Mesoscale Modeling of Cell Membrane-Mediated Trafficking*

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Minimal Models for Intracellular Trafficking based on Coarse-Coarse Graining from Direct Experimental Data

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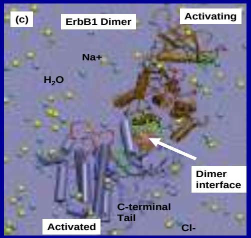

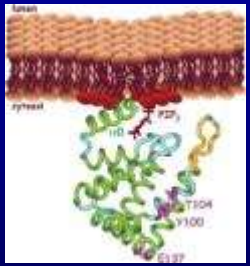

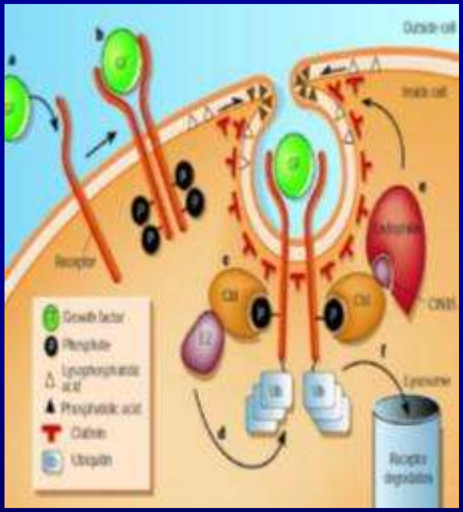

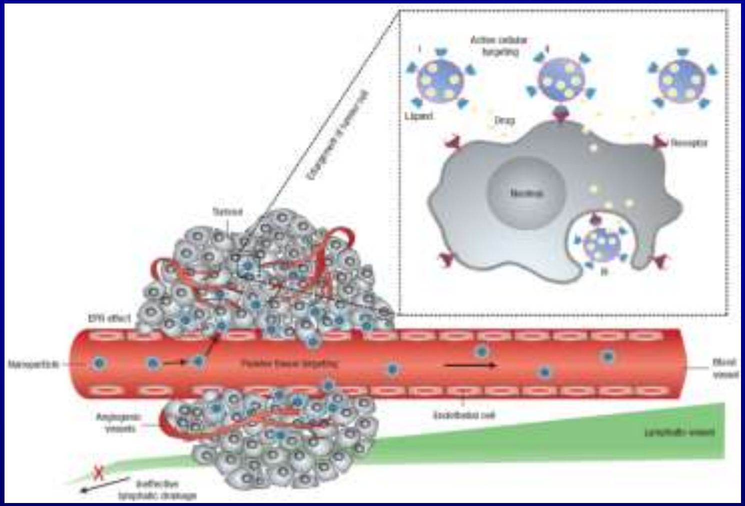

→ Length, Time

Complexity
Simplicity

Acknowledgements

Collaborators


Mark


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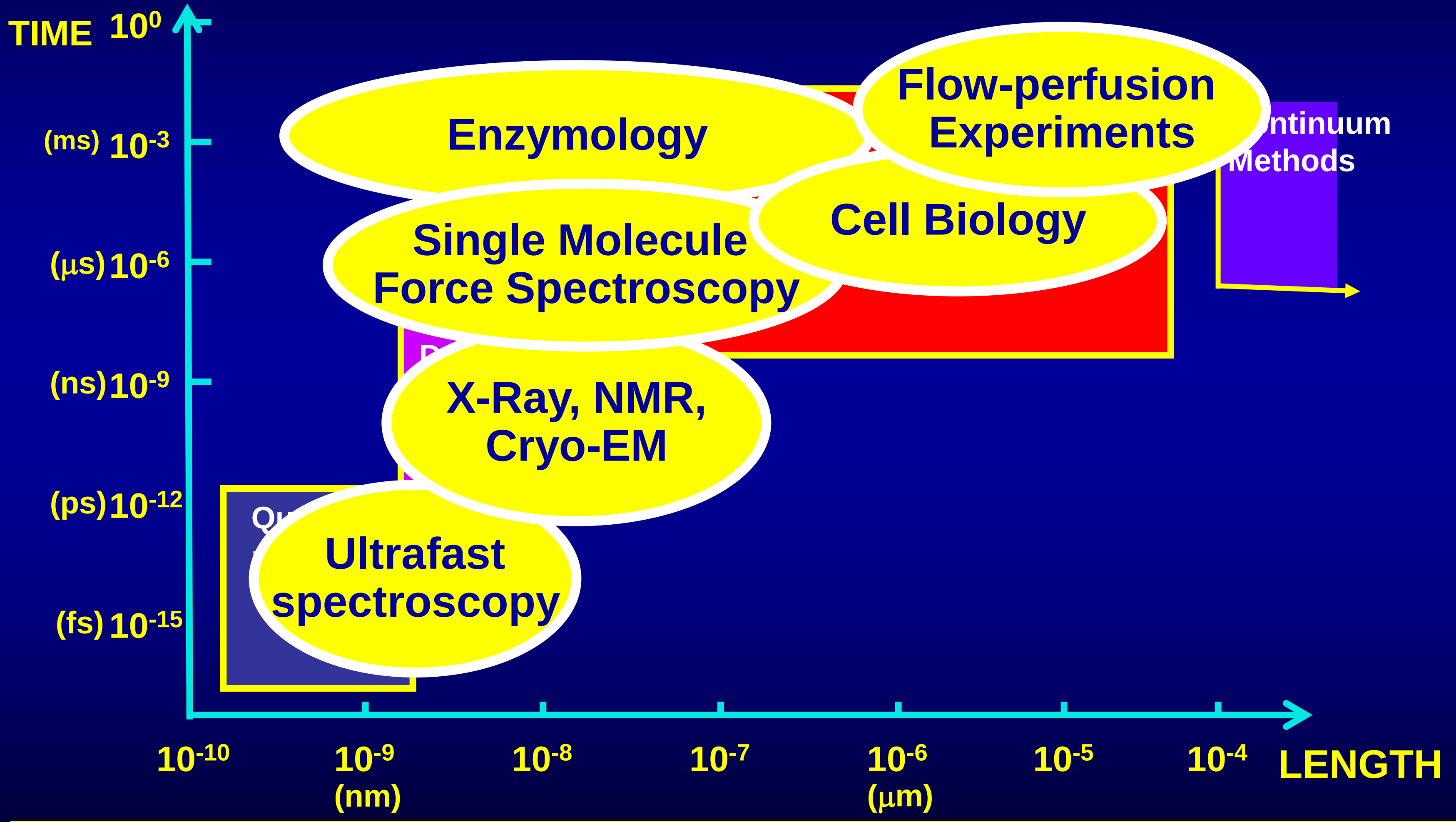
Modeling at Multiple Simulation Scales and Connection with Experiment



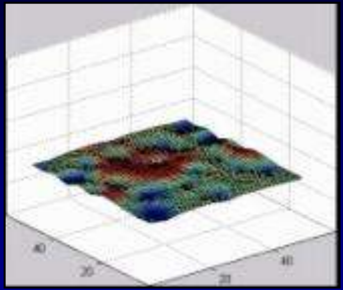
Multiscale Modeling of Membranes

Time scale

s

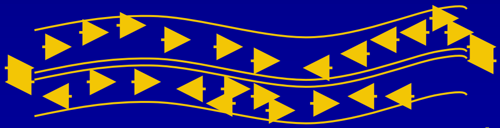
ns

> 1μm, 10^8 atoms



Generalized elastic models

(50 nm) Seifert, 1995

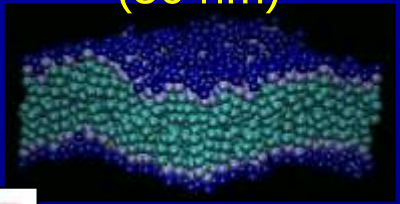


Monolayer viscous dissipation

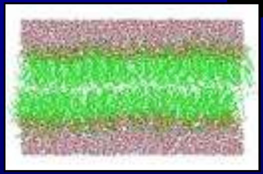
Bilayer slippage

Viscoelastic models

(50 nm)



Coarse-grained MD



Fully-atomistic MD (15 nm, 10^5 atoms)

Molecular Dynamics (MD)

