(almost) All Life occurs in a Plasma of Spherical Ions in water

Na^+, K^+ , Ca^{++} , and Cl^-

each with a different diameter

Ion Diameters *Pauling Diameters*	
Ca^{++}	**1.98 Å**
Na^+	**2.00 Å**
K^+	**2.66 Å**

Ions are involved in most of biology

Ions are controlled by ion channels that are natural nano-valves*

Ions control all electrical activity in cells

Ions produce signals of the nervous system

Ions coordinate contraction in skeletal muscle

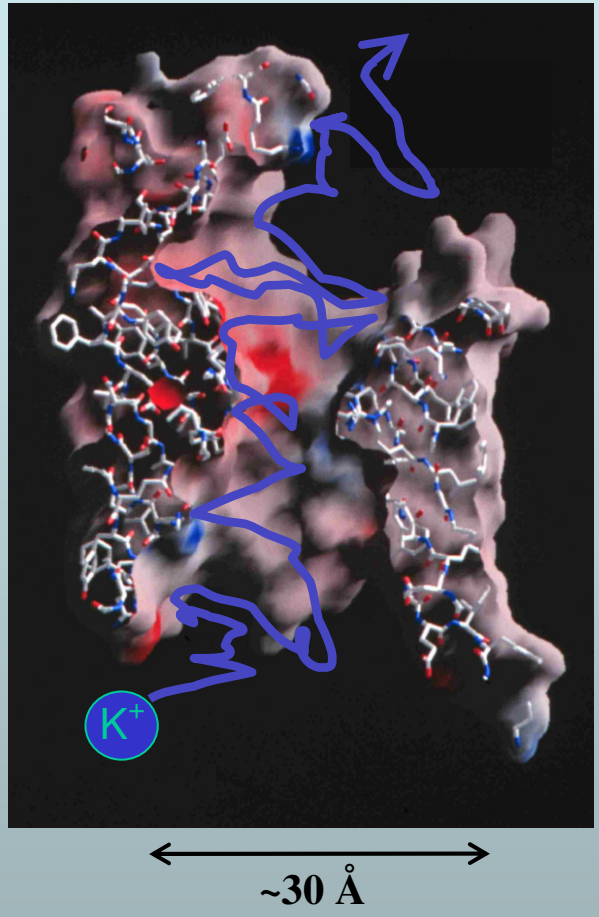
Ions coordinate contraction in the heart, allowing the heart to function as a pump

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

Ion channels are involved in thousands of diseases and many drugs act on channels

Ion channels are proteins whose genes (blueprints) can be manipulated by molecular genetics

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



*nearly pico-valves: diameter is 400 – 900 pico-meters

Charged Particles
in a Dielectric with Friction is

THE

Fundamental Problem in Plasmas,

including

Plasmas of Life

I am not qualified to discuss the importance of this problem in physical plasmas but to an outsider, it seems fundamental.

Seeking a Simple Description of the Brownian Motion of Charged Particles

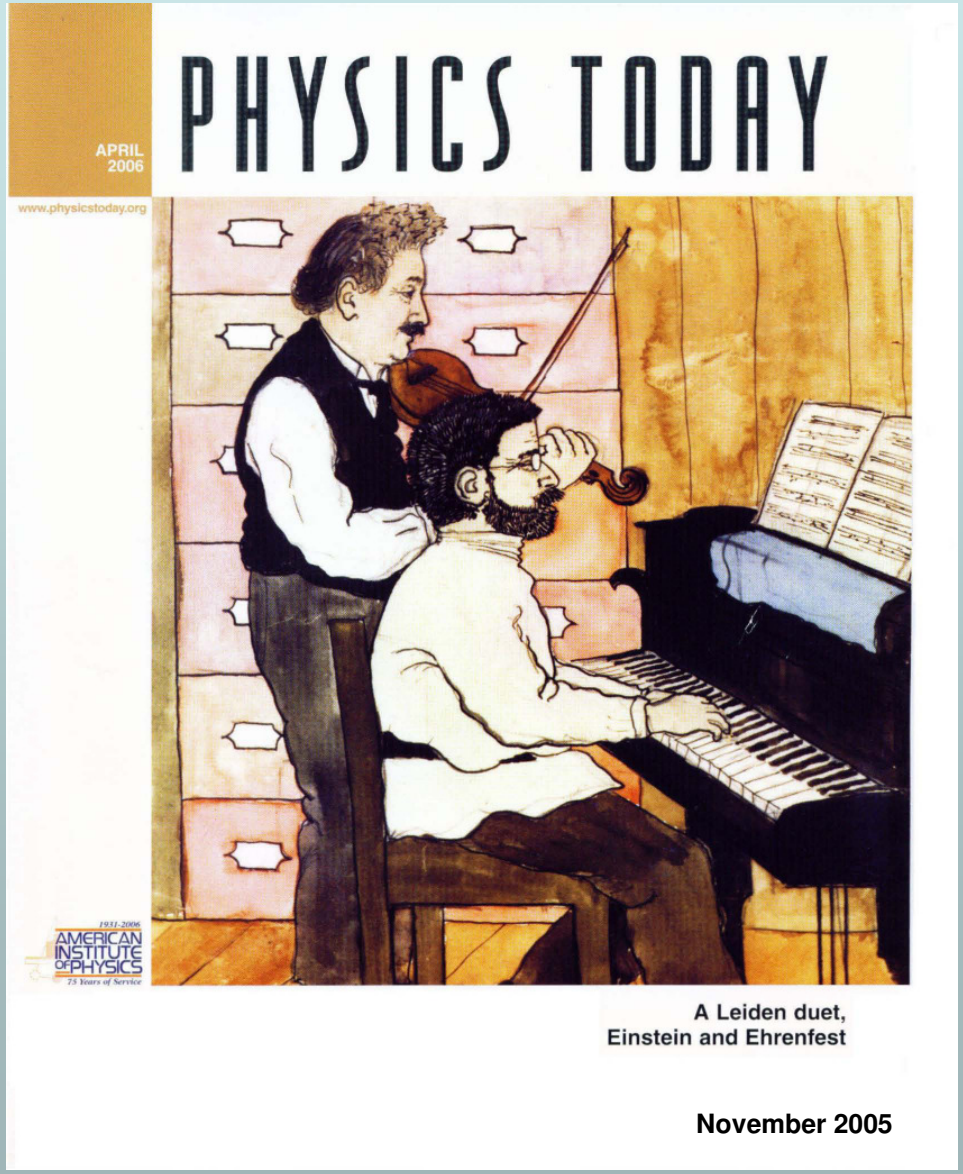
Einstein's Brownian Particles are Uncharged

(nearly)

Everything Dissolved in Water is Charged

(somewhere)

Einstein's Mistakes: Steven Weinberg



<u>Conjecture</u>

Fluctuations in charge density are a significant
–even dominant–
source of Fluctuations in Plasmas

but

Einstein's treatment of Brownian motion does not discuss charge

Simplified Descriptions are Clearly Possible:

Ohm's Law works well for a wide range of ionic solutions

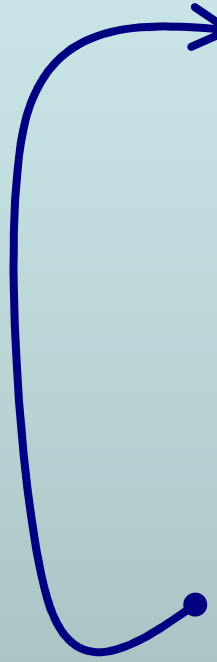
(Ohm's law involves ONLY charge)

Fick's law works well for a wide range of non-ionic solutions

(Fick's law involves only mass)

Self-consistent Simulation

Consider a random process in which charged particles move in an electric field created by their own charge and charge applied by boundary conditions. (No other applied fields are allowed)



1) Start with an overall neutral system
2) Choose a small volume
3) Count the number of particles of each type in that volume
4) Compute the electric field from the location and amount of charges
5) Allow the particles to move a small amount
6) Count again, etc.

Construct graphs of number density (‘concentration’) of particles vs. time and location.

Typical Time Series

$[X]$ = number of X	***Time =***	**1**	**2**	**3**	**...**
Number of Na^+	$[Na^+]$	7	6	$[Na^+]$	...
Number of K^+	$[K^+]$	3	2	$[K^+]$	...
Number of Cl^-	$[Cl^-]$	9	9	$[Cl^-]$	...
Number of Positive Charges		10	8	$[Na^+]+[K^+]$	...
Number of Negative Charges		9	9	$[Cl^-]$	...
Net Charge *Q* *(units: number of charges)*		+1	-1	**$[Na^+]+[K^+]-[Cl^-]$**	...
Number of Particles *N*		19	17	**$[Na^+]+[K^+]+[Cl^-]$**	...

Typical Time Series

	Time =	1	2	3	...
1) Number of Na^+	$[Na^+]$	0	6	$[Na^+]$	...
2) Number of K^+	$[K^+]$	**3**	**2**	$[K^+]$	...
3) Number of Cl^-	$[Cl^-]$	9	9	$[Cl^-]$	...

1) Gives equation for $[K^+]$

2) Gives equation for [Na+]

3) Gives equation for $[Cl^-]$

Variables $[Na^+]$, $[K^+]$, $[Cl^-]$

are **highly correlated**

so we have severe ‘closure’ problems

Time Series of

Time =	**1**	**2**	**3**	**...**
1) Net Charge *Q* *(units: number of charges)*	+1	-1	$[Na^+]+[K^+]-[Cl^-]$	...
2) Number of Particles *N*	19	17	$[Na^+]+[K^+]+[Cl^-]$	...

1) Gives equation for ***Q***

2) Gives equation for ***N***

Variables

$$Q = [Na^+]+[K^+]-[Cl^-]$$

$$N = [Na^+]+[K^+]+[Cl^-]$$

are **almost uncorrelated**
(we know from experiments and common sense)

so (I imagine)
we have almost no closure problems

Challenge

We know PDE's for [Na^+], [K^+], [Cl^-].

What are the PDE's for ***Q, N,*** and [Cl^-]?

Challenge

How do we “change variable”?

How do we construct the counting process for charge and density?

Charged Brownian Motion in Langevin Form

Frictional Force

White Noise

$$\ddot{x}(t)_j^+ + \gamma_j^+ \dot{x}(t)_j^+ = \frac{\boldsymbol{F}_j^+}{m_j^+} + \sqrt{\frac{2\gamma_j^+ k_B T}{m_j^+}}\ \dot{w}(t)_j^+ \qquad j = 1, 2, \ldots N$$

Electrical Force

Similar Equation for location $x(t)_k^-$ of negative species *k*

Electrical Force

$$\boldsymbol{F}_j^+$$

Electrical Force is computed

1) from solution of Poisson's equation,
or by applying
2) Coulomb's law to <u>all</u> other charges

What has been done?

