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Simulations of Membrane Fusion and the Role of Different Lipid Types

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Helfrich Free Energy

$$E = \int_{\partial V} \mathrm{d}A \left\{ 2\kappa \left(H - c_0\right)^2 + \bar{\kappa} K + \sigma \right\} - P \int_V \mathrm{d}V$$

- The κ are the moduli: bending and saddle-splay
- c_0 is spontaneous curvature
- H is the mean curvature
- K is the Gaussian curvature
- σ is the surface tension
- P, V are the pressure and volume

Inputs are moduli κ

Calculation of fluctuations, vesicle shape, fusion energies ....

Free Energy: Lipid Model

$$f_{\mathrm{tot}} = \frac{1}{2}\cdot\kappa\cdot(\mathrm{div}\,\mathbf{n} - \tilde{J}_{\mathrm{s}})^2 + \frac{1}{2}\cdot\kappa_{\mathrm{t}}\cdot\mathbf{t}^2 - \frac{1}{2}\cdot\kappa\cdot\tilde{J}_{\mathrm{s}}^2$$

f_{tot} is monolayer free energy/area

- The κ are the moduli: splay and tilt
- $\boldsymbol{J}_s$ is the spontaneous splay, $\boldsymbol{J}$ = div **n**
- $\boldsymbol{t}$ is the tilt, $\boldsymbol{t}$ = **n** / (**n**·**N**) - **N**

- Kozlovsky & Kozlov, 2002

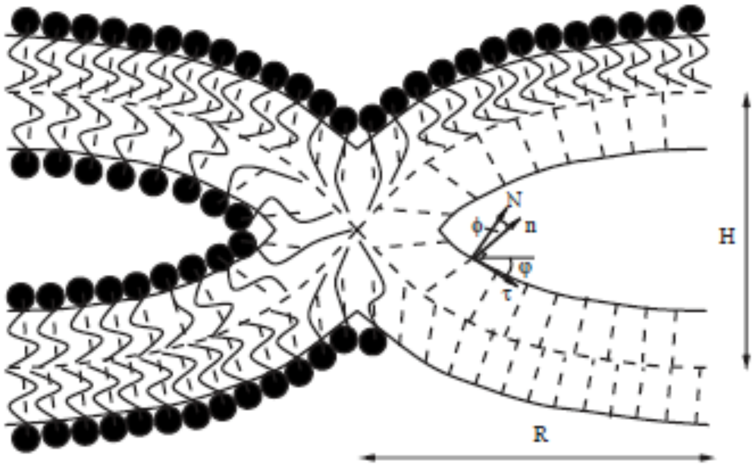

FIGURE 2 Tilt model for stalk and TMC. The shape is axially symmet-

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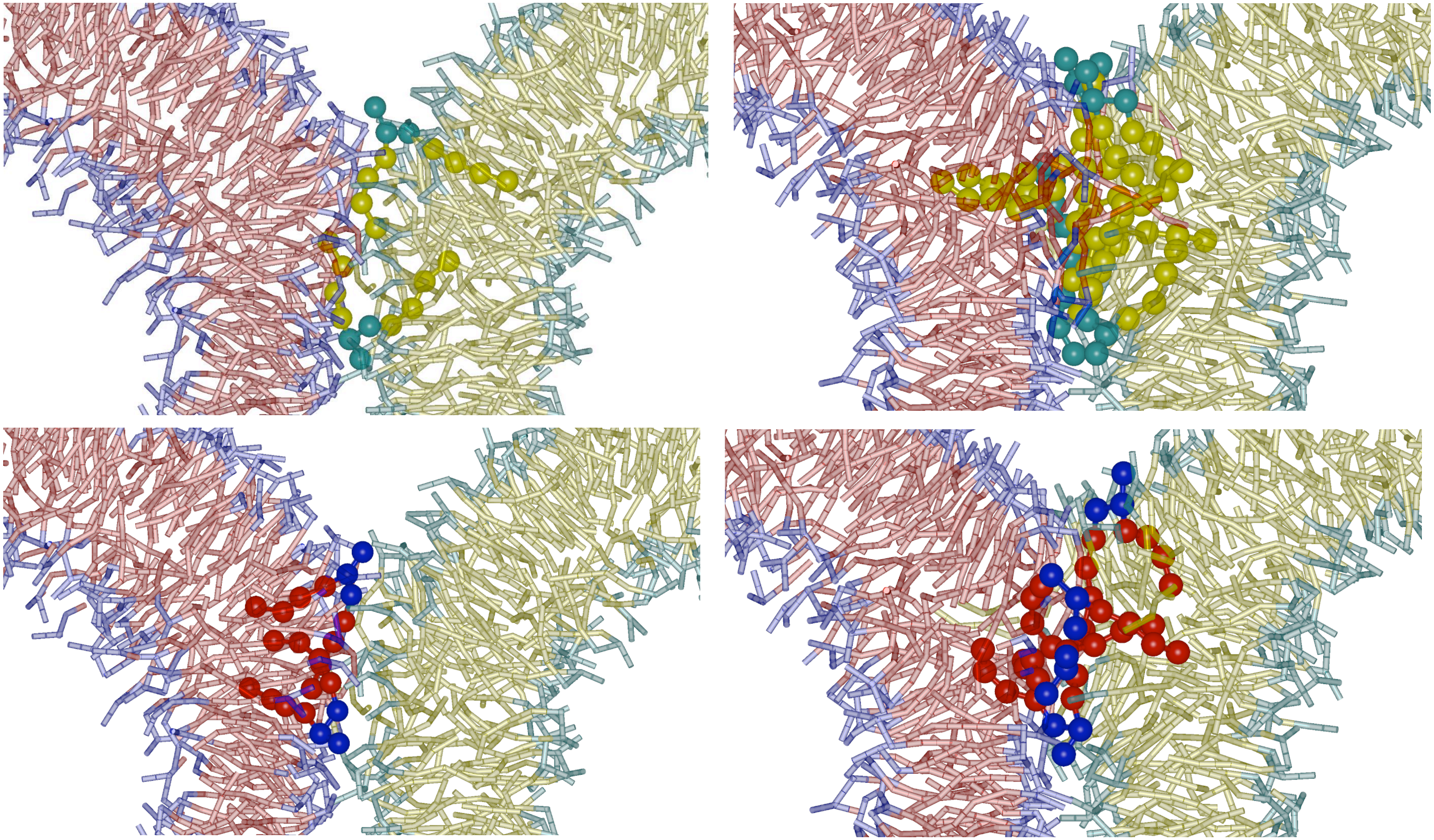
Splayed Lipid Tails Initiate Fusion