Deserno, 2008
Voth, 2008
Baker, 2009
Schulten, 2009

Length scale

nm

μm

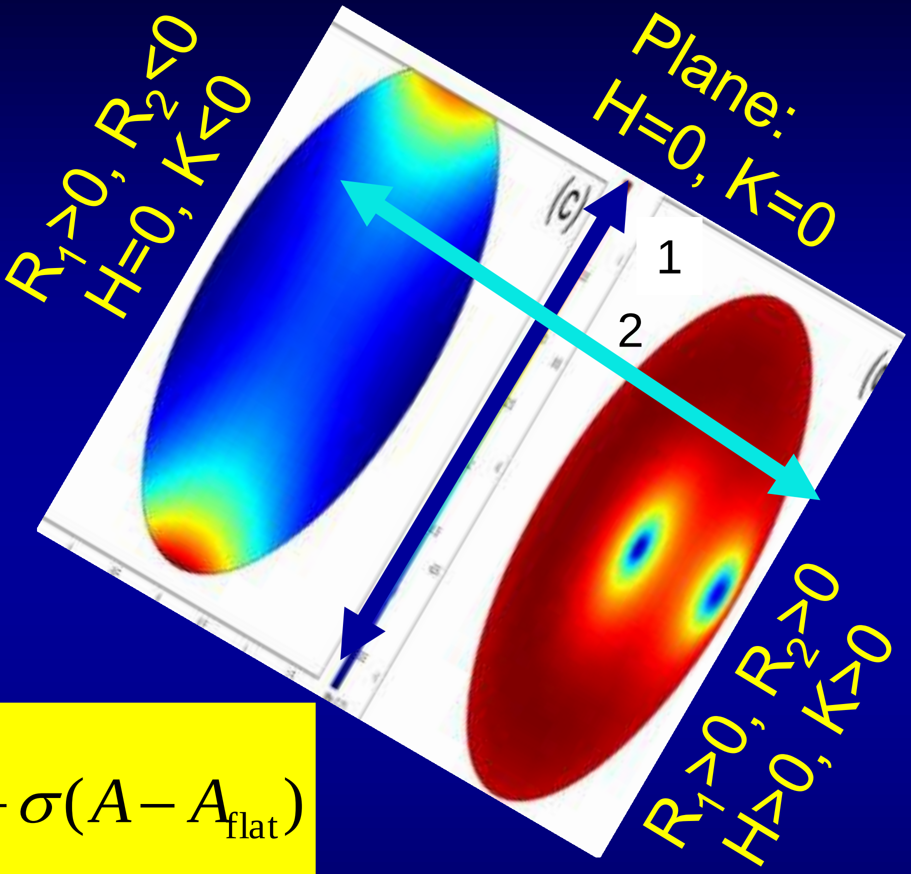
Mesoscale Elastic Model for Membranes

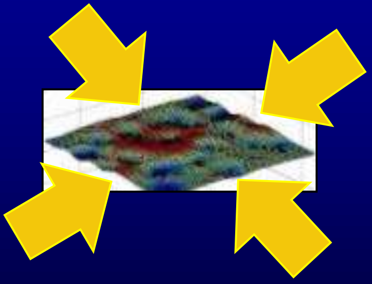
Helfrich Free Energy

Nelson, Piran, Weinberg, 1987

$$f_c = \tfrac{1}{2}k(H - H_0)^2 + \bar{k}K.$$

H_0 :Intrinsic curvature
k: Bending Modulus
$\bar{k}$: Gaussian Curvature Modulus





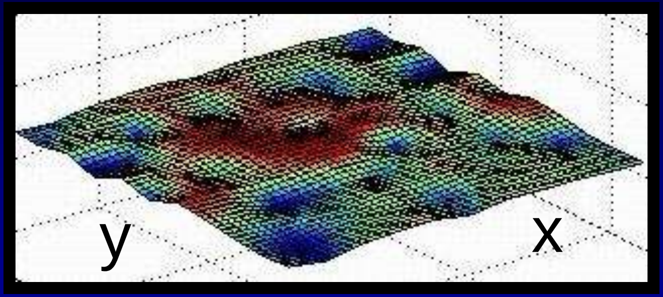
$$E = \int_A \frac{\kappa}{2}(H - H_0)^2 dA + \sigma(A - A_{\text{flat}})$$

Elastic free energy including frame tension on a membrane patch

$H \Rightarrow 1/2[1/R_1 + 1/R_2]$
$K \Rightarrow 1/R_1 \times 1/R_2$

Mesoscale Linearized Elastic Model for Membrane (small deformation limit)

z=h(x,y)



Time-Dependent Ginzburg Landau Eq.

$$\frac{\partial z}{\partial t} = -M\frac{\delta E}{\delta z} + \zeta.$$

Langevin Equation (TDGL)

Hohenberg and Halperin, 1977

Helfrich Free Energy

$$f_c = \tfrac{1}{2}k(H - H_0)^2 + \bar{k}K.$$

Cartesian (Monge) notation: z=h(x,y)

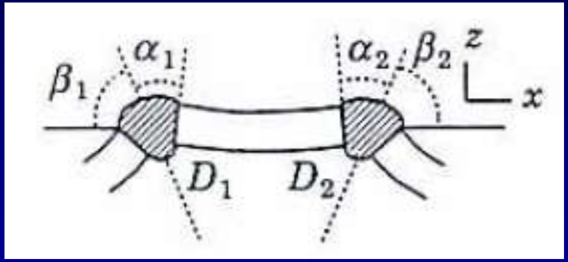
$$H = \frac{(1+h_x^2)h_{yy} + (1+h_y^2)h_{xx} - 2h_x h_y h_{xy}}{2[(1+h_x^2+h_y^2)]^{3/2}},$$

$$K = \frac{h_{xx}h_{yy} - h_{xy}^2}{(1+h_x^2+h_y^2)^2}.$$

$$E = \iint_A \frac{\kappa}{2}\left(\nabla^2 z - H_0\right)^2 + \left(\frac{\kappa}{4}H_0^{\,2} + \frac{\sigma}{2}\right)(\nabla z)^2 + \bar{\kappa}\left(z_{xx}z_{yy} - z_{xy}^{\,2}\right)dxdy$$

$$F_z = -\frac{\delta E}{\delta z} = 2H_0\kappa\left(z_x H_{0,x} + z_y H_{0,y}\right) + \left(\frac{\kappa}{2}H_0^2 + \sigma\right)\left(\nabla^2 z\right) - \kappa\nabla^4 z + \kappa\nabla^2 H_0 + \xi$$

Coarse-Grained Representation of Protein-Membrane Interaction

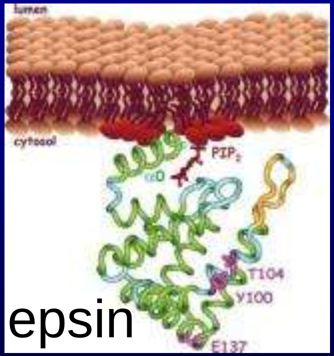


Integral Membrane Proteins
Membrane is attached to the protein at a fixed contact angle
Goulian M, Bruinsma R, Pincus P (1993)
Lubensky T (1997)
Kim KS, Neu J, Oster G (1998)

LOCAL CURVATURE INDUCER MODEL

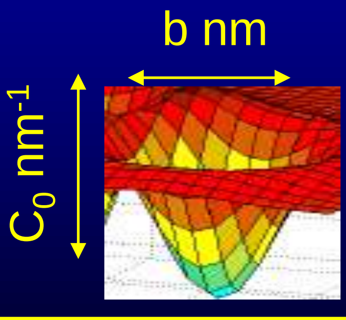
McMahon, 2003, 2005

Tubule diameter=20 nm; $\Delta E_{binding}$= -14 k_BT



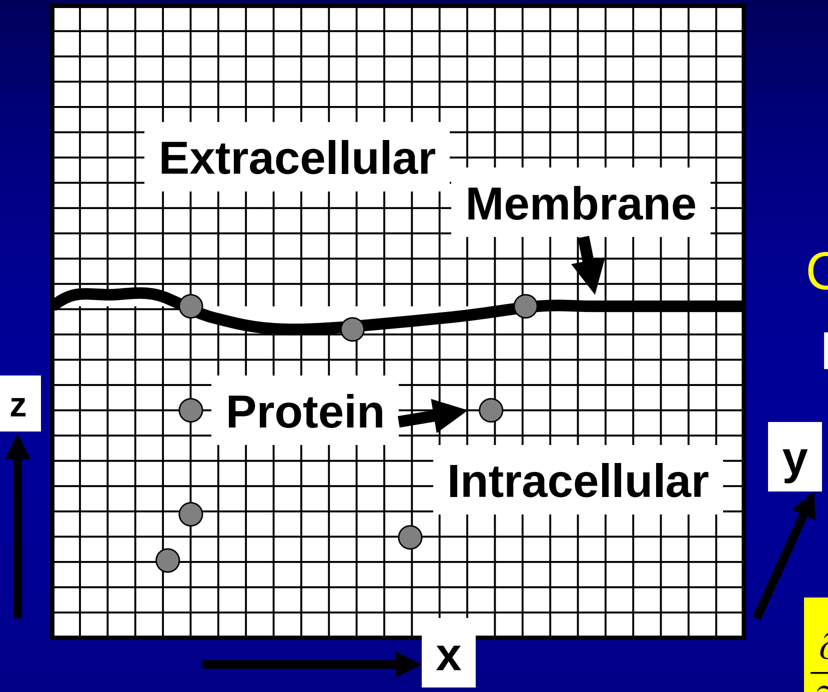
Seifert, et. al. 2006;
Weinstein, Radhakrishnan, 2006;
Agrawal, Weinstein, Radhakrishnan, 2008

C_0=0.1 nm^{-1}; b=8 nm; κ=20 k_BT



$$H_0 = C_0 e^{-s^2/b^2} .$$

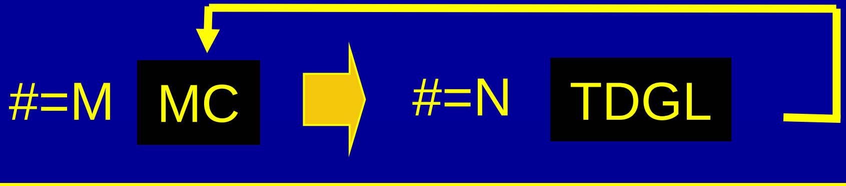
Multiscale Integration: Protein-Mediated Membrane Fluctuations



