Assembly, Architecture, and Collective Function of Membrane Protein Lattices

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Ned S. Wingreen *(Molecular Biology, Princeton)*

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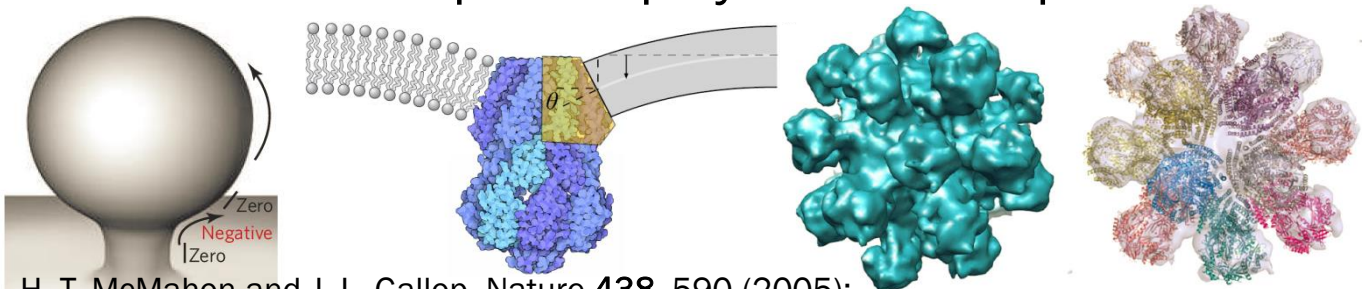
Regulation of membrane shape

1. Membrane protein polyhedral nanoparticles



H. T. McMahon and J. L. Gallop, Nature **438,** 590 (2005);
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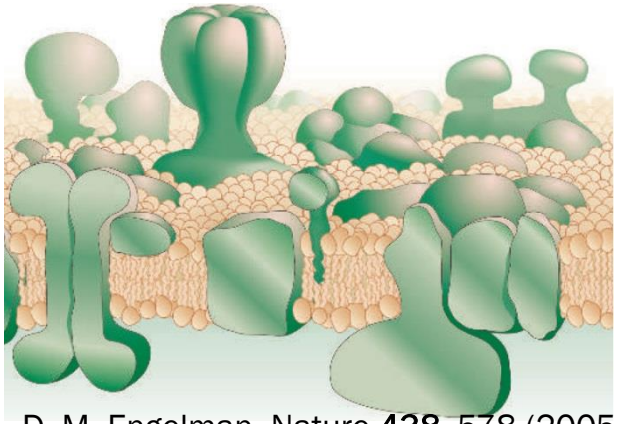
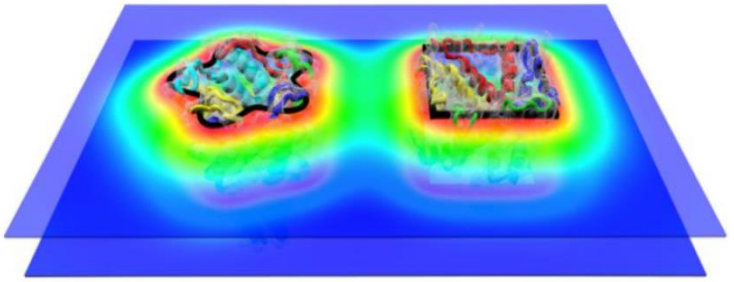
Collective function of proteins in cell membranes





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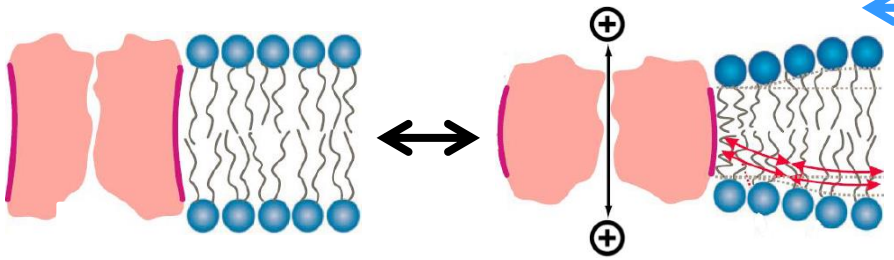
Protein regulation through lipids

2. Mechanosensitive ion channels



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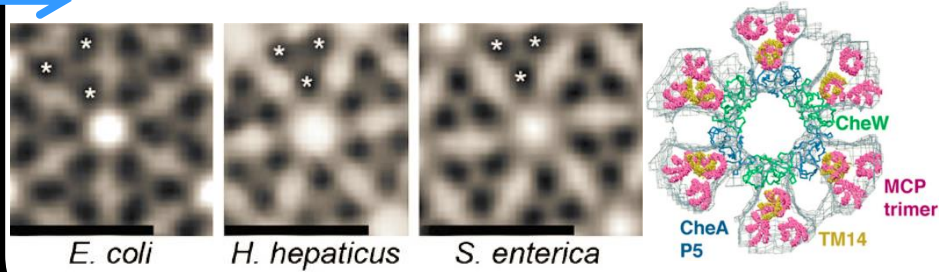
Self-assembled protein clusters

3. Chemoreceptor lattices



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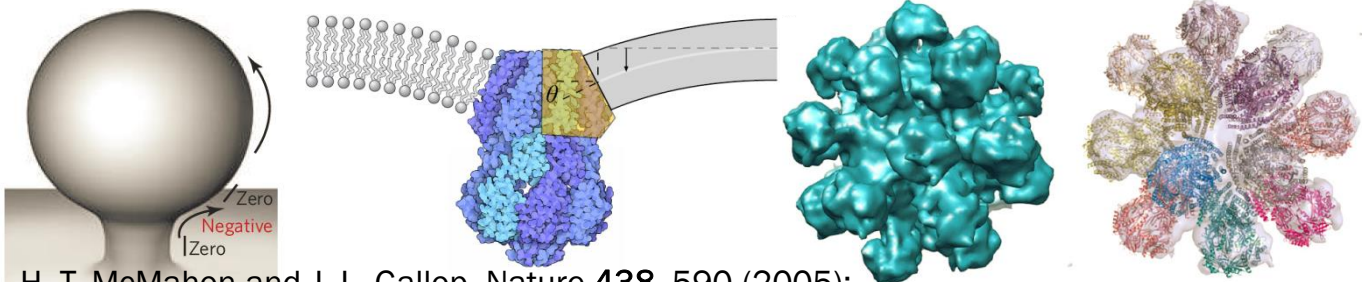

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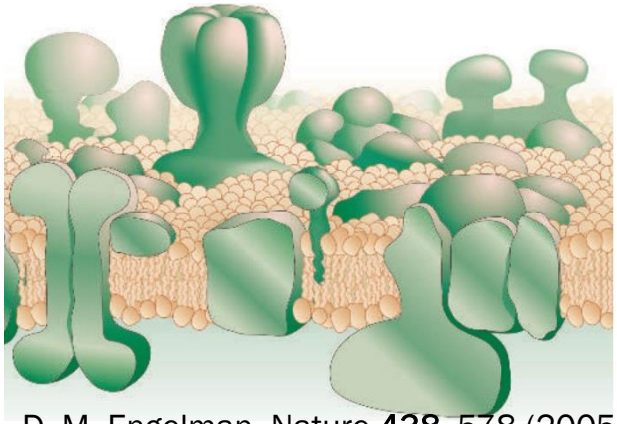

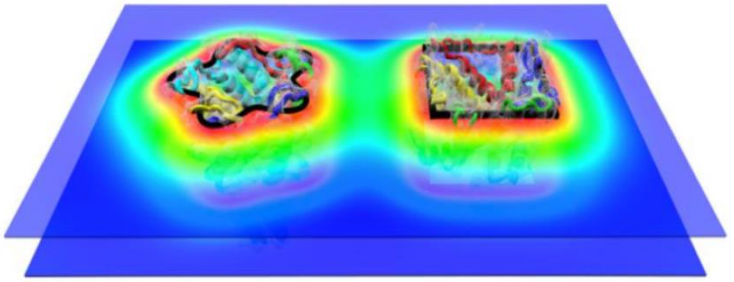

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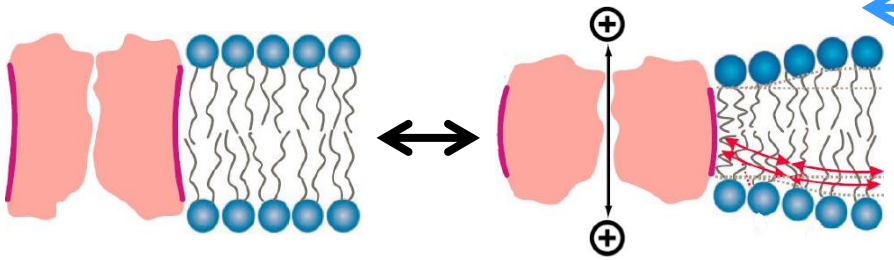

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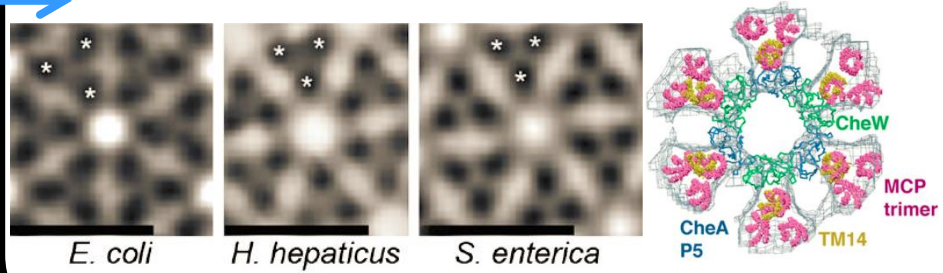
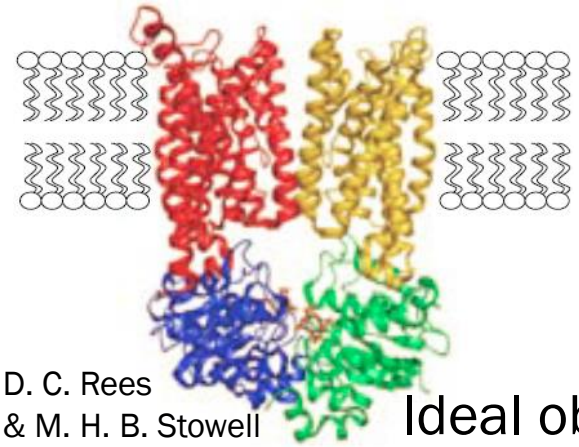


A. Briegel, *et al.*, PNAS **109**, 3766 (2012)

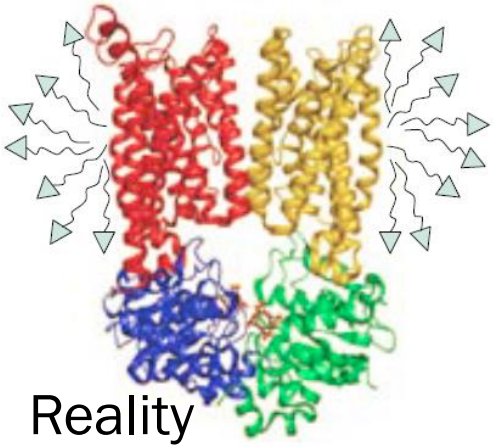
Membrane protein polyhedral nanoparticles (MPPNs)



D. C. Rees
& M. H. B. Stowell

Ideal objective

Remove protein from cell membrane

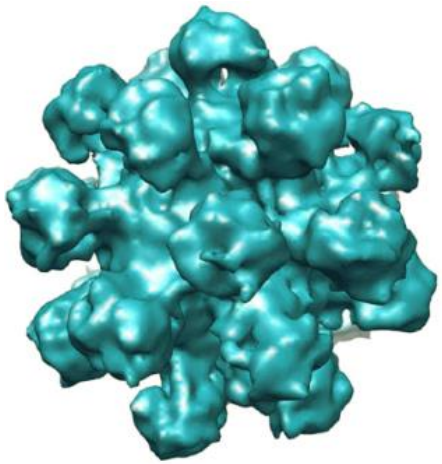


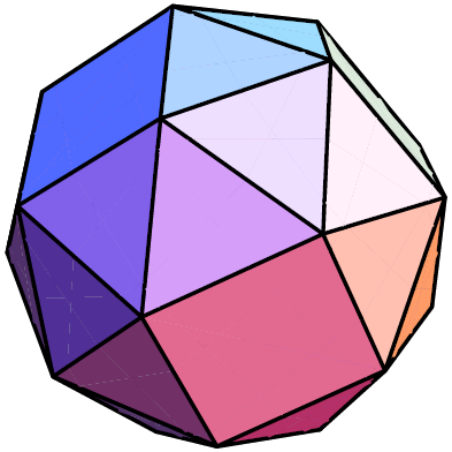
Reality

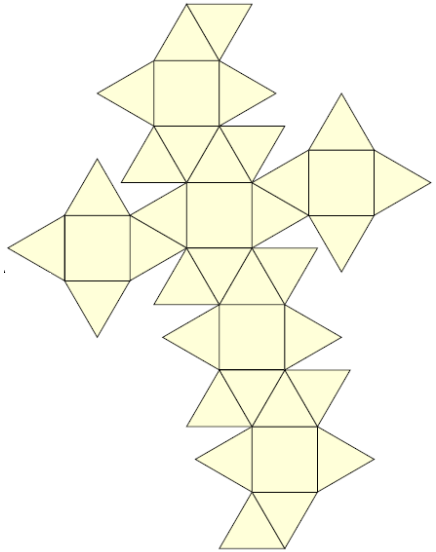
Synchrotron

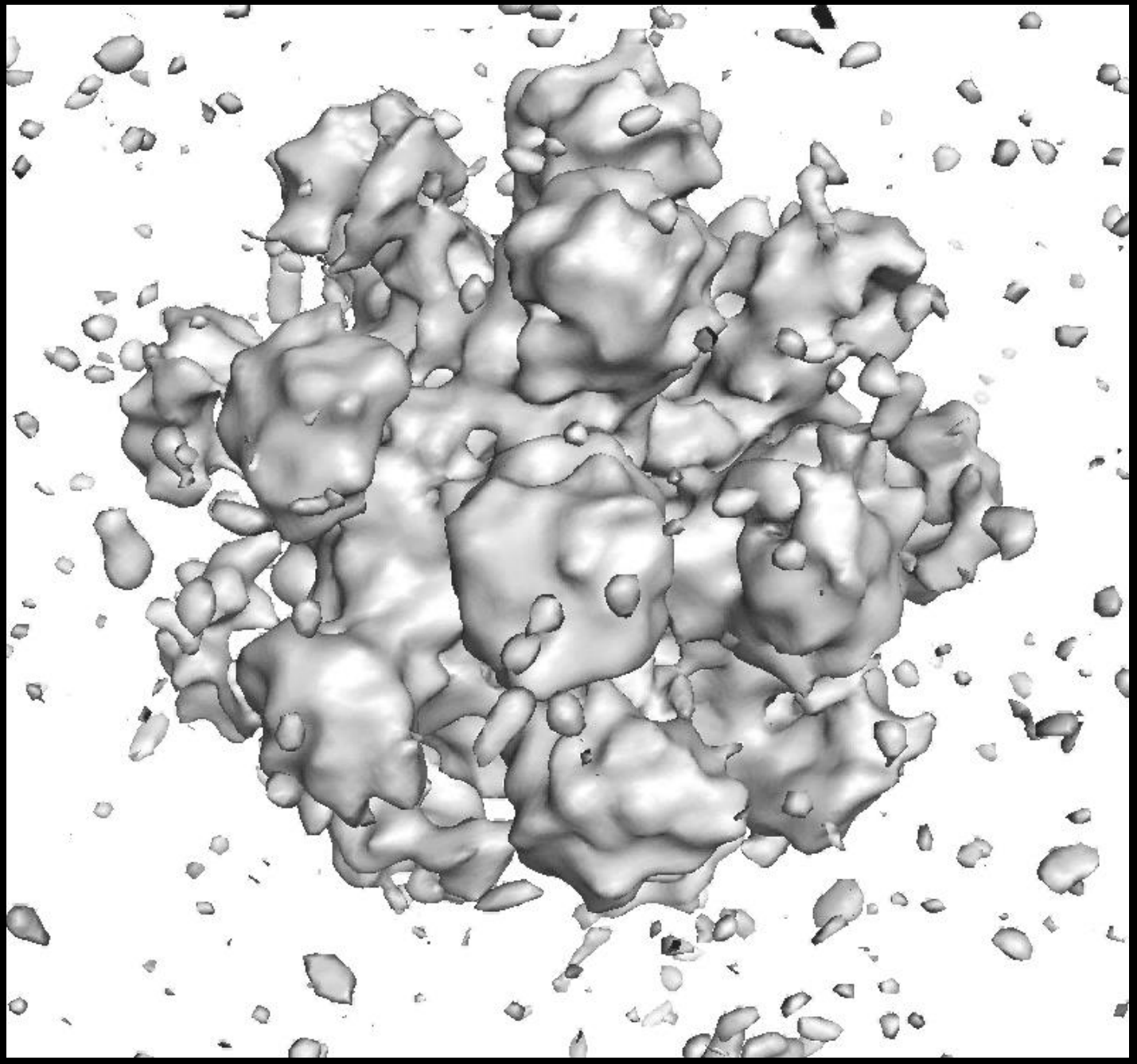
Membrane protein structure in lipid bilayer environments? Ion or chemical transmembrane gradients? Access different conformational states?

Self-assembly of *membrane protein polyhedral nanoparticles (MPPNs)*
[T. Basta, *et al.*, PNAS **111**, 670 (2014)]









T. Basta, *et al.*, PNAS **111**, 670 (2014)

Key experimental features of MPPNs

T. Basta, *et al.*, PNAS **111**, 670 (2014)

- MPPNs self-assemble in aqueous environments
- Proteins embedded in lipid bilayer environment; Closed surface of MPPNs: “Inside” and “outside.”
- Well-defined symmetry: Snub cube with proteins at its 24 vertices
- Characteristic overall radius ≈ 20 nm

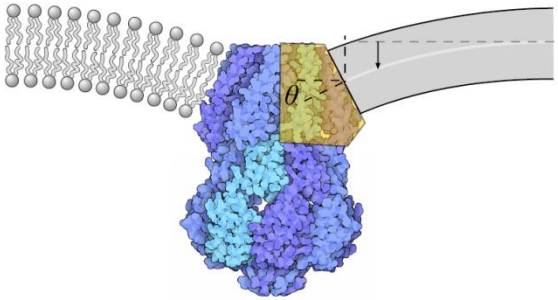
How can MPPN symmetry and size be controlled to allow high-resolution structural studies?
MPPNs formed from general membrane proteins?

What are the physical mechanisms yielding MPPN self-assembly?

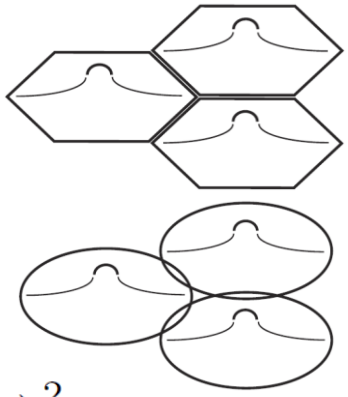
What molecular properties of lipids and proteins determine MPPN symmetry and size?

