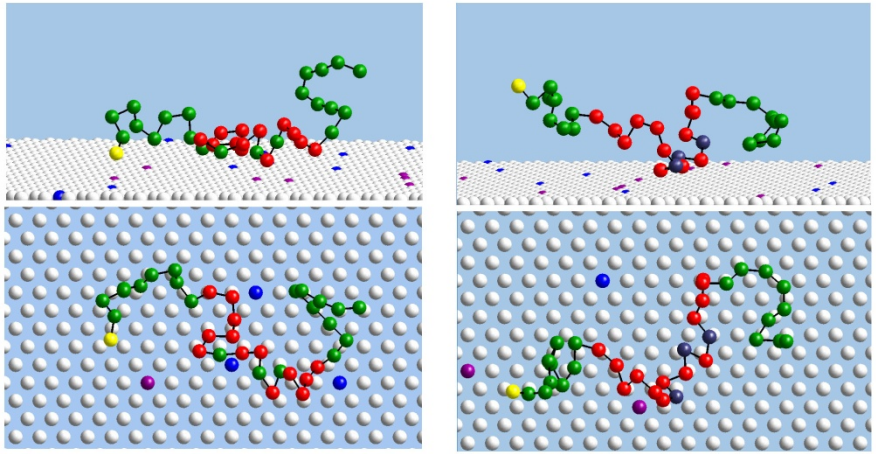
Rigid & Flexible Macroions Interacting with Mixed Fluid Membranes

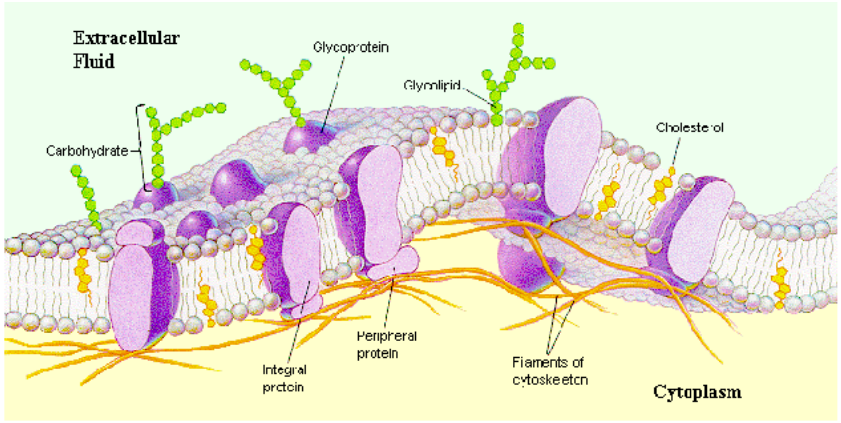
Screening, Overcharging, Macrioion Condensation,
Lipid Demixing, Domain Formation
DNA, Proteins, Polyelectrolytes

Shelly Tzlil, Sylvio May,
Daniel Harries

Bill Gelbart, Emanuel Mbamala



Bio-Membranes are Soft, 2D, Fluid Mixtures



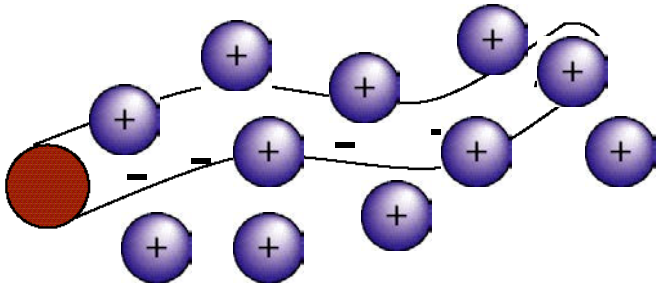
Taken from *Human Biology* by Daniel Chiras

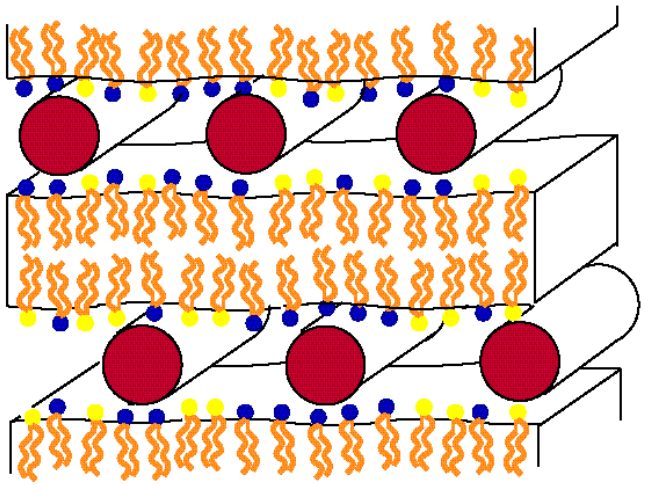
Lipid membranes can respond to interactions with integral and/or peripheral macromolecules by changing:

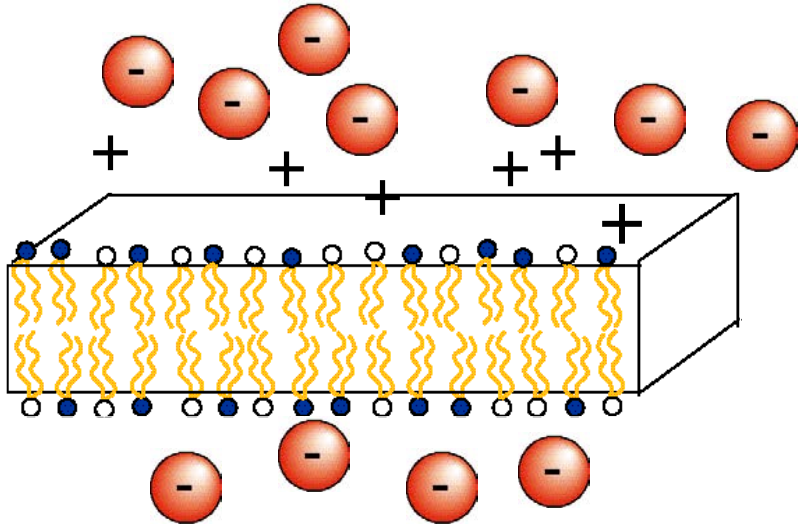
Composition, Curvature, Morphology – Locally or Globally

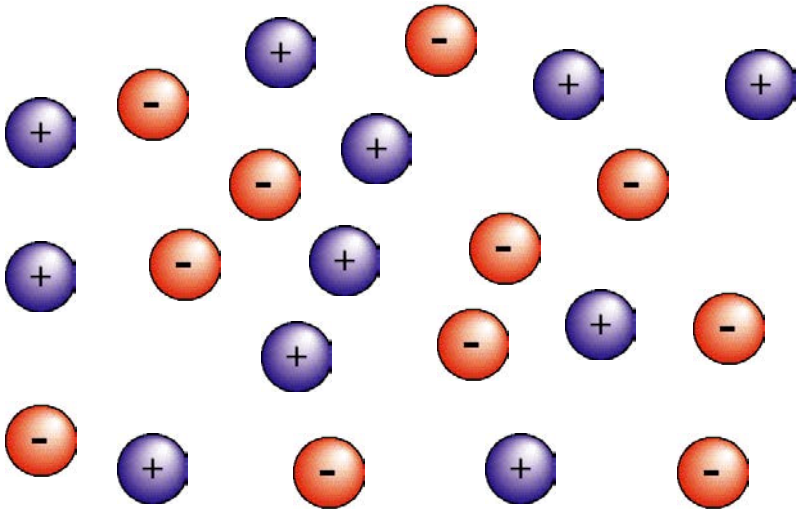
Lipoplexes = Cationic Lipid-DNA Complexes

Driving Force: Counterion Release = Gain of Counterion Translational Entropy



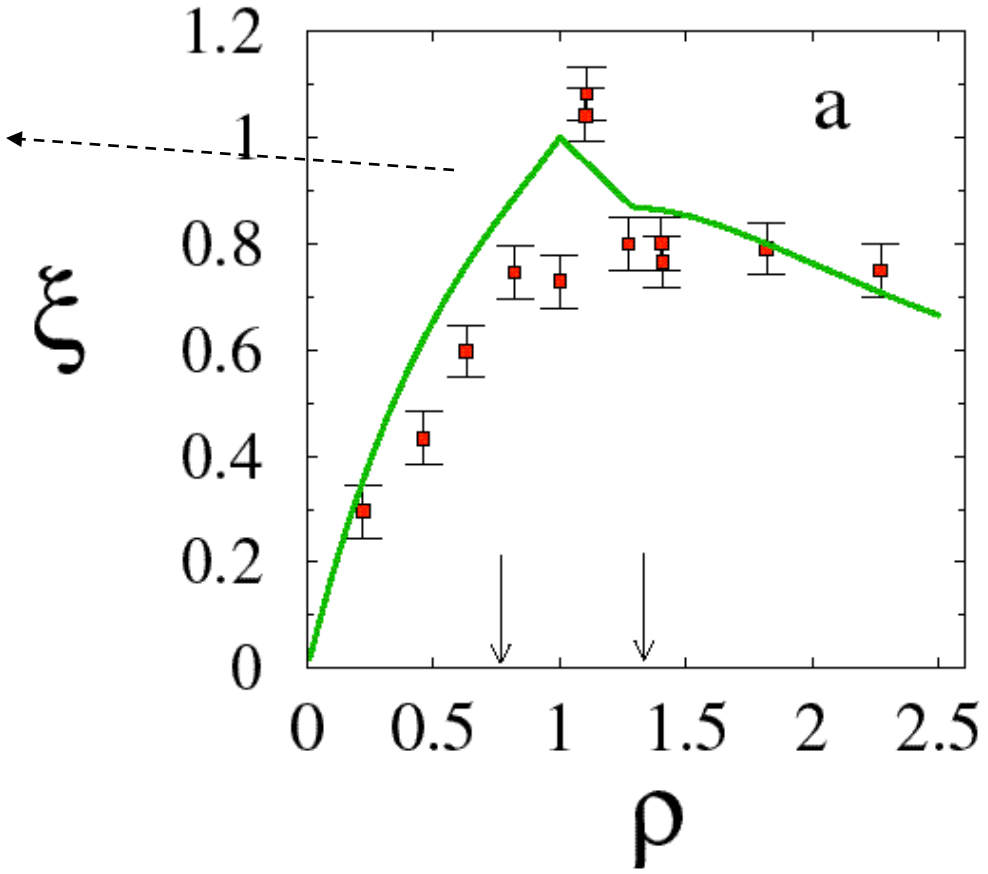






Counterion release; Conductivity measurements

Maximal counterion release at the ***isoelectric point*** (ρ=1)



Experiments: Raedler et al.

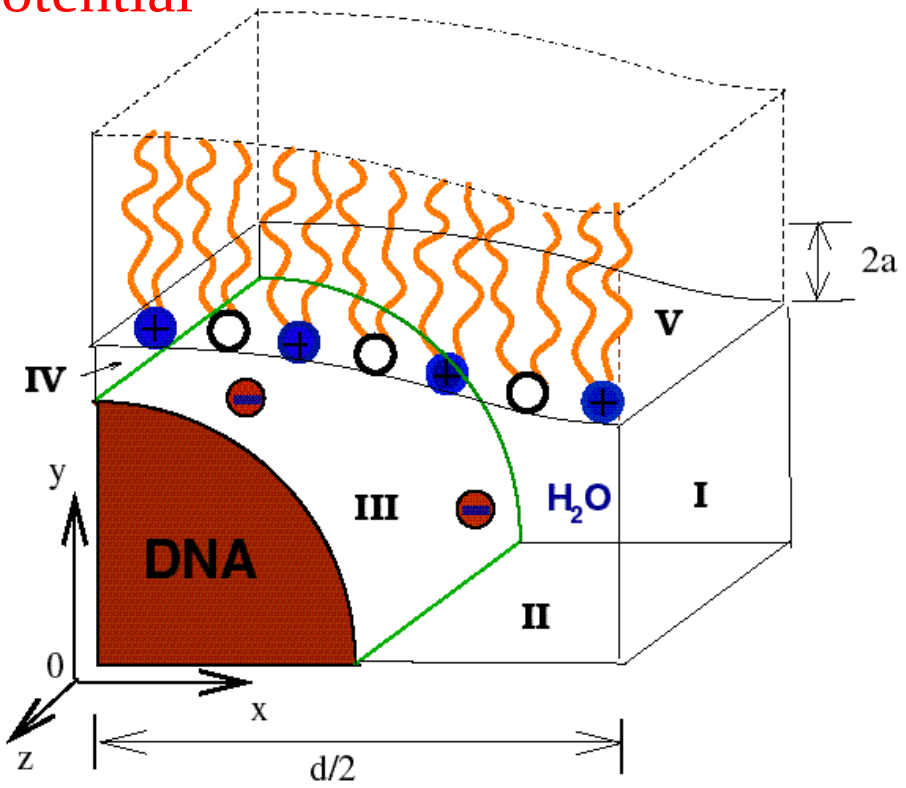
Theory

$$\rho = \frac{\text{Lipid (+) charge}}{\text{DNA (-) charge}}$$

Solve using Poisson-Boltzmann theory

ψ - The (reduced) electrostatic potential

The unit cell



Boundary conditions:

On boundaries I, IV: $\dfrac{\partial \psi}{\partial x} = 0$

On boundary II: $\dfrac{\partial \psi}{\partial y} = 0$

On boundary III: $-\nabla \psi \cdot \hat{\mathbf{n}} = \dfrac{e\sigma^-}{\epsilon_0 \epsilon_r k_B T}$

The Free Energy:

$$F = \int_V \frac{\epsilon}{2}(\nabla\phi)^2 dv$$

Electrostatic energy

$$+ \quad kT \int_V n_+ \ln \frac{n_+}{n_0} + n_- \ln \frac{n_-}{n_0} - (n_+ + n_- + 2n_0) dv$$

Mixing entropy of counterions

$$+ \quad kT \int_{S^V} \eta \ln \eta + (1-\eta) \ln(1-\eta) ds$$

Entropy of lipid demixing

$$+ \quad \int_{S^V} \frac{1}{2}\kappa(\eta)(c - c_0(\eta))^2 ds$$

Bending ("Helfrich") free energy

Minimization of F wrt to n^+, n^-, η , subject to charge conservation:

$$\eta_0 A = \int_{S^V} \eta ds$$

1. The Poisson-Boltzmann Equation:

$$\nabla^2 \psi = l_D^{-2} \sinh \psi$$

l_D - the Debye length

2. A boundary condition for boundary V:

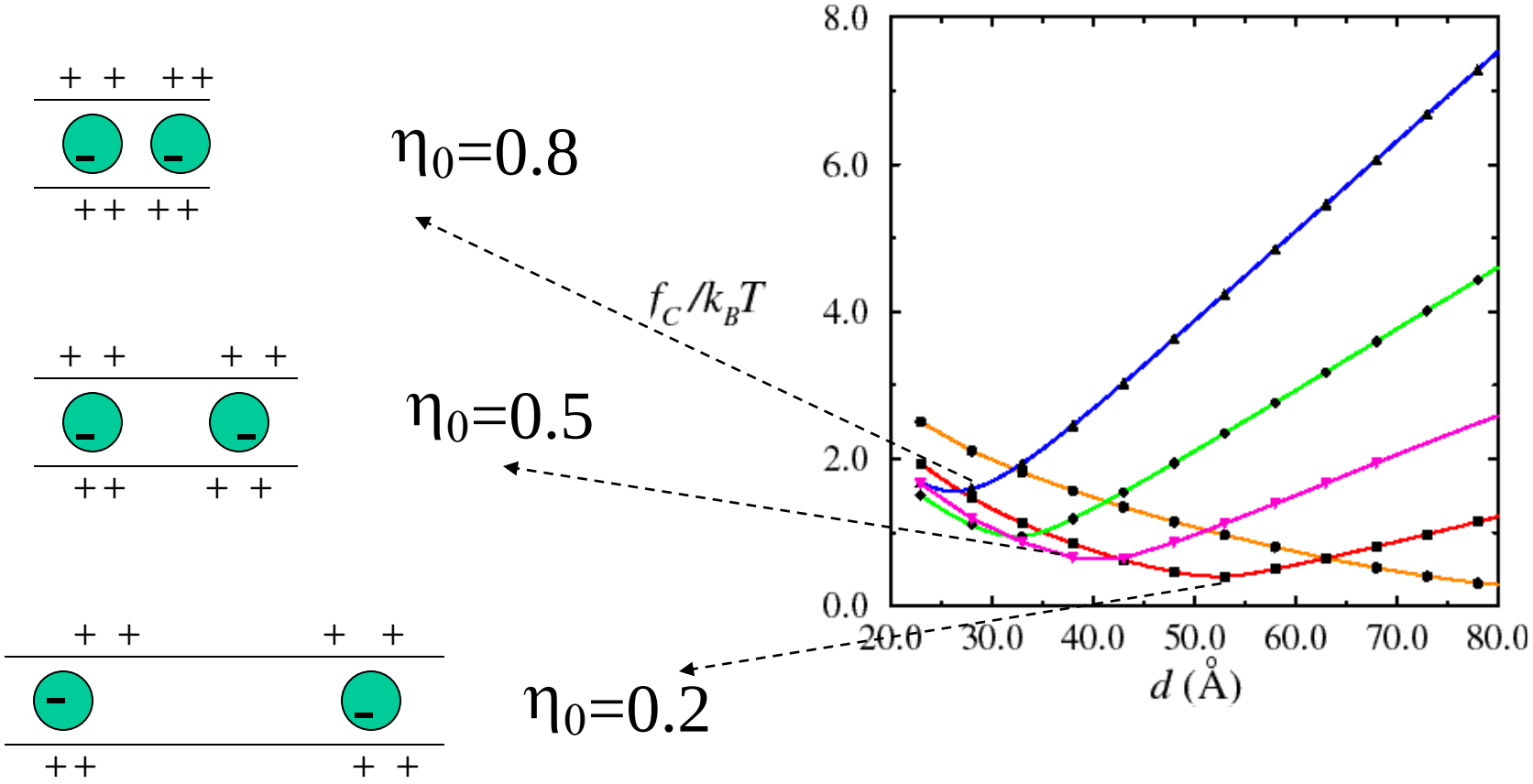
$$\ln \frac{\eta(1-\eta_0)}{\eta_0(1-\eta)} + \psi + \lambda = 0$$

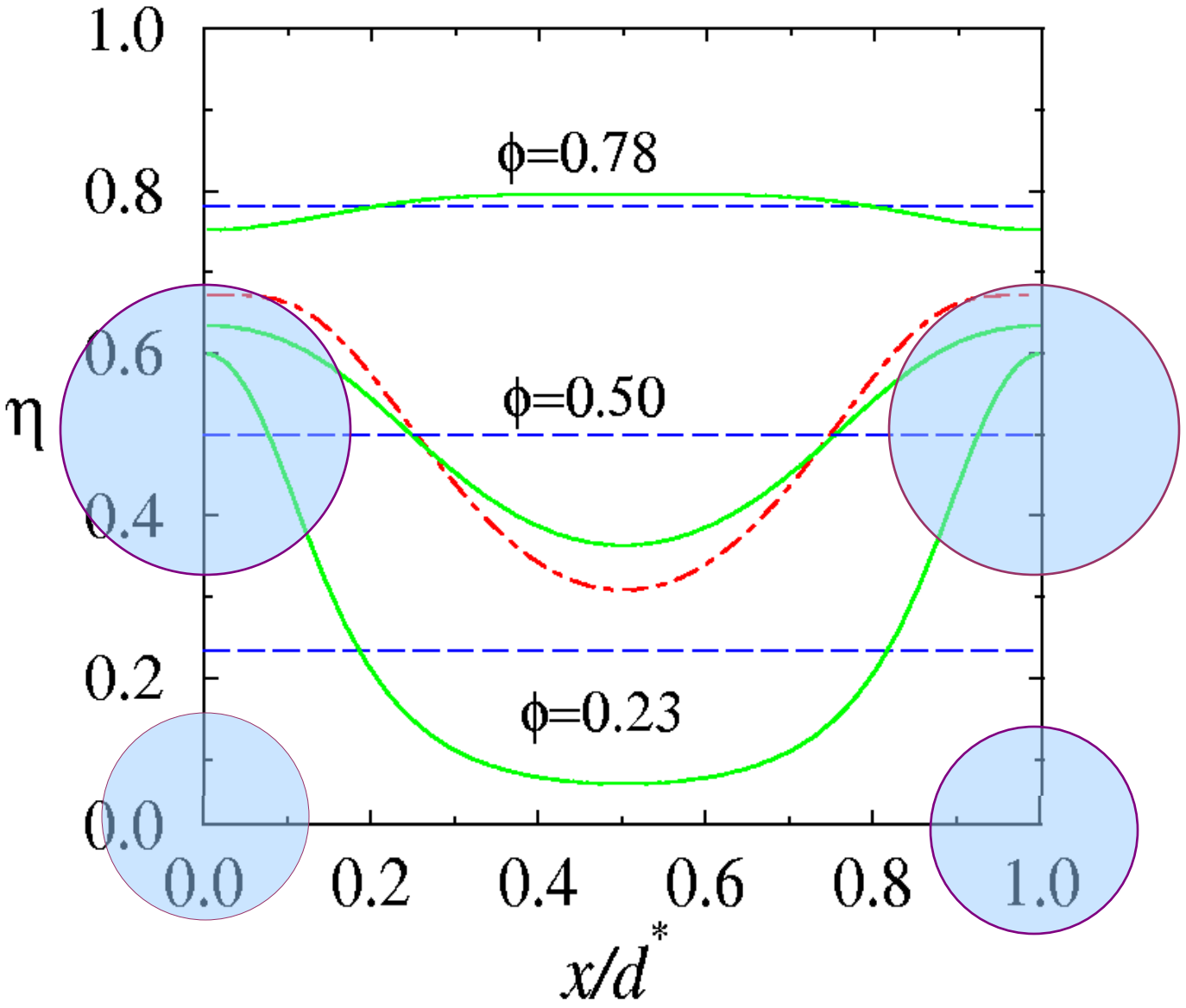
$$- (\kappa_A - \kappa_B)\left(c - (c_{0A}\eta + c_{0B}(1-\eta))\right)^2$$

$$- (\kappa_A \eta + \kappa_B(1-\eta))\left(c - (c_{0A}\eta + c_{0B}(1-\eta))\right)(c_{0A} - c_{0B})$$

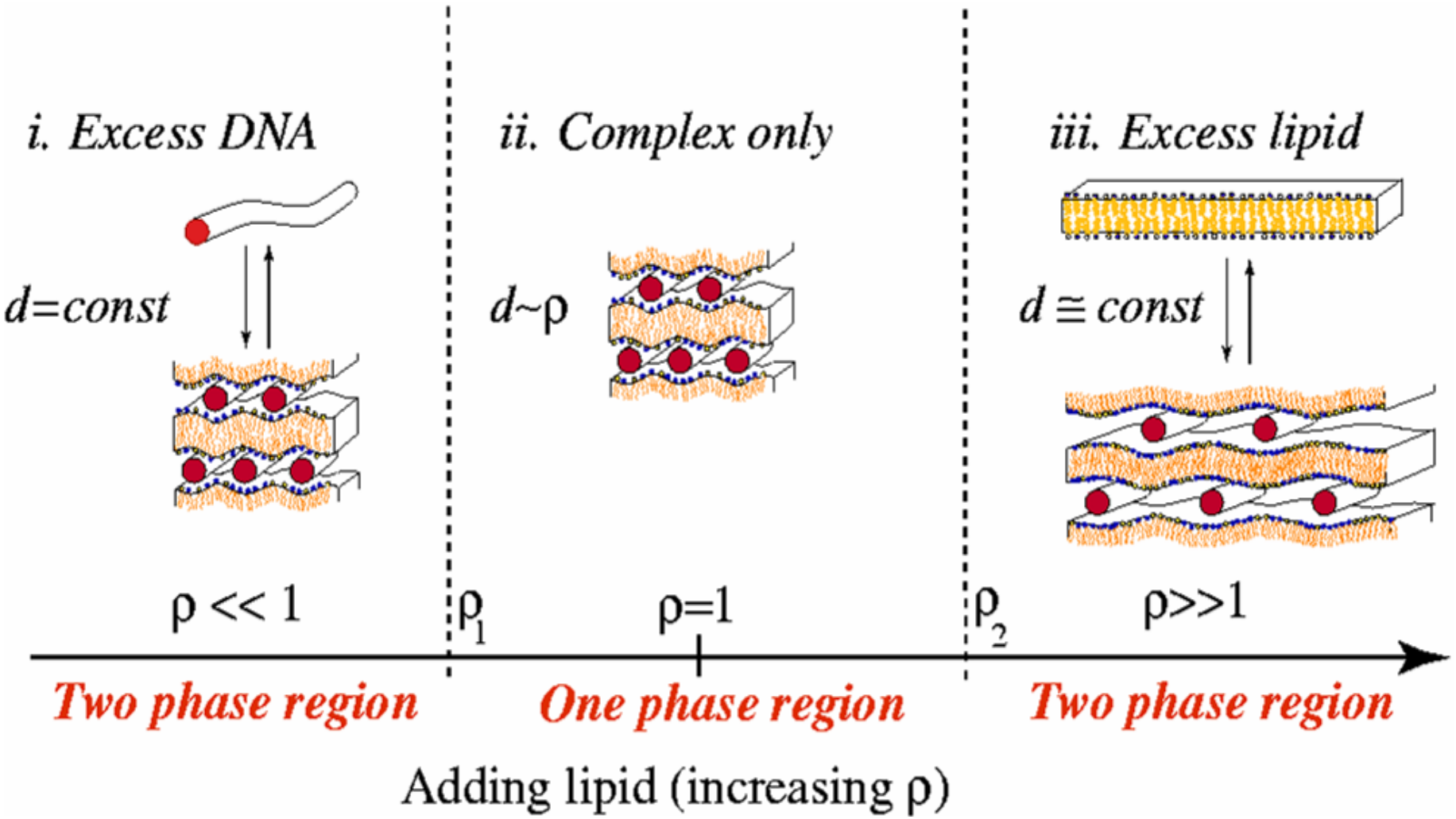
Complex Free energy:

