TIMS National Taiwan University

A Poisson-Fermi Theory for Biological Ion Channels: Models and Methods

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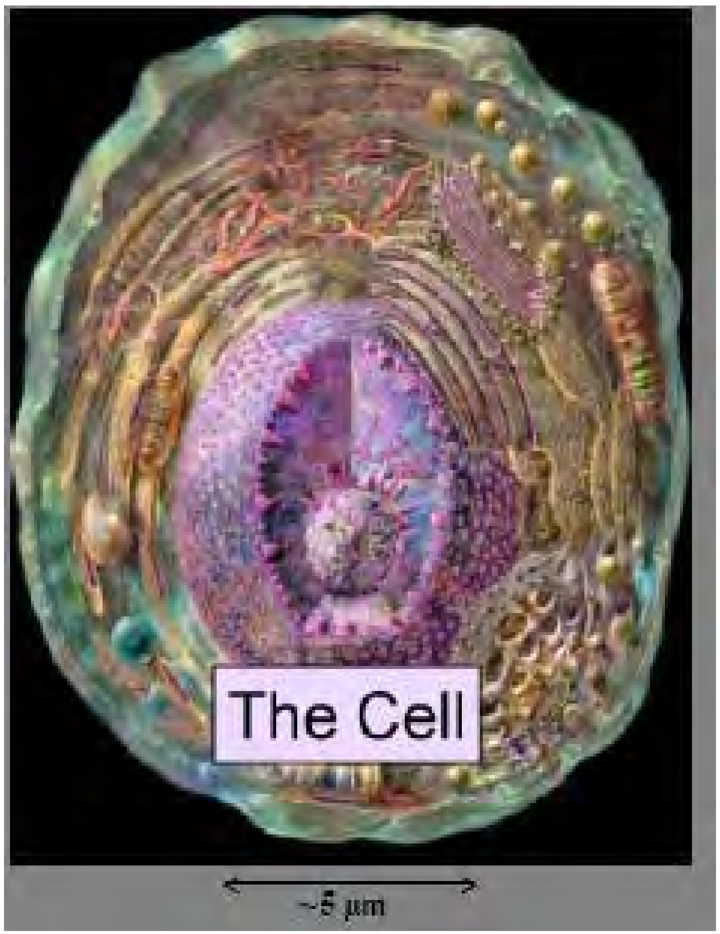
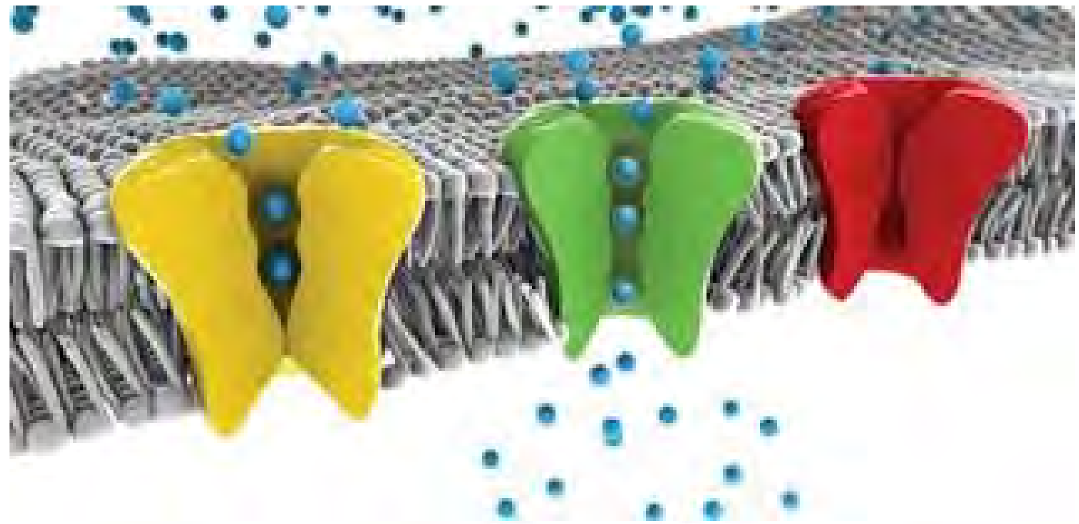
Outline

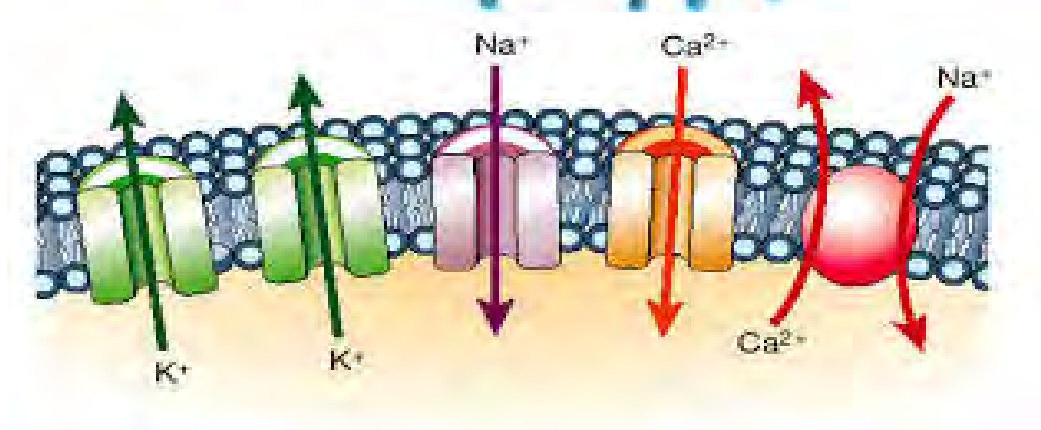
- Ion Channel
- Poisson-Fermi & Nernst-Planck
- Numerical Methods
- Results
- Outlook

Ion Channel

Biological ion channels seem to be a precondition for all living matter.







A. L. Hodgkin & A. Huxley
(Nobel Prize in Physiology or Medicine 1963)
for their discoveries concerning " the ionic mechanisms in the nerve cell membrane ".
(Action Potential)

Hypothesized
Ion Channel

E. Neher & B. Sakmann
(Nobel Prize in Physiology or Medicine 1991)
for their discoveries concerning "the function of single ion channels in cells". (Current Measurement)

Confirmed
Ion Channel

P. Agre & R. MacKinnon
(Nobel Prize in Chemistry 2003)
for their discoveries concerning "channels in cell membranes". (Crystal Structures)

Saw
Ion Channel

Poisson-Fermi*-Nernst*-Planck* (Steric & Correlation)

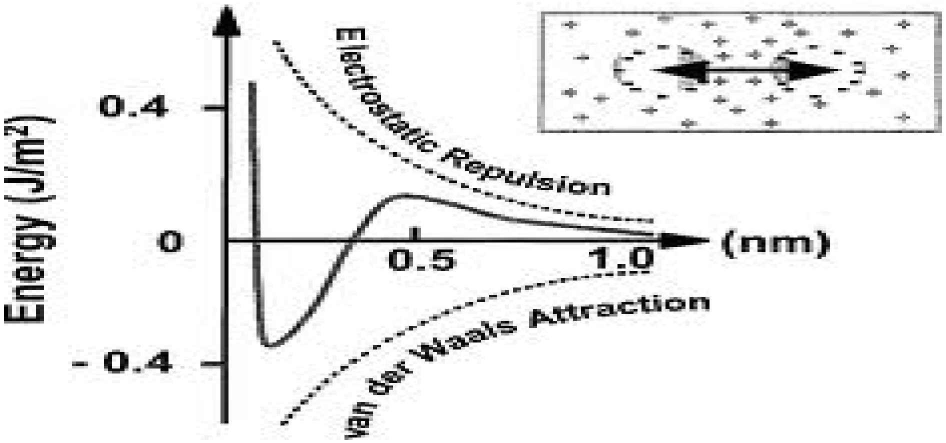
Steric & Correlation in Poisson-Boltzmann: 100-Year Old Problems since Gouy (1910) & Chapman (1913)

Historical Developments: Bjerrum (1918), Debye*-Huckel (1923), Stern* (1924), Onsager * (1936), Kirkwood (1939), Dutta-Bagchi (1950), Grahame (1950), Eigen*-Wicke (1954), Borukhov-Andelman-Orland (1997), Santangelo (2006), Eisenberg-Hyon-Liu (2010), Bazant-Storey-Kornyshev (2011), Wei-Zheng-Chen-Xia (2012)

* Nobel Laureates

Steric Effects

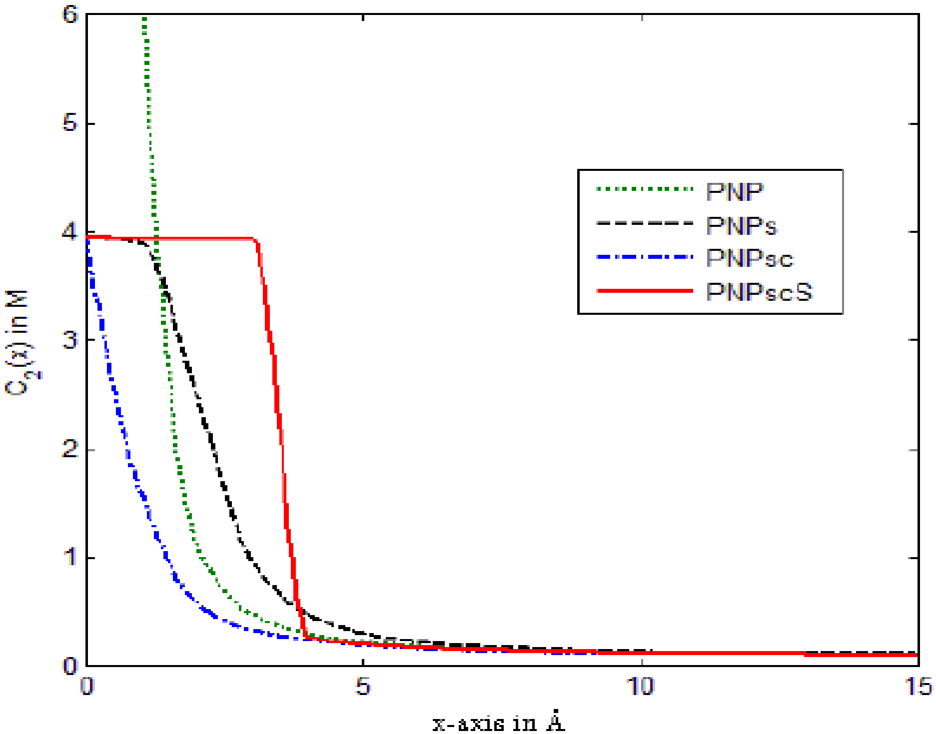
Steric effects arise from the fact that each atom within a molecule occupies a certain amount of space. (Wiki)



Steric stabilization

Electrostatic stabilization

Steric Effects



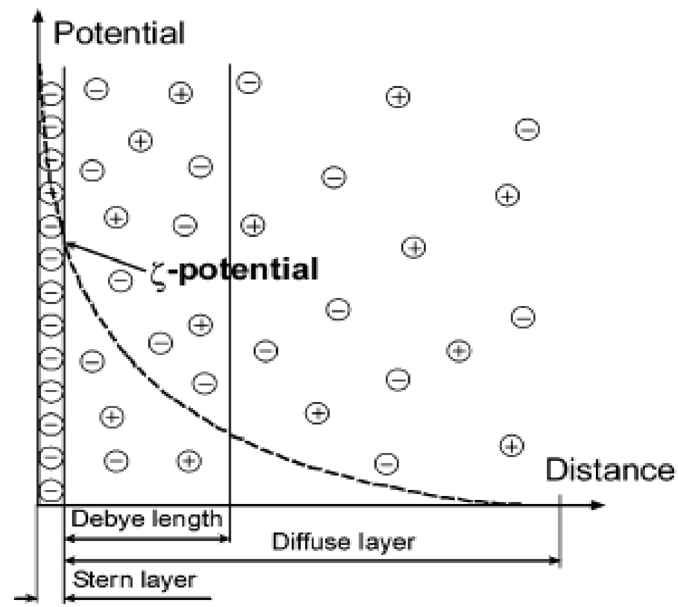


Figure 1. Definitions of Stern layer, Debye length, diffuse layer, and ζ potential. ⊖, positive ion; ⊕, negative ion and potential distribution.