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Lipid Model: Interactions

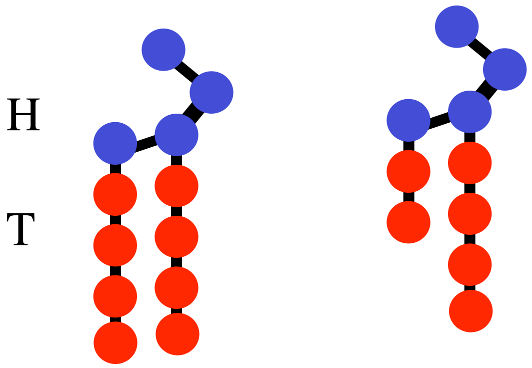
Lipid types

DPPC

DPPC/DPPE mixture (3:1)

asymmetric tail

DOPC



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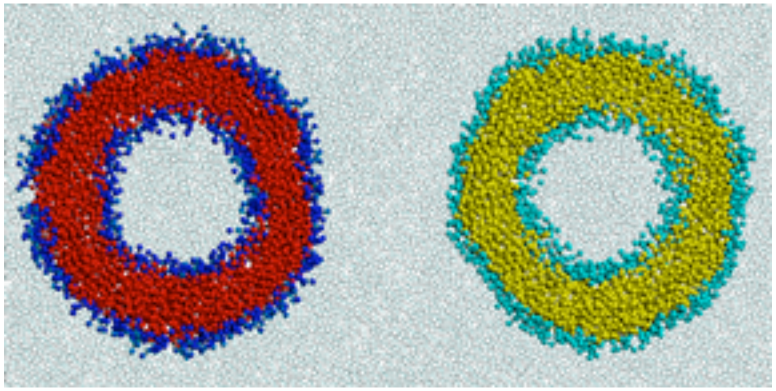
Fusion Simulation Setup

- Two vesicles
- Center of mass separation constrained
- calculate free energy using WHAM
- T = 325K
- Marrink original lipid FF



f *f*

877 lipids per vesicle

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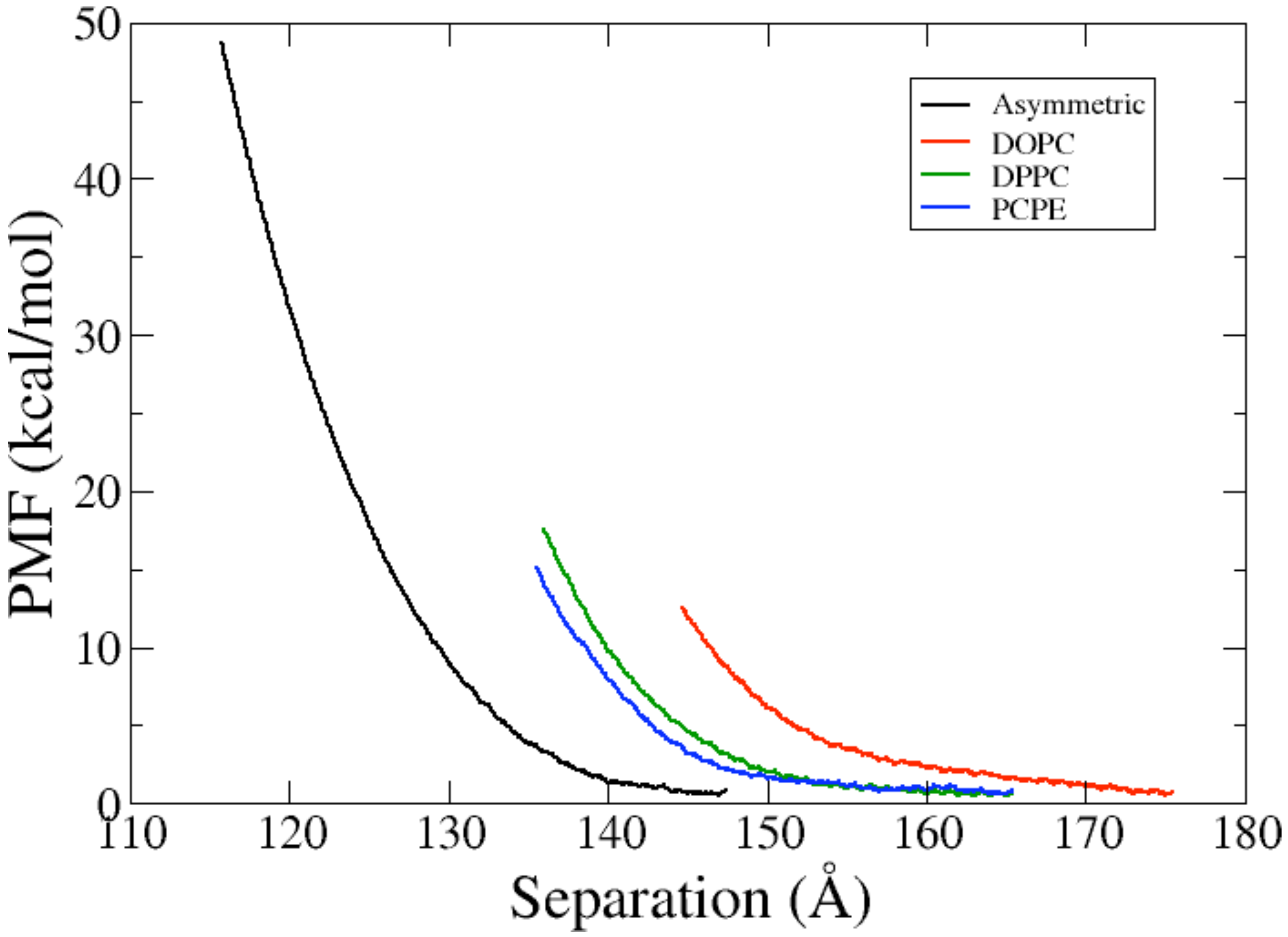
PMF