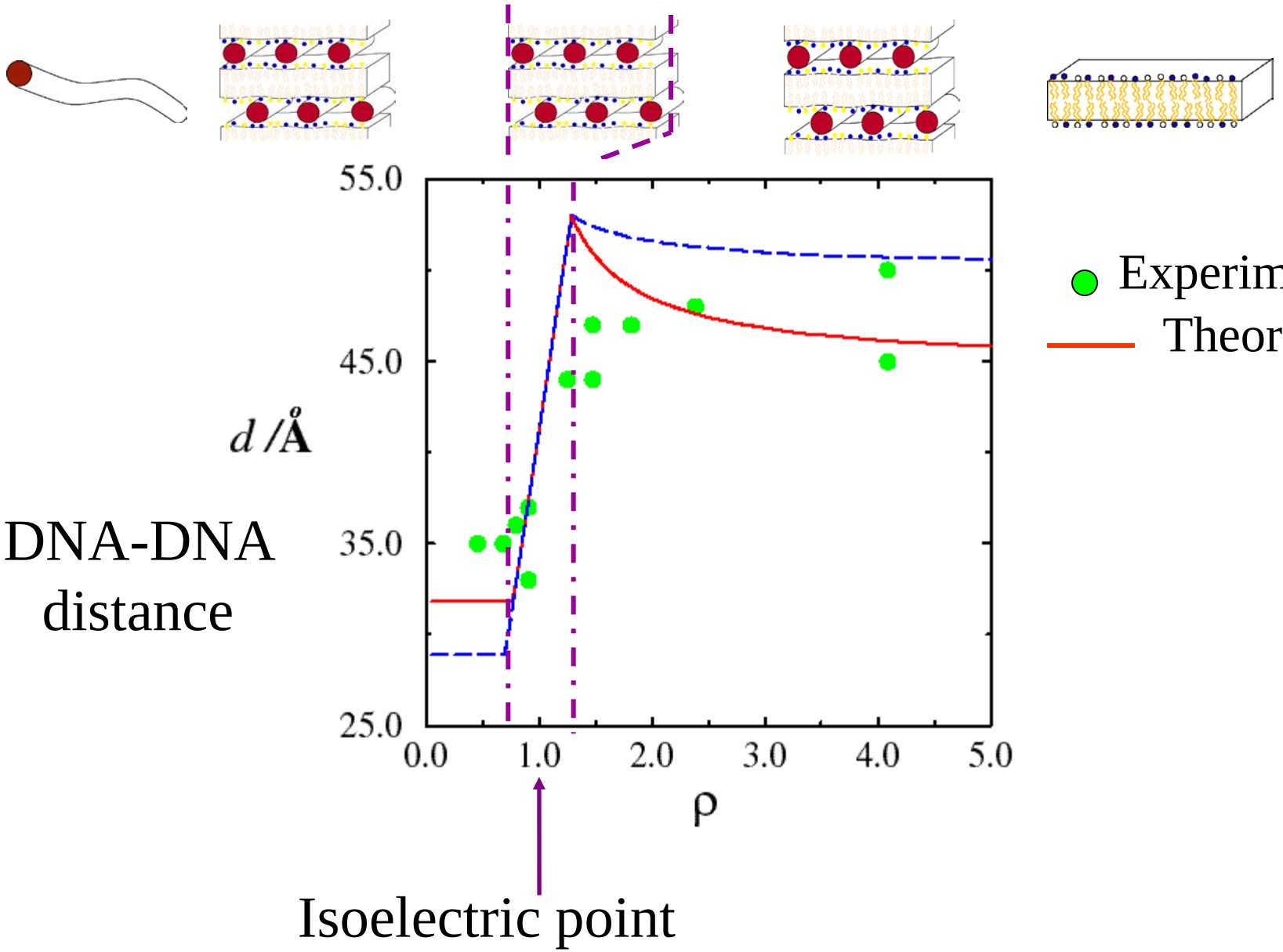
Minimal at the ***isoelectric*** point

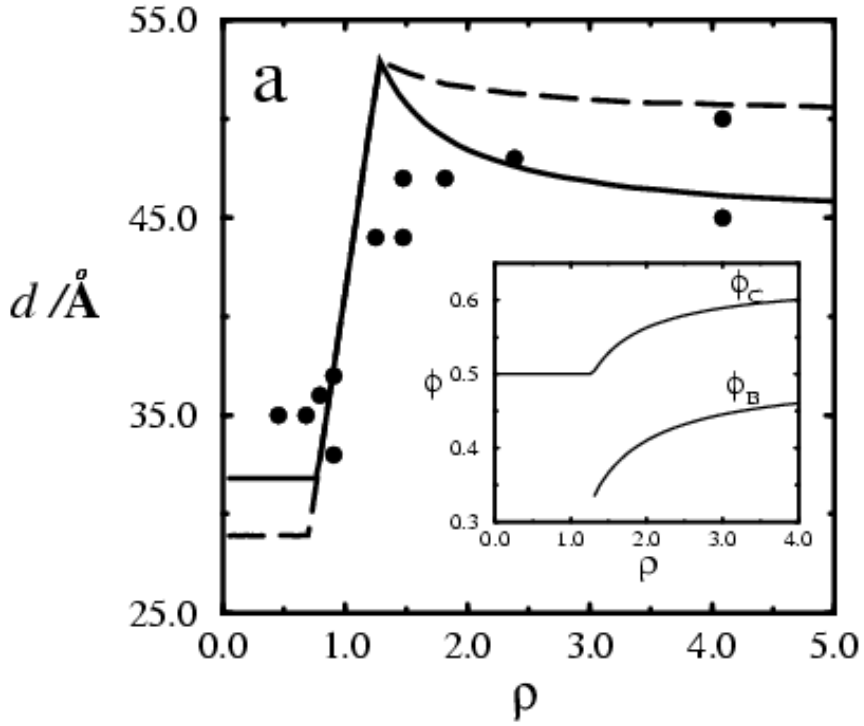


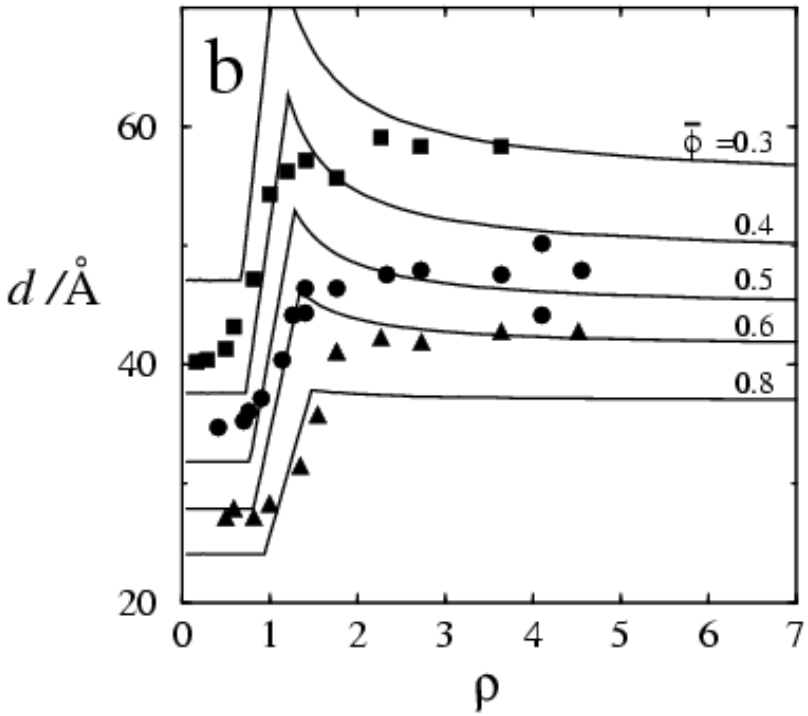

1.0
0.8
0.6
0.4
0.2
0.0
η
ϕ=0.78
ϕ=0.50
ϕ=0.23
0.0
0.2
0.4
0.6
0.8
1.0
x/d*

Phase Evolution of Lamellar Complex

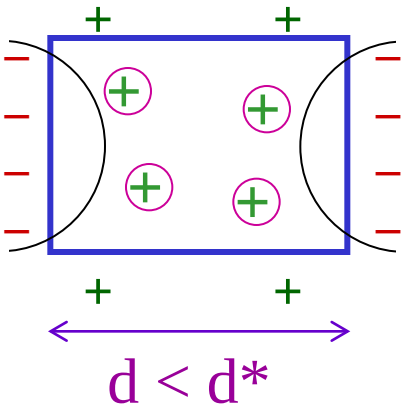



55.0
45.0
35.0
25.0
d /Å
0.0
1.0
2.0
3.0
4.0
5.0
ρ
Experiment
Theory
DNA-DNA distance
Isoelectric point





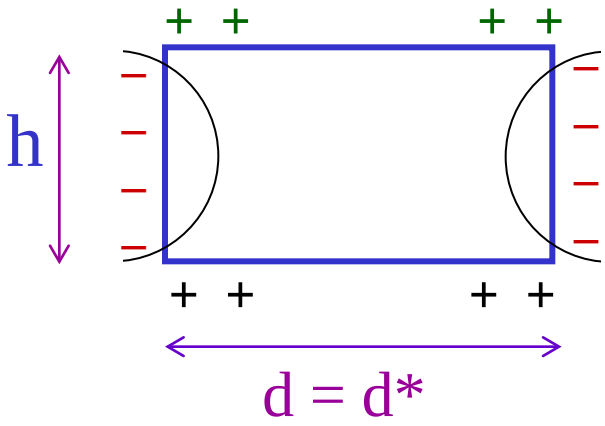
Addition comparisons with experiment (Safinya's group)



"Negative"

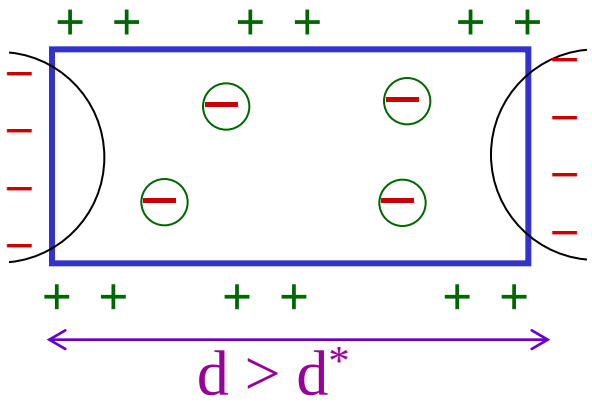
Overcharging,

ρ <1



"Isoelectricity",

ρ =1



"Positive"

Overcharging,

ρ >1

Box Model

(May, Harries, ABS, BJ 1998)

Electrostatic Free Energy of Complex Cell

charging

Membrane Repulsion

$$f_C = Ad\left\{2\Delta\phi\left[\ln(D\Delta\phi)-1\right]+\frac{B}{h}\right\}$$

Excess Charge ($d>d^*$, $\rho>1$)

$$\Delta\phi = \phi^+\left[1-\frac{d^*}{d}\right] \quad ;$$

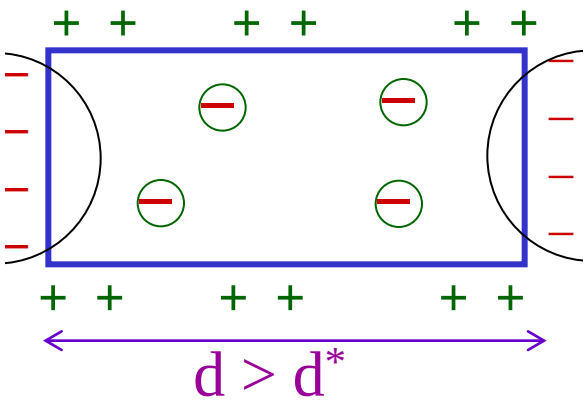
$$\{\ \phi^+ = (a/e)\sigma^+\}$$

σ^+ = lipid charge density

$A,\ D,\ B$ = constants

Bilayer-Complex coexistence, ρ>1

Complex $\Delta\phi$



Bilayer ϕ^+

$$\tilde{f}_B = A2\phi^+\left[\ln(D\phi^+)-1\right]$$

$$f_C = Ad\left\{2\Delta\phi\left[\ln(D\Delta\phi)-1\right]+\frac{B}{h}\right\}$$

$$\Delta\phi = \phi^+\left[1-d^*/d\right]$$

$$F = D_C f_C(d,\Delta\phi)+(L-dD_C)\tilde{f}_B(\phi^+)$$

System Free Energy

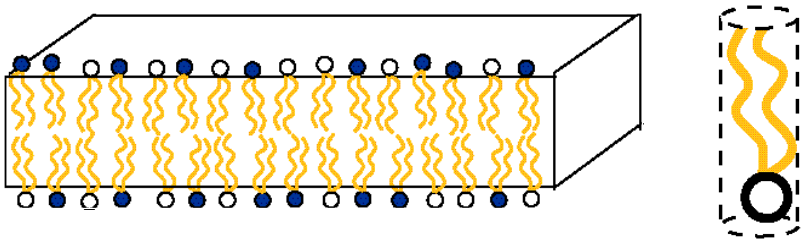
$$\frac{\partial F}{\partial d}=0 \Leftrightarrow \frac{\partial f_C}{\partial d}=\tilde{f}_B$$

← Equality of lipid chemical potentials

$$\hat{d}_2 \simeq d^*/\{1-\exp[-(1+B/2h\phi^+)]\}$$

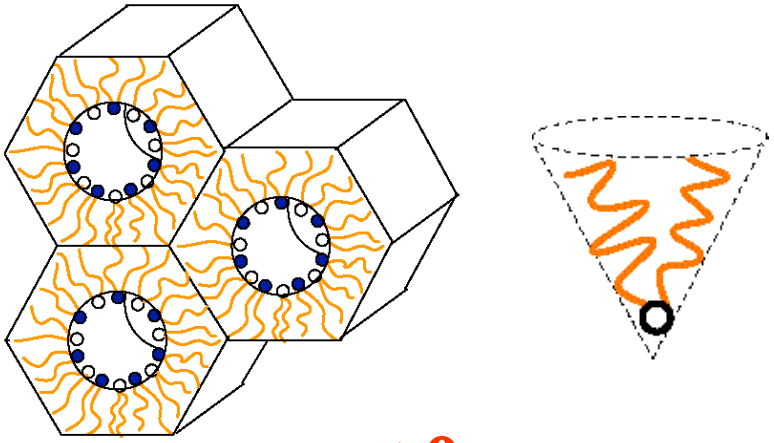
Spontaneous Curvature

Bilayer



The spontaneous curvature $c_0 \sim 0$

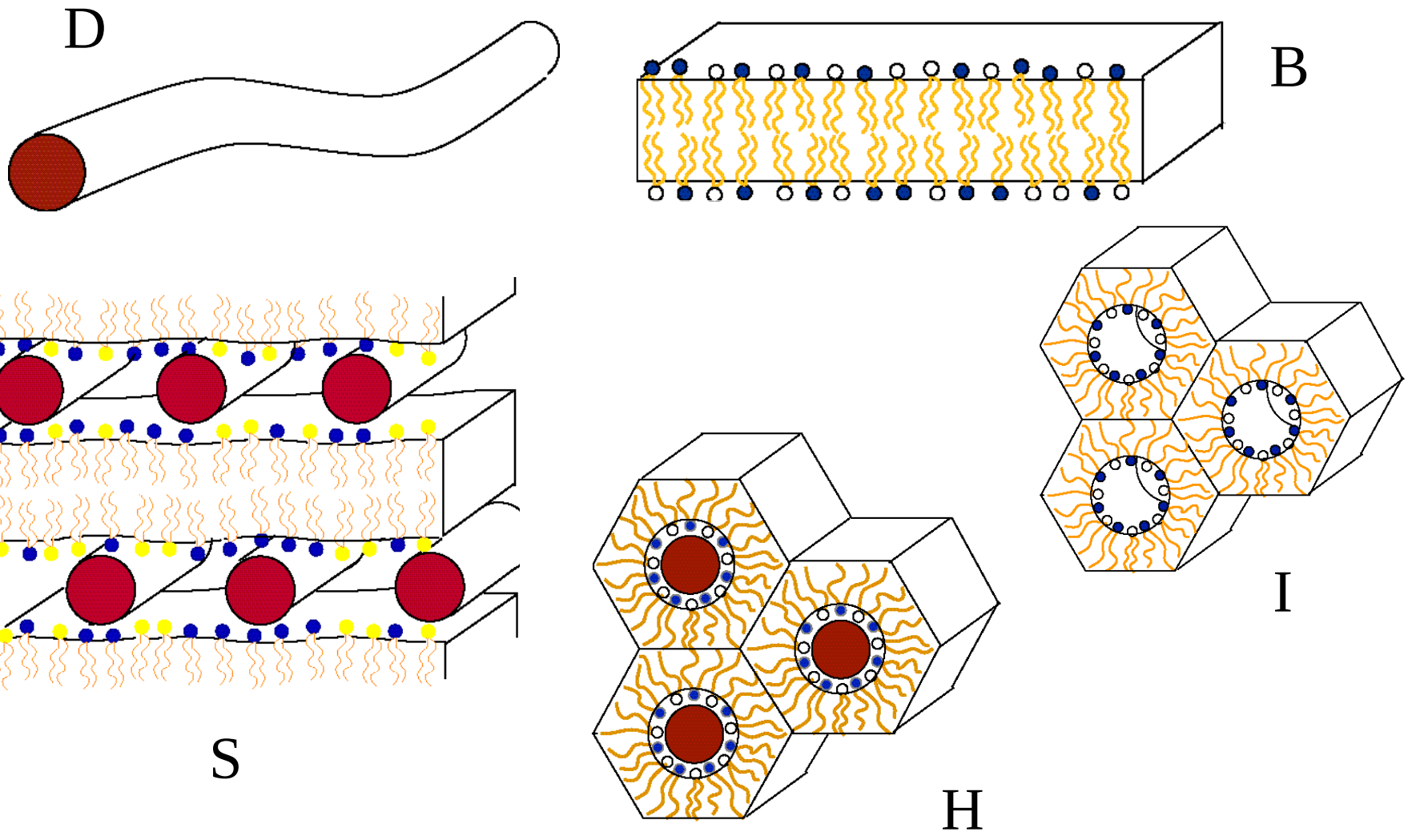
Inverted Hexagonal



$c_0 < 0$

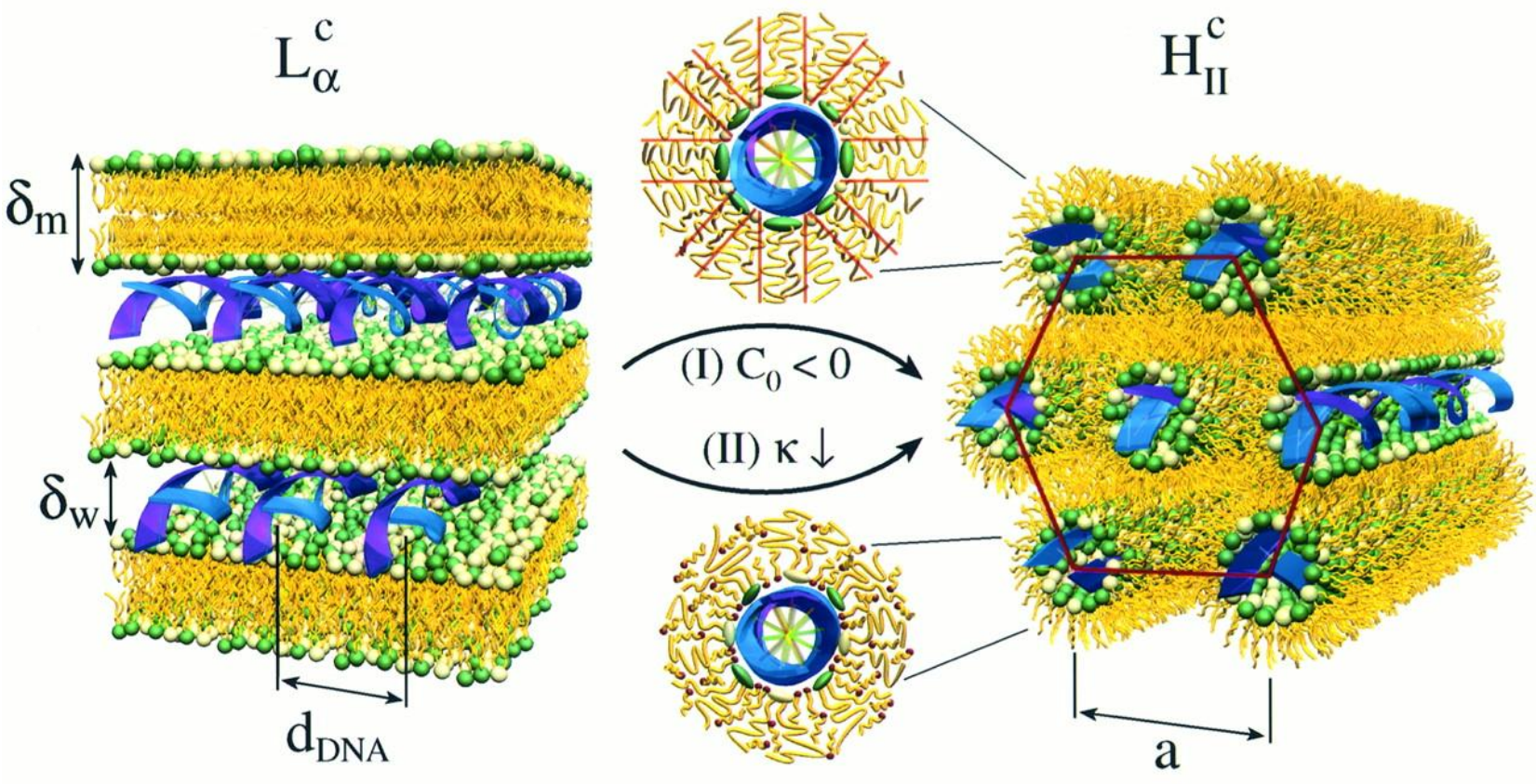
Lipid Layers are Soft

Lipid, DNA and Lipoplex Phases

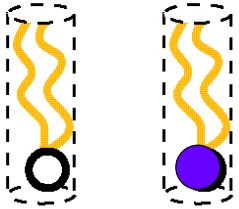


Structure & phase transitions of ***Lipoplexes***

Governed by Electrostatic, Elastic lipid properties



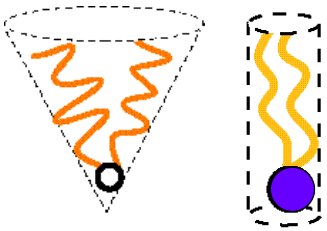
Safinya et al., (Science 97,98)