Boltzmann => Infinity => Unphysical
Fermi => Finite => Saturation

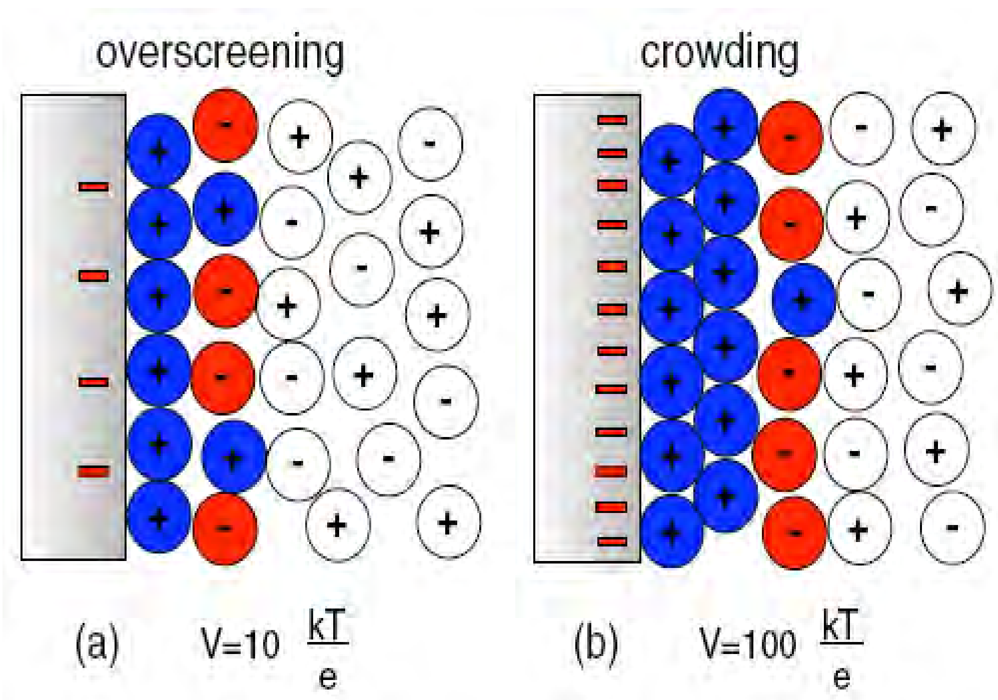
Correlation Effects

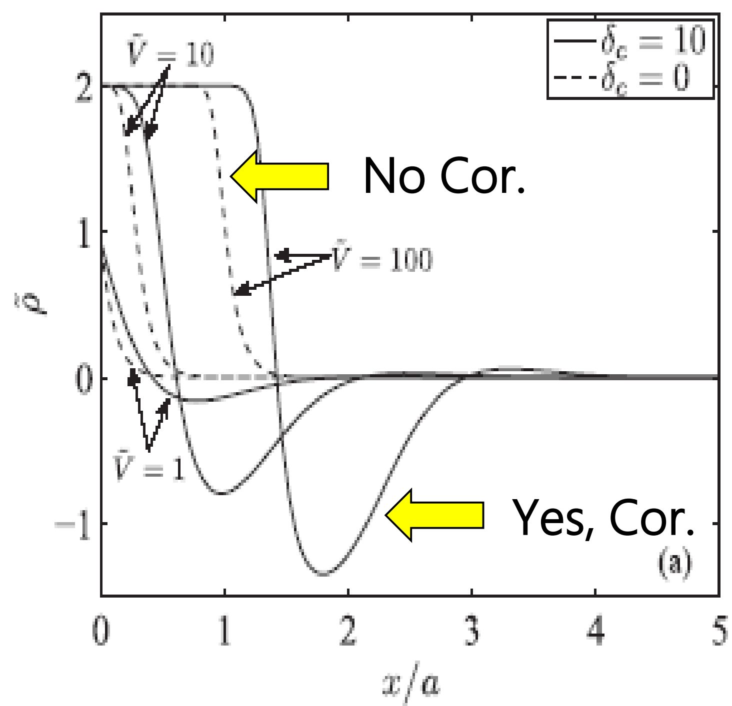
Bazant, Storey, Kornyshev (PRL 2011)

PRL 106, 046102 (2011) PHYSICAL REVIEW LETTERS week ending 28 JANUARY 2011

Double Layer in Ionic Liquids: Overscreening versus Crowding

Martin Z. Bazant,[1] Brian D. Storey,[2] and Alexei A. Kornyshev[3]





Fermi Distribution (Steric)

Borukhov-Andelman-Orland (PRL 1997)

Blow Up?

The entropic contribution $-TS$ is

$$-TS = \frac{k_B T}{a^3} \int d\mathbf{r}[c^+ a^3 \ln(c^+ a^3) + c^- a^3 \ln(c^- a^3) + (1 - c^+ a^3 - c^- a^3) \times \ln(1 - c^+ a^3 - c^- a^3)], \quad (2)$$

$$F = U - TS$$

$$c^-(\mathbf{r}) \to \frac{1}{a^3} \frac{1}{1 + (z+1)\frac{1-\phi_0}{\phi_0} e^{-z\beta e\psi}}$$

Fermi Like Dist.

Problems: 1. Single Size (Same *a*) for all Ions

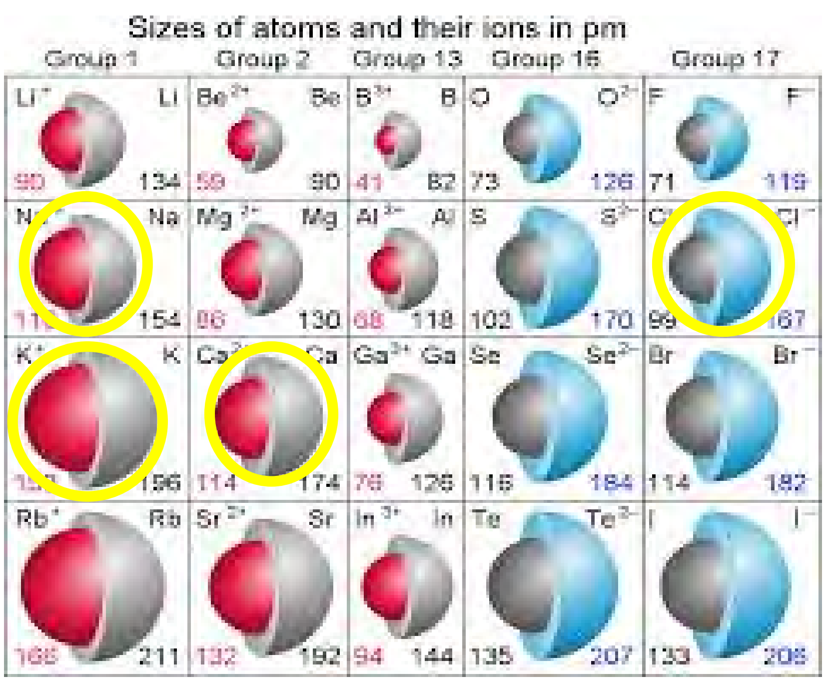
2. Energy functional blows up as *a* goes to 0 (phenomenological or analytical?)

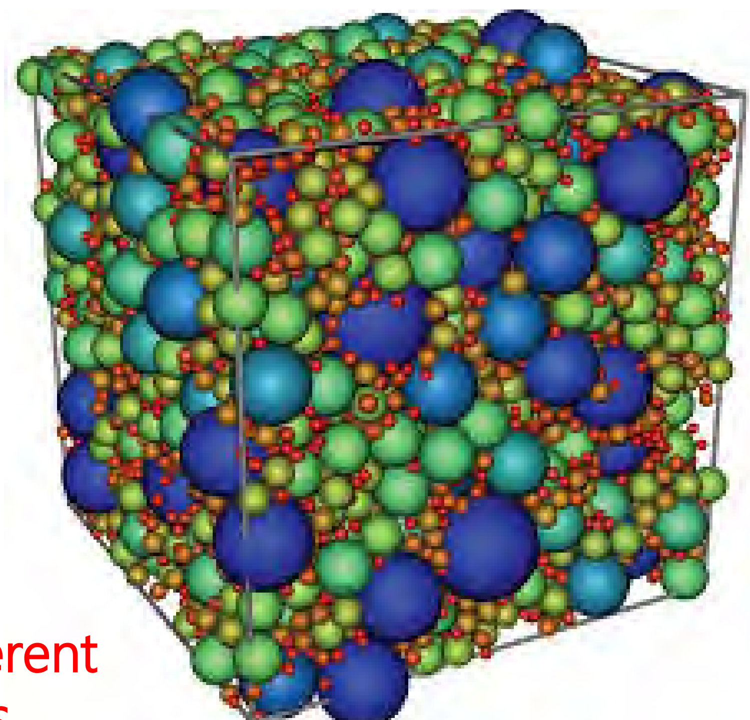
Bazant, Storey, Kornyshev (PRL 2011)

Free Energy of Electrolyte Solutions

$$F = \phi \sum_{j=1}^{K} q_j N_j - k_B T \ln W \qquad W = \prod_{j=1}^{K} W_j = \frac{N!}{(\Pi_{j=1} N_j!)(N - \sum_{j=1}^{K} N_j)!}$$

$$W_1 = N!/(N_1!(N - N_1)!)$$





different sizes

Global Electrochemical Potential

$$\mu_i = \frac{\partial F}{\partial N_i} = q_i\phi + k_B T \ln \frac{N_i/N}{1 - \sum_{j=1}^{K} N_j/N}$$

Global Probabilities

Local Electrochemical Potential

$$\mu_i = q_i\phi(\mathbf{r}) + k_B T \ln \frac{v_i C_i(\mathbf{r})}{1 - \sum_{j=1}^{K} v_j C_j(\mathbf{r})}$$

Local Probabilities

Water Probability New

$$v_{K+1} C_{K+1}$$

Fermi Distribution

$$C_i = \frac{C_i^{\mathrm{B}} \exp\left(-\beta_i \phi\right)}{1 - \sum_{j=1}^{K} v_j C_j^{\mathrm{B}}} \left(1 - \sum_{j=1}^{K} v_j C_j\right) = C_i^{\mathrm{B}} \exp\left(-\beta_i \phi + S_{\mathrm{trc}}\right)$$

New

$$F = \phi \sum_{j=1}^{K} q_j N_j - k_B T \ln W$$

Fermi Distribution

$$C_i = \frac{C_i^{\mathrm{B}} \exp(-\beta_i \phi)}{1 - \sum_{j=1}^{K} v_j C_j^{\mathrm{B}}} \left(1 - \sum_{j=1}^{K} v_j C_j \right) = C_i^{\mathrm{B}} \exp(-\beta_i \phi + S_{\mathrm{trc}})$$

different valences

$$\beta_i = \frac{z_i e}{k_B T}$$

Steric Functional

$$S_{\mathrm{trc}} = \ln\left[\left(1 - \sum_{j=1}^{K} v_j \underline{C_j}\right) \Big/ \left(1 - \sum_{j=1}^{K} v_j C_j^{\mathrm{B}}\right) \right]$$

different sizes

Saturation Condition

New

$$\text{Fermi: } C_i \le \frac{1}{v_i} = C_i^{\mathrm{Max}}, \quad \text{Boltzmann: } C_i = \infty \;\text{ as }\; |\phi| \to \infty$$

Liu-Eisenberg (2013 JPC) improves
Borukhov- Andelman-Orland (1997 PRL)

$$F = \phi \sum_{j=1}^{K} q_j N_j - k_B T \ln W$$

4th-Order Poisson Eq. (Correlation)

Santangelo (PRE 2006)

$$\epsilon\left(l_c^2\nabla^2 - 1\right)\nabla^2\phi = \rho_0 + \sum_i e z_i C_i = \rho$$

$$\rho_0(\mathbf{r}) = \sum_{j=1}^{N_A} q_j \delta(\mathbf{r} - \mathbf{r}_j) \qquad C_i = C_i^{\mathrm{B}} \exp\left(-\beta_i \phi + S_{\mathrm{trc}}\right)$$

$\epsilon = \epsilon_s\epsilon_0$ in Ω_s, $\epsilon = \epsilon_m\epsilon_0$ in Ω_m. ϵ_s, ϵ_m: Dielectric Constants

$l_c \neq 0$ in Ω_s, $l_c = 0$ in Ω_m: Correlation Length (Parameter)

$\hat{\epsilon} = \epsilon(1 - l_c^2\nabla^2)$: **Dielectric Operator**

Cahn-Hilliard: $D\nabla^2(\gamma\nabla^2 C - C^3 + C) = 0$

4th-Order Poisson Eq. (Correlation)

$$H = \frac{1}{2}\int d\mathbf{r}d\mathbf{r}'\rho(\mathbf{r})\left[V_s(\mathbf{r}-\mathbf{r}') + V_l(\mathbf{r}-\mathbf{r}')\right]\rho(\mathbf{r}')$$

$$\rho(\mathbf{r}) = \sigma(\mathbf{r})/z - \delta(\mathbf{r}-\mathbf{r}')q'$$

$\sigma(\mathbf{r})$: Surface Chage Density, $q' = ze$: Ion Charge

$$V(\mathbf{r}) = V_s(\mathbf{r}) + V_l(\mathbf{r}) = \frac{l_B z^2}{r}e^{-r/l_c} + \frac{l_B z^2}{r}(1 - e^{-r/l_c}) = -\frac{l_B z^2}{r}$$

$l_B = e^2/4\pi\epsilon kT$: Bjerrum Length

$l_c = l_B z^2$: Correlation Length

$H \Rightarrow$ Hubbard-Stratonovich Trasformation $\Rightarrow$ Long Range Action

$$\Rightarrow S_l = \frac{1}{l_B}\int d\mathbf{r}\left[\frac{1}{2}(\nabla\phi)^2 + \frac{l_c^2}{2}(\nabla^2\phi)^2\right]$$

$$\epsilon\left(l_c^2\nabla^2 - 1\right)\nabla^2\phi = \rho_0 + \sum_i e z_i C_i = \rho$$

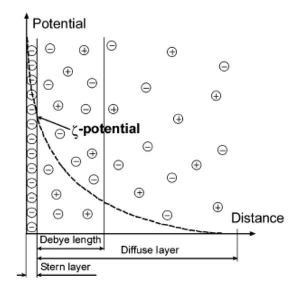


Figure 1. Definitions of Stern layer, Debye length, diffuse layer, and ζ potential. ⊖, positive ion; ⊕, negative ion and potential distribution.

