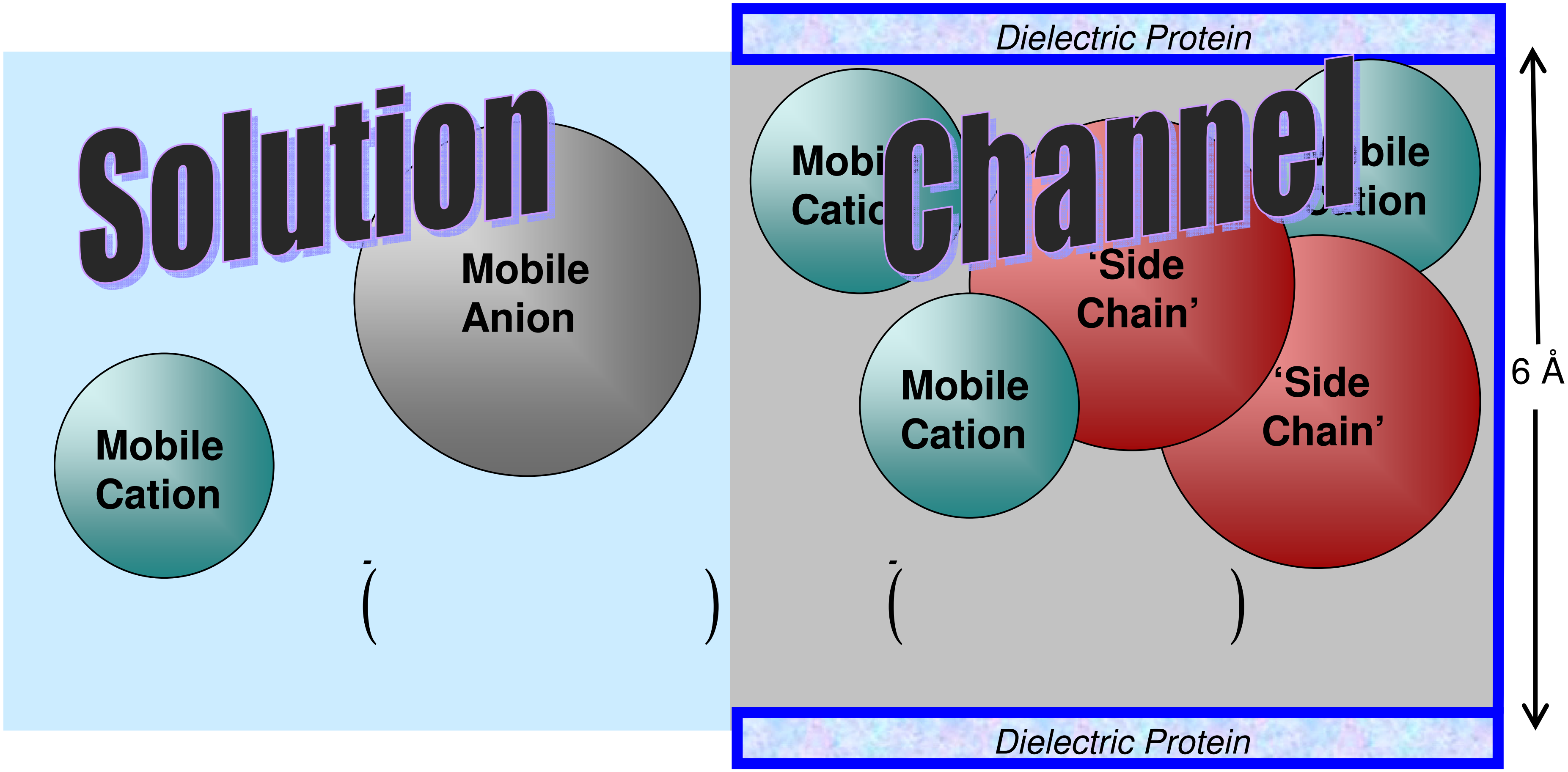
Setup

Ion 'Binding' in Crowded Channel

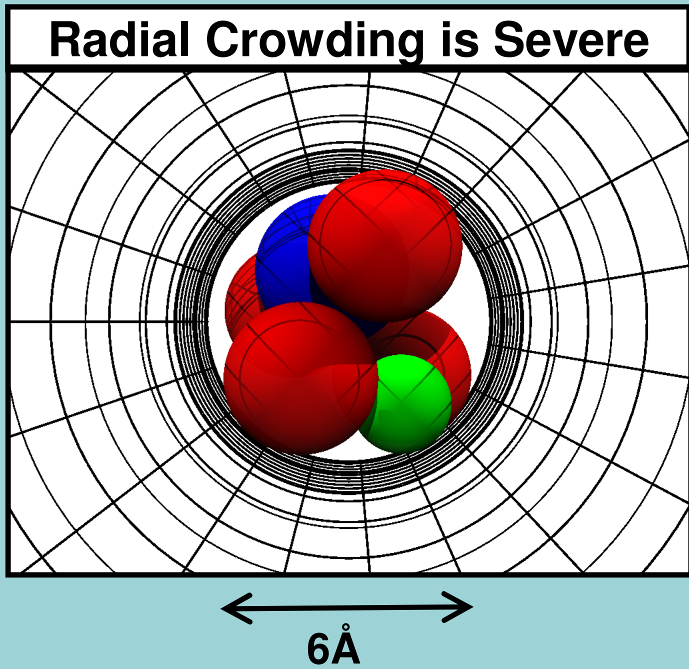