$c_0^h = 0$

$c_0^c = 0$

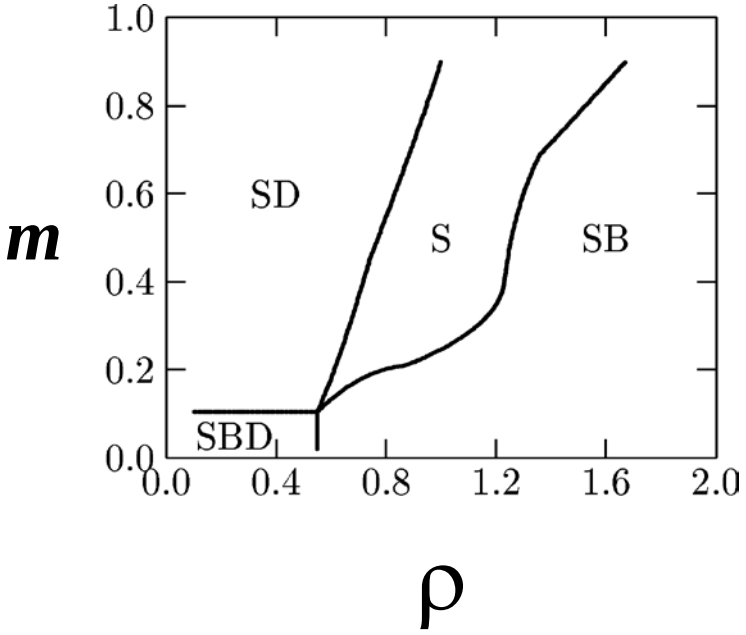
$\kappa = 10\ k_B T$

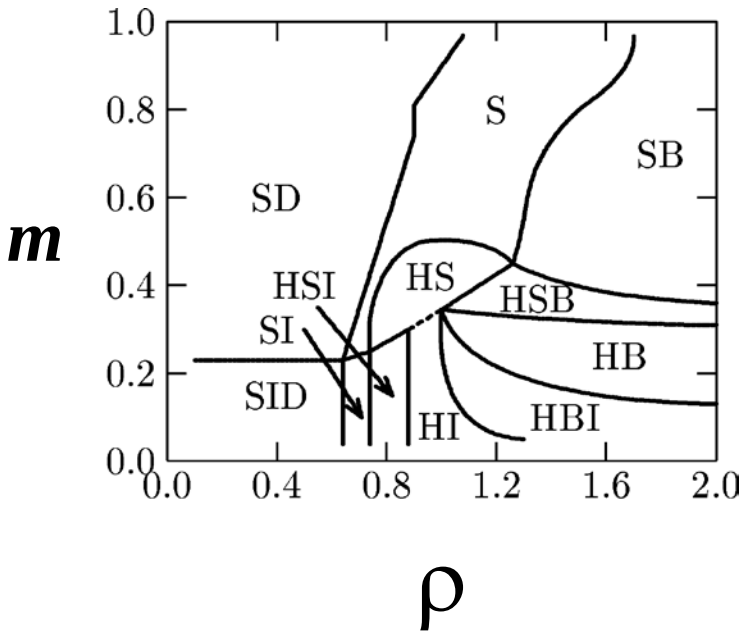


$c_0^h = -1/25A$

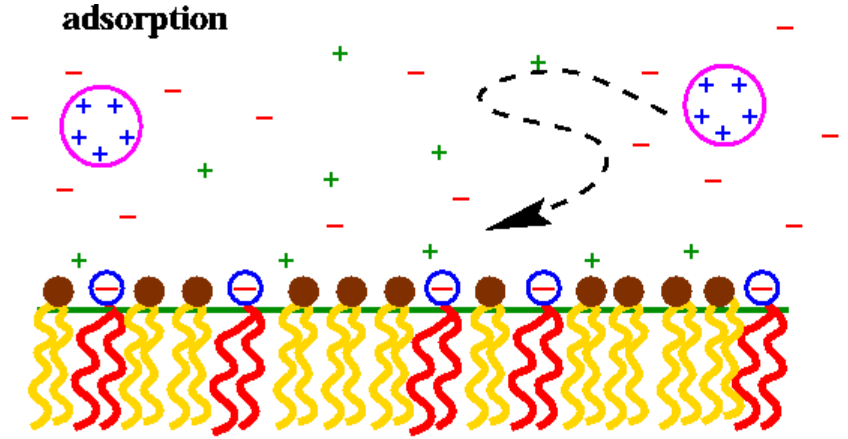
$c_0^c = 0$

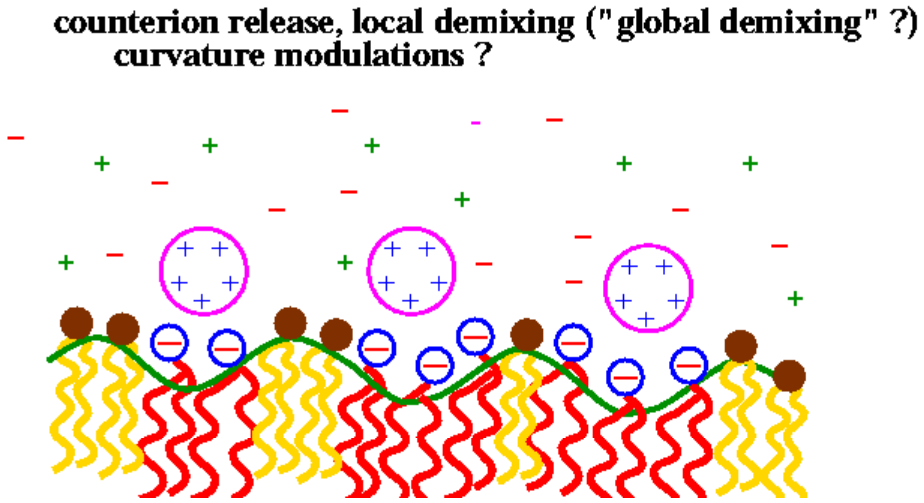
$\kappa = 10\ k_B T$



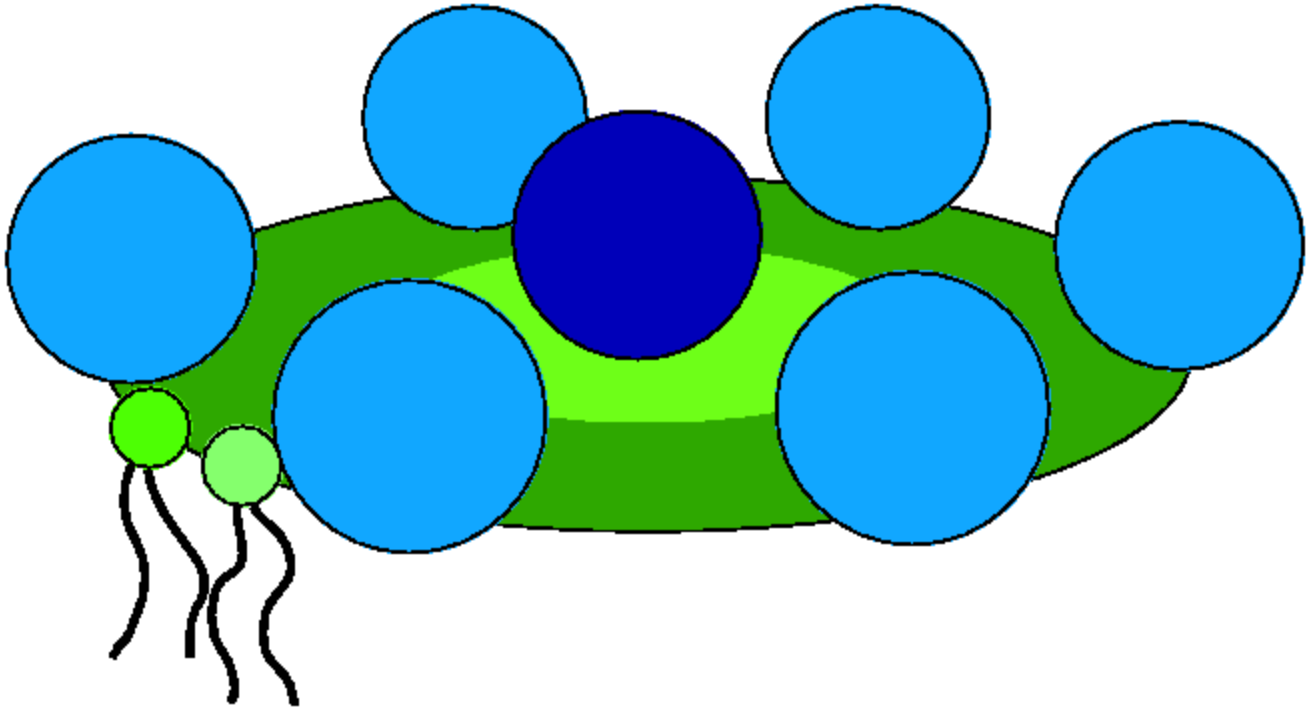


Membrane-Protein Interaction

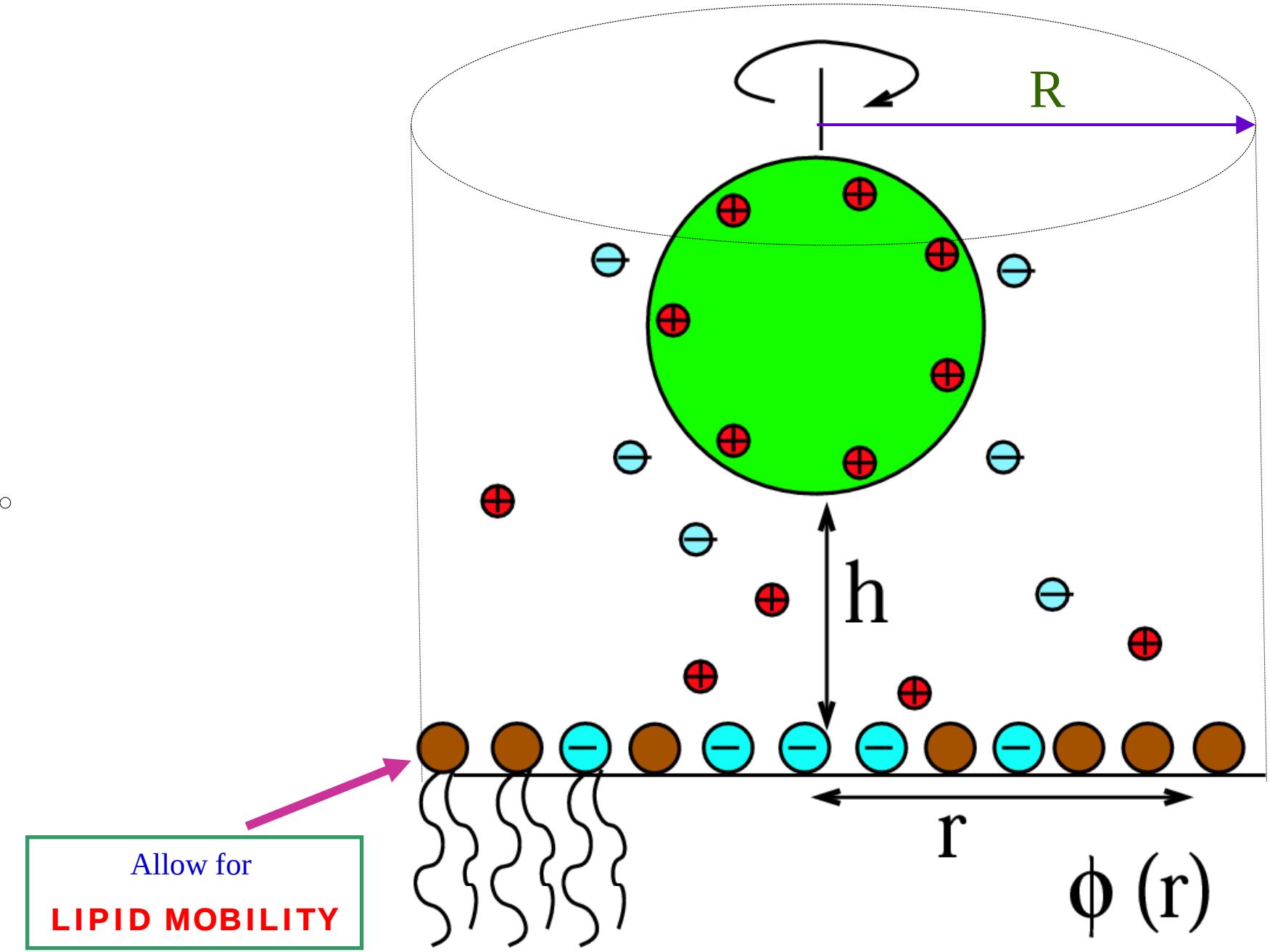




use Cell Model for Protein Adsorption



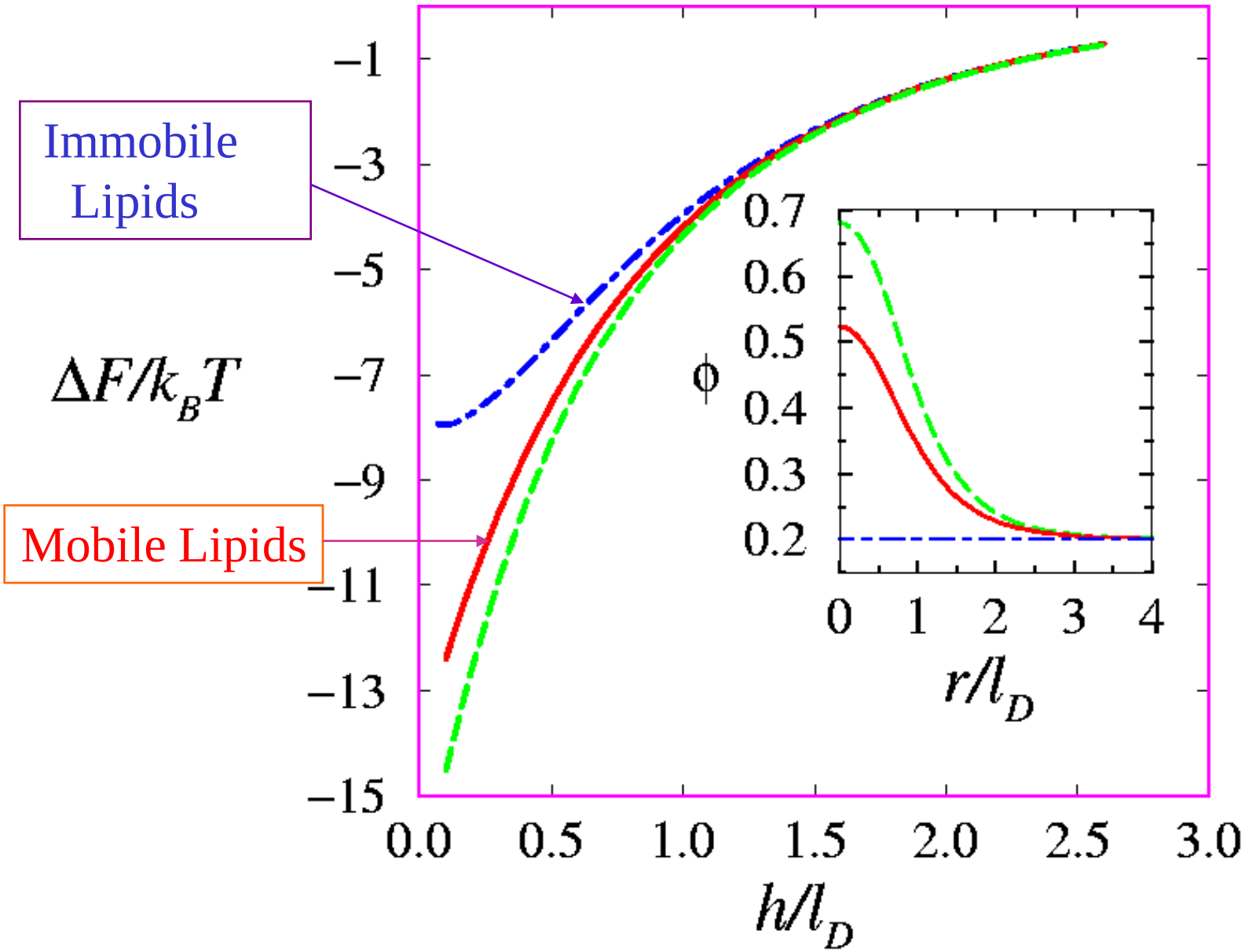
Solve Poisson-Boltzmann Equation



Allow for

LIPID MOBILITY

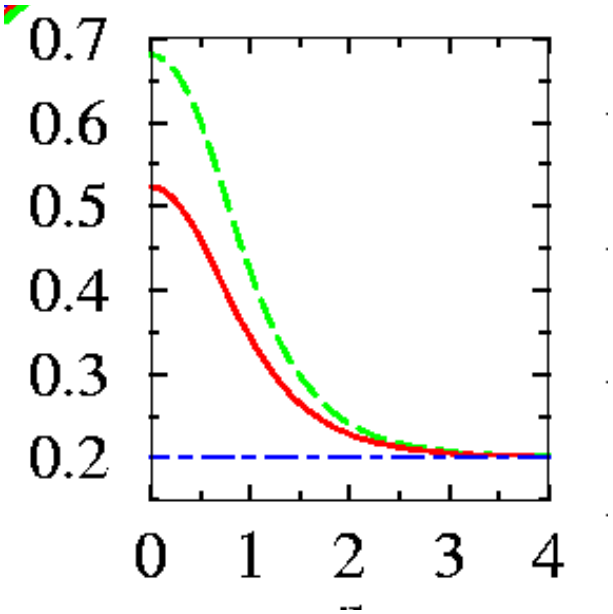
Free Energies and Composition Profiles (isolated protein)



Free Energies and Composition Profiles (isolated protein)

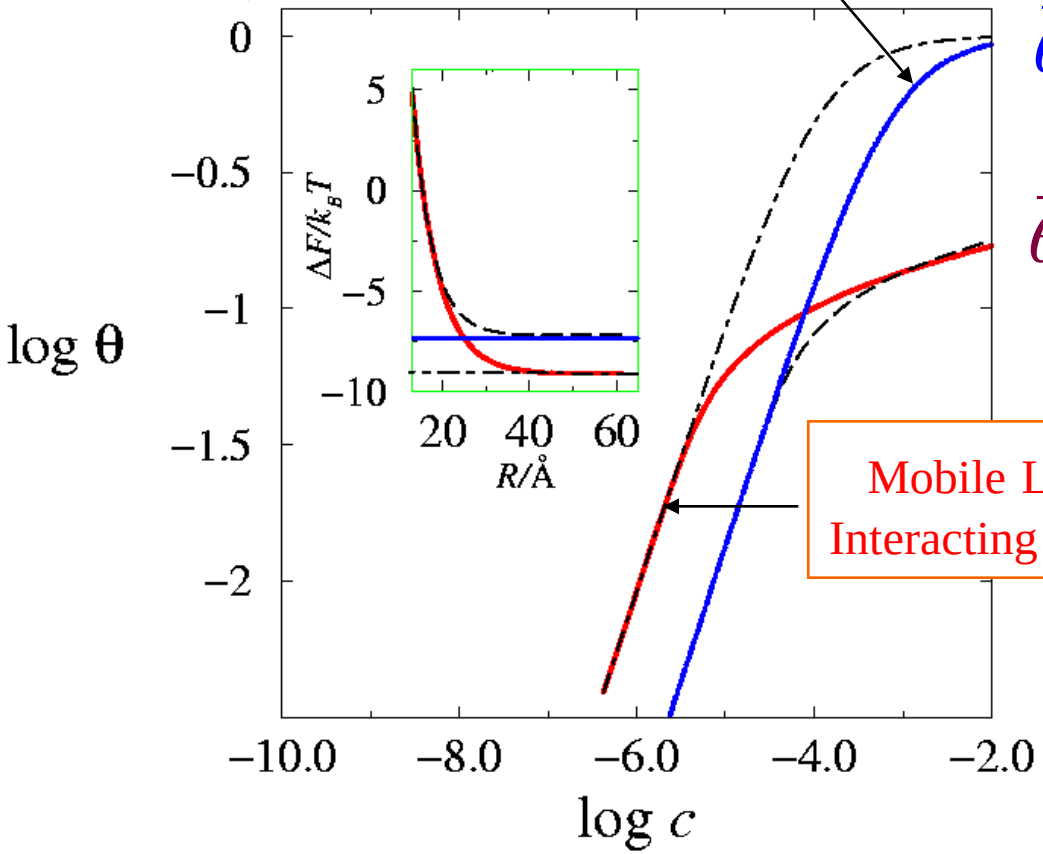
Immobile Lipids

Mobile Lipids



Immobile Lipids, Non-interacting Proteins

$\sigma^+ = 0.2,\ \sigma^- = 0.7$



$\bar{\theta} \approx 1$

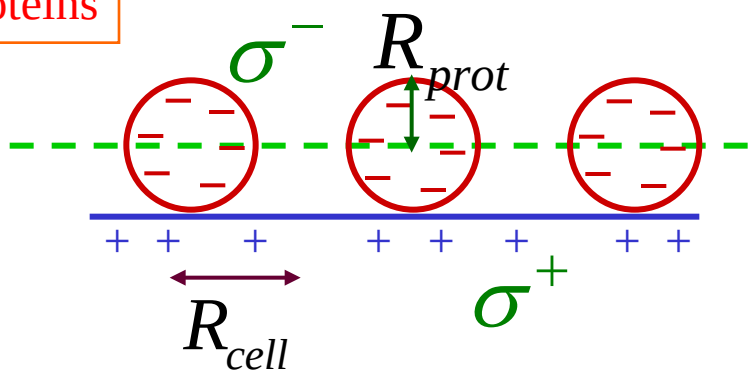
$\bar{\theta} \approx 0.16 \rightarrow$

$\sigma_{net} = -0.25$

$= -1.25\sigma^+$

Charge Inversion

Mobile Lipids, Interacting Proteins



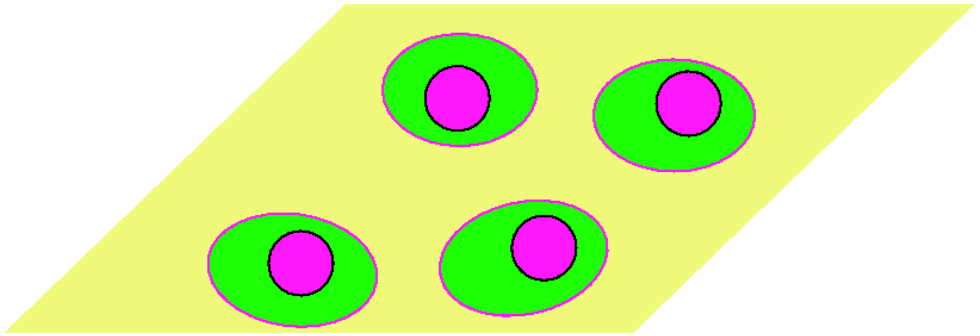
$\sigma_{net} = \sigma^+ - 4\theta\sigma^-$

$\theta = (R_{prot} / R_{cell})^2$

2D Protein-Lipid Condensation:

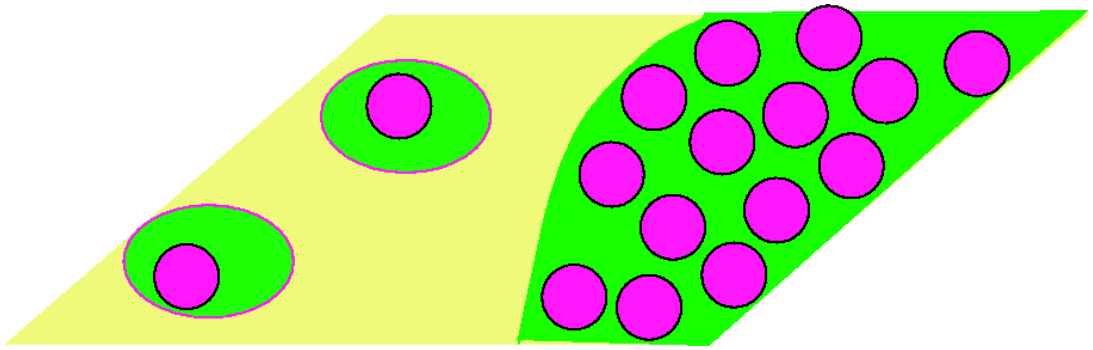
Role of Lipid Nonideal Mixing

Local Demixing

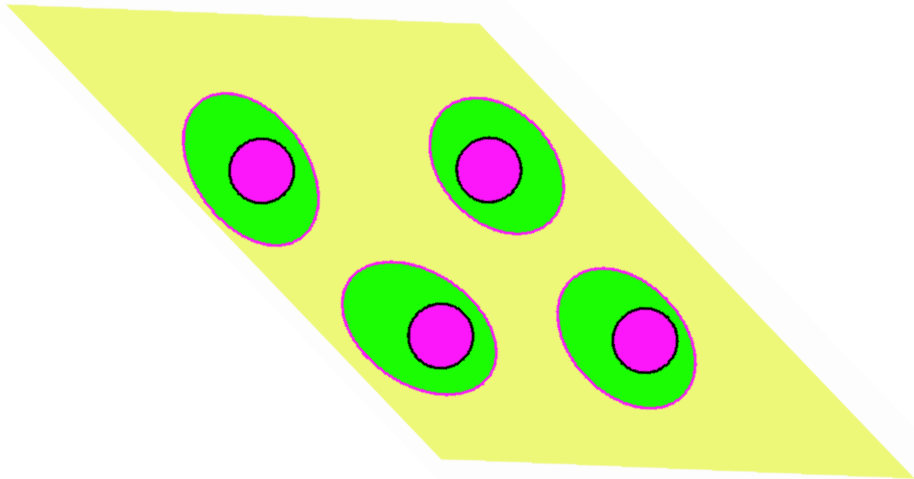


or

Global (phase separation)



or



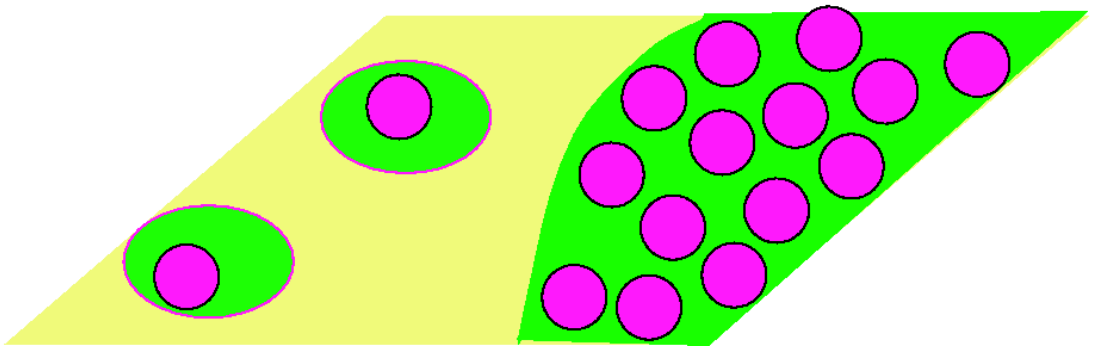
(phase separation)

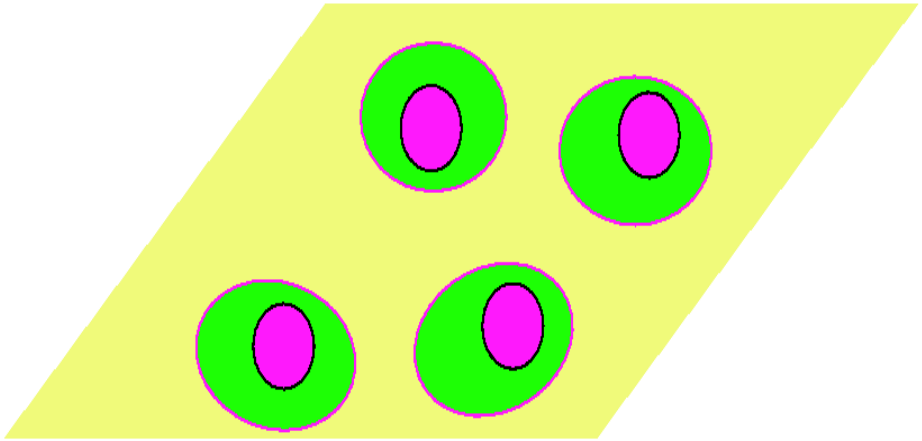
2D Protein-Lipid Condensation:

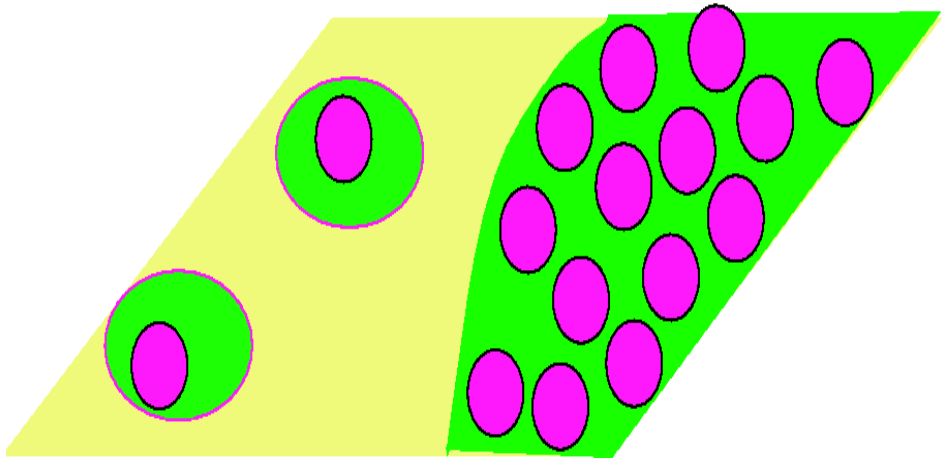
Role of Lipid Nonideal Mixing

or

(phase separation)



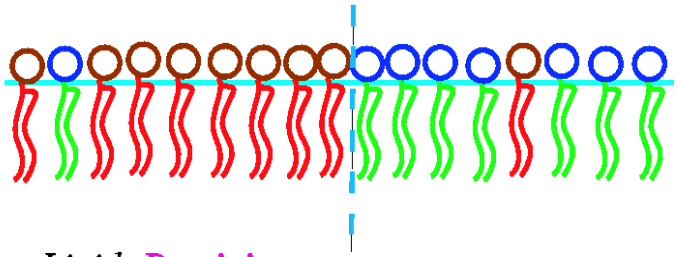




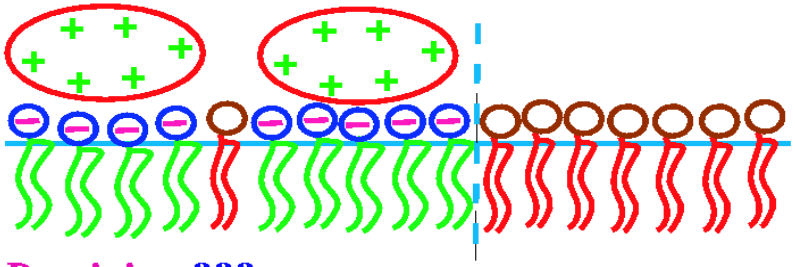
χ = lipid (chain !) nonideality

$$\chi > 0$$

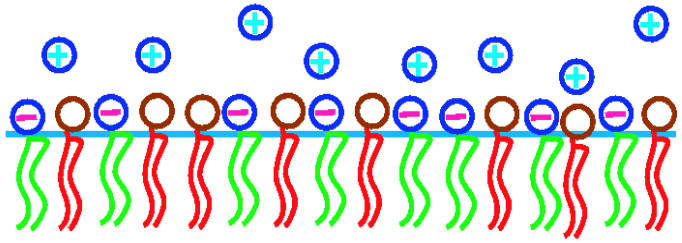
*Two **Uncharged** Lipids : Phase Separation*



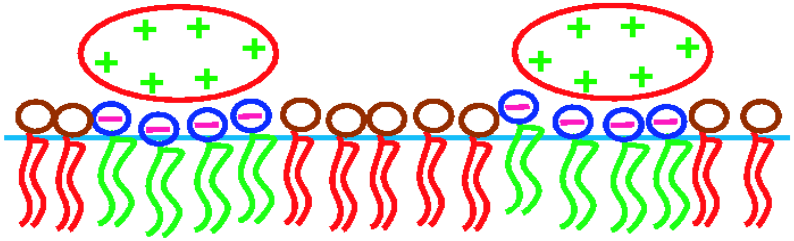
Adding Protein: Neutralization/Phase Separation



*Charging One Lipid: **Demixing***



*Or, **Local Demixing ???***



$$\frac{F}{N_{lip}kT} = \varphi \ln \varphi + (1-\varphi)\ln(1-\varphi) + \chi\varphi(1-\varphi)$$

$$+\left(a_{lip}/a_{prot}\right)\left[\theta\ln\theta + (1-\theta)\ln(1-\theta)\right] + f_{elec}(\theta,\varphi)$$

φ = charged lipid (area) fraction

θ = protein concentration (area fraction)

Cell Model: Electrostatic Free Energy Per Cell

$$F_{el} = N_{lip} f_{el} = \frac{1}{8\pi l_B}\int_{V_c} dV(\nabla\Psi)^2$$

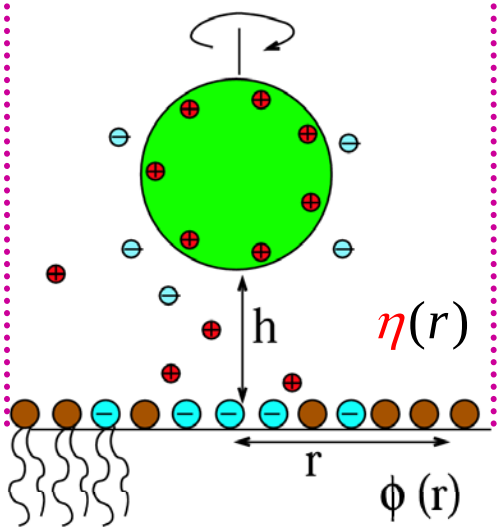
$$+\int_{V_c} dV\left[n_+ \ln\frac{n_+}{n_0} + n_- \ln\frac{n_-}{n_0} - (n_+ + n_- - 2n_0)\right]$$

$$+\frac{1}{a_{lip}}\int_{A_c} dA\left[\eta \ln\frac{\eta}{\varphi} + (1-\eta)\ln\frac{(1-\eta)}{(1-\varphi)} - \chi(\eta-\varphi)^2\right]$$

$$+\frac{\omega}{2}\int_{A_c} dA(\nabla\eta)^2$$

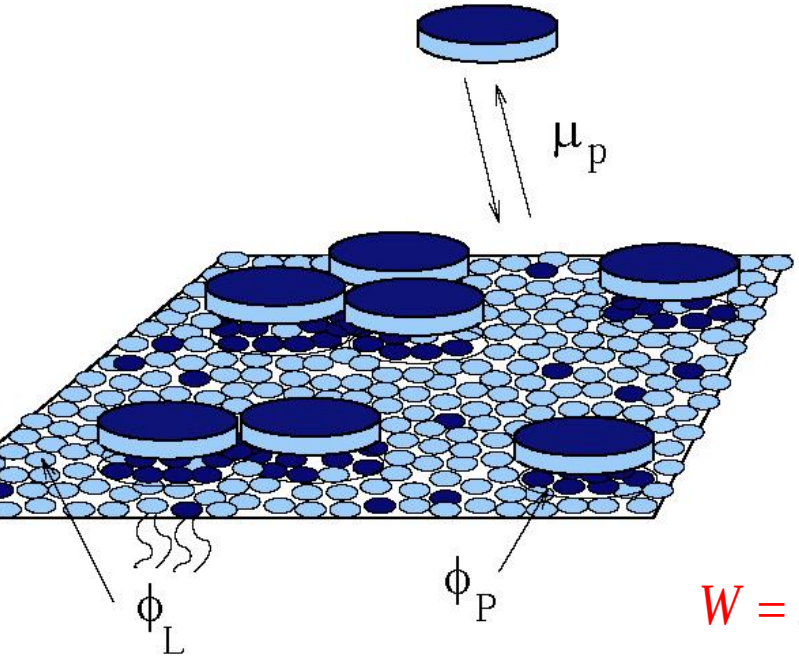
Line Energy

$$\varphi = \frac{1}{A_c}\int_{A_c} \eta dA$$



$$\omega = 2\omega_{AB} - (\omega_{AA} + \omega_{BB}) = (2kT/z)\chi$$

(A, B = the two lipid species)