2^{nd}-Order Poisson-Fermi Eqs

Liu (JCoP 2013)

$$\begin{cases} \epsilon_s \left(l_c^2 \nabla^2 - 1 \right) \Psi = \rho \\ \nabla^2 \phi = \Psi \end{cases}$$

New

$$\text{PB:} \ -\epsilon_s \nabla^2 \phi = \rho \Leftarrow \Psi = -\nabla \cdot \mathbf{E}$$

Charge Neutrality → Boundary Conditions

$$\text{Maxwell:} \ \epsilon_s \nabla \cdot \mathbf{E} = \rho - \nabla \cdot \mathbf{P}$$

$$\eta = -\nabla \cdot \mathbf{P} = -\epsilon_s \Psi - \rho\text{: Polarization Charge Density}$$

$$\widetilde{\epsilon}(\mathbf{r}) \approx \frac{\epsilon_s}{1 + \eta(\mathbf{r})/\rho(\mathbf{r})}\text{: Dielectric Function}$$

New

$$\epsilon \left(l_c^2 \nabla^2 - 1 \right) \nabla^2 \phi = \rho_0 + \sum_i e z_i C_i = \rho \qquad \hat{\epsilon} = \epsilon \left(1 - l_c^2 \nabla^2 \right)\text{: Dielectric Operator}$$

Poisson-Fermi-Nernst-Planck Model

$$-\epsilon\left(l_c^2\nabla^2 - 1\right)\nabla^2\phi = \rho_0 + \sum_i e z_i C_i = \rho$$

$$\frac{\partial C_i}{\partial t} = -\nabla \cdot \mathbf{J}_i,\ \mathbf{J}_i = -D_i(\nabla C_i + \beta_i C_i \nabla\phi - \underbrace{C_i \nabla S_{\text{stc}}}_{\text{New}})$$

New

$$S_{\text{trc}} = \ln\left[\left(1 - \sum_{j=1}^{K} v_j C_j\right) \Big/ \left(1 - \sum_{j=1}^{K} v_j C_j^{\text{B}}\right)\right]$$

Nernst-Planck implies Fermi in Equilibrium

$$\frac{\partial C_i}{\partial t} = -\nabla \cdot \mathbf{J}_i, \mathbf{J}_i = -D_i(\nabla C_i + \beta_i C_i \nabla \phi - C_i \nabla S_{\text{stc}})$$

$$\mathbf{J}_i = 0 \Rightarrow \nabla C_i + \beta_i C_i \nabla \phi - C_i \nabla S_{\text{trc}} = 0 \Rightarrow$$

$$\nabla \left[C_i \exp(\beta_i \phi - S_{\text{trc}}) \right] = 0$$

$$\exp(\beta_i \phi - S_{\text{trc}}) \nabla C_i + \exp(\beta_i \phi - S_{\text{trc}}) C_i \left[\beta_i \nabla \phi - \nabla S_{\text{trc}} \right] = 0$$

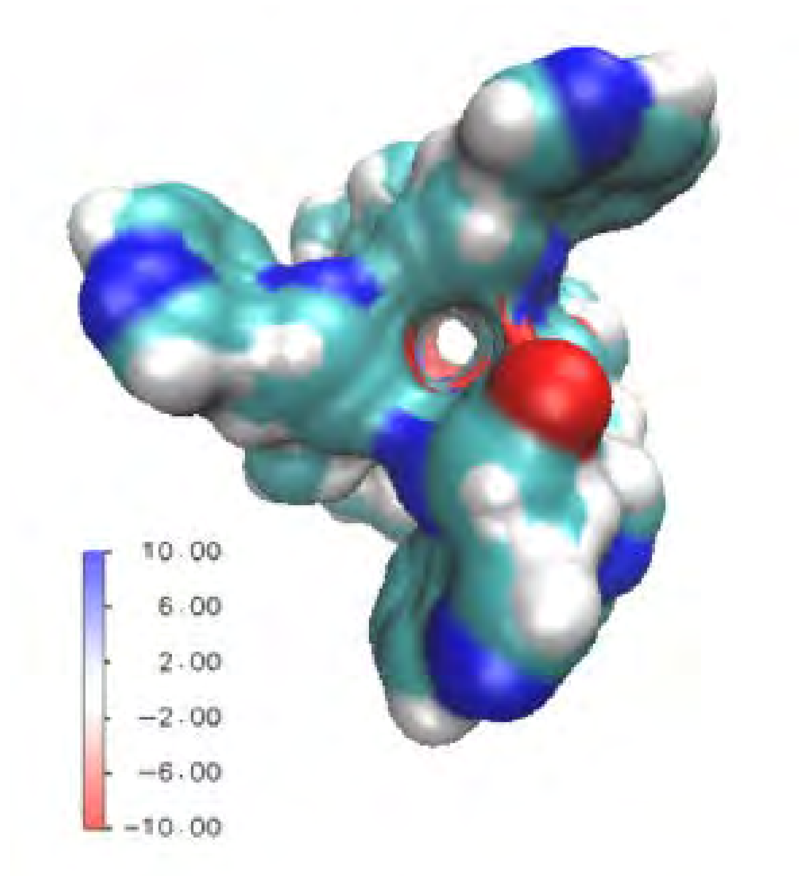
$$\nabla C_i + \beta_i C_i \nabla \phi - C_i \nabla S_{\text{trc}} = 0$$

$$C_i \exp(\beta_i \phi - S_{\text{trc}}) = \text{const} = C_i^{\text{B}} \Rightarrow$$

$$C_i = C_i^{\text{B}} \exp(-\beta_i \phi + S_{\text{trc}}) : \text{Fermi}$$

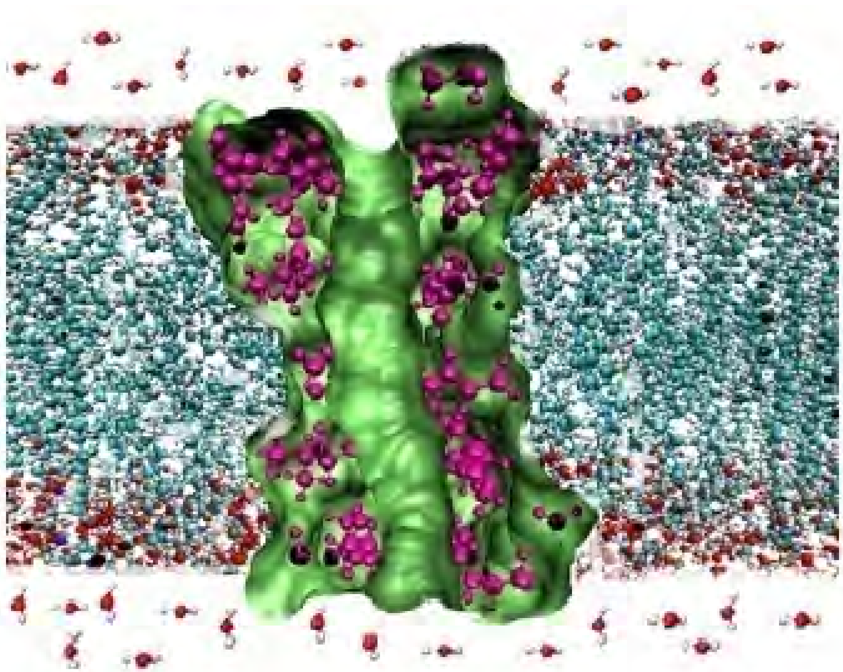
Numerical Methods

Gramicidin A (GA) Channel

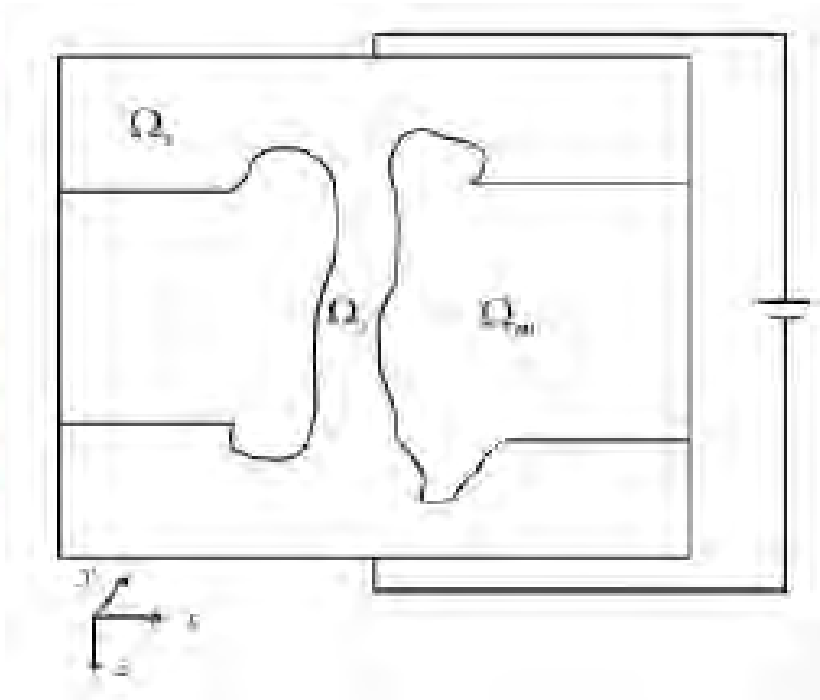


Simulation Domain

$$\text{Box} = \Omega = (-20\text{Å}, 20\text{Å}) \times (-20\text{Å}, 20\text{Å}) \times (-20\text{Å}, 20\text{Å})$$



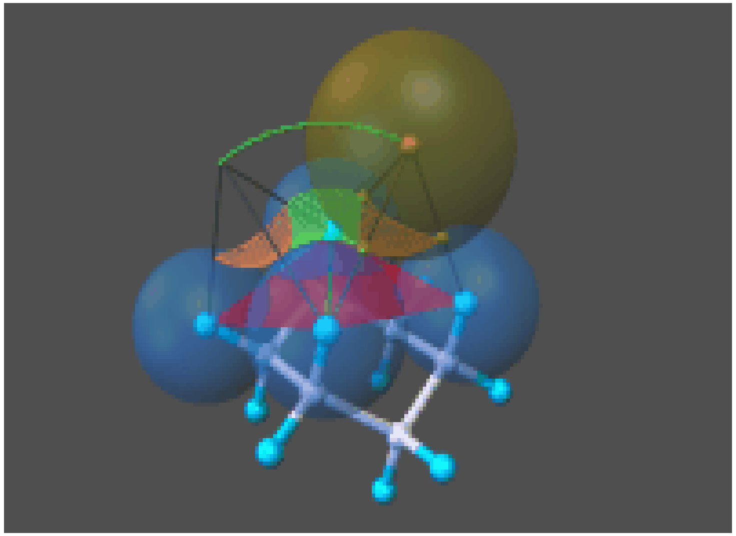
Zheng, Chen, Wei (JCoP 2011)



$$\rho_0(\mathbf{r}) = \sum_{j=1}^{N_A} q_j \delta(\mathbf{r} - \mathbf{r}_j)$$

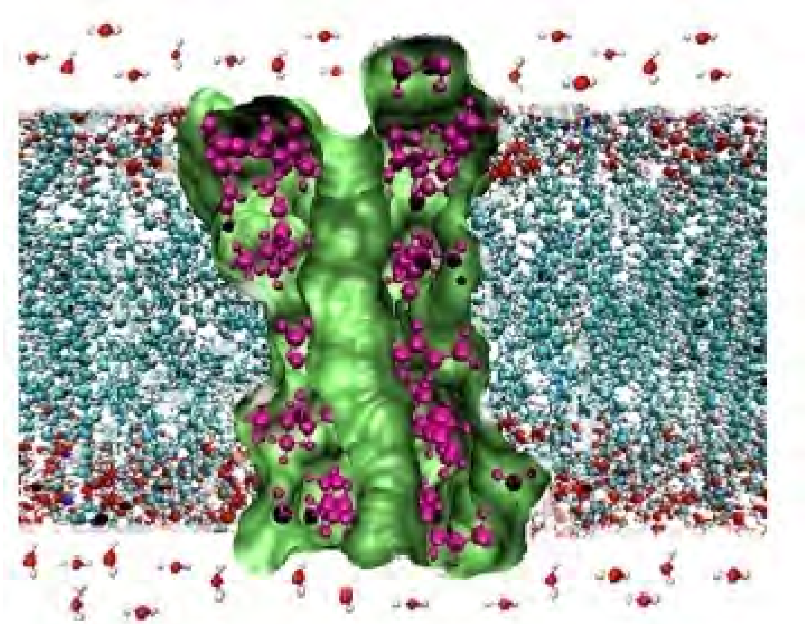
Molecular Surface

- Molecular Surface (MS) generated in 3D uniform grid by a probe ball



Rolling Ball Algorithm
Shrake-Rupley (1973)

Error: 1-3 Å²



Ball (Water) Radius: 1.4Å

Numerical Methods

- Rolling Ball Method for MS
- 7-Point Finite Difference Method
- Wei's Matched Interface and Boundary Method (MIB)
- Linear Solver: SOR
- Chern-Liu-Wang's Method for Singular Charges
- Newton's Method
- Continuity Method on Steric Functional and Correlation Length

Simplified MIB

$$-\frac{\partial}{\partial x}\left(\epsilon(x)\frac{\partial \phi(x)}{\partial x}\right) = f$$

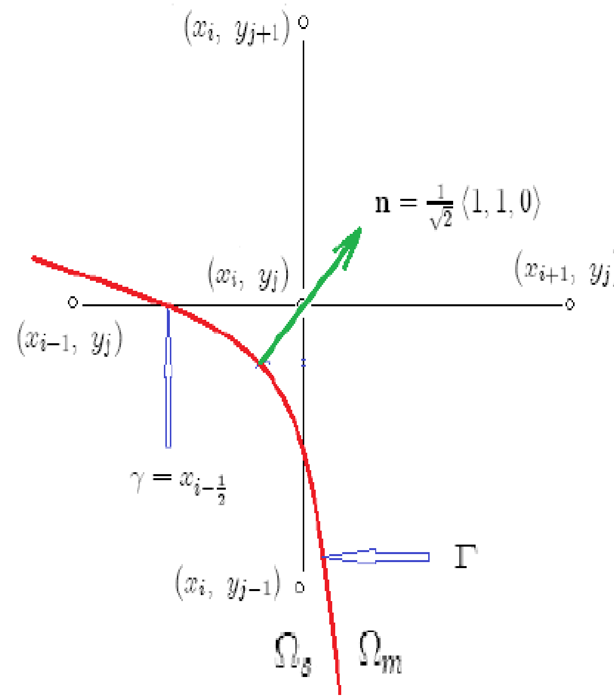
$$x_{i-1} < \gamma = x_{i-\frac{1}{2}} < x_i,$$

$$\frac{-\epsilon_{i-\frac{3}{2}}\phi_{i-2} + \left(\epsilon_{i-\frac{3}{2}} + (1-A_1)\epsilon^-_{i-\frac{1}{2}}\right)\phi_{i-1} - A_2\epsilon^-_{i-\frac{1}{2}}\phi_i}{\Delta x^2} = f_{i-1} + \frac{\epsilon^-_{i-\frac{1}{2}}A_0}{\Delta x^2}$$

$$\frac{-B_1\epsilon^+_{i-\frac{1}{2}}\phi_{i-1} + \left((1-B_2)\epsilon^+_{i-\frac{1}{2}} + \epsilon_{i+\frac{1}{2}}\right)\phi_i - \epsilon_{i+\frac{1}{2}}\phi_{i+1}}{\Delta x^2} = f_i + \frac{\epsilon^+_{i-\frac{1}{2}}B_0}{\Delta x^2},$$