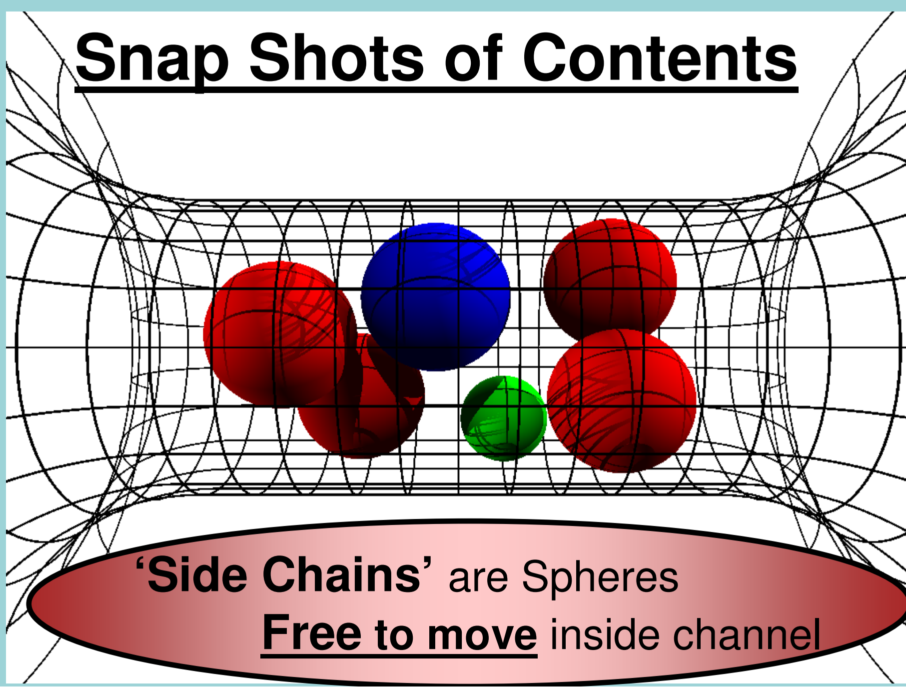
Classical Donnan Equilibrium of Ion Exchanger