Weinstein, Radhakrishnan, 2006;
Agrawal, Weinstein, Radhakrishnan, 2008

Canonical Ensemble (Constant Temperature)

MC-MD algorithm of La Berge and Tully, 2001

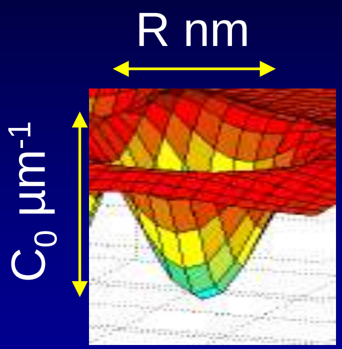


$$\frac{\partial E}{\partial x_{0i}} = -\frac{\kappa C_i}{R_i^2}\iint_A e^{-\frac{(x-x_{0i})^2+(y-y_{0i})^2}{2R_i^2}}\left(\nabla^2 z - H_0 + \frac{H_0(\nabla z)^2}{2}\right)(x-x_{0i})\,dxdy$$

Proteins perform a random walk on membrane surface with a membrane mediated force field

$$\frac{\partial z}{\partial t} = -M\frac{\delta E}{\delta z} + \zeta.$$

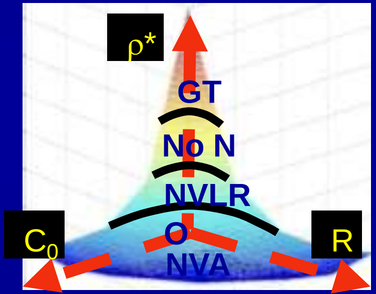
State Diagram: Protein-Mediated Membrane Fluctuations



- ρ^*, Surface Density 1-100 per μm^2
- R=b/2, Range 10-50 nm
- C_0 or H_0, Intrinsic Curvature 0-40 μm^{-1}
- Radial Distribution, Orientational Correlation
- Membrane Height Autocorrelation

J. Weinstein, R. Radhakrishnan, 2006

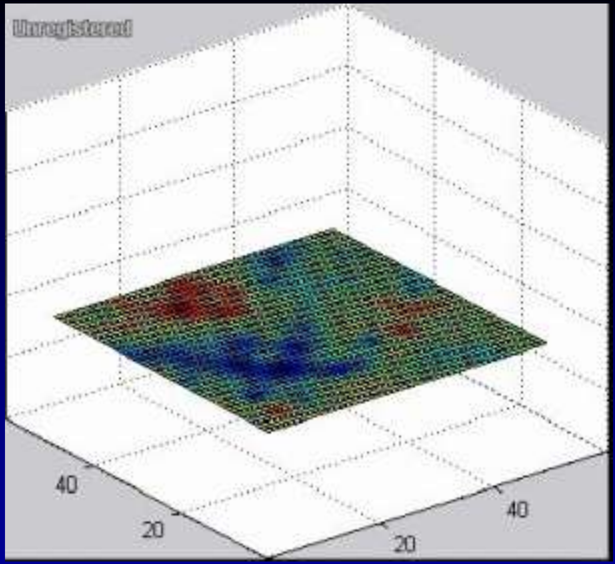
N. J. Agrawal, J. Weinstein, R. Radhakrishnan, 2008.



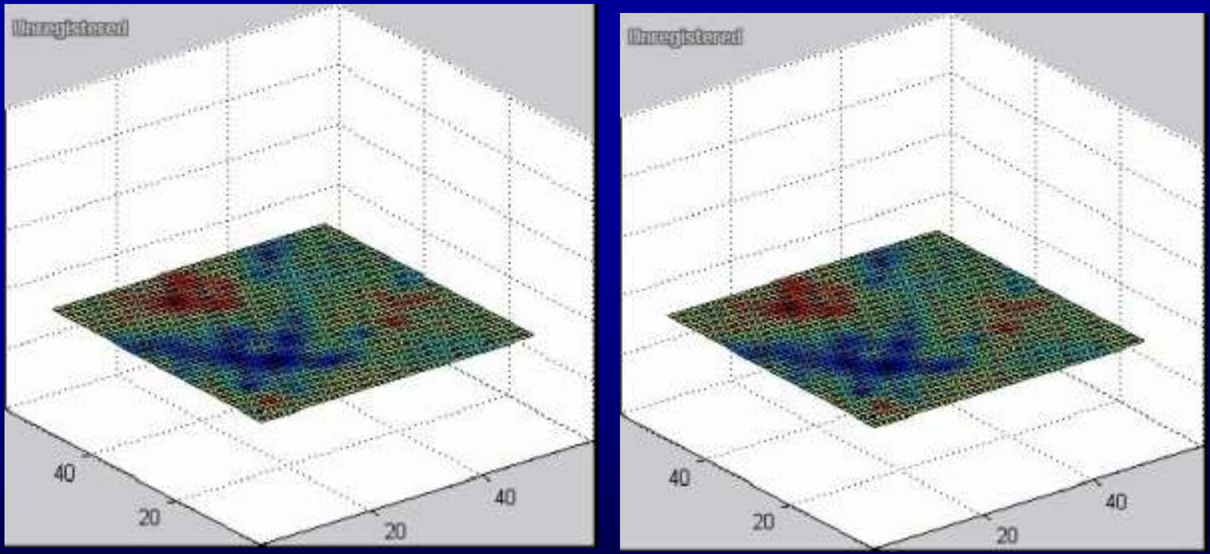
How does the protein induced curvature affect the equilibrium properties and conformations of the membrane ?

State Diagram

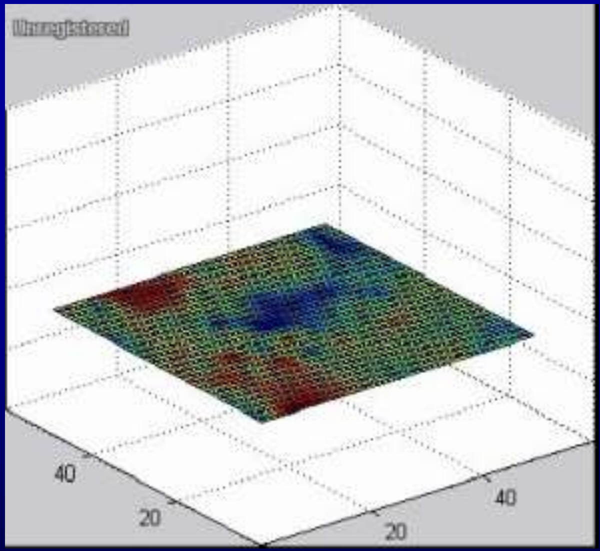
RU: Repressed Undulations;
No N: No nucleation
NVOO: Nucleation via orientational ordering
NVA: Nucleation via diffusional association