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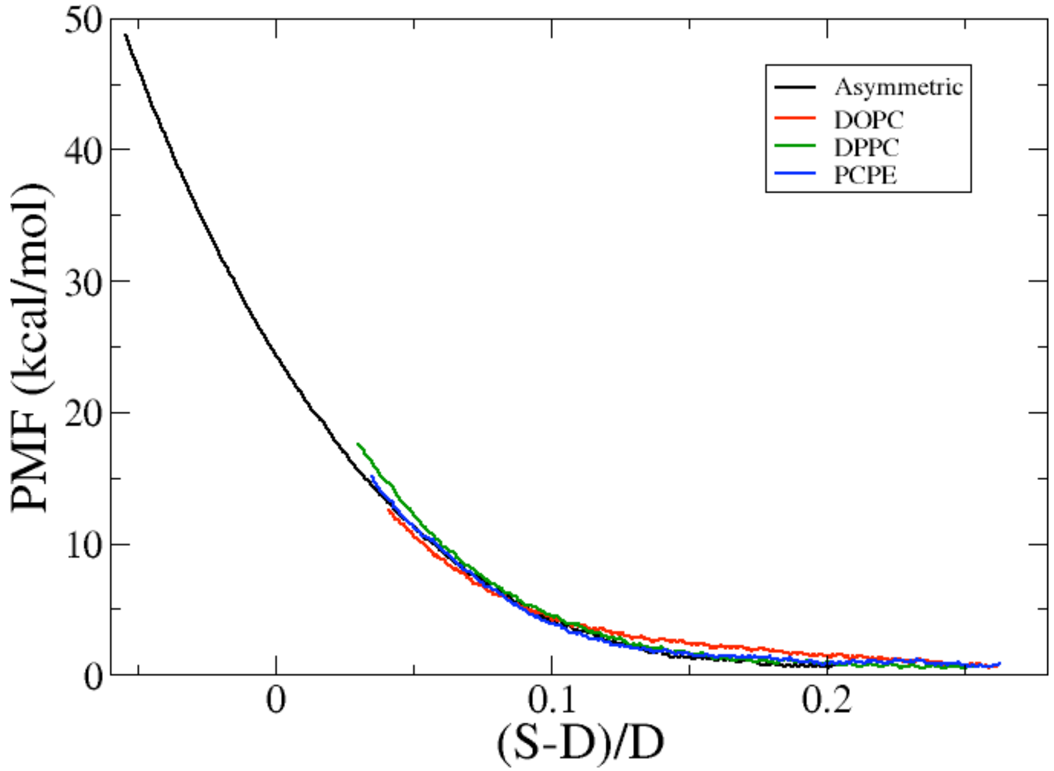
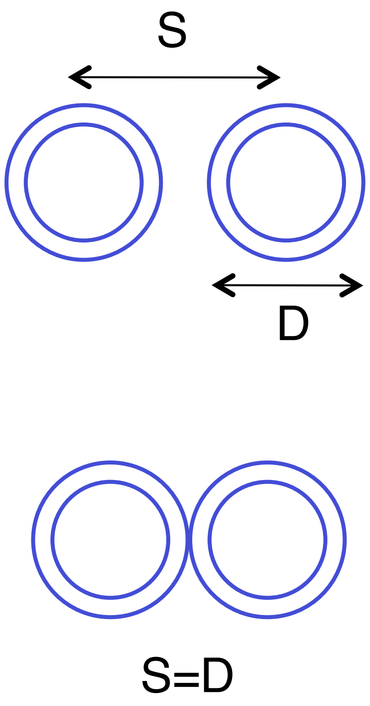
scaled PMF



- moving water between vesicles
- deformation of vesicles
- lipid dynamics



type	D(fit)	D(calc
DPPC	132 Å	130 Å
PC/PE	131 Å	130 Å
DOPC	139 Å	138 Å
Asymm	122 Å	122 Å

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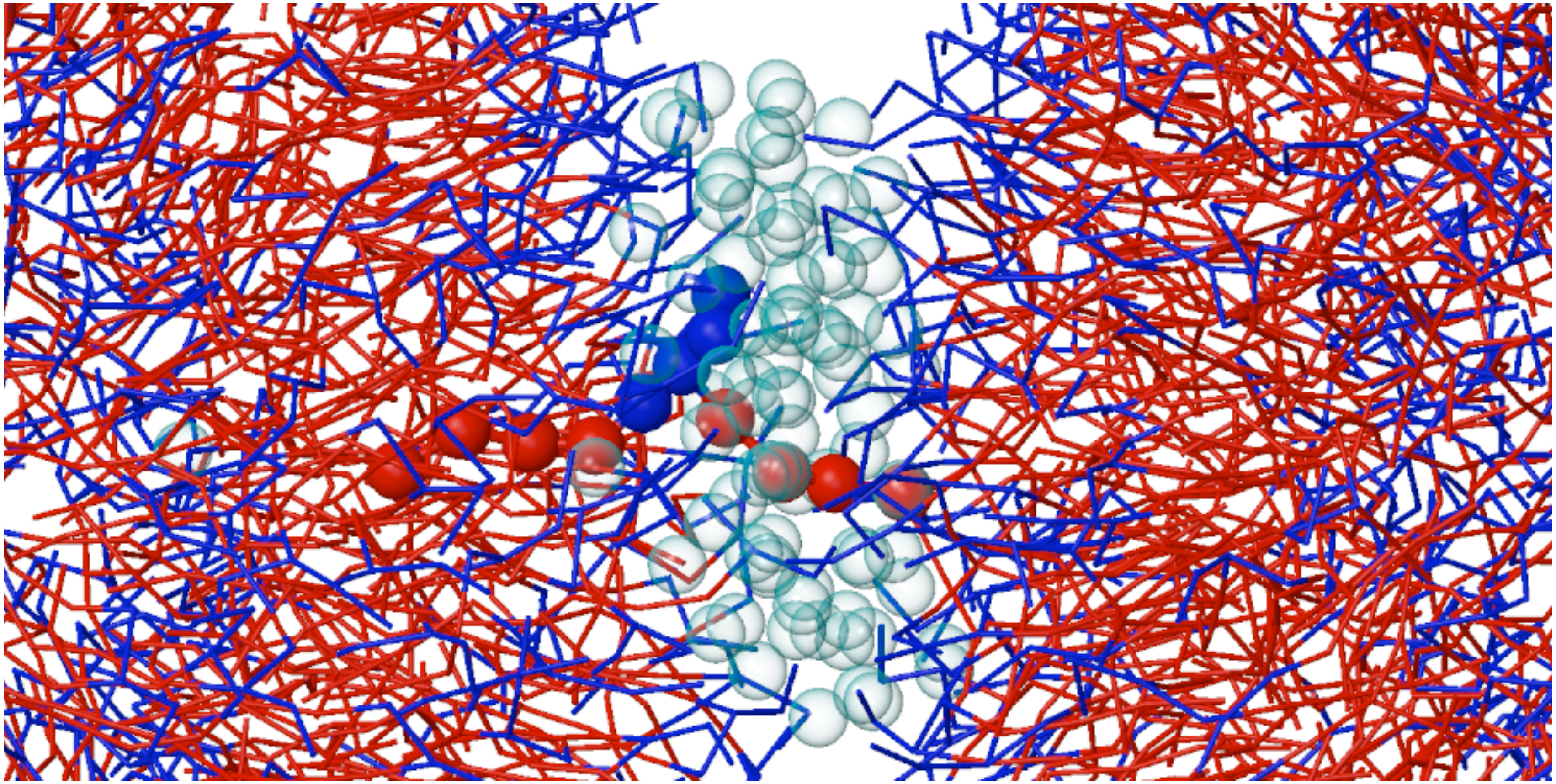
Fusion Initiation: DPPC