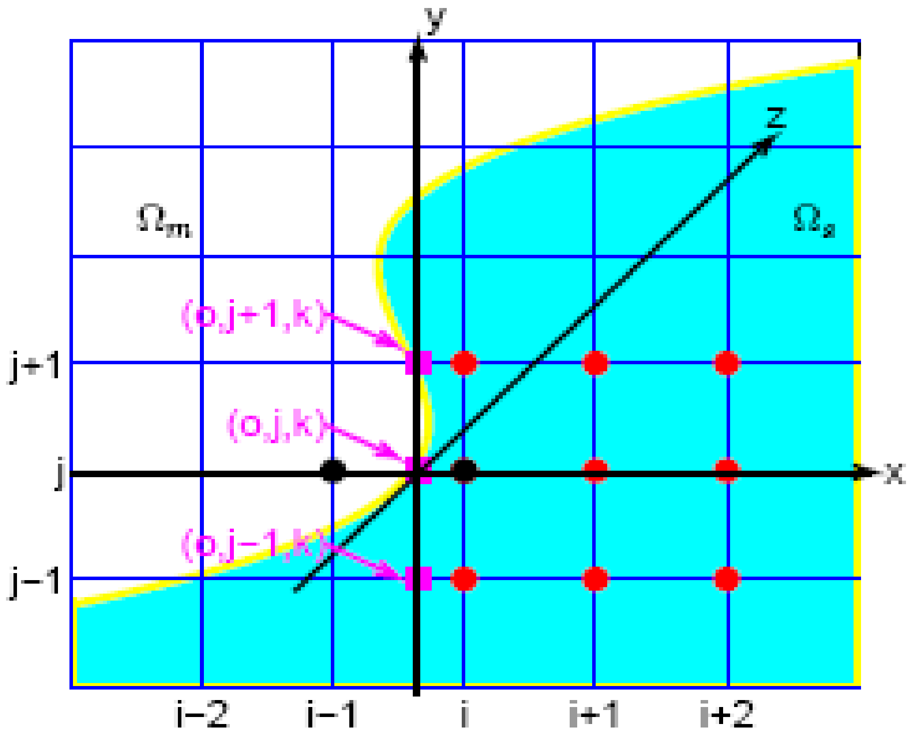
$$A_1 = \frac{-(\epsilon_m - \epsilon_s)}{\epsilon_m + \epsilon_s},\ A_2 = \frac{2\epsilon_m}{\epsilon_m + \epsilon_s},\ A_0 = \frac{-2\epsilon_m[\phi] - \Delta x[\epsilon\phi']}{\epsilon_m + \epsilon_s}$$

$$B_1 = \frac{2\epsilon_s}{\epsilon_m + \epsilon_s},\ B_2 = \frac{\epsilon_m - \epsilon_s}{\epsilon_m + \epsilon_s},\ B_0 = \frac{2\epsilon_s[\phi] - \Delta x[\epsilon\phi']}{\epsilon_m + \epsilon_s}.$$



Results (SMIB vs MIB)

MIB: Zheng, Chen, Wei (JCoP 2011)



MIB > 27-pt FDM

SMIB = 7-pt FDM

h= 0.25Å

Matrix Size = 4,096,000

MS Error: 1-3 Å^2

SMIB vs MIB (Ex)

Poisson Eq for GA Channel				
	SMIB		MIB	
h in Å	E_∞	Order	E_∞	Order
2.00	0.4466			
1.00	0.0922	2.28	0.1400	
0.50	0.0228	2.02	0.0271	2.36
0.25	0.0057	2.00	0.0152	0.84

SMIB is simpler, efficient, accurate but mid-point interface.

Ca channel pore radius is only ~1Å. May not have sufficient pts for high order MIB.

Order and Time of SMIB (Ex)

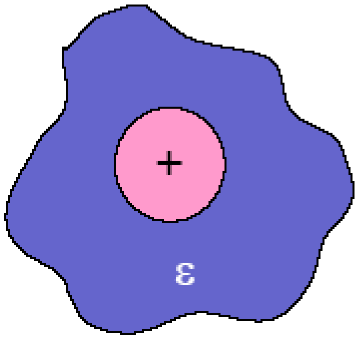
Nonlinear PNP for GA w. Exact Solutions & Singular Charges								
h in Å	P	Ord	NP1	Ord	NP2	Ord	Iter#	Time
2.00							∞	
1.00	0.0925		0.0327		0.0168		5	
0.50	0.0228	2.02	0.0074	2.14	0.0037	2.18	4	4m20s
0.25	0.0057	2.00	0.0018	2.04	0.0009	2.04	4	37m44s

Born Ion Model (Ex)
Classic Example of Solvation

$$\Delta G_{\text{Ex}} = \frac{q^2}{8\pi\epsilon_0 a}\left(\frac{1}{\epsilon_{\text{W}}} - \frac{1}{\epsilon_{\text{V}}}\right) = -81.98 \quad [\text{kcal/mol}]$$

Table 4.2. ΔG				
h (Å)	PBEQ	APBS	MIBPB	SMIB
1.000	-83.57	-83.44	-81.95	-82.06
0.500	-85.78	-85.85	-81.98	-81.98
0.250	-82.84	-82.58	-81.98	-81.98
0.125	-82.49	-82.27	-81.98	-81.98

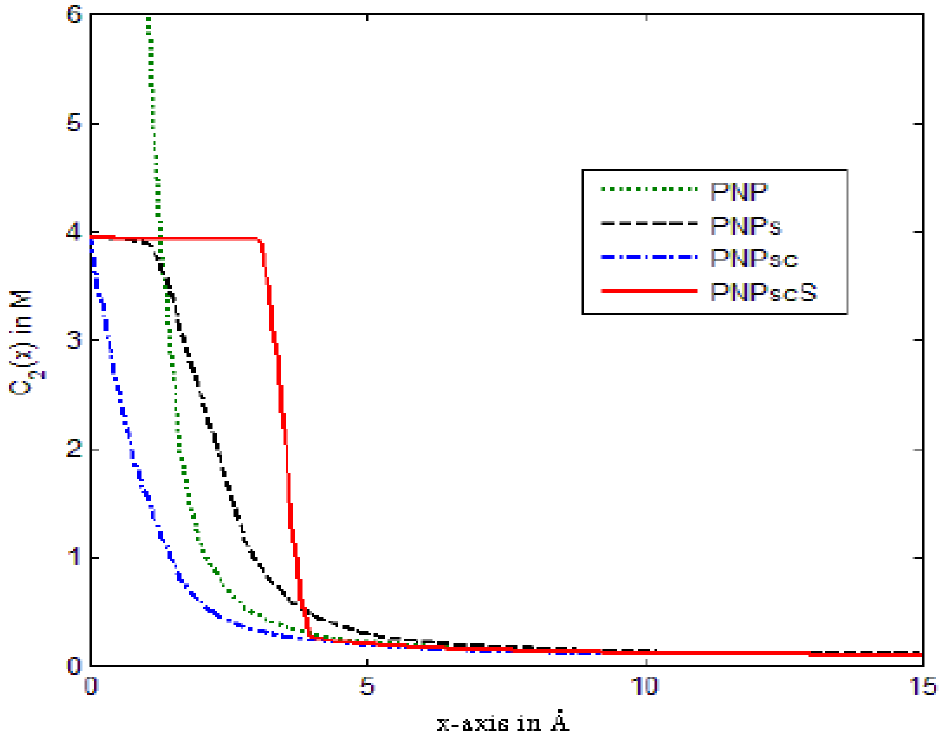
$\epsilon_m = 1,\ \epsilon_s = 80$



$a = 2.0$ Å $\quad q_1 = +e$

MIBPB: Geng, Yu, Wei (JChP 2007)

Charged Wall Models



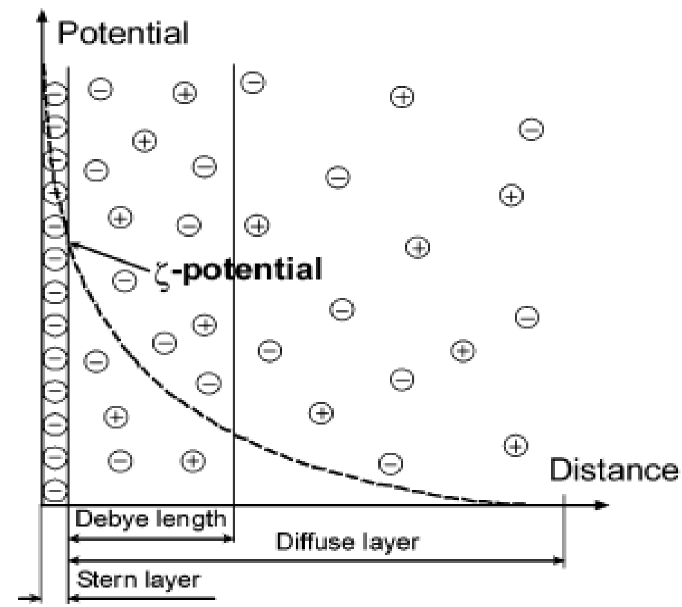
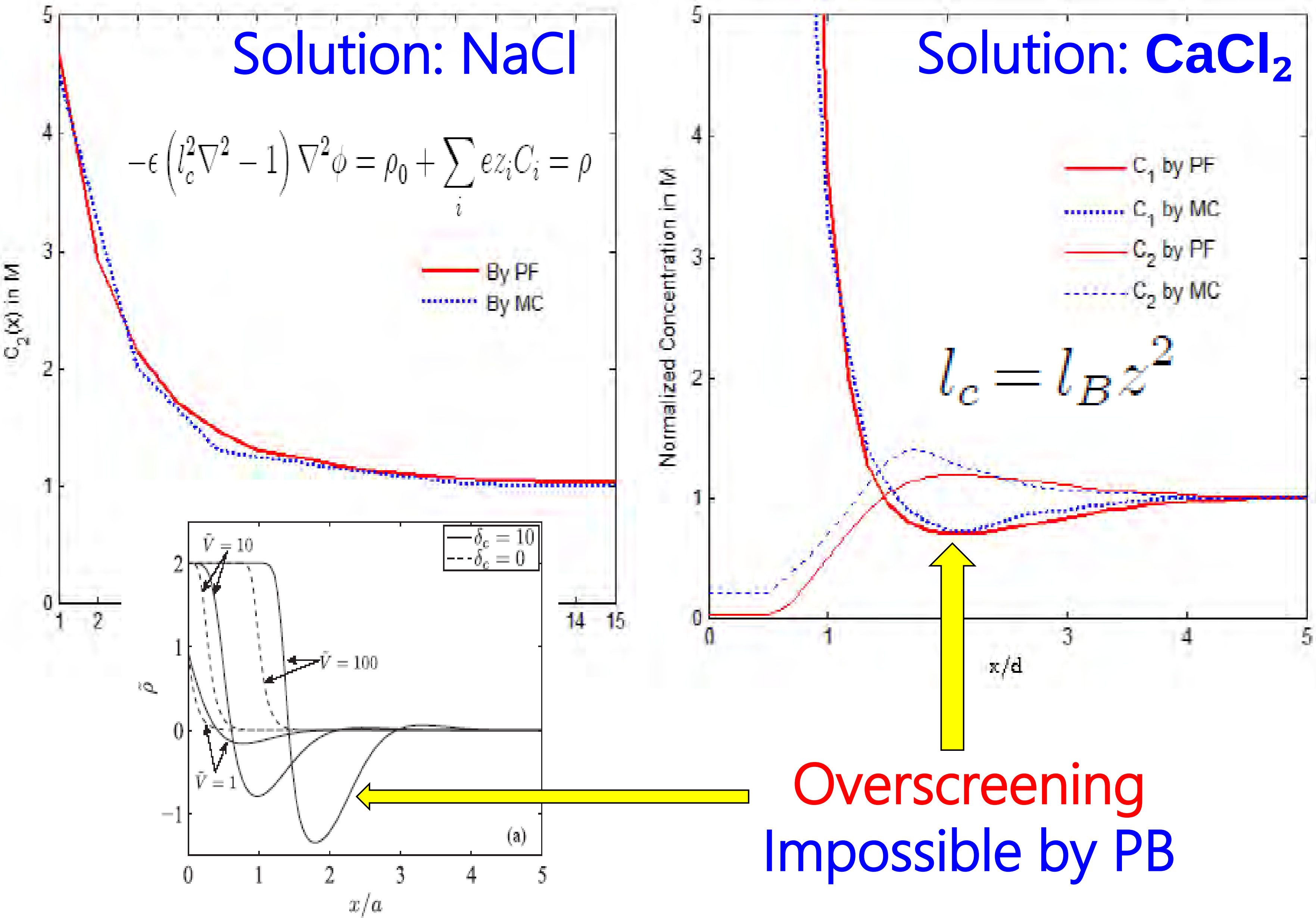


Figure 1. Definitions of Stern layer, Debye length, diffuse layer, and ζ potential. ⊖, positive ion; ⊕, negative ion and potential distribution.