NVA



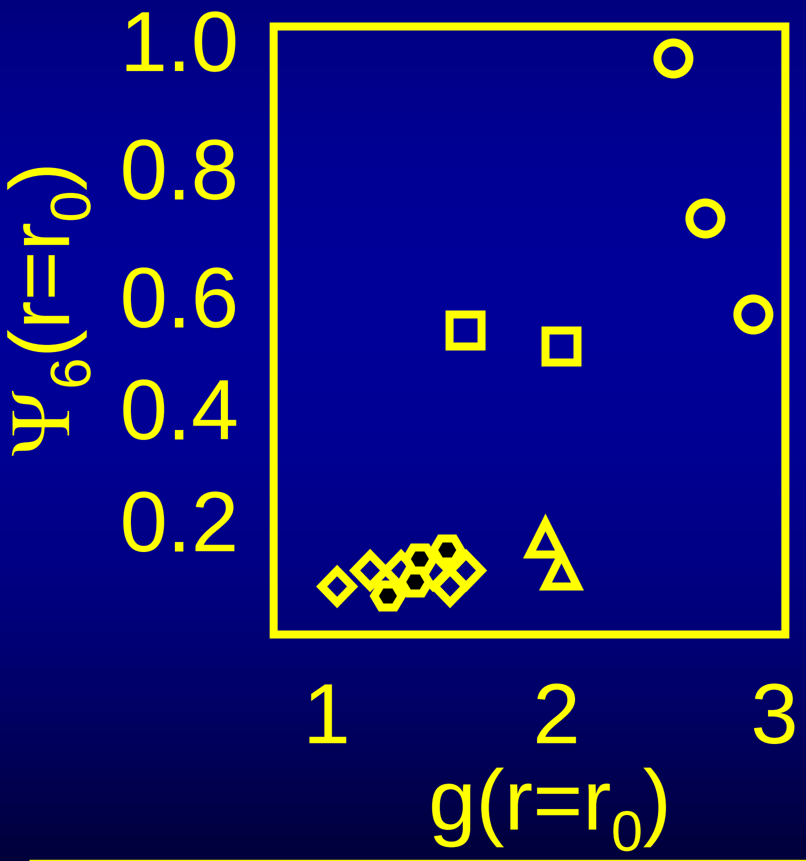
NVOO

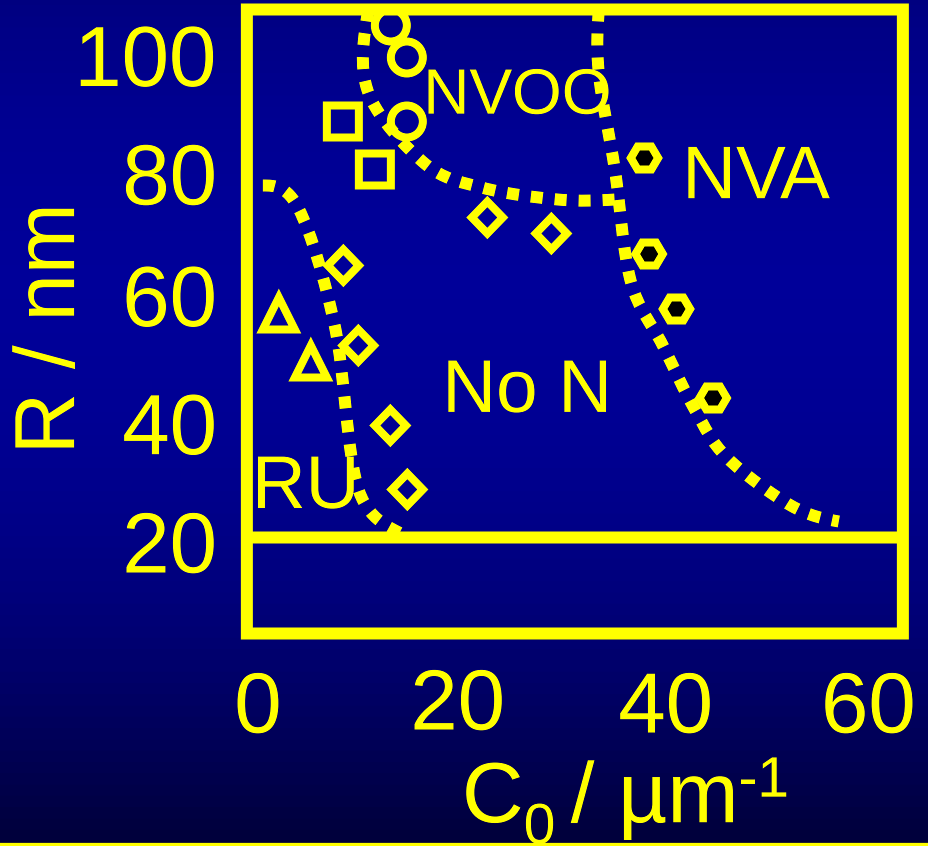


RU

State Diagram

RU: Repressed Undulations; **No N:** No nucleation
NVOO: Nucleation via orientational ordering
NVA: Nucleation via diffusional association

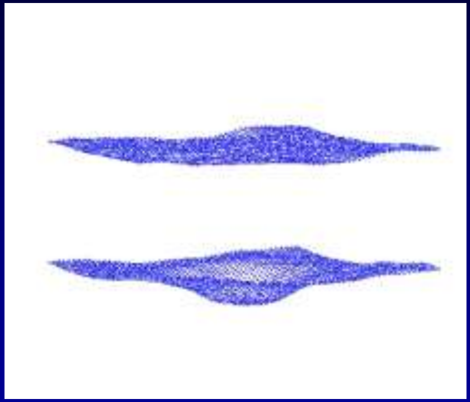




Free Energy Calculations via Thermodynamic Integration

$$\begin{tikzcd}
(s_0,0) \arrow[r, "\Delta F_0=0"] \arrow[d, "\Delta F_1"'] & (s_1,0) \arrow[d, "\Delta F_2"] \\
(s_0,C_0) \arrow[r, "\Delta F"] & (s_1,C_0)
\end{tikzcd}$$

Free energy change with spatial extent of the curvature function



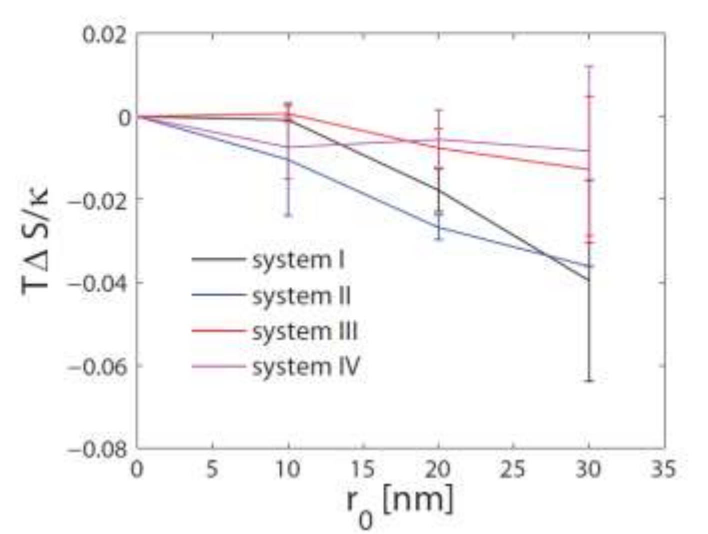
Agrawal, Radhakrishnan, 2009

$$\left(\frac{\partial F}{\partial \lambda}\right)_{N,V,T} = -\frac{1}{\beta}\frac{\partial}{\partial \lambda}\ln Q = \left\langle \frac{\partial E}{\partial \lambda} \right\rangle_{\lambda}$$

By choosing $\lambda = C_0$,

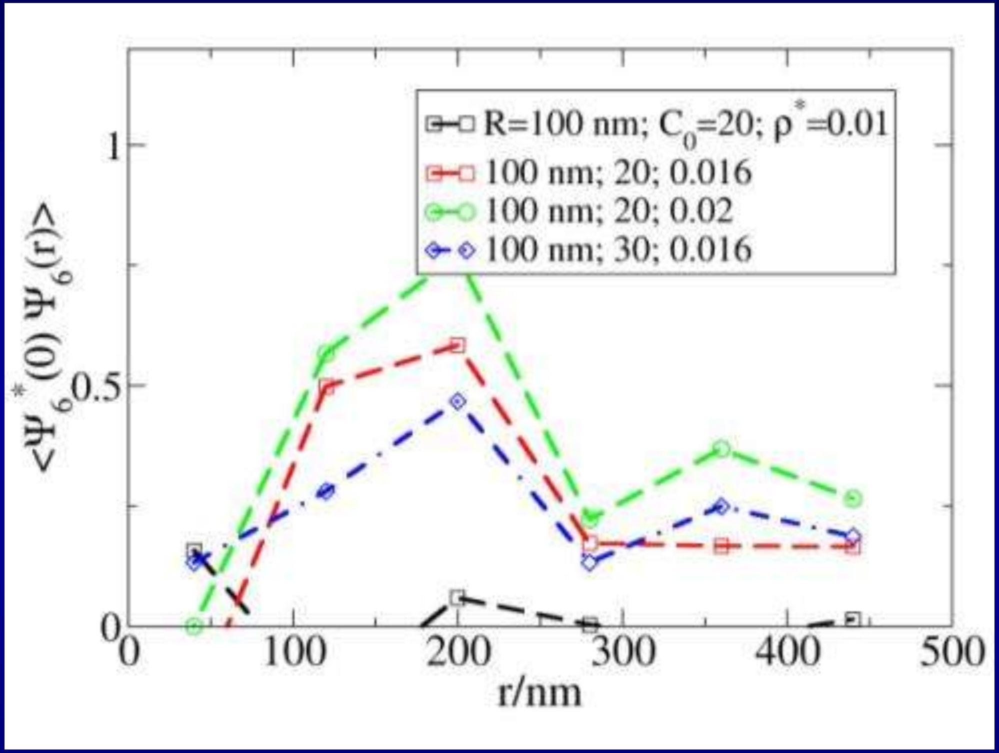
$$\frac{\partial F}{\partial C_0} = \left\langle \Gamma(r_0)\kappa \sum_{N} \left[-\left(\nabla^2 z_i - \lambda \Gamma(r_0)\right) + \frac{\lambda}{2}(\nabla z_i)^2 \right] (\Delta r_i)^2 \right\rangle$$

