties of Ionic Solutions

Goal:

Make a Calcium Channel

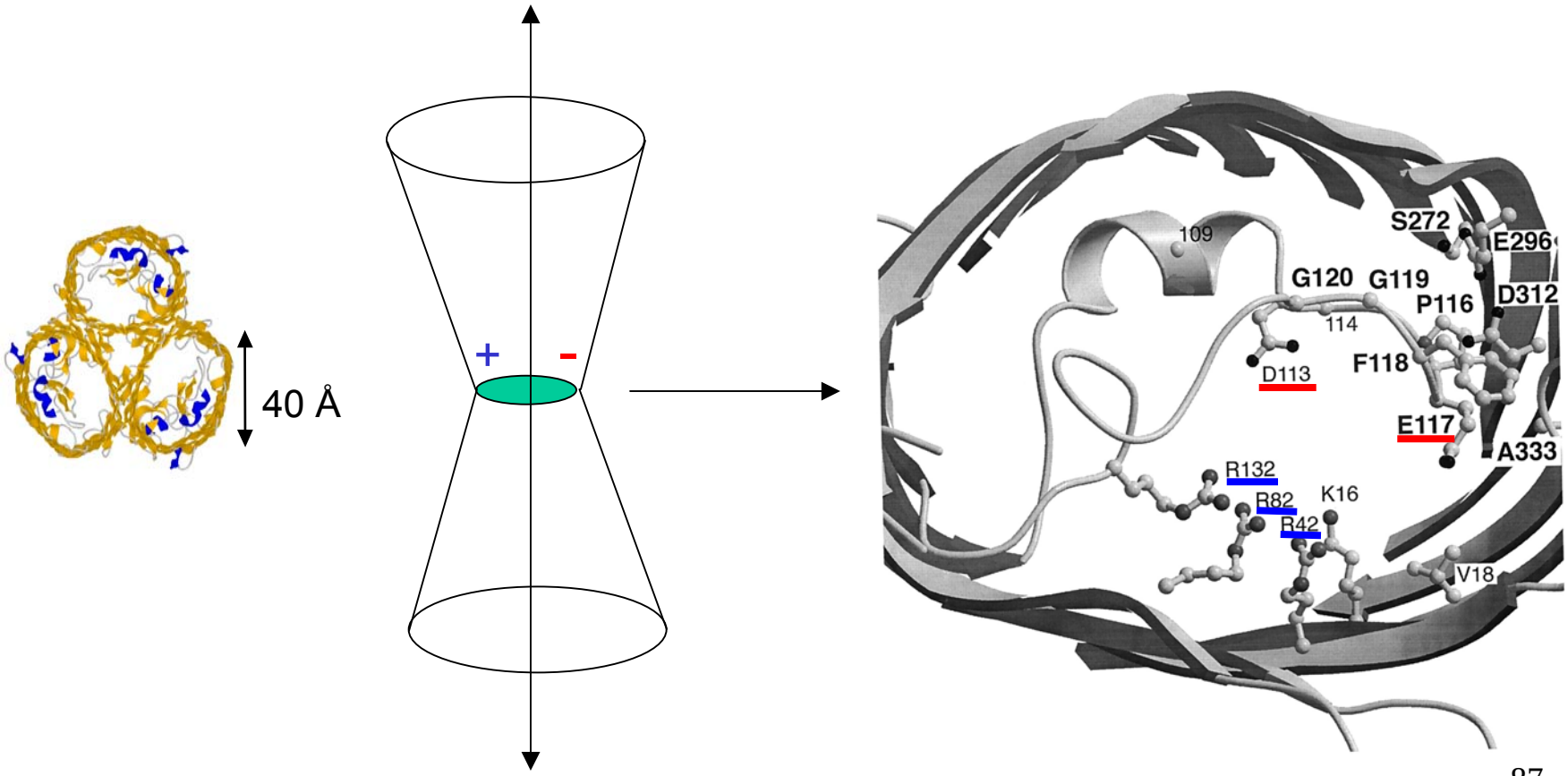
using techniques of molecular genetics, site-directed Mutagenesis

George Robillard, Henk Mediema, Wim Meijberg

BioMaDe Corporation, Groningen, Netherlands

Goal

Switch the essentially non-selective porin (OmpF) into a calcium-selective ion channel by mimicing the dielectric environment found in Ca^{2+} channels

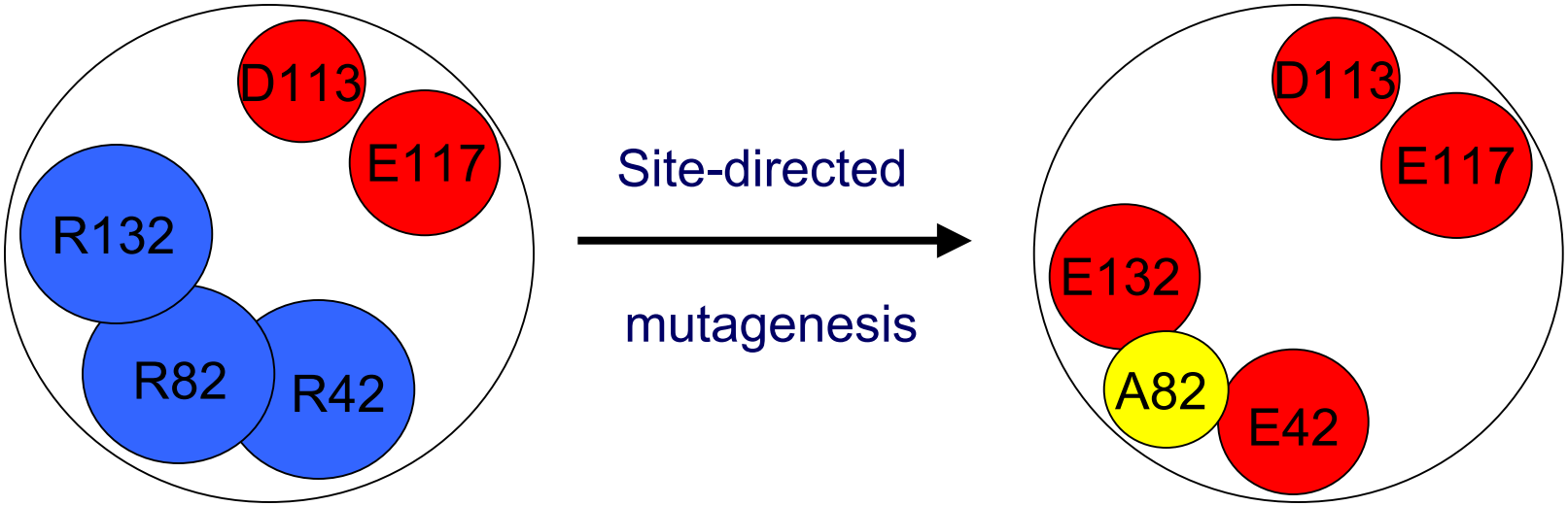


George Robillard, Henk Mediema, Wim Meijberg
BioMaDe Corporation, Groningen, Netherlands