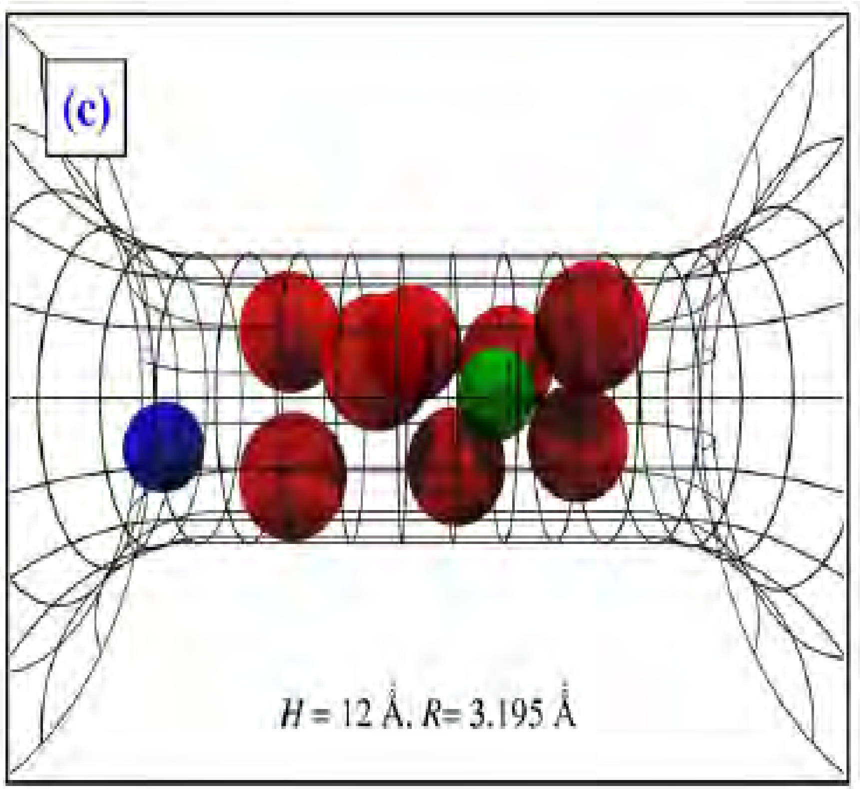
$$\text{Fermi: } C_i \leq \frac{1}{v_i} = C_i^{\text{Max}}, \quad \text{Boltzmann: } C_i = \infty \ \text{ as } \left|\phi\right| \to \infty$$

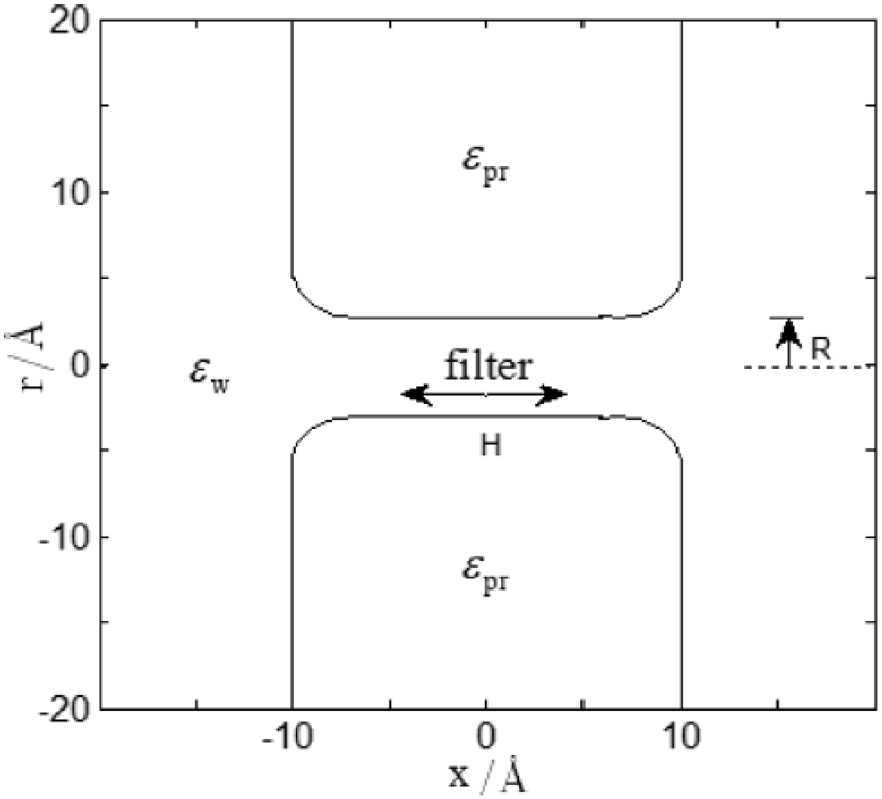
Charged Wall Models (MC)



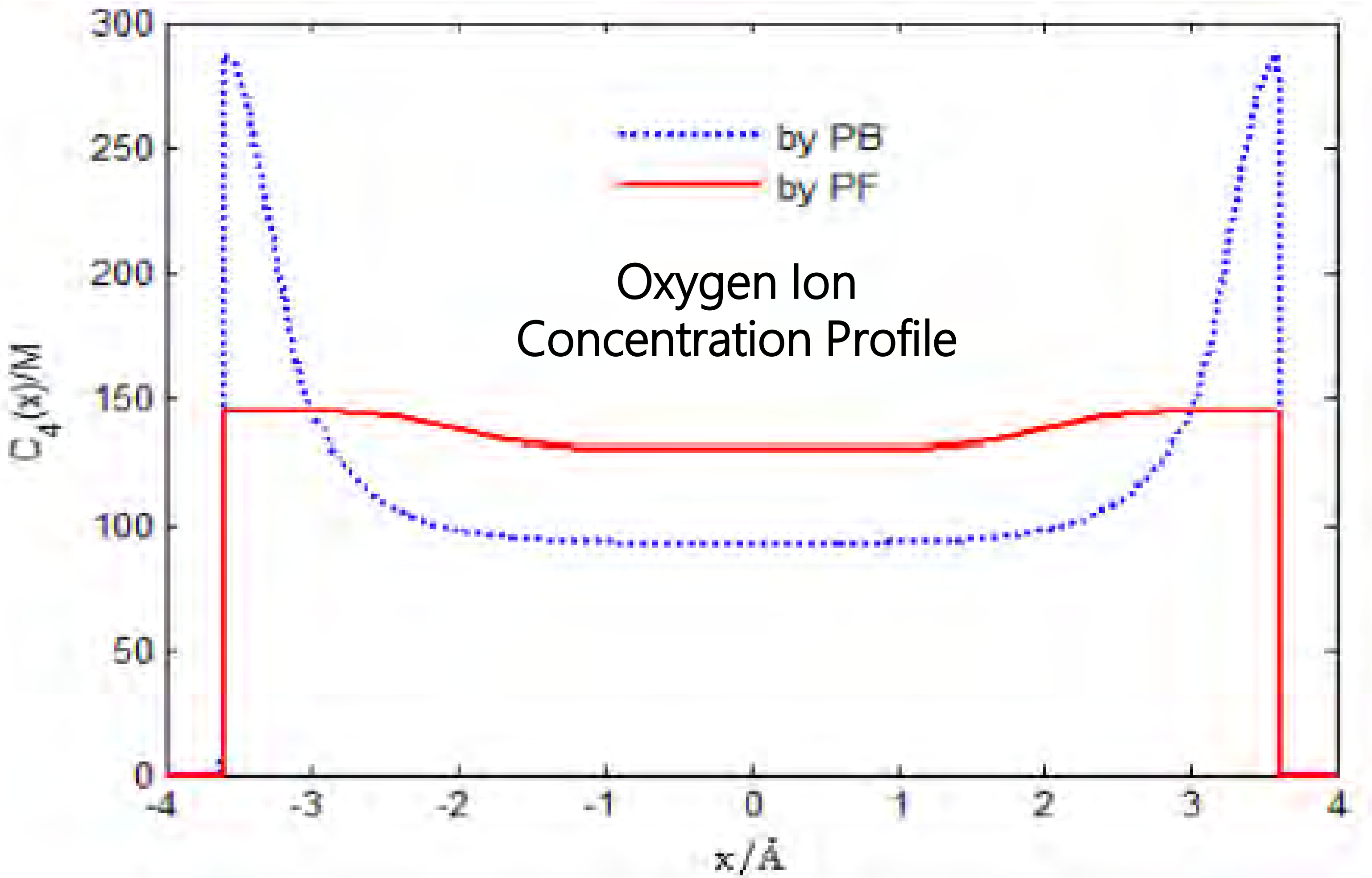
L-Type Ca Channel Model 1

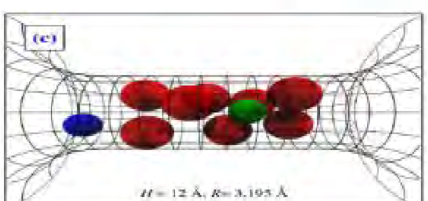
Boda, Valiskó, Henderson, Eisenberg, Gillespie, Nonner (JGenPhysio 2009)



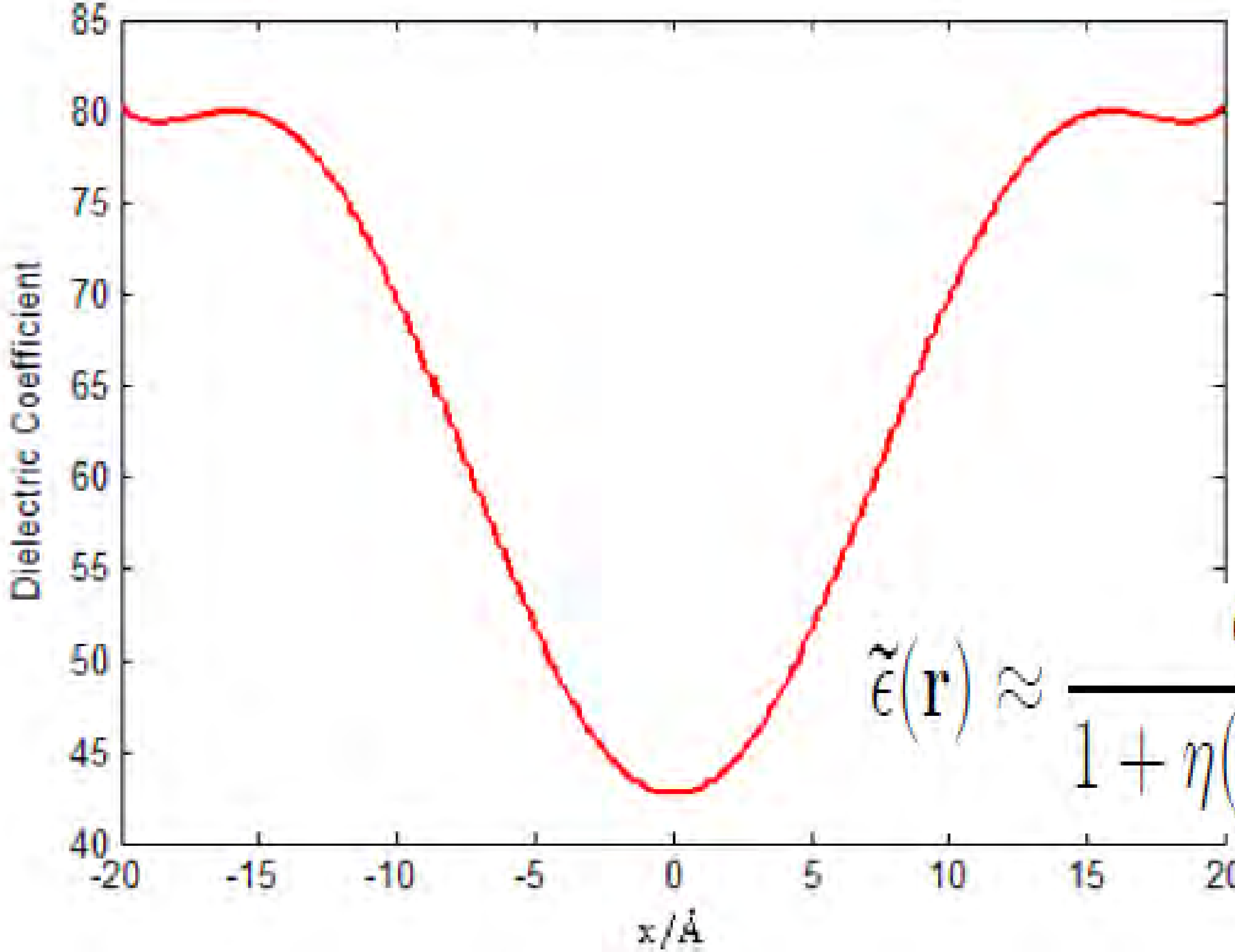


PF vs PB


300
250
200
150
100
50
0
-4
-3
-2
-1
0
1
2
3
4
$C_4(x)$/M
x / Å
by PB
by PF
Oxygen Ion
Concentration Profile

