Pathway and free energy barriers of rupturing the hemi-fission intermediate under tension

A Wang-Landau sampling study

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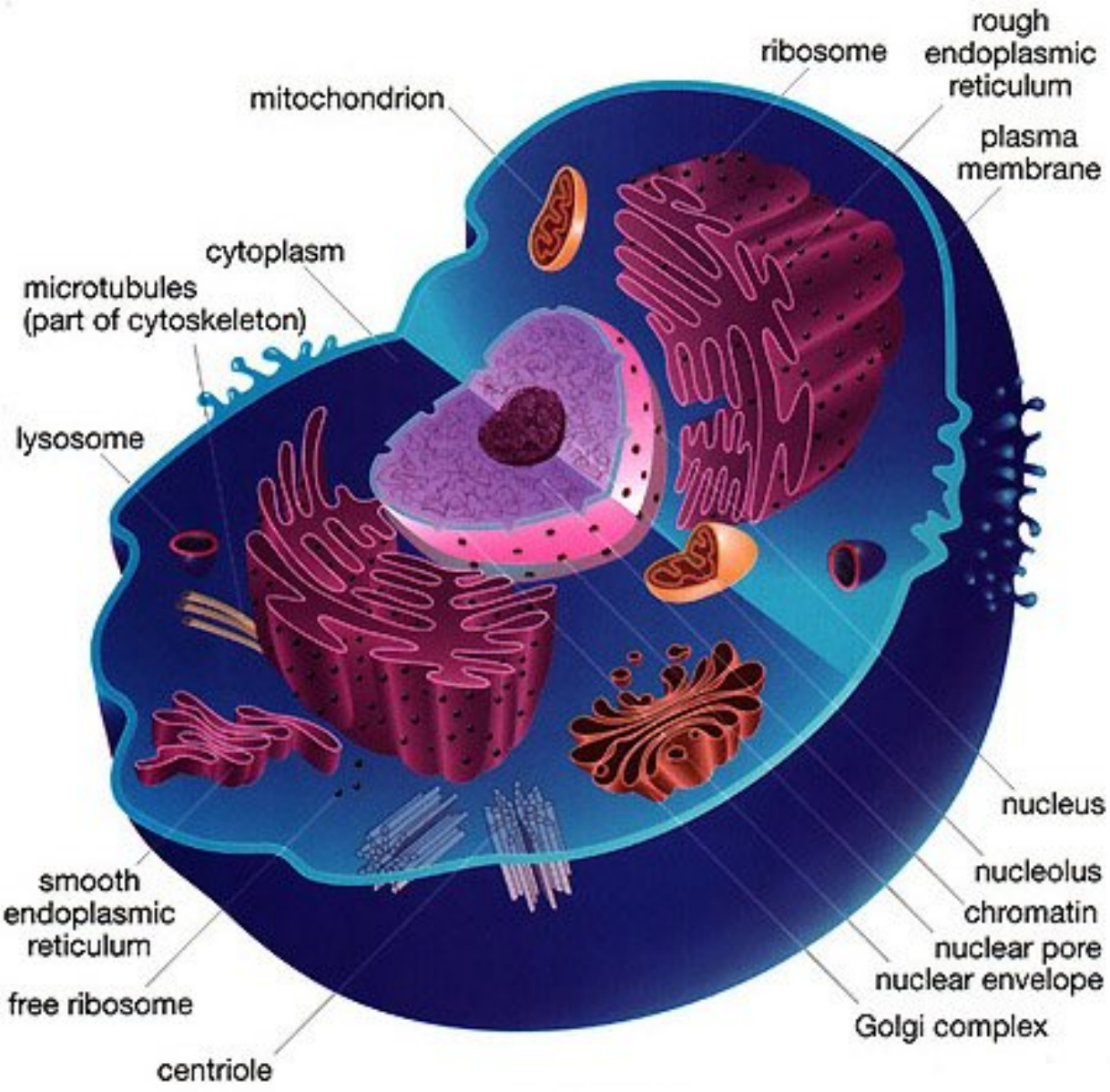
Workshop of "Bridging time-scale techniques and their applications in atomistic computational science"
at Max-Planck-Institute for the Physics of Complex Systems
12-15 Sep. 2016, Dresden