We start with Langevin equations of charged particles

Simplest stochastic trajectories
are
Brownian Motion of Charged Particles

Gouy-Chapman, (nonlinear) Poisson-Boltzmann, Debye-Hückel,
are models with similar resolution
but constrained to equilibrium, i.e., zero flux of all species.
Devices do not exist at equilibrium

Once we learn to count Trajectories of Brownian Motion,
we can count trajectories of Molecular Dynamics

Equilibrium

Configurations

Boltzmann Distribution

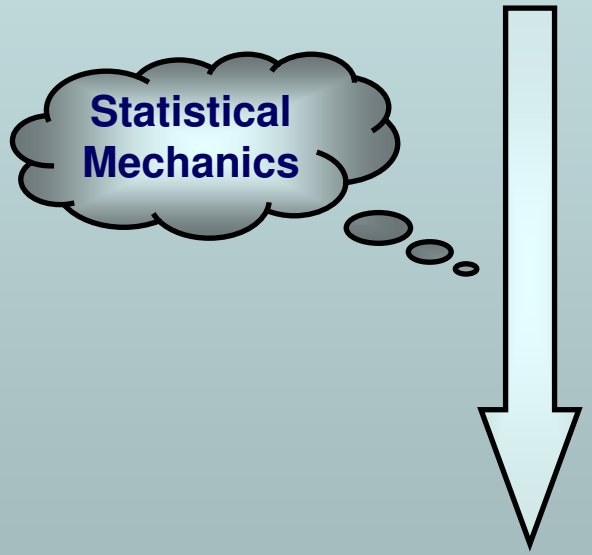
$\lim N, V \to \infty$

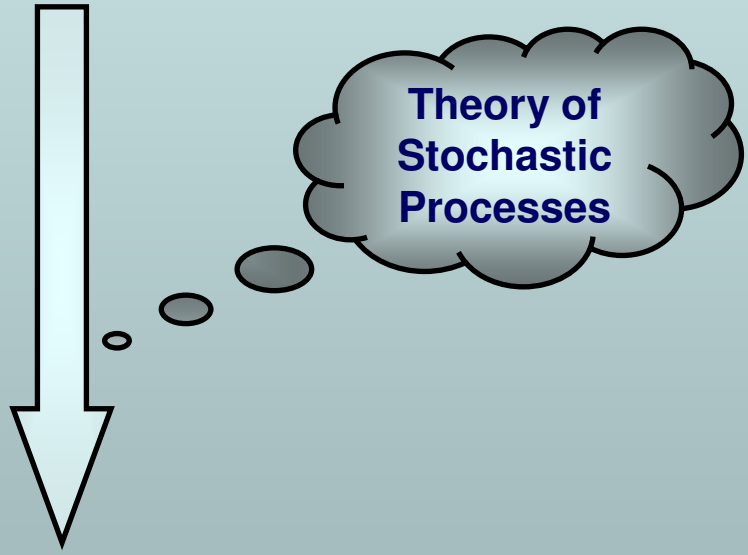
Nonequilibrium

Trajectories

Fokker Planck Equation

Finite OPEN System





Thermodynamics

Device Equation

Schuss, Nadler, and Eisenberg

Langevin Equations

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

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

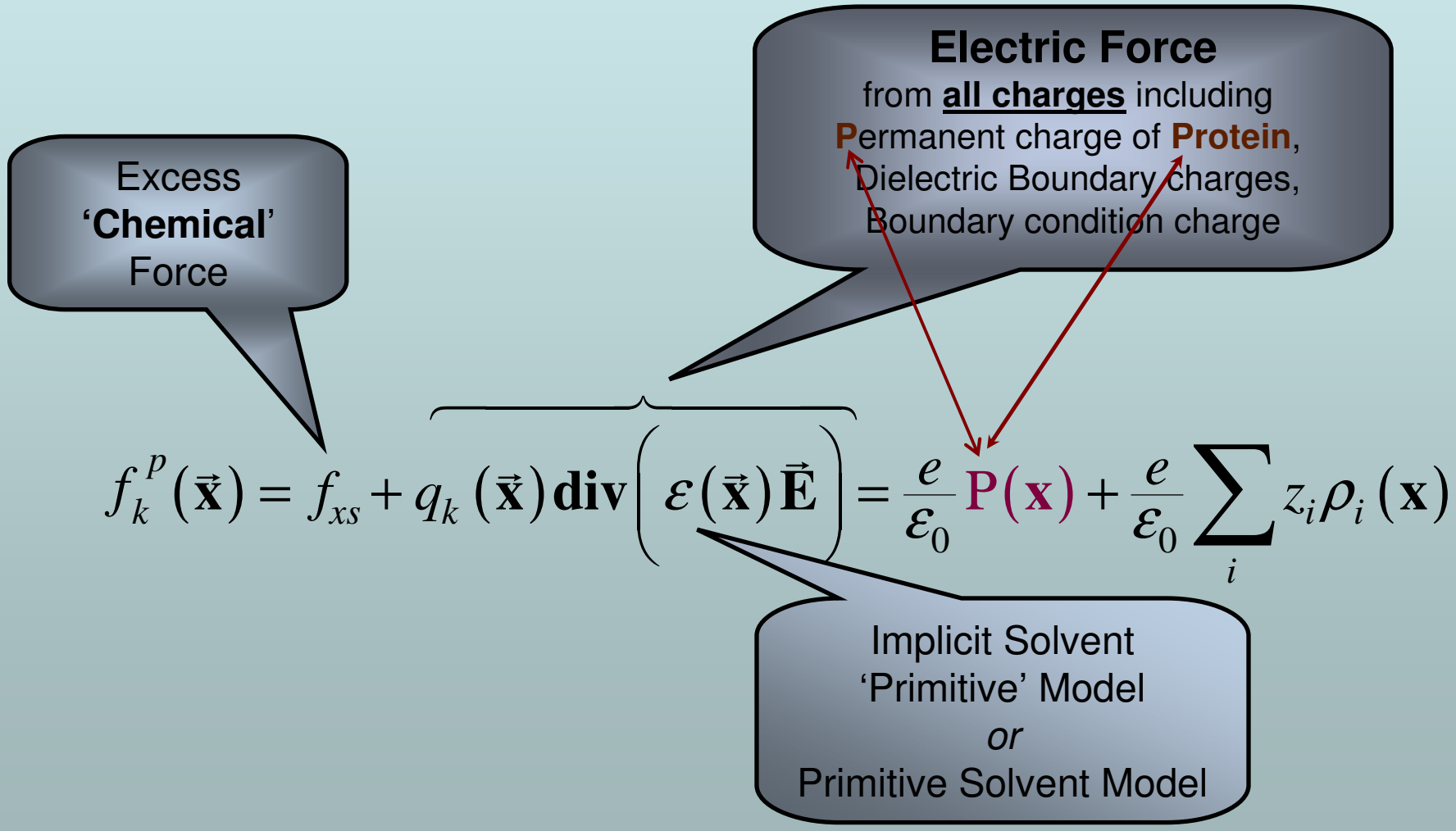
Negative ***an*ion**,
e.g., n = Cl^-

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

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

Schuss, Nadler, Eisenberg

Electric Force from Poisson Equation



Schuss, Nadler, Eisenberg

From Trajectories to Probabilities

Main Result: Theory of Stochastic Processes

Joint probability density of position and velocity

$$p(\tilde{x},\tilde{v}) = \mathbf{Pr}\left\{\left\{x_j, v_j\right\}_{j=1}^{2N}\right\}; \quad N = \text{Number of Particles}$$

satisfies a Fokker Planck equation

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

with Fokker Planck Operator

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

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

Schuss, Nadler, and Eisenberg

Conditional PNP

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

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

Channel Protein

Closures or **Approximations** Needed

Nernst-Planck gives UNconditional Density of Charge

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

Mass

Friction

Schuss, Nadler, Eisenberg

Closure by Hand

Counting at low resolution gives
‘Semiconductor Equations’

Poisson-Nernst-Planck (PNP)

Only contains correlations of means

Gouy-Chapman, (nonlinear) Poisson-Boltzmann,
Debye-Hückel,
are siblings with similar resolution
but without current or flux of any species
Devices do not exist at equilibrium

PNP in 3D

Poisson's Equation

$$-\varepsilon_0 \nabla \cdot \left(\varepsilon(\mathbf{x}) \nabla \phi(\mathbf{x}) \right) = eP(\mathbf{x}) + e\sum_i z_i \rho_i(\mathbf{x})$$

Channel Protein

Drift-diffusion & Continuity Equation

$$\nabla \cdot \mathbf{J}(\mathbf{x}) = 0; \quad -\mathbf{J}_i(\mathbf{x}) = D_i(\mathbf{x}) \rho_i(\mathbf{x}) \frac{1}{kT} \nabla \mu_i(\mathbf{x})$$

Chemical Potential

Closure by Hand

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

Special Chemistry

Solving semiconductor equations requires a trick

Poisson Equation

and

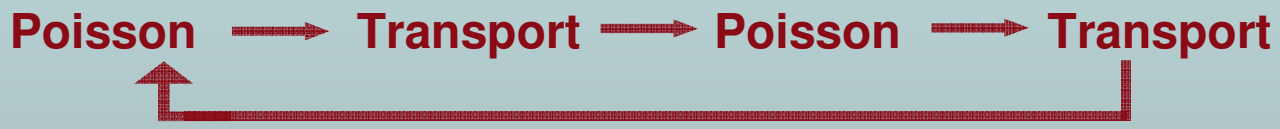
Nernst Planck Equation

(Fick's Law for charged particles)

are solved together

by

Gummel iteration



Or much better

(but much harder)

Newton Iteration

Electrodiffusion of charged, hard spheres

Correlations put in by Hand

Closure by Hand

How well can we do biology with correlations done by hand?

Goal:
Understand Selectivity

Selectivity Differs in Different Types of Channels

Wolfgang Nonner, Dirk Gillespie, Douglas Henderson, Dezso Boda

Selectivity of Different Channel Types Studied in Many Solutions

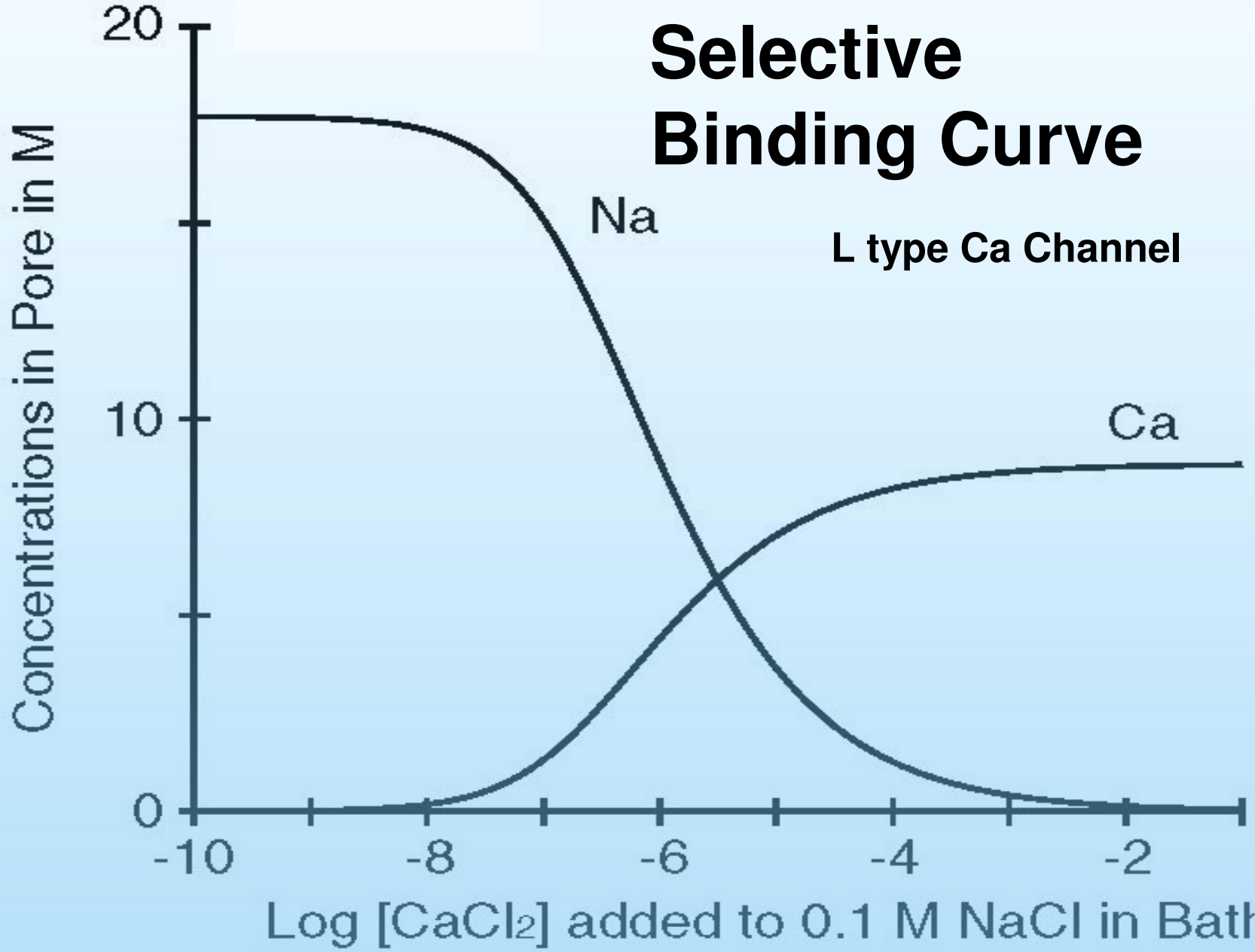
RyR Channel	Calcium Channel	Sodium Channel	Synthetic Ca Channel
Selectivity filter ***DDDD*** 4 – charges	**Selectivity filter** ***EEEE*** 4 – charges	**Selectivity filter** ***DEKA*** 2 –, 1+ charge	**Selectivity filter** ***Various*** many – charges
PNP/DFT	PNP/DFT Monte Carlo	Monte Carlo	PNP/DFT