2D Protein Lattice Gas (MF) Model

$$\frac{F}{kT} = \theta \ln \theta + (1-\theta)\ln(1-\theta) + \Lambda\,\theta(1-\theta)$$

$$W = 2W_{PM} - (W_{PP} + W_{MM}) = (\pi / z)\left(\frac{a_{prot}}{a_{lip}}\right)^{\frac{1}{2}} \omega(\phi_L - \phi_P)^2$$

Two state approximation:

$\phi_P \quad \phi_L$

$$\Lambda = \left(\frac{z}{2kT}\right) W \cong \chi \left(\frac{a_{prot}}{a_{lip}}\right)^{\frac{1}{2}} (\phi_L - \phi_P)^2$$

$$\Lambda_c = 2 \quad \Rightarrow \quad \chi_c = \frac{2(a_{lip} / a_{prot})^{1/2}}{(\phi_L - \phi_P)^2}$$

S. May, D. Harries and ABS. PRL (2002) E. Mbamala, ABS and S. May, BJ (2005)

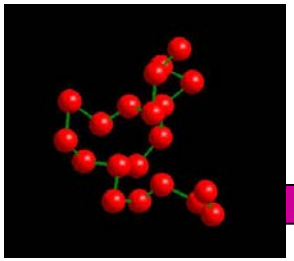
* Lipid mobility allows compositional modulations ➡ Enhanced adsorption energy

* Protein lateral interactions determine saturation coverage (Debye length)

* Overcharging/Charge Inversion Depend on Protein Shape

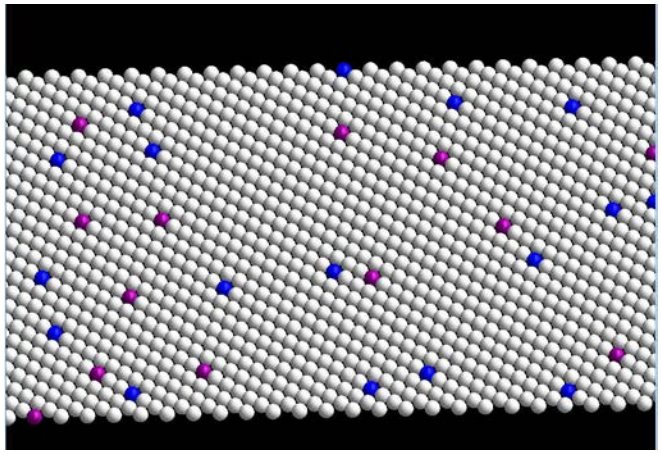
* Phase separation ⟺ Nonideal lipid mixing

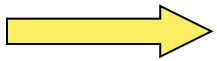
* Critical lipid nonideality (possibly) smaller than for bare Membrane

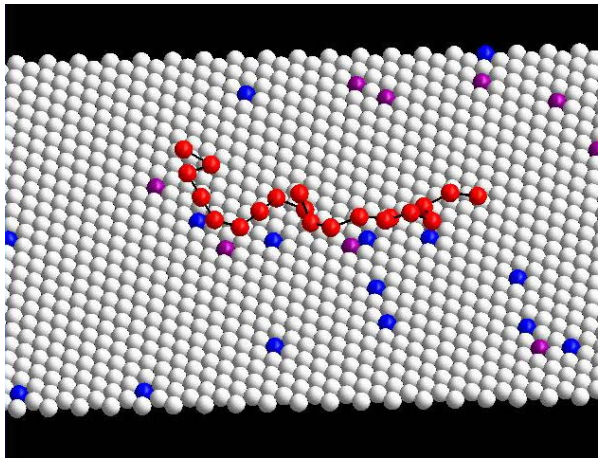


Flexible Macromolecules (Macroions) Interacting with Mixed Fluid Surfaces

Tzlil@ABS BJ(in press)







$$\Delta S < 0$$

Rigid Macrolecule & Frozen Membrane: $\Delta F = \Delta E_{\text{int}}$

Polymer & Frozen/Uniform Membrane: $\Delta F = \Delta E_{\text{int}} + \Delta E_p - T\Delta S_p$

Polymer & fluid membrane: $\Delta F = \Delta E_{\text{int}} + \Delta E_p - T\Delta S_p + \Delta E_m - T\Delta S_m$

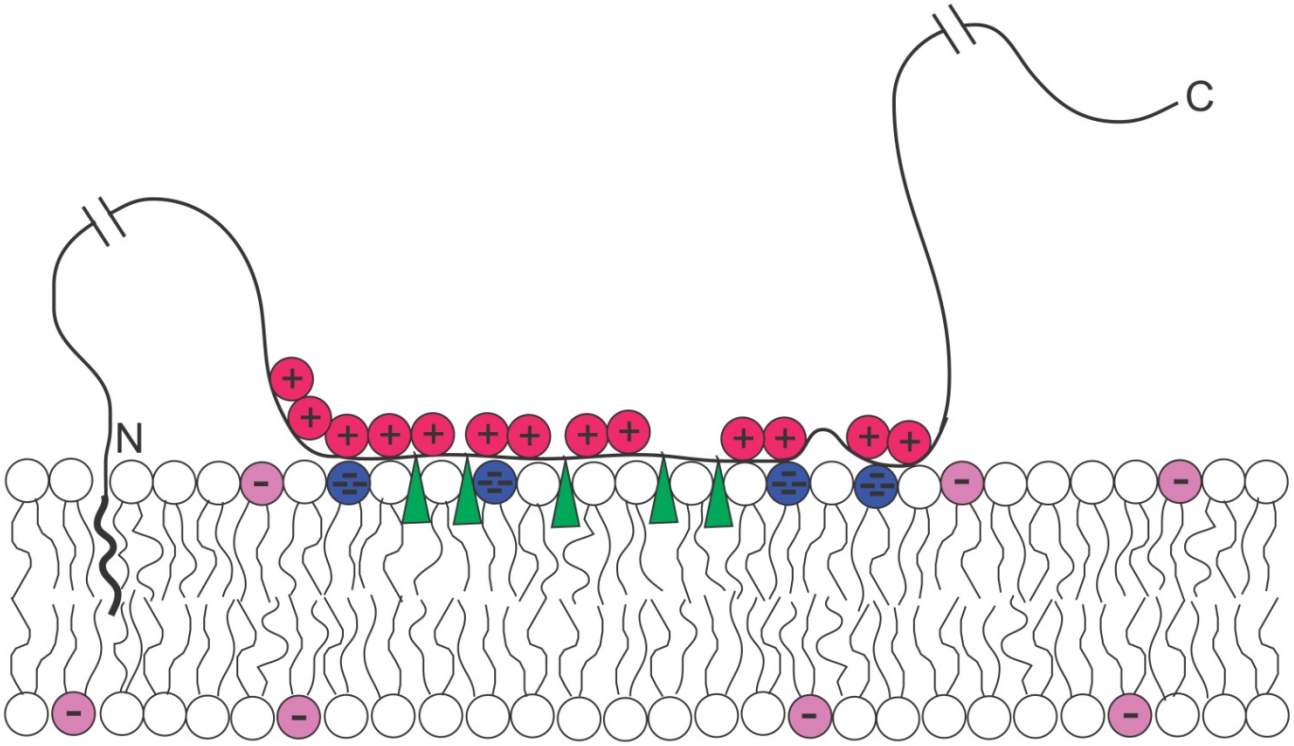
MARCKS

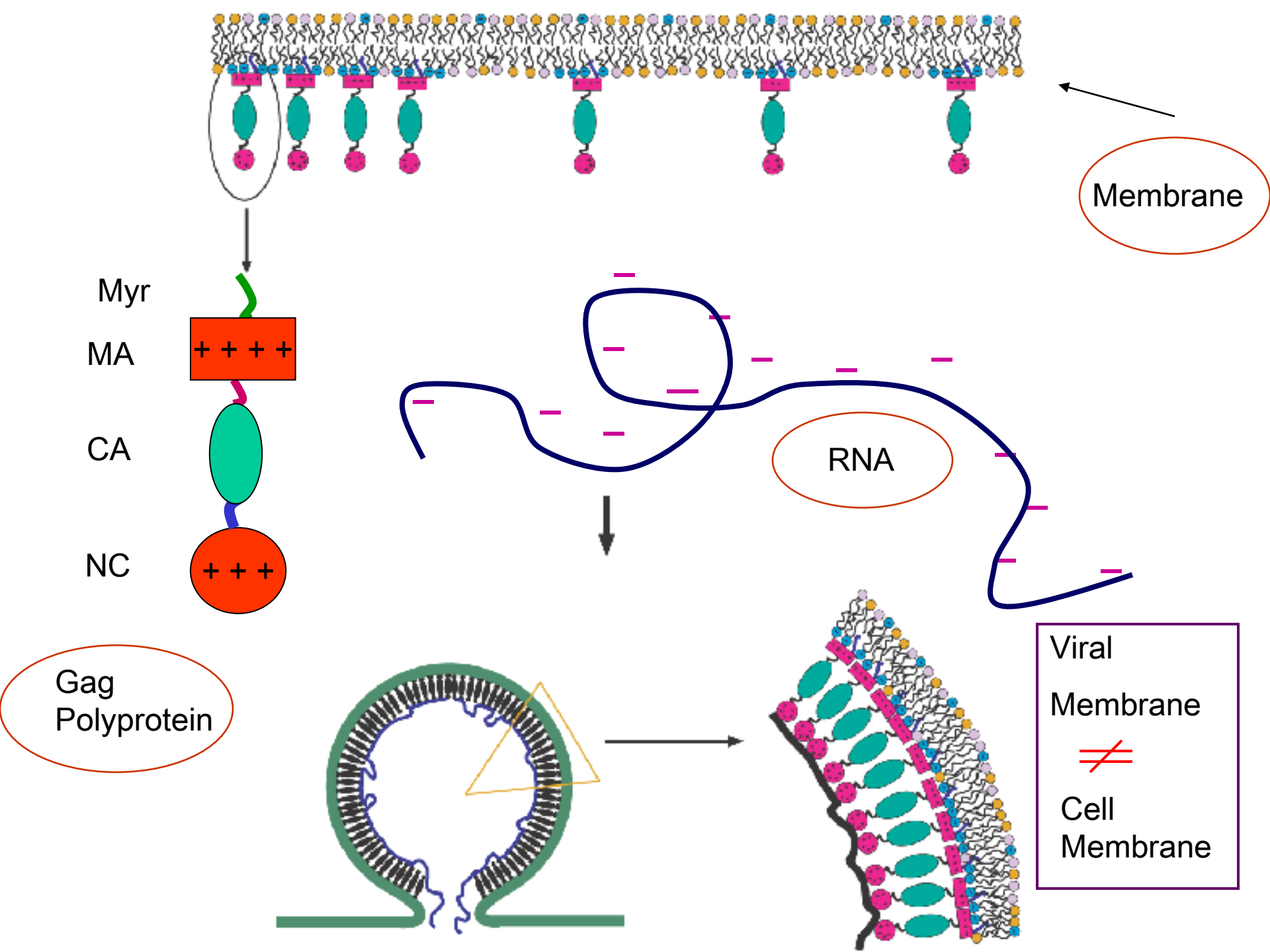
(Myristoylated Alanine-Rich C Kinase Substrate)

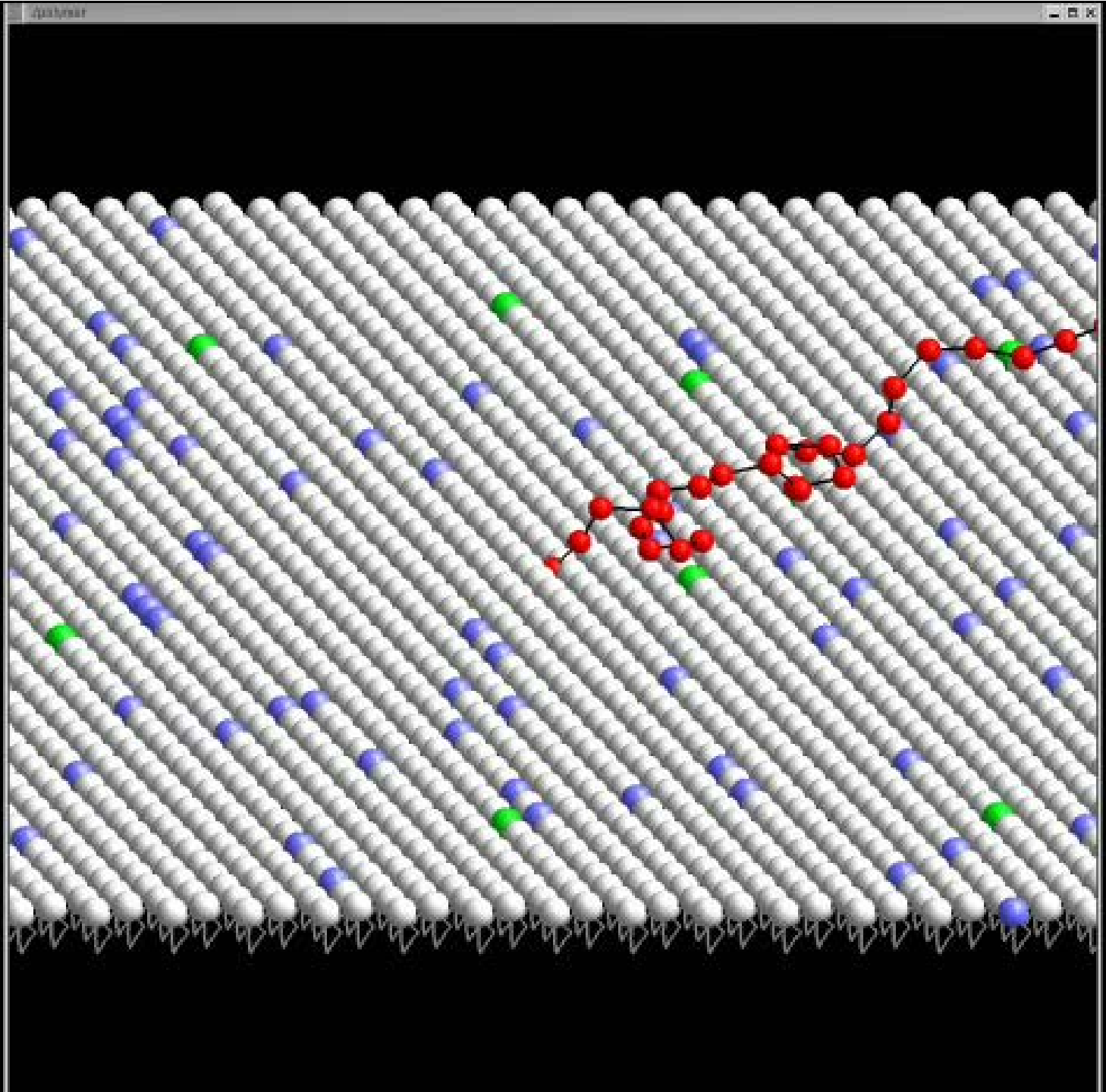
"electrostatic switch"

Hydrophobic interaction
(Myristoyl chain+phenyl alanine groups)

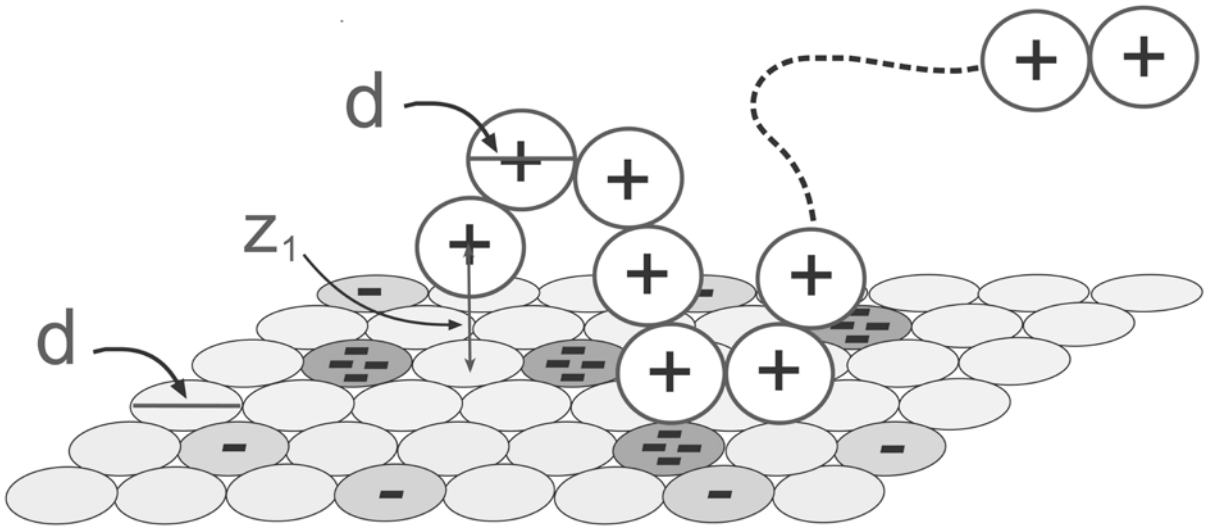
Electrostatic interaction




Membrane
Myr
MA
+ + + +
CA
NC
+ + +
RNA
Gag
Polyprotein
Viral
Membrane
≠
Cell
Membrane



Model



Hexagonal lattice of interacting disks

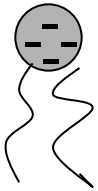
Freely jointed chain of beads.

Lennard-Jones repulsion
(excluded-volume)

PC

PS

PIP_2



Polymer segment +

Debye-Hückel interactions between charged particles

Simulation Conditions

"Physiological Conditions"

Area per head group = 64Å^2

⇩

Lattice constant = 8.66Å=polymer segment diameter

[PS] = 0.01, 0.1 [PIP_2] = 0. 01

Debye-Hückel potential

$$U(r) = \frac{z_1 z_2 l_B e^{-r/l_D}}{r}$$

Beujrum Length (l_B) = 7.14Å (T = 300 K)

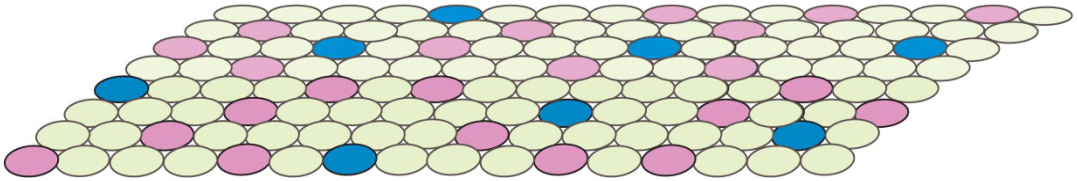
Debye Length (l_D) = 10 Å

All energies are in kT.

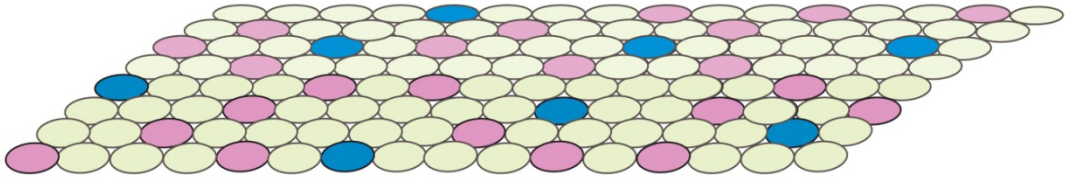
All distances in polymer segment diameter

Three types of membranes

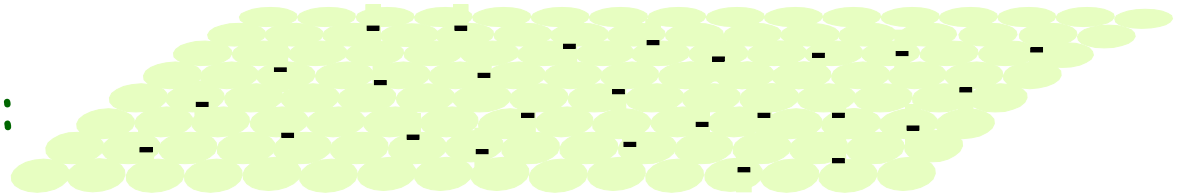
Fluid membrane:



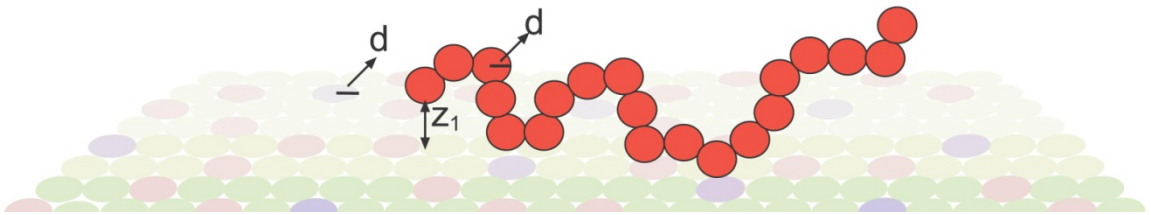
Frozen membrane:

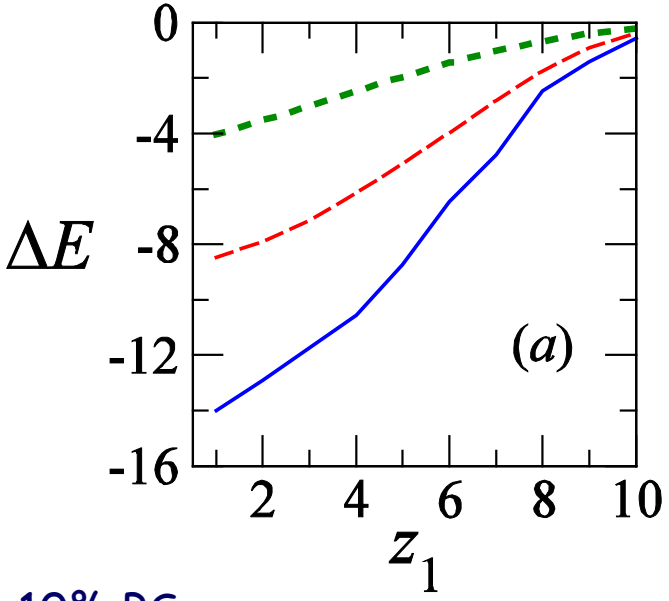


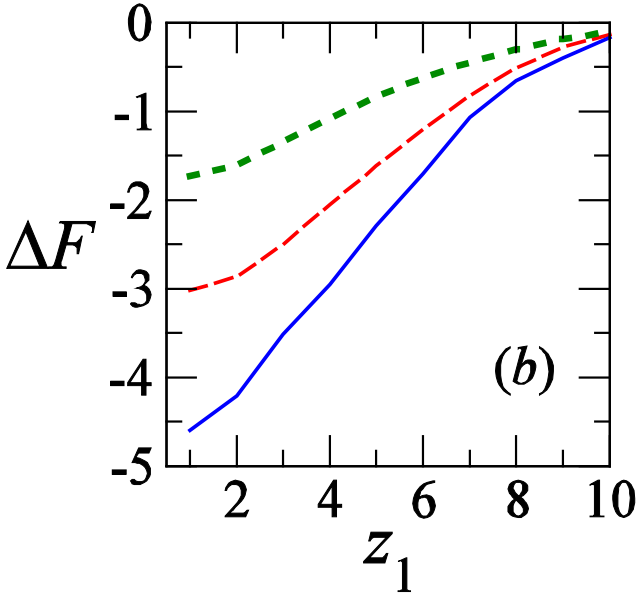
Uniform membrane:



"Potential of Mean Force"







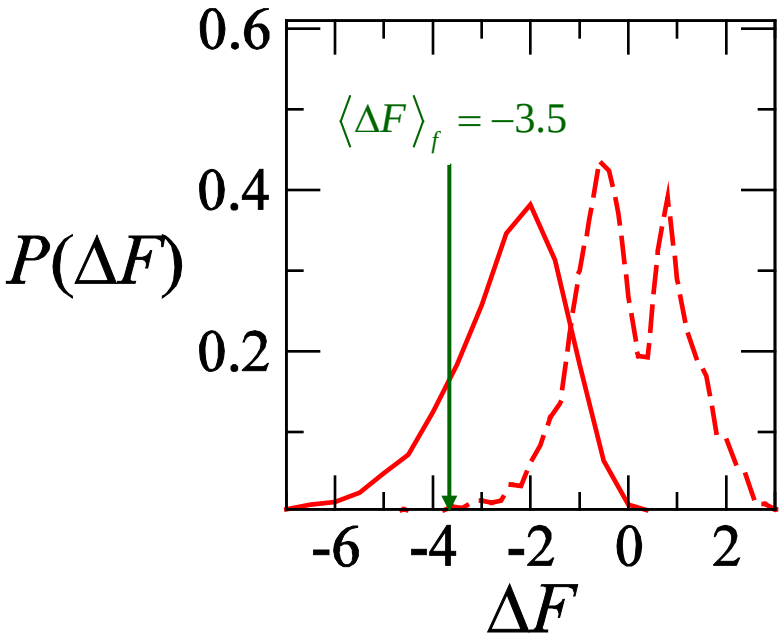
1% PIP_2, 10% PS

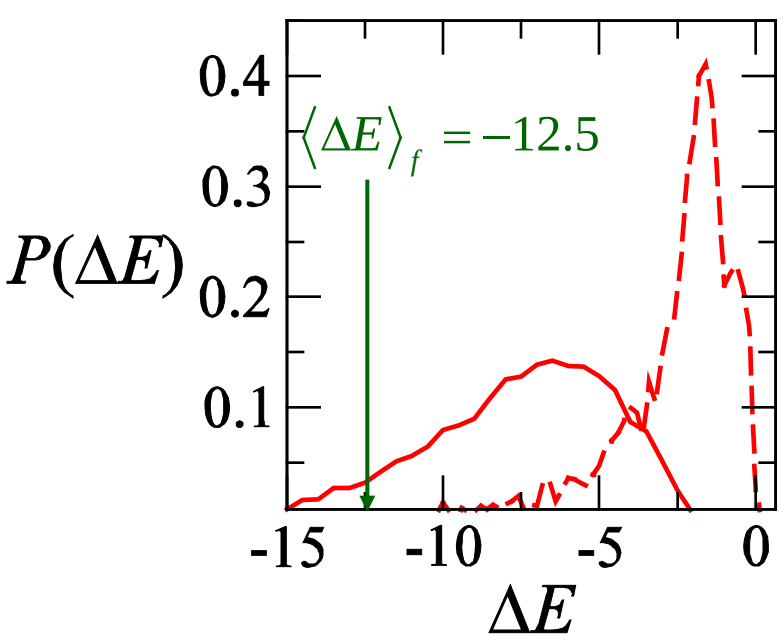
Fluid membrane: $\Delta F < 0 \iff$ adsorption

Frozen membrane: $\langle \Delta F \rangle \cong 0 \iff$ weak adsorption

Uniform membrane: $\Delta F > 0 \iff$ depletion

Distribution of Adsorption Energies on Frozen Membrane





1% PIP2, 1% PS

1% PIP2, 10% PS

Some quenched membranes are repulsive
Others are strongly attractive
(More than the mobile membrane!
No loss of lipid entropy…)