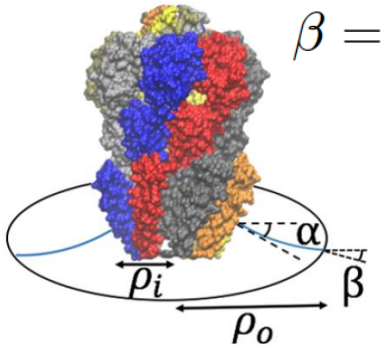
Minimal analytic (mean-field) model of MPPNs

MPPN bending energy [Membrane budding: T. Auth and G. Gompper, PRE **80**, 031901 (2009)]



R. Phillips, *et al.*, Nature **459**, 379 (2009)





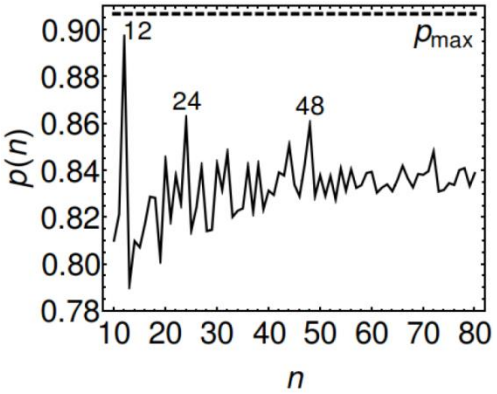
$$\beta = \arccos[(n-2)/n],$$

$$\rho_o = R\sin\beta,$$

diC14:0 lipids: $K_b \approx 14\ k_B T.$

$$G_{\text{Helfrich}} = \frac{K_b}{2}\int dxdy\,(\nabla^2 h)^2 \quad \xrightarrow{\text{Minimize}} \quad E_b(n,R) = \frac{2n\pi K_b(b\rho_o - a\rho_i)^2}{\rho_o^2 - \rho_i^2}$$

MPPN defect energy [Viral capsid self-assembly: R. F. Bruinsma, *et al.*, PRL **90**, 248101 (2003)]



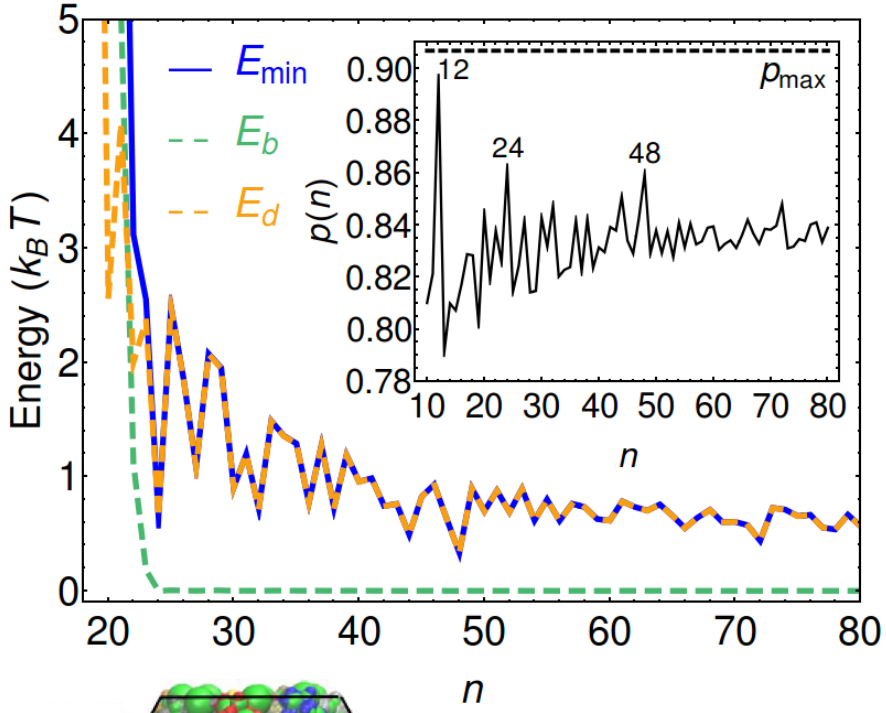
Defects in protein packing yield deviations from hexagonal packing of protein-induced bilayer deformations.

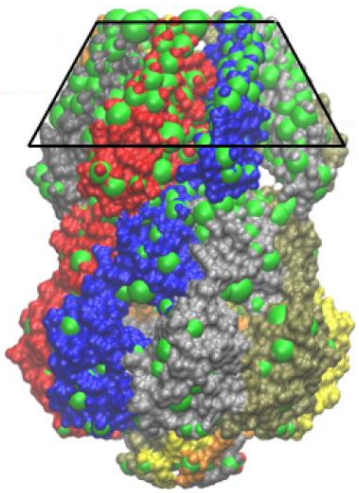
Tammes Problem: Fraction of the surface of a sphere enclosed by *n* identical non-overlapping circles at closest packing, *p*(*n*).

$$E_d(n,R) = 2\pi K_s R^2\left[\frac{p_{\max} - p(n)}{p_{\max}}\right]^2, \quad \text{where} \quad K_s = \frac{\pi K_b}{2\sqrt{3}}\frac{\min(a^4,b^4)}{|a^2-b^2|\rho_i^2}.$$

MPPN mean-field energy versus number of proteins

Total MPPN energy: $E = E_b + E_d$





Protein radius and bilayer-protein contact angle for MscS:

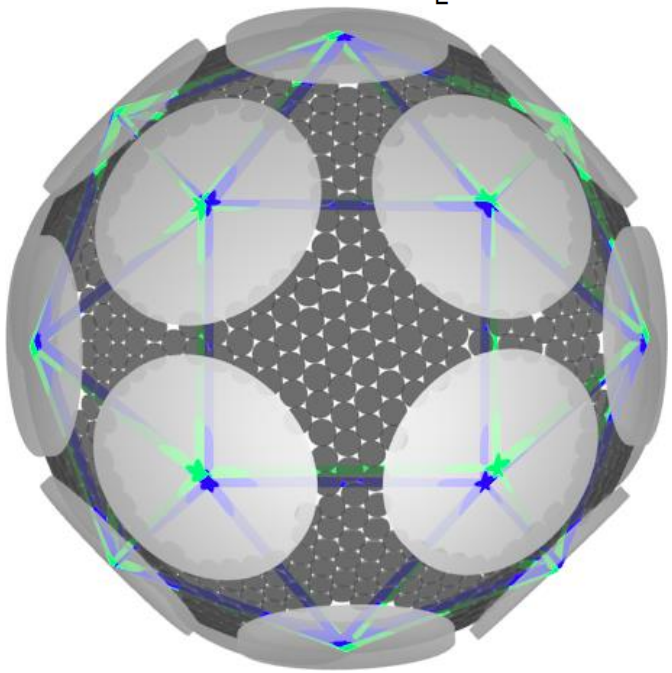
$\rho_i \approx 3.5$ nm,

$\alpha \approx 0.46$–0.54 rad.

Testing the mean-field model: Minimal molecular model of MPPNs

[Viral capsid structure: R. Zandi, *et al.*, PNAS **101**, 15556 (2004)] Proteins at centers of circular patches? Close packing of membrane patches?

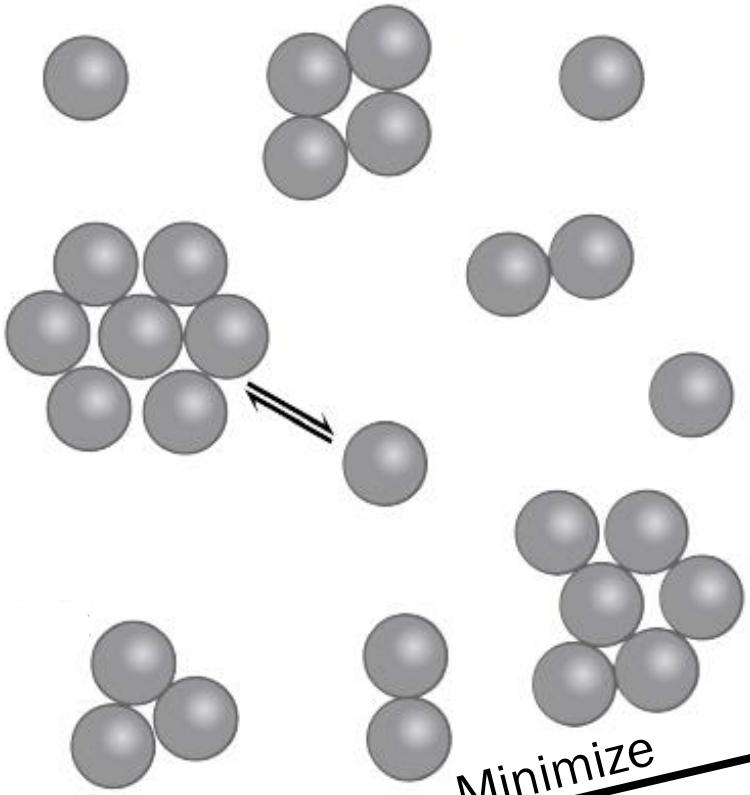
$$\text{Lennard-Jones}: V_i(r) = 4\epsilon_i \left[\left(\frac{\sigma_i}{r} \right)^{12} - \left(\frac{\sigma_i}{r} \right)^{6} \right]$$



Group	Polyhedron	Fit error Å^2
A	Snub cuboctahedron (dextro)	420
A	Truncated cuboctahedron	3725
C	Pentagonal hexecontahedron (levo)	5849

Statistical thermodynamics of MPPN self-assembly

Amphiphile self-assembly in dilute aqueous solutions [e.g., A. Ben-Shaul and W. M. Gelbart, in *Micelles, Membranes, Microemulsions, and Membranes* (Springer New York, 1994); J. N. Israelachvili, *Intermolecular and Surface Forces* (Academic press, 3rd ed., 2011); R. F. Bruinsma, *et al.*, PRL **90**, 248101 (2003)]. MPPN distribution in thermal equilibrium?



$N_n \ldots$ total number of proteins bound in MPPNs with n proteins each;

$N_w \ldots$ total number of solvent molecules;

Protein number fraction:
$c = \sum_n N_n/N_w \approx 7.8 \times 10^{-8}$.

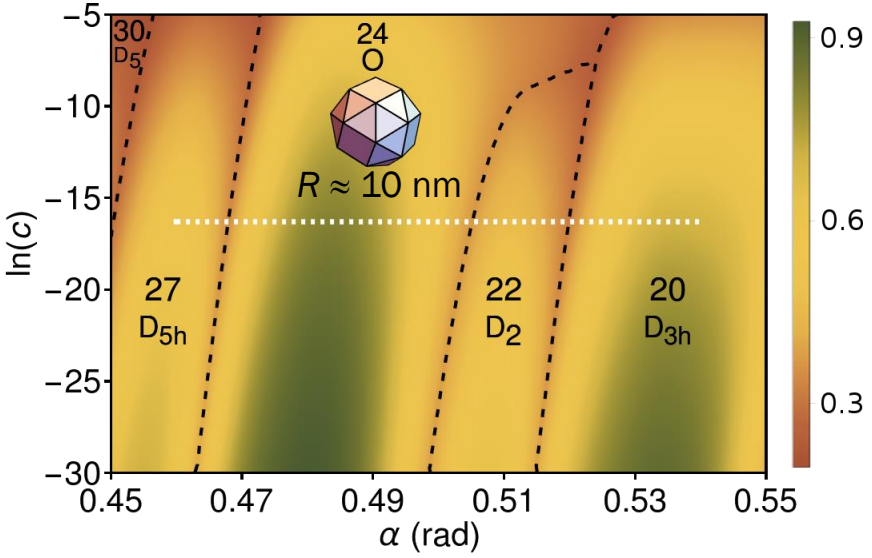
Mixing entropy in dilute limit $c \ll 1$:
$S = -N_w k_B \sum_n \Phi(n)[\ln\Phi(n) - 1]$,
where MPPN number fraction $\Phi(n) = \frac{N_n}{nN_w}$.

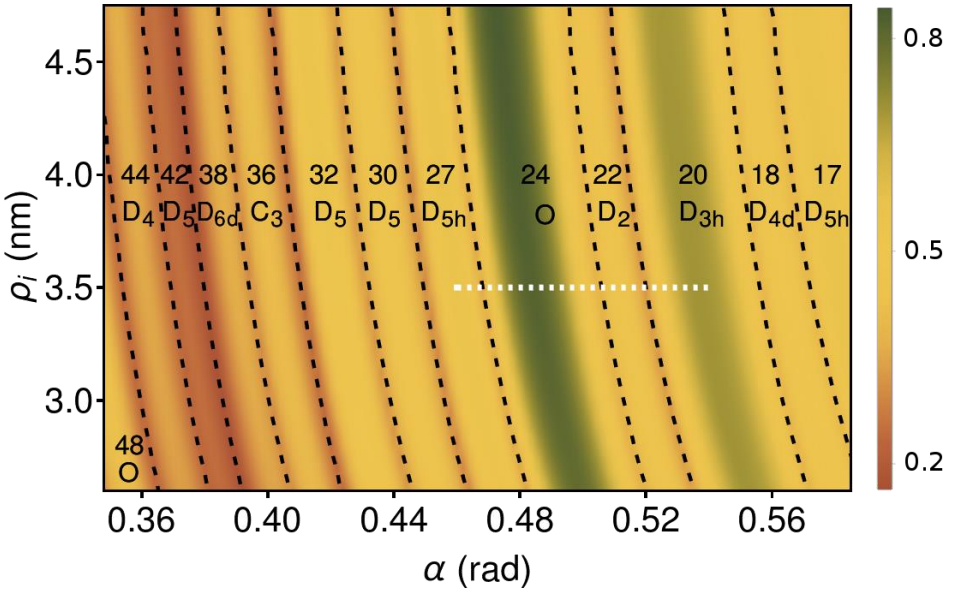
Helmholtz free energy $F = E - TS$ with
total MPPN energy $E = N_w \sum_n \Phi(n) E_{\min}(n)$.

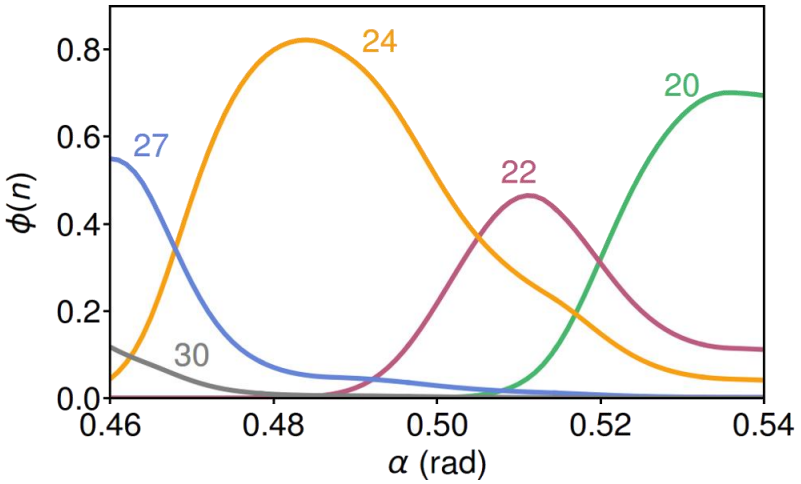
Minimize

$\Phi(n) = e^{\beta[\mu n - E_{\min}(n)]}$ with $\sum_n n\Phi(n) = c$. $\Longrightarrow$ MPPN distribution: $\phi(n) = \dfrac{\Phi(n)}{\sum_n \Phi(n)}$

MPPN self-assembly phase diagram







- For α, ρ_i, c, and K_b associated with experiments on MPPNs, predict observed n, MPPN symmetry & size.

- Do smaller observed MPPNs correspond to predicted MPPNs with dihedral symmetry?

- Model suggests how key lipid and protein properties can be modified to produce a range of MPPN symmetries & sizes.

Membrane shape regulation is a collective phenomenon: MPPN symmetry and size emerge from the interplay of protein-induced lipid bilayer deformations, topological defects in protein packing, and thermal effects.

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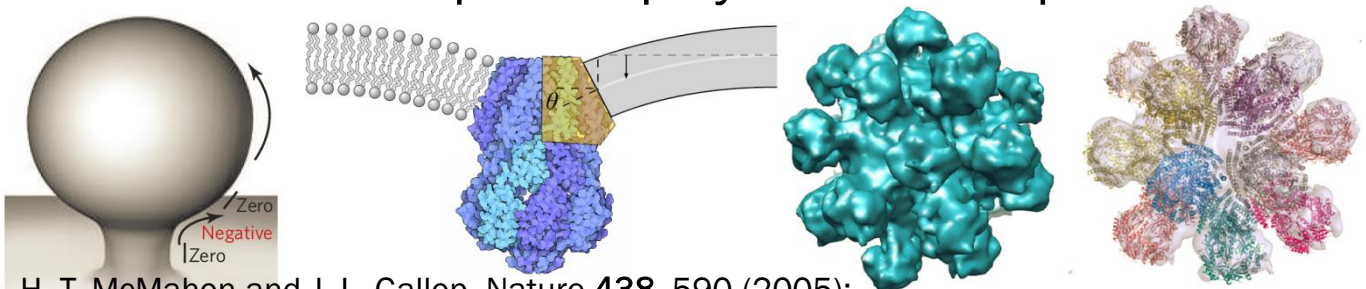

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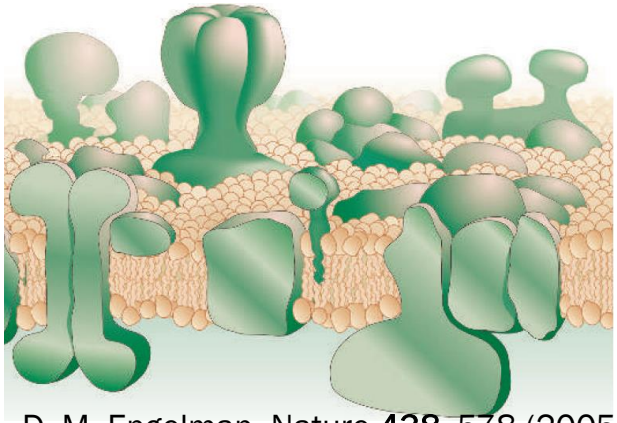

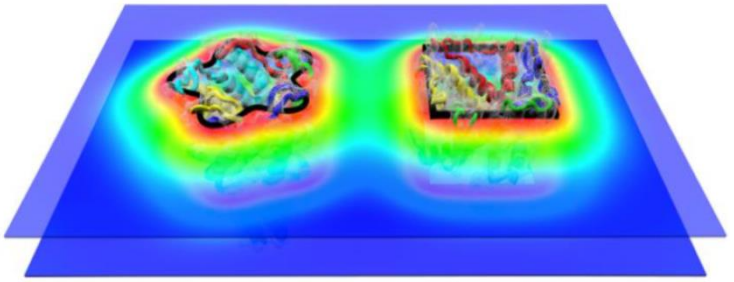

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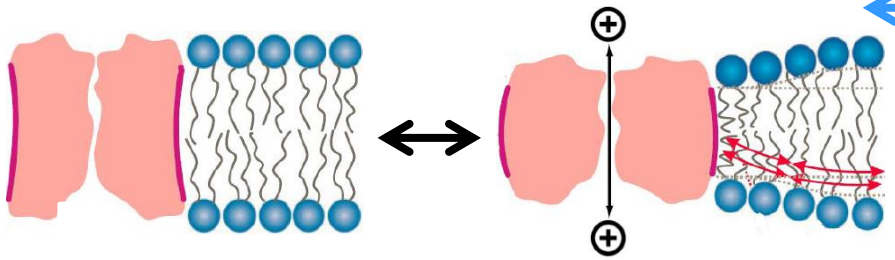

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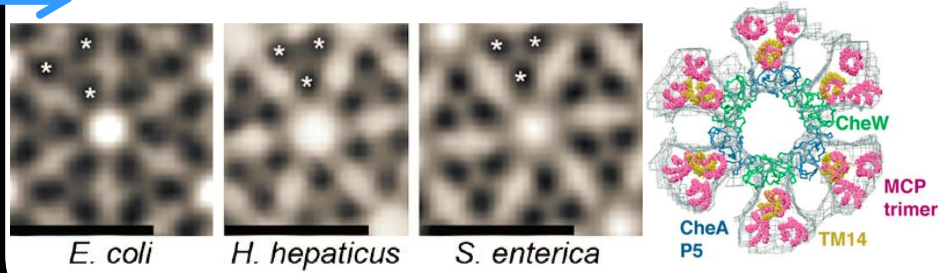

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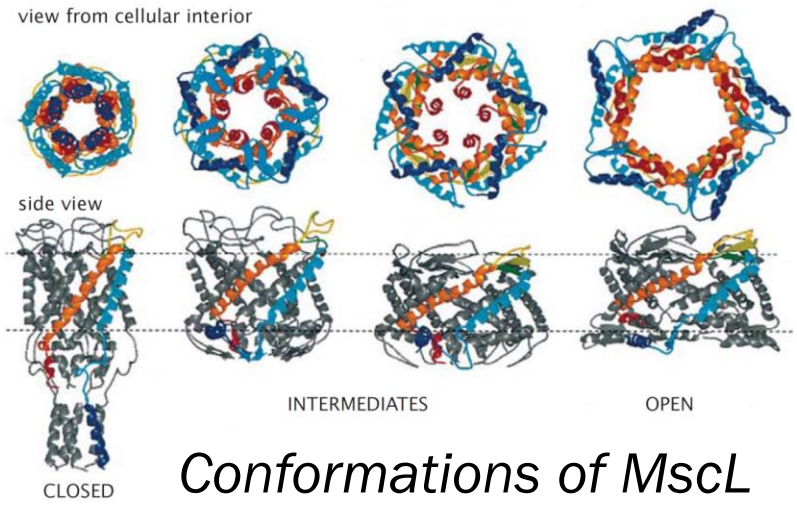
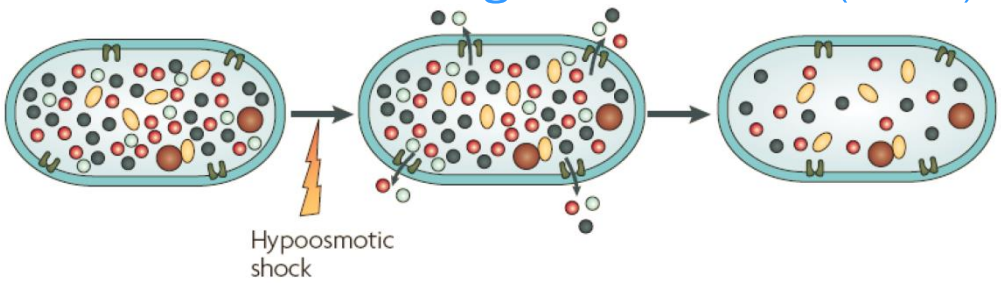
MscL as a model system for bilayer-protein interactions

Structure & biology (?) of the mechanosensitive channel of large conductance (MscL):

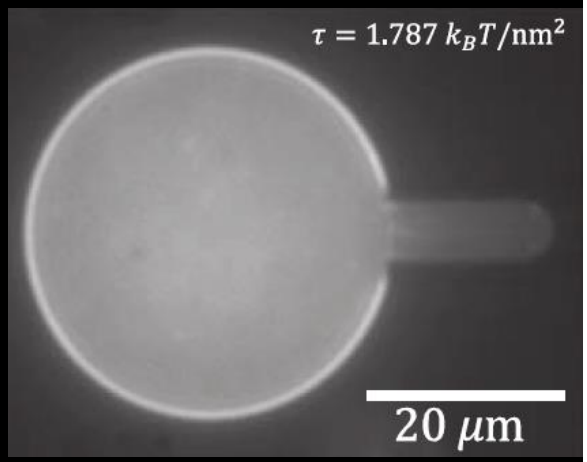


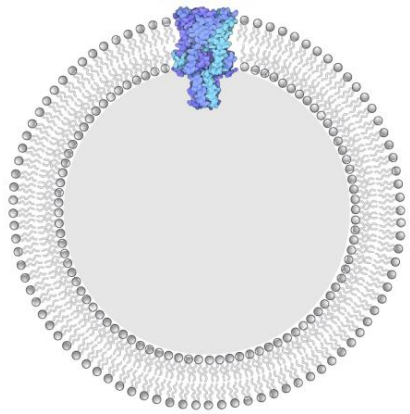
Conformations of MscL



I. R. Booth *et al.*, Nat. Rev. Microbiol. **5**, 431 (2007); G. Chang *et al.*, Science **282**, 2220 (1998); Z. Liu, C. S. Gandhi, and D. C. Rees, Nature **461**, 120 (2009). S. I. Sukharev et al., Nature **414**, 720 (2001); Biophys. J. **81**, 917 (2001). E. Perozo *et al.*, Nature **418**, 942 (2002); M. Betanzos *et al.*, Nat. Struct. Biol. **9**, 704 (2002); E. Perozo *et al.*, Nat. Struct. Biol. **9**, 696 (2002).