Strategy

Use site-directed mutagenesis to put in extra **glutamates**

and create an **EEEE locus** in the selectivity filter of OmpF

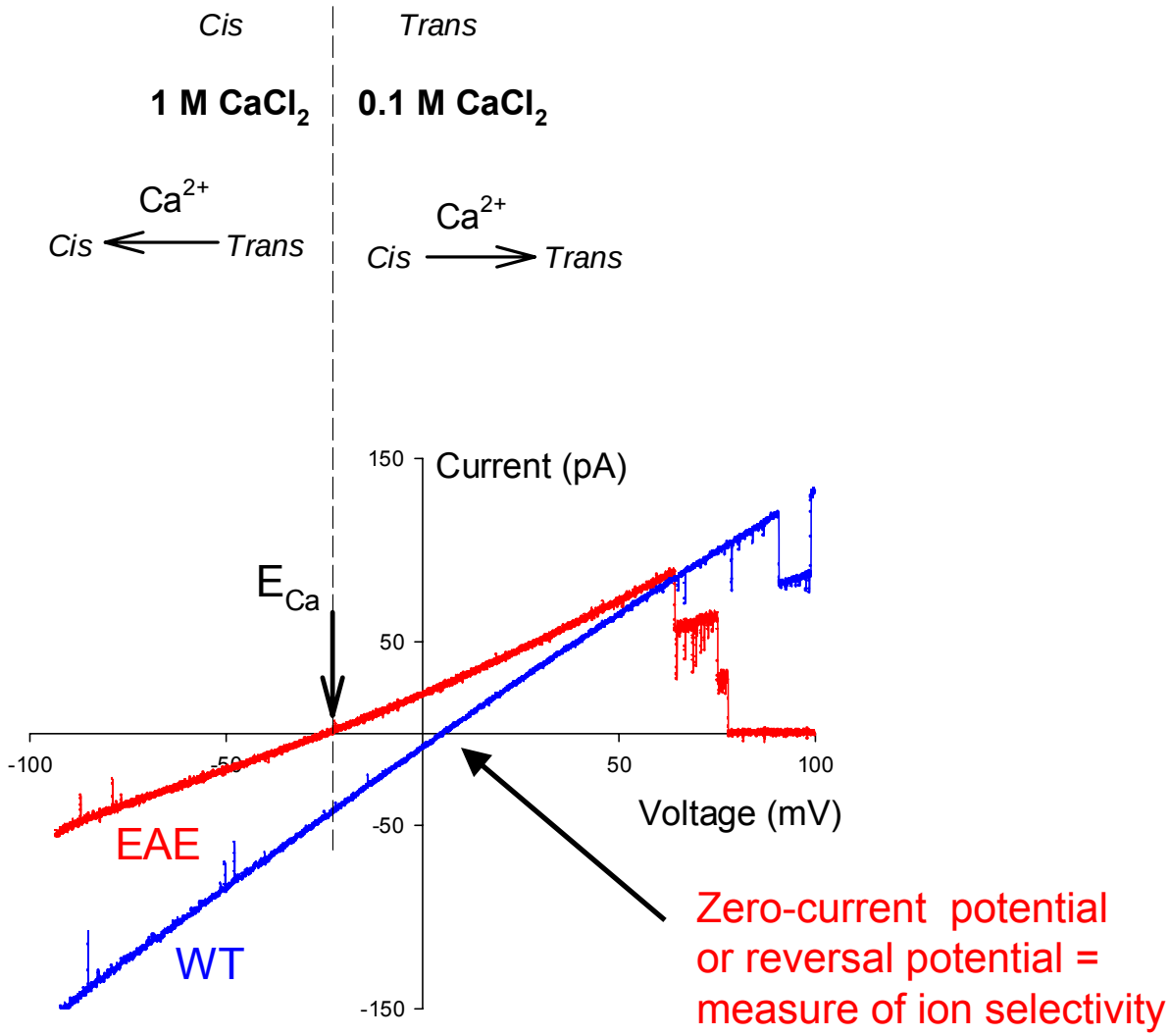


Wild type

EAE mutant

George Robillard, Henk Mediema, Wim Meijberg
BioMaDe Corporation, Groningen, Netherlands

IV-PLOT



IV-plot EAE: current reverses at equilibrium potential of Ca^{2+} (E_{Ca}), indicating the channel can discriminate between Ca^{2+} and Cl^-

Henk Mediema
Wim Meijberg

SUMMARY OF RESULTS (1)

Ca^{2+} over Cl^- selectivity (P_{Ca}/P_{Cl})
recorded in 1 : 0.1 M $CaCl_2$

	P_{Ca}/P_{Cl}
WT	2.8
AAA	25
EAE	>100

Henk Mediema
Wim Meijberg

Conclusions:

- Taking positive charge out of the constriction zone (👎= -3, *see* control mutant AAA) enhances the cation over anion permeability.

- Putting in extra negative charge (👎= -5, *see* EAE mutant) further increases the cation selectivity.

Henk Mediema
Wim Meijberg

SUMMARY OF RESULTS (2)

Ca^{2+} over Na^{+} selectivity (P_{Ca}/P_{Na})
recorded in 0.1 M NaCl : 0.1 M $CaCl_2$

	P_{Ca}/P_{Na}
WT	2.2
AAA	3.7
EAE	4.2

Work in Progress!

Conclusion:

- Compared to WT, EAE shows **just a moderate** increase of the Ca^{2+} over Na^{+} selectivity.

- To further enhance P_{Ca}/P_{Na} may require additional negative charge and/or a change of the 'dielectric volume'.

Selectivity Differs in Different Types of Channels

Wolfgang Nonner
Dirk Gillespie

Selectivity of Different Channel Types

Ca channel	Na channel	Cl channel	K channel
prefers **Small ions** $Ca^{2+} > Na^{+}$	prefers **Small ions** $Na^{+} > Ca^{2+}$ Na^{+} over K^{+}	prefers **Large ions**	prefers **$K^{+} > Na^{+}$**
Selectivity filter ***EEEE*** 4− charges	**Selectivity filter** ***DEKA*** 2−, 1+ charge	**Selectivity filter** hydrophobic partial charges	**Selectivity filter** single filing partial charges
PNP/DFT	Monte Carlo	Bulk Approx	Not modeled *yet*

The same crowded charge mechanism can explain all these different channel properties.

Calcium Channel

Highly Charged (4 negative charges in 0.25 nm^3)

High Ca^{2+} selectivity

- 1 μM $CaCl_2$ in 0.1 M NaCl reduces Na^+ current 50%

Current/voltage curves

- are linear when no Ca^{2+} is present
- are superlinear >100 mV when Ca^{2+} is present

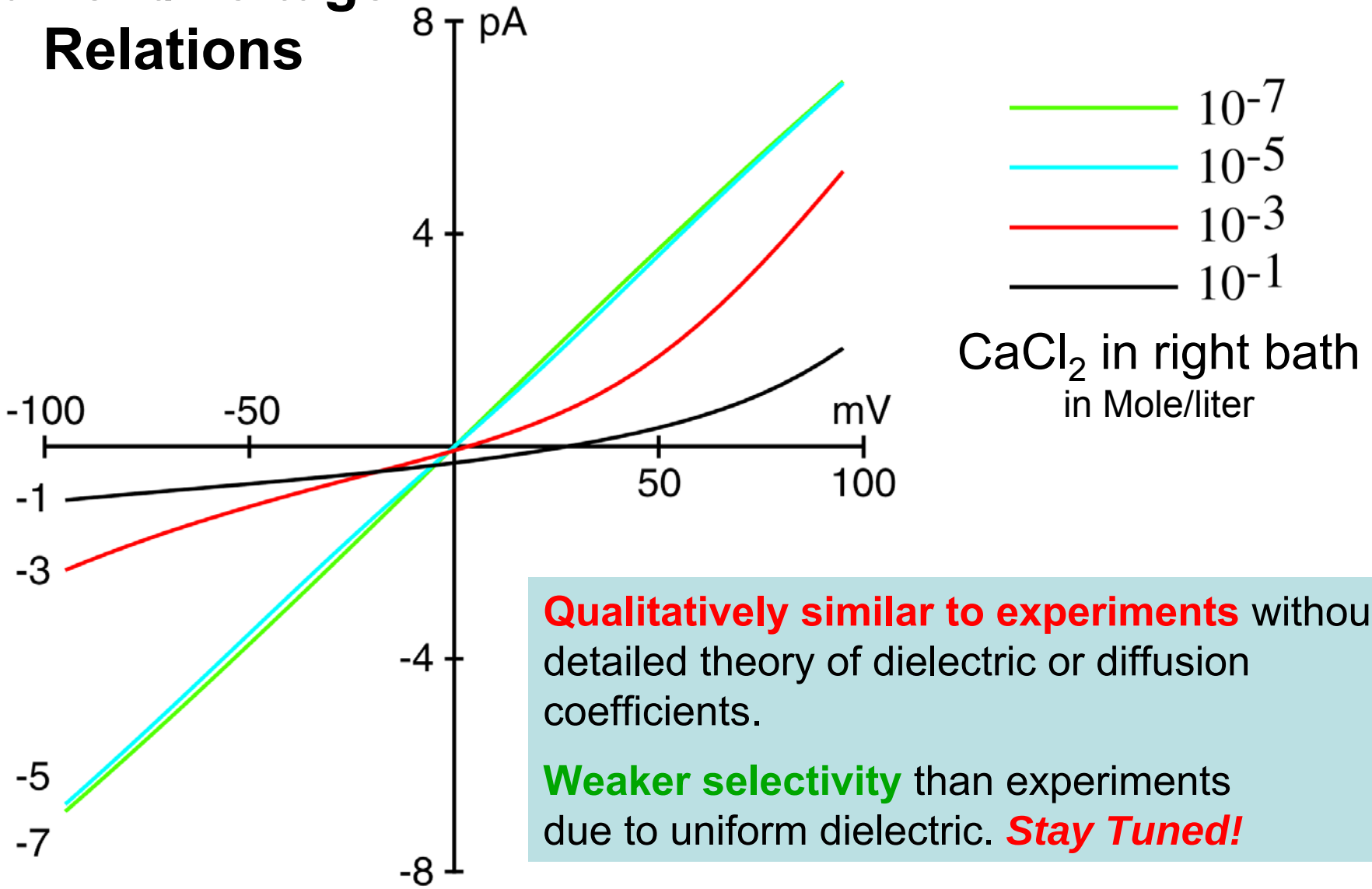
With the PNP/DFT method, we can calculate ion flux. This is the **first time this has been done for ions of finite size**.

So far, we are limited to a uniform dielectric in the system.

Stay tuned!