RyR model of Gillespie is best worked out, most data
K channel model of Benoit Roux is Similar
Quantum Water/K^+ Model of Susan Rempe is Similar, ***but***
Neither K model has yet been computed in a range of solutions

Nonner, Gillespie, Henderson, Boda

Selective Binding Curve

L type Ca Channel



Wolfgang Nonner

Goal:

Understand Selectivity

well enough to

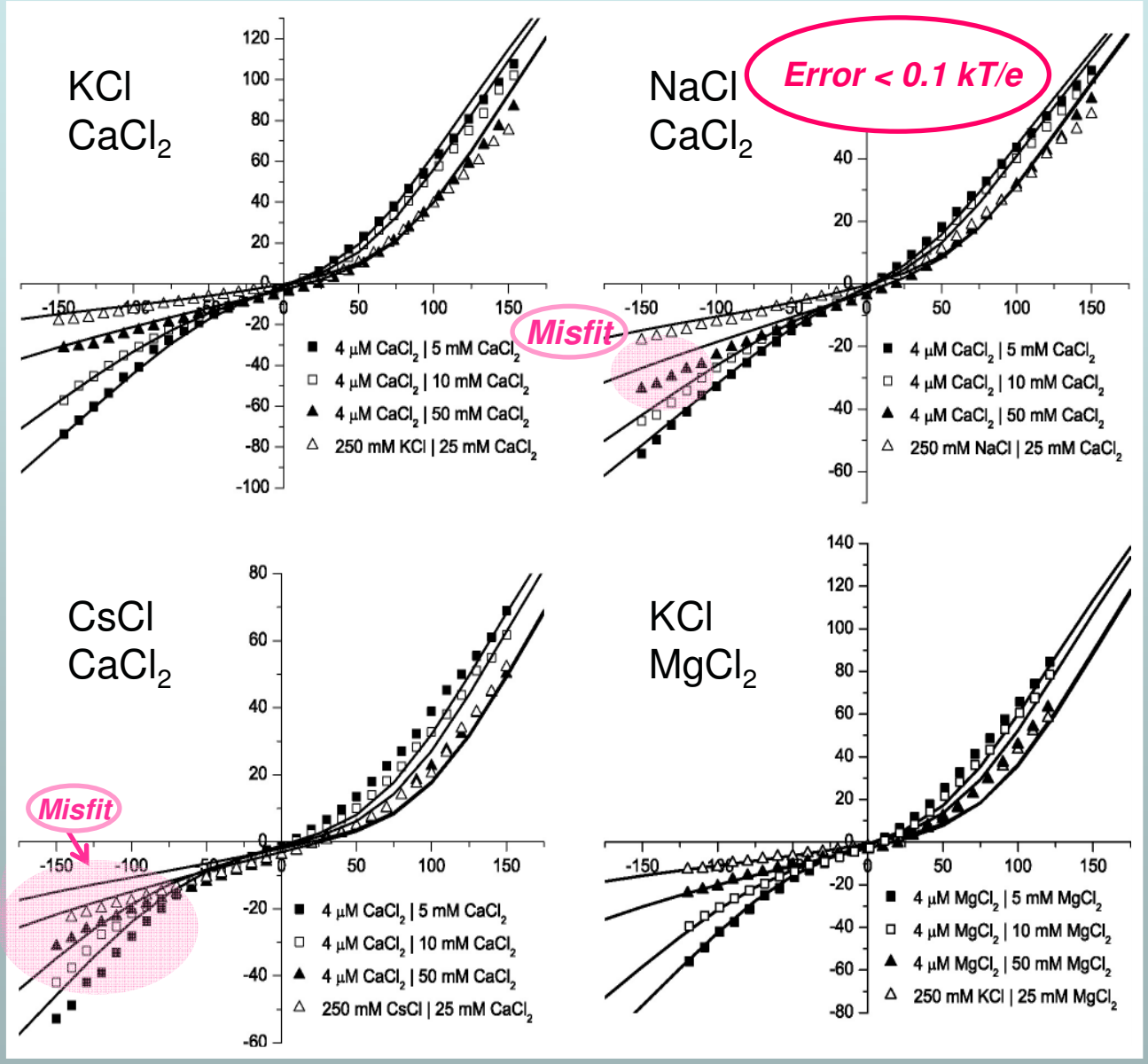
Fit Large Amounts of Data

and to

Make a Calcium Channel

Divalents in RyR: fits with a few parameters:

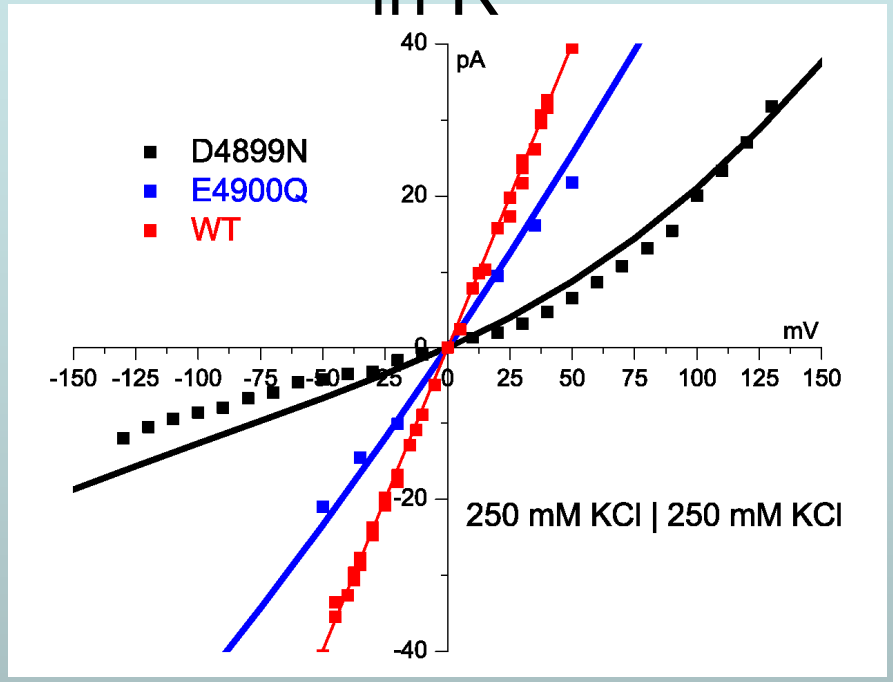
Gillespie, Meissner, Le Xu, not Bob Eisenberg