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

Ca and Na Channels

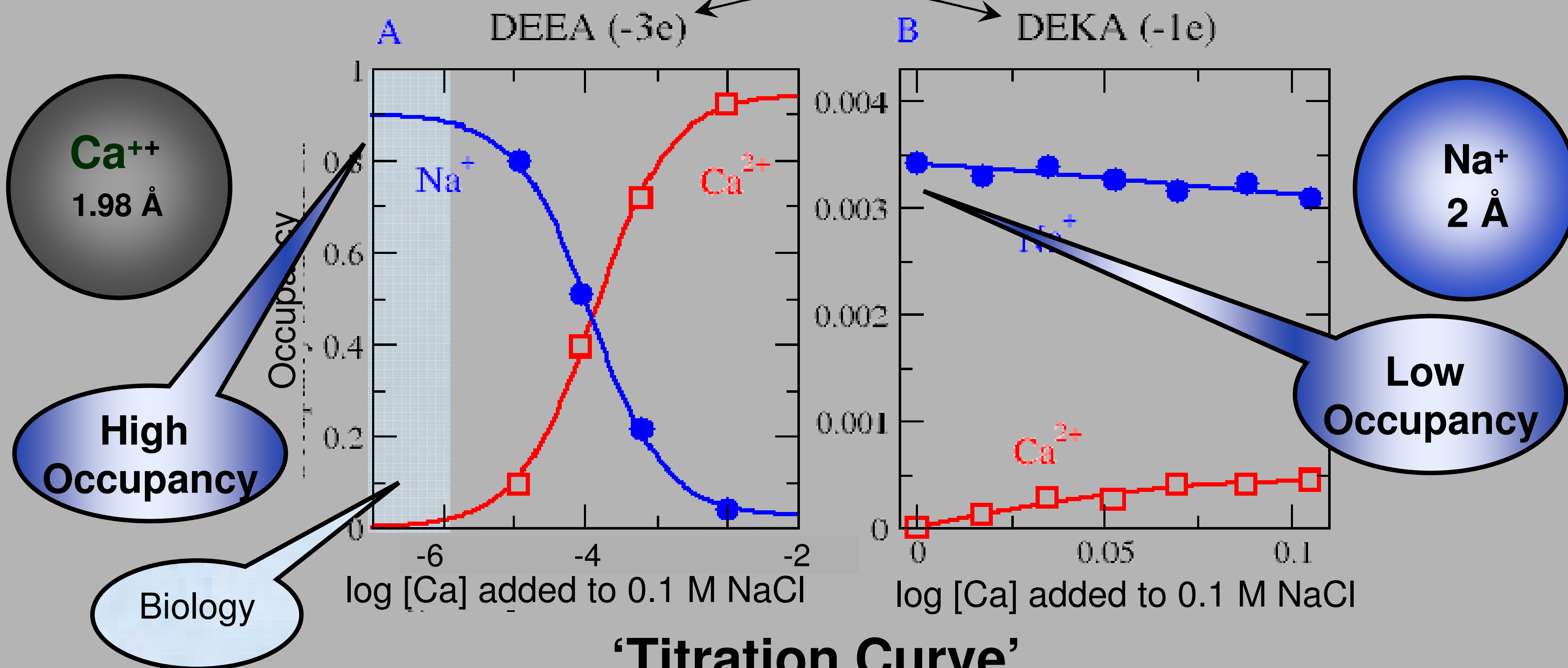
Calcium Channel 6Å
3 electron charges
High Occupancy

Aspartate E
acid (negative)

Mutation

Lysine K
basic (positive)