Tail Splay



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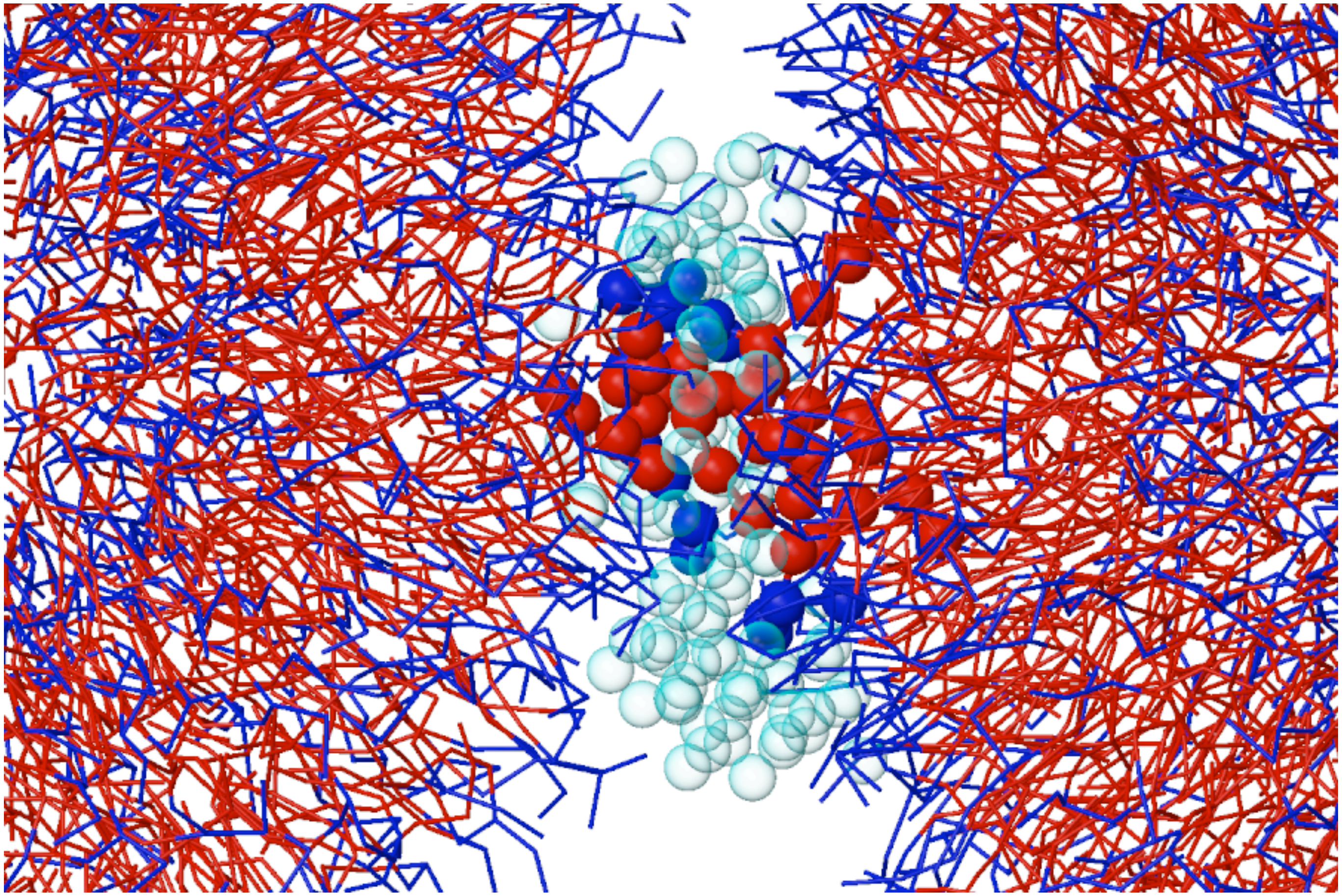
Fusion Initiation: PC/PE

Multiple lipids



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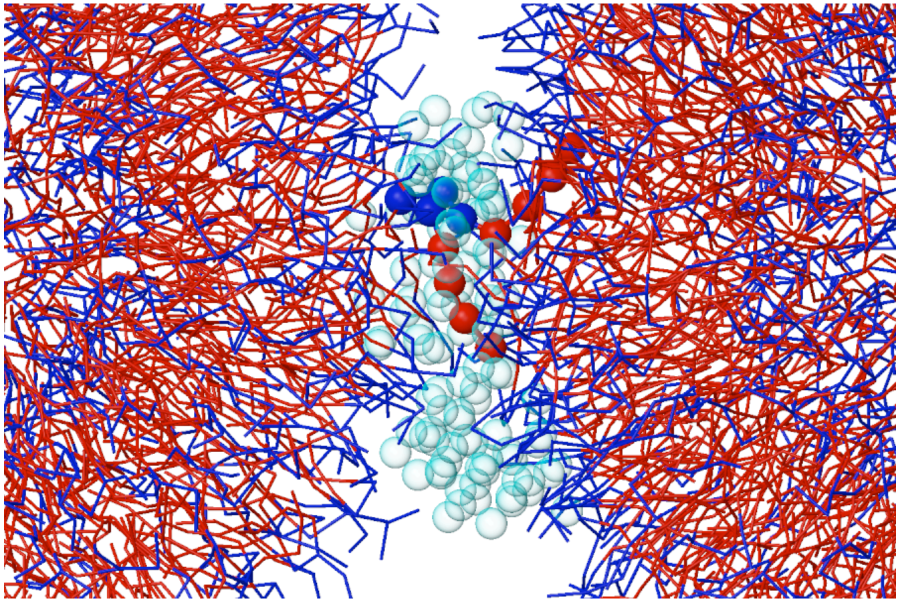
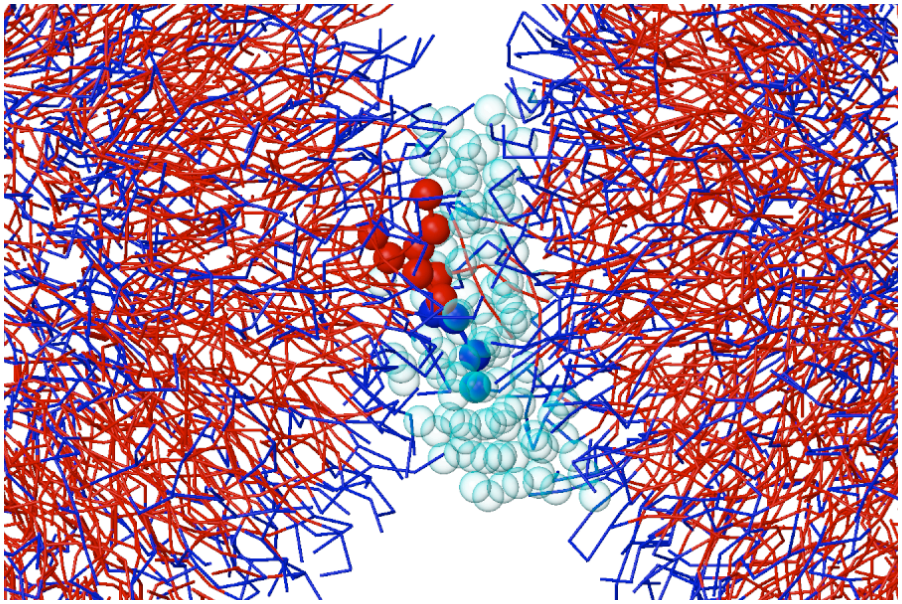
Fusion Initiation: PC/PE