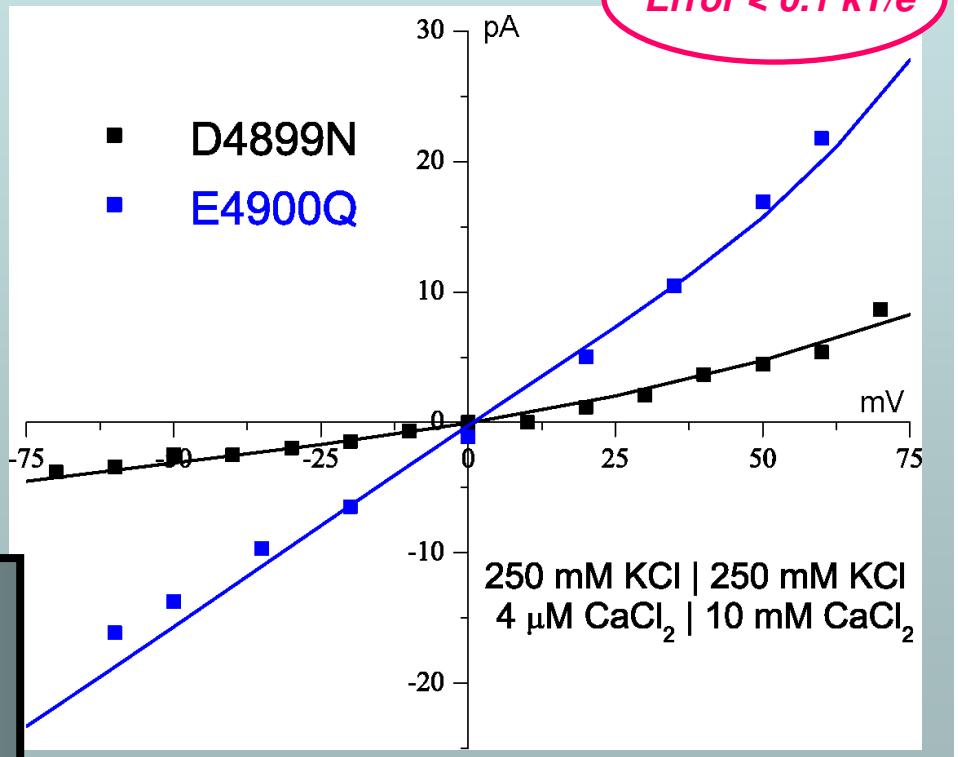
Theory fits Mutation with Zero Charge

No parameters adjusted

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

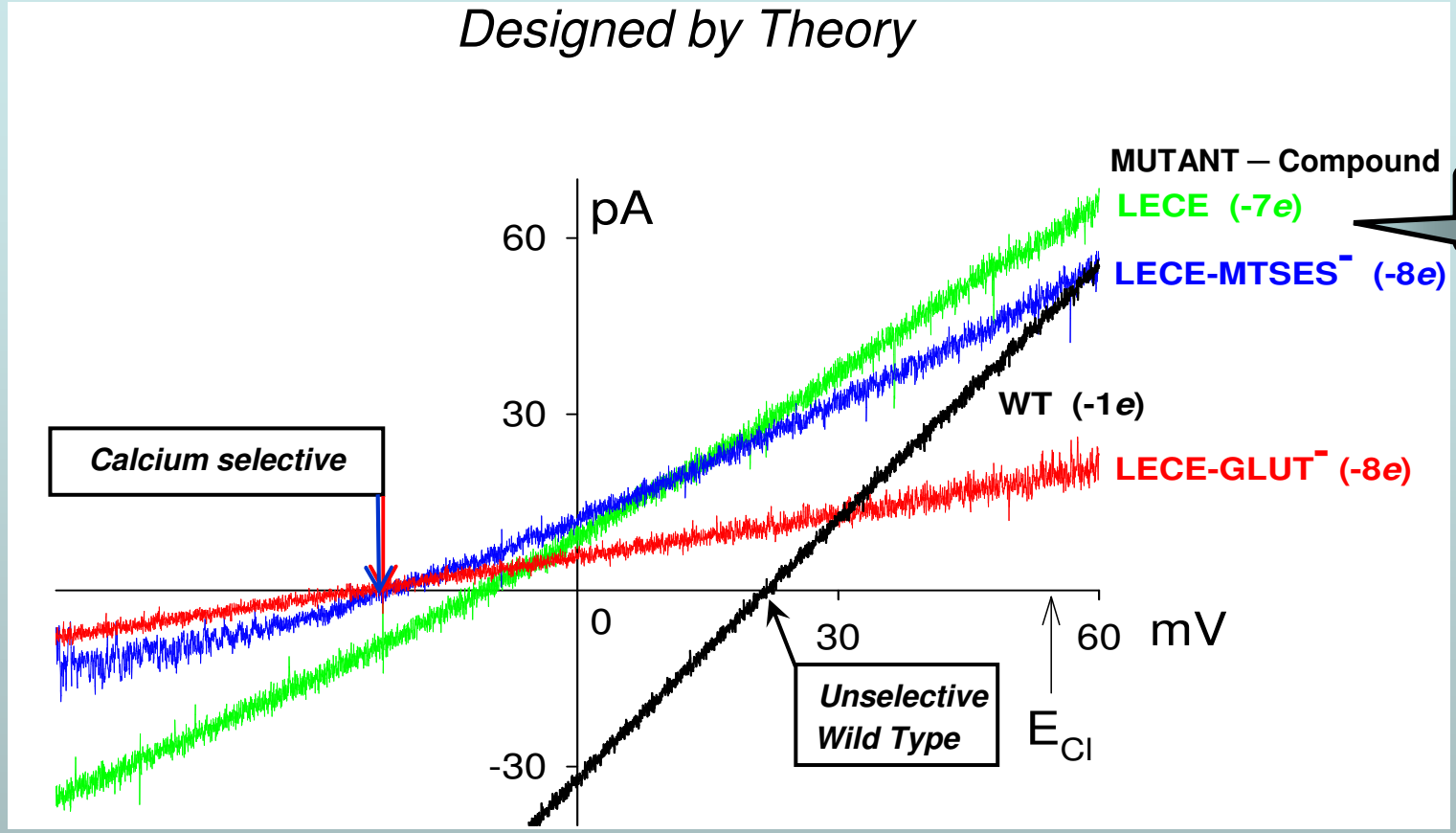
some wild type curves not shown, 'off the graph'

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

Experiment

Two Synthetic Calcium Channels

Designed by Theory



As charge density increases, channel becomes calcium selective

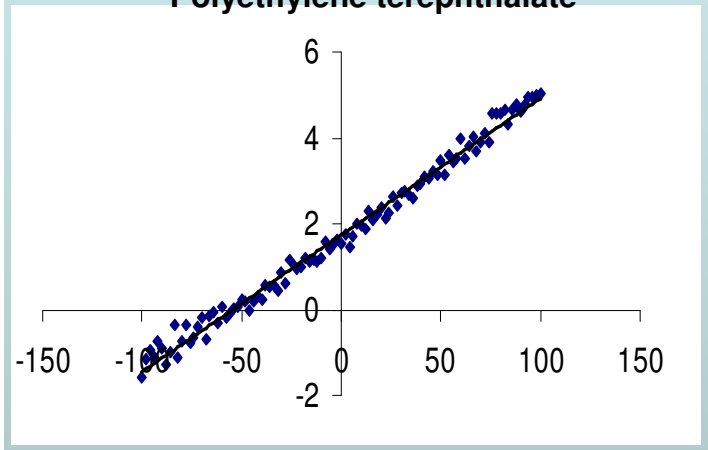
$E_{rev} \rightarrow E_{Ca}$

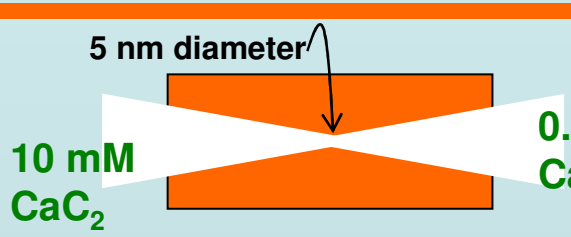
built by Henk Miedema, Wim Meijberg of BioMade Corp.,Groningen, Netherlands

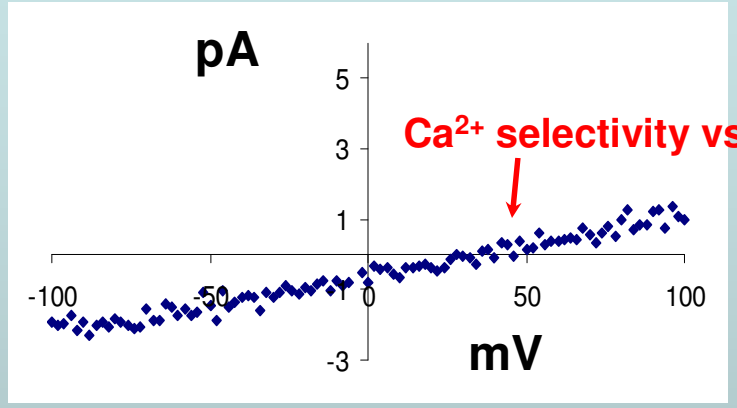
Miedema** et al**, Biophys J 87: 3137–3147 (2004)

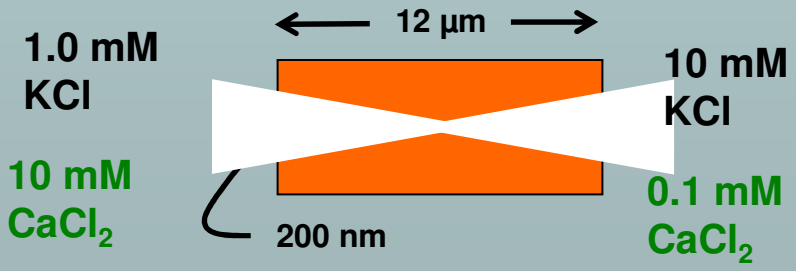
Hole in Plastic: Synthetic Nanopore NO PROTEIN

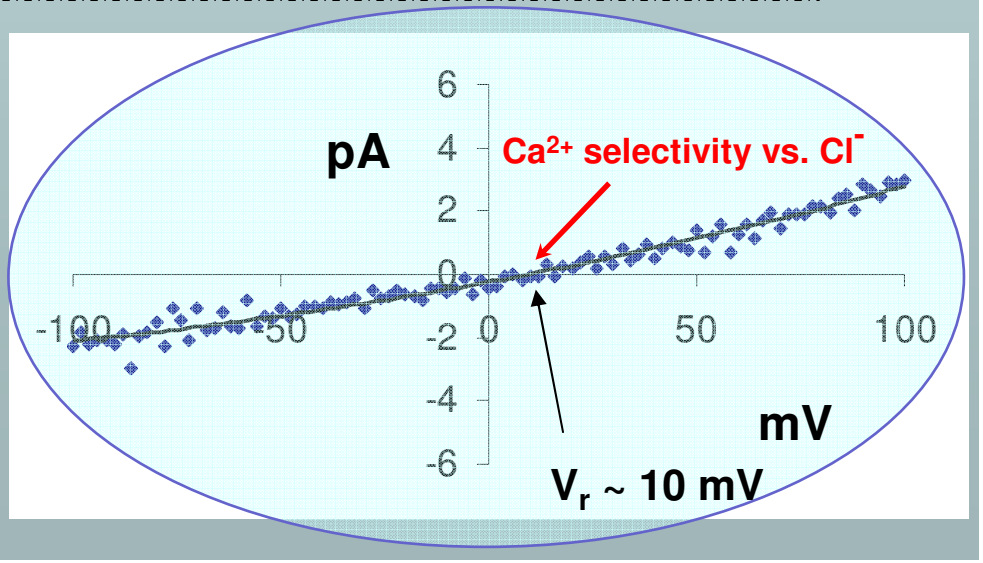
Polyethylene terephthalate











Zuzanna Siwy & Yan He, UC Irvine

How do we understand selectivity?

Where do we start?