Sodium Channel 6Å
1 electron charge
Low Occupancy



‘Titration Curve’
Classical Definition of Selectivity

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

Boda, Nonner, Valisko, Henderson, Eisenberg & Gillespie

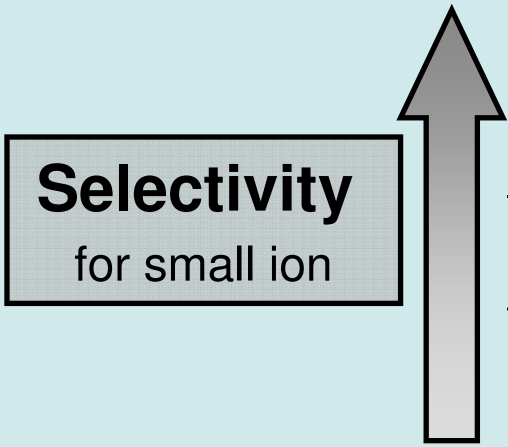
<u>Size</u> Selectivity

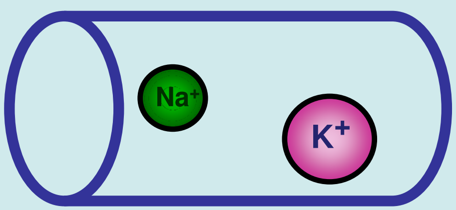
Na^+ *vs* K^+

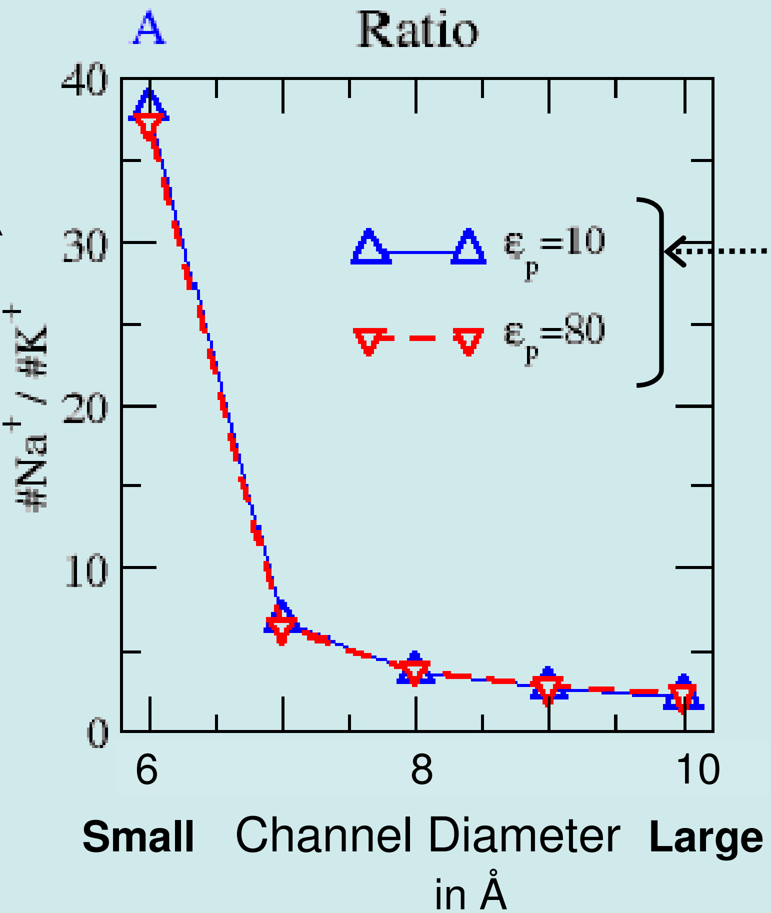
in the DEKA Na Channel

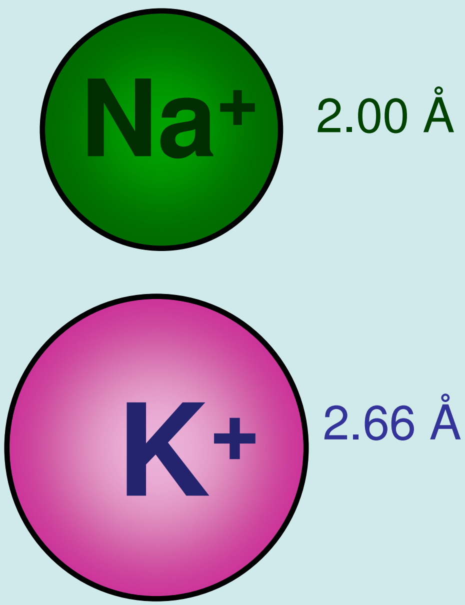
<u>Nothing was changed</u> *in the model*