are these PC or PE lipids?

Splay



Rotated



Hydrophobic 'pore' is composed of 4 lipids.
The splayed lipid does not span between two vesicles.

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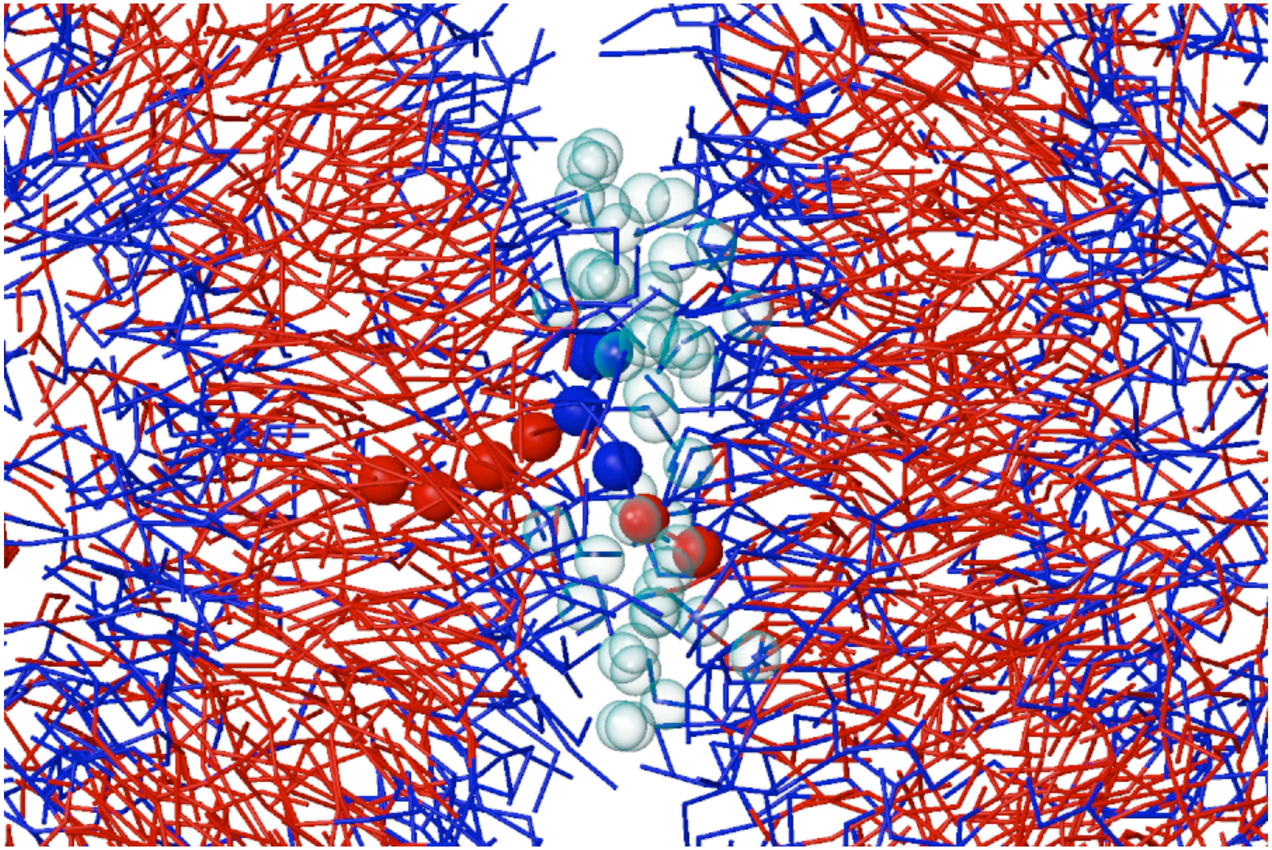
Fusion Initiation: Asymmetric

Tail Splay



Shorter span by assymmetric tails leads to shorter separation between vesicles for fusion.