Wolfgang Nonner
Dirk Gillespie

Current/Voltage Relations

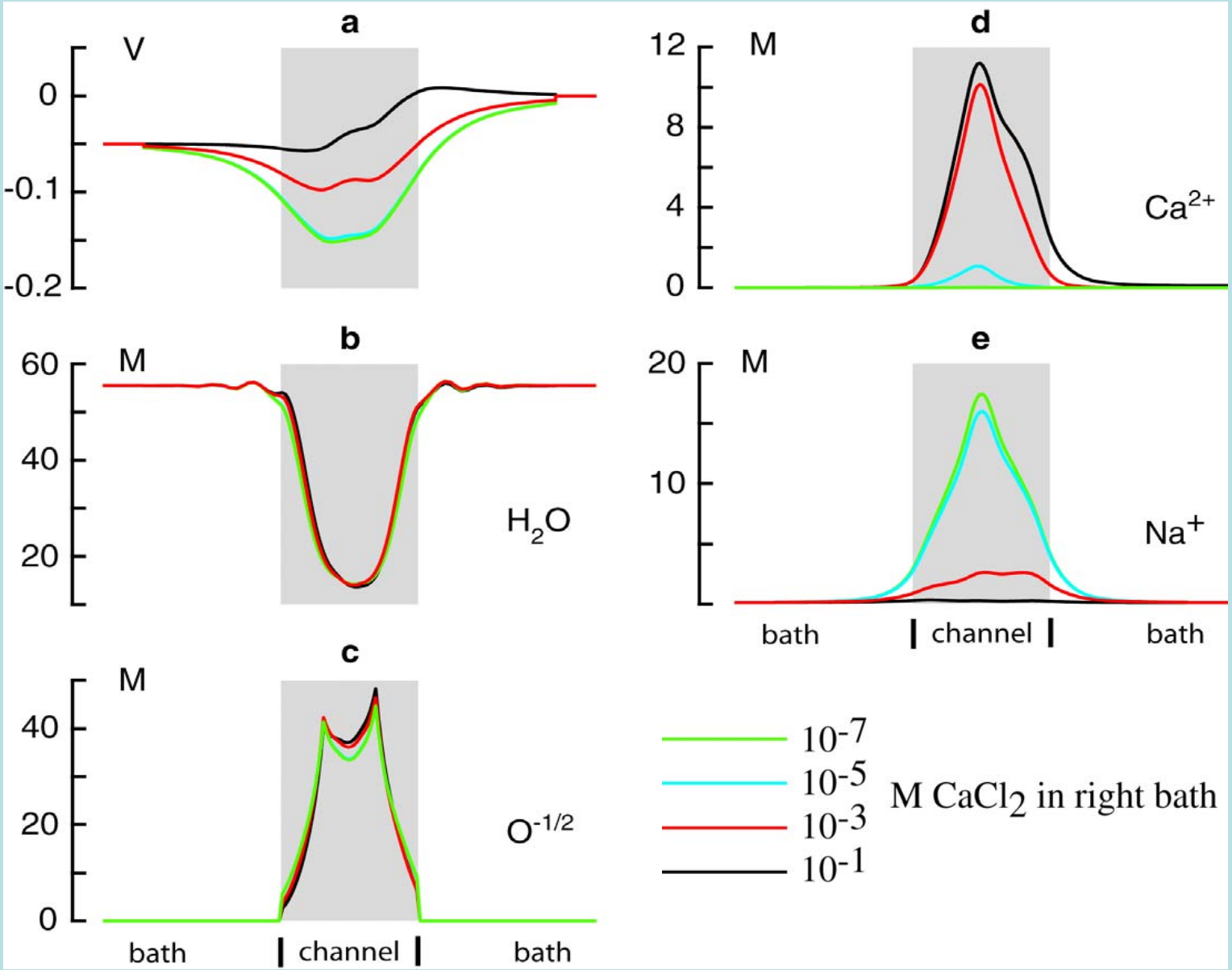


Qualitatively similar to experiments without detailed theory of dielectric or diffusion coefficients.

Weaker selectivity than experiments due to uniform dielectric. ***Stay Tuned!***

Wolfgang Nonner
Dirk Gillespie

Potential and Concentration Profiles at -50 mV



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Sodium Channel

(with D. Boda, D. Busath, and D. Henderson)

Related to Ca^{++} channel

- removing the positive lysine (K) from the **DEKA** locus makes calcium-selective channel

High Na^{+} selectivity

- 1 mM $CaCl_2$ in 0.1 M NaCl gives all Na^{+} current (compare to calcium channel)
- only >10 mM $CaCl_2$ gives substantial Ca^{++} current

Monte Carlo method is limited (so far) to a uniform dielectric

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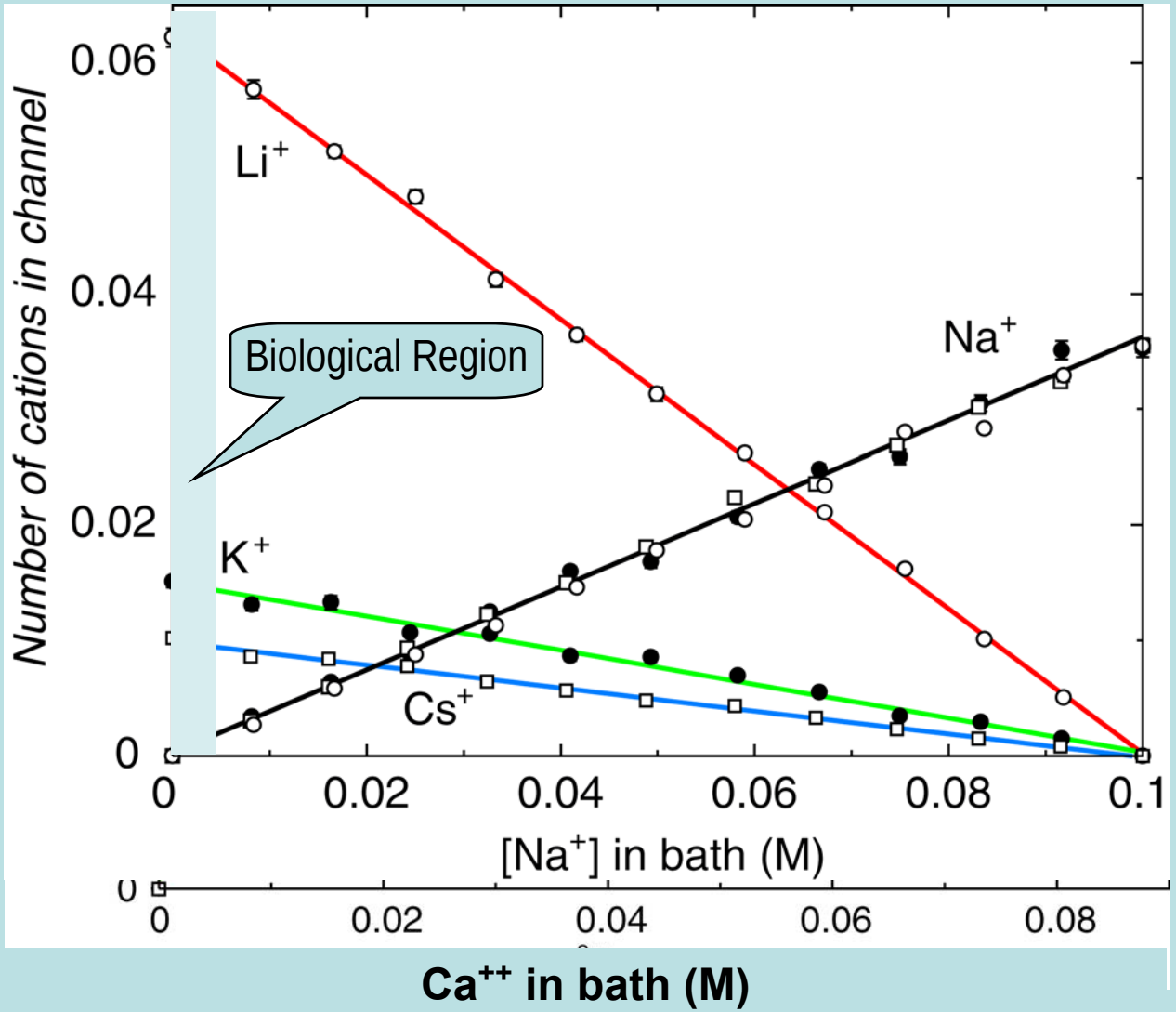
Na^+/Ca^{2+} Competition in the Sodium Channel