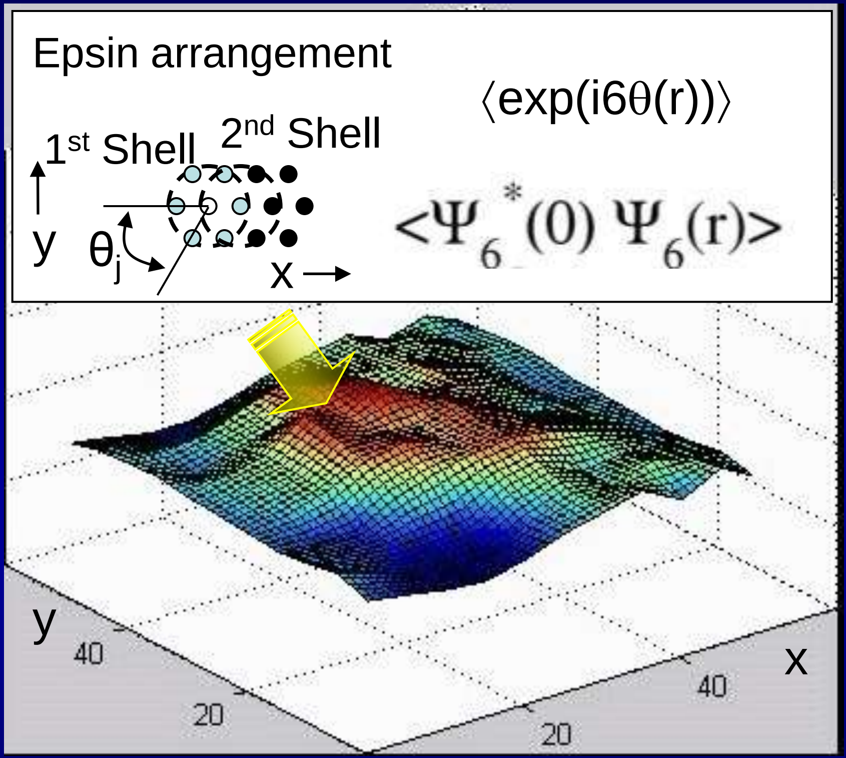
$$\Delta F = F(C_0) - F(0) = \int_0^{C_0} \frac{\partial F}{\partial C_0}\, dC_0$$



Entropy change is small (<5% of the Energy change) but is of order $k_B T$

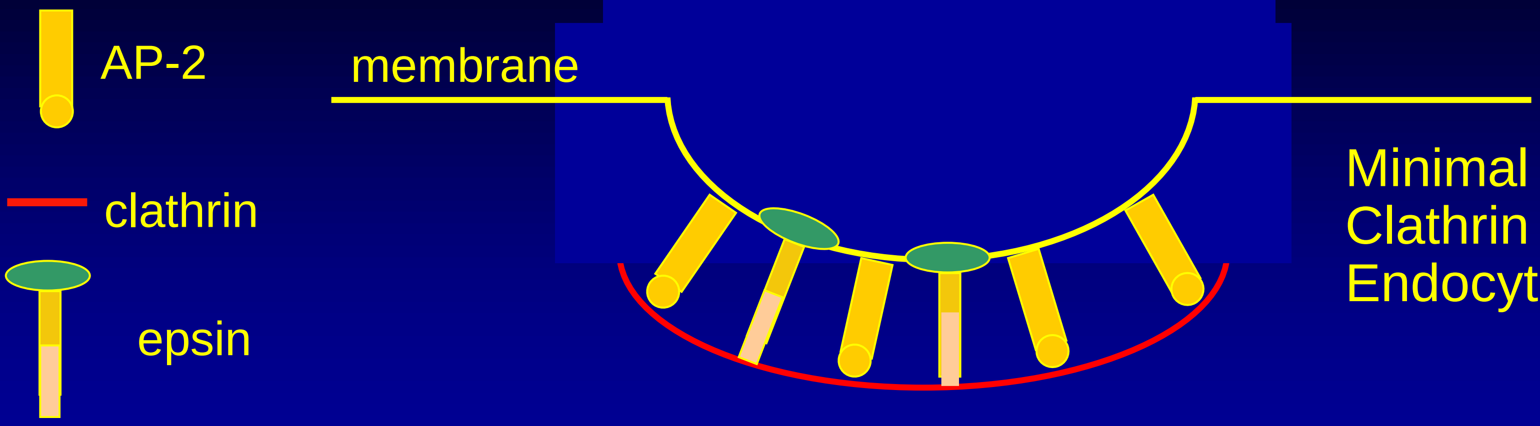
Nucleation via Hexatic Orientational Ordering: NVOO





Sustained orientational correlations beyond nearest-neighbors drives nucleation

Clathrin-Mediated Endocytosis: Inference-Based Model



Minimal Model of Clathrin Mediated Endocytosis

Recent Experimental Observations

- HeLa Cells: In absence of clathrin, AP-2 and accessory proteins form curvature lacking sub-domain. Hinrichsen, PNAS 2006.
- HeLa Cells: Knockdown of AP-2 significantly reduces the number of clathrin coated pits (CCP) at the plasma membrane. Hinrichsen, J. Biol. Chem. 2003.
- Neurons: epsin antibodies change the morphology of CCP. Jakobsson, PNAS, 2008.
- Effect of accessory proteins is receptor (cargo) dependent.

Surface Evolution

- ❑ Exact minimization of Helfrich energy possible for any (axisymmetric) membrane deformation.
- ❑ Energy is minimized instead of Free Energy
- ❑ Membrane parameterized by arc length, s and angle ψ.

Seifert, 1995

For topologically invariant transformations,

$$E = \iint_M \left\{ \frac{\kappa}{2}\left(H - H_0\right)^2 + \sigma \right\} dA$$

σ Frame tension

κ Bending modulus

H_0: Spontaneous curvature

$$\psi'' = \frac{\cos\psi \sin\psi}{R^2} - \frac{\psi' \cos\psi}{R} + \frac{\gamma \sin\psi}{R\kappa} + H_0'(s)$$

$$\gamma' = \frac{\kappa}{2}\left(\psi' - H_0(s)\right)^2 - \frac{\kappa \sin^2\psi}{2R^2} + \sigma$$

$$R' = \cos\psi$$

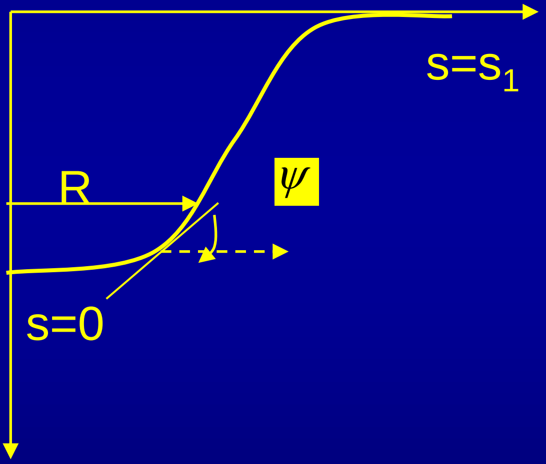
$$R(s=0) = 0$$

$$\psi(s=0) = 0$$

$$R(s=s_1) = R_0$$

$$\psi(s=s_1) = 0$$

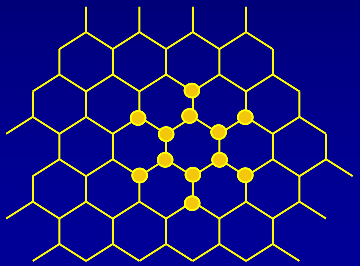
$$\gamma(s=s_1) = \sigma R_0$$



Surface evolution provides a route to compute the profiles and energetics associated with minimum energy conformations of membranes subject to extreme curvature

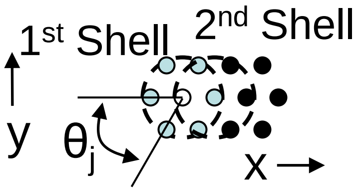
Bond-Orientational Patterning of Epsin on Clathrin Lattice Leads to a Mature Vesicle Formation