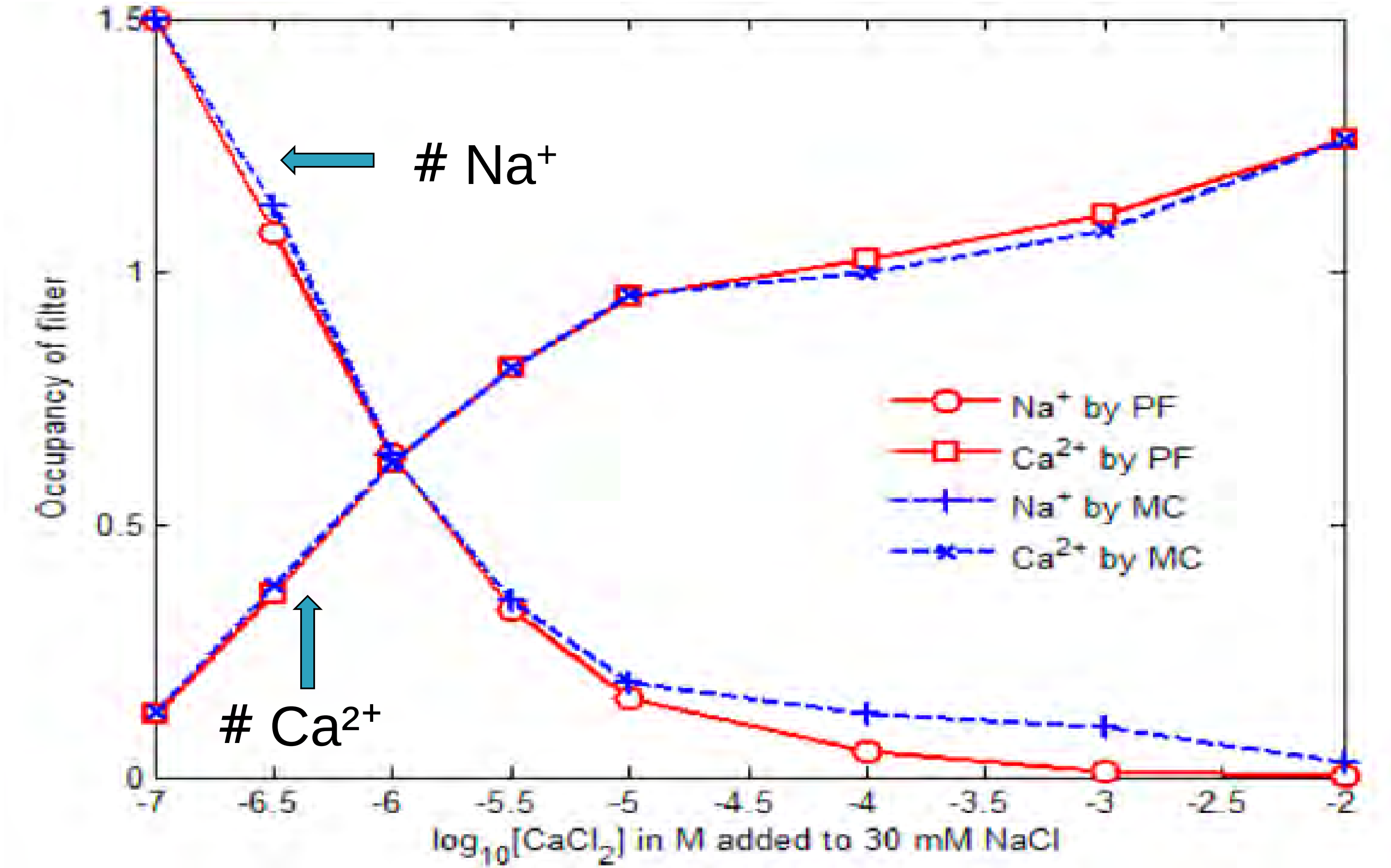

(c)
H = 12 Å, R = 3.195 Å

Dielectric Function $\tilde{\varepsilon}(\mathbf{r})$

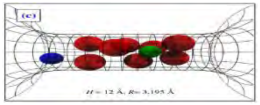


$$\tilde{\epsilon}(\mathbf{r}) \approx \frac{\epsilon_s}{1 + \eta(\mathbf{r})/\rho(\mathbf{r})}$$

Ca Binding Curves (MC)



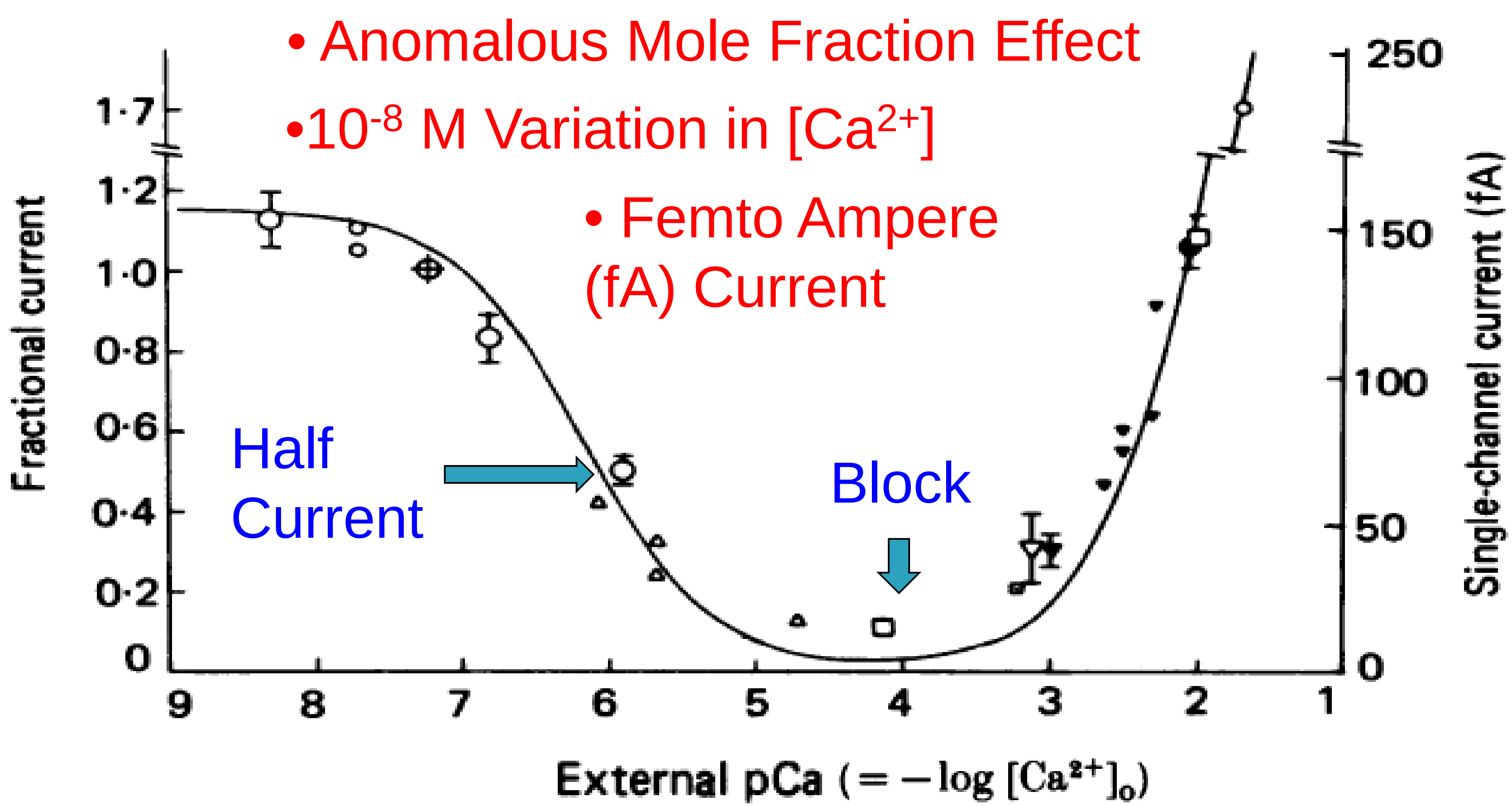
$$C^{B}_{Ca^{2+}} = 10^{-2} \sim 10^{-7}\ \mathrm{M} : \text{Large Variation of Bath Concentrations}$$



L-Type Ca Channel Model 2
(All Spheres-PF Model)

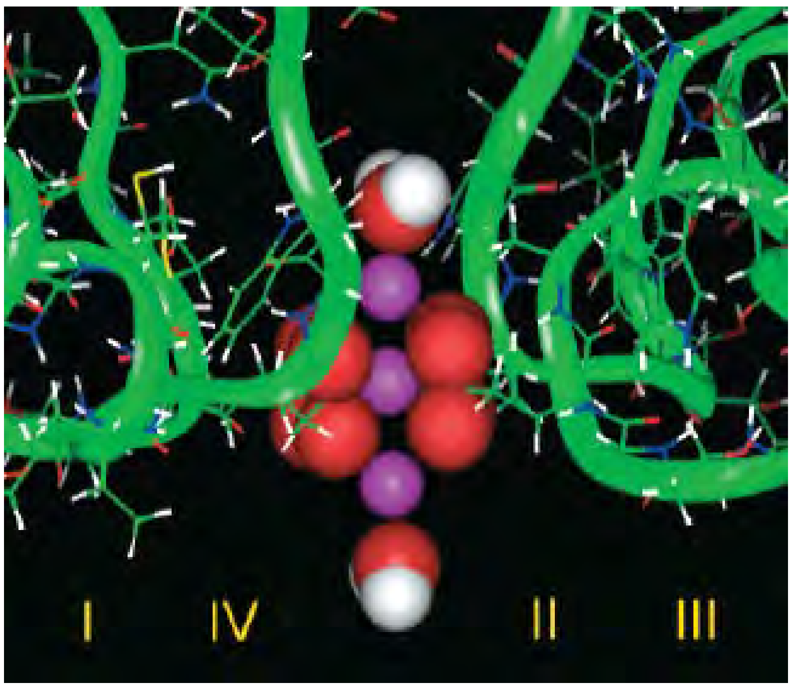
Experiments: Almers, McCleskey, Palade (JPhysio 1984)

$[Na^+]_i = [Na^+]_o = 32$ mM

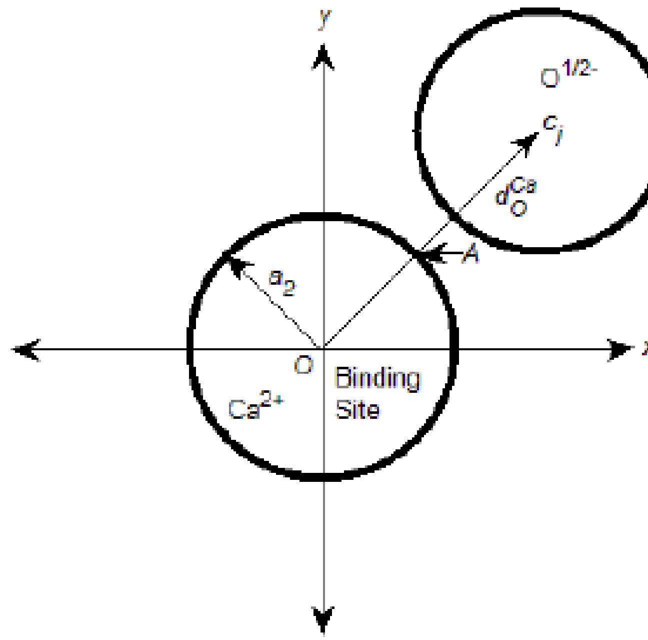


All Spheres-PF Model

Molecular Dynamics:
Lipkind, Fozzard (Biochem. 2001)
Barreiro, Guimaraes, Alencastro (Protein Eng. 2002)