Physical Models of Selectivity

Balance between Electrostatic Attraction and Hard Sphere Repulsion

Crowded Charge

that depends on surrounding solutions

INDUCED FIT MODEL

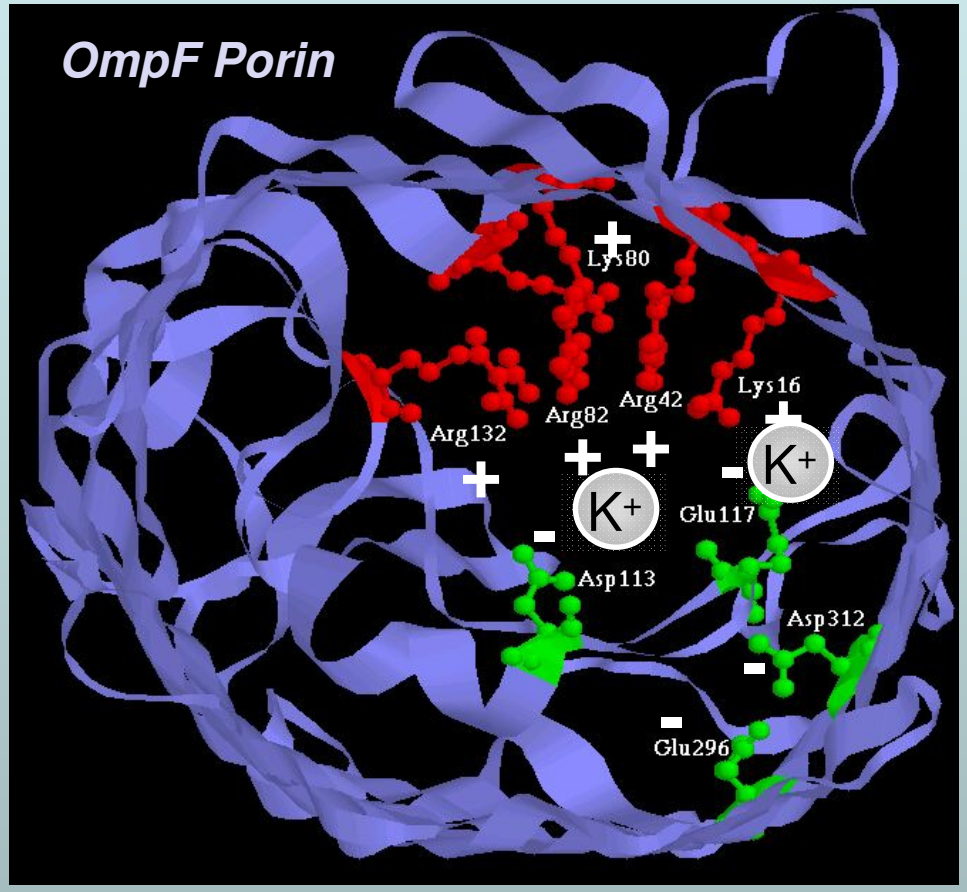
of

Selectivity

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

e.g. 7 charges ~ **20 M net charge = 1.2×10^{22} cm^{-3}**

1 nM = 10 Å



Ions are Crowded

Figure adapted from Tilman Schirmer

Selectivity Filters and Gates of Ion Channels are

Active Sites

Finite Size Effects

Working Hypothesis

Fundamental
Chemically Specific Properties

of ions (e.g. activity= free energy per mole)
come from their

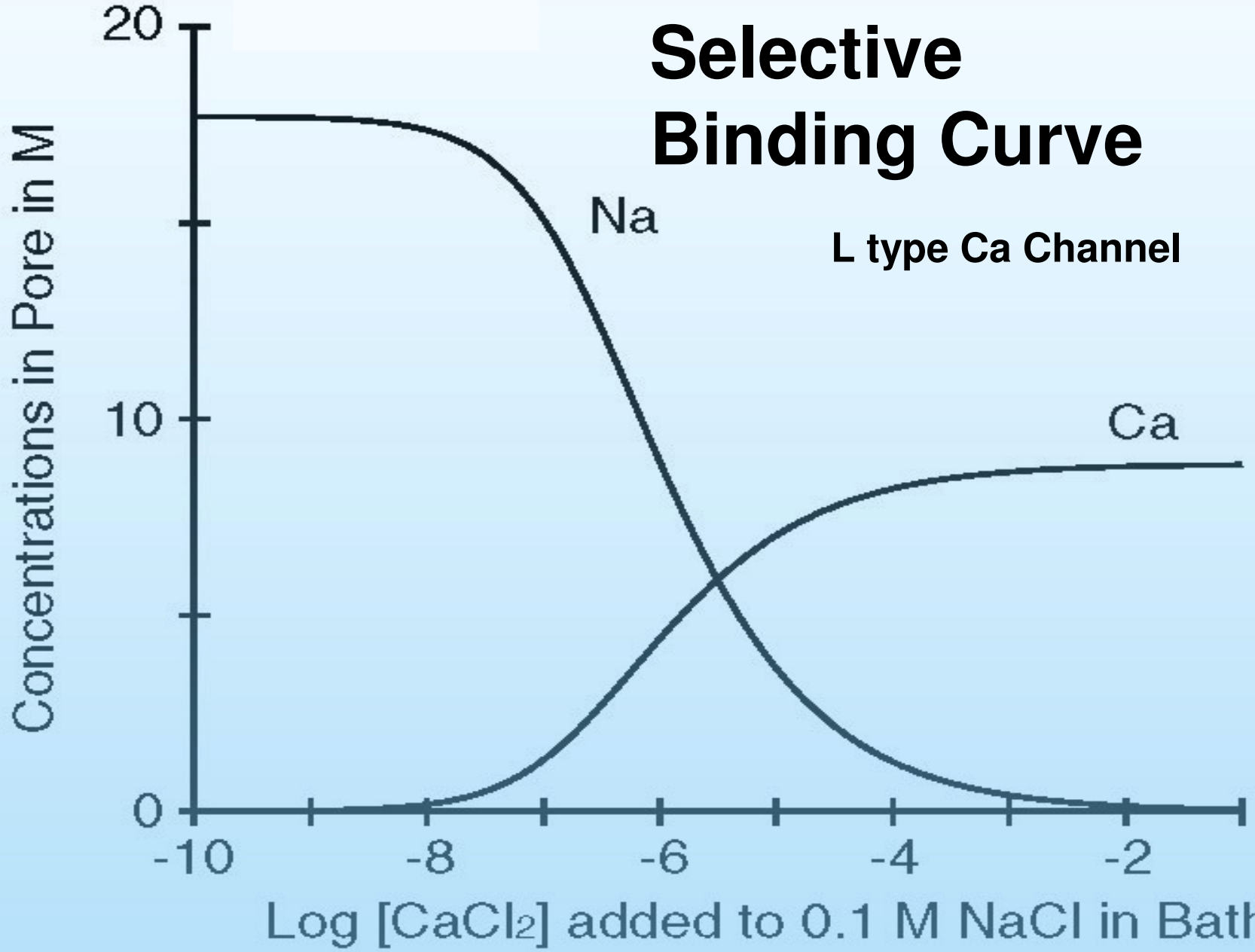
Diameter and Charge

not vaguely defined hydration shells or
‘chemical’ bonds

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

Selective Binding Curve

L type Ca Channel

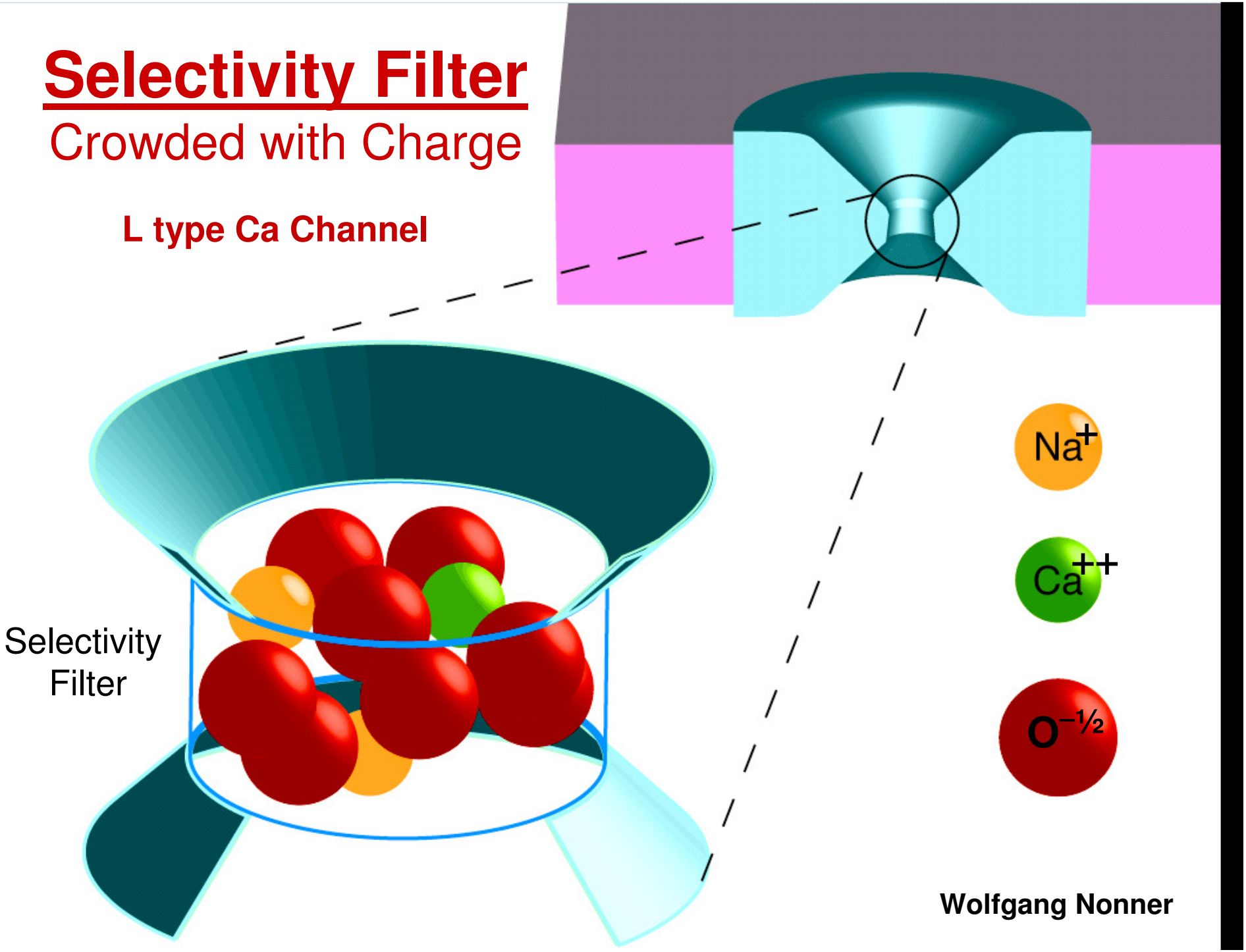


Wolfgang Nonner

Selectivity Filter

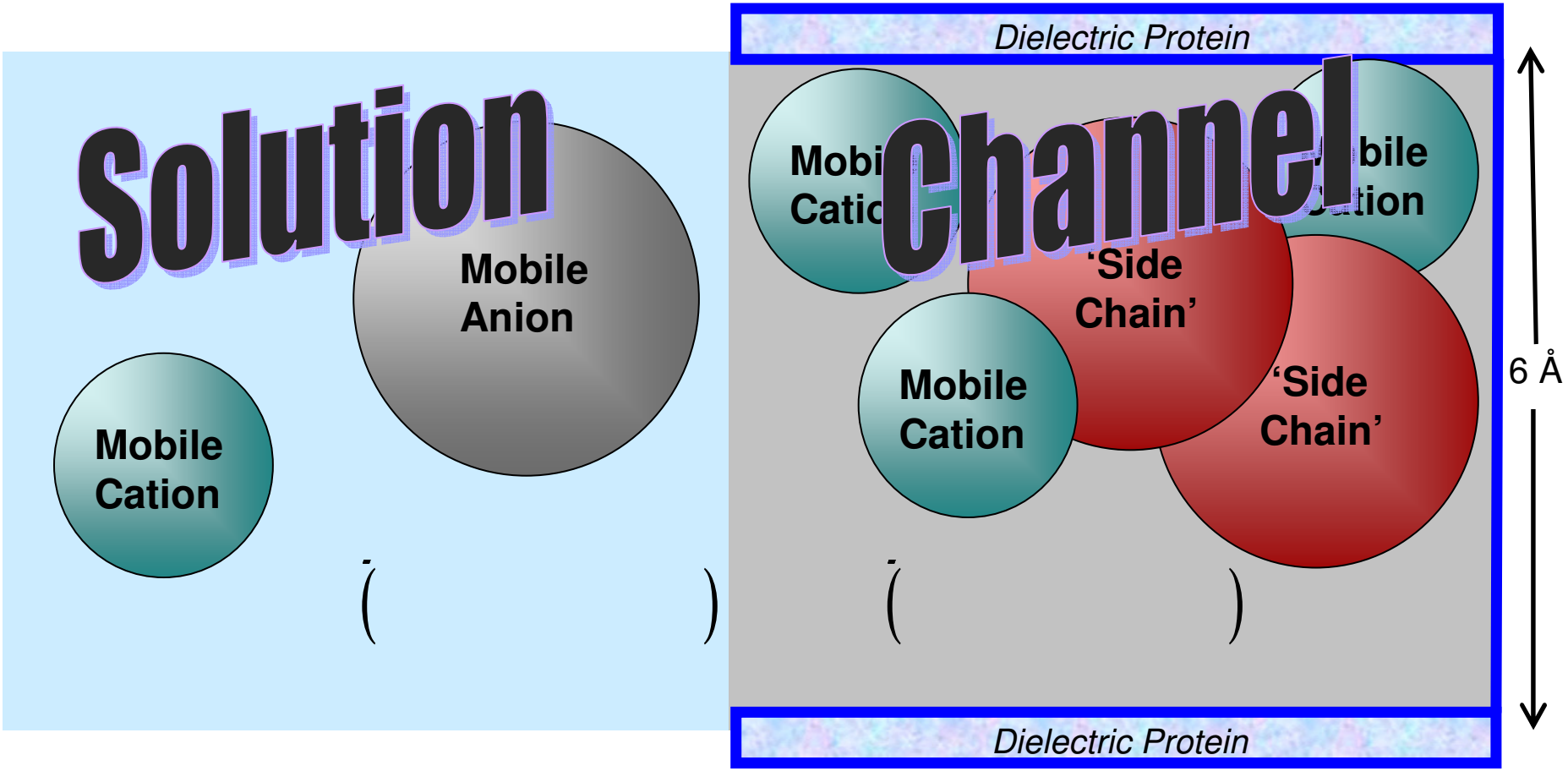
Crowded with Charge

L type Ca Channel



Wolfgang Nonner

Ion 'Binding' in Crowded Channel

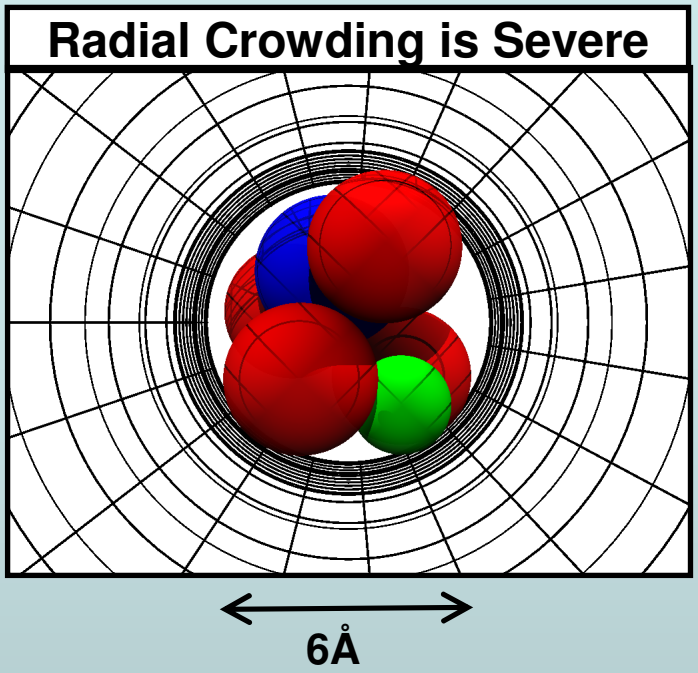


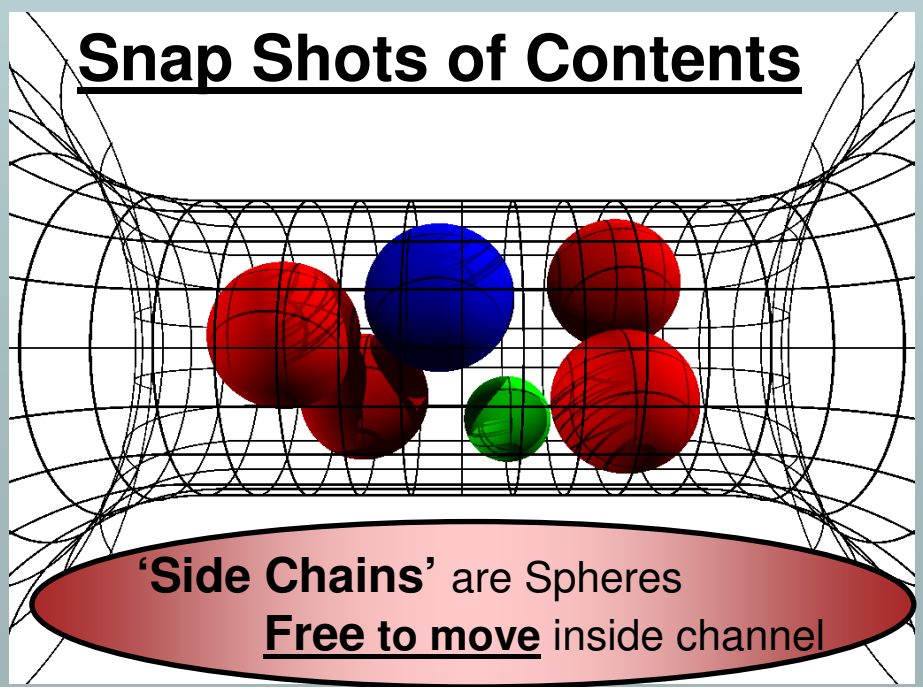