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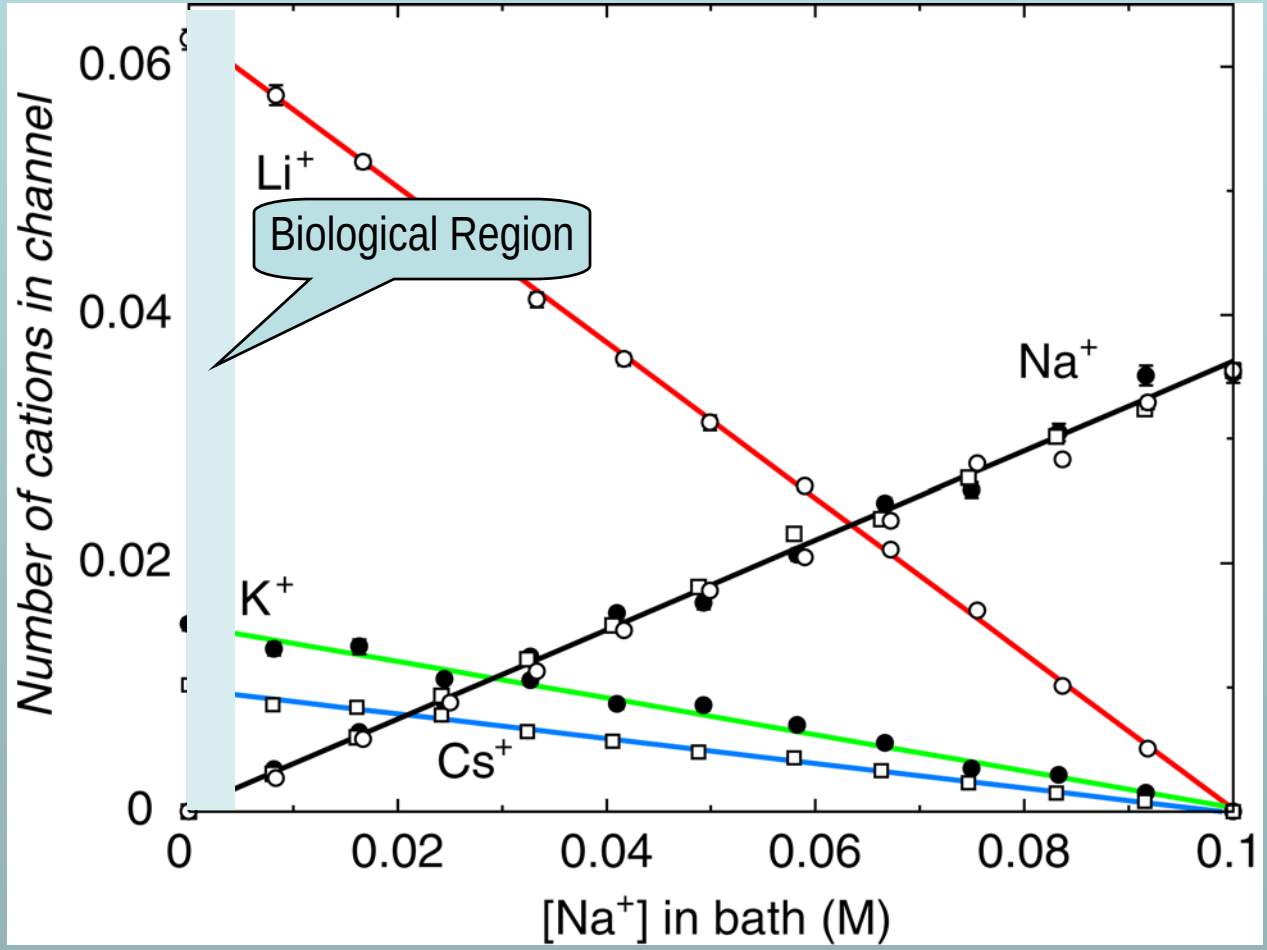
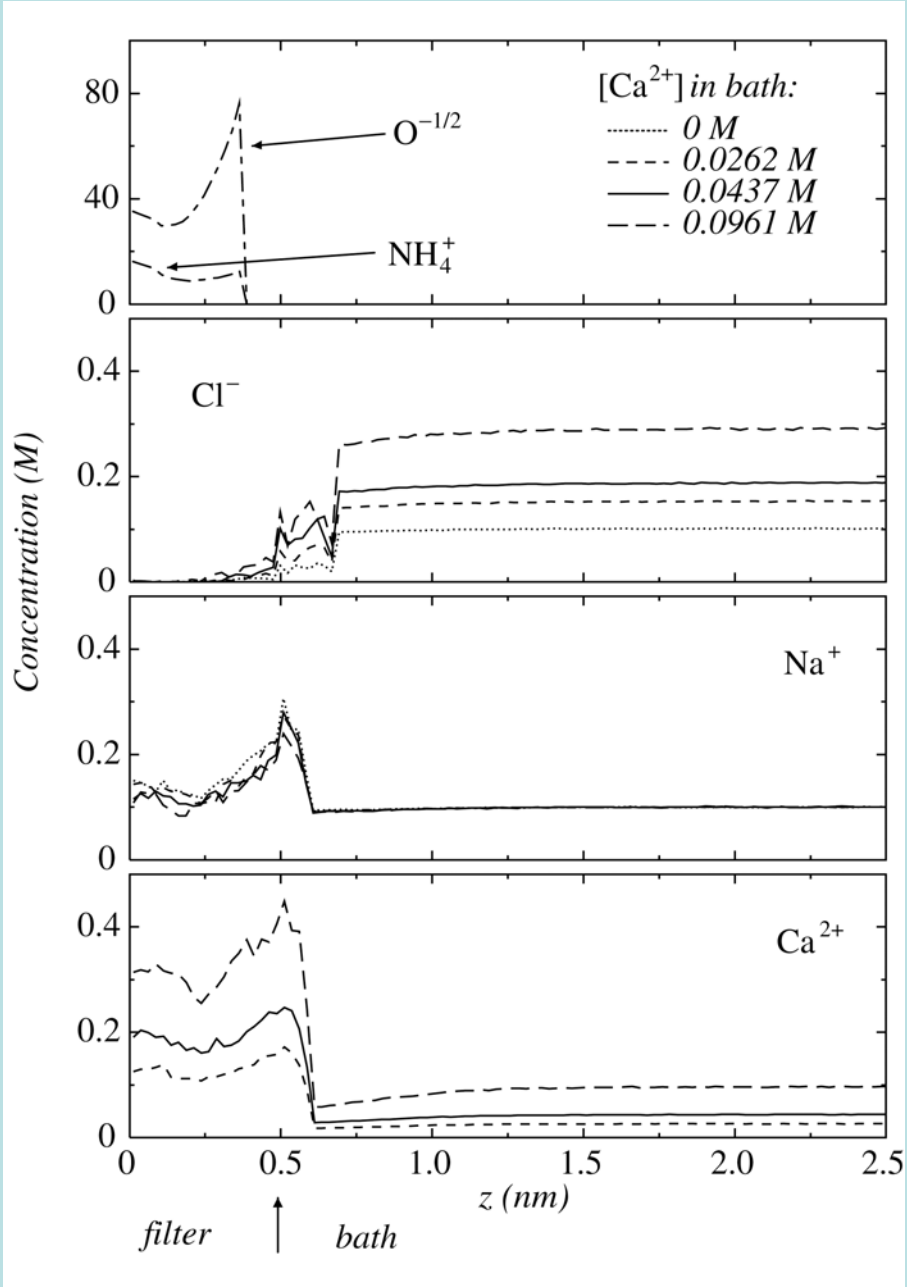
Na^+/Alkali Metal Competition in Na^+ Channel

- Model gives small-ion selectivity.
- Result also applies to the calcium channel.