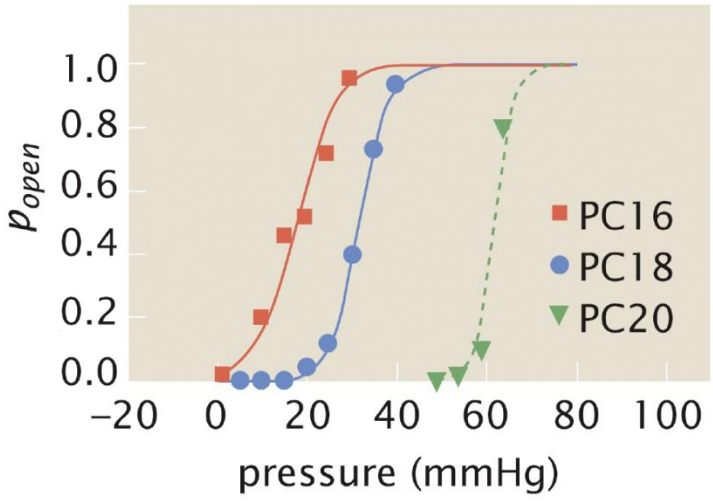
Biophysics of MscL:





$$P_o = \frac{1}{1 + e^{\beta(\Delta\mathcal{G} - \tau\Delta A)}}$$

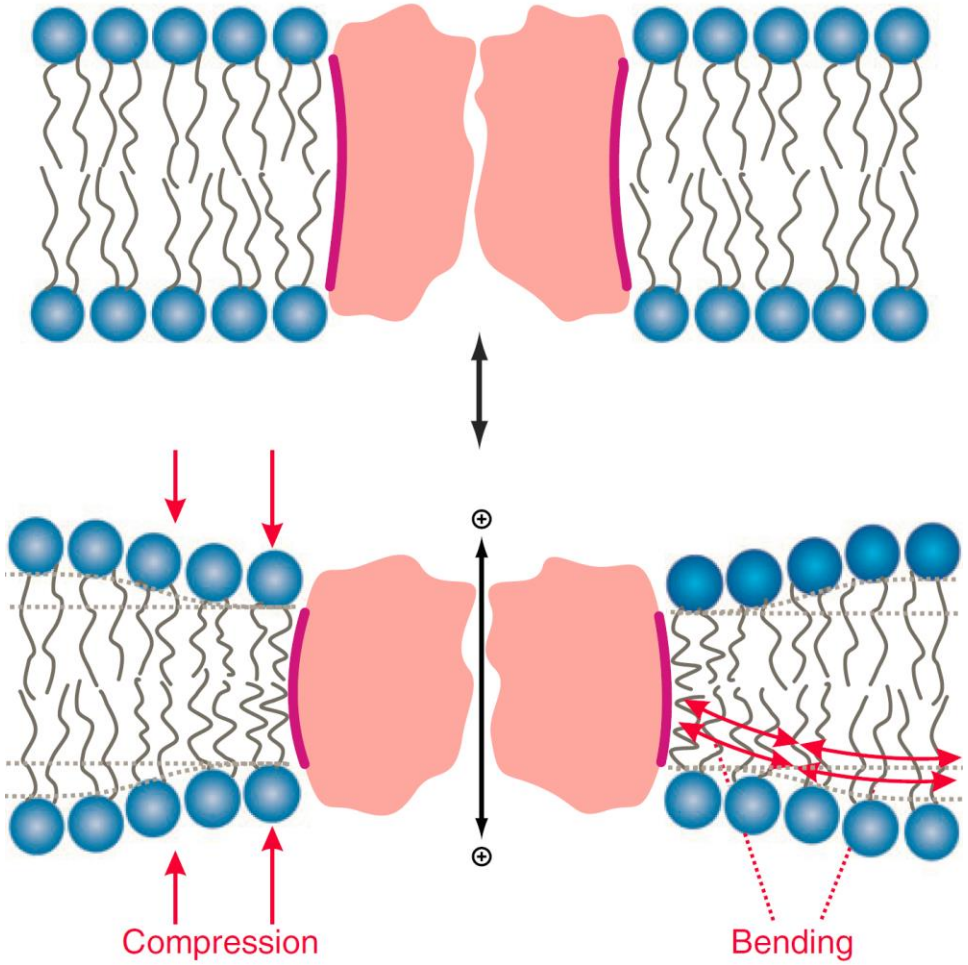
R. Phillips *et al.*, Nature **459**, 379 (2009)



E. Perozo *et al.*, Nat. Struct. Biol. **9**, 696 (2002); Nat. Rev. Mol. Cell Biol. **7**, 109 (2006).

Regulation of protein function by bilayer mechanics

O. S. Andersen and R. E. Koeppe, II, Annu. Rev. Biophys. Biomol. Struct. **36**, 107 (2007); A. Anishkin, *et al.* PNAS **111**, 7898 (2014); S. G. Brohawn, *et al.,* PNAS **111**, 3614 (2014); ...



Coupling of protein function to bilayer mechanical properties: Bilayer serves as a "splint" stabilizing certain protein conformations.

- Function of many membrane proteins affected by bilayer mechanical properties.

- Biphasic changes in protein function with changes in bilayer properties (thickness, curvature, cholesterol,...).

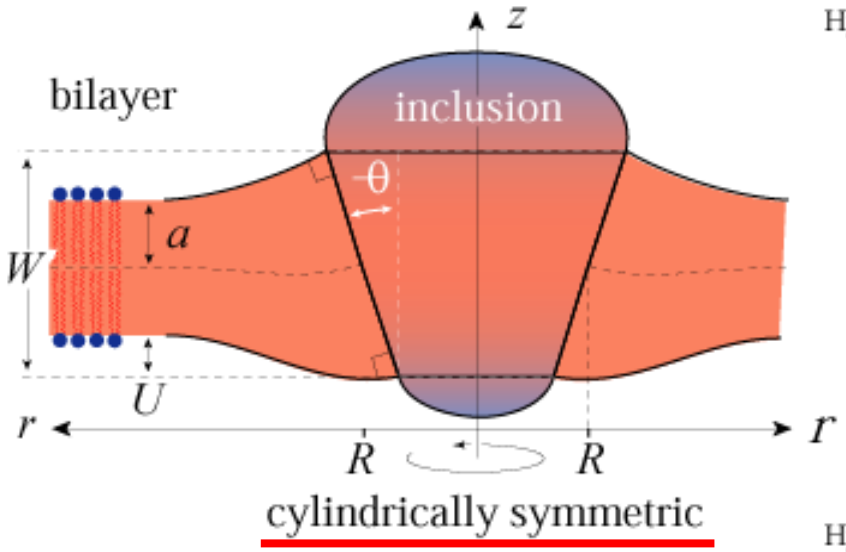
- 1000s different lipid species; but robust protein function.

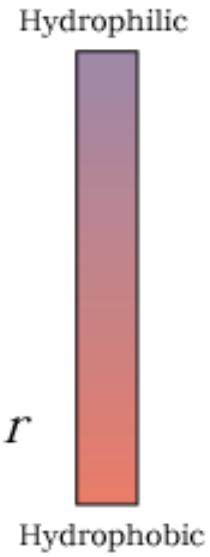
Caveats: Specific (chemical) lipid-protein interactions; Internal protein degrees of freedom (point mutations, etc.).

A (beautiful) 0th-order theory of bilayer-protein coupling

"Lipid bilayer:" Two elastic fields describing the two bilayer leaflets.
"Membrane protein:" Boundary conditions on these fields.

Modeling bilayer-protein interactions (~1980s onwards): H. W. Huang; O. S. Andersen; M. Goulian; R. Bruinsma; P. Pincus; S. E. Safran; R. Lipowsky; F. L. H. Brown; T. R. Weikl; W. Helfrich; O. G. Mouritsen; M. Ø. Jensen; N. Dan; J.-B. Fournier; M. Deserno; R. Golestanian; P. C. Jordan; ...





Bilayer Parameters:
$2a$ = Thickness
K_B = Bending Modulus
K_A = Thickness Deformation Modulus
C = Spontaneous Curvature

Inclusion geometry:
R = Radius
W = Thickness
θ = Interface Angle

P. Wiggins and R. Phillips, Biophys. J. **88**, 880 (2005)

$$u(x,y) = \frac{1}{2}\left[h_+(x,y) - h_-(x,y) - 2a\right], \qquad h(x,y) = \frac{1}{2}\left[h_+(x,y) + h_-(x,y)\right].$$

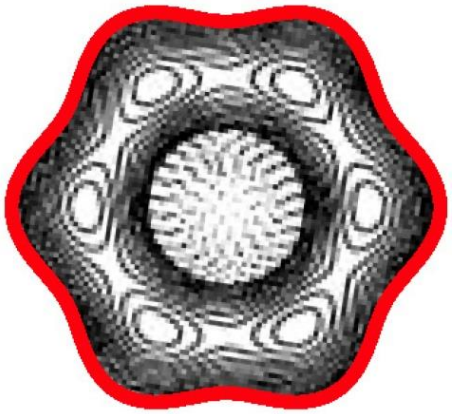
$$G_u[u] = \frac{1}{2}\int dxdy\left[K_b\left(\nabla^2 u\right)^2 + K_t\left(\frac{u}{a}\right)^2 + \tau\left(\nabla u\right)^2\right],$$

$$G_h[h] = \frac{1}{2}\int dxdy\left[K_b\left(\nabla^2 h\right)^2 + \tau(\nabla h)^2\right].$$

Minimum elastic energy = *G*(bilayer material properties, protein conformation)

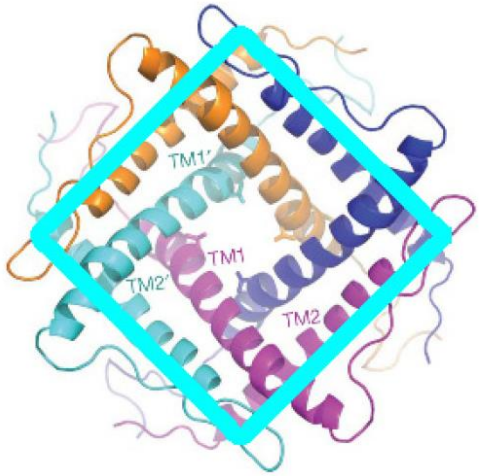
Oligomeric state and hydrophobic shape of MscL?

Oligomeric state and structure of MscL are (still!) a matter of debate.

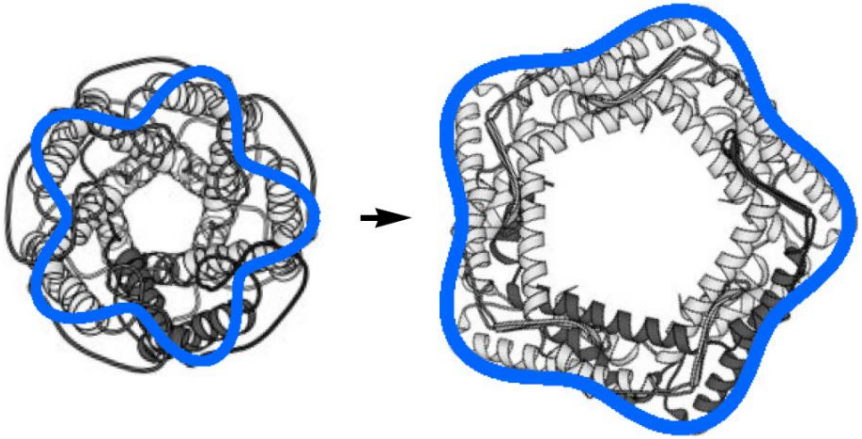


N. Saint, *et al.*, J. Biol. Chem. **273**, 14667 (1998)

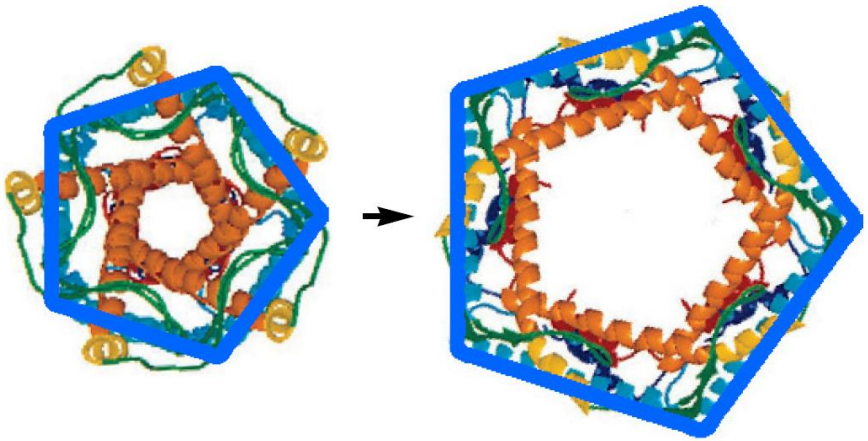
Protein crystallography, electron microscopy, and various biochemical approaches yield different oligomeric states of MscL; Mixture of oligomeric states? [T. A. Walton, *et al.*, Pflügers Arch. – Eur. J. Physiol. **467**, 15 (2015); E. S. Haswell, *et al.* Structure **19**, 1356 (2011); M. R. Dorwart, *et al.* PLoS Biol. **8**, e1000555 (2010)]



Z. Liu, *et al.*, Nature **461**, 120 (2009)



G. Chang, *et al.*, Science **282**, 2220 (1998); S. I. Sukharev, *et al.*, Nature **414**, 720 (2001); Biophys. J. **81**, 917 (2001).



S. I. Sukharev, *et al.*, Biophys. J. **81**, 917 (2001)

Also: P. Blount *et. al.*, EMBO J. **15**, 4798 (1996); S. I. Sukharev, *et al.*, J. Membrane Biol. **171**, 183 (1999); E. Perozo, *et al.*, Nature **418**, 942 (2002).

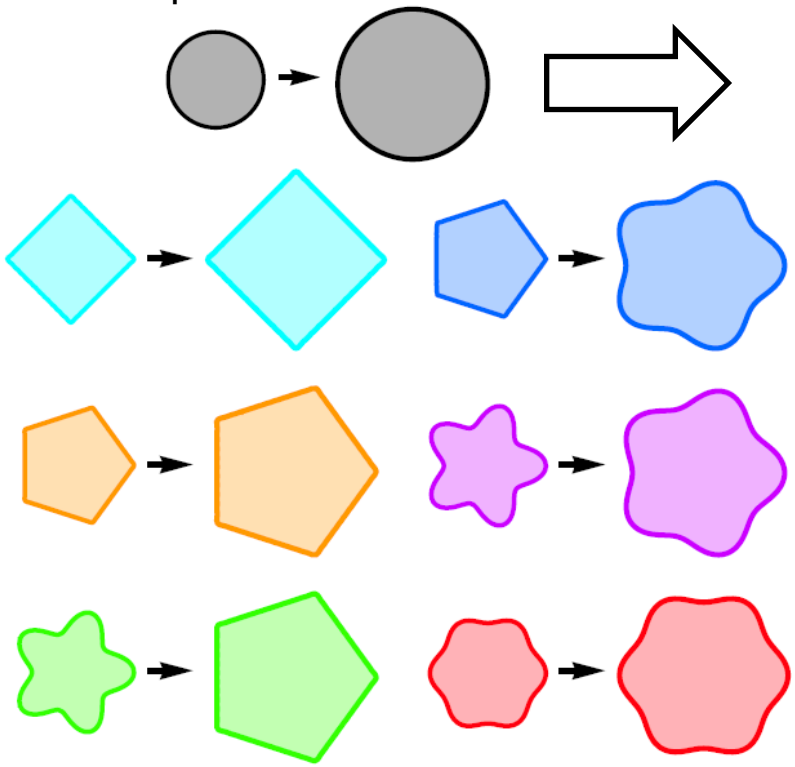
What is the role of protein symmetry in MscL gating?

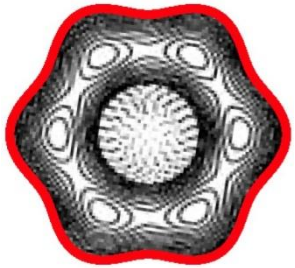
Generalized elastic theory of bilayer-protein interactions

General boundary curve:

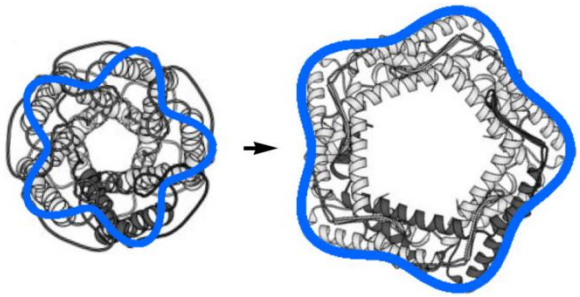
$$r_B(\theta) = R\left[1 + \epsilon \sum_{i=1}^{N} \left(a_i \cos i\theta + b_i \sin i\theta\right)\right], \quad \sum_{i=1}^{\infty} \left(|a_i| + |b_i|\right) = 1 .$$

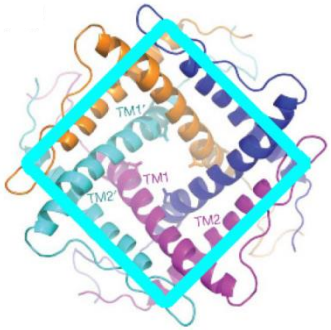
From “spherical cows” to “cubical cows:”



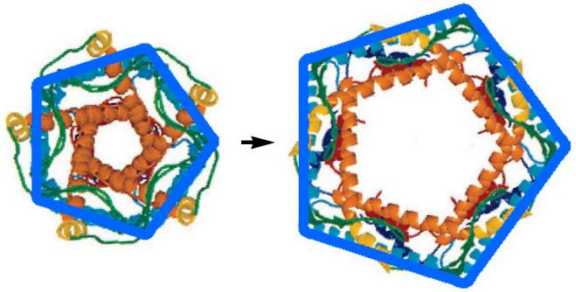


N. Saint, *et al.*, J. Biol. Chem. **273**, 14667 (1998)





Z. Liu, *et al.*, Nature **461**, 120 (2009)



G. Chang, *et al.*, Science **282**, 2220 (1998); S. I. Sukharev, *et al.*, Nature **414**, 720 (2001); Biophys. J. **81**, 917 (2001).