Classical Donnan Equilibrium of Ion Exchanger

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

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

Boda, Nonner, Valisko, Henderson, Eisenberg & Gillespie

Calcium Channel First

Calcium Channel 6Å

3 electron charges

High Occupancy

Aspartate E
acid (negative)

Mutation

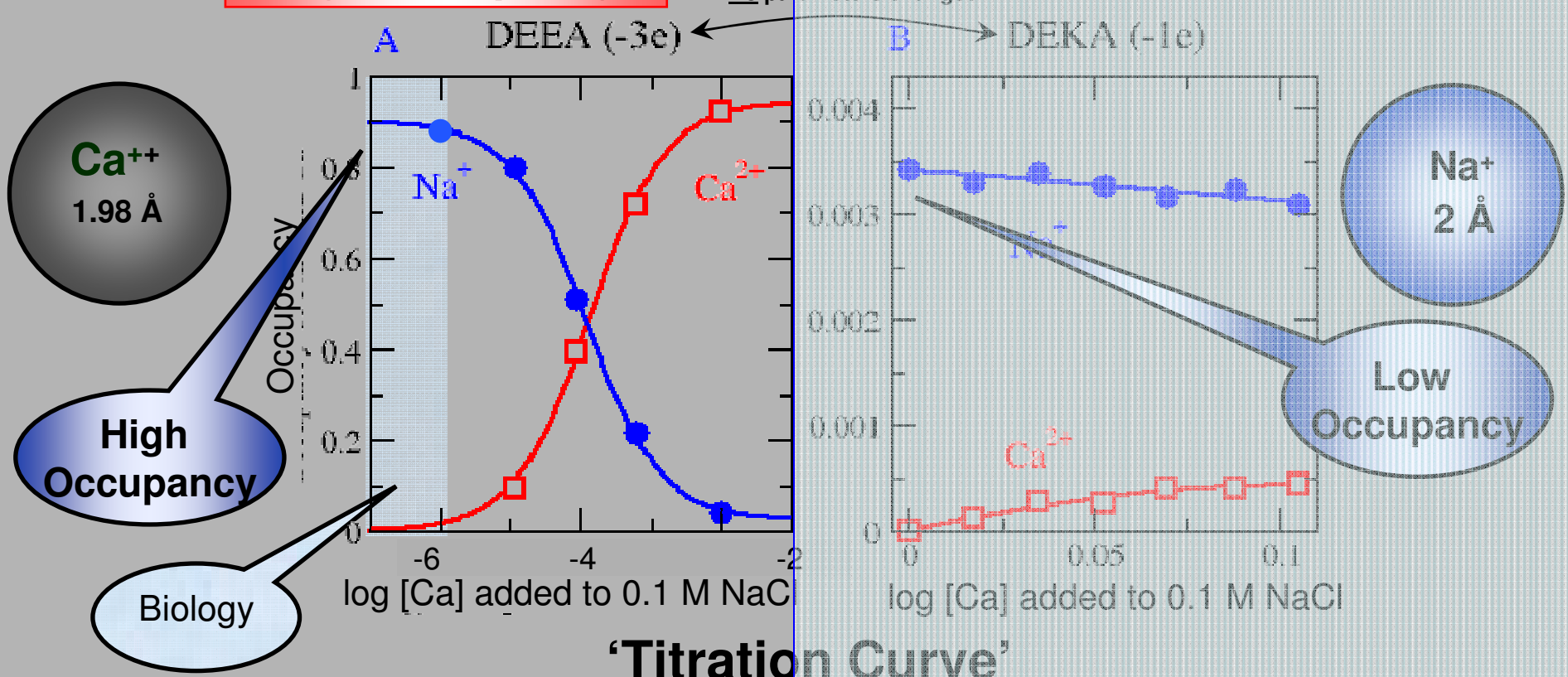
Lysine K
basic (positive)

Sodium Channel 6Å

1 electron charge

Low Occupancy

No parameters changed



'Titration Curve'
Classical Definition of Selectivity

We believe curves like these must be reproduced by a useful theory

Boda, Nonner, Valisko, Henderson, Eisenberg & Gillespie

Calcium Channel

has been examined in ~30 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
http://www2.phys.rush.edu/RSEisenberg/physioeis.html

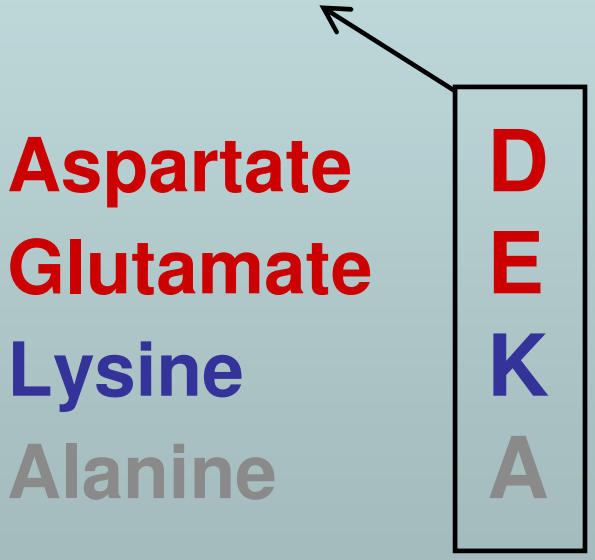
Now, the Sodium Channel

Now, the

Sodium Channel

specifically, the

DEKA Sodium Channel 6 Å



Aspartate	D	Acid	Negative
Glutamate	E	Acid	Negative
Lysine	K	Basic	Positive
Alanine	A	Aliphatic	Neutral

Calcium Channel 6Å
3 electron charges
High Occupancy

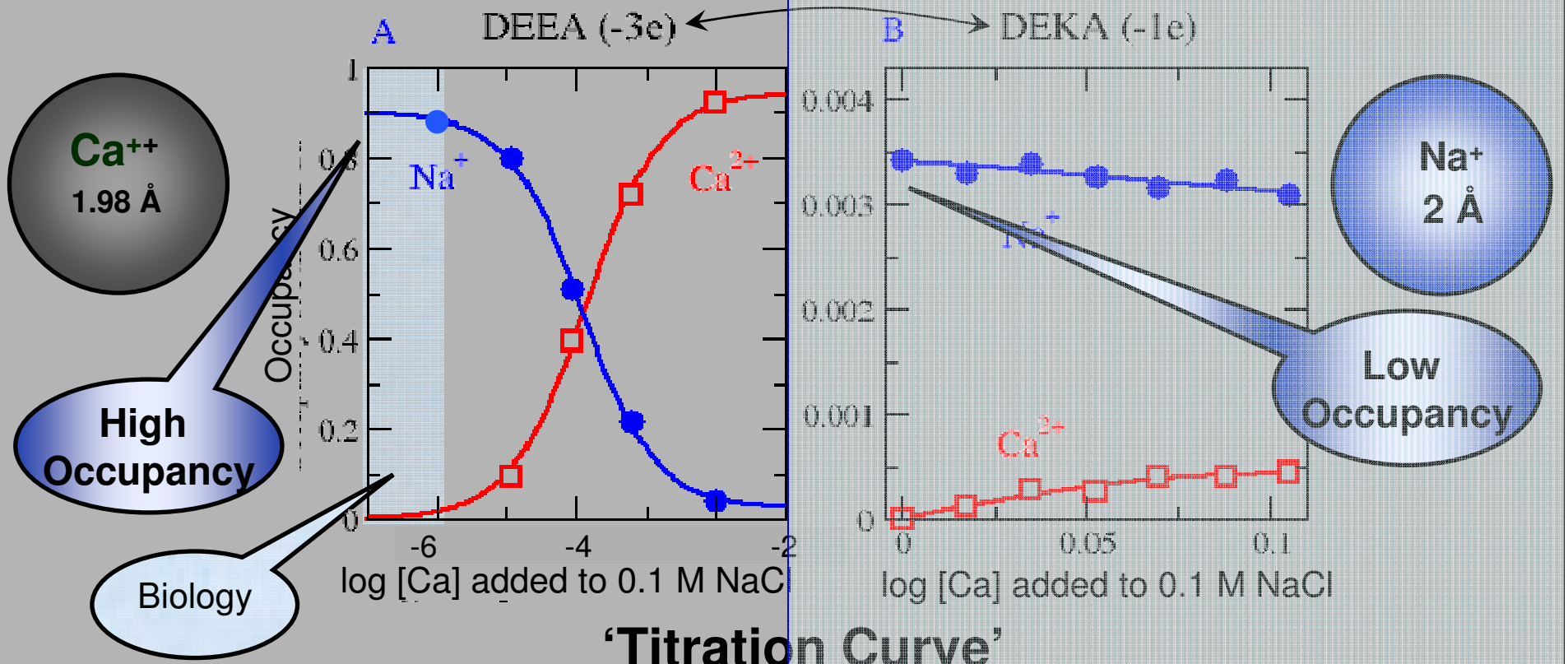
Aspartate E
acid (negative)