Spatial Nonuniformity in Na^+ Channel



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Na^+ *vs* K^+ Selectivity

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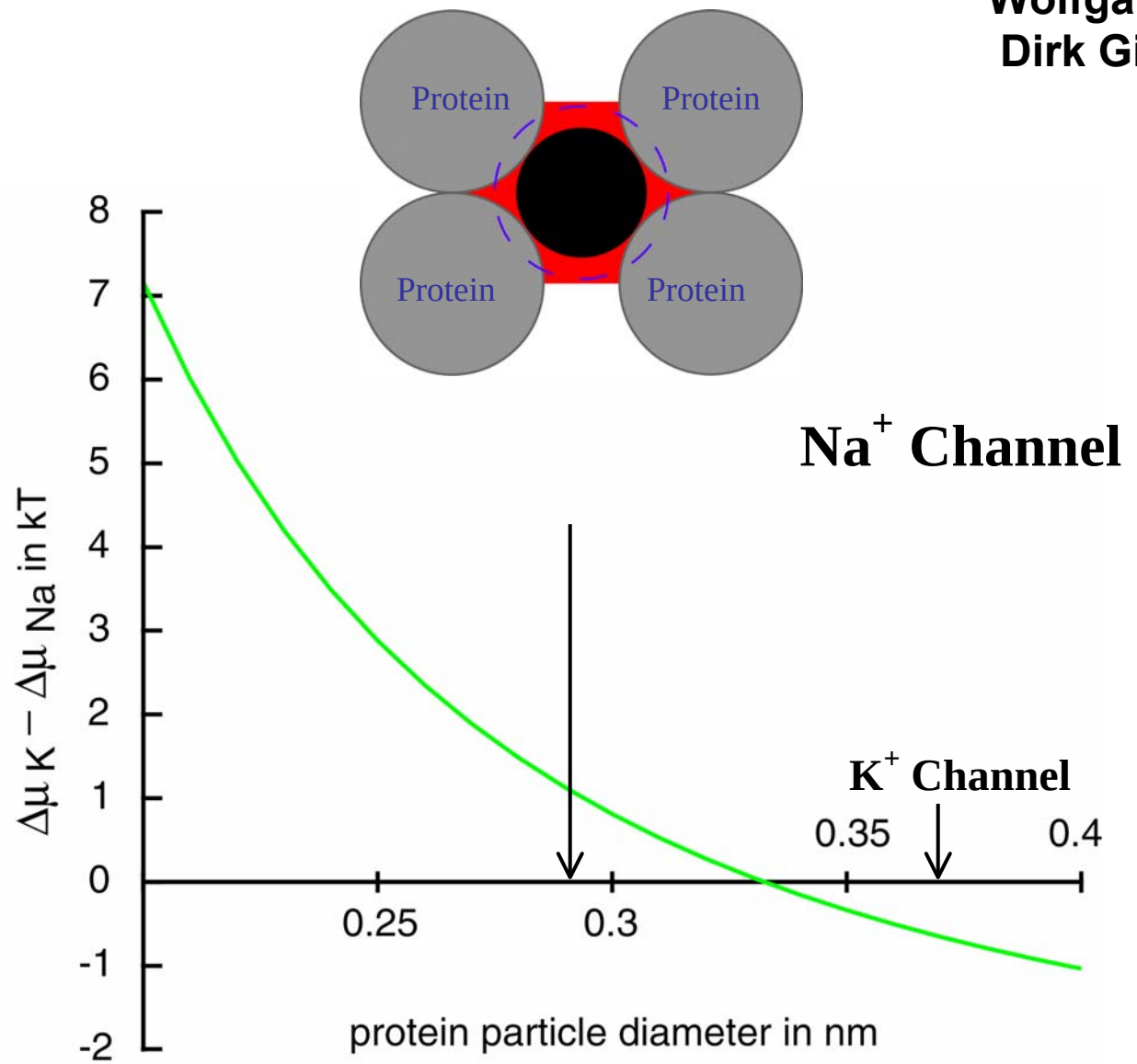
Dirk Gillespie



Na^+ Channels Select

Small Na^+ over Big K^+

because

Protein side chains are small

allowing

Small Na^+ to Pack into Niches

K^+ is too big for the niches!

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Dirk Gillespie

Sodium Channel Summary

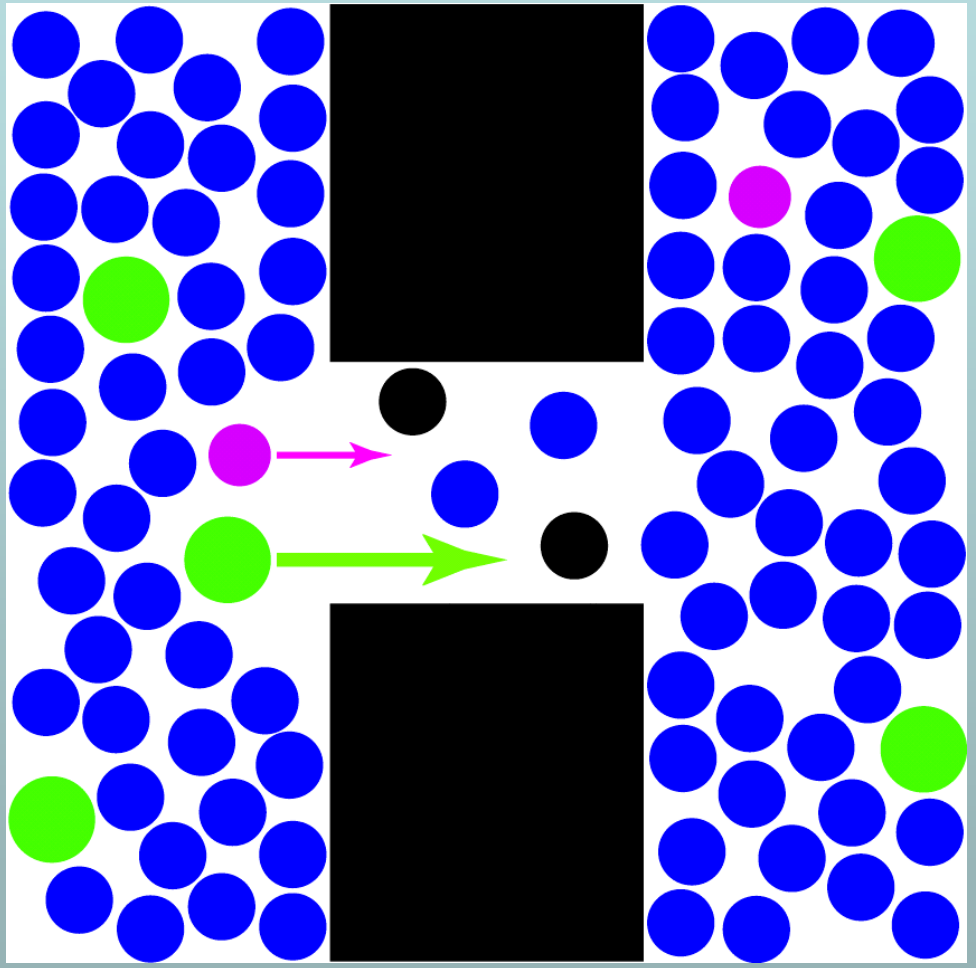
Na channel is a
Poorly Selective
Highly Conducting Calcium channel,

which is Roughened
so it prefers
Small Na over big K

Wolfgang Nonner
Dirk Gillespie

Cl Selective Channel

Selective for Larger Anions



The Dilute Channel

Wolfgang Nonner
Dirk Gillespie

Chloride Channel

(with D. Henderson)

Channel prefers large anions in experiments,

Low Density of Charge (several partial charges in 0.75 nm^3)

Selectivity Filter contains hydrophobic groups

- these are modeled to (slightly) repel water
- this results in large-ion selectivity

Conducts only anions at low concentrations

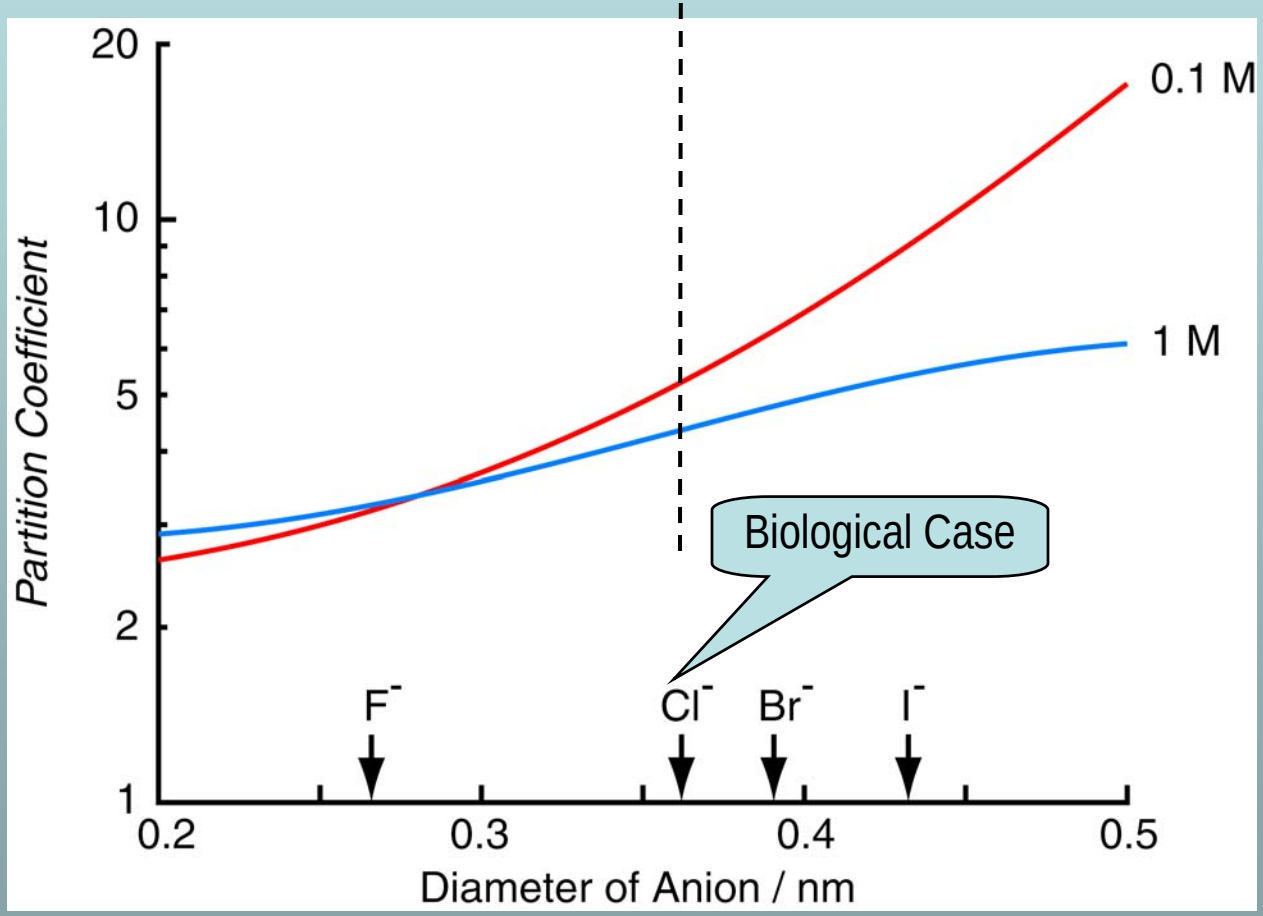
- Conducts both anions and cations at high concentration