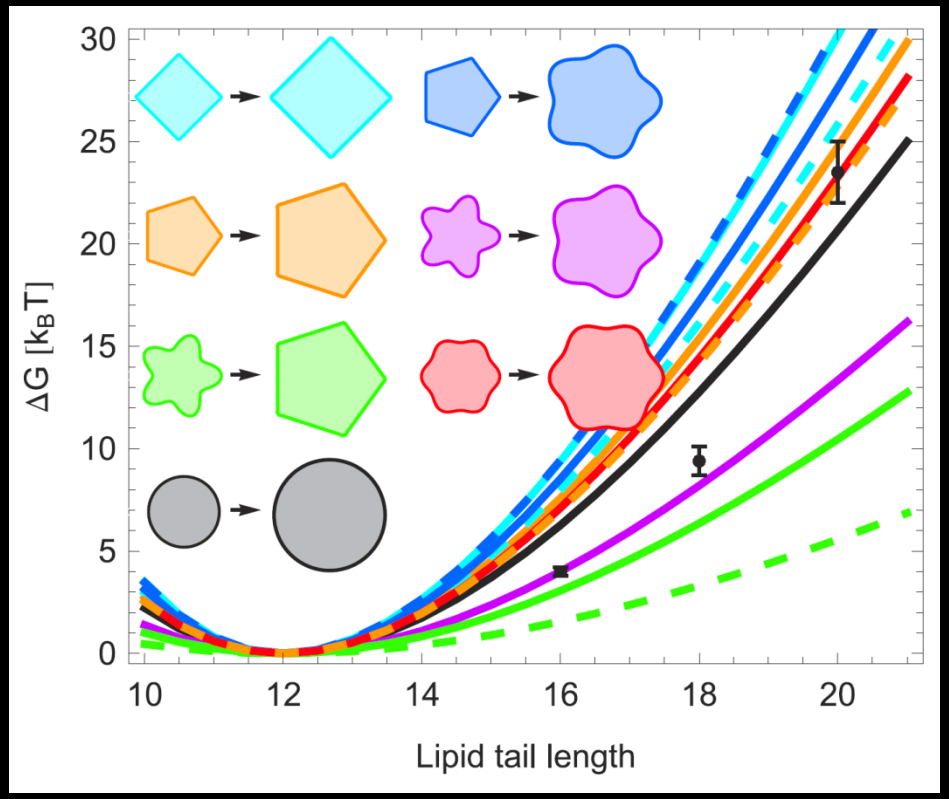
Boundary conditions:

$$\begin{aligned} u(r_B,\theta) &= U , \\ \hat{\mathbf{n}} \cdot \nabla u(r_B,\theta) &= U' . \end{aligned}$$

Obtain analytic expression for deformation energy:

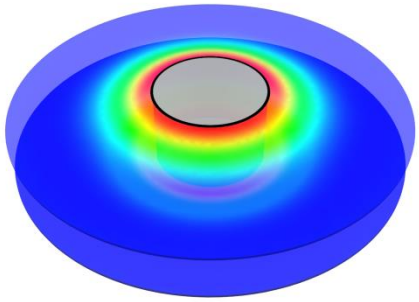
$$G_u[u] = \frac{1}{2}\int dxdy \left\{ K_b \left(\nabla^2 u\right)^2 + K_t \left(\frac{u}{a}\right)^2 + \tau \left[2\frac{u}{a} + (\nabla u)^2\right] \right\} .$$

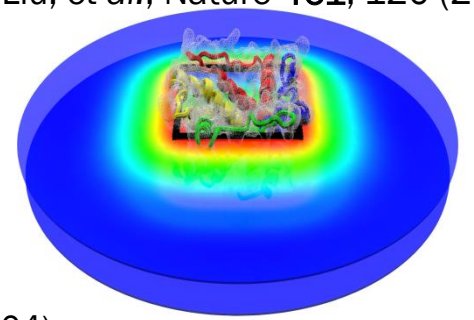
Analytic solutions for general protein shapes

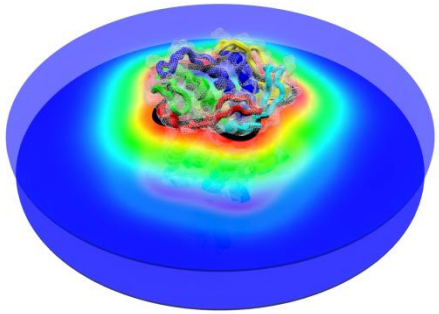


$\Delta G_{symmetry} \approx \Delta G_{bilayer} \approx \Delta G_{total}$

Z. Liu, *et al.*, Nature **461**, 120 (2009)







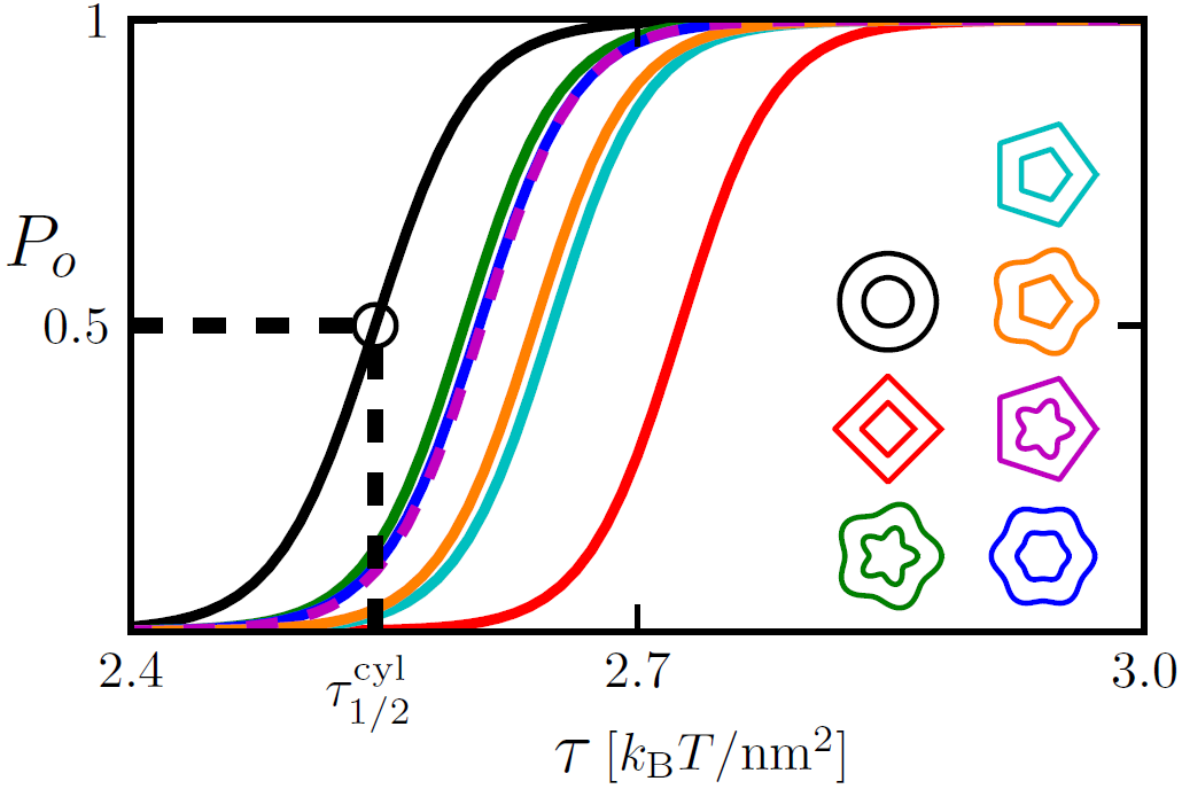
P. Wiggins and R. Phillips, PNAS **101**, 4071 (2004)

G. Chang, *et al.*, Science **282**, 2220 (1998)

Signatures of MscL structure in MscL gating curves

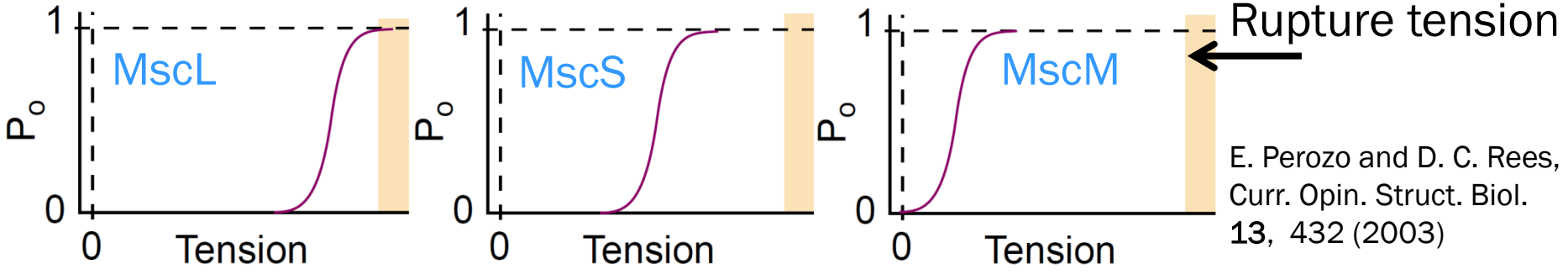
Two-state Boltzmann model [P. Wiggins and R. Phillips, PNAS **101**, 4071 (2004); Biophys. J. **88**, 880 (2005)]:

$$P_o = \frac{1}{1 + e^{\beta(\Delta \mathcal{G} - \tau \Delta A)}}$$



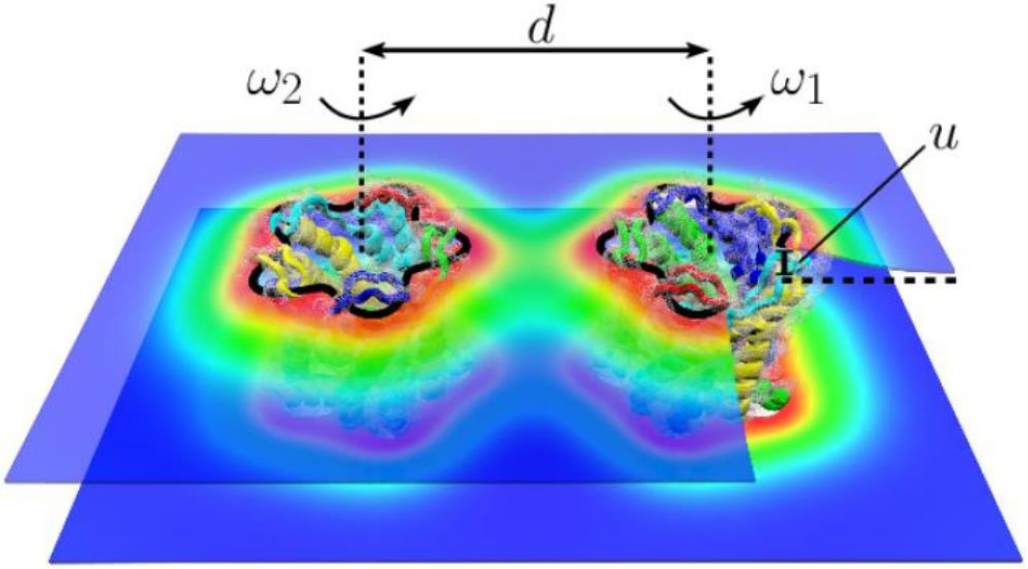
- All model parameters determined by MscL structures and bilayer mechanical properties.

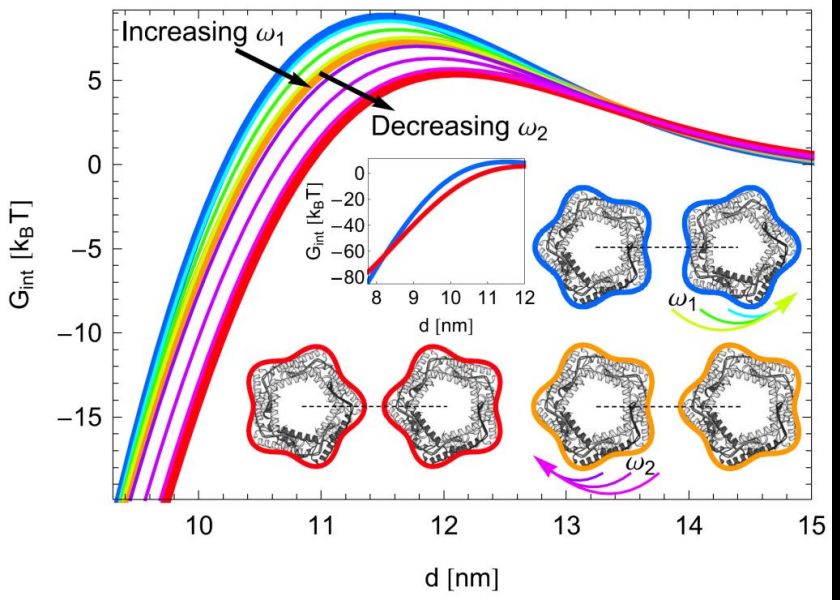
- Distinct oligomeric states of MscL yield distinct MscL gating tensions.

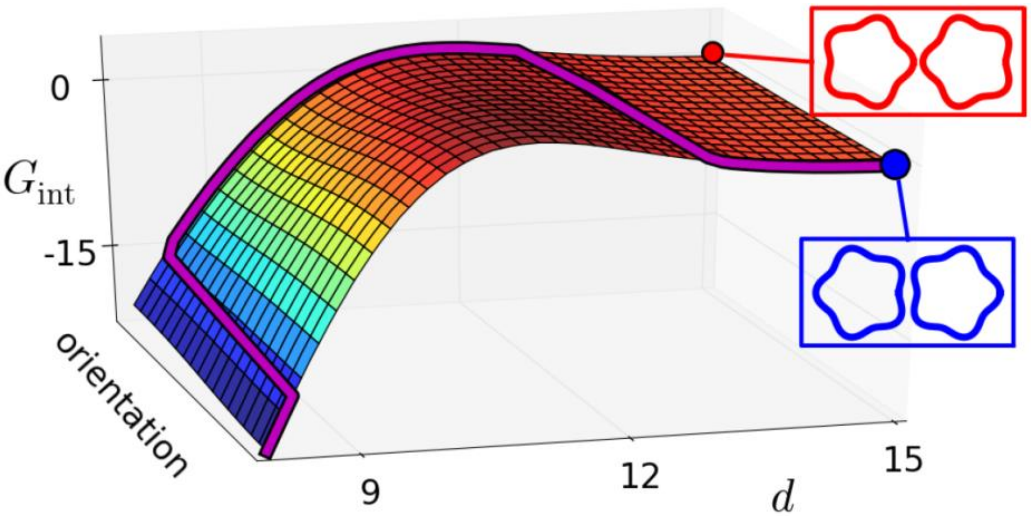


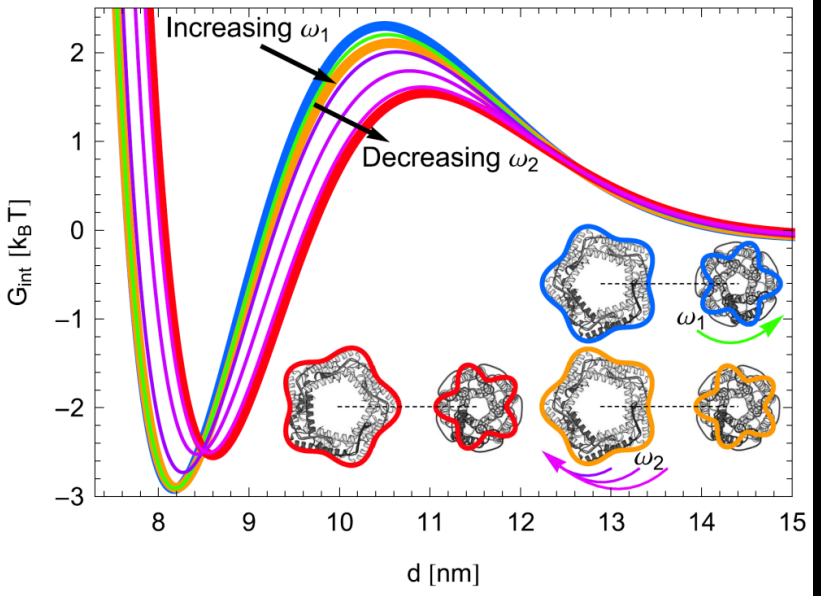
E. Perozo and D. C. Rees, Curr. Opin. Struct. Biol. **13**, 432 (2003)

Observed MscL structures imply directional interactions



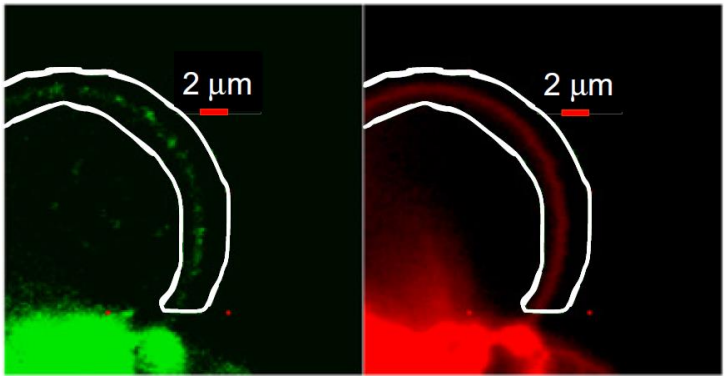


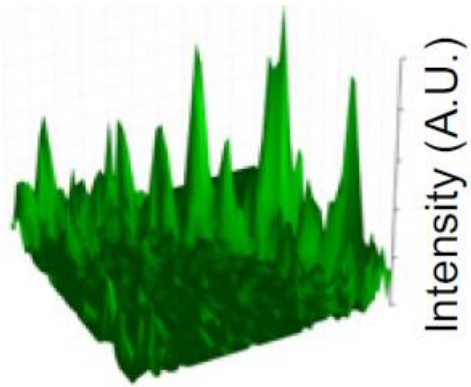


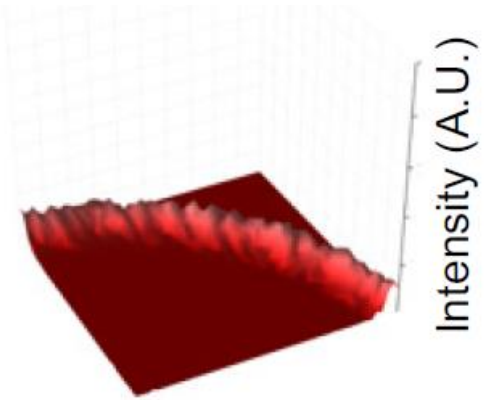


Clustering & collective response of MscL: Experiments

Confocal microscopy, patch-clamp electrophysiology, neutron scattering, and atomic force microscopy [S. L. Grage, *et al*., Biophys. J. **100**, 1252 (2011); *E. coli*: T. T. Nomura, *et al*. PNAS **109**, 8770 (2012)]:

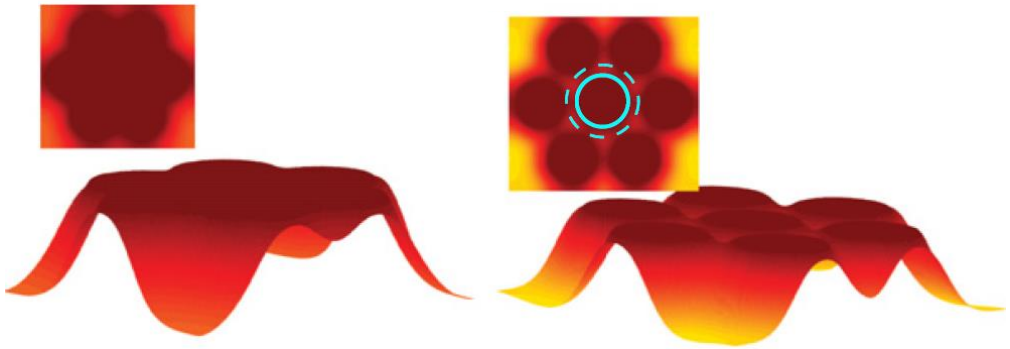






- MscL form clusters composed of ≈ 100s MscL; Clustering driven by thickness-mediated interactions.

- MscL activation is affected by clustering: Activation barrier competes with bilayer-mediated cooperativity.



Do bacteria use MscL clustering to modulate MscL function?
MscL number is surprisingly large *in vivo* (≈ 300–1,400 MscL/*E. coli*) [M. Bialecka-Fornal, *et al*., PLoS One **7**, e33770 (2012)]

What is the relation between MscL structure, the lattice architecture of MscL clusters, and the collective gating of MscL lattices?

Calculation of bilayer-mediated protein interactions

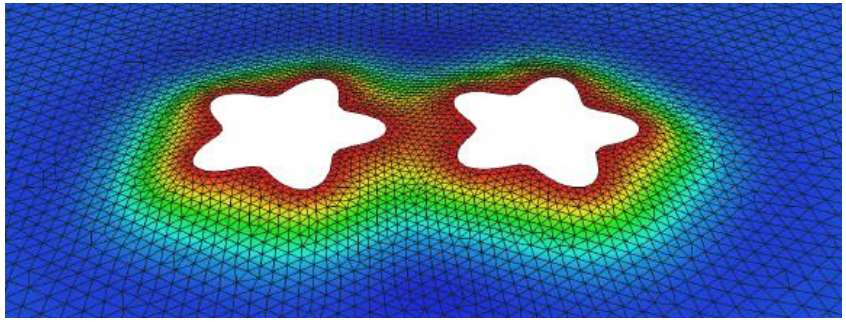
(1) Predict bilayer-mediated interactions between 100s of proteins;
(2) Account for the protein shapes implied by structural studies.