Mutation

Lysine K
basic (positive)

Sodium Channel 6Å
1 electron charge
Low Occupancy

No parameters changed



'Titration Curve'
Classical Definition of Selectivity

We believe curves like these must be reproduced by a useful theory

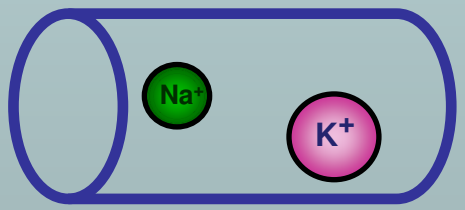
Boda, Nonner, Valisko, Henderson, Eisenberg & Gillespie

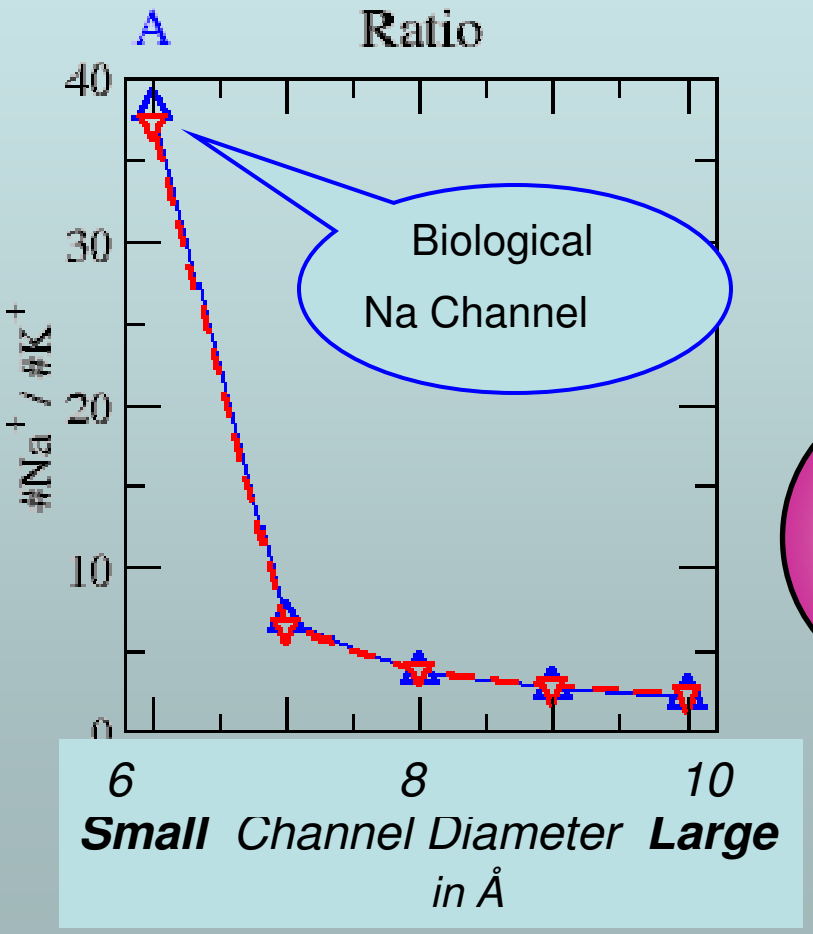
DEKA Channel is Selective for Na

using model & parameters of a <u>Ca channel</u> DEEA (!)

No Changes!

Selectivity
for small ion





Na+ 2.00 Å

K+ 2.66 Å

Boda, et al

Size Selectivity

Na^+ *vs* K^+

in the DEKA Na Channel

Nothing was changed

in the model

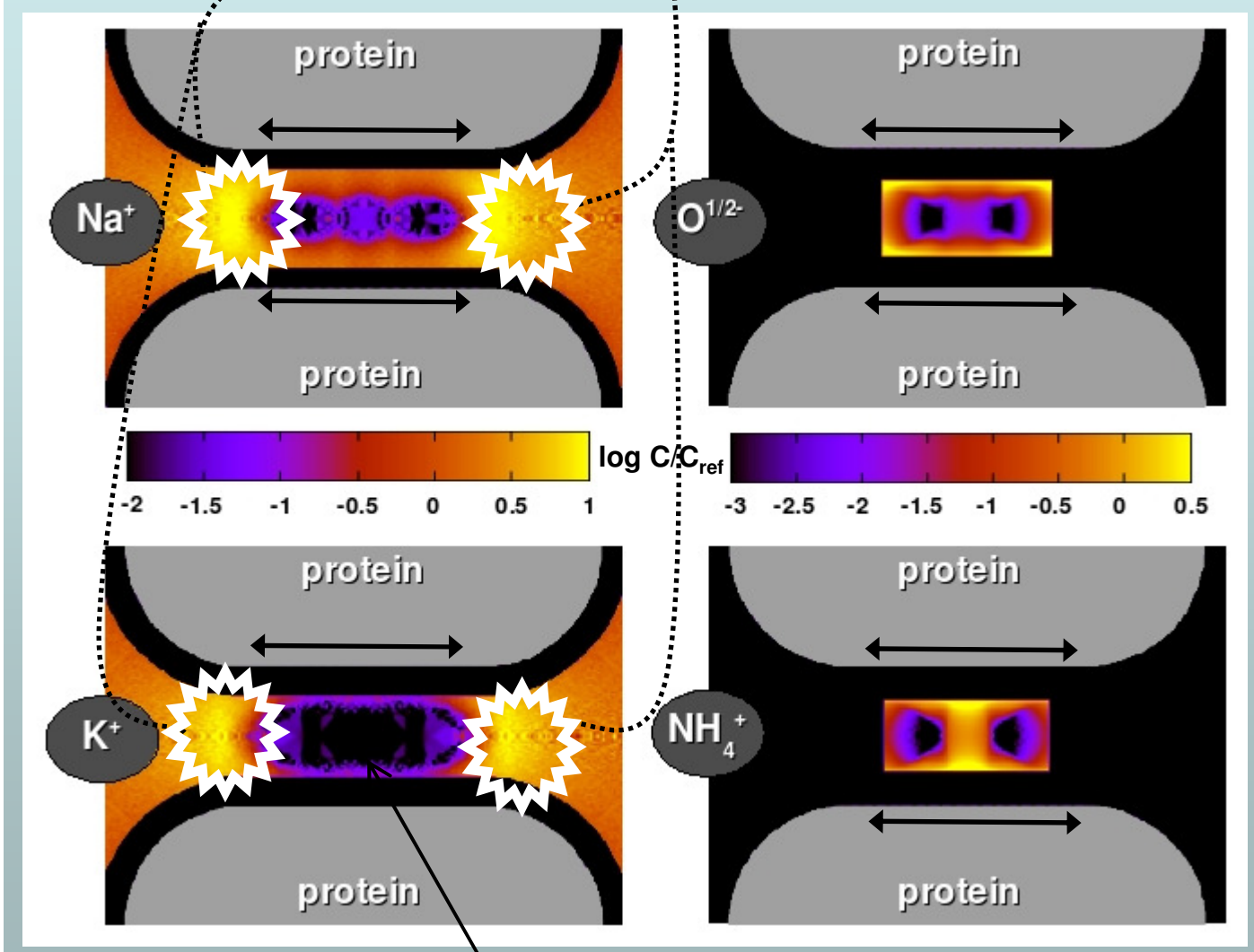
of the EEEA Ca channel

except the amino acids

Size Selectivity

Binding Sites

NOT selective



Na vs K Size Selectivity is in

Depletion Zone

BLACK = Depletion=0

Boda, et al

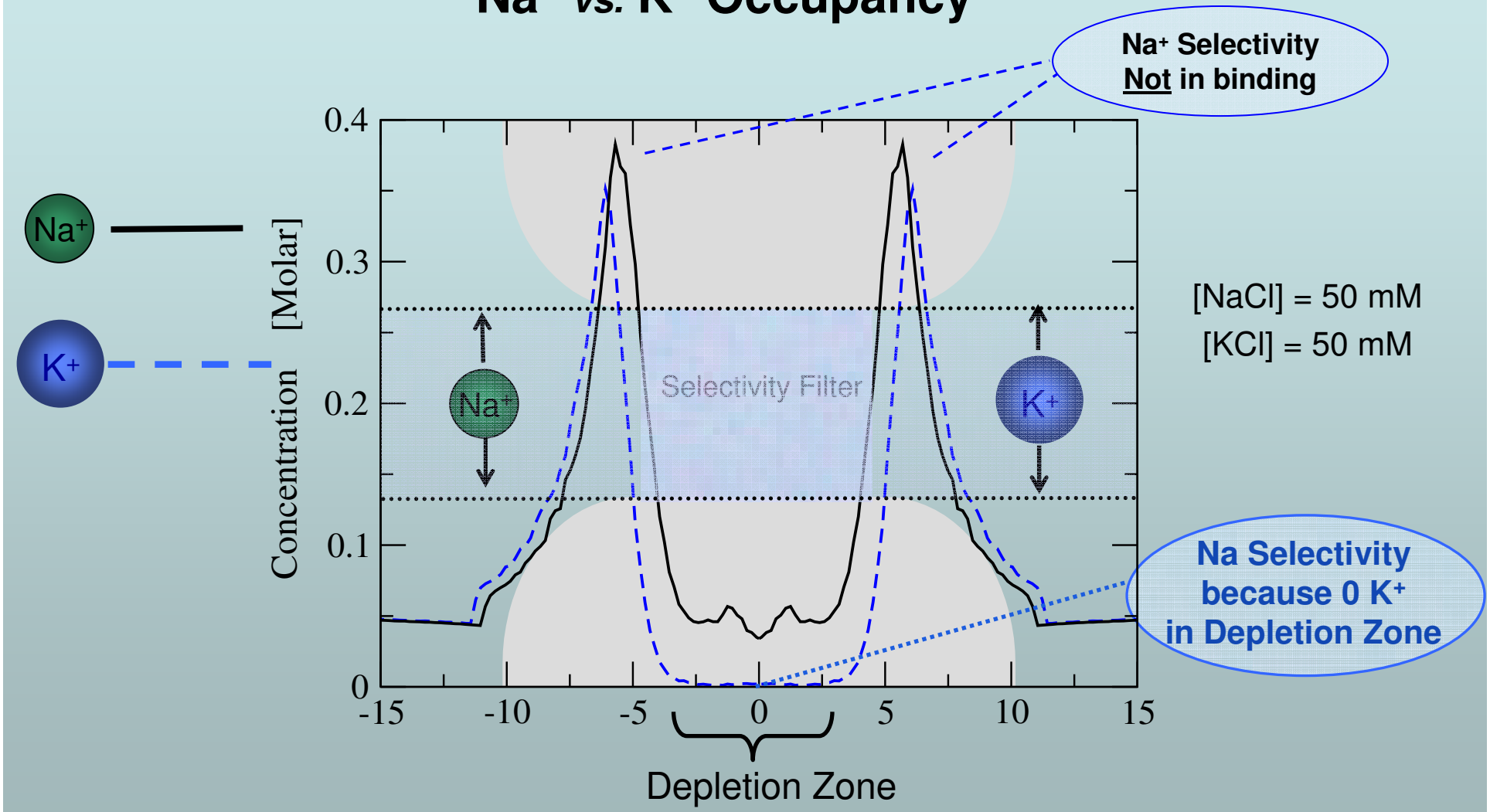
*Binding Sites are outputs of our INDUCED FIT Model of Selectivity, ***not*** *structural inputs*