Conductance depends on anion type and concentration

Wolfgang Nonner
Dirk Gillespie

Chloride Channel

Selectivity depends Qualitatively on concentation



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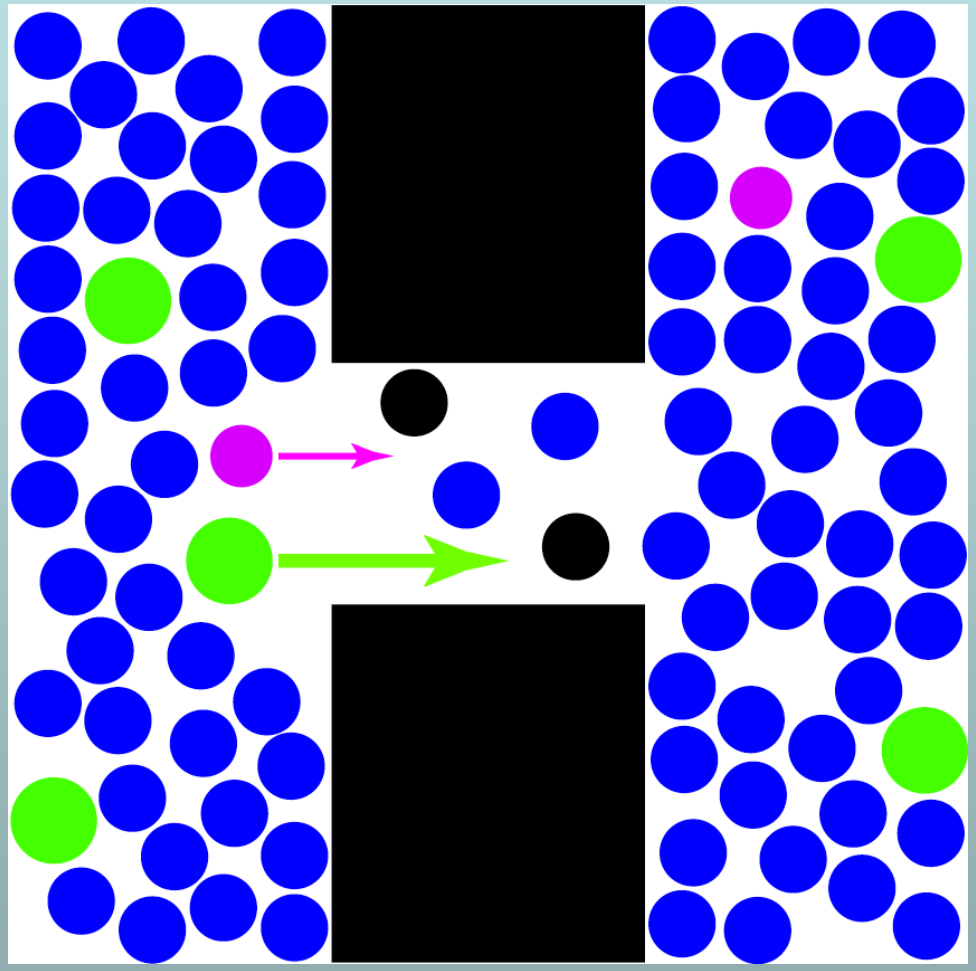
Dirk Gillespie

The Dilute Channel: Anion Selective



Channel protein creates a

Pressure difference between bath and channel

Large ions like Cl^- are Pushed into the channel more than smaller ions like F^-

Wolfgang Nonner
Dirk Gillespie

Chloride Channel

Key: **Hydrophobic Residues Repel Water**
giving

- **Large-ion selectivity**
  (in both anion and cation channels).
- Peculiar non-monotonic conductance properties
  and IV curves observed in experiments

Hydrophobic repulsion can give gating.
'Vacuum lock' model of gating
(D. Henderson; J.-P. Hansen; Sergei Sukarev)

Wolfgang Nonner
Dirk Gillespie

Conclusion

Selectivity

of Calcium, Sodium, and Chloride channels
arises from

Crowding of Ions

(including side chains of the channel protein)

near Fixed Charge
of the Channel Protein

Results were verified by three different computational methods.

Wolfgang Nonner
Dirk Gillespie

Conclusion

Each channel type is a variation on a theme,

Each channel types uses particular physics as a variation.

Function
can be predicted
From Structure
given
Fundamental
Physical Laws
Sometimes, in some cases
using low resolution models

Systematic Improvement

of calculations requires

Standards for Computational Biology of Channels and Proteins

We need

Standards for Computational Biology of Channels and Proteins

More?

DFT

Density Functional
and
Poisson Nernst Planck
model of
Ion Selectivity
in
Biological Ion Channels

Dirk Gillespie
Wolfgang Nonner

Department of Physiology and Biophysics
University of Miami School of Medicine

Bob Eisenberg

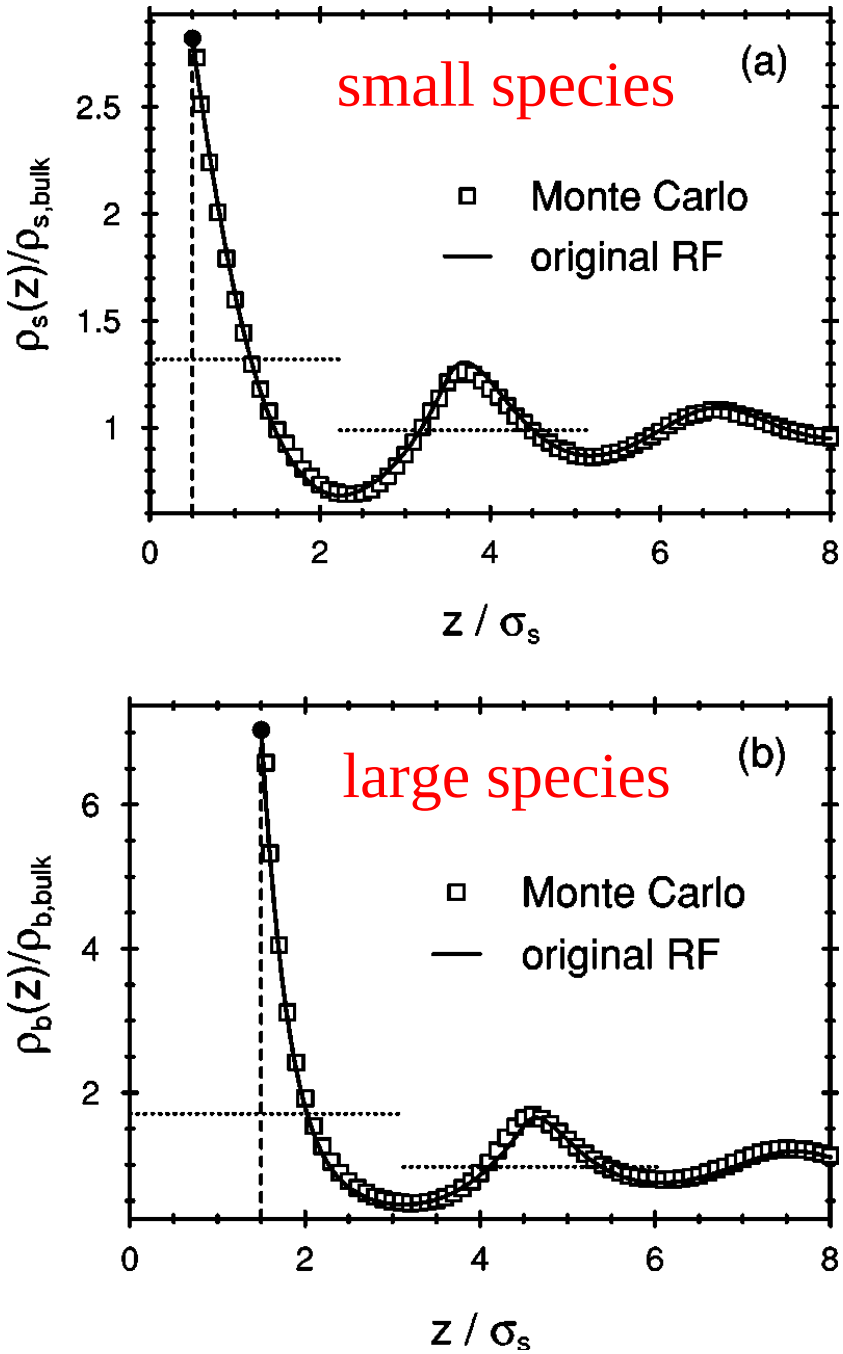
Department of Molecular Biophysics and Physiology
Rush Medical College, Chicago

Example of an Inhomogeneous Liquid

A two-component hard-sphere fluid near a wall in equilibrium (a small and a large species).