- Analytic theory: Exact solutions for arbitrary protein symmetries and separations [C. A. Haselwandter and R. Phillips, EPL **101**, 68002 (2013)]

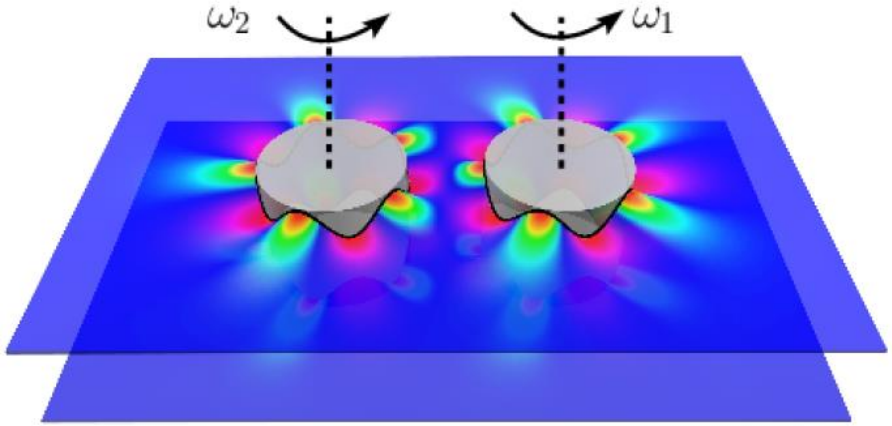
Based on previous far-field solutions for conical/cylindrical proteins: M. Goulian; R. Bruinsma; P. Pincus; S. A. Safran; N. Dan; T. R. Weikl; M. M. Kozlov; W. Helfrich;...]

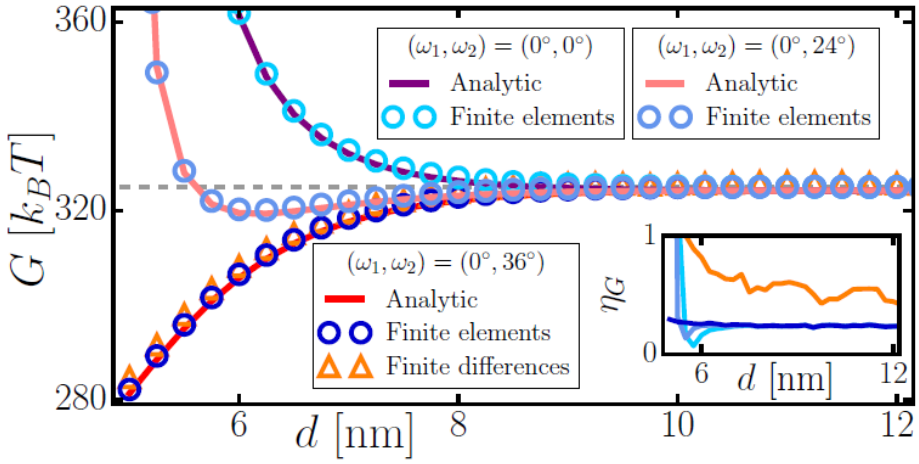
- Hybrid finite element approach:

Discrete Kirchhoff triangle method for bending terms & Lagrange interpolation for thickness stretch and gradient terms [O. Kahraman, *et al*., Sci. Rep. **6**, 19214 (2016); EPL **107**, 48004 (2014)]

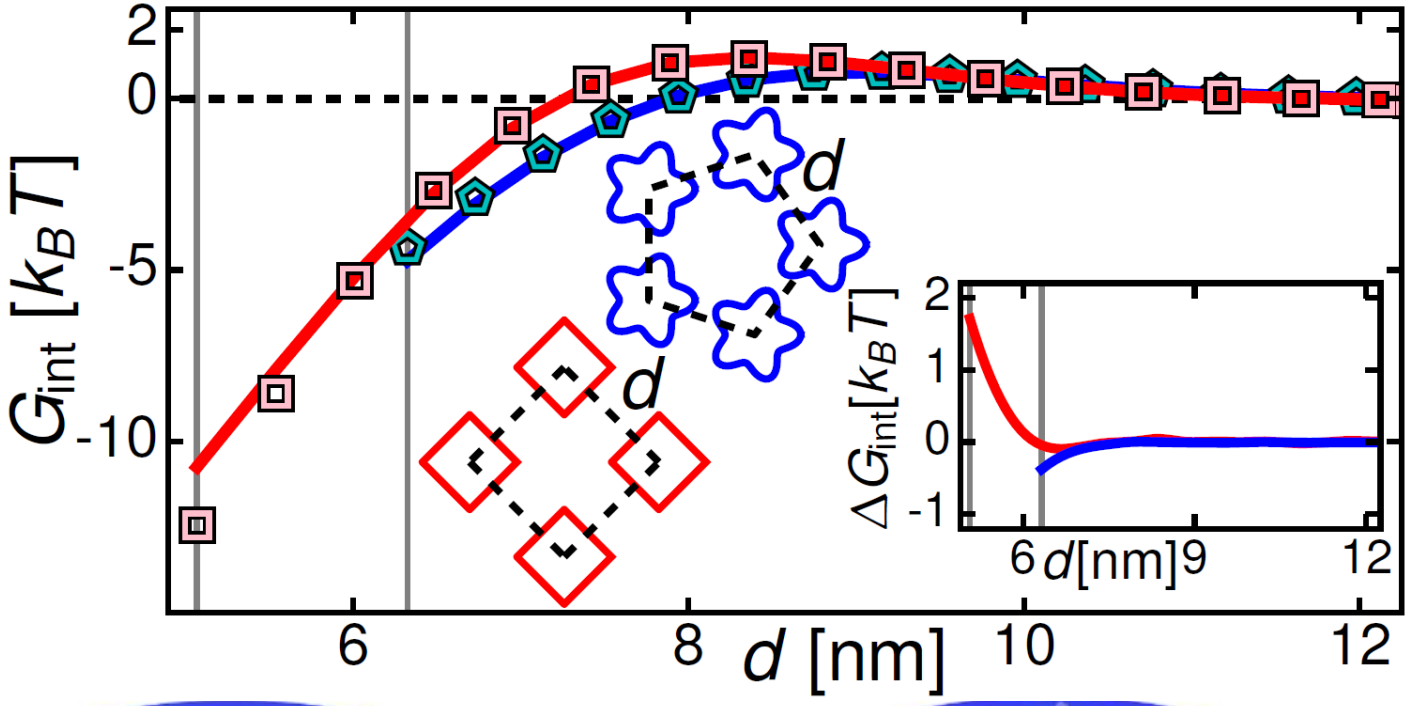


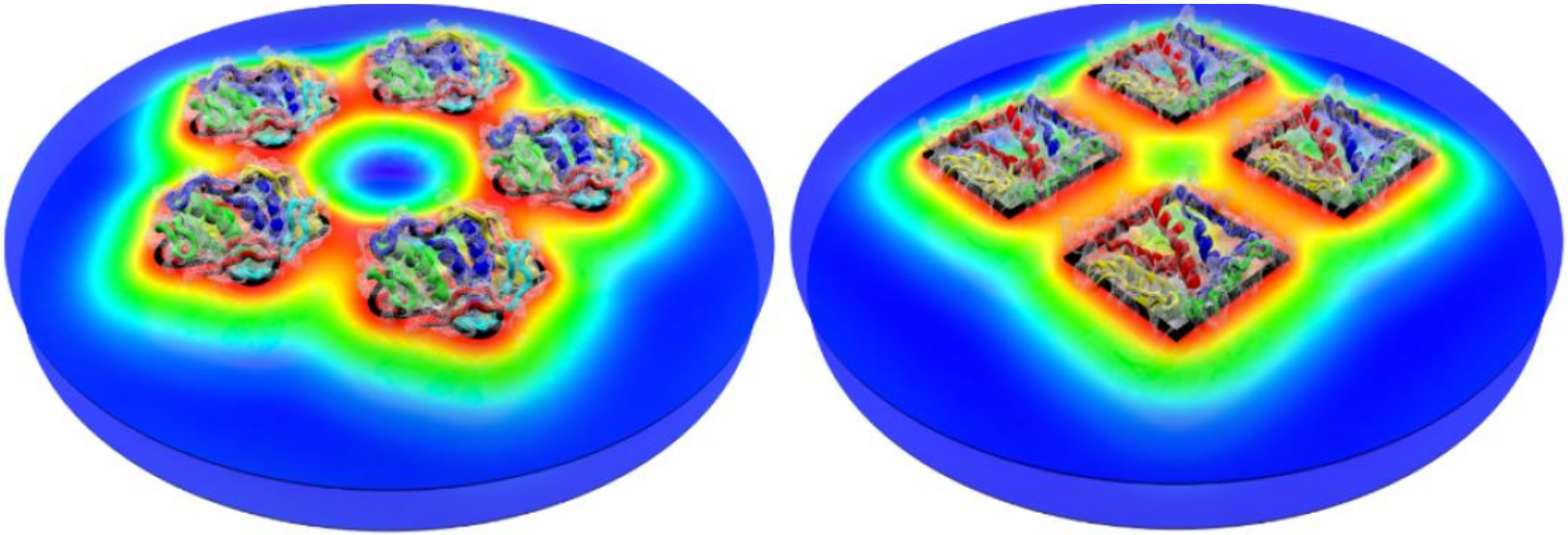
Test validity of combined analytic and numerical framework for, e.g., "crown model" of membrane proteins:





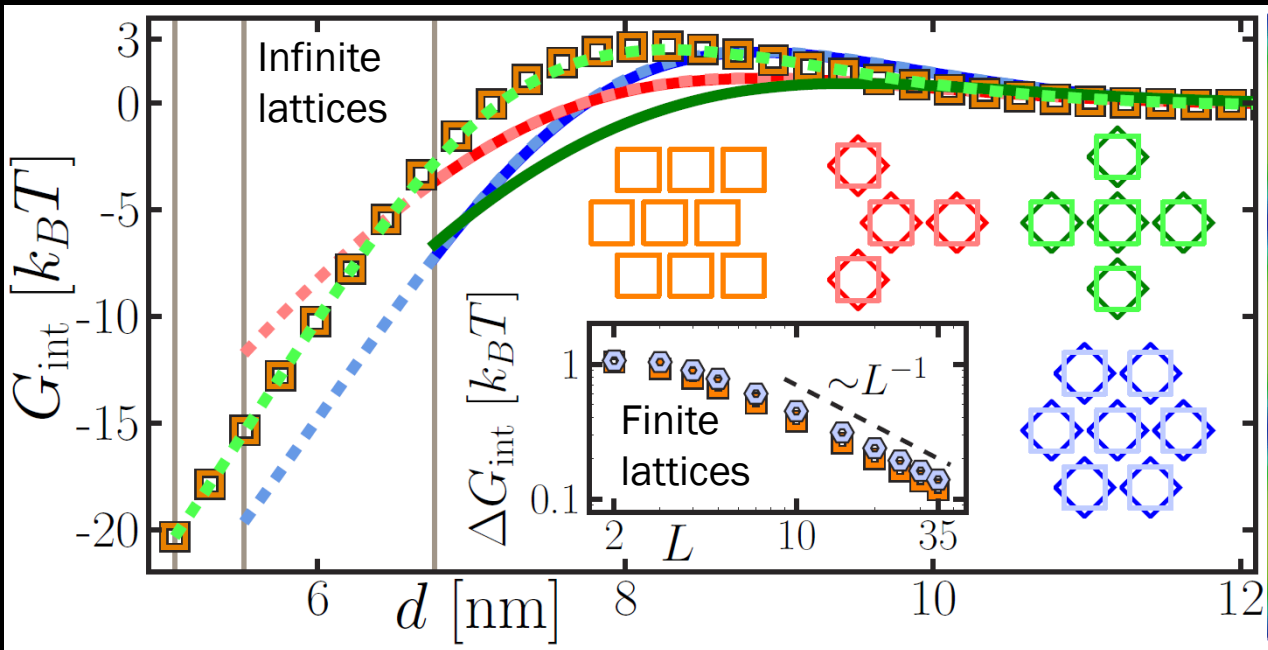
Are thickness-mediated interactions pairwise additive?

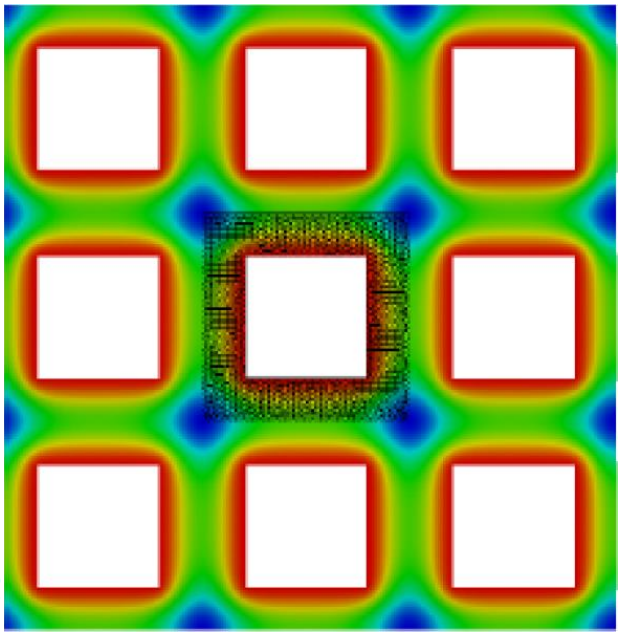


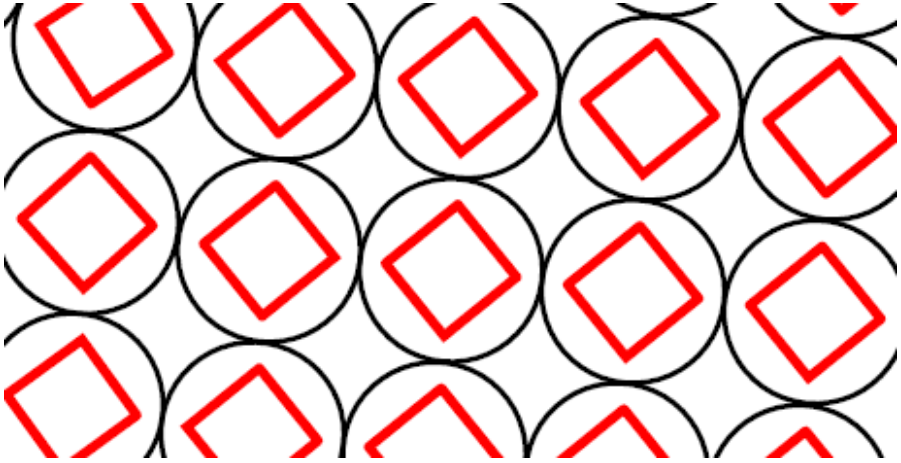


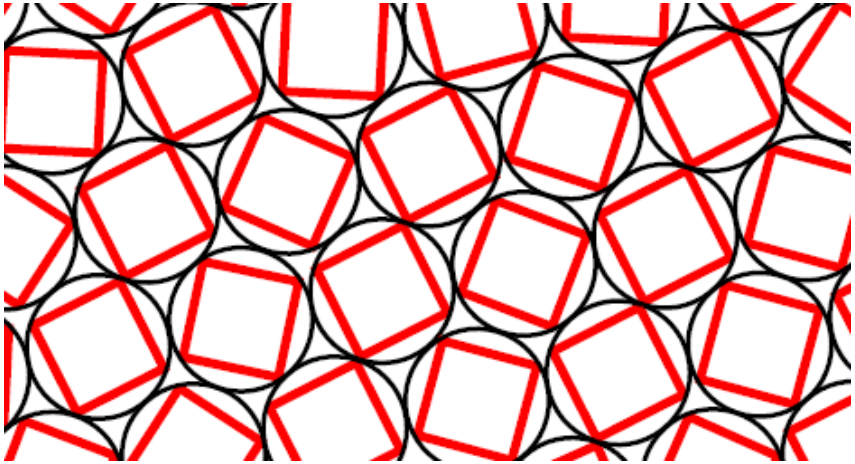
Lattices of tetrameric MscL: Multi-body interactions

Shape of tetrameric MscL is manifested in MscL lattice architecture.

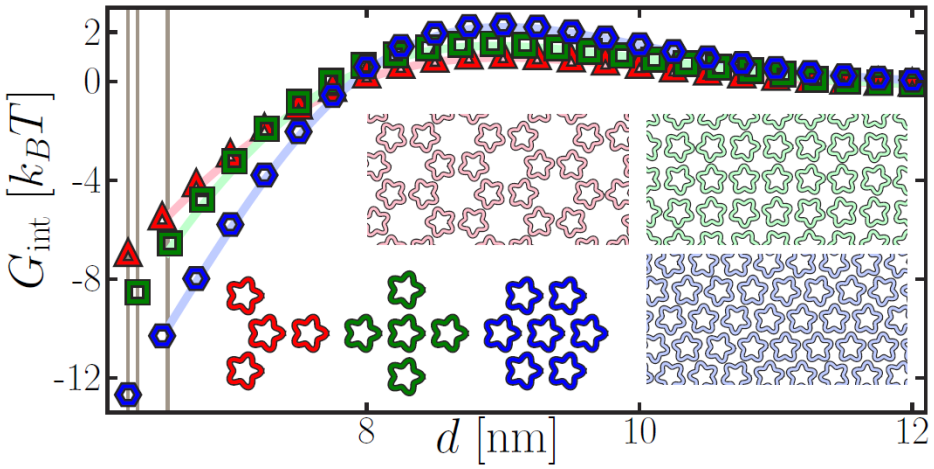






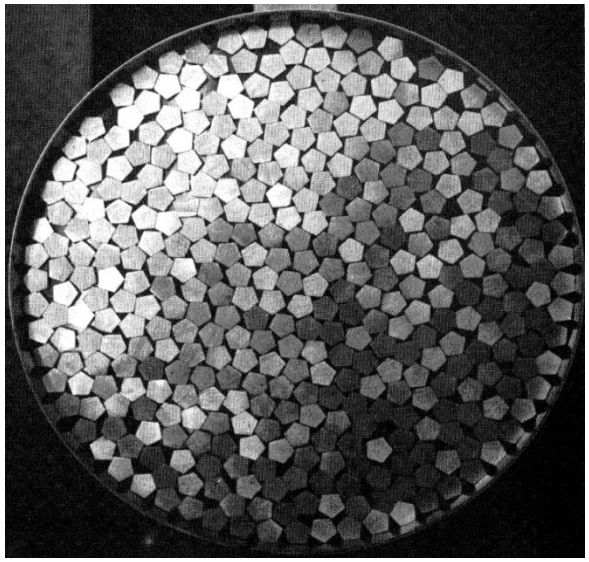


Lattices of pentameric MscL: Multi-body interactions

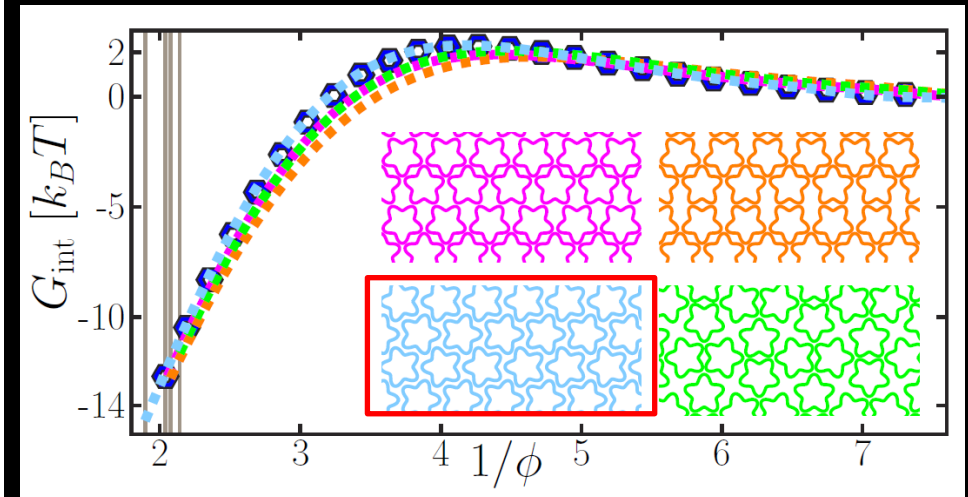


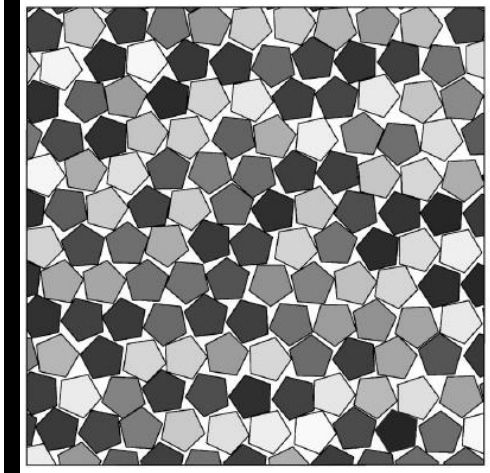
Competition between 2D lattice architectures as if no directional interactions were present: Hexagonal lattice for small *d*, honeycomb lattice for large *d*.