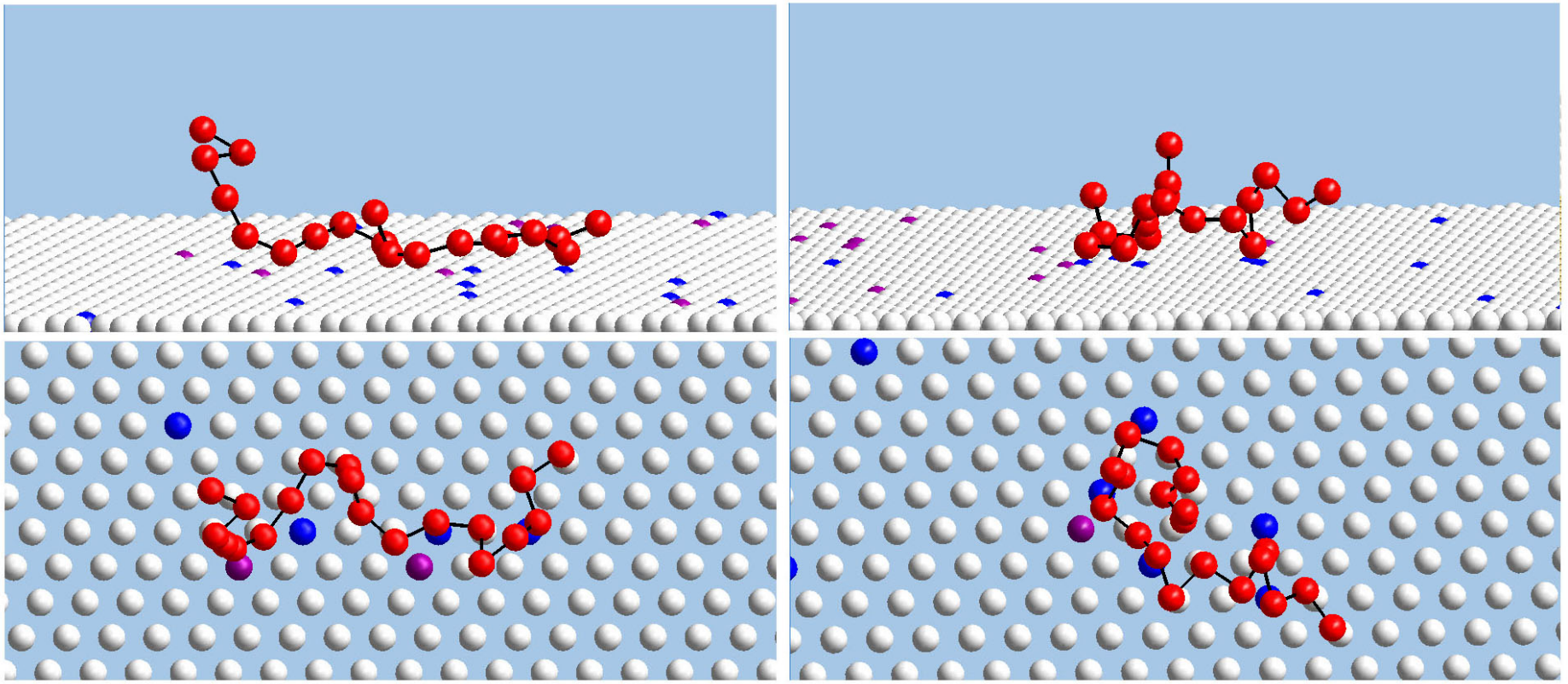
Fluid membrane

$\langle \Delta F \rangle_f = -0.7$

$\langle \Delta E \rangle_f = -5.0$

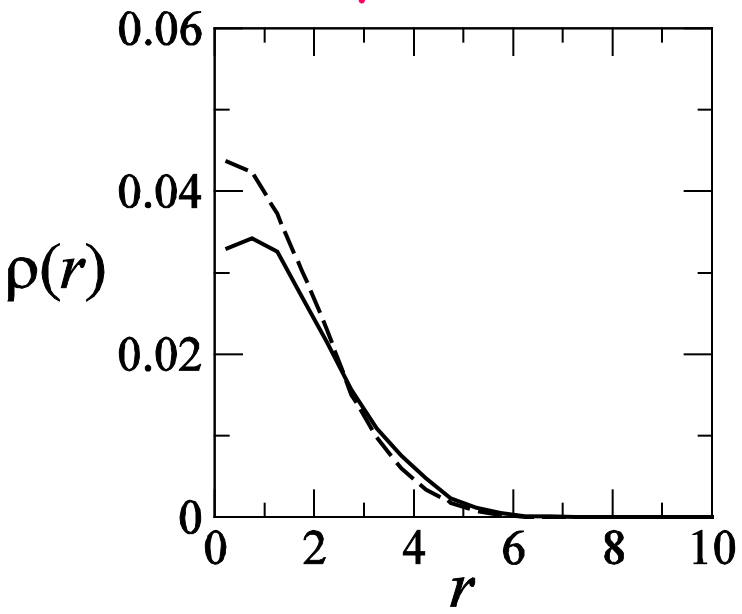
$\langle \Delta F \rangle_f = -3.5$

$\langle \Delta E \rangle_f = -12.5$

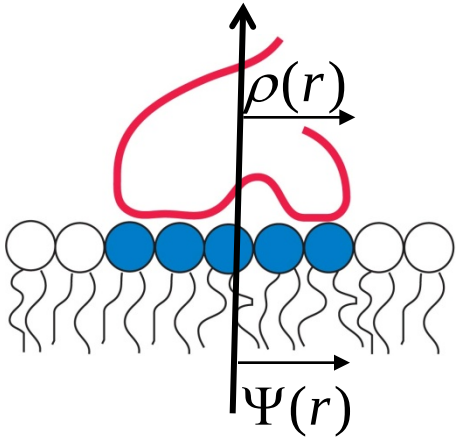


2D Distribution Of:

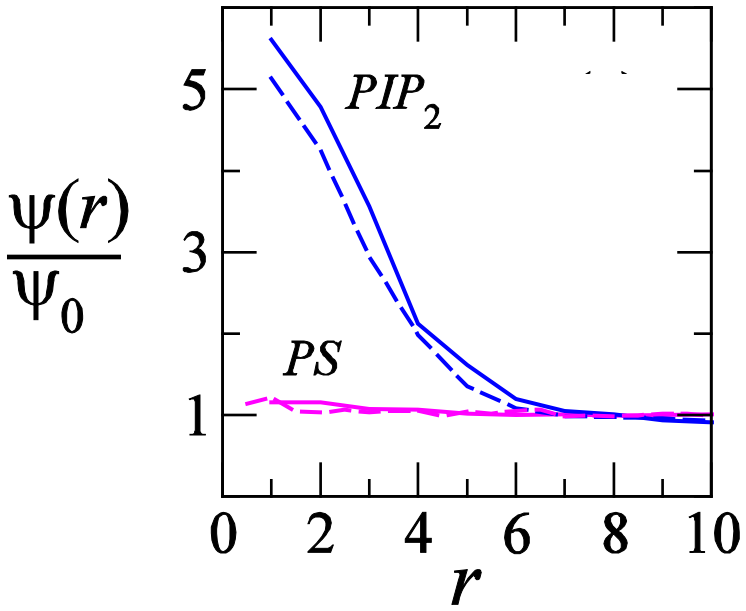
Polymer



Lateral distribution of polymer segments.



Lipid



PIP_2 ($Z=-4$) localize near polymer

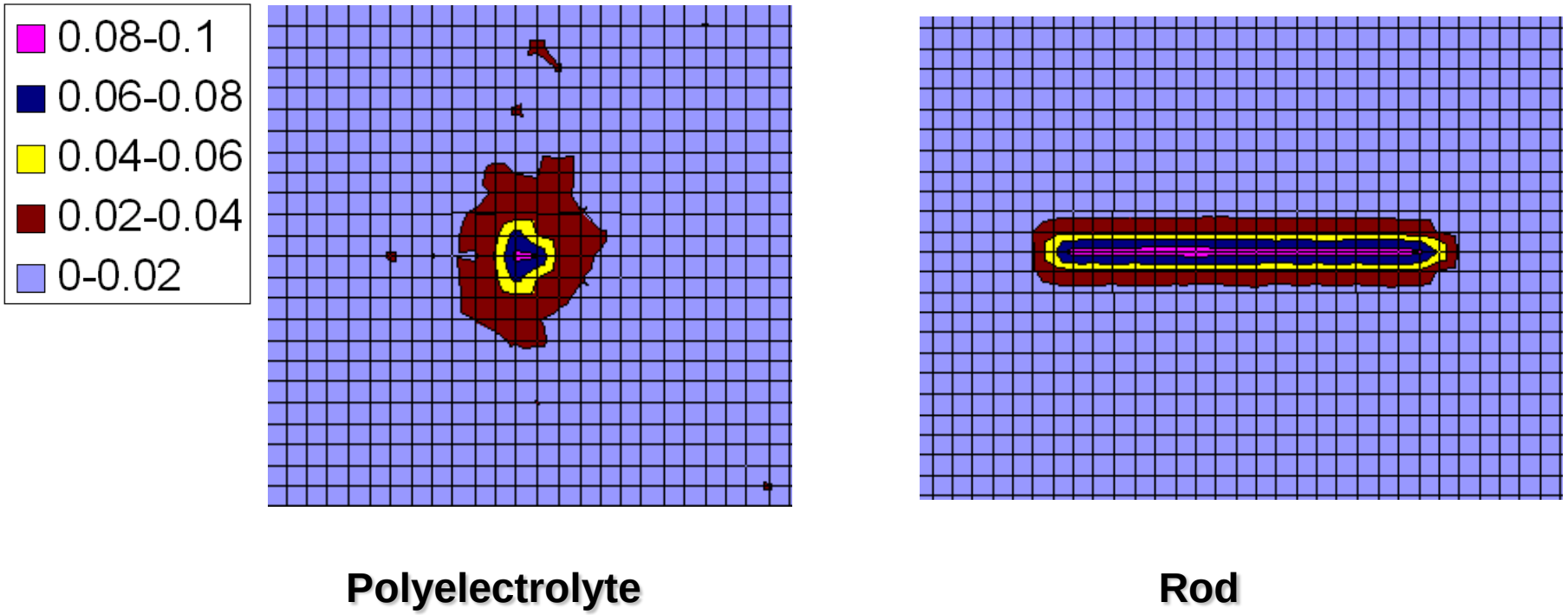
PS ($Z=-1$) distribution not affected.

Charge Matching ⟷ Smaller Entropy Loss by Multivalent Lipid

$$\Delta S_z \sim \frac{1}{z}\ln\left(\frac{\psi_z^*}{\psi_z^0}\right) \sim \frac{1}{z}\ln\left(\frac{1/z}{\psi_z^0}\right)$$

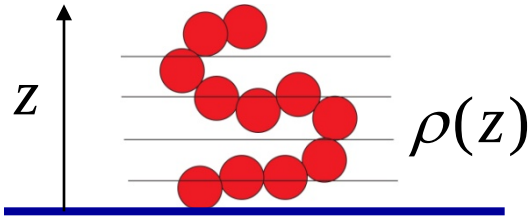
Lipid Distribution

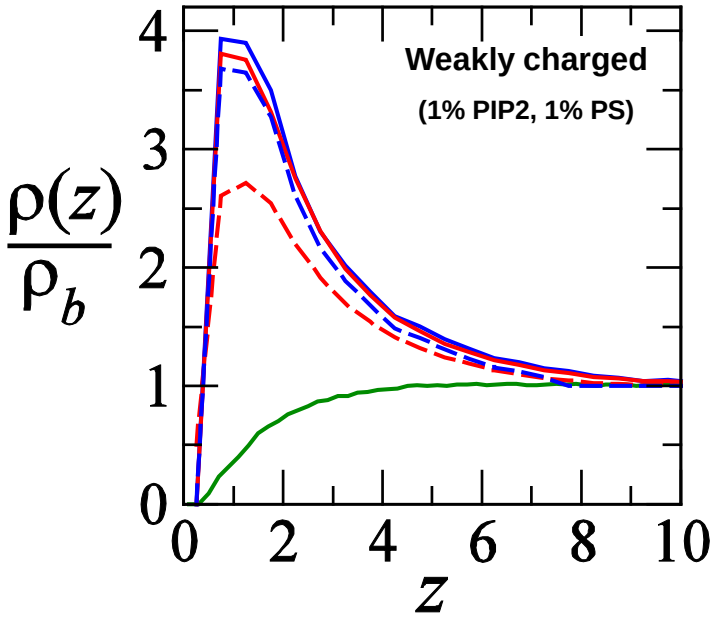
PIP_2 lipids concentrate "under" the macromolecule (isoelectricity)

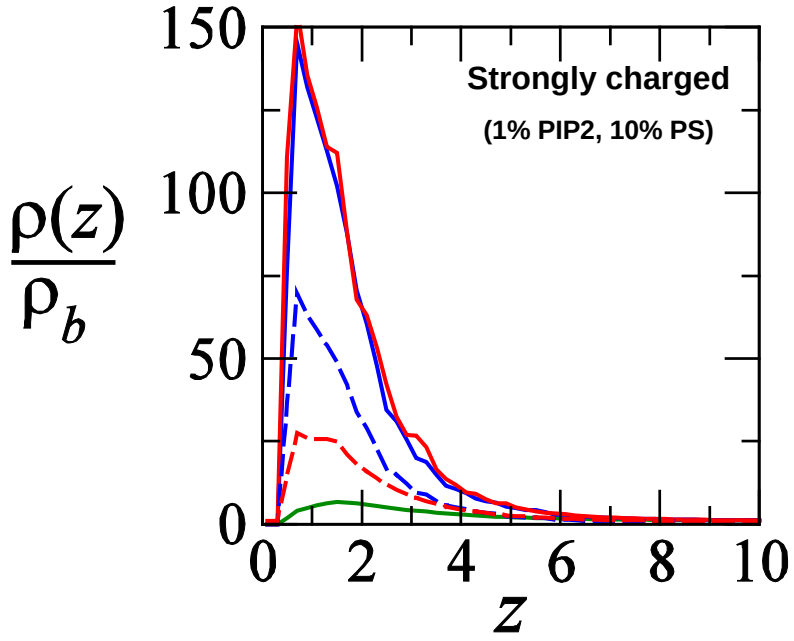


Polyelectrolyte **Rod**

Polymer density profile







$\varphi_b = 0.034$

$\varphi_b \to 0$ (vanishing surface concentration)

Fluid

Frozen

Uniform

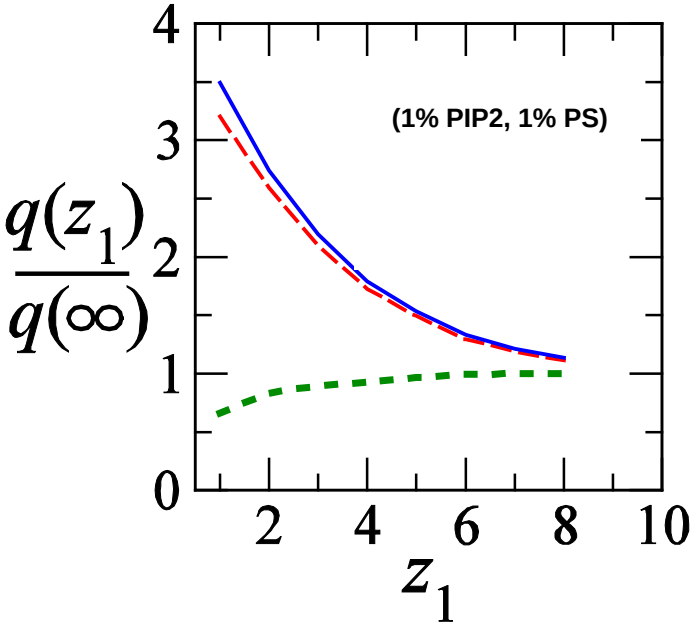
$$\rho(z) = \theta \int_0^{\lambda} \frac{q(z_1)}{q^{(1)}} n(z \mid z_1) dz_1 = \frac{\tilde{\varphi}_b (1-\theta)}{\lambda} \int_0^{\lambda} \frac{q(z_1)}{q(\infty)} n(z \mid z_1) dz_1$$

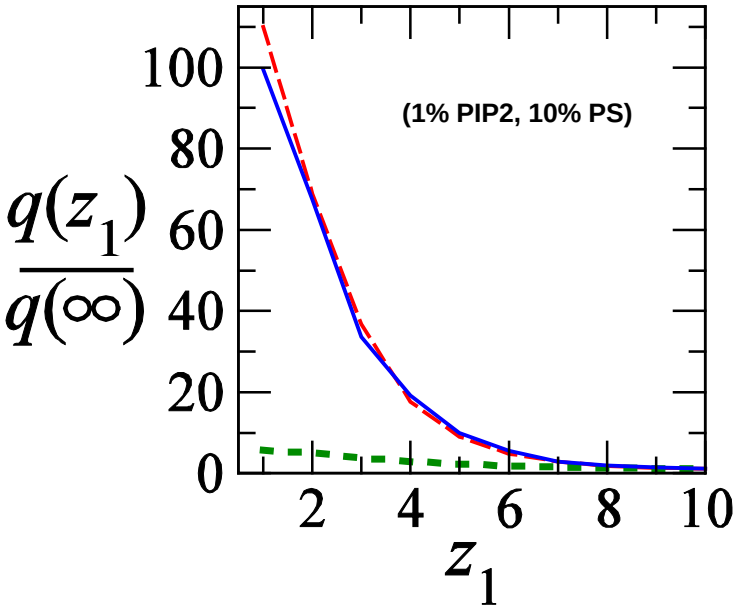
Partition function of a single polymer on a fluid membrane = Average Partition function of polymers on quenched membranes.

Fluid membrane

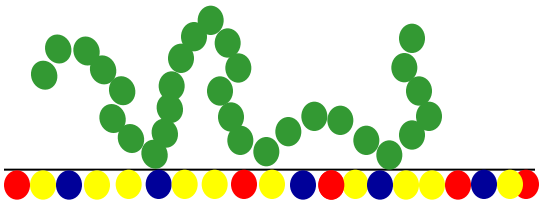
Frozen

Uniform





p = polymer conformation



m =membrane lipid configuration

$$\left(\frac{q}{q_\infty}\right)_f = \frac{q_f^{(1)}}{q_f^{(0)} q_b} = \frac{\sum_{m,p} e^{-u(m,p)}}{\sum_m e^{-u(m)} \sum_p e^{-u(p)}} = \frac{\sum_m e^{-u(m)} \sum_p e^{-u(p|m)}}{\sum_m e^{-u(m)} \sum_p e^{-u(p)}} =$$

$$= \sum_m P(m) \frac{\sum_p e^{-u(p|m)}}{\sum_p e^{-u(p)}} = \sum_m P(m) \frac{q_m}{q_b} = \left\langle \frac{q_m}{q_\infty} \right\rangle_q$$

Properly weighted, simulation runs for a single polymer on a (Boltzmann distributed) ensemble of frozen membranes reproduce the result for a fluid membrane

$$\langle A \rangle_f = \frac{\sum_{m,p} e^{-u(m,p)} A(m,p)}{\sum_{m,p} e^{-u(m,p)}}$$

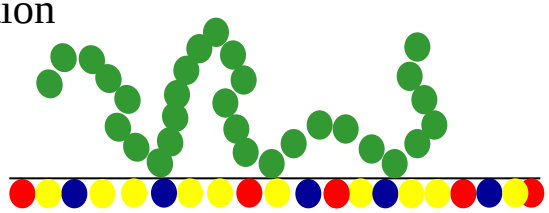
$$= \frac{\sum_m P(m) q_m A(m)}{\sum_m P(m) q_m}$$

$$= \sum_m P(m) A(m) \frac{q_m}{\langle q_m \rangle_q}$$

$$\neq \sum_m P(m) A(m) = \langle A_m \rangle_q$$

p = polymer conformation

m =membrane lipid configuration



$$u(m,p) = u(m) + u(p \mid m)$$

$$P(m) = \frac{e^{-u(m)}}{q_m}$$

$$q_m = \sum_p e^{-u(p|m)}$$

$$A(m) = \frac{\sum_p A(m,p) e^{-u(p|m)}}{q_m}$$

In the limit $\theta \to 0$ (vanishing surface density) $q_m \sim \theta_m$

$$\langle A \rangle_{fluid} = \frac{\sum_{m,p} e^{-u(m,p)} A(m,p)}{\sum_{m,p} e^{-u(m,p)}}$$