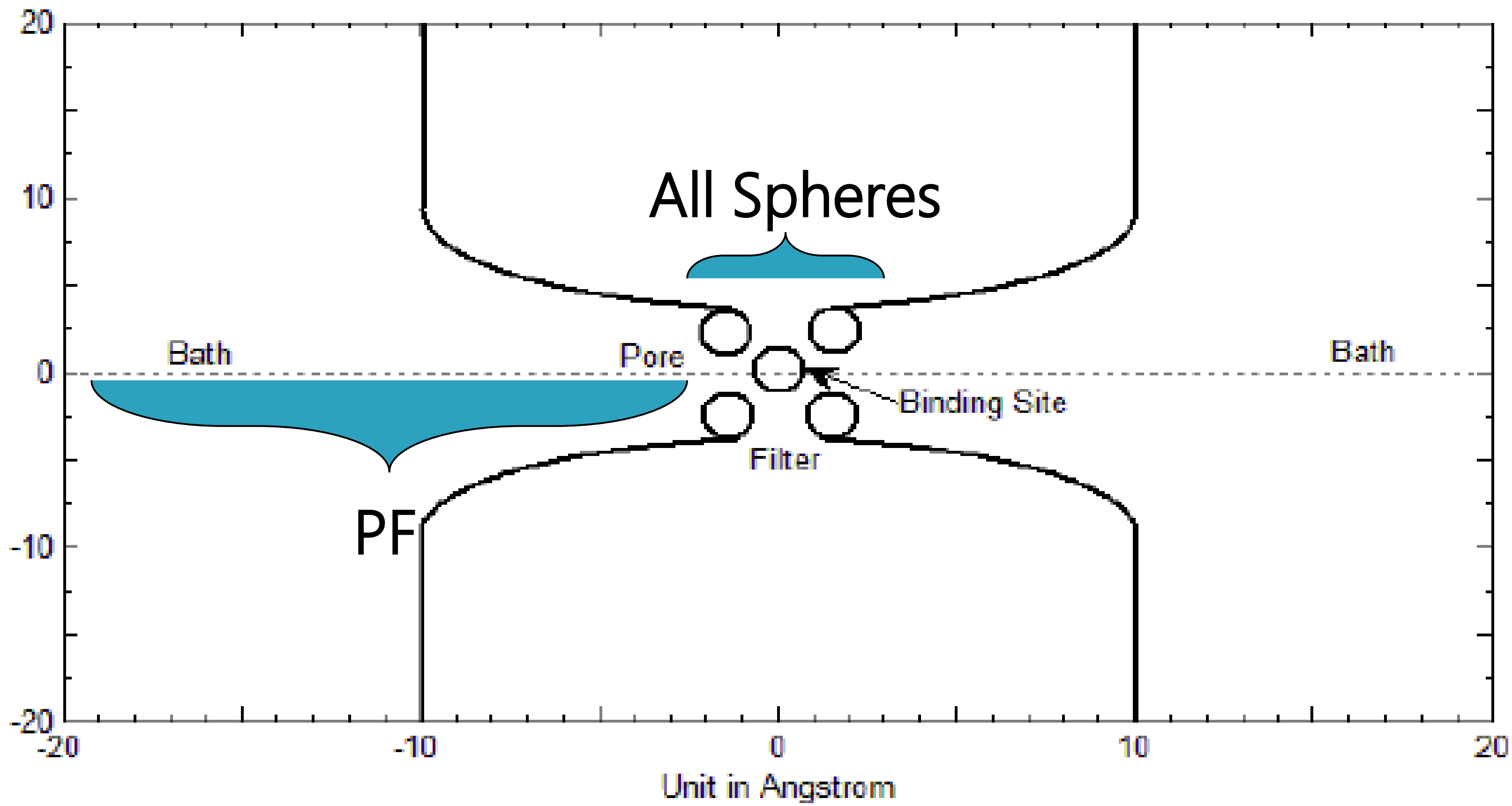


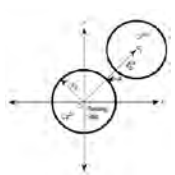
Lipkind-Fozzard Binding Site

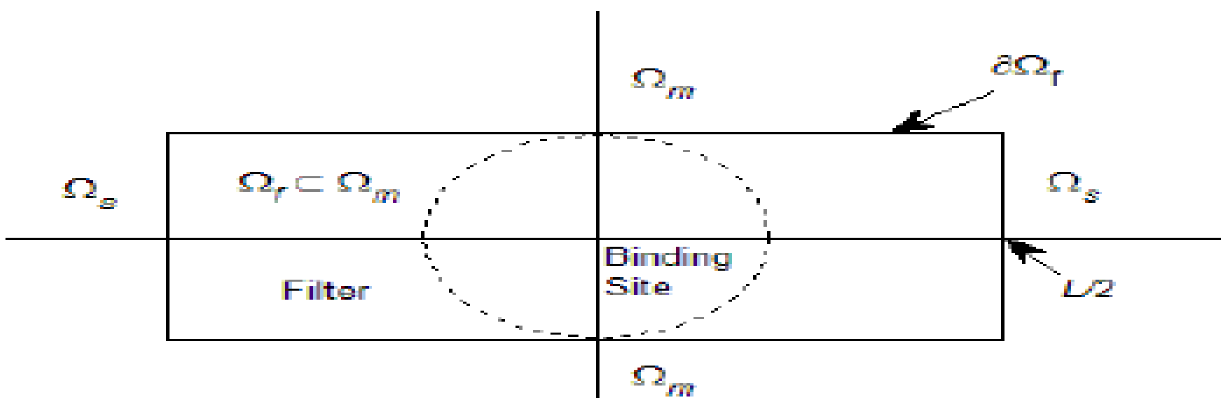


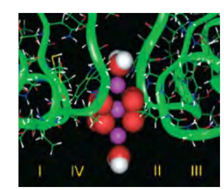
All Spheres

All Spheres-PF (Molecular-Continuum)

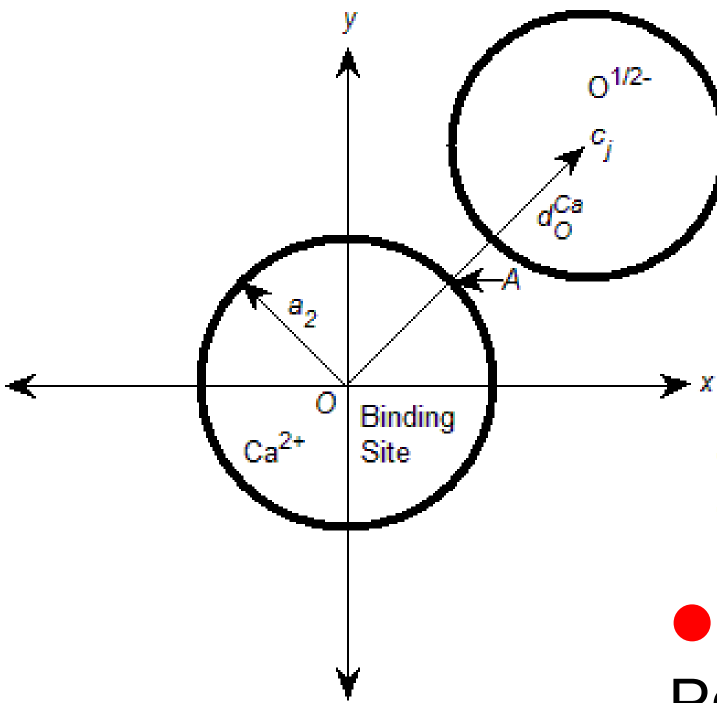








PF Results (w. MD)



Experimental Data (Halved Current)

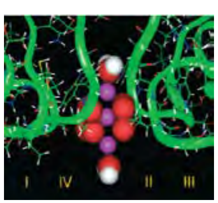
$$C^{\mathrm{B}}_{\mathrm{Na}^+} = 32\ \mathrm{mM},\ C^{\mathrm{B}}_{\mathrm{Ca}^{2+}} = 0.9\ \mu\mathrm{M},$$

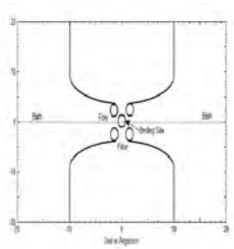
$$\begin{cases} 0.5 = P_1 = v_f C_1(X) = v_f C_1^{\mathrm{B}} \exp\left(-\beta_1 \phi^{\mathrm{Exact}}(X) + S_{\mathrm{trc}}^{\mathrm{Na}}\right), \\ 0.5 = P_2 = v_f C_2(X) = v_f C_2^{\mathrm{B}} \exp\left(-\beta_2 \phi^{\mathrm{Exact}}(X) + S_{\mathrm{trc}}^{\mathrm{Ca}}\right). \end{cases}$$

$$1 = P_1 + P_2 = v_f\left(C_1^{\mathrm{B}} \exp(-\beta_1 \bar{\phi}) + C_2^{\mathrm{B}} \exp(-\beta_2 \bar{\phi})\right)$$

- PF Shows Flexibility of Side Chains: Pore Radius Variation = 2.3 Å (2 Å by MD)
- Steric is Critical:

$$S_{\mathrm{trc}}^{\mathrm{Na}} = -0.6 \quad S_{\mathrm{trc}}^{\mathrm{Ca}} = 1.75$$

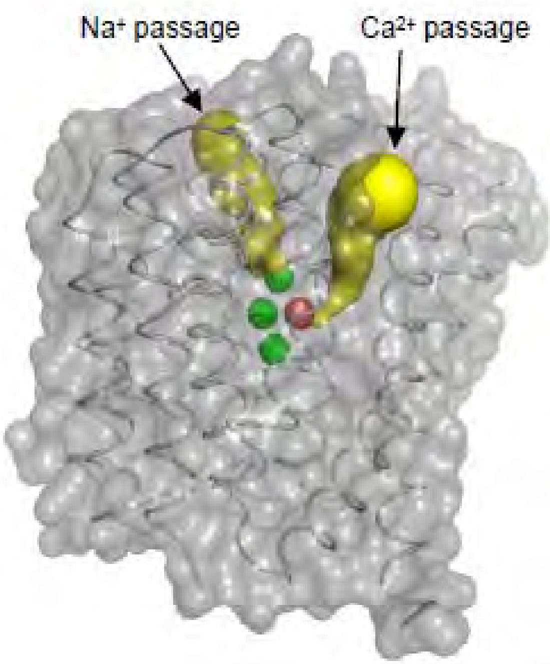


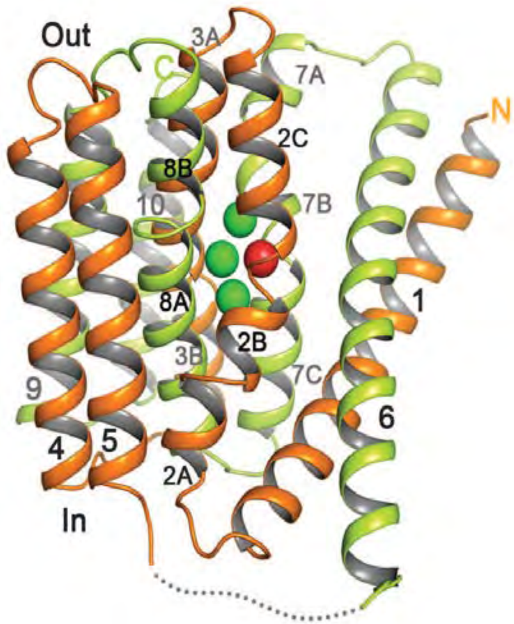


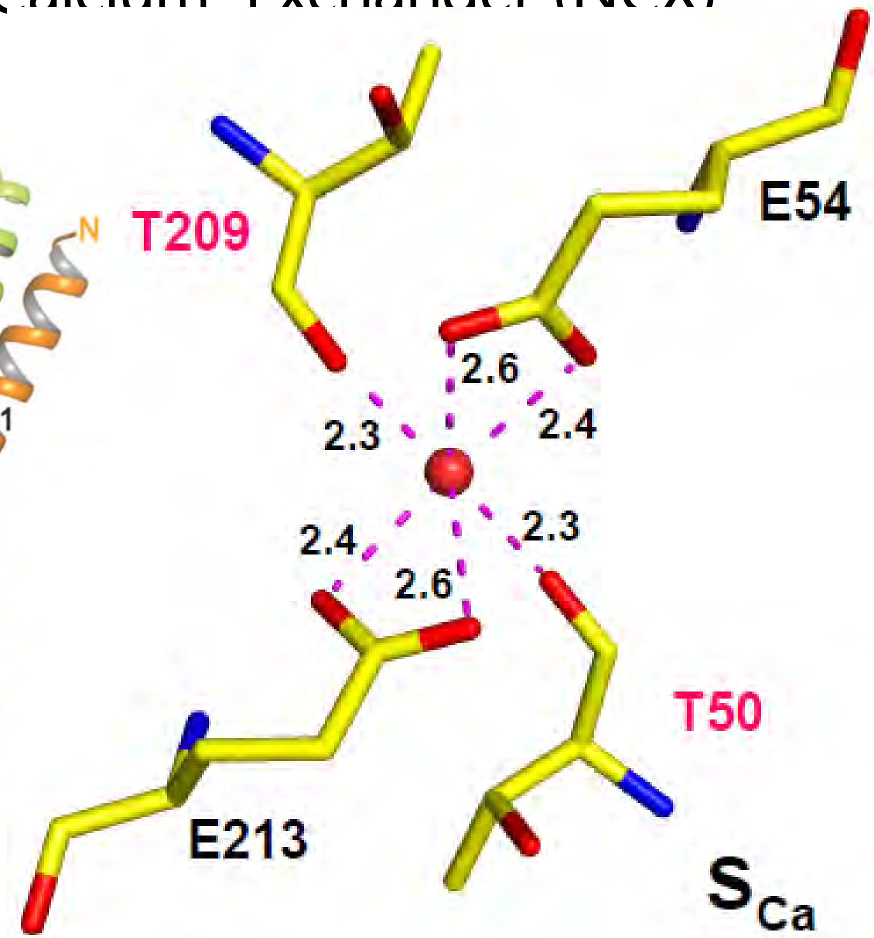
PF Results (w. NCX Exp)

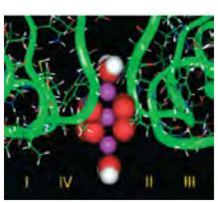
J. Liao, ..., Y. Jiang (Science 2012)

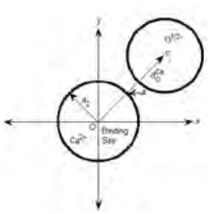
Crystal Structure of Sodium /Calcium Exchanger (NCX)