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









Boda, et al

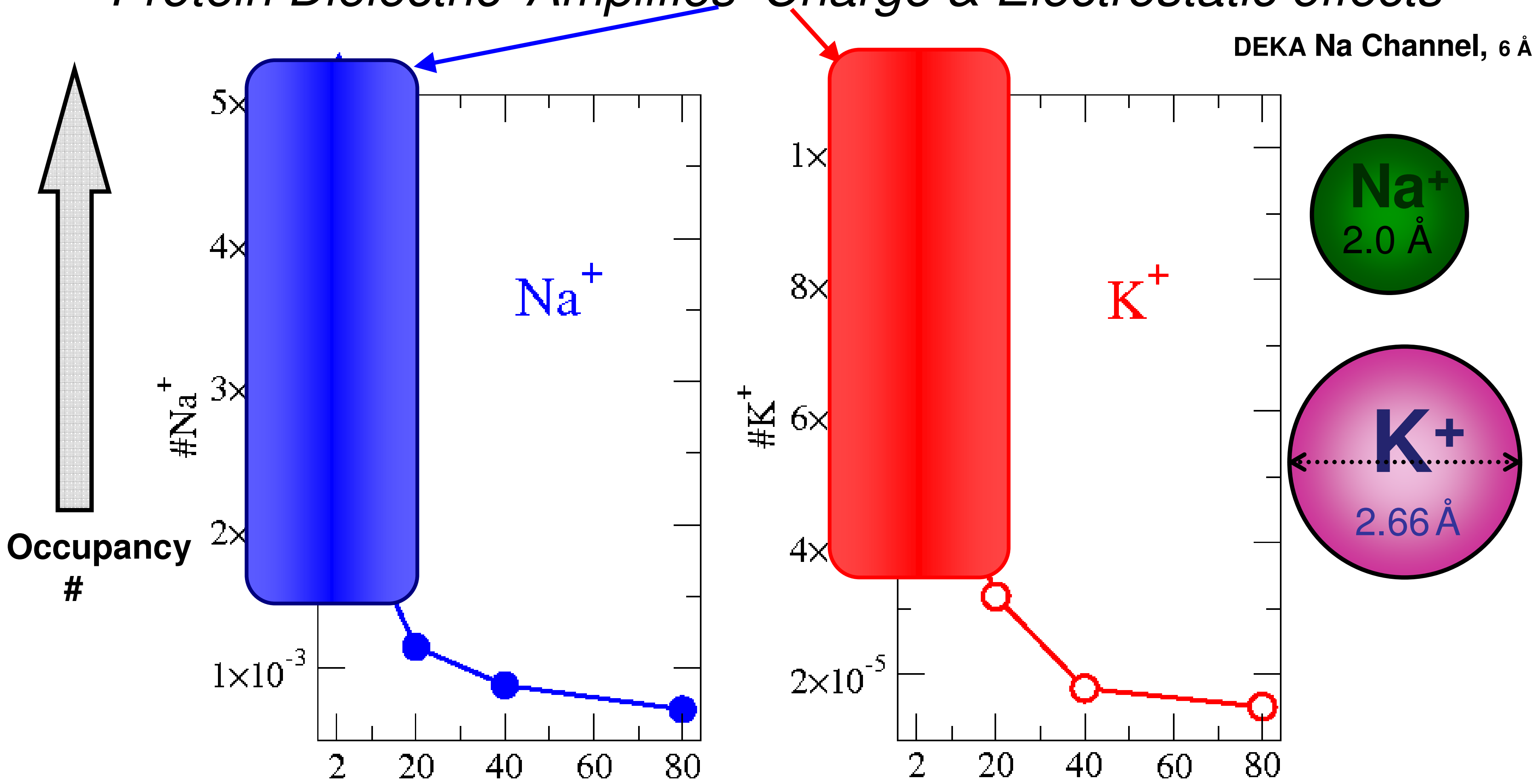
in **DEKA** 6Å Na Channel

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



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

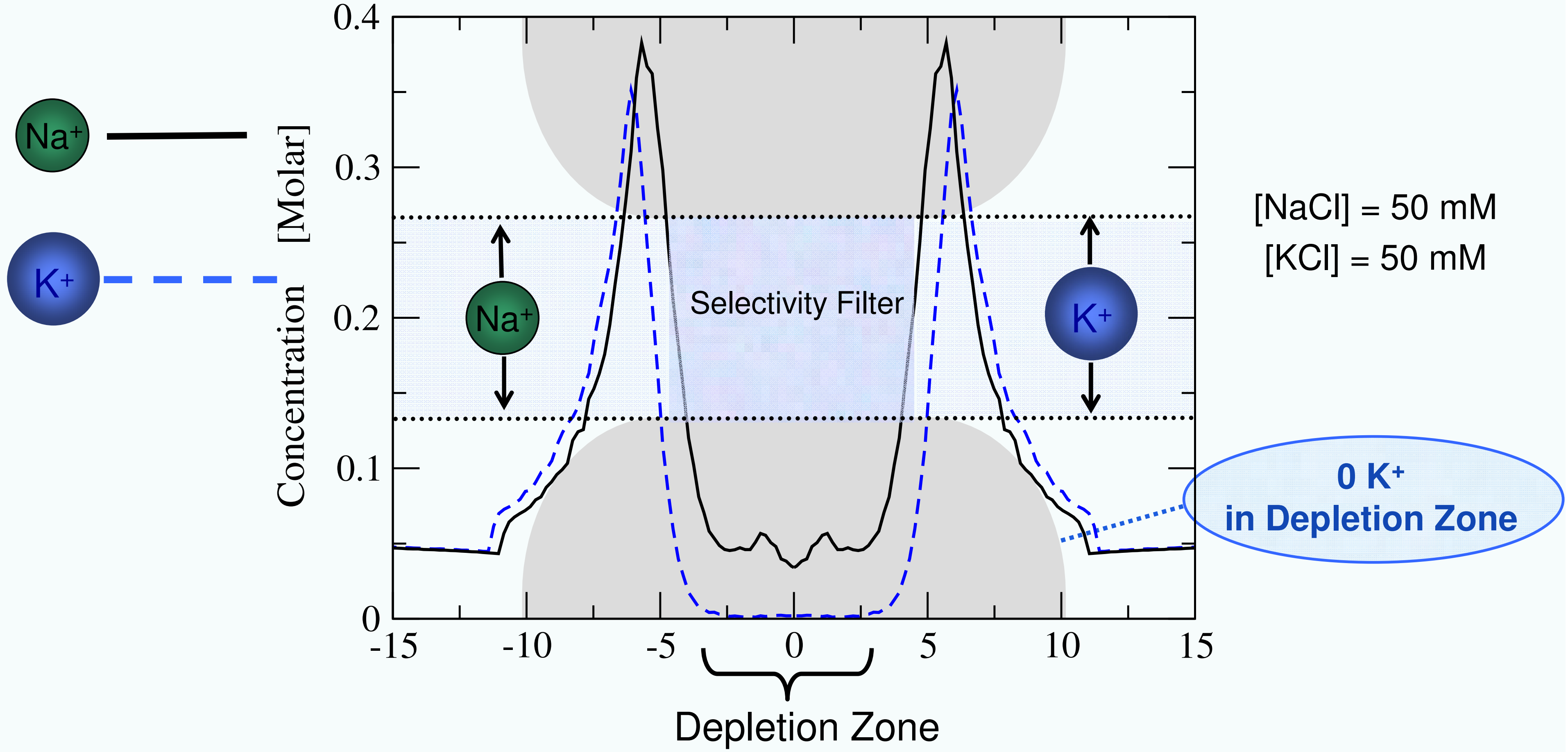
$\varepsilon_{solvent} = 80$

Boda, et al

Selectivity is in the Depletion Zone not the binding site