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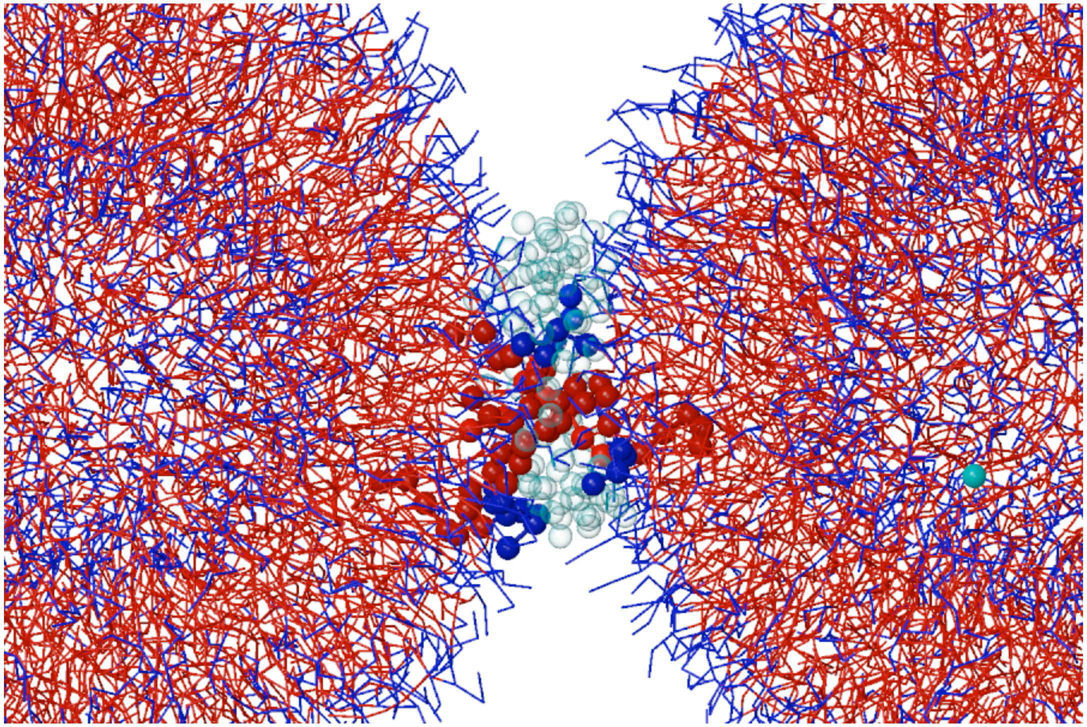
Fusion Initiation: DOPC

Hydrophobic pore: 5 lipids
1 is spans and splayed
3 splay with one tail in pore
1 with head group across to other vesicle



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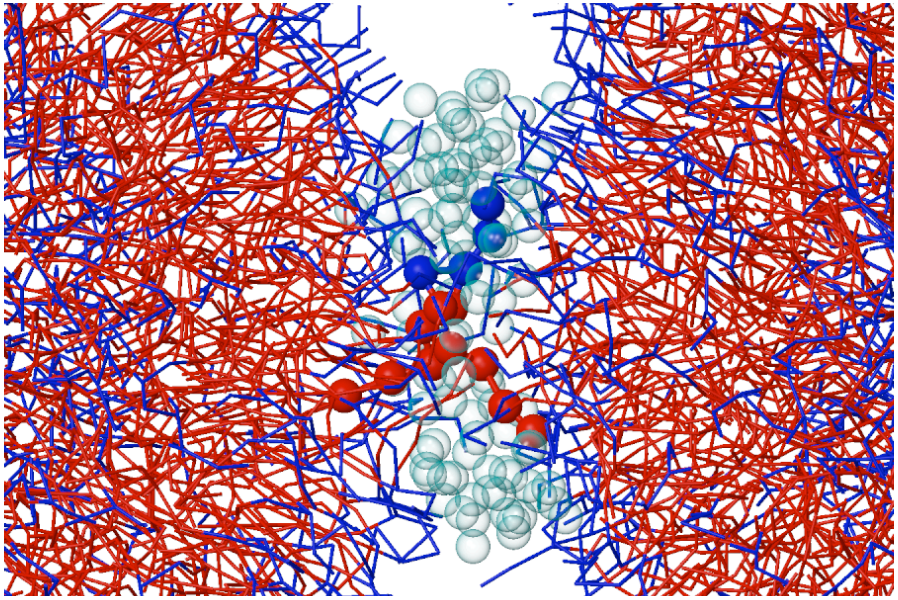
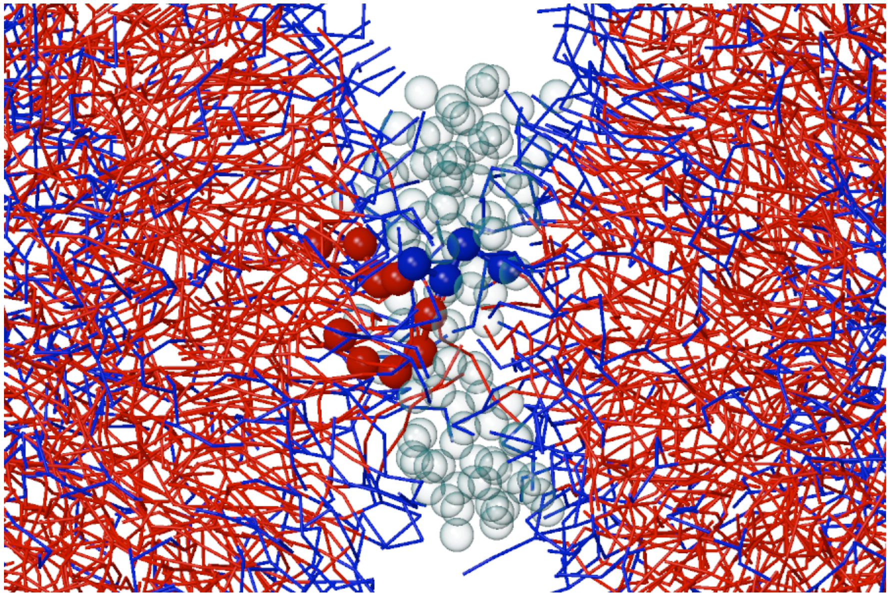
Fusion Initiation: DOPC

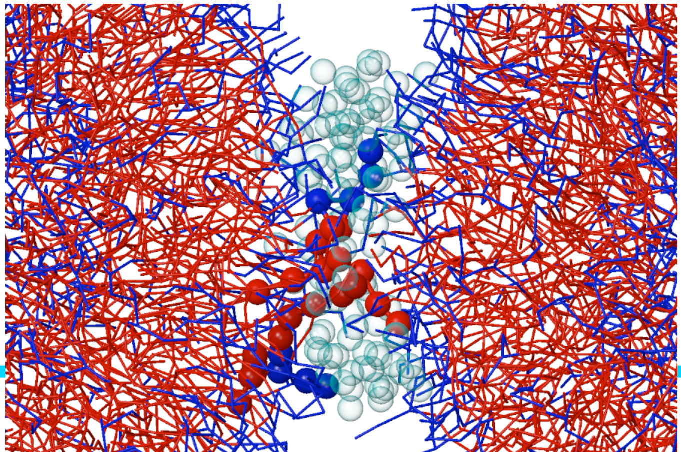
Span & Splay



'Translation'