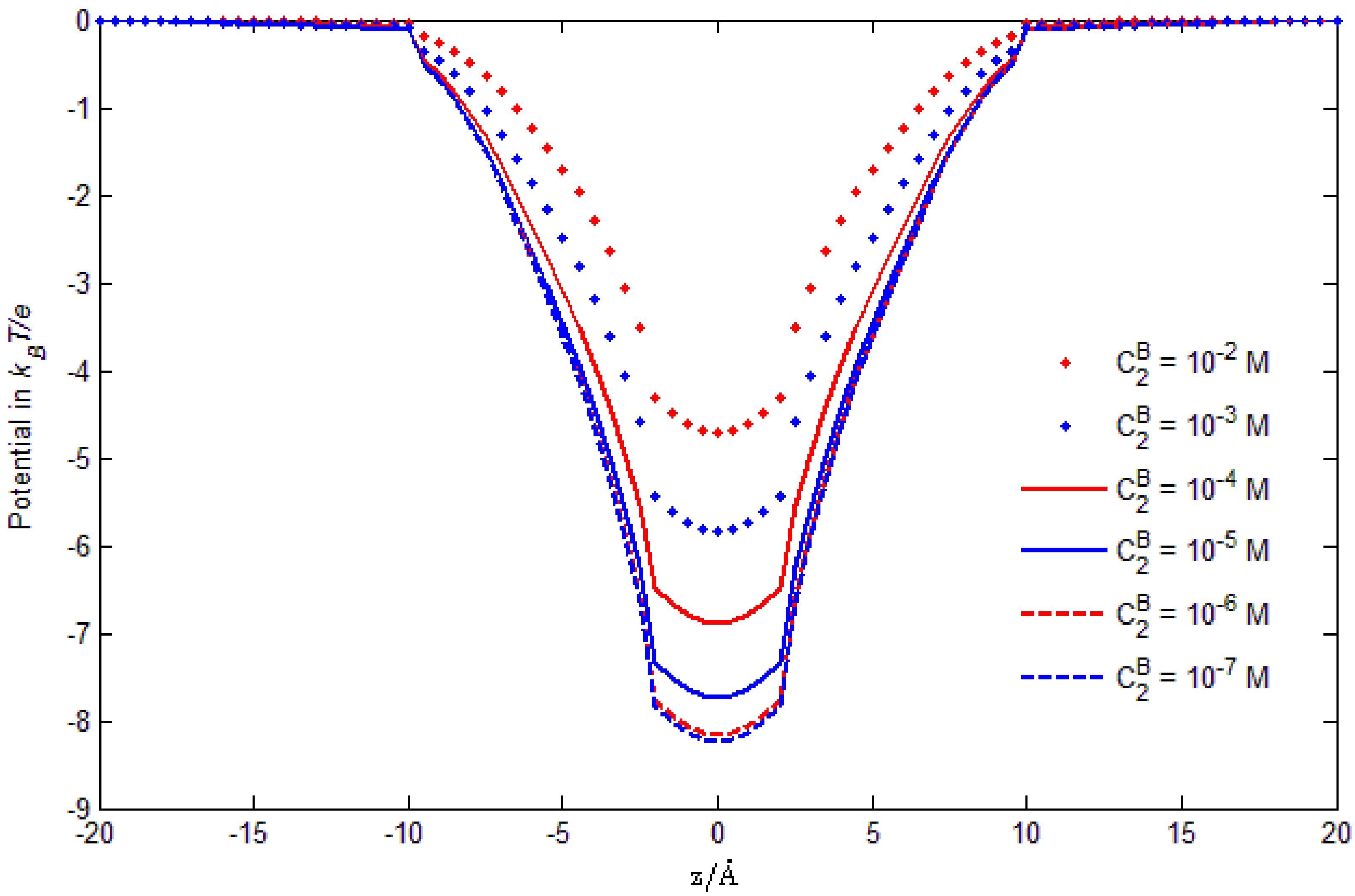




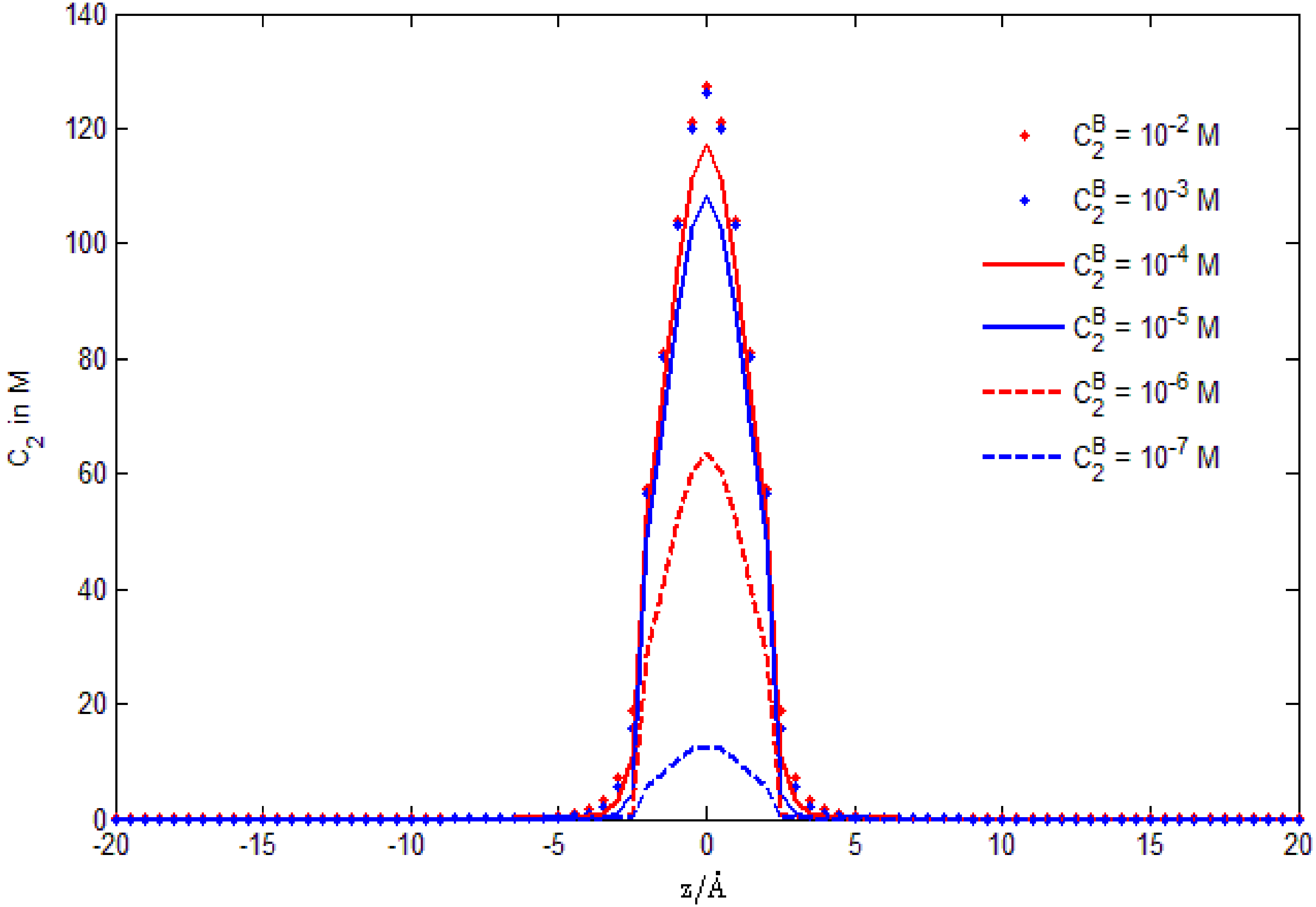
PF = 2.3 Å

Exp = 2.4 Å

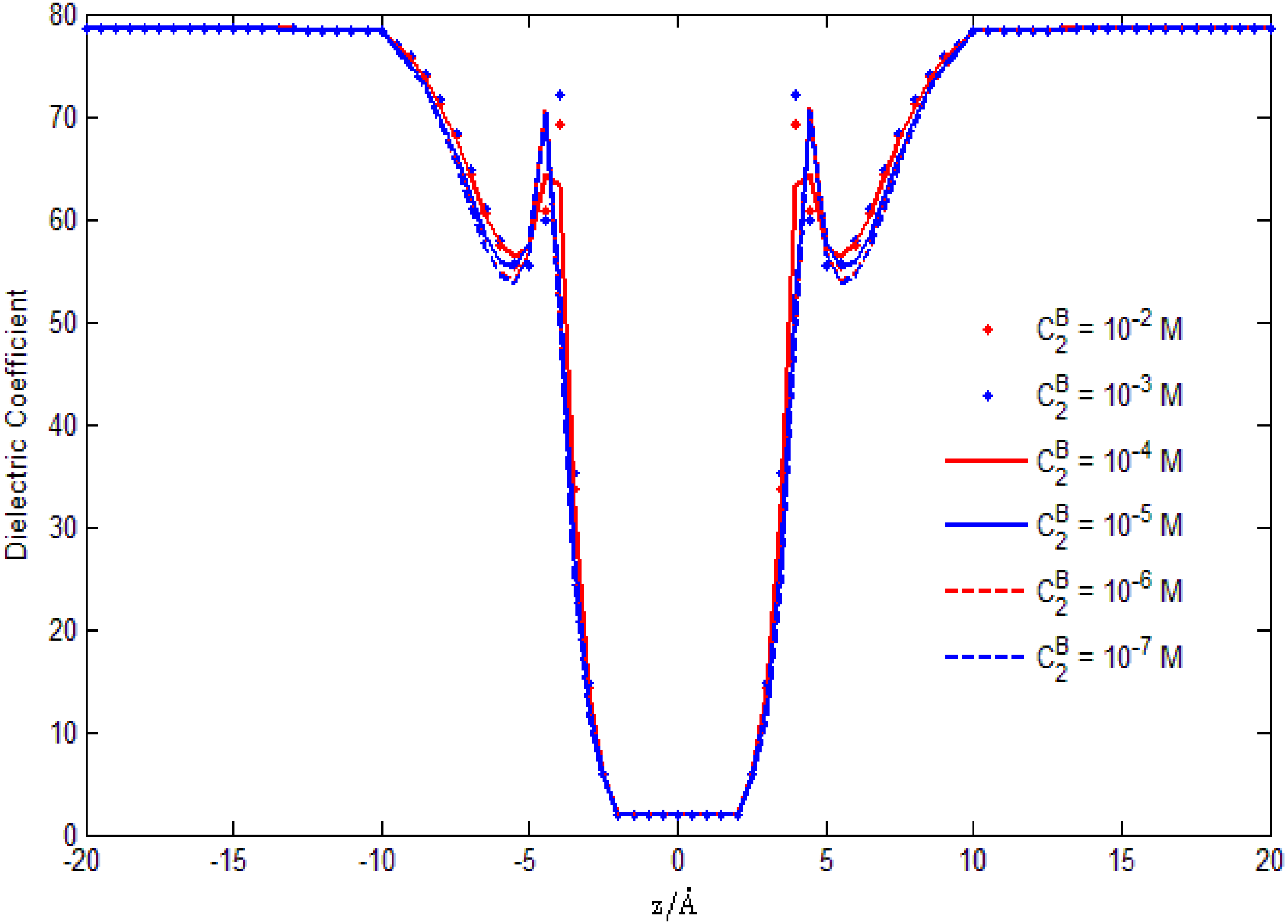
Mol-PF Potential Profile



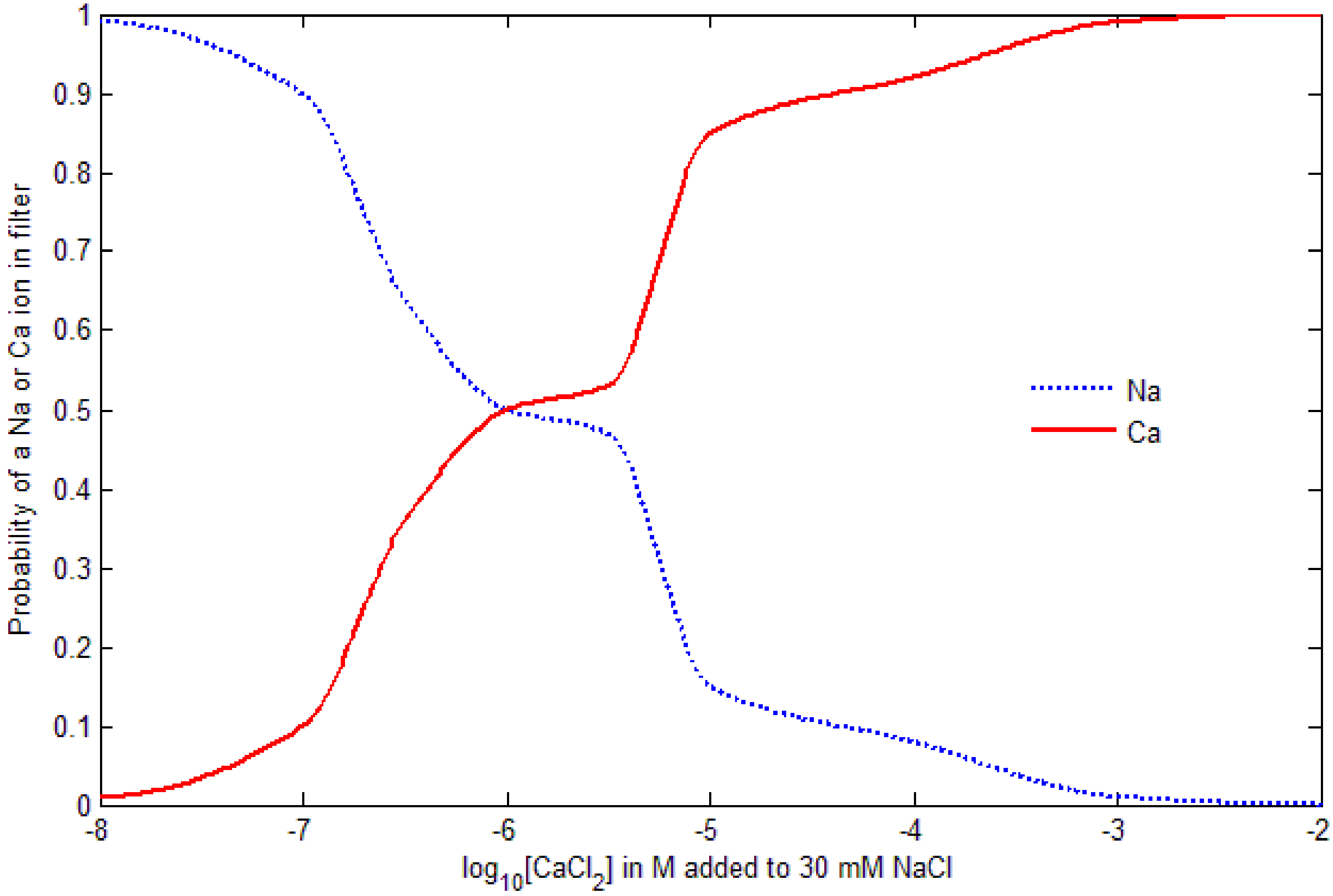
Mol-PF Concentration Profile



Mol-PF Dielectric Profile



Mol-PF Binding Curve



Outlook

- Equilibrium and Nonequilibrium Systems
- PFNP vs Experiments
- Ca, Na, KcsA Channels
- Sodium Calcium Exchanger (NCX)
- Mathematical and Numerical Analysis
- Biophysical Analysis

Thank You