Near the wall there are **excluded-volume effects** that cause the particles to pack in layers.

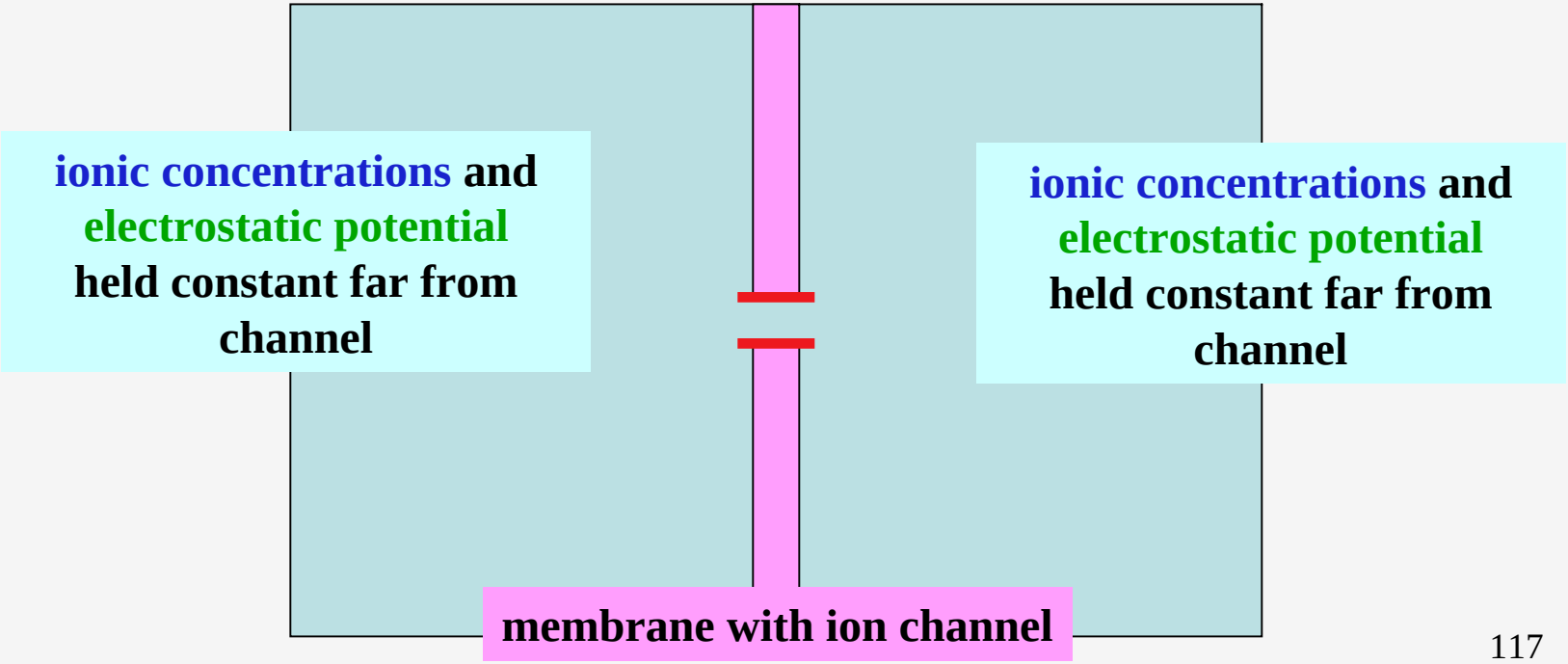
These effects are very nonlinear and are amplified in channels because of the high densities.



The Problem

We are interested in **computing the flux of ions** between **two baths of fixed ionic concentrations**. Across the system an **electrostatic potential is applied**.

Separating the two baths is a lipid membrane containing an ion channel.



Modeling Ion Flux

The flux of ion species *i* is given by the constitutive relationship

$$-\mathbf{J}_i = \frac{1}{kT} D_i(\mathbf{x})\rho_i(\mathbf{x})\nabla\mu_i(\mathbf{x})$$

where **D_i is the diffusion coefficient**

ρ_i is the number density

μ_i is the total chemical potential of species *i*

The flux follows the gradient of the total chemical potential.

The chemical potential has three components

$$-\mathbf{J}_i = \frac{1}{kT} D_i(\mathbf{x}) \rho_i(\mathbf{x}) \nabla \mu_i(\mathbf{x})$$

$$\mu_i^0(\mathbf{x}) + \mu_i^{\mathrm{id}}(\mathbf{x}) + \mu_i^{\mathrm{ex}}(\mathbf{x})$$

concentration-independent
- geometric restrictions
- solvation (Born) terms

excess chemical potential
the "rest": the difference between the "real" solution and the ideal solution

ideal term
- electrochemical potential of point particles in the electrostatic mean-field
- **includes Poisson equation**

When ions are charged, hard spheres the excess chemical potential is split into two parts

$$-\mathbf{J}_i = \frac{1}{kT} D_i(\mathbf{x}) \rho_i(\mathbf{x}) \nabla \mu_i(\mathbf{x})$$

$$\mu_i^0(\mathbf{x}) + \mu_i^{\mathrm{id}}(\mathbf{x}) + \mu_i^{\mathrm{ex}}(\mathbf{x})$$

$$\mu_i^{\mathrm{HS}}(\mathbf{x}) + \mu_i^{\mathrm{ES}}(\mathbf{x})$$

Hard-Sphere Component
describes the effects of excluded volume

the centers of two hard spheres of radius R cannot come closer than 2R

Electrostatic Component
describes the electrostatic effects of charging up the ions

The HS Excess Chemical Potential

Density Functional Theory

The HS excess chemical potential is derived from a **free energy functional**

$$\Omega_{HS}\left(\left\{\rho_k\left(\mathbf{x}\right)\right\}\right)=\int\Phi_{HS}\left(\left\{n_\alpha\left(\mathbf{x}'\right)\right\}\right)\,d\mathbf{x}'$$

where the energy density is given in terms of **"non-local densities"**:

$$\Phi_{HS}\left(\left\{n_\alpha\ \left(\mathbf{x}'\right)\right\}\right)=-n_0\ln\left(1-n_3\right)+\frac{n_1n_2-\mathbf{n}_{V1}\cdot\mathbf{n}_{V2}}{1-n_3}$$

$$+\frac{n_2^3}{24\pi\left(1-n_3\right)^2}\left(1-\frac{\mathbf{n}_{V2}\cdot\mathbf{n}_{V2}}{n_2^2}\right)^3$$

The **non-local densities** (α = 0, 1, 2, 3, V1, V2) **are averages of the local densities**:

$$n_\alpha(\mathbf{x}) = \sum_i \int \rho_i(\mathbf{x}')\,\omega_i^{(\alpha)}(\mathbf{x}'-\mathbf{x})\;d\mathbf{x}'$$

$$\omega_i^{(2)}(\mathbf{r}) = \delta(|\mathbf{r}| - R_i) \qquad \omega_i^{(3)}(\mathbf{r}) = H(R_i - |\mathbf{r}|)$$

$$4\pi R_i^2 \omega_i^{(0)}(\mathbf{r}) = 4\pi R_i \omega_i^{(1)}(\mathbf{r}) = \omega_i^{(2)}(\mathbf{r})$$

$$\omega_i^{(V2)}(\mathbf{r}) = \frac{\mathbf{r}}{|\mathbf{r}|}\delta(|\mathbf{r}| - R_i) \qquad 4\pi R_i \omega_i^{(V1)}(\mathbf{r}) = \omega_i^{(V2)}(\mathbf{r})$$

where δ is the Dirac delta function, H is the Heaviside step function, and R_i is the radius of species i.

Then the HS excess chemical potential is

$$\mu_i^{HS}(\mathbf{x}) = \frac{\delta\Omega_{HS}(\{\rho_k(\mathbf{x}')\})}{\delta\rho_i(\mathbf{x})}$$

$$= kT \sum_\alpha \int \frac{\partial\Phi_{HS}}{\partial n_\alpha}(\{n_\alpha(\mathbf{x}')\})\, \omega_i^{(\alpha)}(\mathbf{x}-\mathbf{x}')\, d\mathbf{x}'$$

The basic formulation of the free energy functional is due to Rosenfeld with minor modifications made later. **It is mathematically imperfect, but considered solved for almost all practical purposes.**

The double convolution makes it numerically expensive.

The ES Excess Chemical Potential

Density Functional Theory

We use Rosenfeld's perturbation approach to compute the electrostatic component.