$$\to \frac{\sum_m P(m)\theta(m)A(m)}{\sum_m P(m)\theta(m)}$$

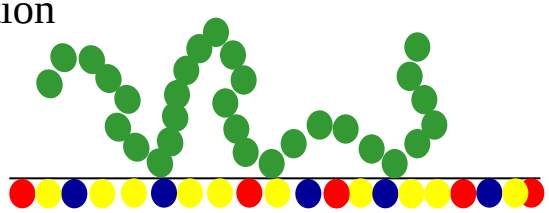
$$\equiv \sum_m f(m)A(m)$$

$$= \langle A(m) \rangle_{quenched\ (\theta-weighted)}$$

$$f(m) = \frac{P(m)\theta(m)}{\sum_m P(m)\theta(m)}$$

p = polymer conformation

m =membrane lipid configuration



$$u(m,p) = u(m) + u(p \mid m)$$

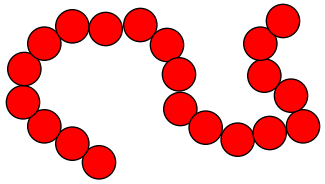
$$P(m) = \frac{e^{-u(m)}}{q_m}$$

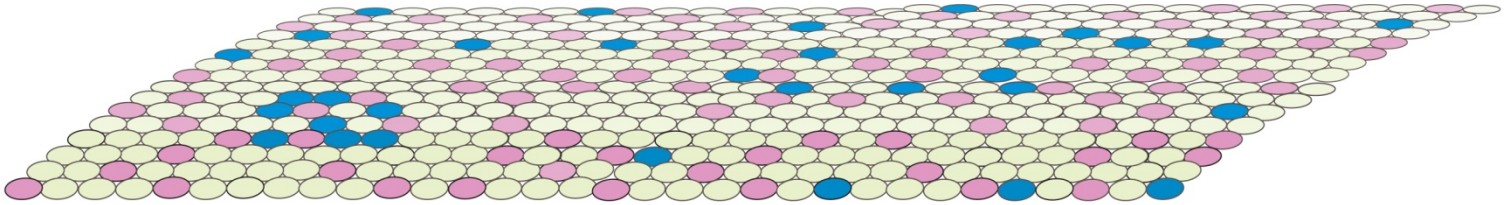
$$q_m = \sum_p e^{-u(p|m)}$$

$$A(m) = \frac{\sum_p A(m,p) e^{-u(p|m)}}{q_m}$$

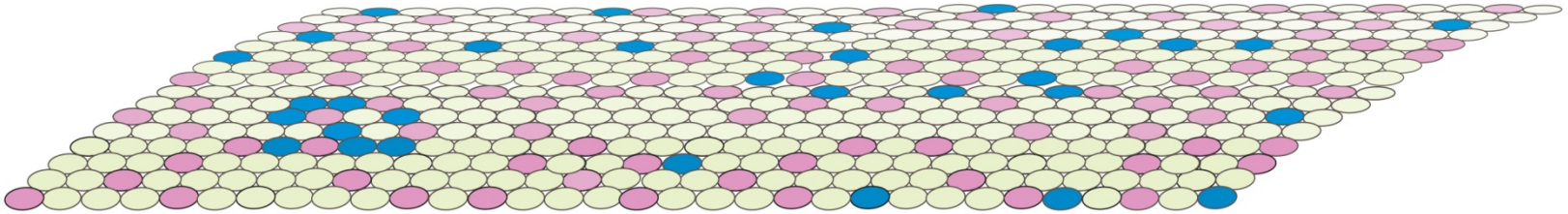
Low polymer concentration

Fluid membrane



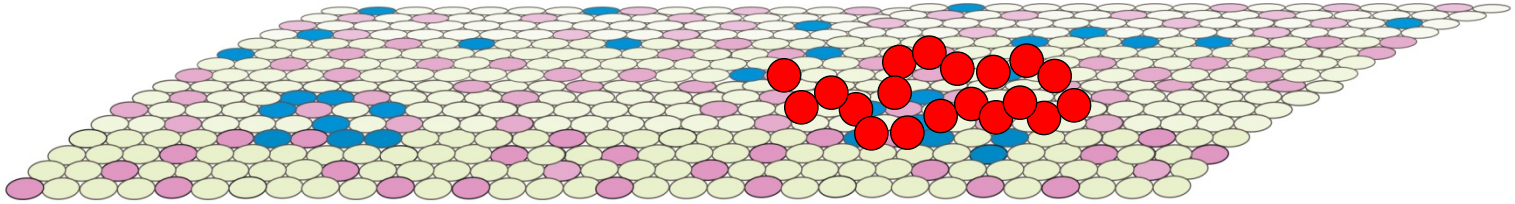


Frozen membrane

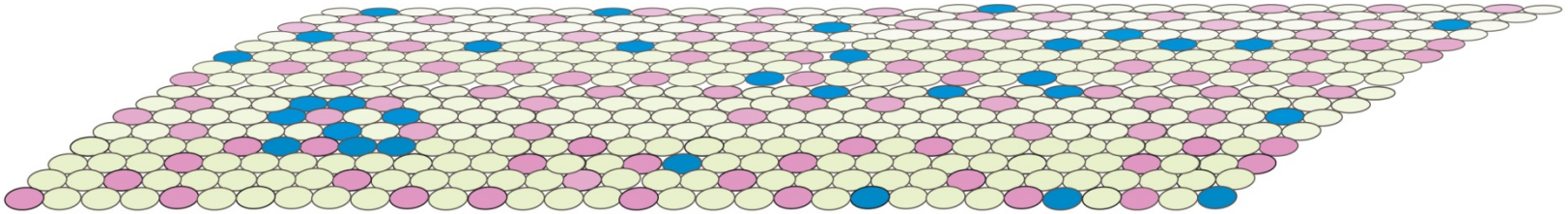


Low concentration

Fluid membrane

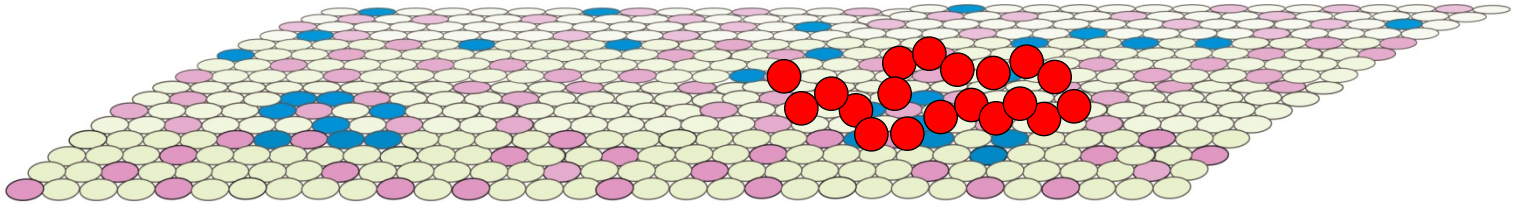


Frozen membrane

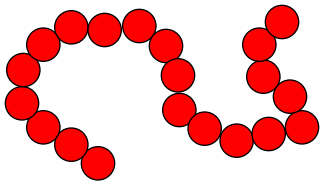


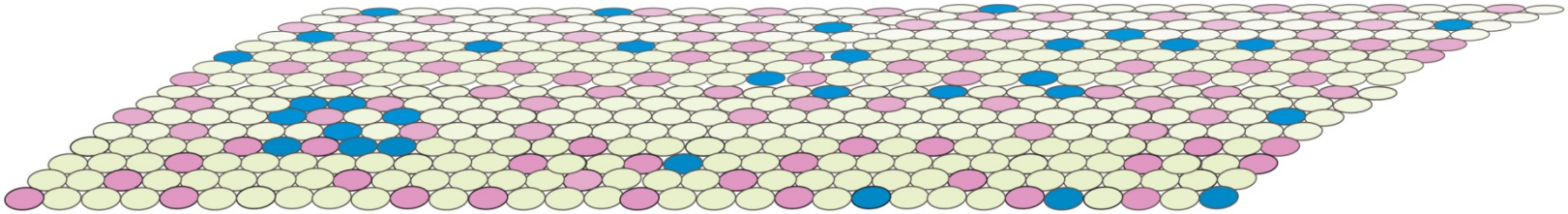
Low concentration

Fluid membrane



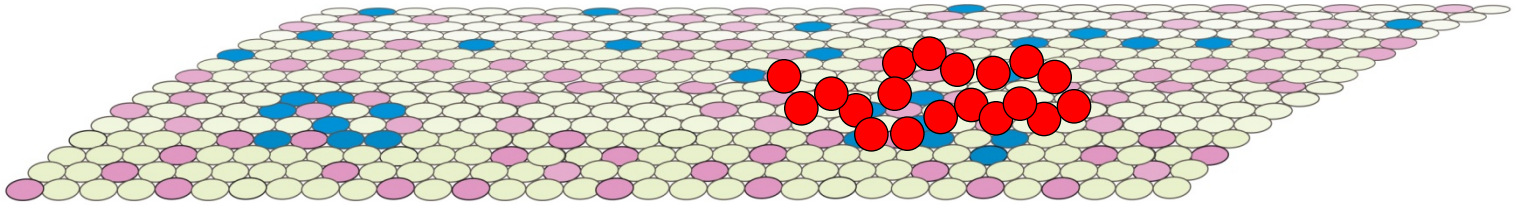
Frozen membrane



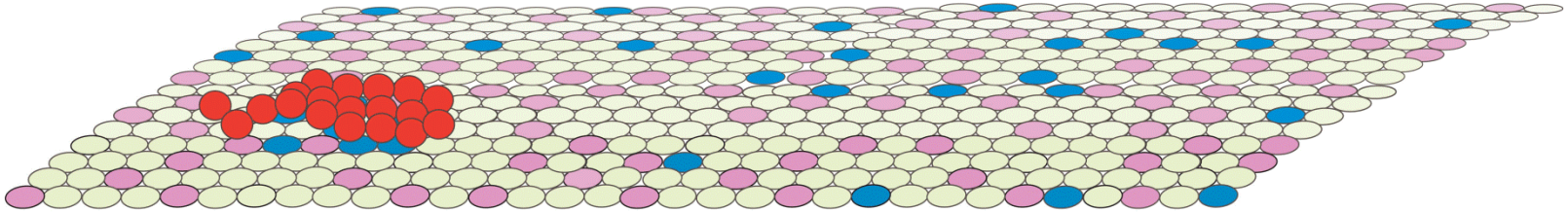


Low concentration

Fluid membrane

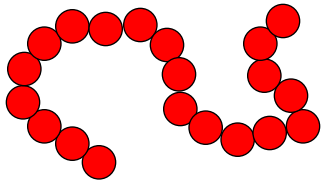


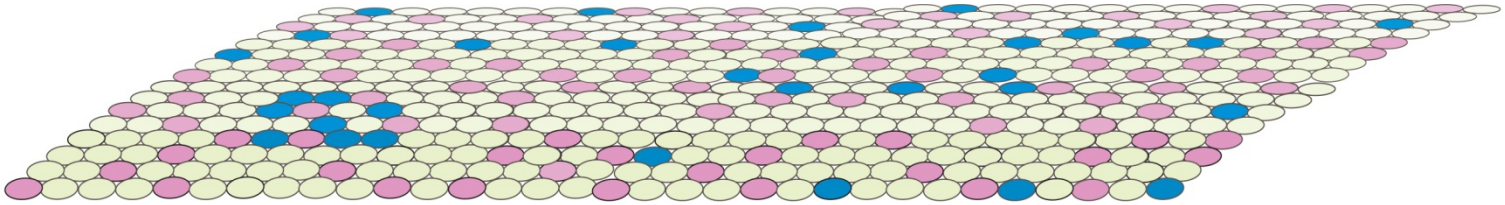
Frozen membrane



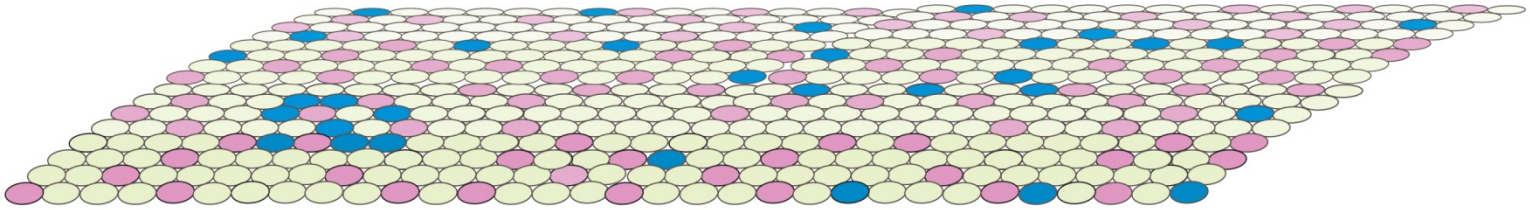
Higher concentration

Fluid membrane



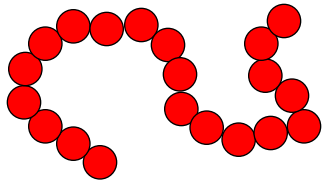


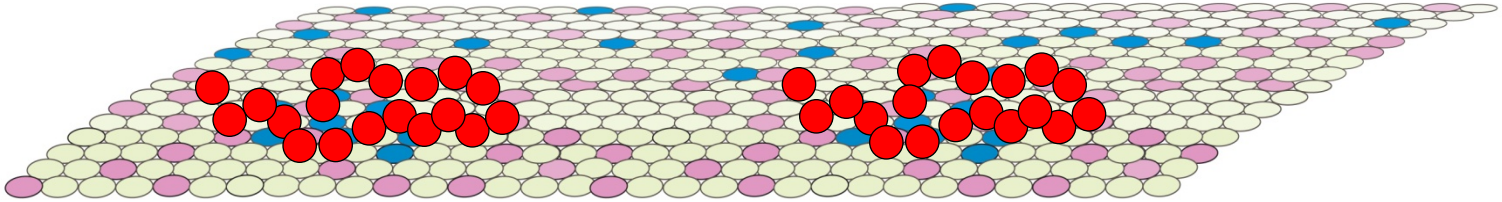
Frozen membrane



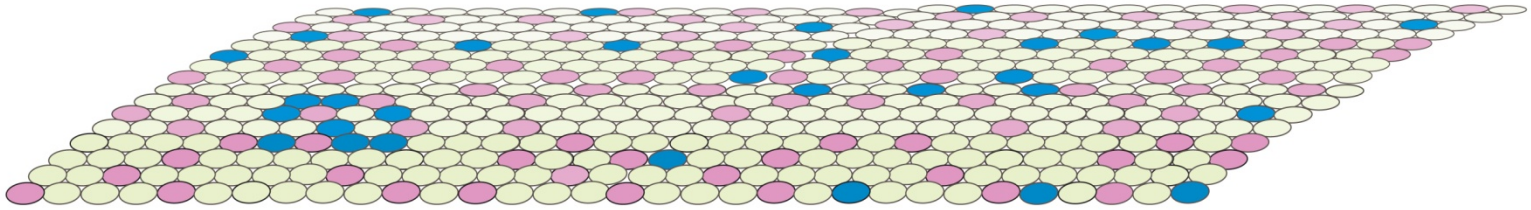
High concentration

Fluid membrane



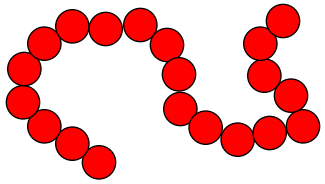


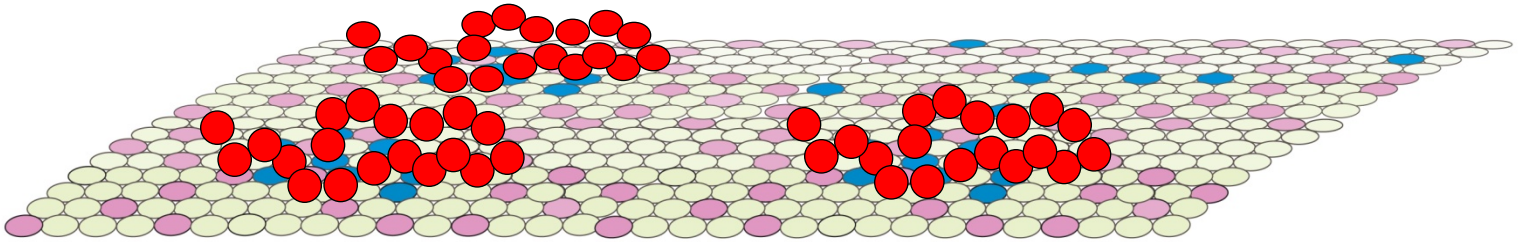
Frozen membrane



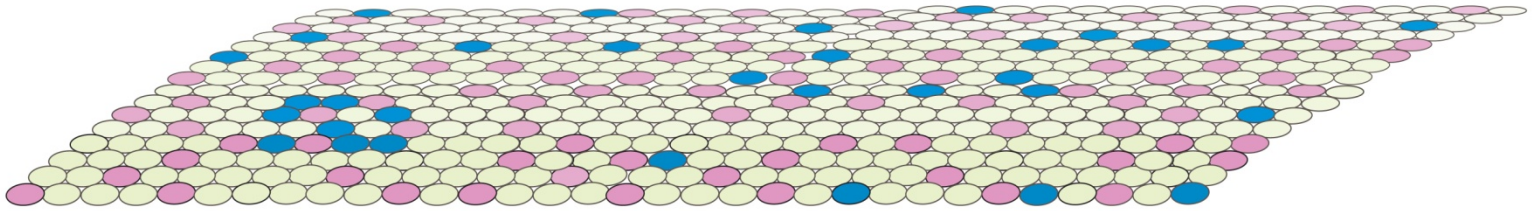
High concentration

Fluid membrane



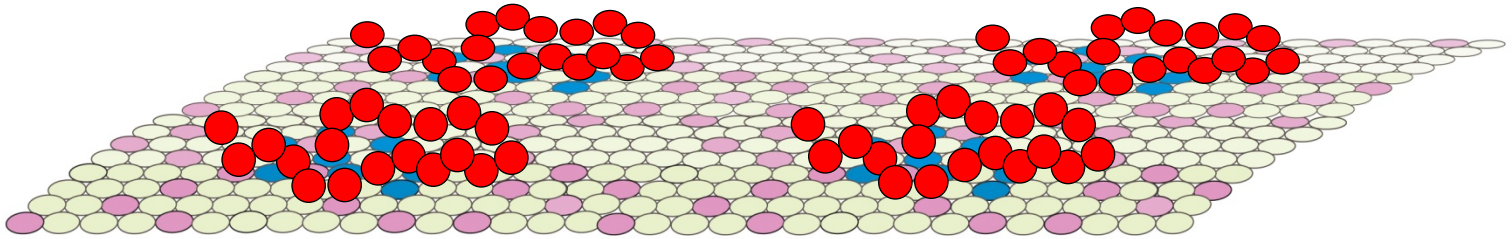


Frozen membrane

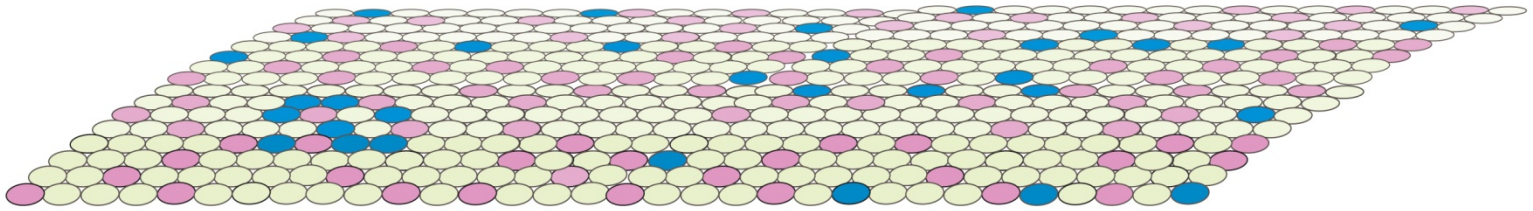


High concentration

Fluid membrane

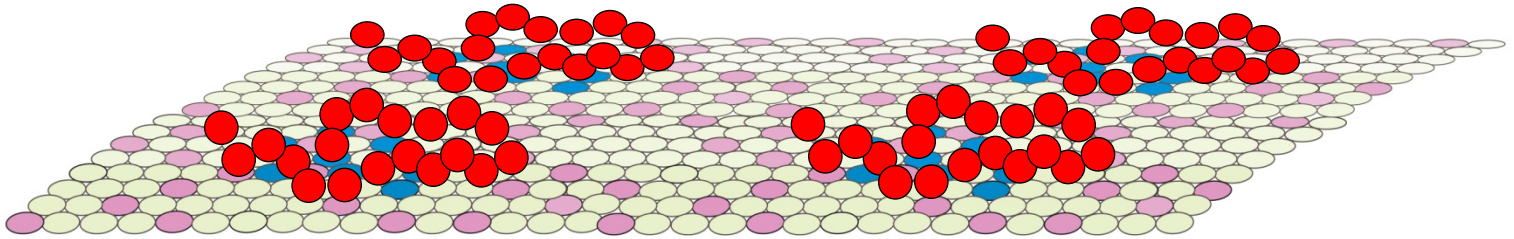


Frozen membrane

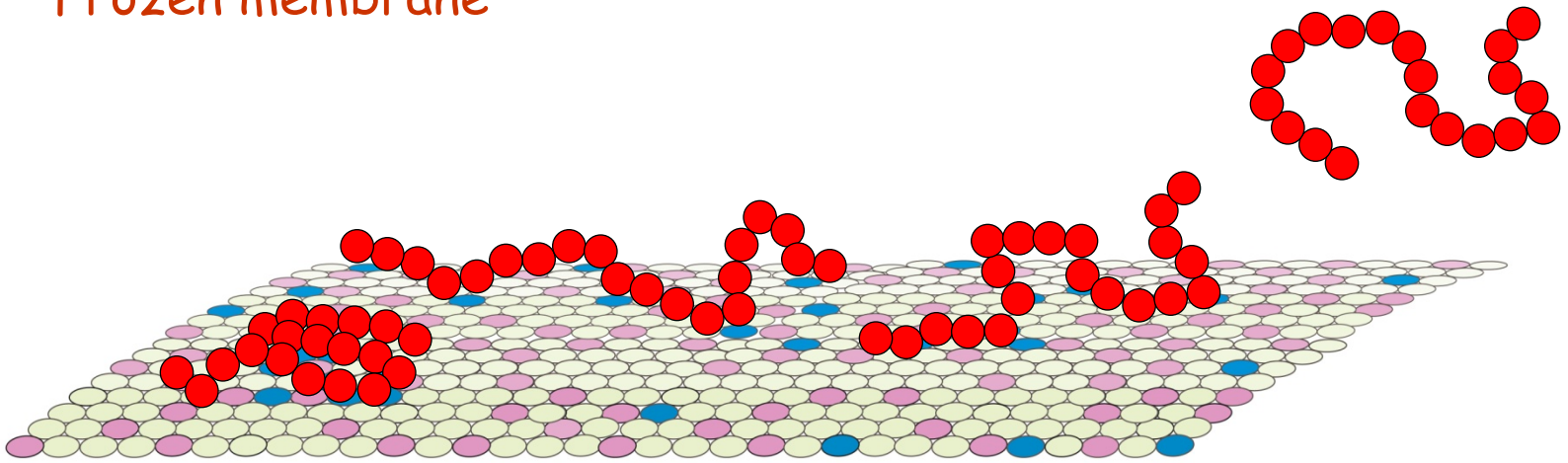


High concentration

Fluid membrane

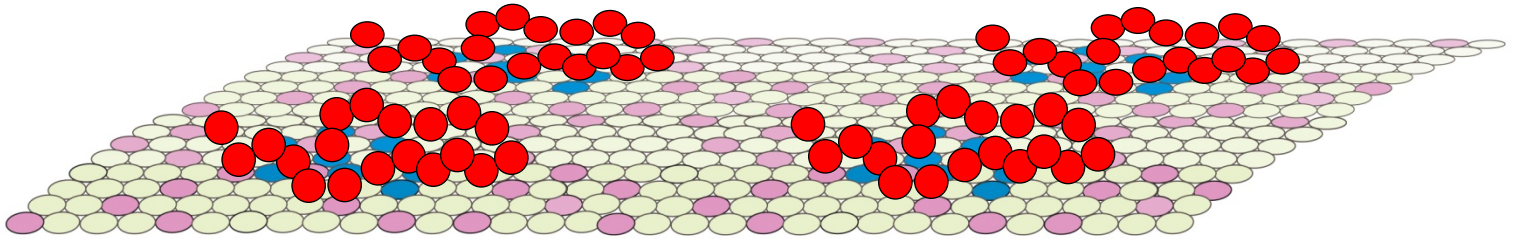


Frozen membrane

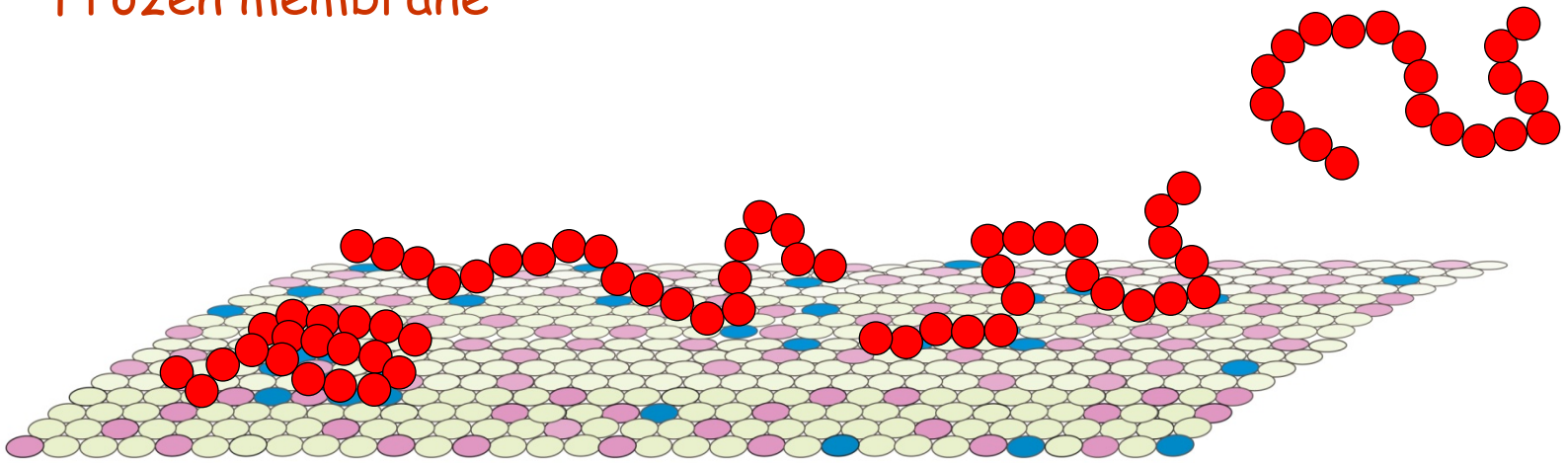


High concentration

Fluid membrane

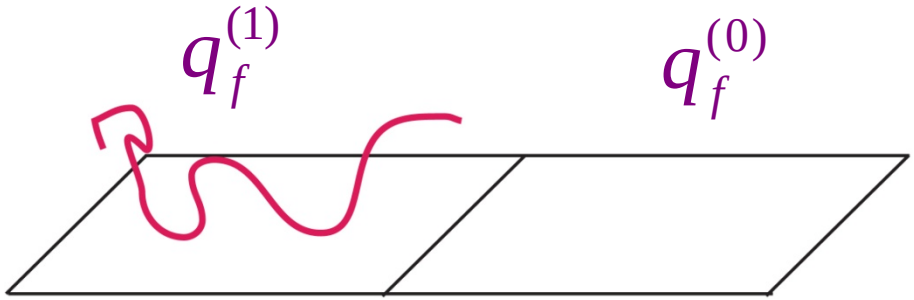


Frozen membrane



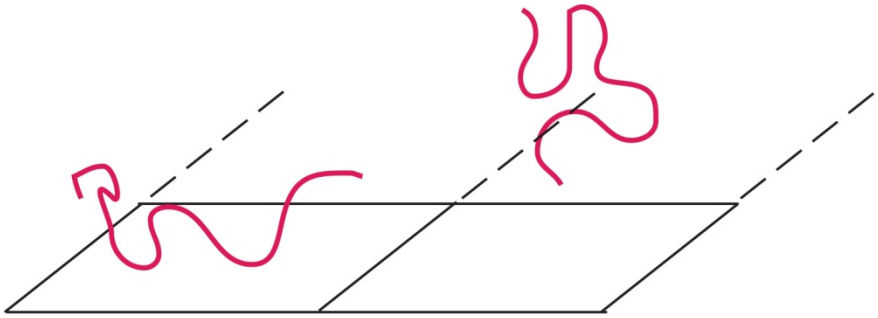
Surface Concentration Effects -- Cell Model

$$\mu = -\ln q_b + \ln \varphi_b$$



Mobile Membrane $\quad \Xi_f = (\xi_f)^M = [q_f^{(0)} + \gamma q_f^{(1)}]^M$

Frozen Membrane $\quad \Xi_q = \prod_m (\xi_m)^{M_m} = \prod_m [1 + \gamma q_m^{(1)}]^{M_m}$



Lattice Cell Model

Frozen Membrane

$$\frac{\theta_m}{1-\theta_m} = \gamma q_m^{(1)} = \varphi_b \frac{q_m^{(1)}}{q_b} = \tilde{\varphi}_b e^{-\Delta F_m}$$

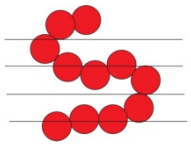
Fluid Membrane

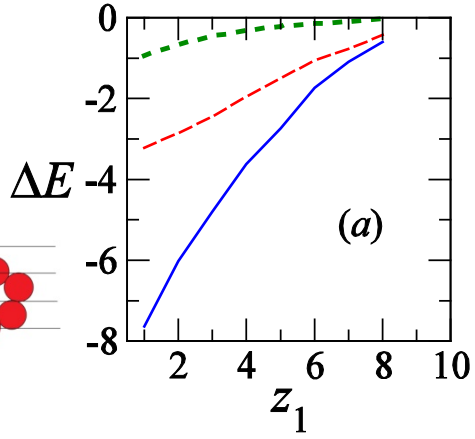
$$\frac{\theta_f}{1-\theta_f} = \frac{\gamma q_f^{(1)}}{q_f^{(0)}} = \frac{\varphi_b}{q_b}\frac{q_f^{(1)}}{q_f^{(0)}} = \tilde{\varphi}_b e^{-\Delta F_f}$$

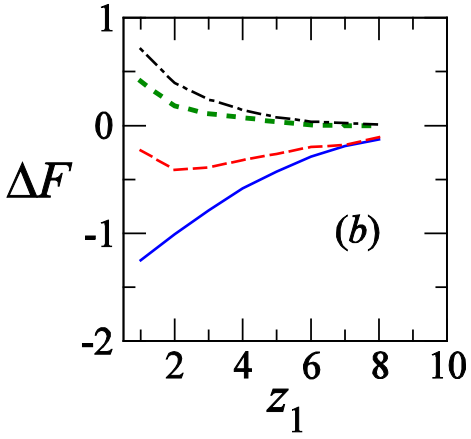
$$\frac{\theta_f}{1-\theta_f} = \sum_m P(m)\frac{\theta_m}{1-\theta_m} = \left\langle \frac{\theta_m}{1-\theta_m} \right\rangle_q \geq \frac{\langle \theta_m \rangle_q}{1-\langle \theta_m \rangle_q}$$

$\theta_f \geq \langle \theta_m \rangle_q$ The equality holds in the limit $\theta \to 0$

A **flexible** macromolecule adjusts its conformation(s) according to the local configuraion of the quenched membrane.
Not so for a uniform surface.

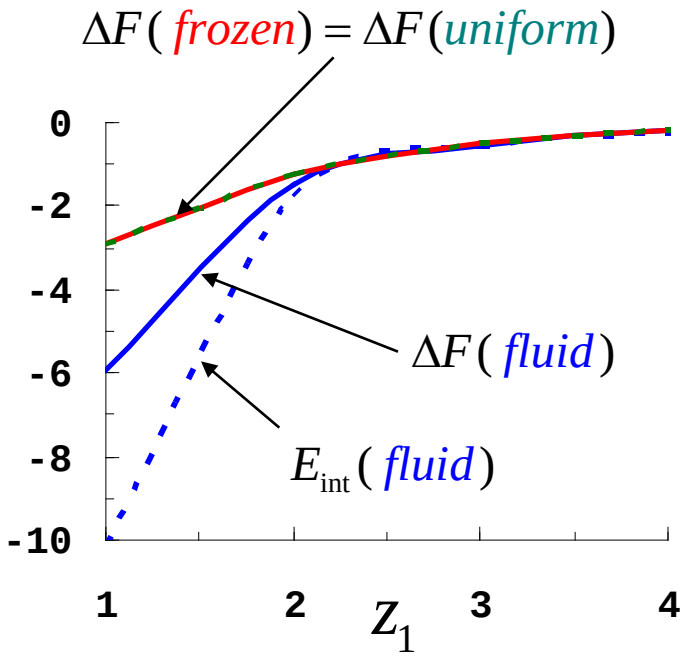


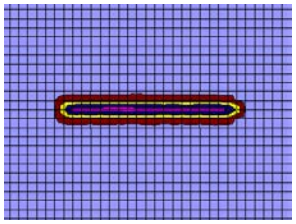




Fluid
Frozen
Uniform

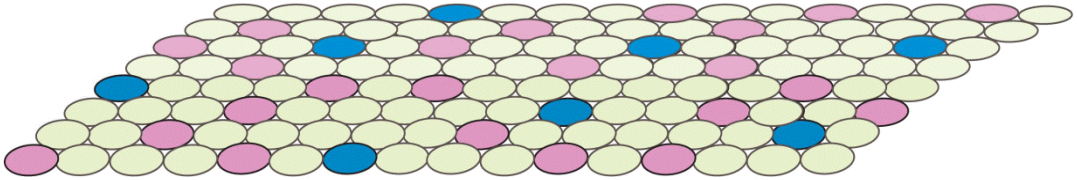
A **rigid** body (e.g., a rod), cannot adjust its conformations ; on average – the frozen membrane binds like a uniformly charged surface.