Cell membranes



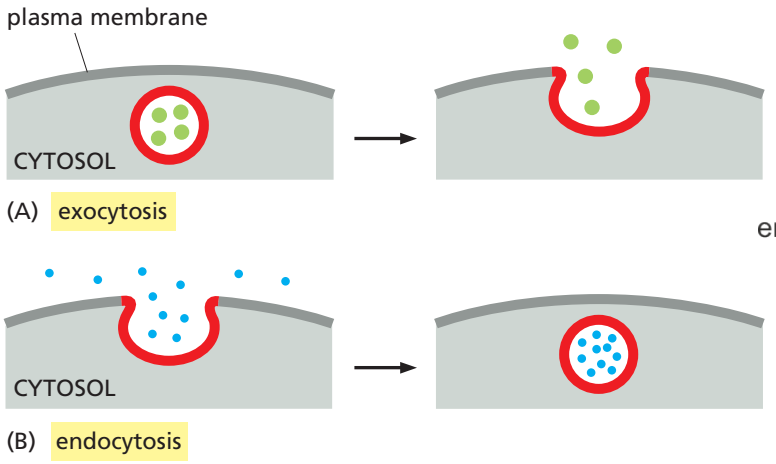
Everything you see here is membrane!

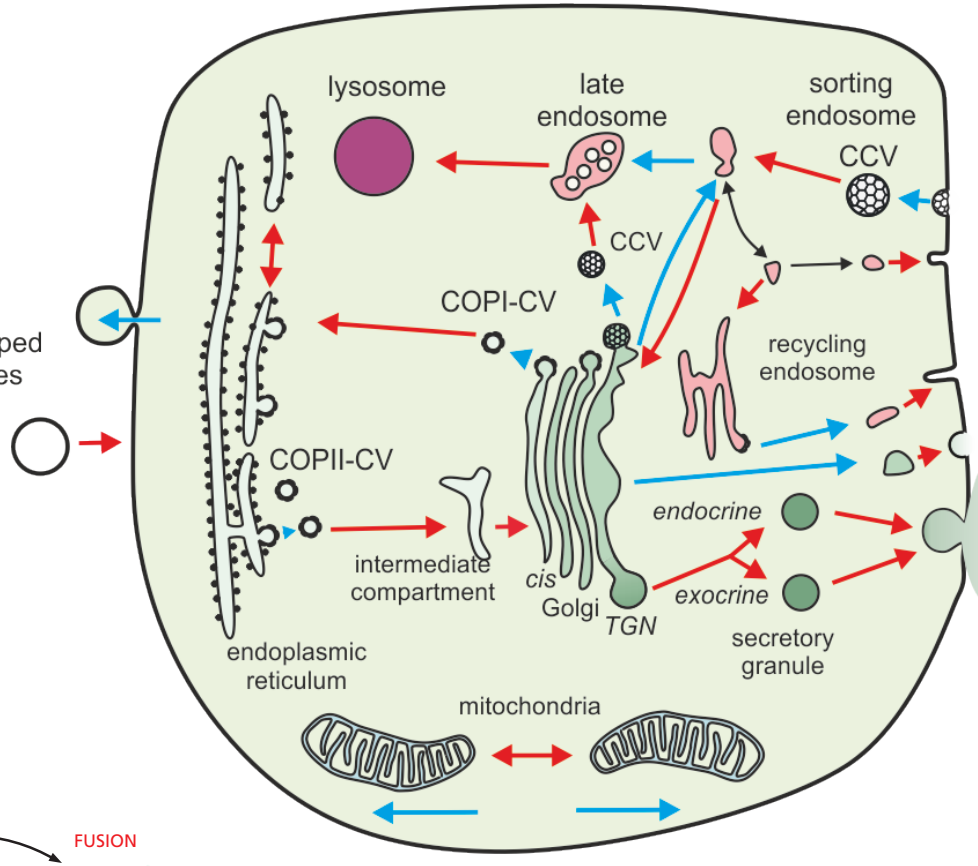
Cell must eat via fusion and fission

To make itself alive, cell must exchange materials between intracellular compartments or the outside of the cell.