Clathrin Coat



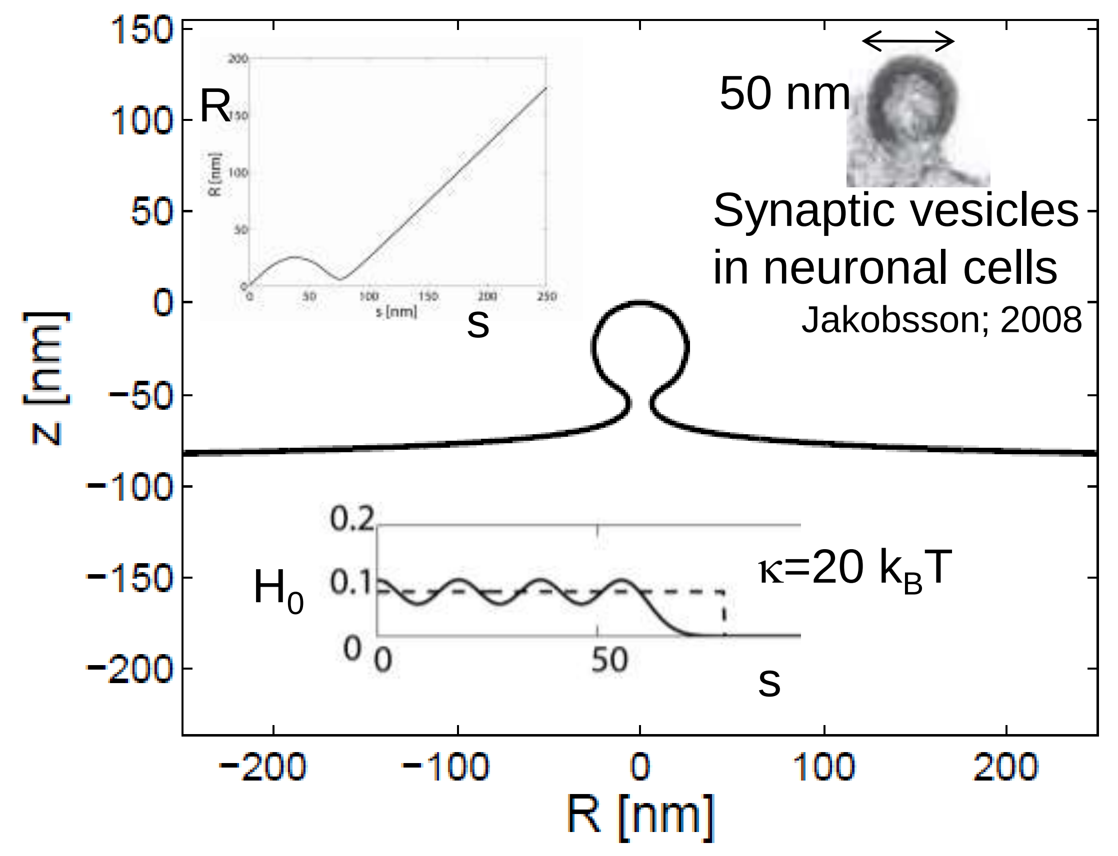
Area=A_a

Epsin arrangement



$\langle \exp(i6\theta(r)) \rangle$

$<\Psi_6^*(0)\,\Psi_6(r)>$



50 nm

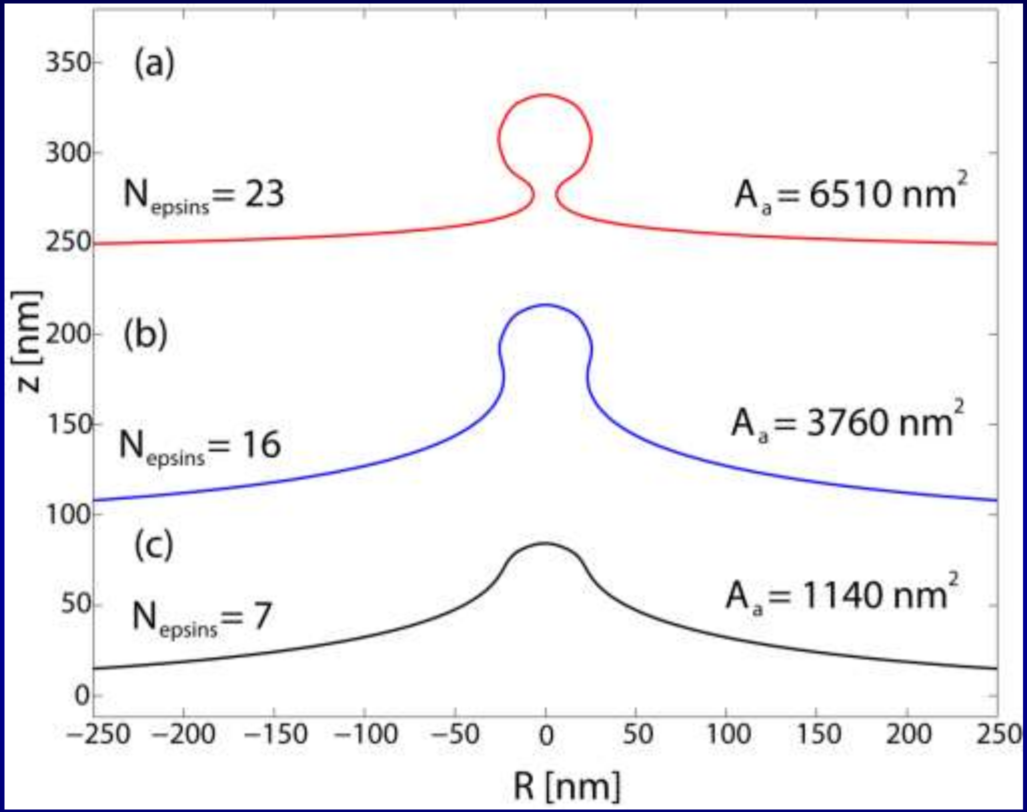
Synaptic vesicles in neuronal cells

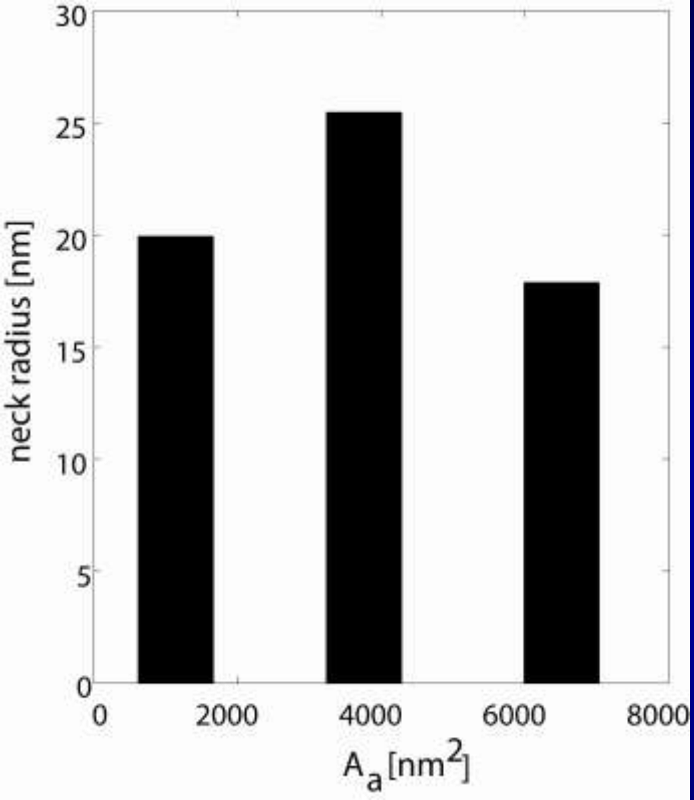
Jakobsson; 2008

κ=20 k_BT

Agrawal, Radhakrishnan, Submitted

Effect of Clathrin-Coat Size on Membrane Vesiculation

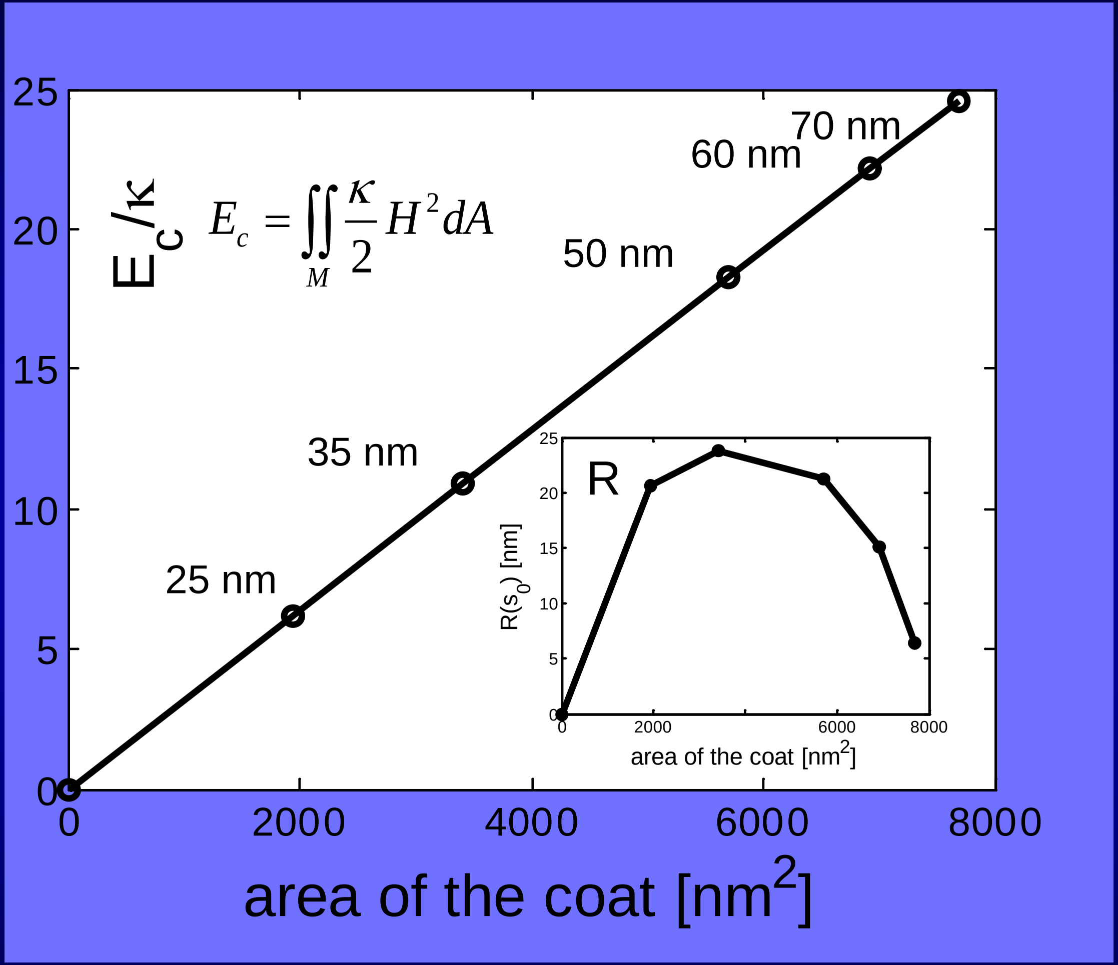




Critical size of a growing clathrin coat leads to membrane invagination

Agrawal, Radhakrishnan, Submitted

Energy Considerations in Clathrin Induced Membrane Vesiculation



For $\kappa=20k_BT$, $E_C \sim 500\ k_BT$

E_a

$-20\ k_BT$ ⇨

Nossal, Traffic, 2001.