[NaCl] = [KCl] = 50 mM

Ion Diameter	
Ca^{++}	1.98 Å
Na^{+}	2.00 Å
K^{+}	2.66 Å
'Side Chain' Diameter	
NH_4^+ Lys or K	3.00 Å
$O^{1/2-}$ D or E	2.80 Å
Na Channel DEKA ***6 Å***	

Size Selectivity is in the Depletion Zone

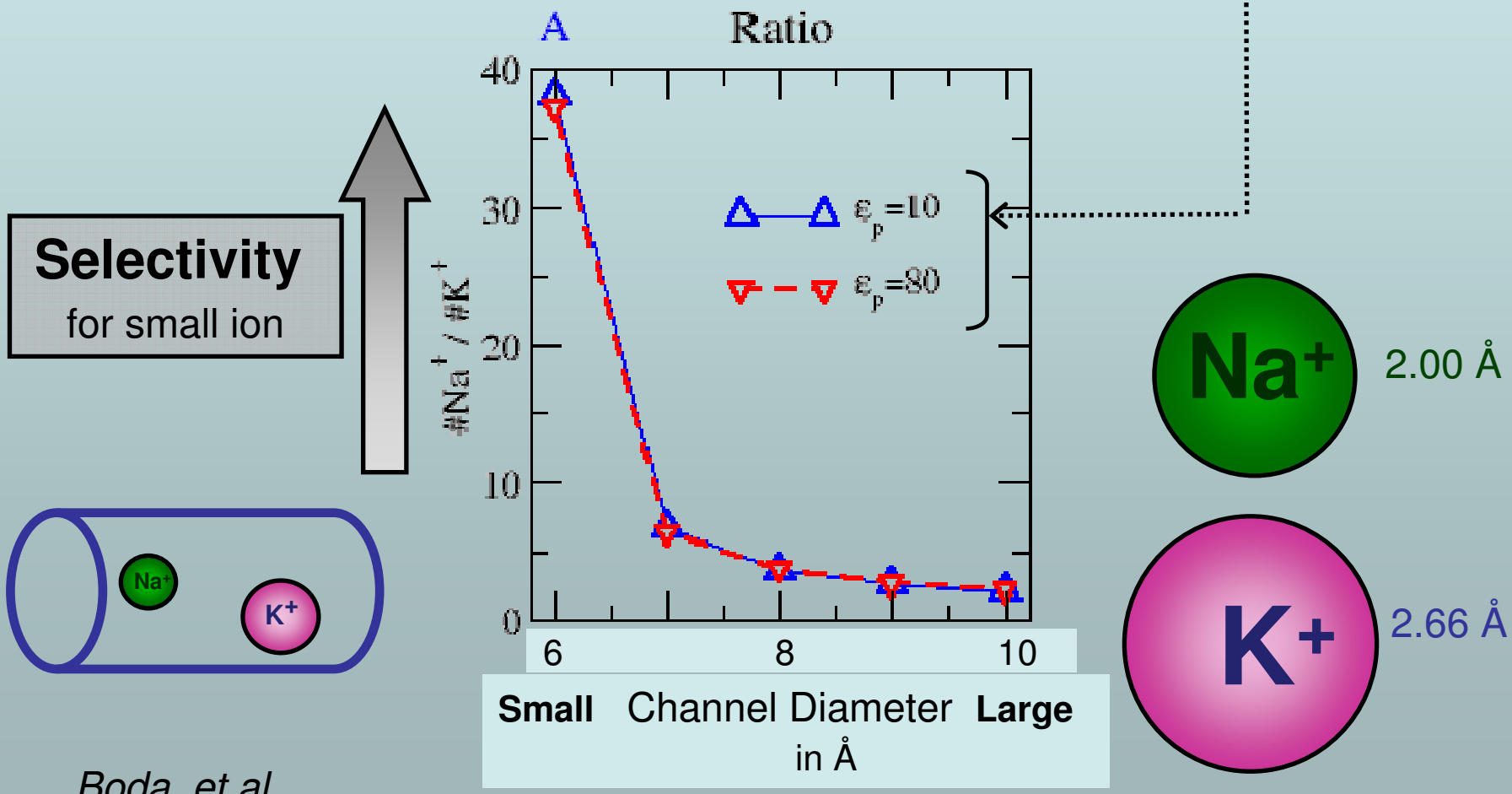
Na^+ *vs.* K^+ Occupancy



of the **DEKA** Na Channel, **6 Å**

Boda, et al

Size Selectivity *(ratio)* Depends on Channel Size, *not* Protein Dielectric Coefficient



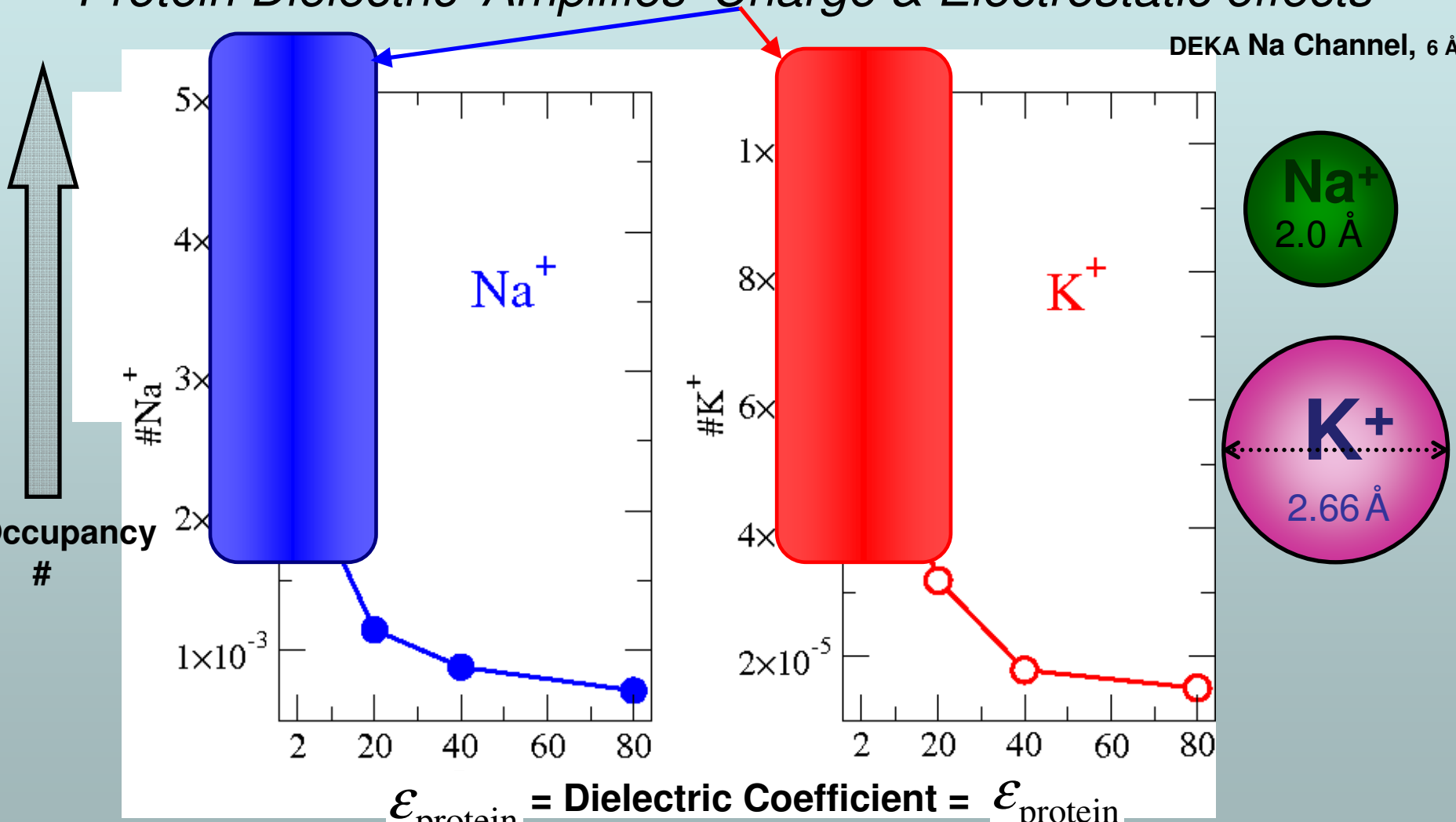
Boda, et al

Size Selectivity *ratio* does not depend on protein dielectric

Occupancy # Depends on Protein Dielectric

Protein Dielectric 'Amplifies' Charge & Electrostatic effects

DEKA Na Channel, 6 Å



$\varepsilon_{protein}$ = Dielectric Coefficient = $\varepsilon_{protein}$
of Protein

$\varepsilon_{solvent} = 80$

Boda, et al

Binding & Depletion Sites* are
Outputs of our Calculations

Our model has no preformed structural binding sites

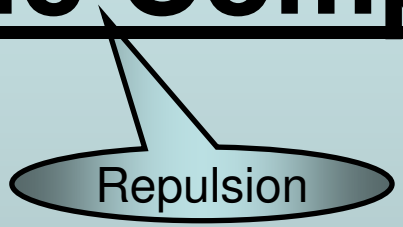
but

Selectivity is very Specific

Induced Fit Model of Selectivity

*Selectivity is in the Depletion Zone,
NOT IN THE BINDING SITE
of the DEKA Na Channel

Binding Sites use Electrostatic Attraction Steric Competition for Space



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

What does the protein do?

Selectivity arises from
Electrostatics and Crowding of Charge

Certain MEASURES of structure are

Powerful DETERMINANTS of Function

e.g., Volume, Dielectric Coefficient, etc.

Induced Fit Model of Selectivity
Atomic Structure is not pre-formed
Atomic Structure is an important output of the simulation

Nonner and Eisenberg

What does the protein do?

Protein maintains

Mechanical Forces*

Volume of Pore

Dielectric Coefficient/Boundary

Permanent Charge

Induced Fit Model of Selectivity

** Driving force for conformation changes ??*

Nonner and Eisenberg

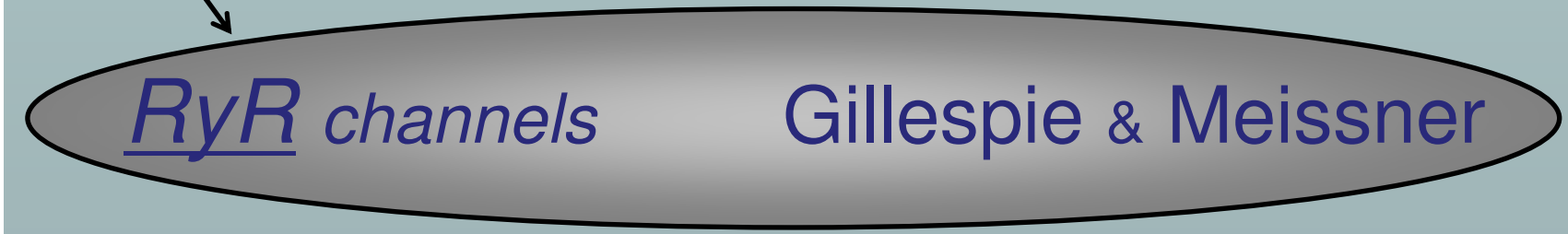
Conclusion

Selectivity can be understood by Reduced Models

K channels — Benoit Roux, Susan Rempe

Na & *Ca channels* — Nonner, *et al,*

Best Evidence



RyR channels — Gillespie & Meissner

Questions?