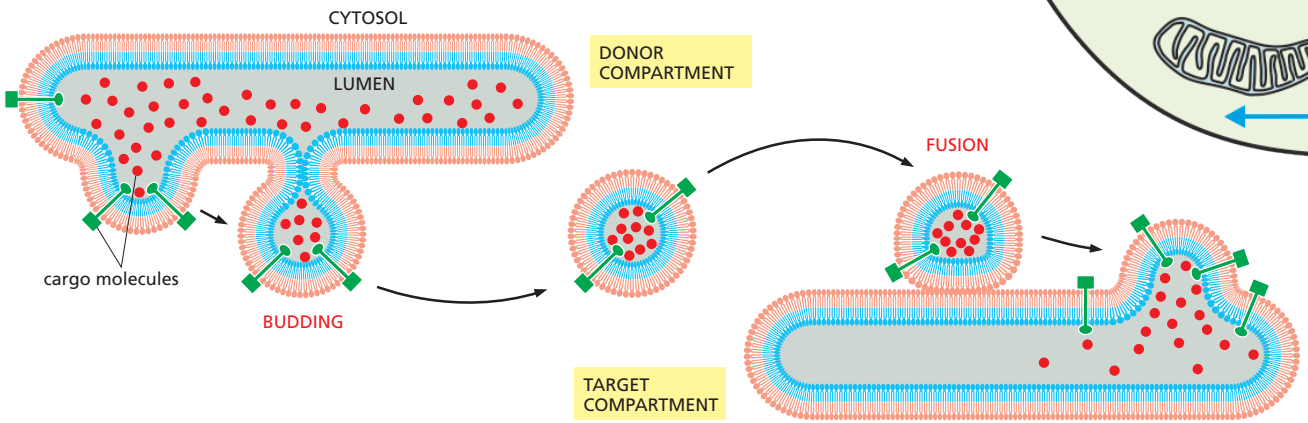
fusion fission

✧ Exocytosis and endocytosis



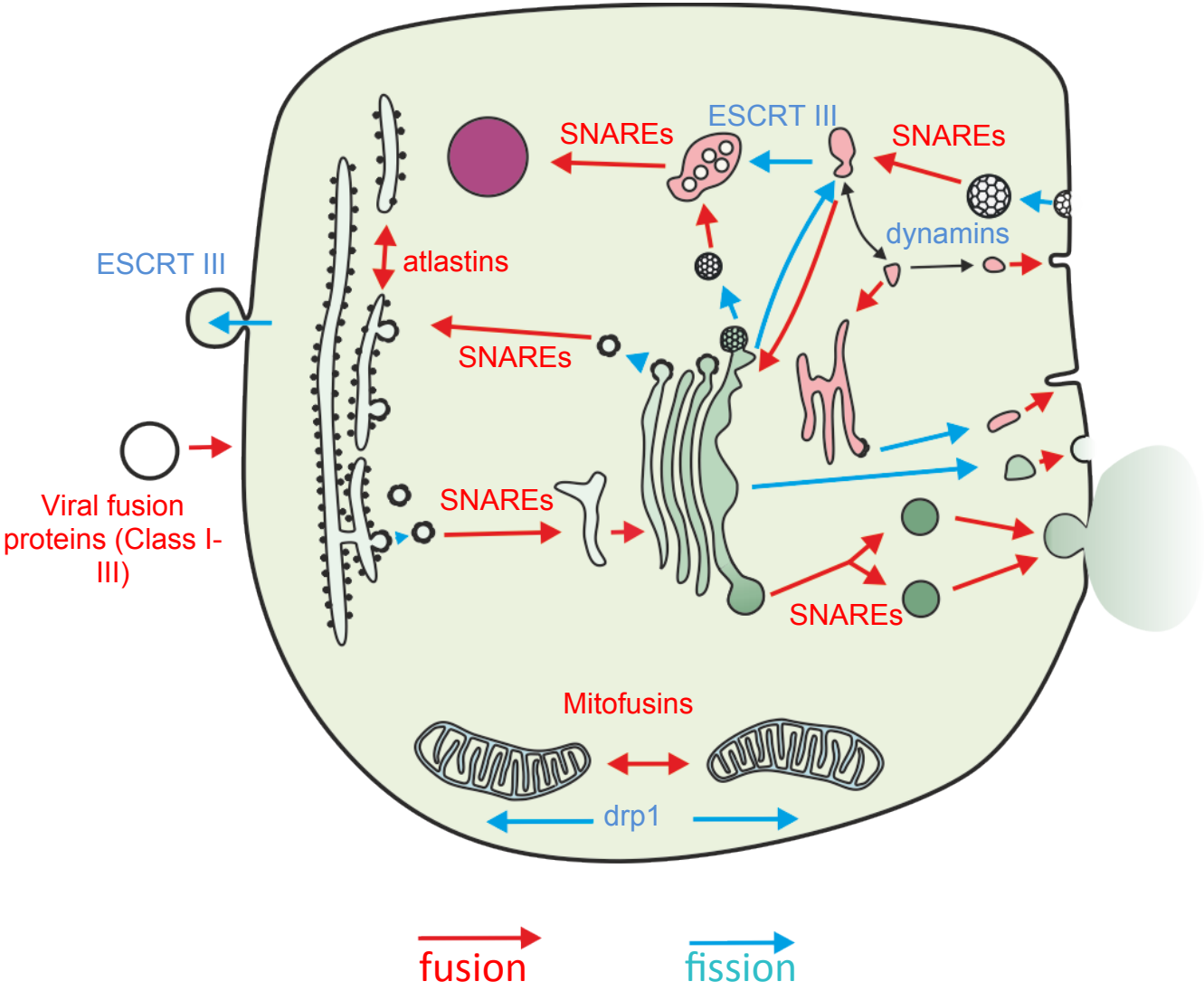


✧ Fission and fusion in vesicle transport



Alberts, et al.
Molecular biology of the cell, 6th Ed.
Garland Science (2015).