Specifically, we assume that **the local density $\rho_i(\mathbf{x})$ is a perturbation of a reference density $\rho_i^{\mathrm{ref}}(\mathbf{x})$**:

$$\rho_i(\mathbf{x}) = \rho_i^{\mathrm{ref}}(\mathbf{x}) + \Delta\rho_i(\mathbf{x})$$

The ES Excess Chemical Potential

Density Functional Theory

The electrostatic free energy functional **Ω_{ES} is then approximated by the first three terms of its Taylor series around this reference fluid.**

The ES excess chemical potential is the functional derivative of Ω_{ES} with respect to density:

$$\mu_i^{ES}(\mathbf{x}) = \frac{\delta \Omega_{ES}}{\delta \rho_i(\mathbf{x})}$$

The ES Excess Chemical Potential

Density Functional Theory

This leads to

$$\mu_i^{\mathrm{ES}}(\mathbf{x}) = \underbrace{\mu_i^{\mathrm{ES}}\left(\left\{\rho_k^{\mathrm{ref}}(\mathbf{x})\right\}\right)}_{\text{ES excess chemical potential of reference fluid}} - kT\sum_j \int \underbrace{c_{ij}^{(2),\mathrm{ES}}(\mathbf{x},\mathbf{x}')}_{\text{ES correlation function of reference fluid for which we used a bulk (MSA) formulation}} \Delta\rho_j(\mathbf{x}')d\mathbf{x}'$$

The Reference Fluid

In previous implementations, the reference fluid was chosen to be a bulk fluid. This was both appropriate for the problem being solved and made computing its ES excess chemical potential straight-forward.

However, **for channels a bulk reference fluid is not sufficient**. The channel interior can be highly-charged and so 20+ molar ion concentrations can result. That is, **the ion concentrations inside the channel can be several orders of magnitude larger than the bath concentrations**.

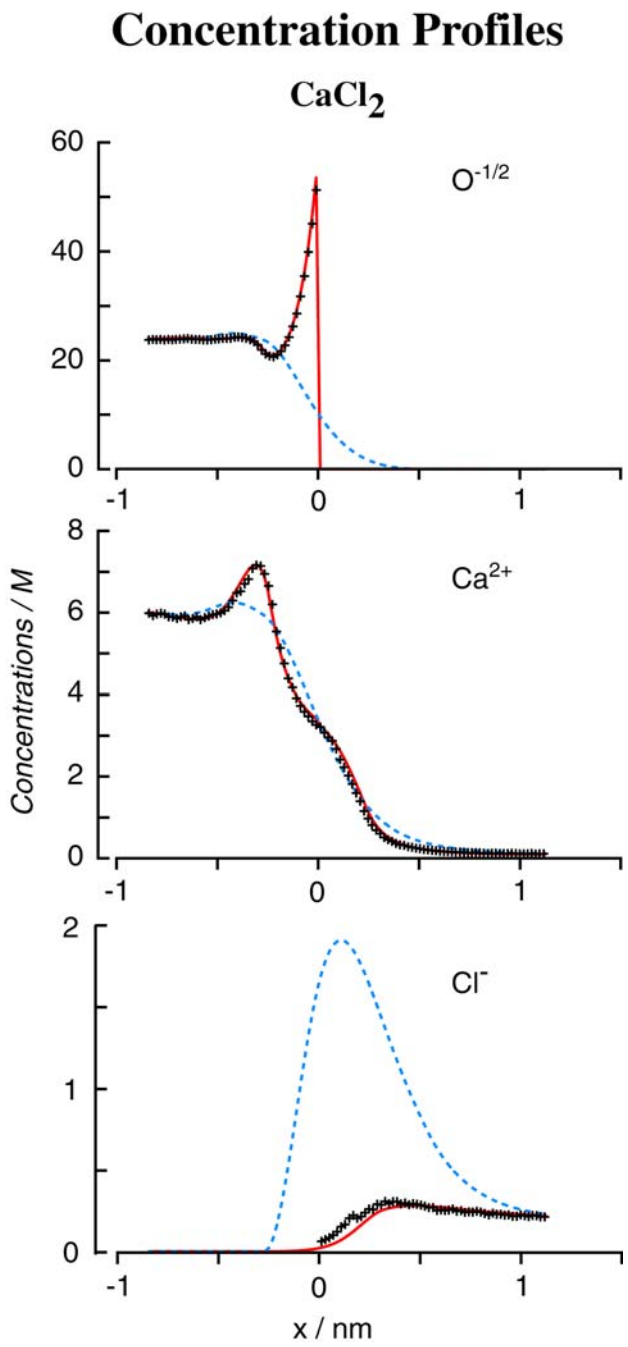
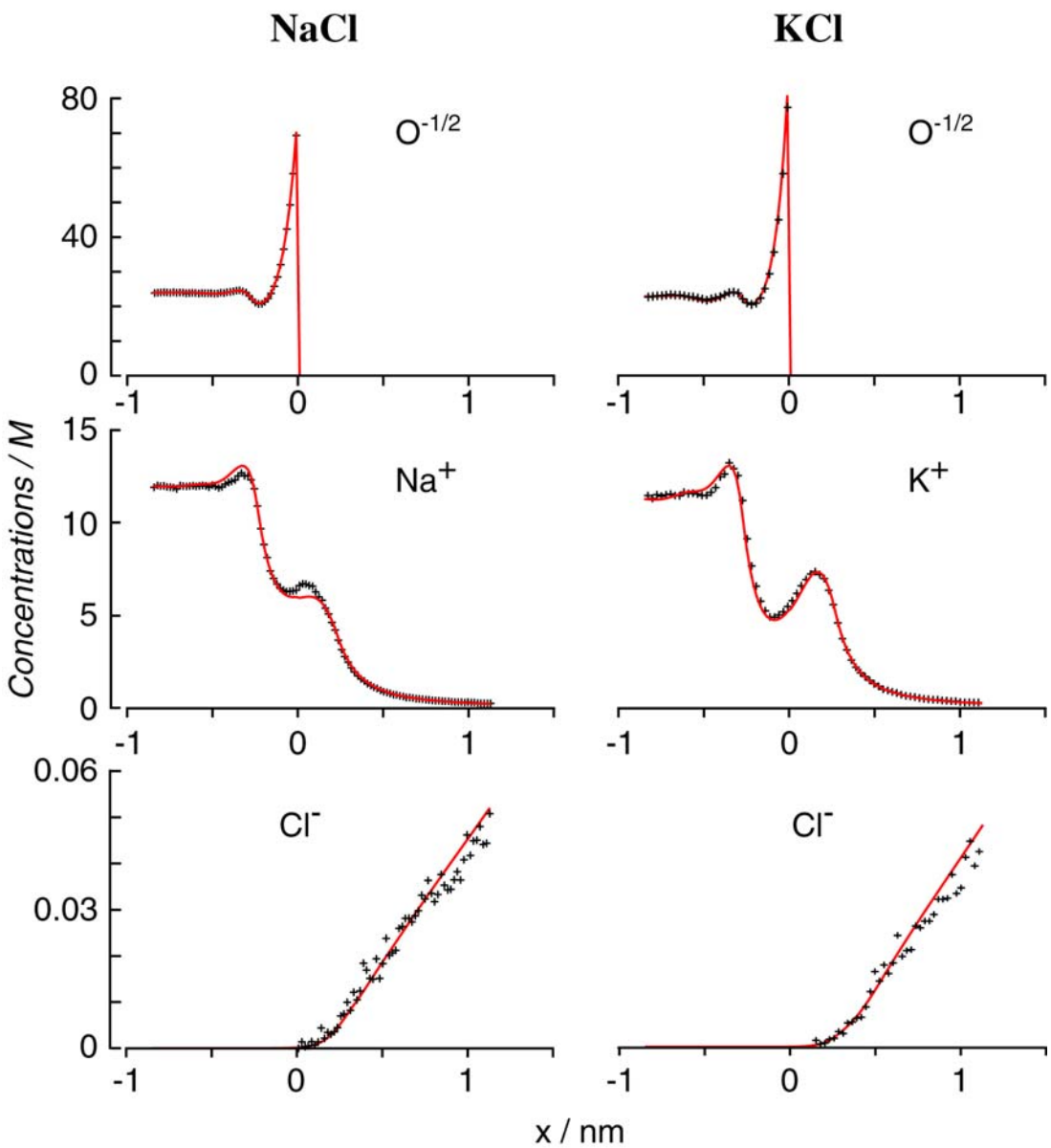
For this reason we developed a formulation of the ES functional that could account for such large concentration differences.

Test of ES Functional

To test our ES functional, we considered an equilibrium problem designed to mimic a calcium channel.

two compartments were equilibrated
edge effects fully computed

The dielectric constant was 78.4 throughout the system.


Concentration Profiles
CaCl2
O-1/2
Ca2+
Cl-
Concentrations / M
x / nm
60
40
20
0
8
6
4
2
0
2
1
0
-1
0
1

Concentration Profiles