E_r EPSIN McMahon 2003

ENTH — UIM — CLAP — NPF

\+ membrane ⇩ $-14\ k_BT$

\+ clathrin ⇩ $-9\ k_BT$

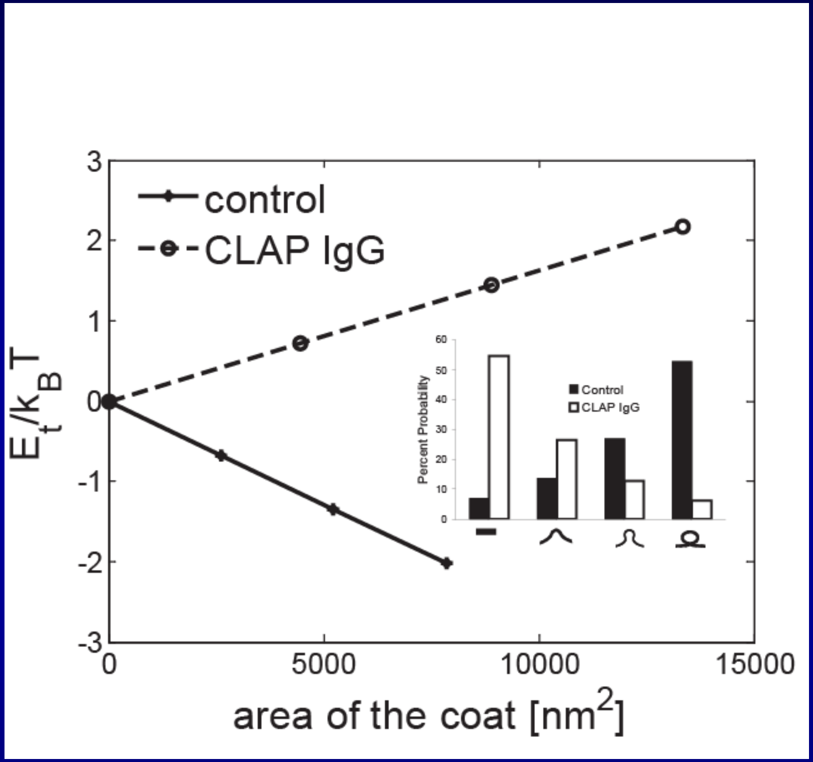
$E_t = E_c + E_a + E_r$; $E_r = n_e*\varepsilon_e$

$E_t = E_c + E_a + n_e*\varepsilon_e$

Agrawal, Radhakrishnan, Submitted

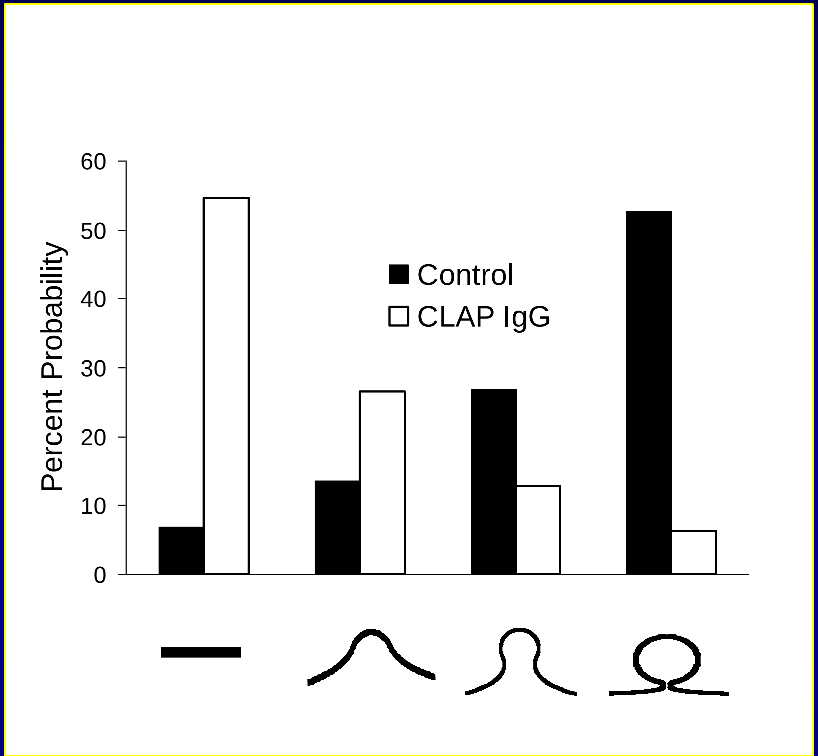
Energy Considerations in Clathrin Induced Membrane Vesiculation

Calculated



Agrawal, Radhakrishnan, submitted

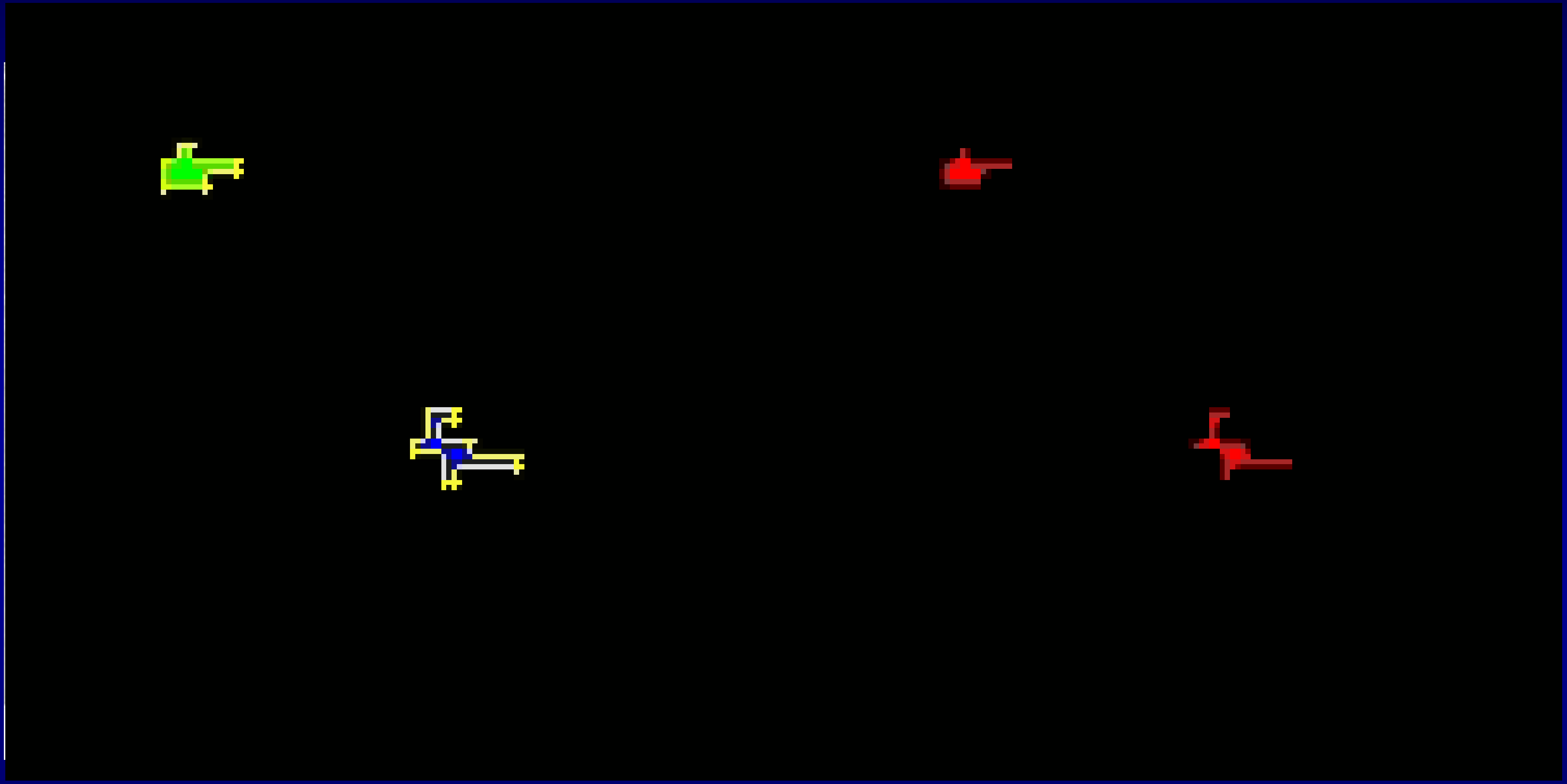
Experimental



Jakobsson, J.; PNAS 2008, 6445.