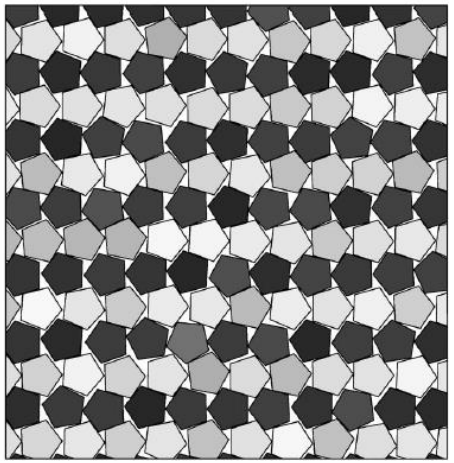
Frustration of orientational ordering in 2D lattices [S. Sachdev and D. R. Nelson, Phys Rev. B **32**, 1480 (1985)].



Pentameric MscL yield a distorted hexagonal lattice architecture.

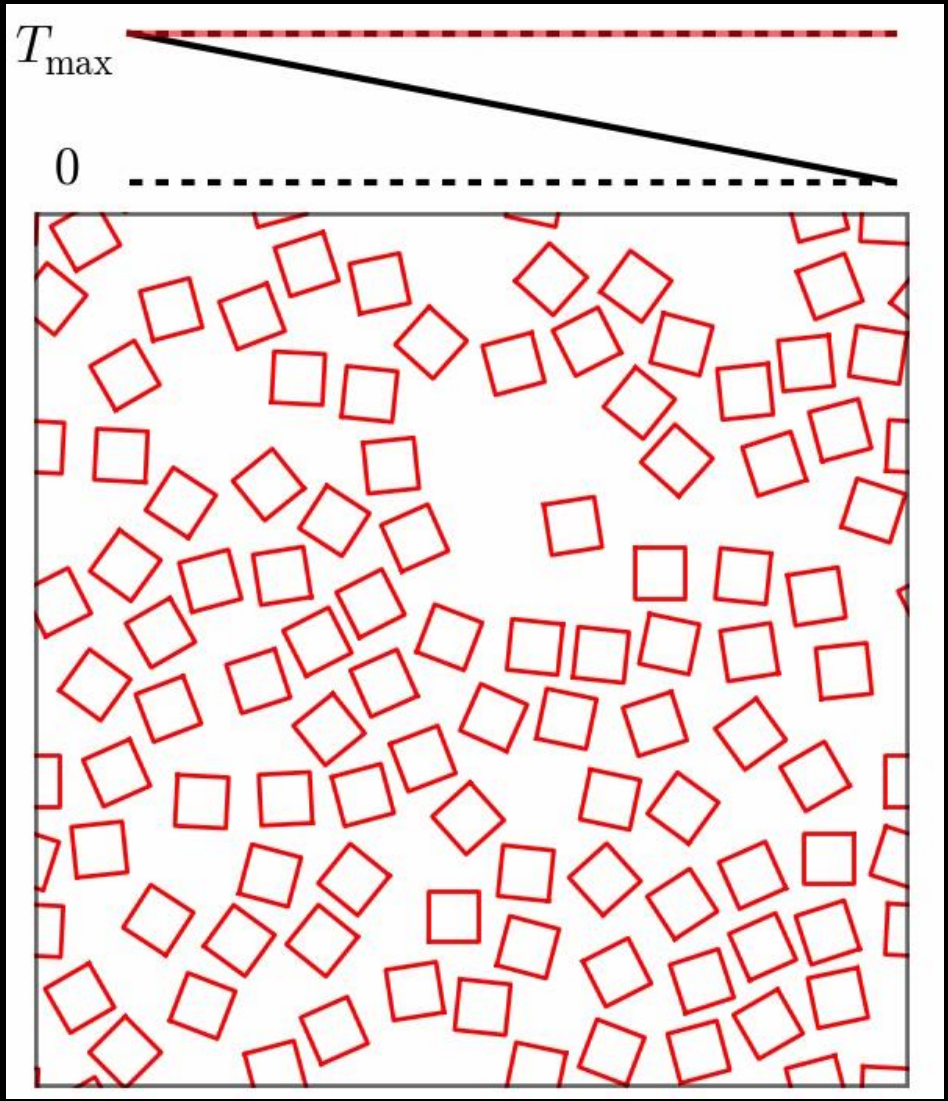


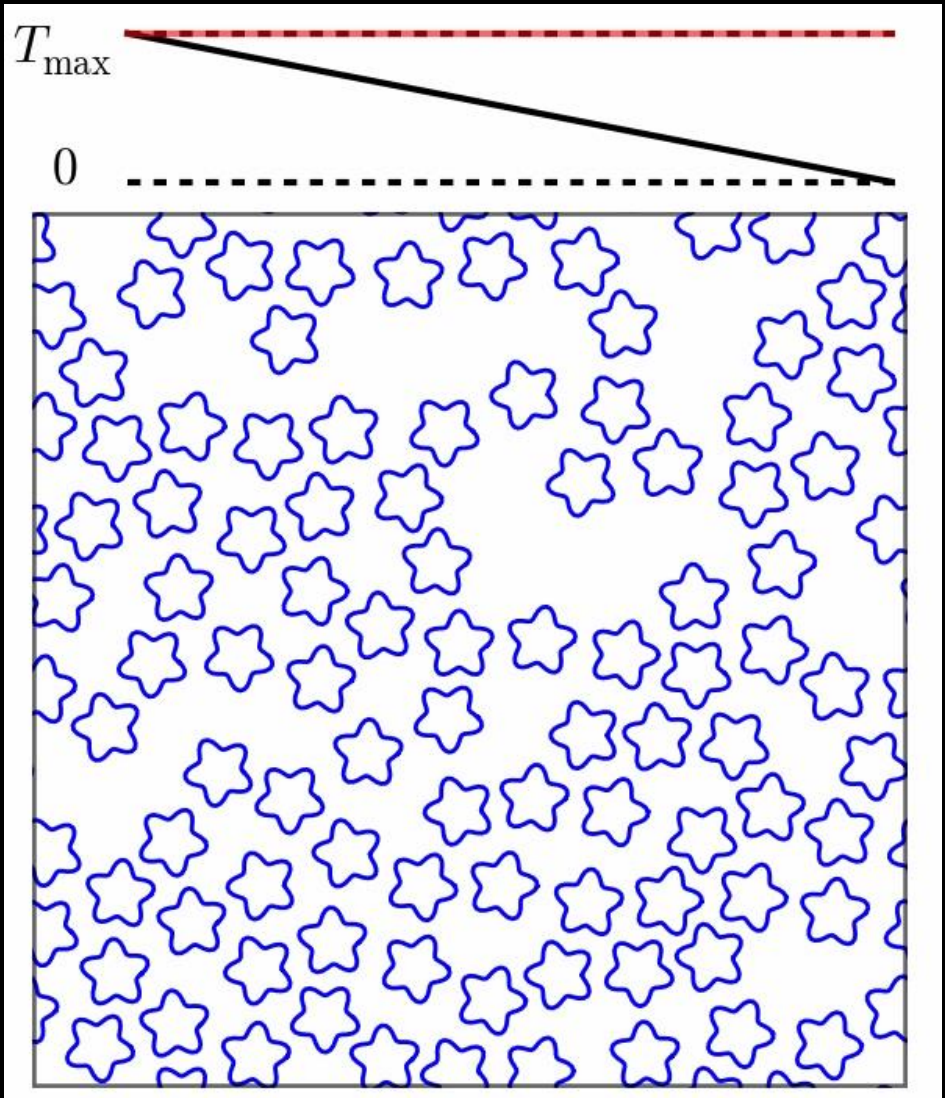




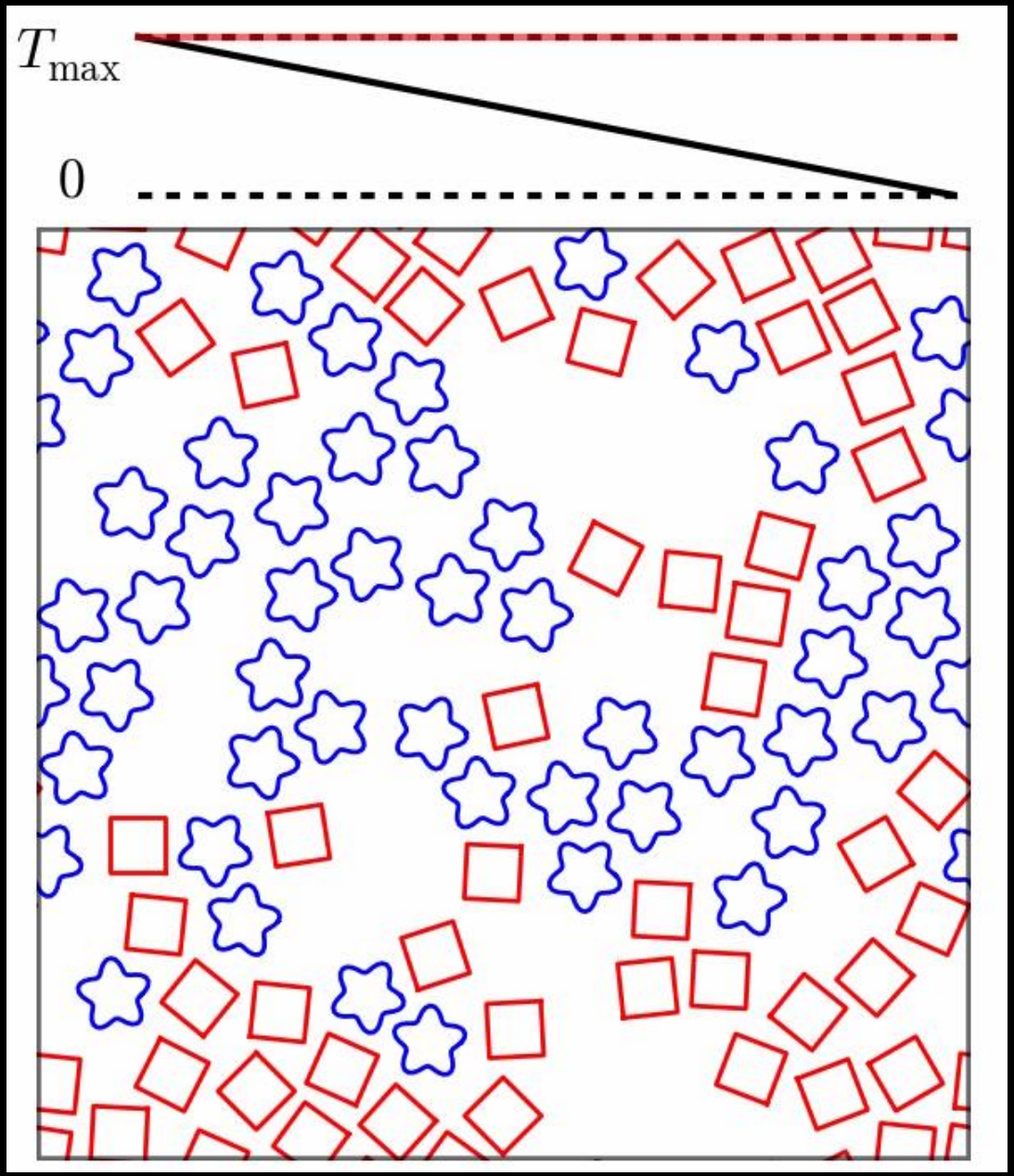
Crystalline packings of pentagons [C. L. Henley, Phys Rev. B **34**, 797 (1986); T. Schilling, *et al.*, Phys. Rev. E **71**, 036138 (2005); ...]

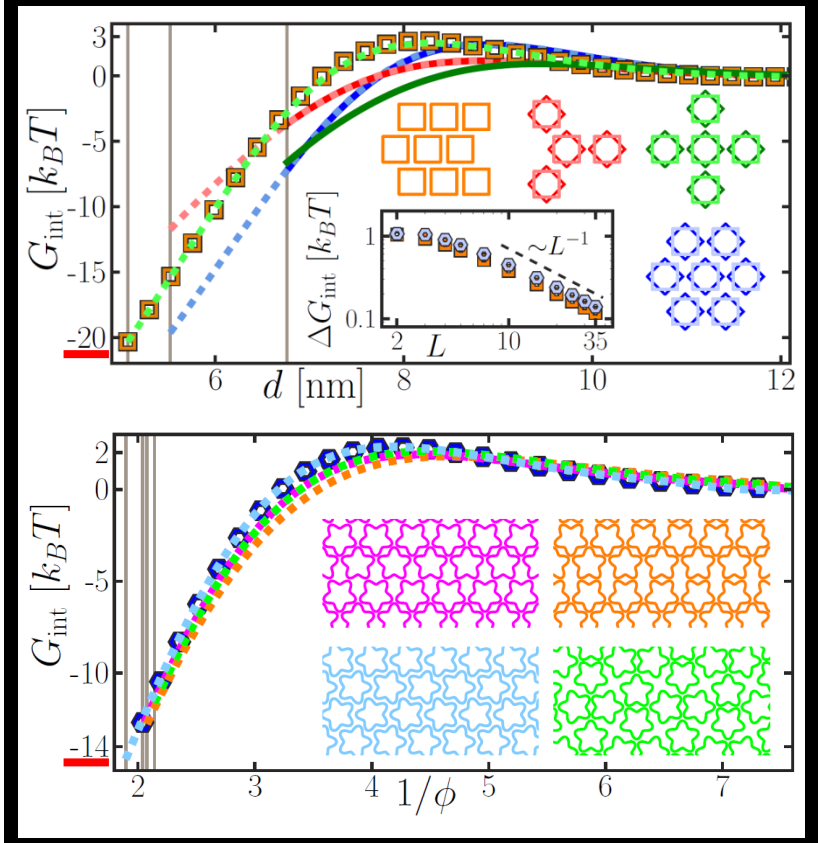
Simulated annealing of MscL pair interactions



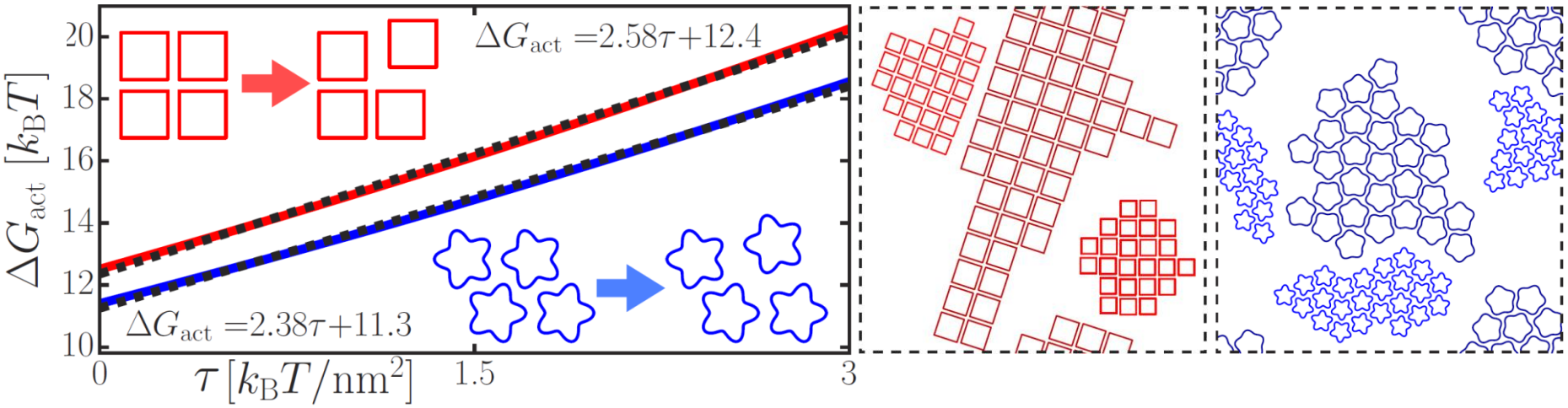


Simulated annealing of MscL pair interactions



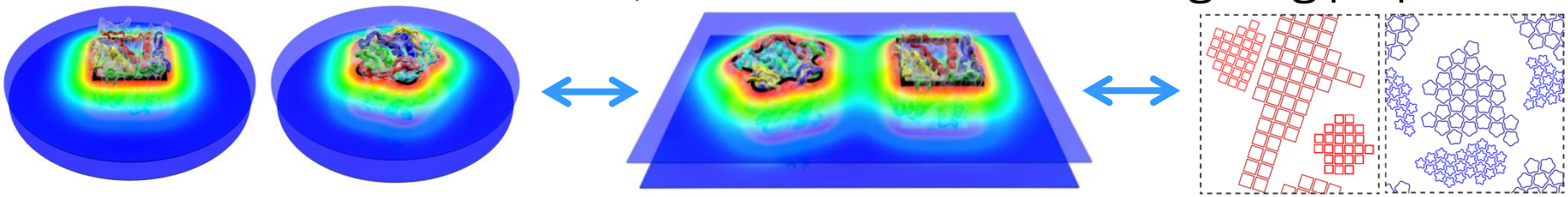


Activation of tetrameric and pentameric MscL lattices



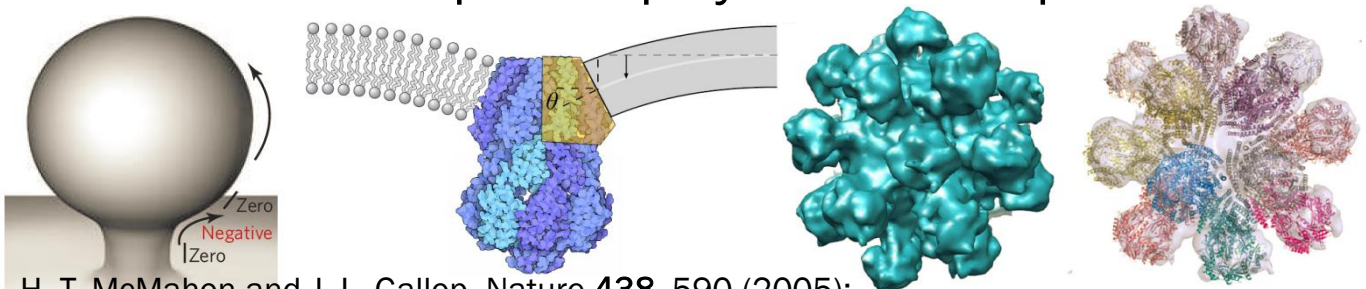
- Activation of tetrameric MscL lattices ≈ 10 times slower than activation of pentameric MscL lattices.
- Composite but segregated clusters of open & closed MscL [as observed in experiments]; Characteristic sub-cluster separation ≈ 10 nm.

Membrane proteins can be regulated through the interplay of protein structure, lipid properties, and protein lattice architecture: The observed four- and five-fold symmetric states of MscL yield characteristic lattice architectures of MscL clusters, with distinctive collective gating properties.



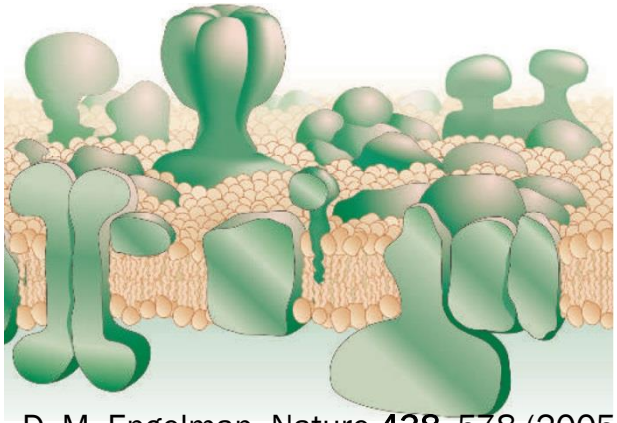
Regulation of membrane shape

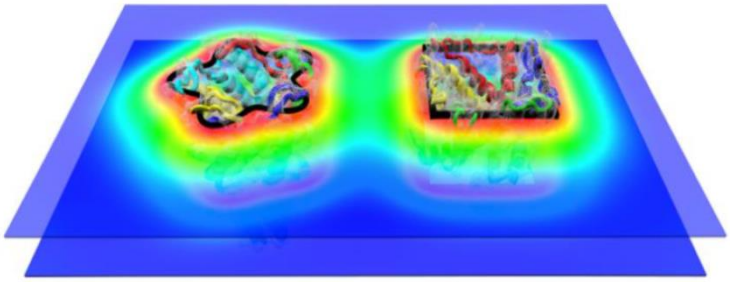
1. Membrane protein polyhedral nanoparticles



H. T. McMahon and J. L. Gallop, Nature **438,** 590 (2005);
R. Phillips, *et al.*, Nature **459**, 379 (2009); T. R. Basta, *et al.*, PNAS **111**, 670 (2014).