Splay & Bridge



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Conclusions

Splayed lipid tails promotes fusion initiation

Future

- Temperature affect: $T\text{-}T_m$?
- Vesicle size
- Force-field/model
- experiment

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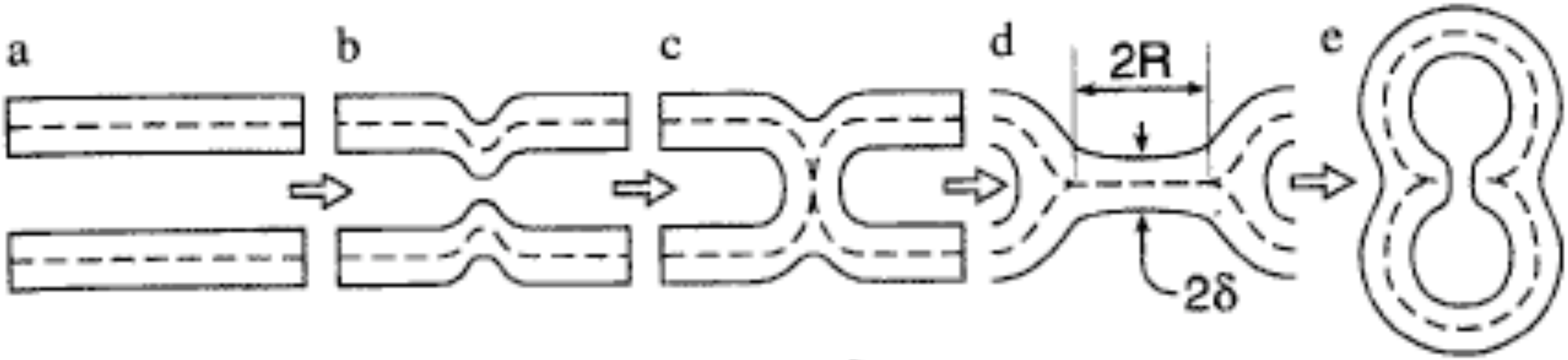
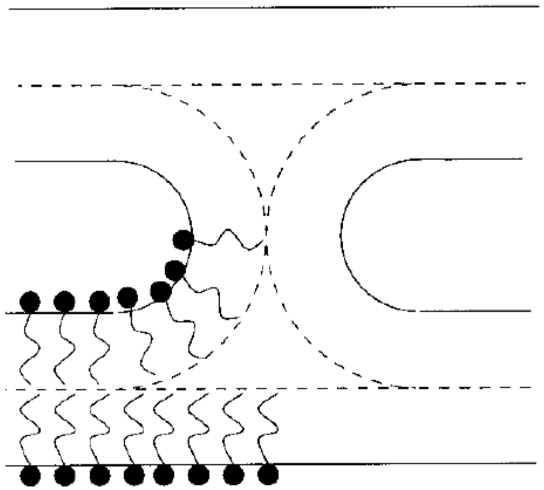
National Institute of
General Medical Sciences