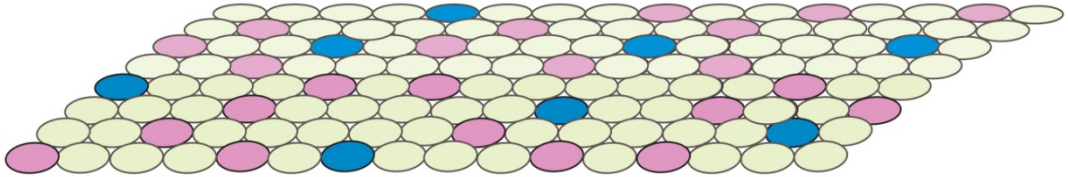


1% PIP_2, 1% PS

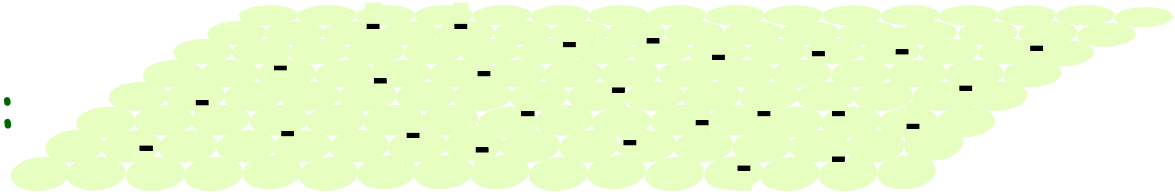
Fluid membrane:



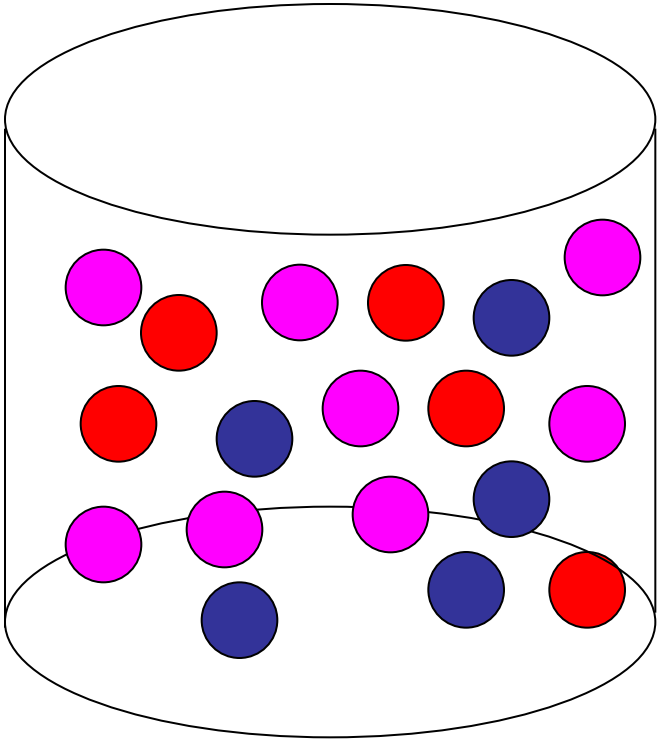
Frozen membrane:



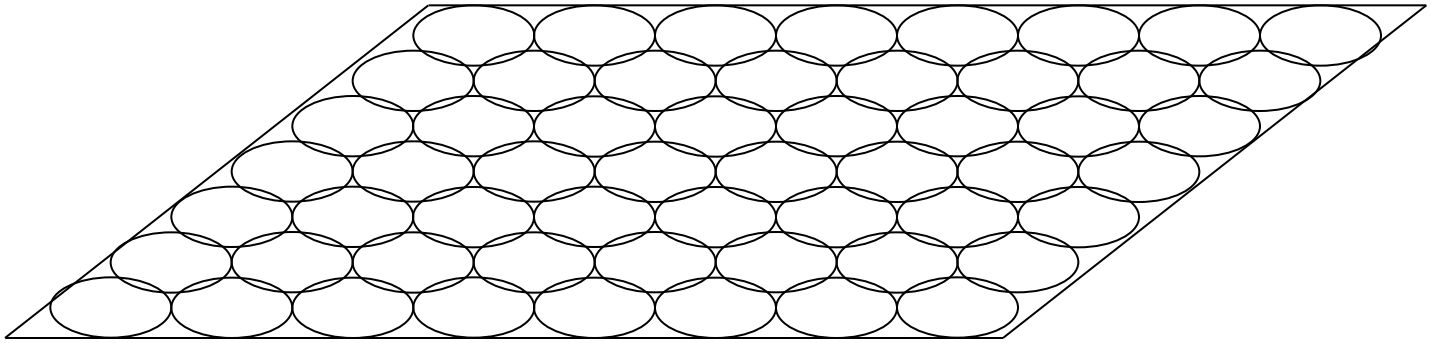
Uniform membrane:



Simulation Method



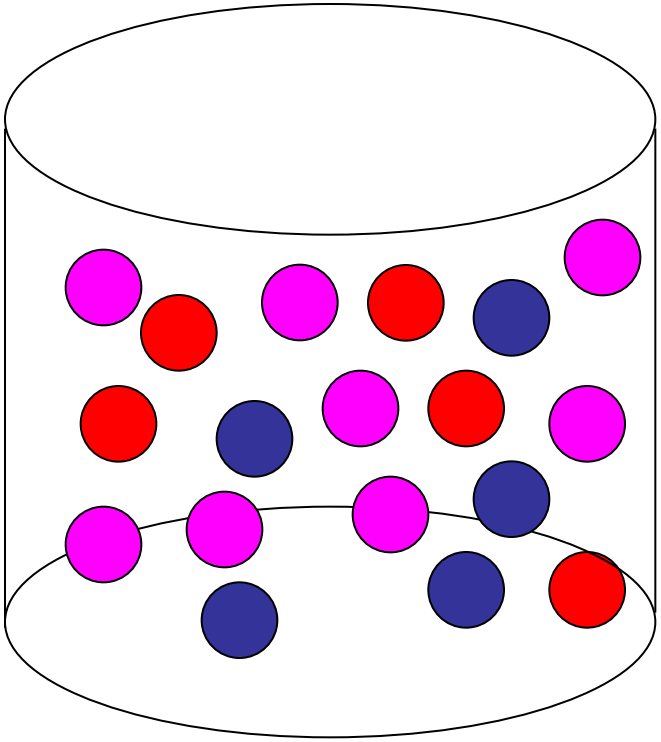
Extended Rosenbluth Scheme



PS lipid, z= -1

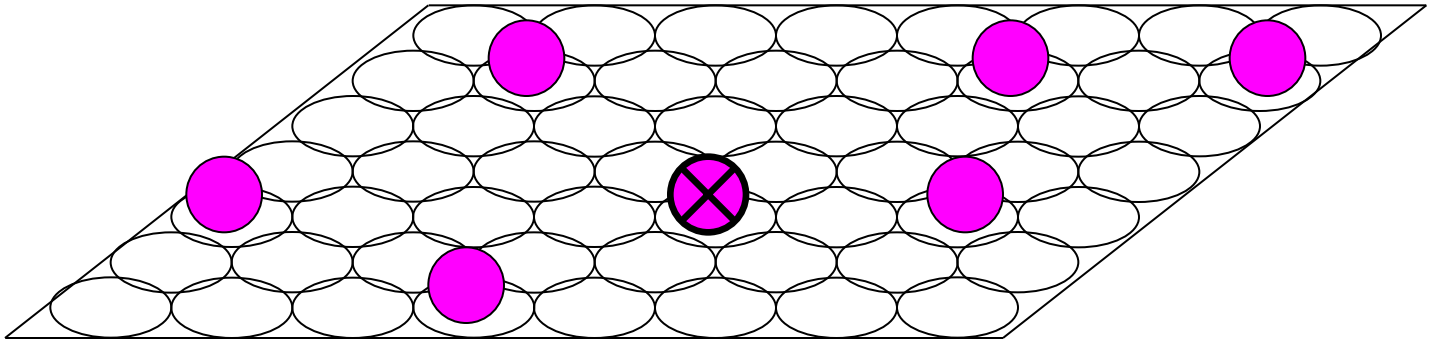
PIP_2 lipid, z= -4

Polymer segment, z= +1



$$w_1^m = \sum_{j=1}^{k_m} e^{-u_j / kT}$$

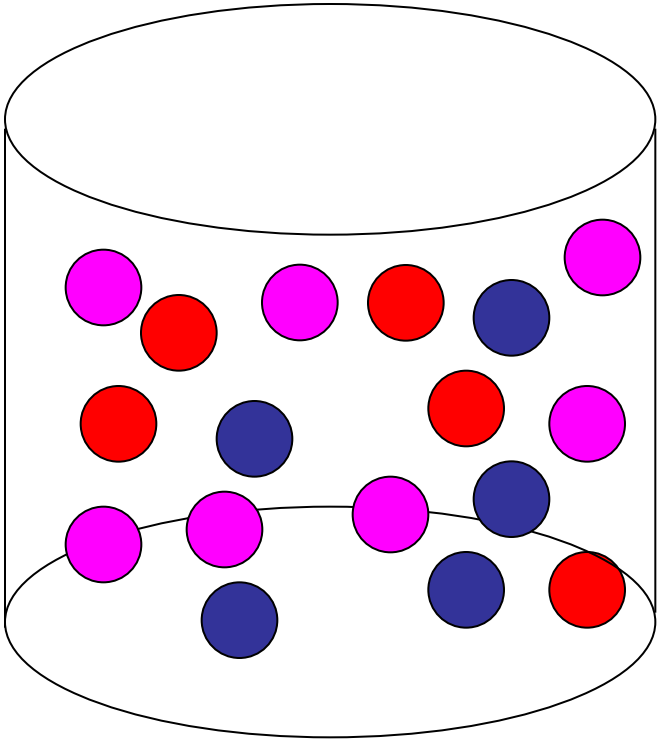
$$P_j = \frac{e^{-u_j / kT}}{w_1^m}$$



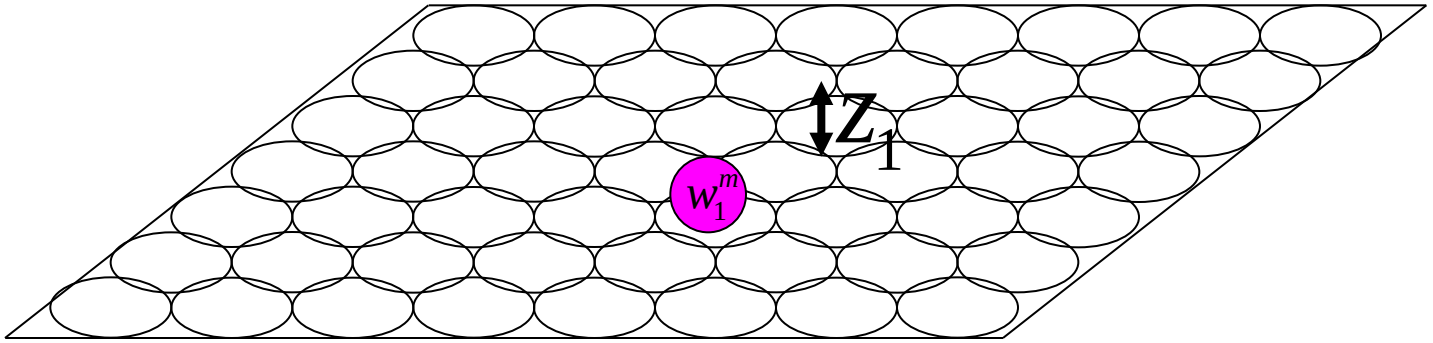
PS lipid, z= -1

PIP_2 lipid, z= -4

Polymer segment, z= +1



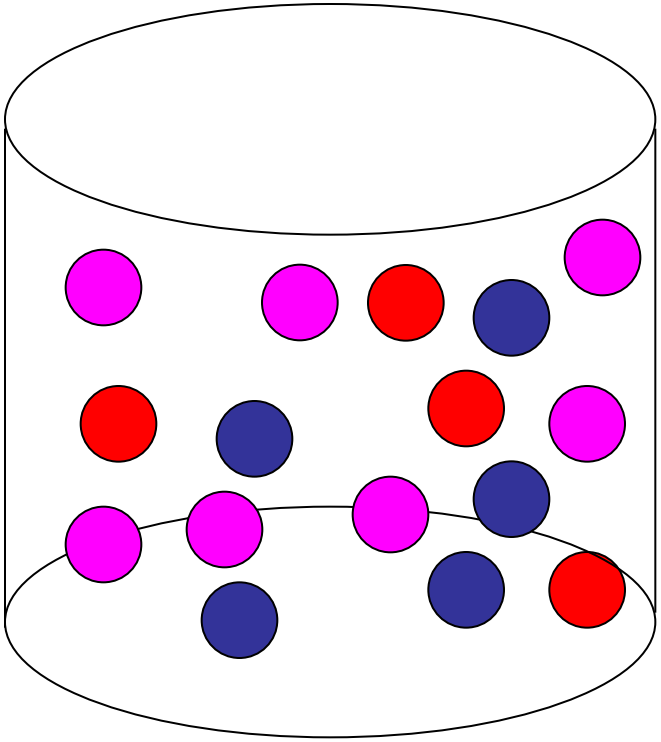
$$w_1^p = ke^{-u/kT}$$



PS lipid, z= -1

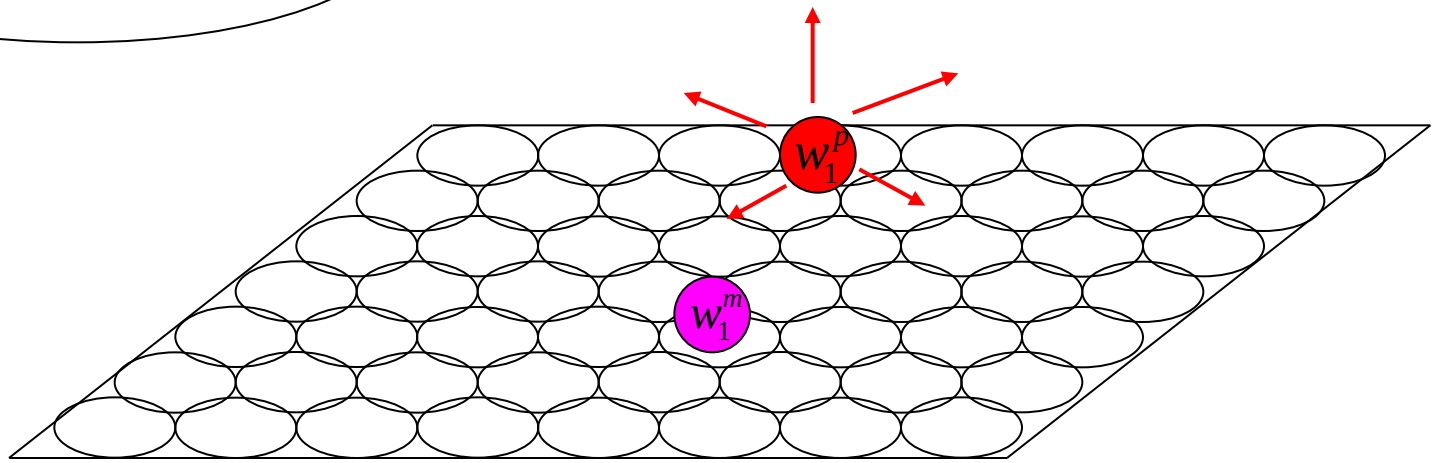
PIP_2 lipid, z= -4

Polymer segment, z= +1



$$w_2^p = \sum_{j=1}^{k} e^{-u_j / kT}$$

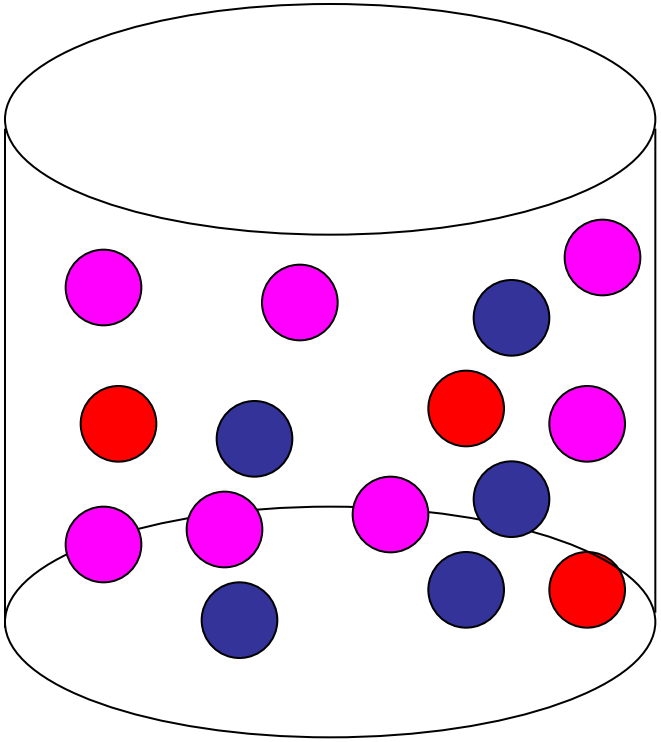
$$P_j = \frac{e^{-u_j / kT}}{w_2^p}$$



PS lipid, z= -1

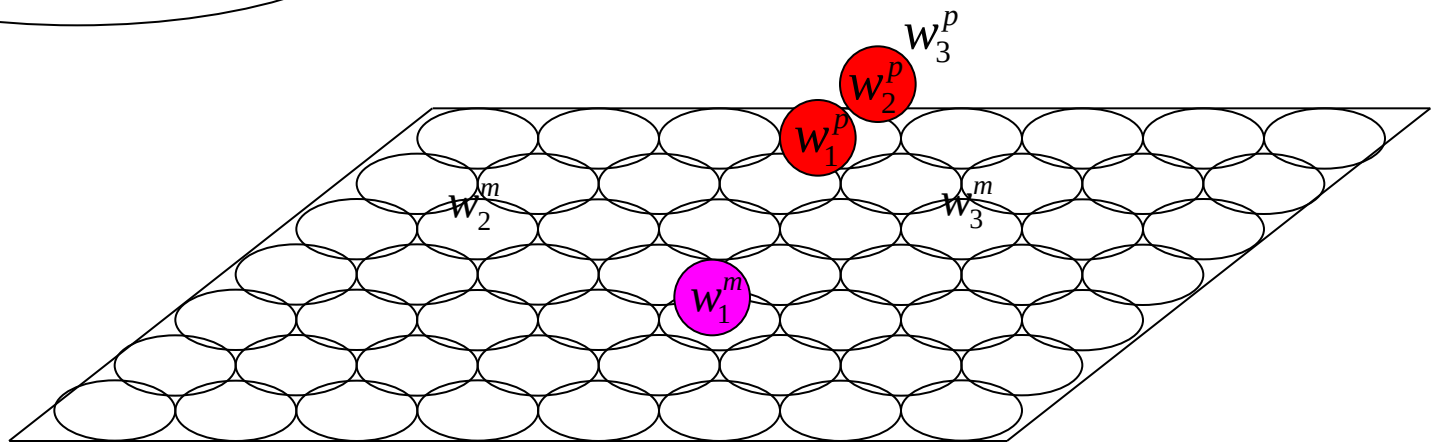
PIP_2 lipid, z= -4

Polymer segment, z= +1



$$W = \prod_{j=1}^{N} \frac{w_j^p}{k^{N-1}} \prod_{j=1}^{N_{PS}+N_{PIP_2}} \frac{w_j^m}{k_m^{N_{PS}+N_{PIP_2}}}$$

Rosenbluth Factor

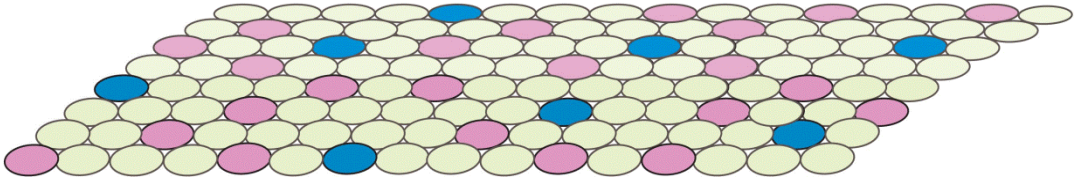


PS lipid, z= -1

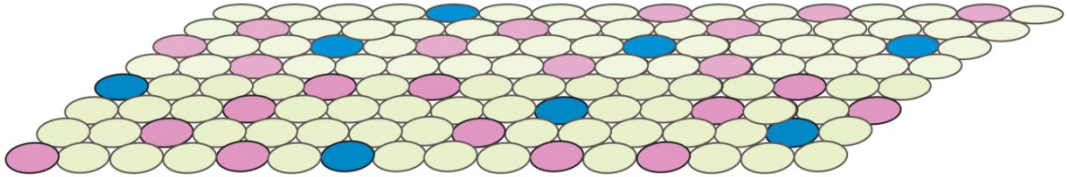
PIP_2 lipid, z= -4

Polymer segment, z= +1

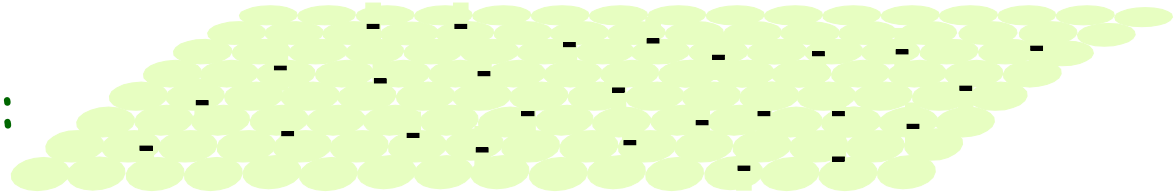
Fluid membrane:



Frozen membrane:



Uniform membrane:



Free Energy Calculation

Fluid membrane: $$\Delta F = -\ln \frac{\langle W \rangle_{m,p}}{\langle W_p \rangle \langle W_m \rangle}$$

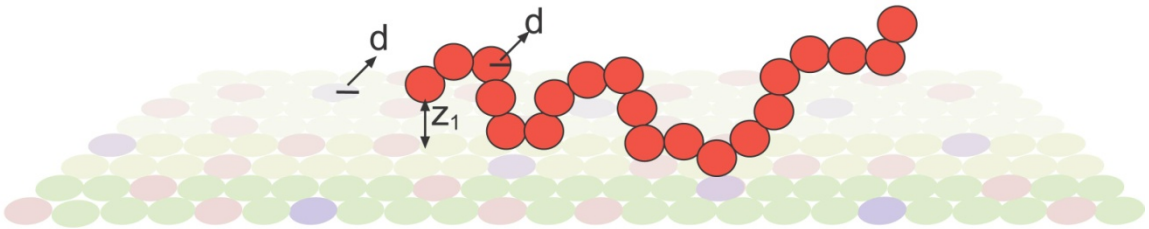
Uniform membrane: $$\Delta F = -\ln \frac{\langle W_p | m \rangle}{\langle W_p \rangle}$$

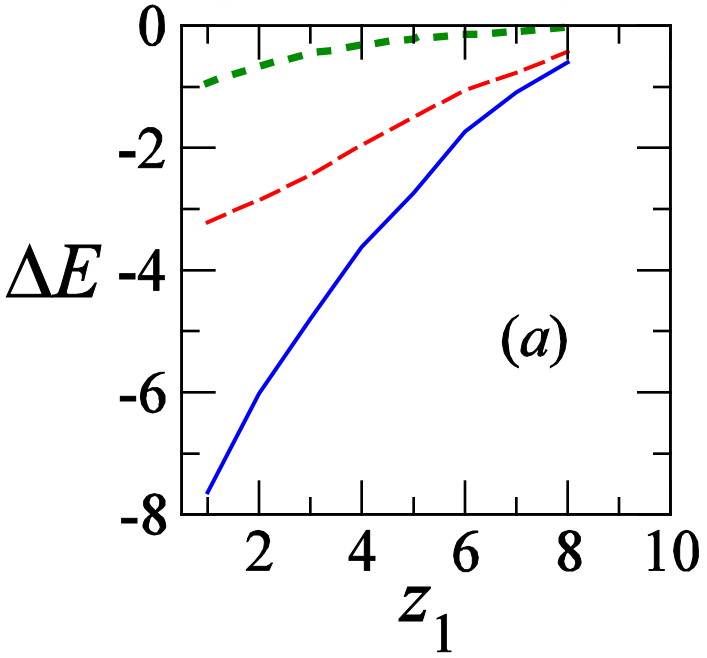
Frozen membrane: $$\Delta F = -\left\langle \ln \frac{\langle W_p | m \rangle}{\langle W_p \rangle} \right\rangle_m$$

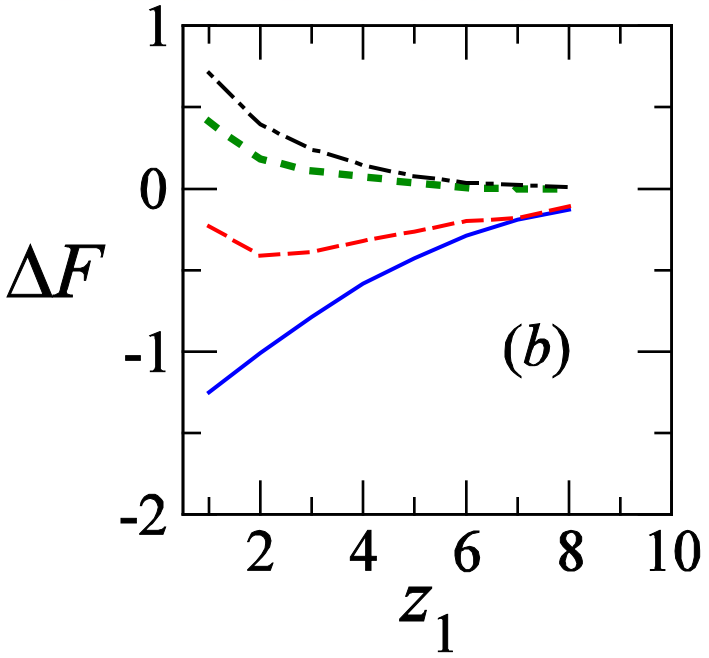
Calculating Thermodynamic Averages

$$P_i = \frac{e^{-U_i}}{W_i} \qquad \langle A \rangle = \frac{\sum_i W_i A_i}{\sum_i W_i}$$

"Potential of Mean Force"







Fluid membrane: $\Delta F < 0$ $\Longleftrightarrow$ adsorption

Frozen membrane: $\Delta F \cong 0$ $\Longleftrightarrow$ weak adsorption

Uniform membrane: $\Delta F > 0$ $\Longleftrightarrow$ depletion

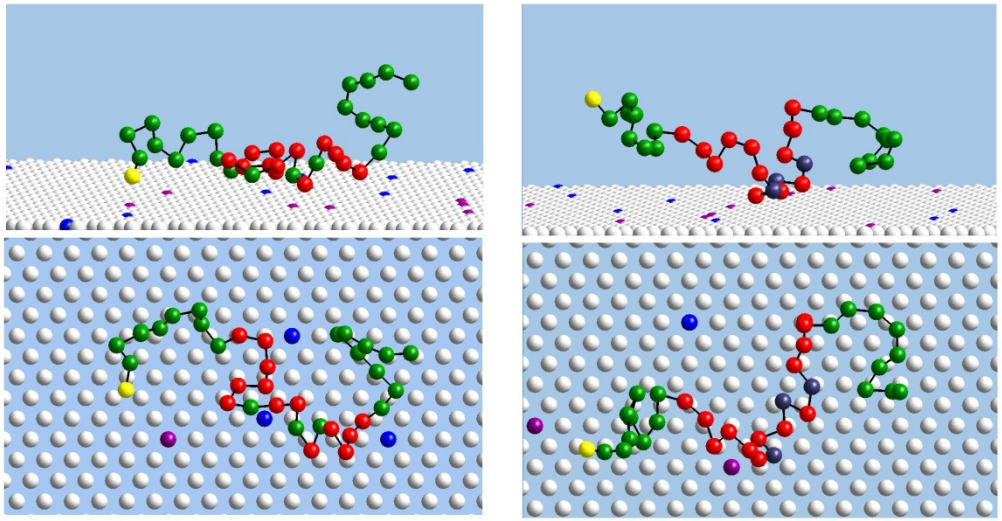
Summary

Lipid mobility, polymer flexibility play a crucial role in Membrane-Macromolecule interaction.

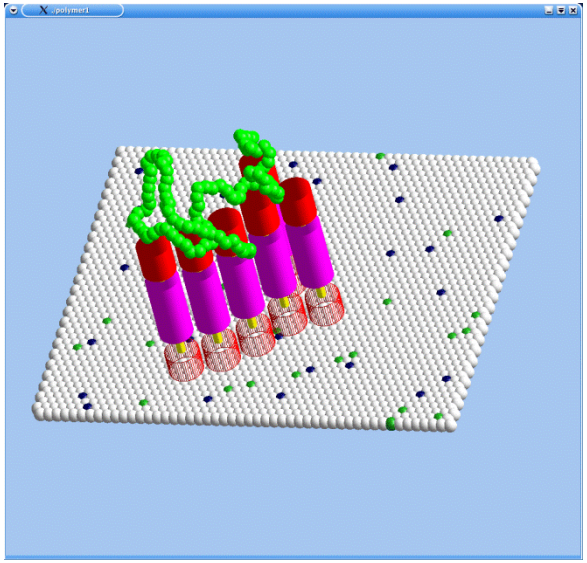
Relevant in signal transduction, viral assembly.