Collective function of proteins in cell membranes

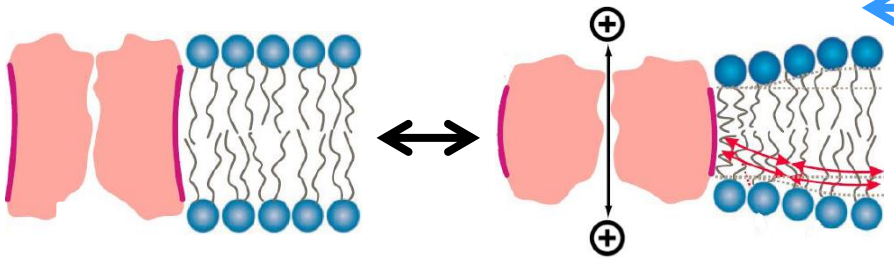




D. M. Engelman, Nature **438,** 578 (2005)

Protein regulation through lipids

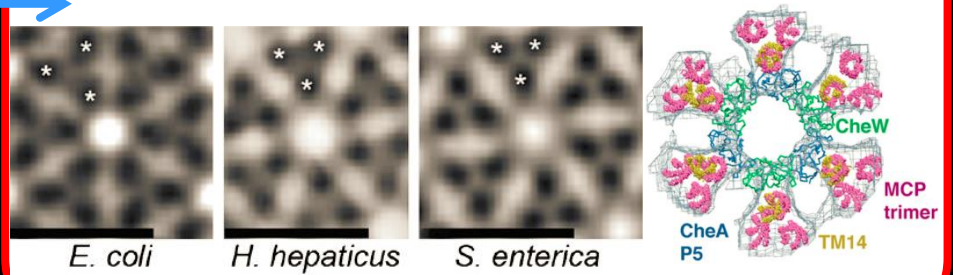
2. Mechanosensitive ion channels



O. S. Andersen and R. E. Koeppe, II, Annu. Rev. Biophys. Biomol. Struct. **36**, 107 (2007)

Self-assembled protein clusters

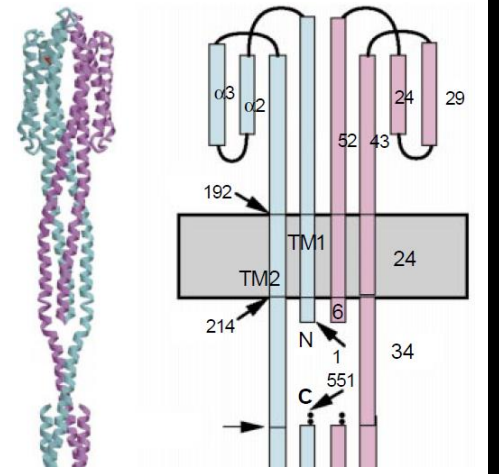
3. Chemoreceptor lattices



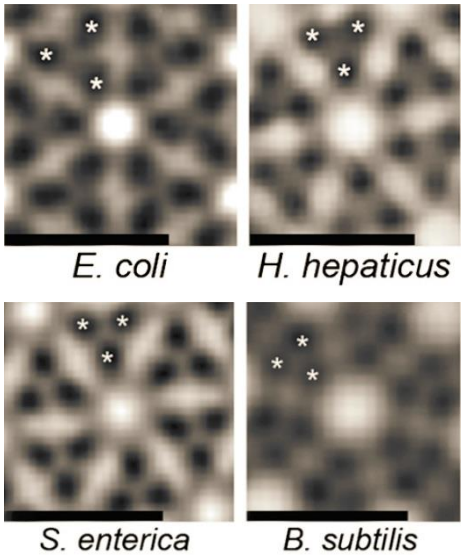
A. Briegel, *et al.*, PNAS **109**, 3766 (2012)

Assembly and architecture of chemoreceptor lattices

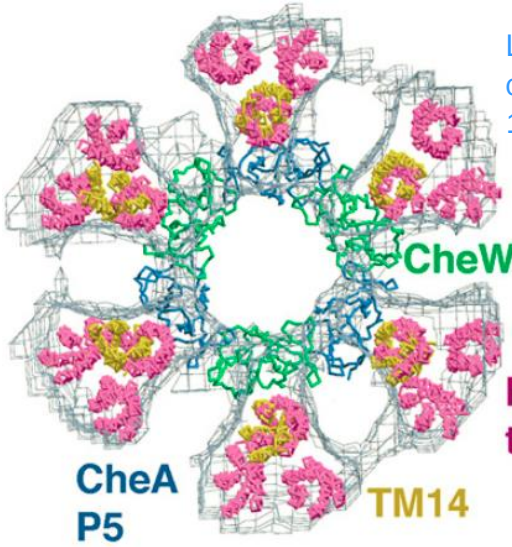
Organization of chemoreceptor dimers: trimers & honeycomb lattices



K. K. Kim, *et al.*, Nature **400**, 787 (1999).

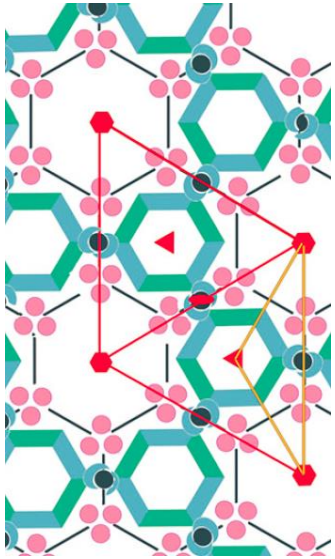


A. Briegel, *et al.*, PNAS **109**, 3766 (2012); J. Liu, *et al.*, PNAS **109**, E1481 (2012); C. M. Khursigara,*et al.*, J. Bacteriol. **190**, 6805 (2008);...

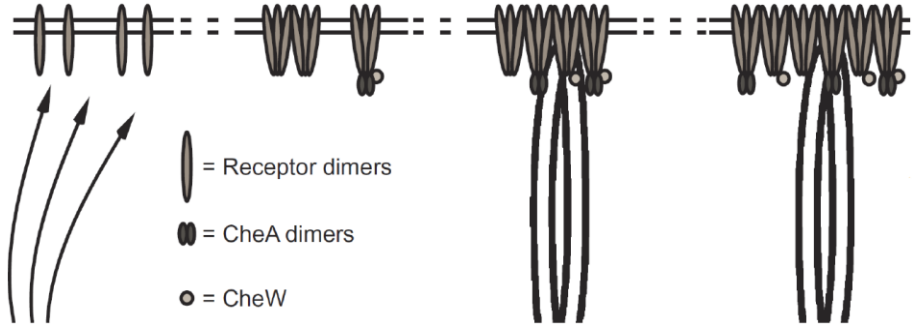


Lattice constant, 12 nm.

MCP trimer

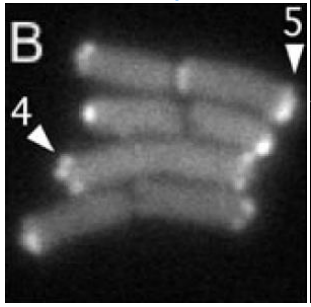


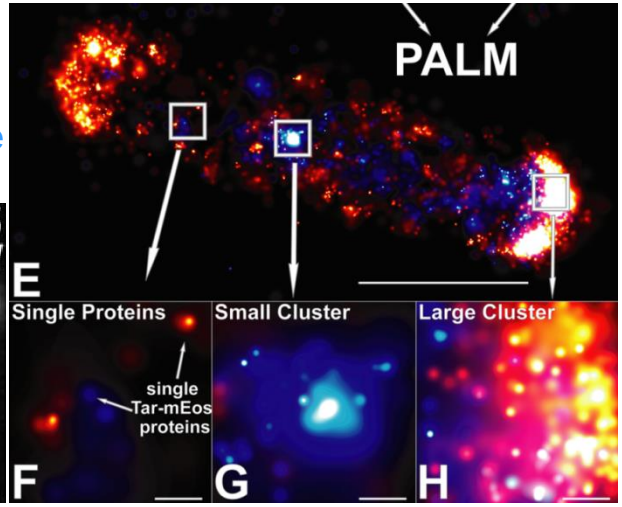
Self-assembly of chemoreceptor clusters via attractive receptor interactions (nucleation & growth):



D. Kentner, *et al.*, Mol. Microbiol. **61**, 407 (2006); S. Thiem and V. Sourjik, Mol. Microbiol. **68**, 1228 (2008);...

No CheA & CheW required for (diff-use) clusters and localization of large clusters to poles.





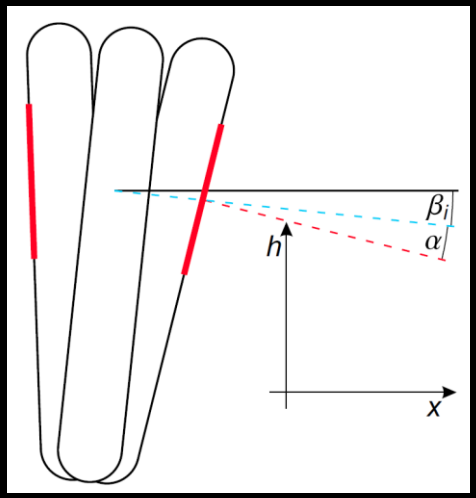
D. Greenfield, *et al.*, PLoS Biol. **7**, e1000137 (2009)

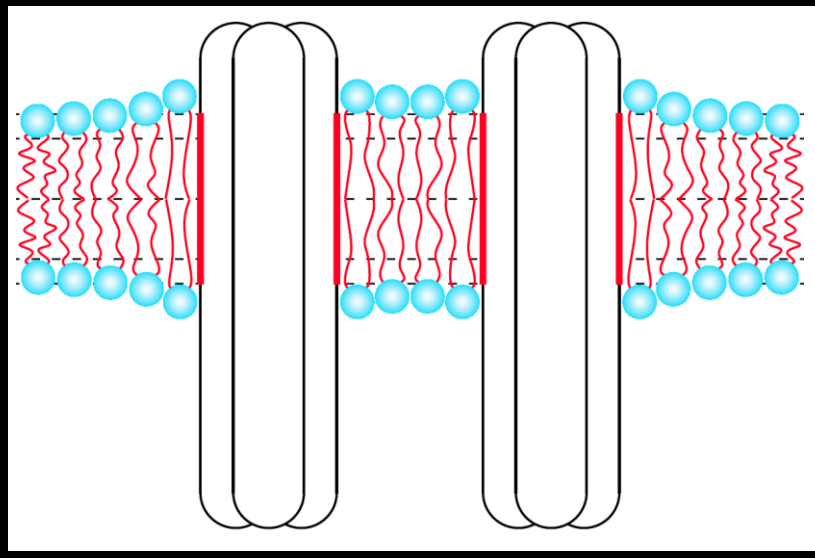
What drives the nucleation, and correct assembly, of chemoreceptor lattices?

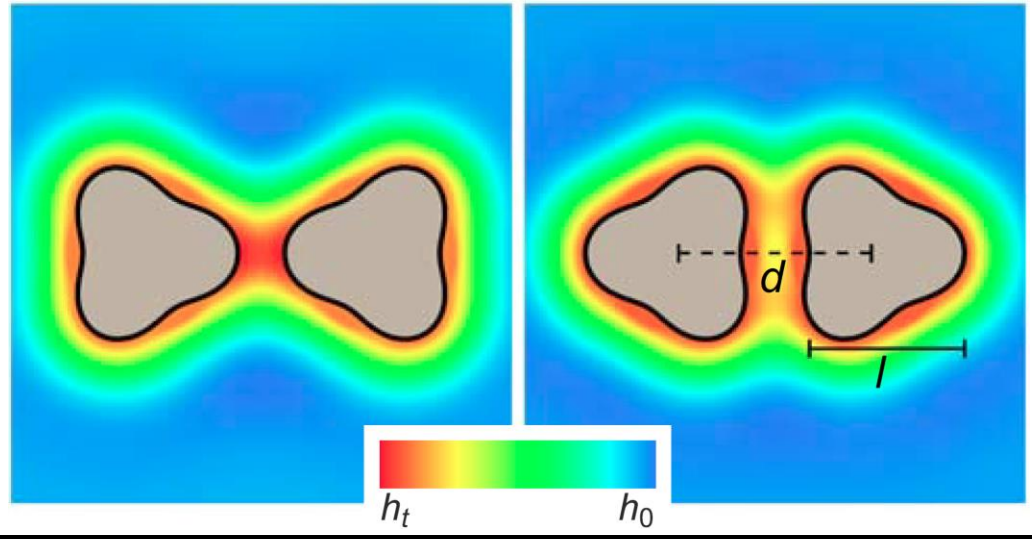
Mechanisms for assembly of chemoreceptor clusters

Bilayer-mediated or direct protein-protein interactions?
(1) Long-range (~nm) versus short-range (~Å); (2) Weak versus strong (?).

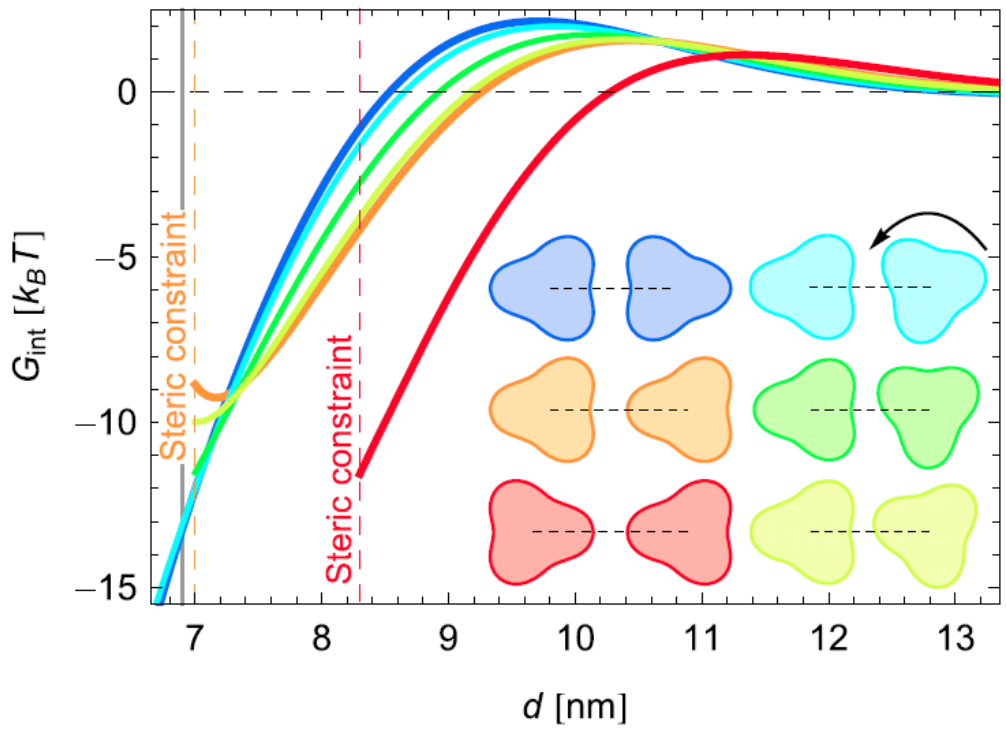
Thickness-mediated or curvature-mediated interactions?
(1) Potentially large hydrophobic mismatch:
Hydrophobic thickness of Trg up to $U \approx 4.5$ nm; U of *E. coli* cytoplasmic membrane ~ 3.4 nm. [*But:* Variation of U? Lipid segregation? Trimers flexible?]
(3) For cone angle $\alpha \approx 0.17$ [A. Vaknin and H. C. Berg, PNAS **103**, 592 (2006)], curvature-mediated interactions < 1 k_BT.



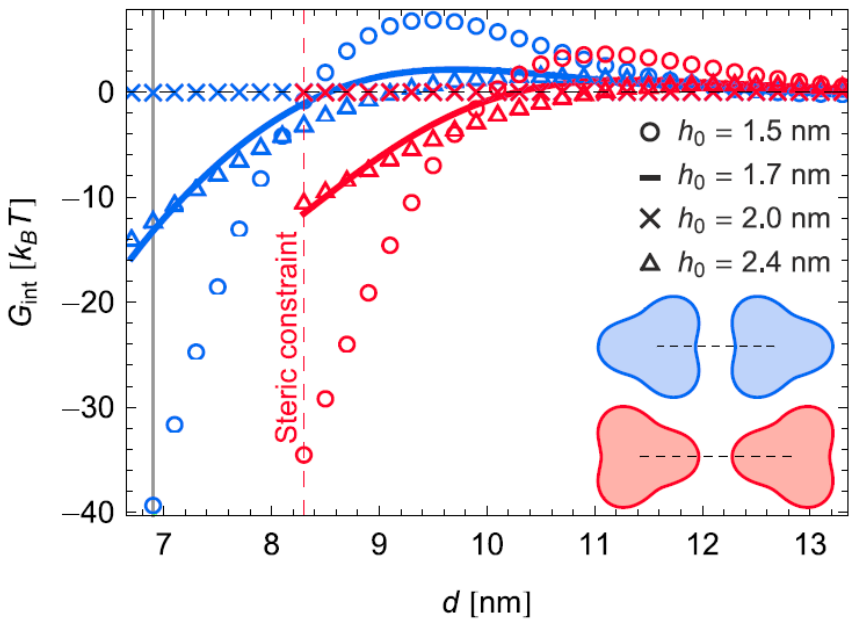


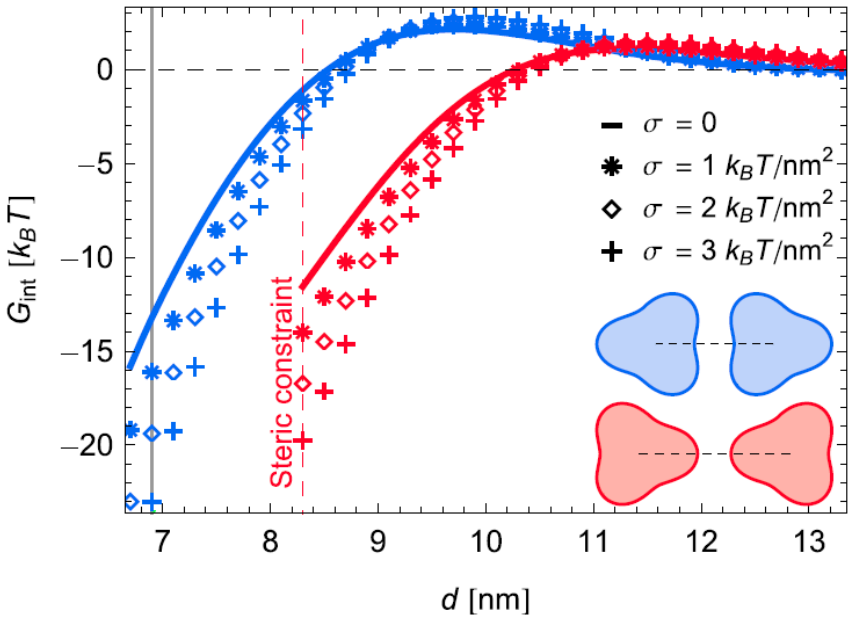


Cluster nucleation by bilayer-mediated interactions

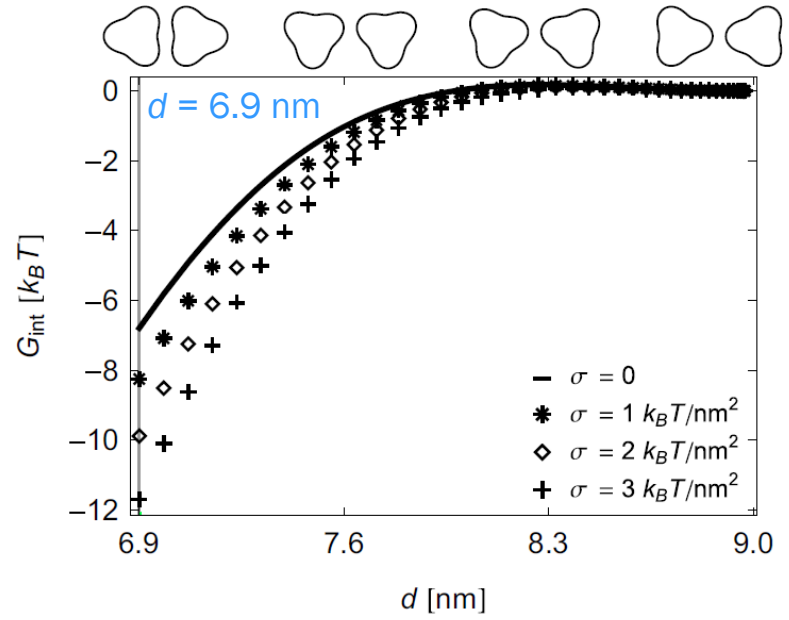


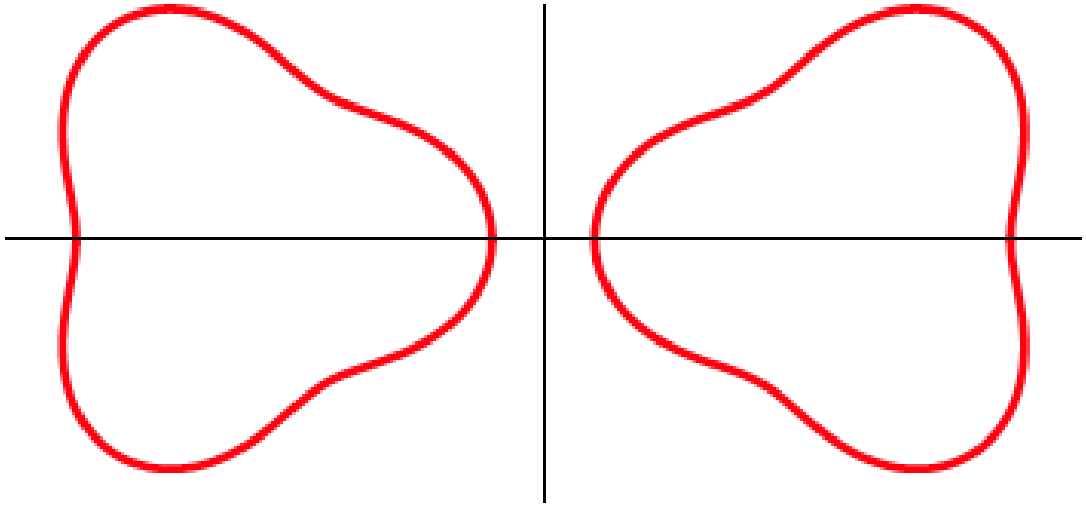
- Attractive interactions over $d \approx 10$ nm.
- Cluster nucleation already with ≈ 15 trimers in cytoplasmic membrane.
- Biphasic dependence of interaction strength on hydrophobic mismatch.
- Interaction strength increases with membrane tension.