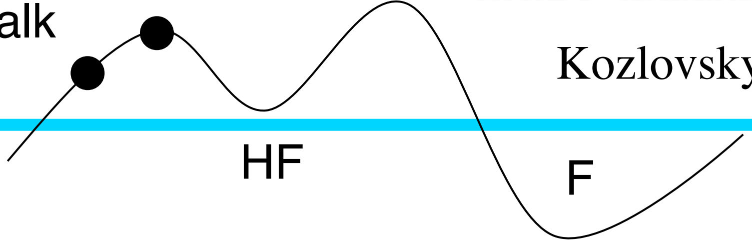
Fusion and the Stalk

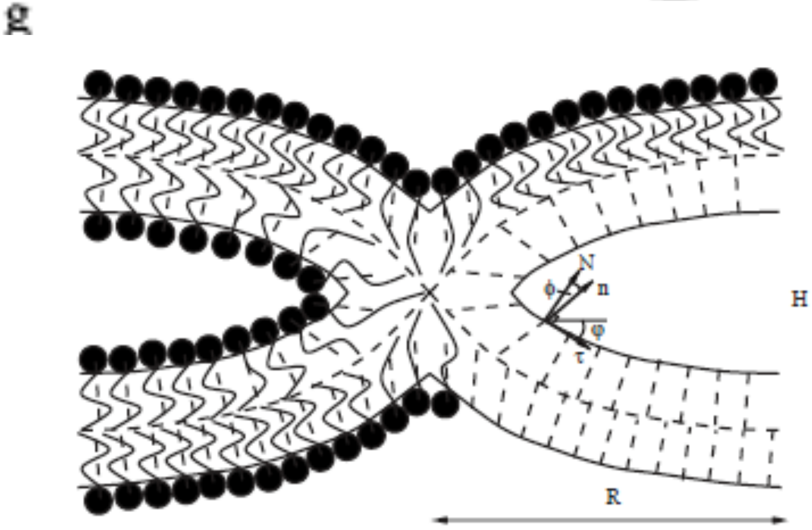


Chernomordik et al. 1995



original stalk geometry





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Kozlovsky & Kozlov, 2002

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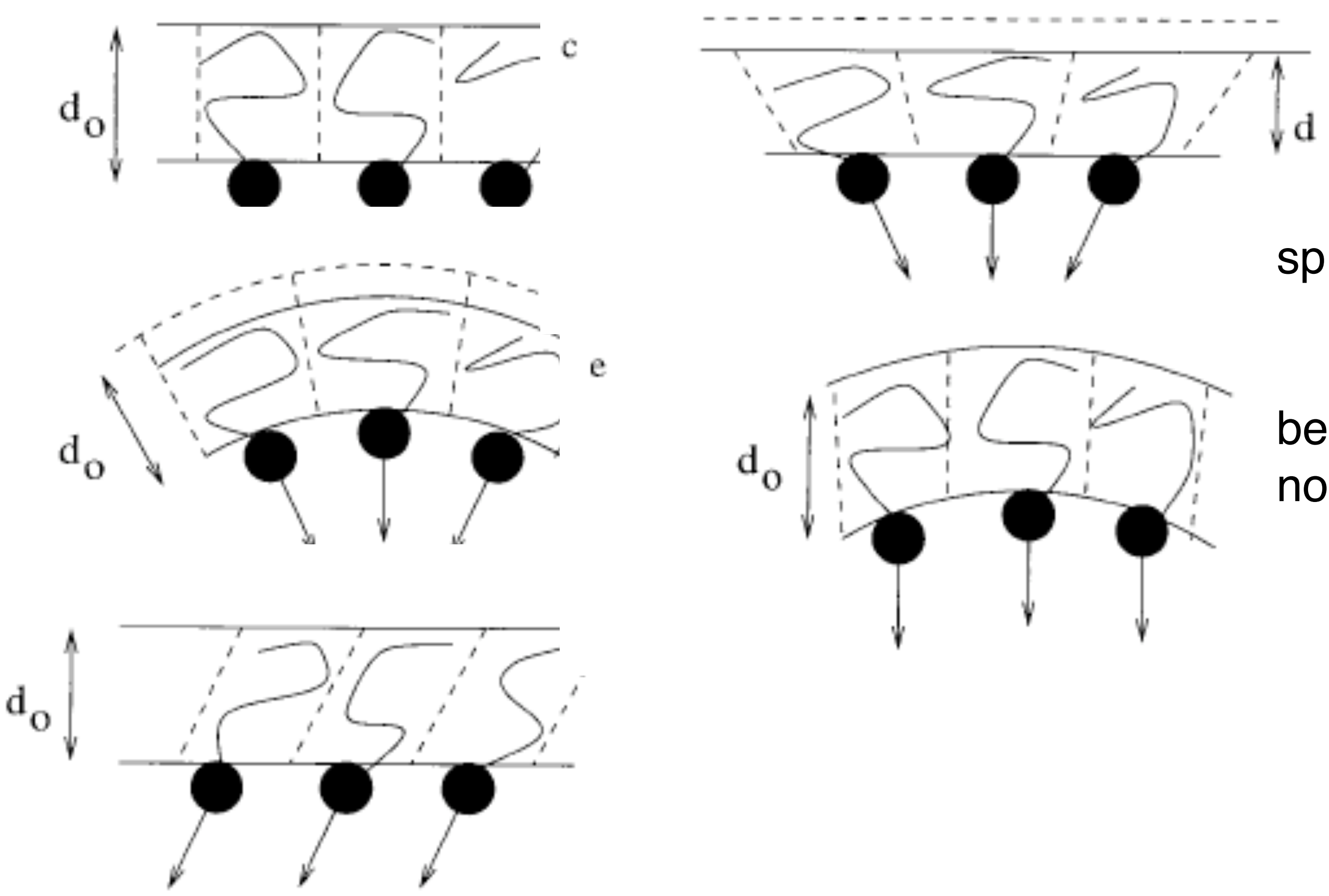
Membrane Deformations



undeformed

bend

tilt

splay

bend & tilt
no splay

Kozlovsky & Kozlov, 2002

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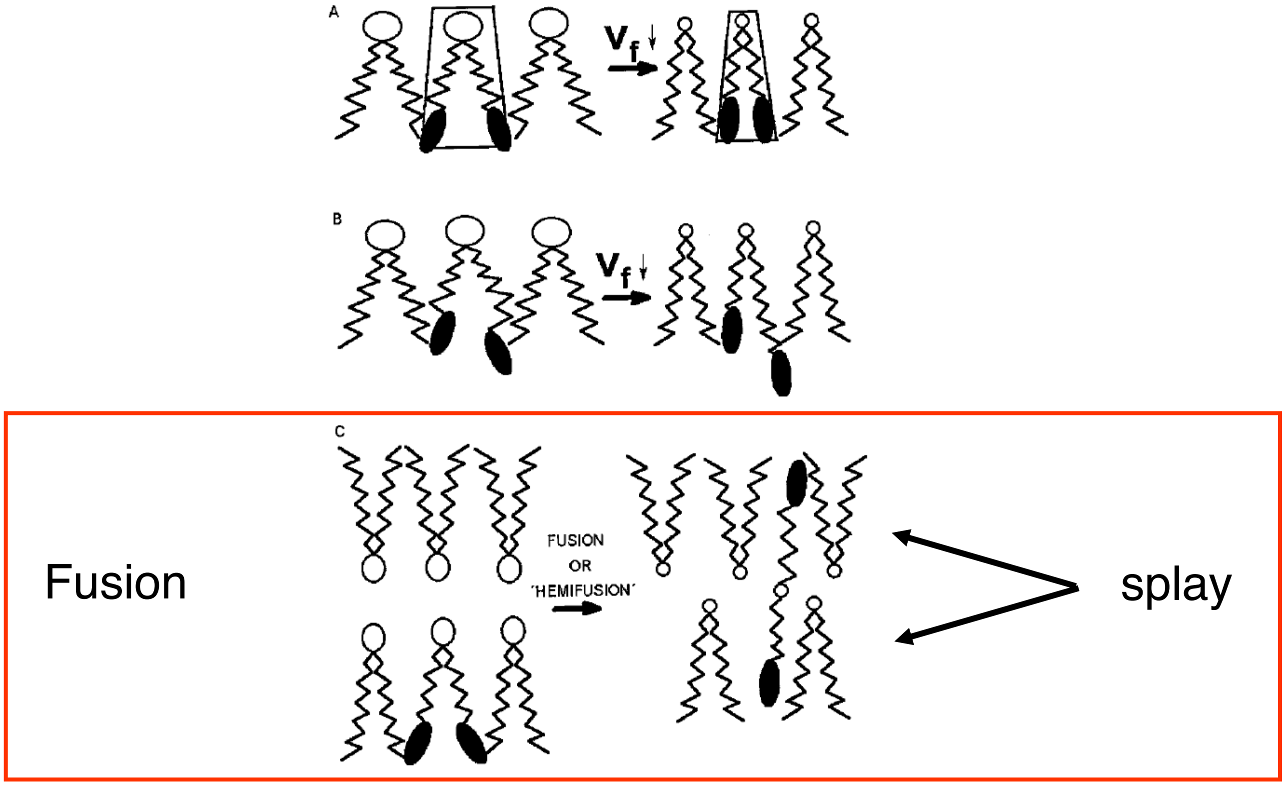
Fluorescence Experiments

J.M. Holopainen, J.Y.A. Lehtonen and P.K.J. Kinnunen, Biophysical J. **76**, 2111 (1999).



Fusion

splay

FIGURE 7 A schematic illustration of the changes in the acyl chain alignment for bis-PDPC (*A*) and PDPTPC (*B*) upon decreasing the membrane free volume by dehydration of the polar headgroup by PEG or Me^{2+}. Hemifusion of bilayers and the adoption of the extended conformation by bis-PDPC is depicted in *C*. The pyrene moiety is represented by the filled black ellipse.

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