Size Selectivity is in the Depletion Zone

Na^+ *vs.* K^+ Occupancy



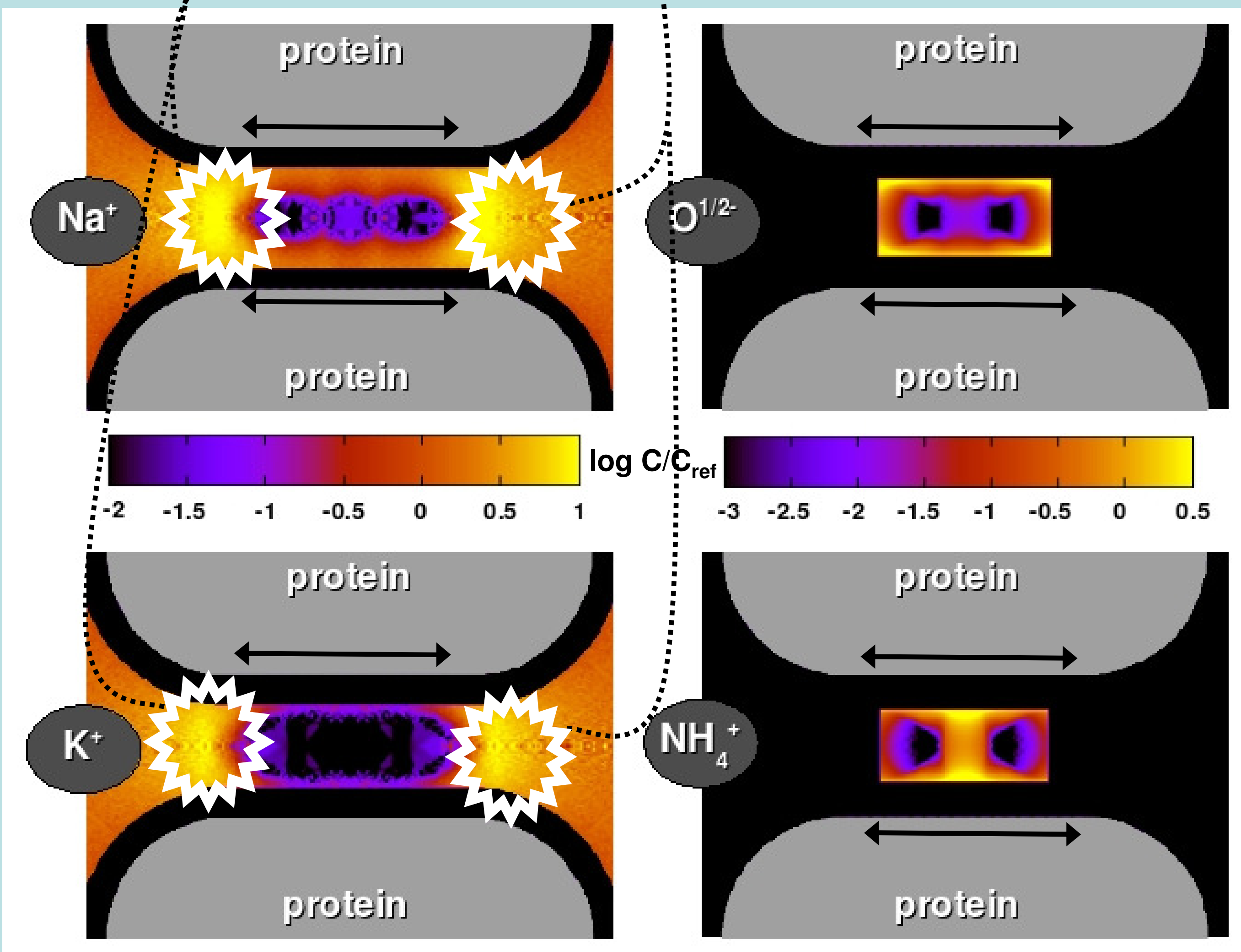
of the **DEKA** Na Channel, **6 Å**

Boda, et al

Size Selectivity

Binding Sites*

Size Selectivity



*Binding Sites are outputs of our model, ***not*** *structural inputs*

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*	

[NaCl] = [KCl] = 50 mM