Future Planes

MARCKS

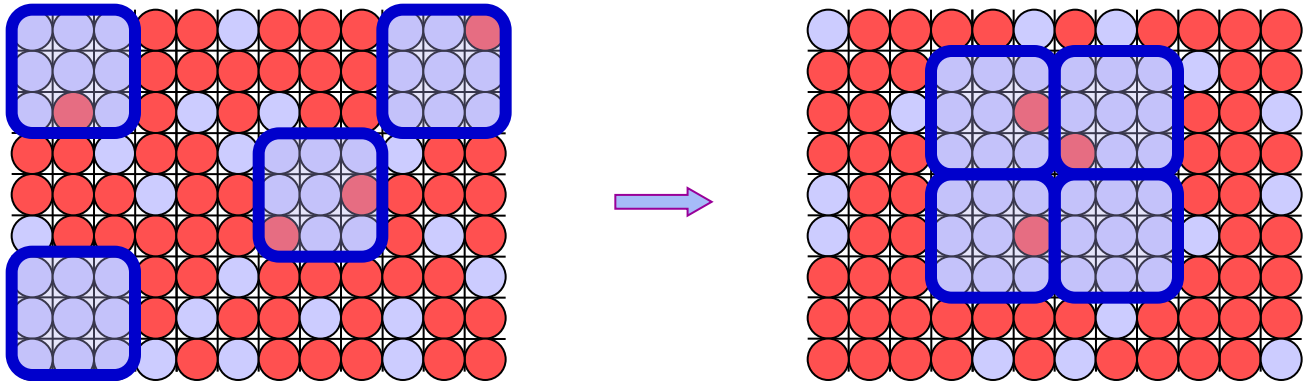


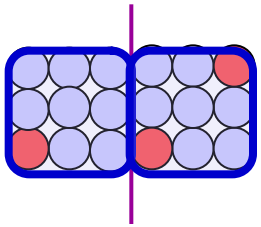
Viral Budding



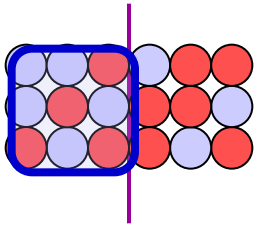
Below are additional slides –
some explaining the basics of lateral phase separation,

Phase Separation of Protein-Dressed Membrane

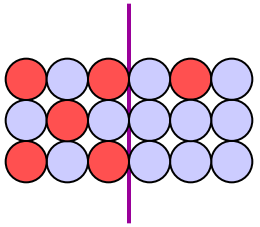




W_{PP}



W_{PM}



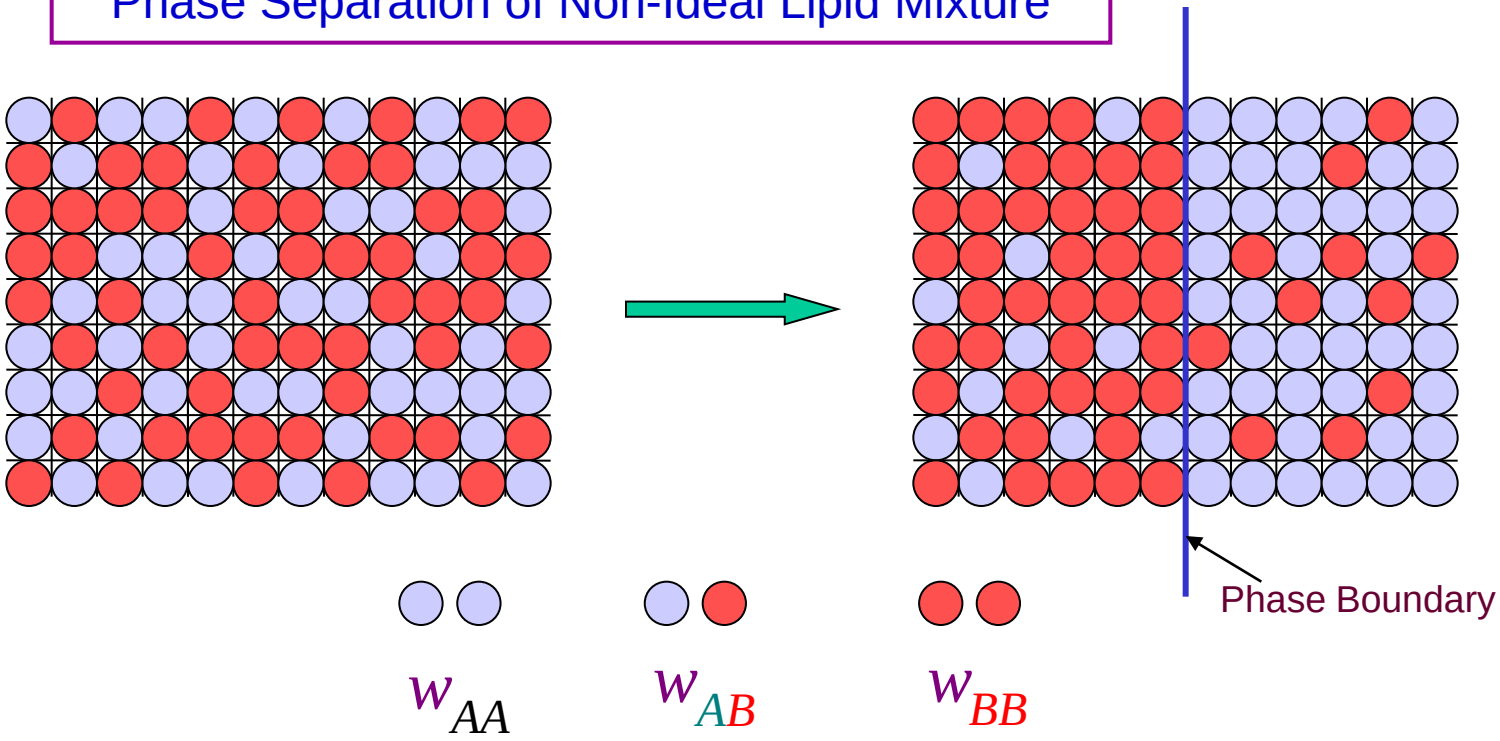
W_{MM}

$$\frac{F}{kT} = \theta \ln \theta + (1-\theta) \ln (1-\theta) + \Lambda \theta (1-\theta) \qquad (\theta = \theta_{\text{protein}})$$

$$\left(\frac{2kT}{z}\right)\Lambda = W = 2W_{PM} - (W_{PP} + W_{MM})$$

Dressed Membrane Phase Separates if: $\Lambda \geq \Lambda_C = 2$

Phase Separation of Non-Ideal Lipid Mixture



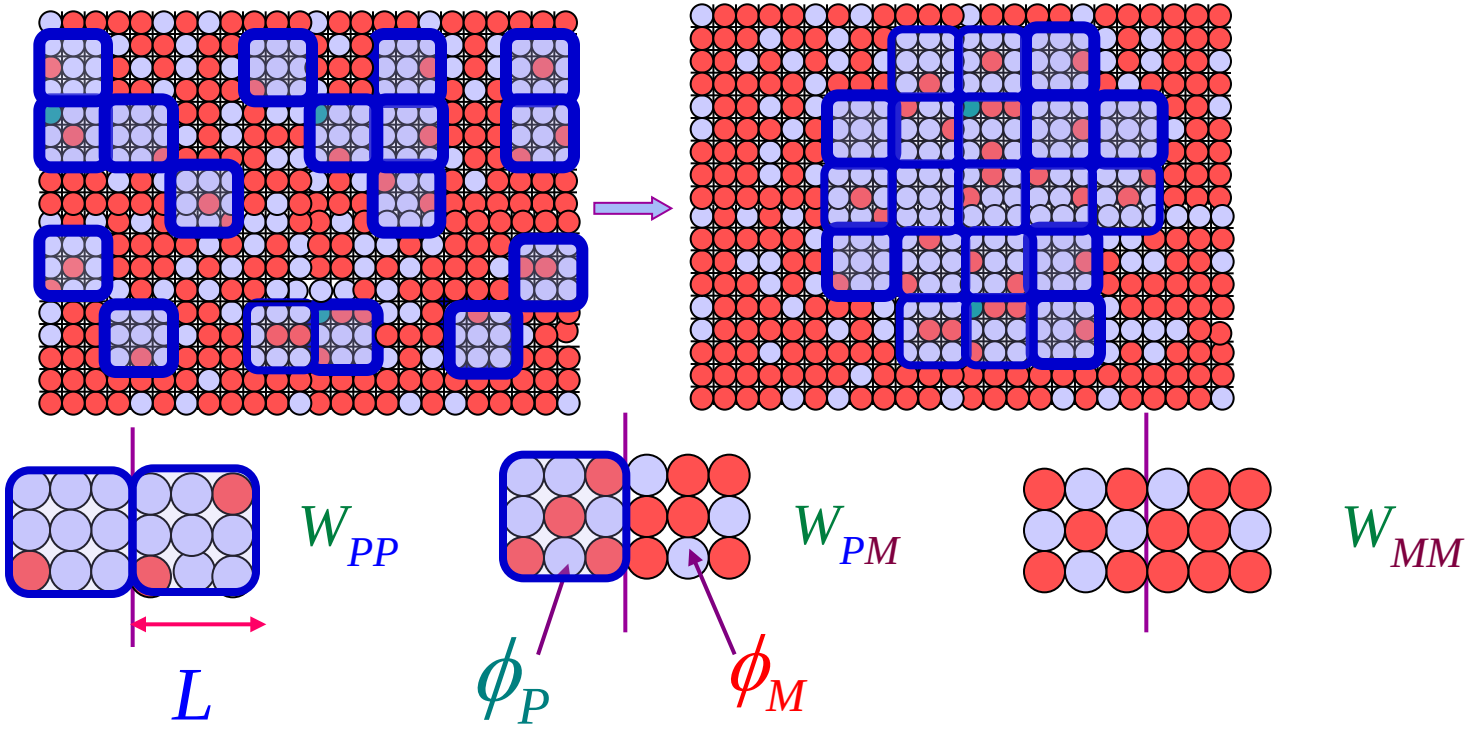
$$\frac{F}{kT} = \varphi \ln \varphi + (1-\varphi) \ln (1-\varphi) + \chi \varphi (1-\varphi)$$

$$\left(\frac{2kT}{z}\right)\chi = w = 2w_{AB} - (w_{AA} + w_{BB})$$

Mixture Phase Separates if: $\chi \geq \chi_C = 2$

(Mean Field)

$\Lambda_C = 2$



$$W_{PM} = L\{\phi_P \phi_M w_{AA} + (1-\phi_P)(1-\phi_M) w_{BB} + [\phi_P(1-\phi_M) + \phi_M(1-\phi_P)] w_{AB}\}$$

etc.

$$\Lambda = \left(\frac{z}{2kT}\right)\left(2W_{PM} - (W_{PP} + W_{MM})\right) = 2\chi L(\phi_P - \phi_M)^2$$

Critical Lipid Nonideality for Phase Separation of Dressed Membrane,

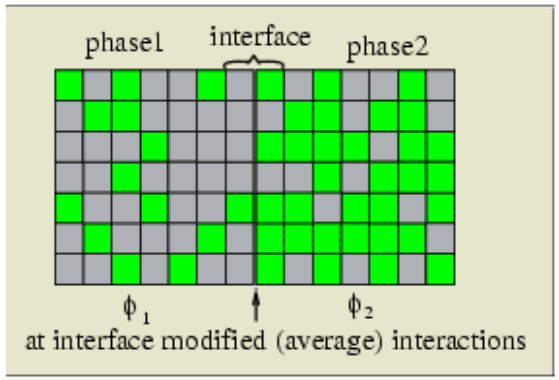
$\Lambda_C = 2 \longrightarrow$

$$\chi^*_{crit} = \frac{1}{L(\phi_P - \phi_M)^2}$$

may be Smaller than that of Bare Membrane: $\chi_C = 2$

RE-EXAMINATION OF REGULAR SOLUTION THEORY

For **microphase separation** regular solution theory predicts a **line tension** contribution



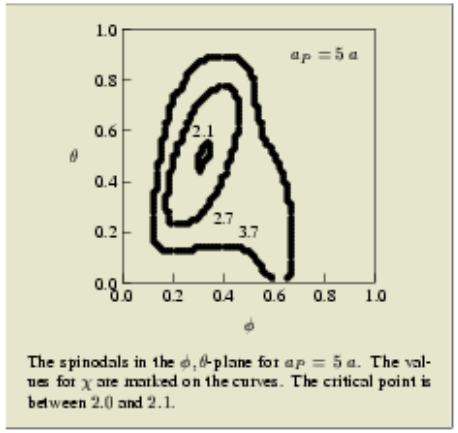
The modified interactions at interface give rise to a line tension contribution

The line tension energy for a single (circular) protein can be calculated and is:

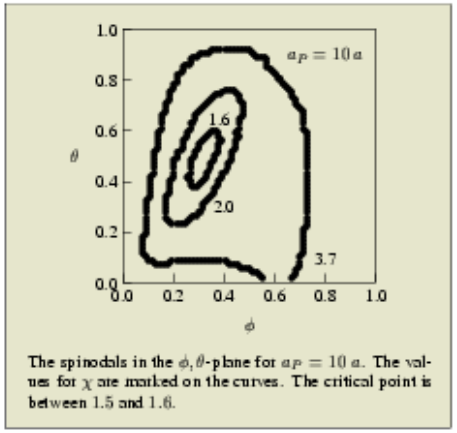
$$\chi_P = 2\chi\sqrt{\frac{a_P}{a}}\,(\phi_S - \phi_L)^2$$

Free energy: $f(\phi,\theta) = \theta f_S(\phi_P,\phi_S) + (1-\theta) f_L(\phi_L) + \theta(1-\theta)\frac{a}{a_P}\chi_P(\phi_S,\phi_L)$

Results based on numerical solution of 1D-PB equation (for $\phi_P = 0.6$ and $h = 3$ Å):



The spinodals in the ϕ,θ-plane for $a_P = 5\,a$. The values for χ are marked on the curves. The critical point is between 2.0 and 2.1.



The spinodals in the ϕ,θ-plane for $a_P = 10\,a$. The values for χ are marked on the curves. The critical point is between 1.5 and 1.6.

Remarkable conclusion: Critical point can fall below 2

The slides below outline the free energy of macroion-membrane interaction

The Free Energy:

$$F = \int_V \frac{\epsilon}{2} (\nabla \Phi)^2 \, dv$$

Electrostatic Energy

$$+ kT \int_V \left[n_+ \ln \frac{n_+}{n_0} + n_- \ln \frac{n_-}{n_0} - (n_+ + n_- + 2n_0) \right] dv$$

Mixing Entropy of Counterions

$$+ \frac{1}{a} kT \int_S \left[\eta \ln \eta + (1 - \eta) \ln (1 - \eta) \right] ds$$

Lipid, 2D, Mixing Entropy

$$+ \frac{\chi}{a} kT \int_S \eta (1 - \eta) ds$$

Non-ideal ("Bragg-Williams") Mixing

$$+ \frac{\chi}{3} kT \int_S (\nabla \eta)^2 ds$$

Line Tension Energy

$$+ \int_S \frac{1}{2} \kappa(\eta) \left(c - c_0(\eta) \right)^2 ds$$

Membrane Bending Energy

Charge Conservation Condition

$$\frac{1}{a} \int_S \eta ds = \langle \eta \rangle$$

For Ideal Planar Lipid Mixture:

$$F = \int_V \frac{\epsilon}{2} (\nabla \Phi)^2 \, dv$$

Electrostatic Energy

$$+ kT \int_V \left[n_+ \ln \frac{n_+}{n_0} + n_- \ln \frac{n_-}{n_0} - (n_+ + n_- + 2n_0) \right] dv$$

Mixing Entropy of Counterions

$$+ \frac{1}{a} kT \int_S [\eta \ln \eta + (1 - \eta) \ln(1 - \eta)] \, ds$$

Lipid, 2D, Mixing Entropy

Lipid Charge Conservation

$$\frac{1}{a} \int_S \eta ds = \langle \eta \rangle$$

Minimize F $\Longrightarrow$

$$\nabla^2 \Phi = \kappa^2 \sinh \Phi; \qquad \kappa = \frac{1}{l_D} = \left(\frac{2 n_0 e^2}{\epsilon_0 \epsilon_r k_B T} \right)^{1/2}$$

and, at membrane surface

$$\eta = \frac{1}{1 + \left(\frac{1 - \langle \eta \rangle}{\langle \eta \rangle} \right) e^{(\Phi + \lambda)}} = - \frac{a \epsilon k_B T}{e^2} \hat{n} \nabla \Phi$$

a) Assume

Uniform lipid charge distribution (no charge modulation)

No protein-protein repulsion

Protein lowers membrane charge:

$\phi_{eff} \equiv \phi - Z_P(a/a_P)\theta$

Set $\theta = \theta(\phi)$ from $\mu_{P,bulk} = \mu_{P,surface}(\theta, \phi)$

$\Longrightarrow$spinodal equation

$$\chi_{sp} = \frac{1}{2\phi(1-\phi)} + \frac{p_0}{q + 2p_0\theta(1-\theta)z_P^2 a/a_P}$$

$$p = p_0\phi_{eff}; \qquad q = (1+p^2)^{1/2}$$

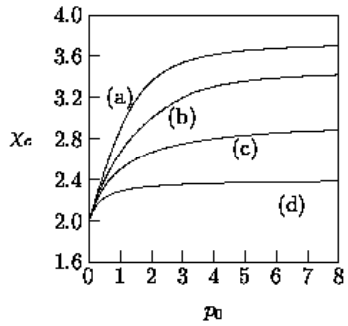
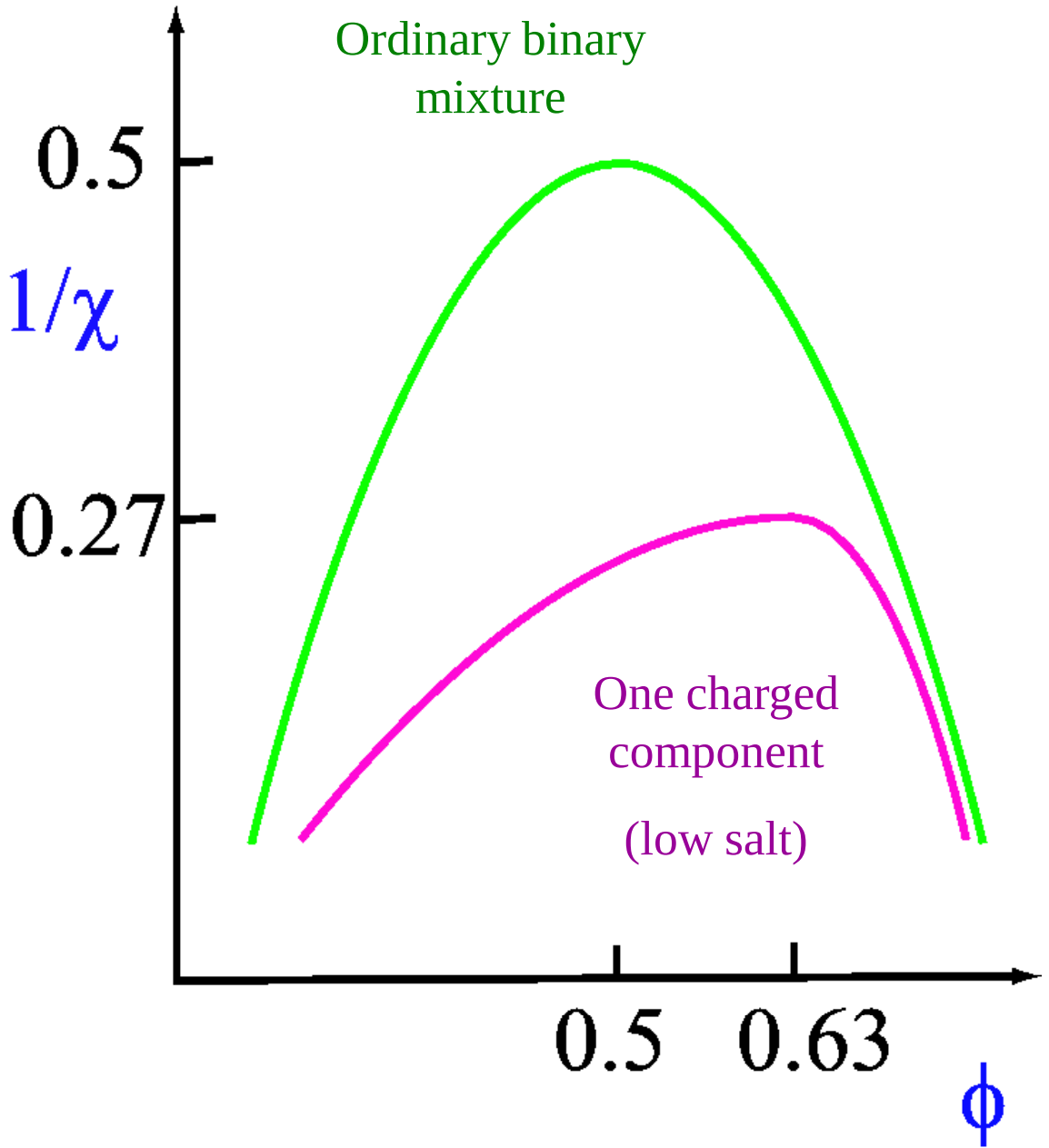


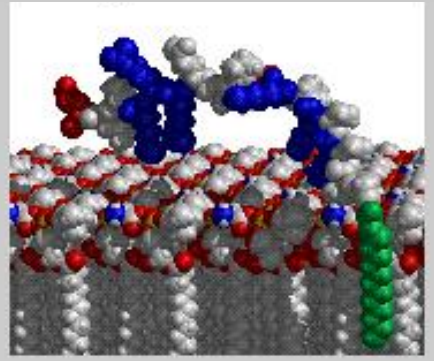
Figure 1: The critical point χ_c of a mixed membrane with an adsorbed protein layer as a function of $p_0 = 2\pi l_B l_D/a$ for no adsorbed proteins (a), $a_P = a$ and $z_p = 1$ (b), $a_P = 2a$ and $z_p = 2$ (c), and $a_P = 5a$ and $z_p = 5$ (d).

Spinodal curves for binary mixture

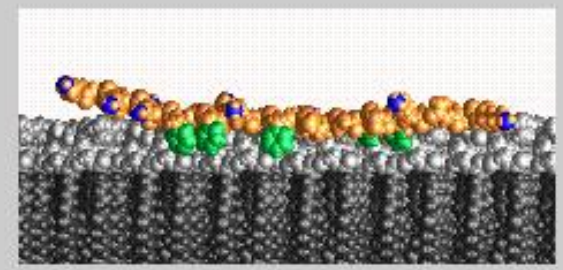


Electrostatic and hydrophobic interactions in membrane adsorption

Unstructured sequences

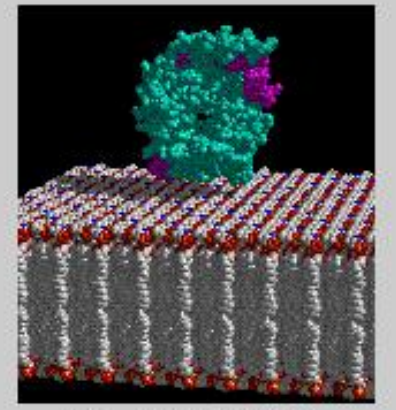


Src, K-ras, Rap-1a

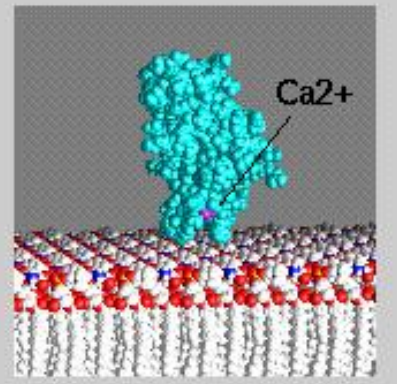


MARCKS- cytoskeletal
Caveolin- caveolae
Numb- asymmetric division
AKAP79- scaffold

Basic surface patches

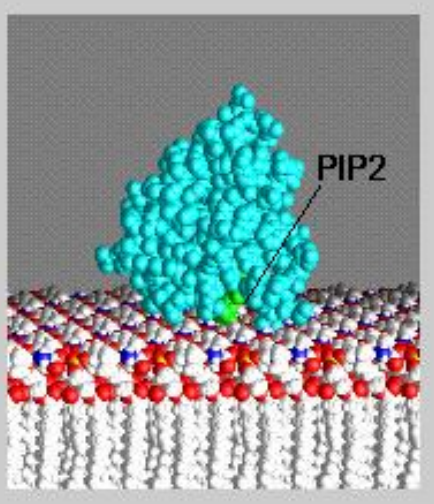


Gβγ, HIV-1 Gag



C2 domains
Retroviral matrix domains

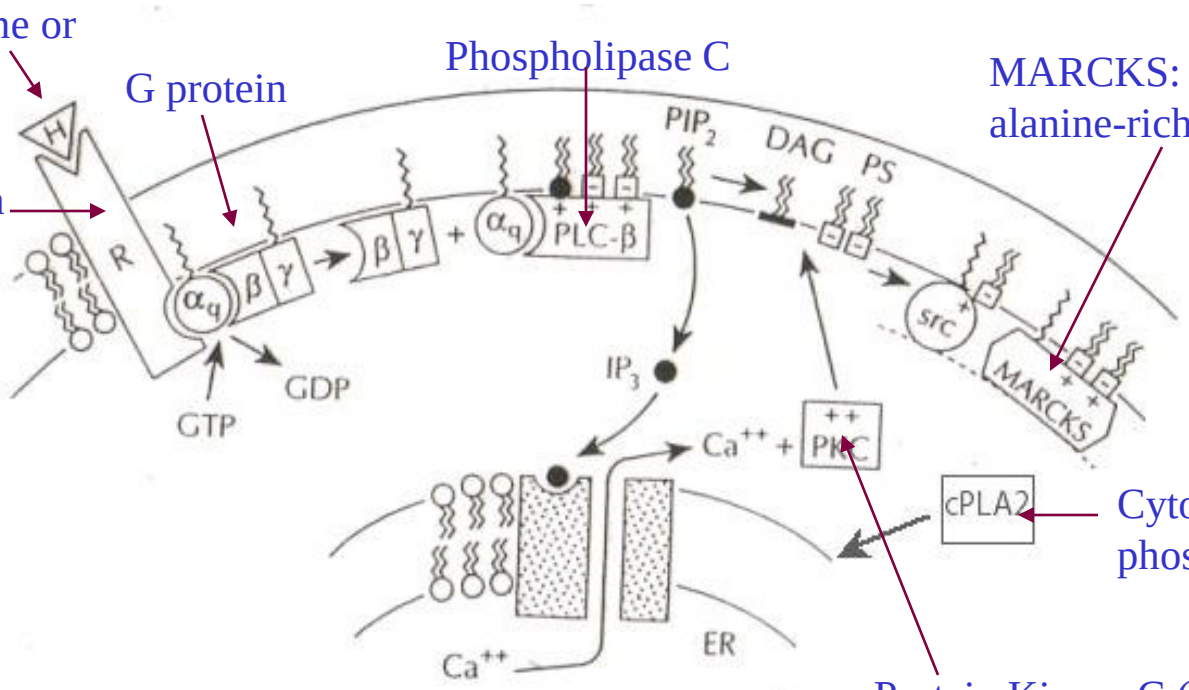
Specific interactions



PH domains
C1 domains
FYVE domains
Catalytic domains

Diana Murray, (Barry Honig, Stauart McLaughlin, …)

Calcium/phospholipid second messenger system



Protein Kinase C (PKC):
C1 domain interacts with DAG
Calcium-bound C2 domain recruits protein to the plasma membrane;
Ser/Thr kinase that phosphorylates serines with the basic effector domain of MARCKS leading to the "myristoyl/electrostatic switch".

Diana Murray