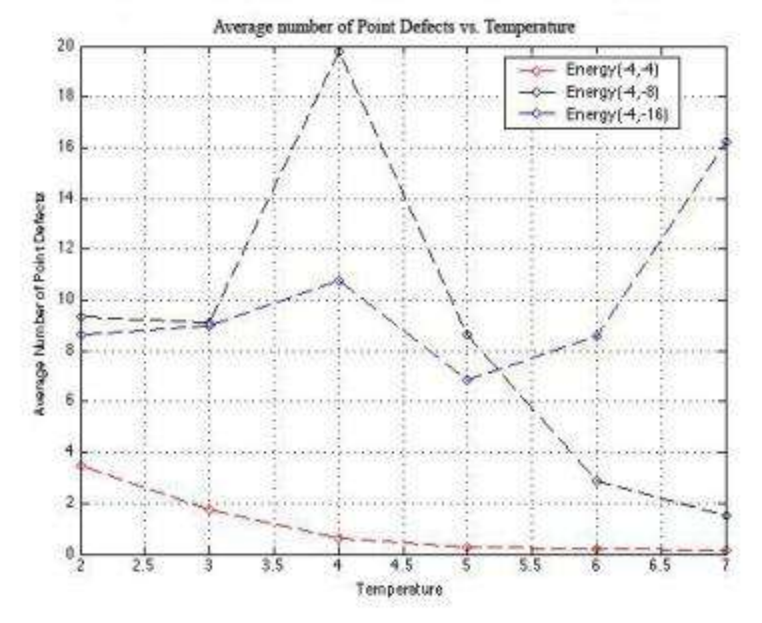
Our results highlight the unique and central role played by epsin in the process of vesicle nucleation during endocytosis

Minimal Model for Clathrin Coat Nucleation

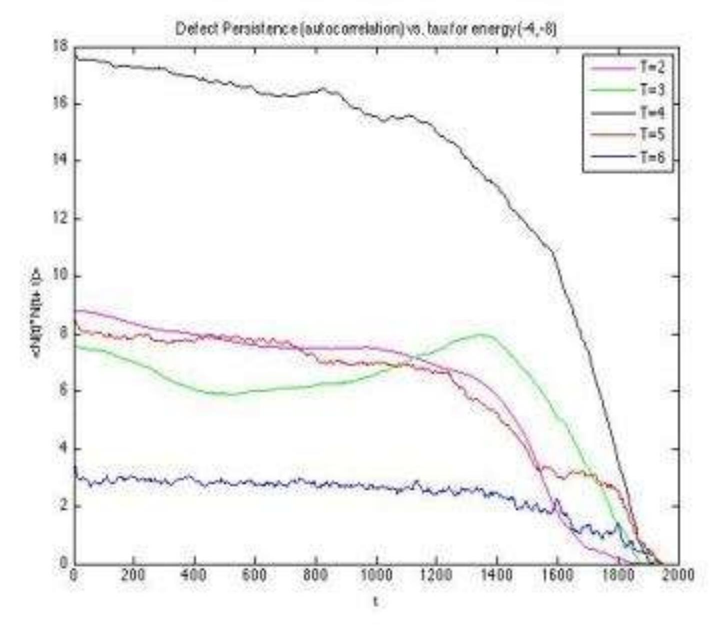


Point defects serve the role of disclinations in a hexagonal lattice and enable the coat to adaptively assume a curvilinear scaffold

Minimal Model for Clathrin Coat Nucleation



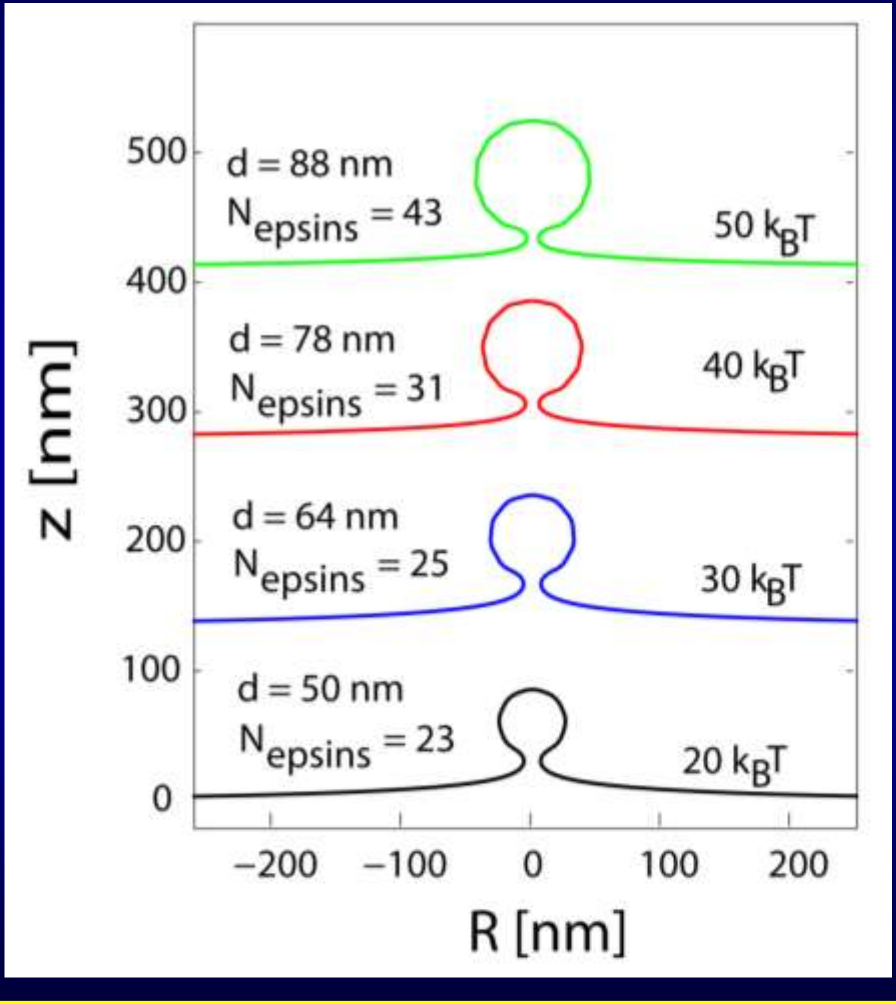
Effect of Interaction Energy Variation on Number of Point Defects



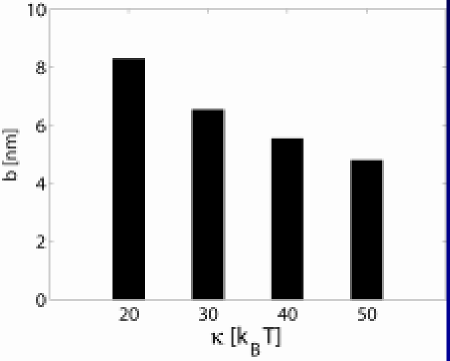
Autocorrelation and Persistence Time

Effect of Bending Rigidity on Membrane Vesiculation

Diameter of the budding vesicle depends strongly on membrane bending rigidity

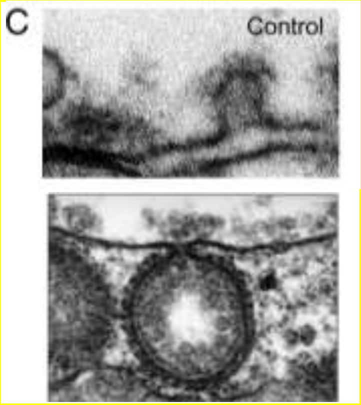


b



κ

Due to cell-cell variability, diameter of clathrin-coated vesicles range from 50-100 nm



Neuronal Cells

d=50 nm

Epithelial Cells

d=100 nm

Integrated Molecular-Systems Model for ErbB Signaling, Trafficking

Clathrin adaptor	Cargo motif recognized	Ubiquitin binding	Membrane component bound
AP2 complex	ΦxxYxxΦ [DE]xxxL[LI]	Yes	PtdIns(4,5)P_2
AP1 complex	ΦxxYxxΦ [DE]xxxL[LI]	Yes	PtdIns4P
GGA	DxxLL	Yes	ArfGTP
Epsin		Yes	PtdIns(4,5)P_2
HRS/Vps27		Yes	PtdIns3P
DAB2/ARH	[FY]xNPxY	Yes	PtdIns(4,5)P_2
Arrestin	GPCRs	Yes	PtdIns(4,5)P_2
AP180/CALM		Yes	PtdIns(4,5)P_2
Amphiphysin		Yes	Acidic phospholipid including PtdIns(4,5)P_2

E

TOFMS

Survival

Activation of downstream effectors of cellular response is specific to the molecular context

- ErbB1-4 internalize at different rates

-- FYRALM recognition motif

-- Receptor:AP-2 in 2:2 is optimal

- Some ErbB1 mutants internalize slowly
- Link to altered downstream signaling: Erk vs. Akt vs. STAT5

-- Akt activation is optimal in membrane-bound receptor

-- Erk signaling occurs for internalized as well as membrane-bound receptors

-- STAT5 activation could be mutually exclusive of internalization