BLACK = Depletion=0

Boda, et al

Na vs K Size Selectivity is in Depletion Zone

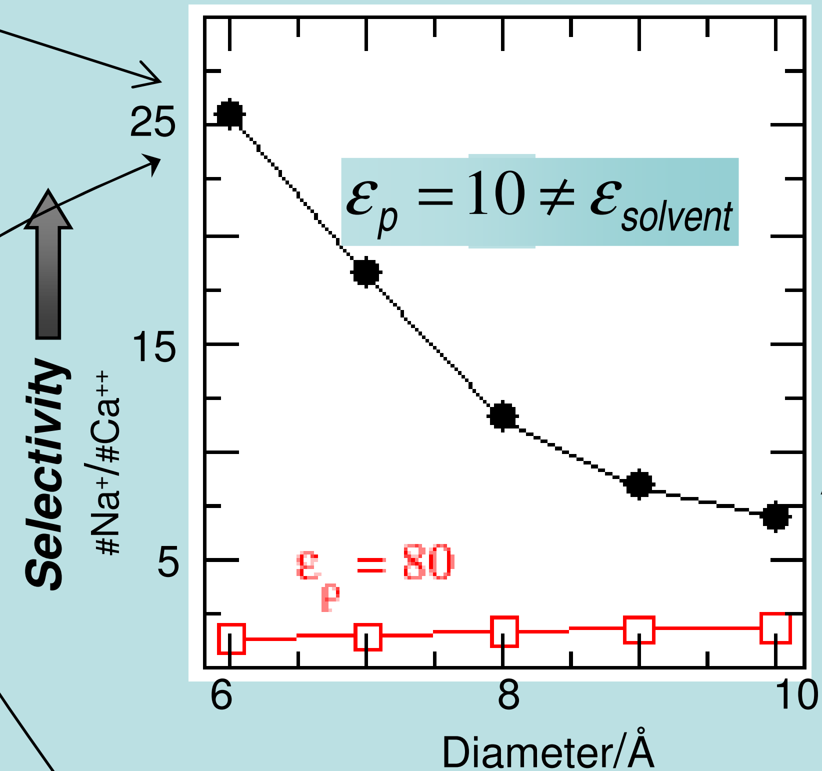
Charge Selectivity

<u>Charge</u> Selectivity Na^+ *vs* Ca^{++}
Depends on Dielectric

Dielectric Boundary Force = DBF

***Small Size** and*
Large Dielectric Boundary Force

DEKA Na Channel, 6 Å



Na+ 2.0 Å

Ca++ 1.98 Å

<u>Dielectric is a Charge Amplifier</u>

$$DBF = f\left(\frac{\varepsilon_{solvent} - \varepsilon_{protein}}{\varepsilon_{solvent} + \varepsilon_{protein}} Q_{ion}^2\right)$$

<u>Large</u> Dielectric Boundary Force

$\varepsilon_{\mathbf{protein}} \neq \varepsilon_{\mathbf{solvent}}$

<u>Zero</u> Dielectric Boundary Force

$\varepsilon_{\mathbf{protein}} = \varepsilon_{\mathbf{solvent}}$

Small Size ⟹ Greater Charge Selectivity

Boda et al