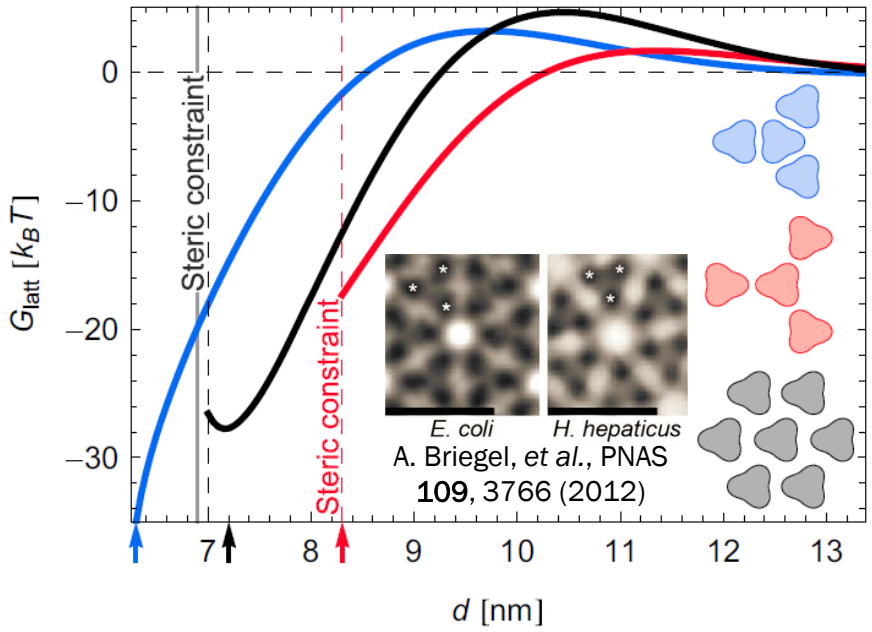




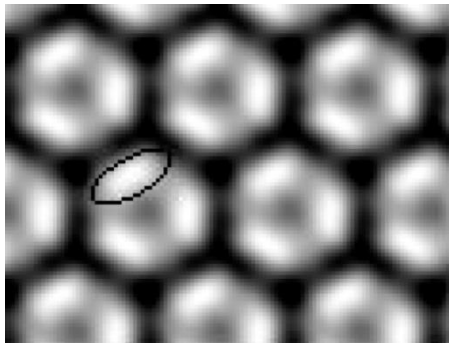
Gateway to chemoreceptor lattice architecture

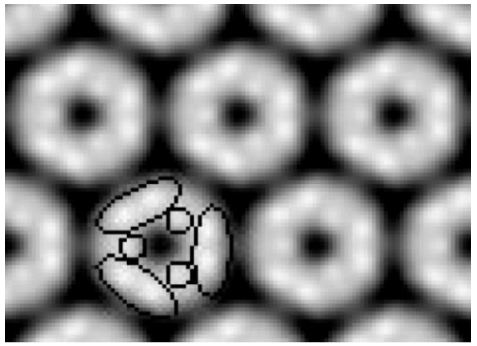






Close-packed hexagonal lattice metastable if clustering constrained by membrane area, as observed in overexpression experiments.



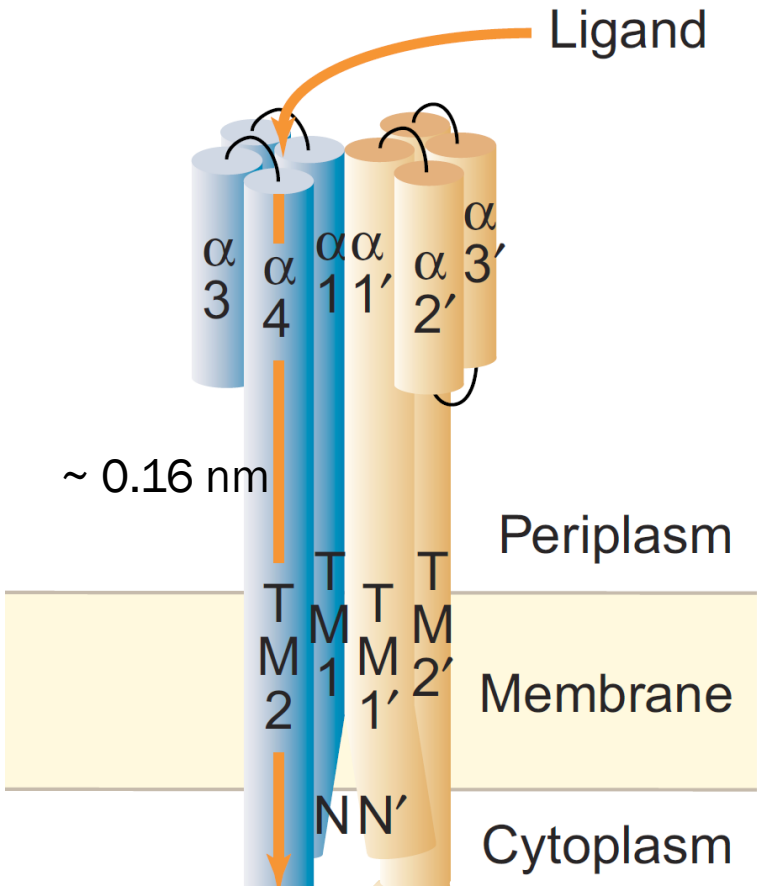


R. S. McAndrew, *et al.*, Microsc. Microanal. **10**, 416 (2004); M. D. Manson, in *Sensory Mechanisms in Bacteria: Molecular Aspects of Signal Recognition* (Caister, 2010), 107.

Chemoreceptor signaling and cooperativity

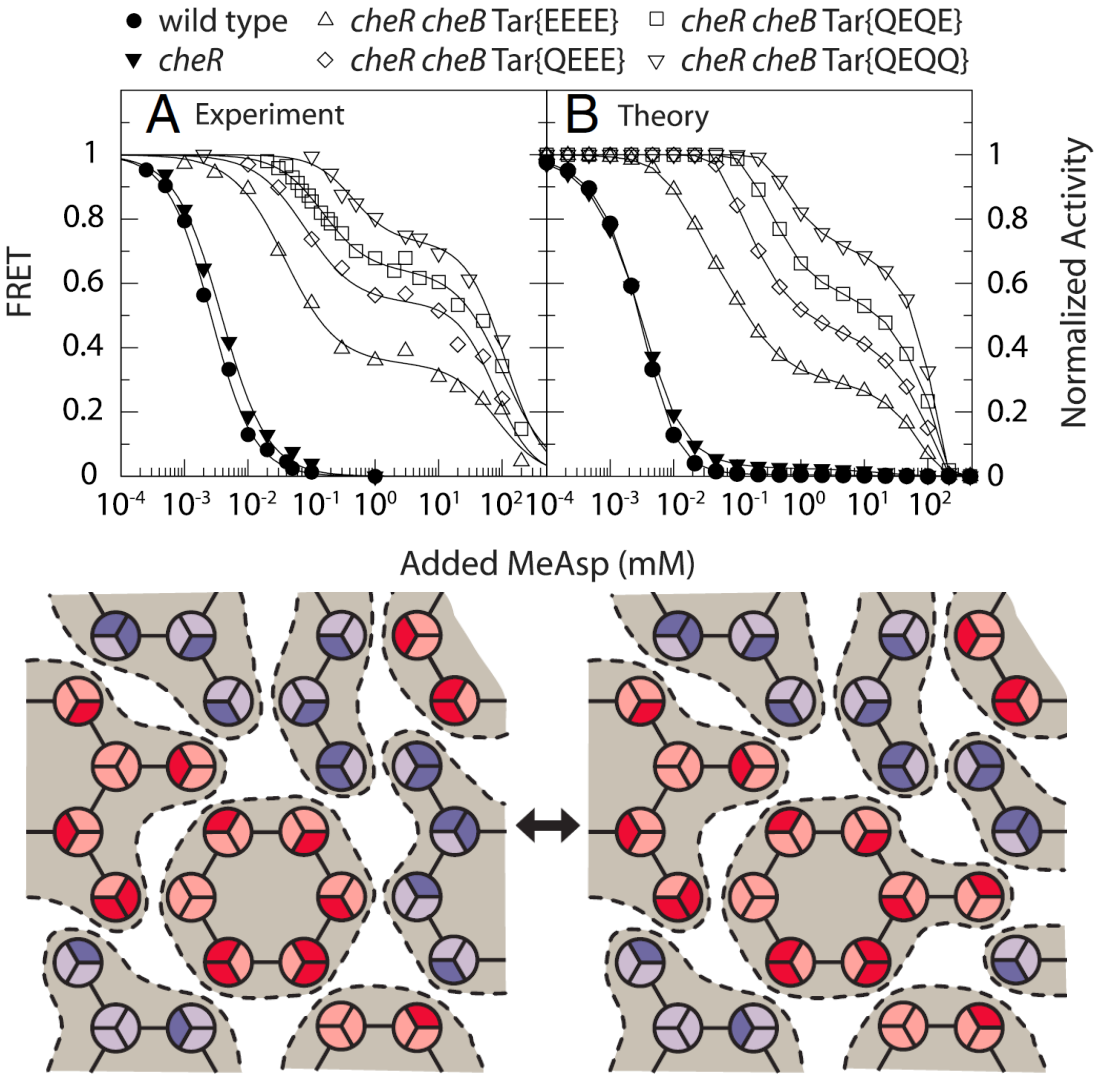
Piston model of signaling:

[S. A. Chervitz and J. J. Falke, PNAS **93**, 2545 (1996); A. G. Hughson and G. L. Hazelbauer, PNAS **93**, 11546 (1996); K. M. Ottemann, *et al*., Science **285**, 1751 (1999); J. J. Falke and G. L. Hazelbauer, Trends Biochem. Sci. **26**, 257 (2001); J. J. Falke and A. H. Erbse, Structure **17**, 1149 (2009); ...]



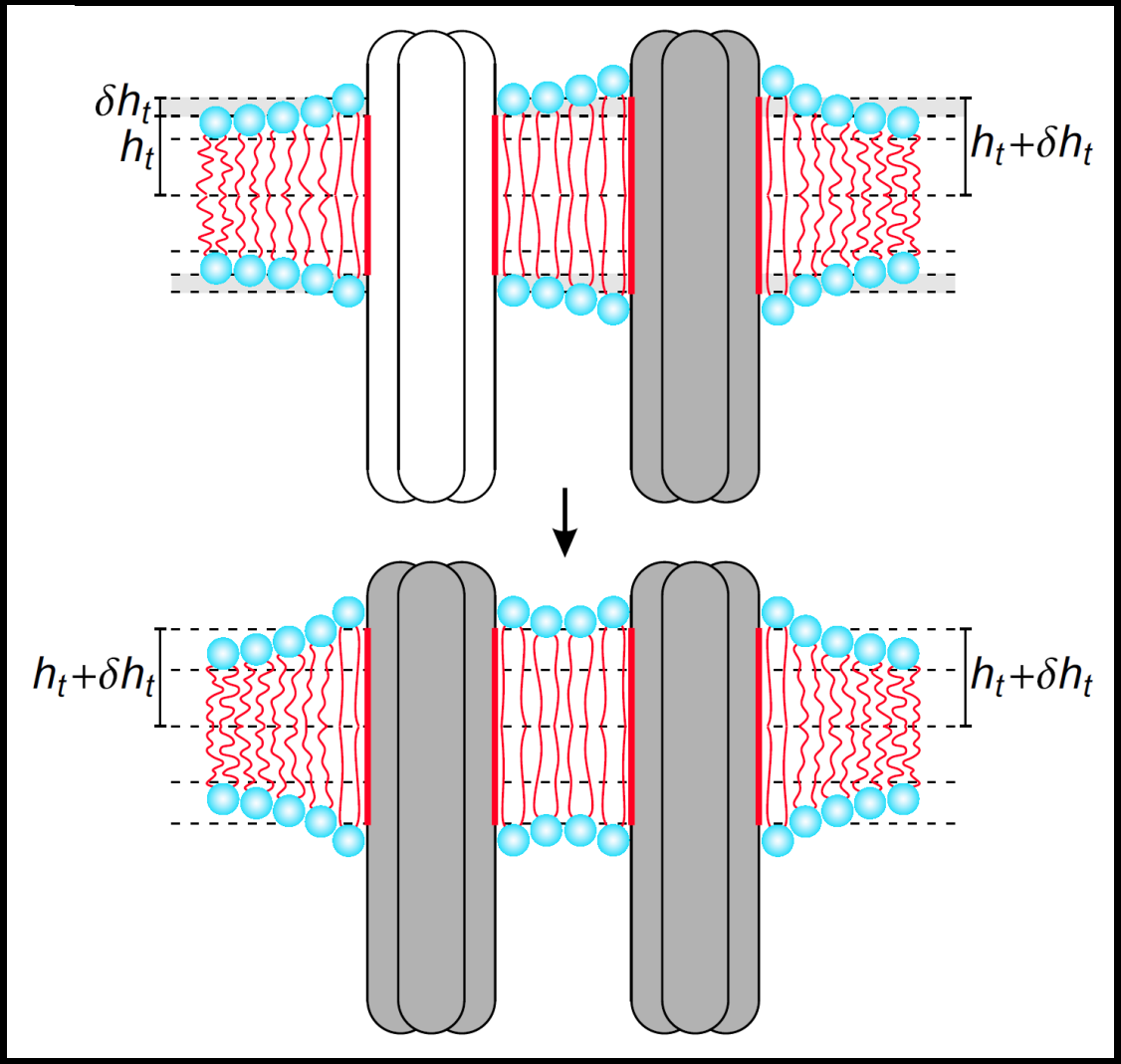
Cooperativity of chemoreceptor lattices:

[V. Sourjik and H. C. Berg, PNAS **99**, 123 (2002); V. Sourjik and H. C. Berg, Nature **428**, 437 (2004); B. A. Mello and Y. Tu, PNAS **100**, 8223 (2003); C. H. Hansen, *et al*., PNAS **107**, 17170 (2010); ...]



Do bilayer-trimer interactions play a role in chemotactic signaling?

A simple model for bilayer-mediated cooperativity

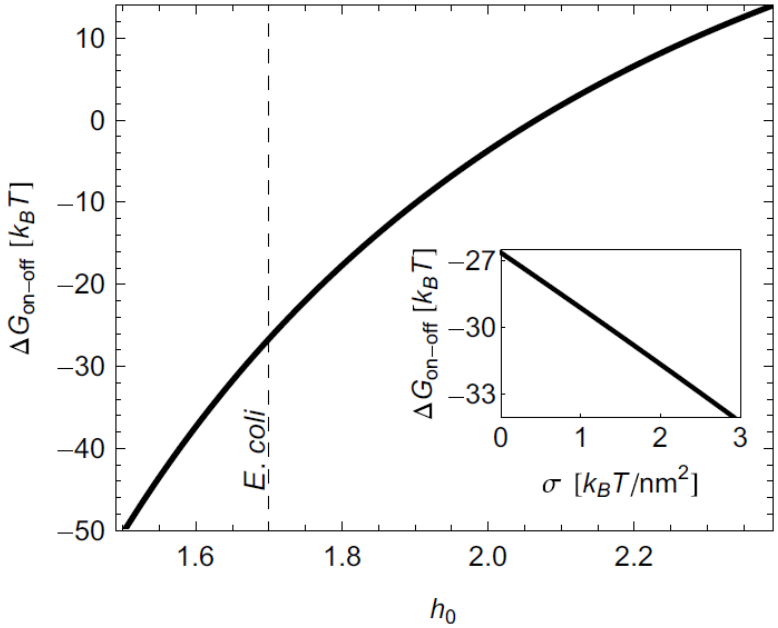


Assume that trimers switch collectively; Uniform shift δh_t = 0.16/2 nm.

[Variations in shift along trimer circumference? Tilts? Hydrophobic surface?]

A role for bilayer-trimer interactions in signaling?

Single trimer in dilute membranes:



- Total free energy contribution > 20 k_BT.

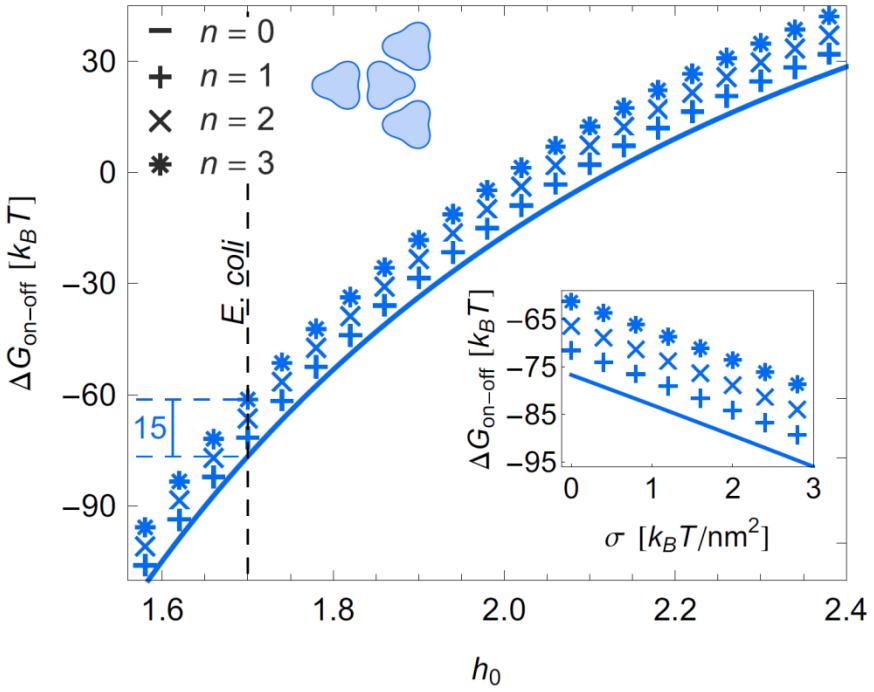
- Contribution *v*aries over ~ 60 k_BT with bilayer thickness and ~ 6 k_BT with tension.

C.f., shifts in chemoreceptor energy due to methylation ~ 1 k_BT per modification site. [T. S. Shimizu, *et al*., Mol. Sys. Biol. **6**, 1 (2010)]

Experiments: Bias signaling state by changing lipid composition/bilayer-receptor interface.

[D. N. Amin and G. L. Hazelbauer, J. Biol Chem. **287**, 41697 (2012); E. Bogonez and D. E. Koshland, Jr, PNAS **82**, 4891 (1985); R. R. Draheim, *et al*., Biochemistry **45**, 14655 (2006)].

Trimer in chemoreceptor lattice:



- Each nearest-neighbor trimer in off state lowers transition energy by ~ 5 k_BT.

- Cooperative shift robust with respect to perturbations in bilayer hydrophobic thickness and membrane tension.

Mechanism for cooperativity in presence of lattice defects, complementary to interactions mediated by CheA and CheW?

[M. Skoge, *et al*., Phys. Rev. Lett. **107**, 178101 (2011)]

Conclusions and outlook

1. Many key aspects of cell membrane function emerge from the collective properties of protein structure, lipid bilayer-protein interactions, the supramolecular organization of proteins, and large-scale membrane shape.

2. Model systems: MPPNs (membrane shape regulation); MscL (protein regulation through lipids); Chemoreceptor lattices (self-assembled protein clusters).

3. Collective membrane properties only rely on certain key molecular features of cell membranes; Physical models of collective membrane function can help to identify what these key molecular features are.

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