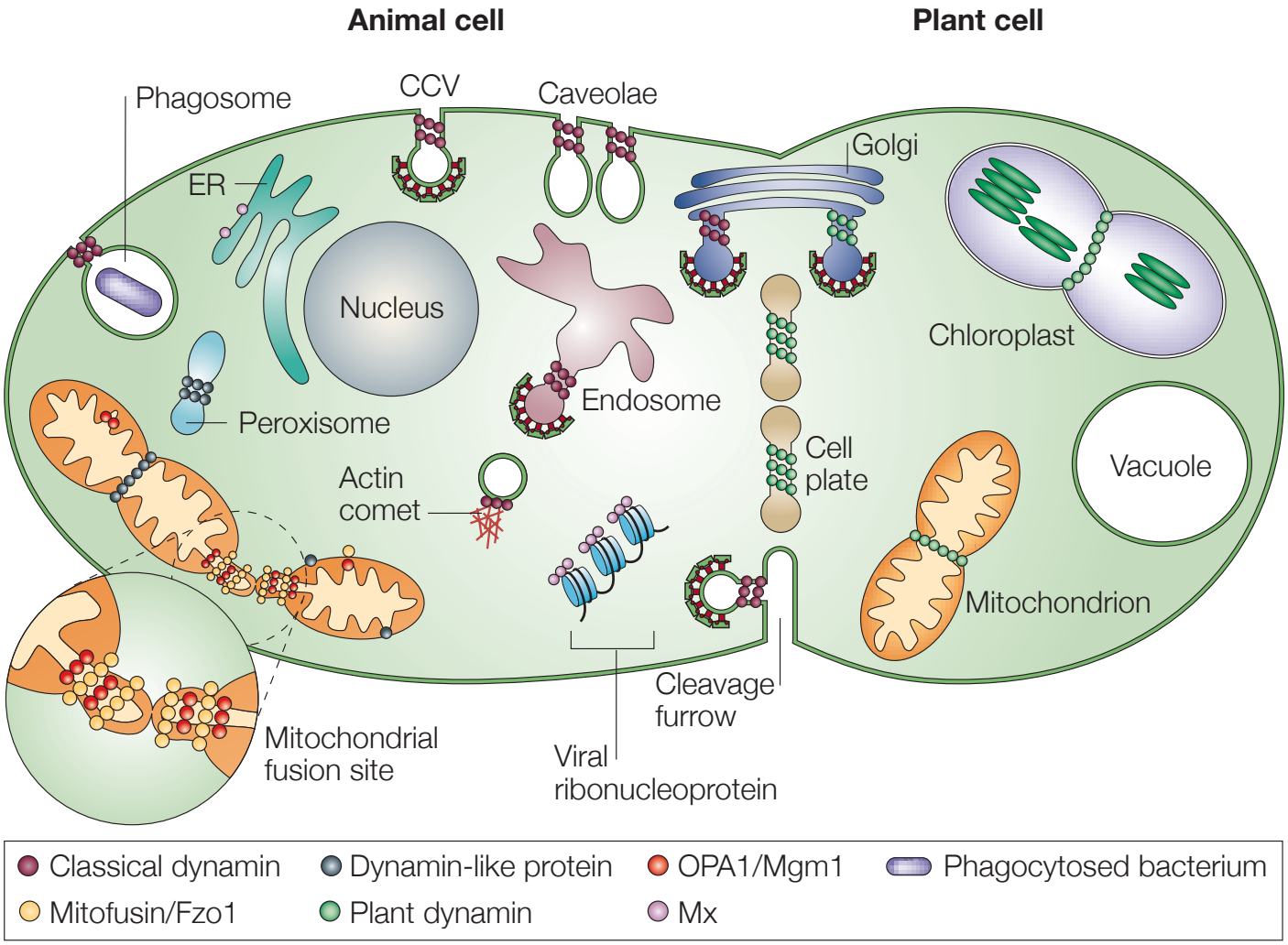
Membrane fusion and fission



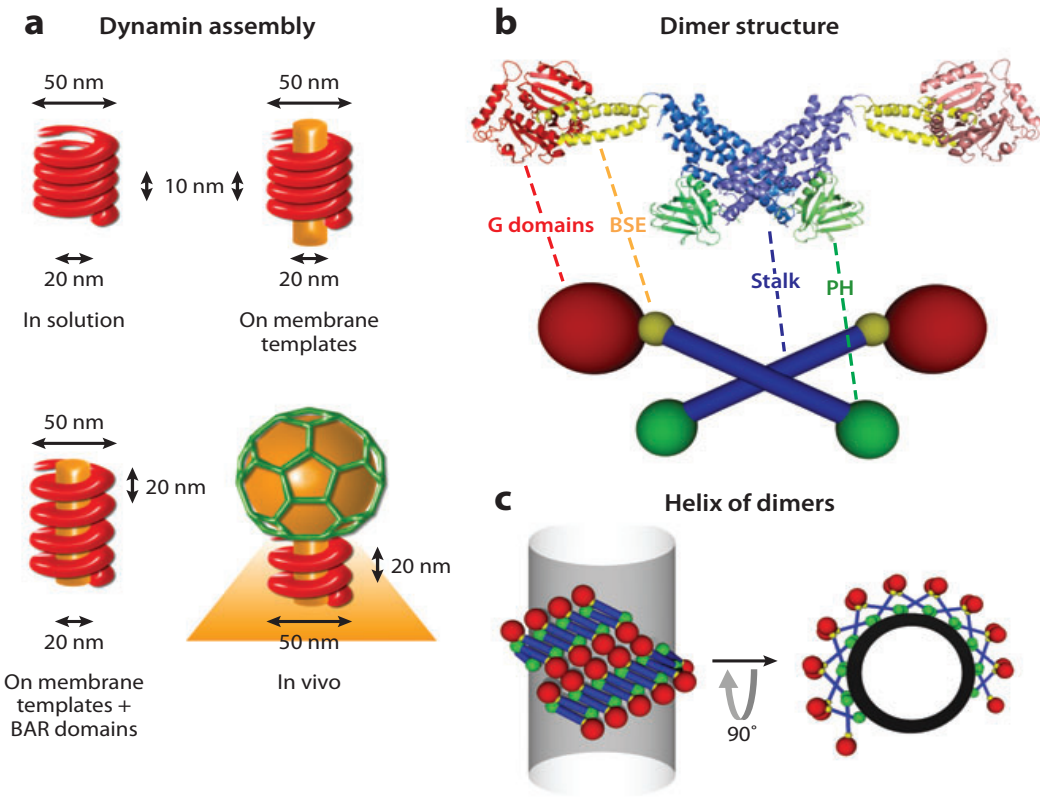
Membrane fusion and fission are *mediated by proteins*, e.g. SNAREs for fusion, and dynamin for fission.

Protein-mediated membrane fission

Membrane fission: A process by which a bud separates from a lipid membrane, and which is mostly mediated by (dynamin-family) proteins.



Self-assembly of dynamin around the neck of a budding vesicle



What we know:

- ✧ Existence as tetramer in solution
- ✧ Self-assembly (into rings/helices)
- ✧ Inner diameter of helices independent from membrane template.
- ✧ Membrane tube is constricted by PH domain insertion of dynamin rings.
- ✧ Constriction is necessary, but insufficient for completing fission.

Nat. Rev. Mol. Cell Biol. 5, 133 (2004)
Annu. Rev. Cell Dev. Biol. 27, 79 (2011)
Annu. Rev. Biochem. 81, 407 (2012)
Annu. Rev. Biophys. 42, 629 (2013)

Questions:

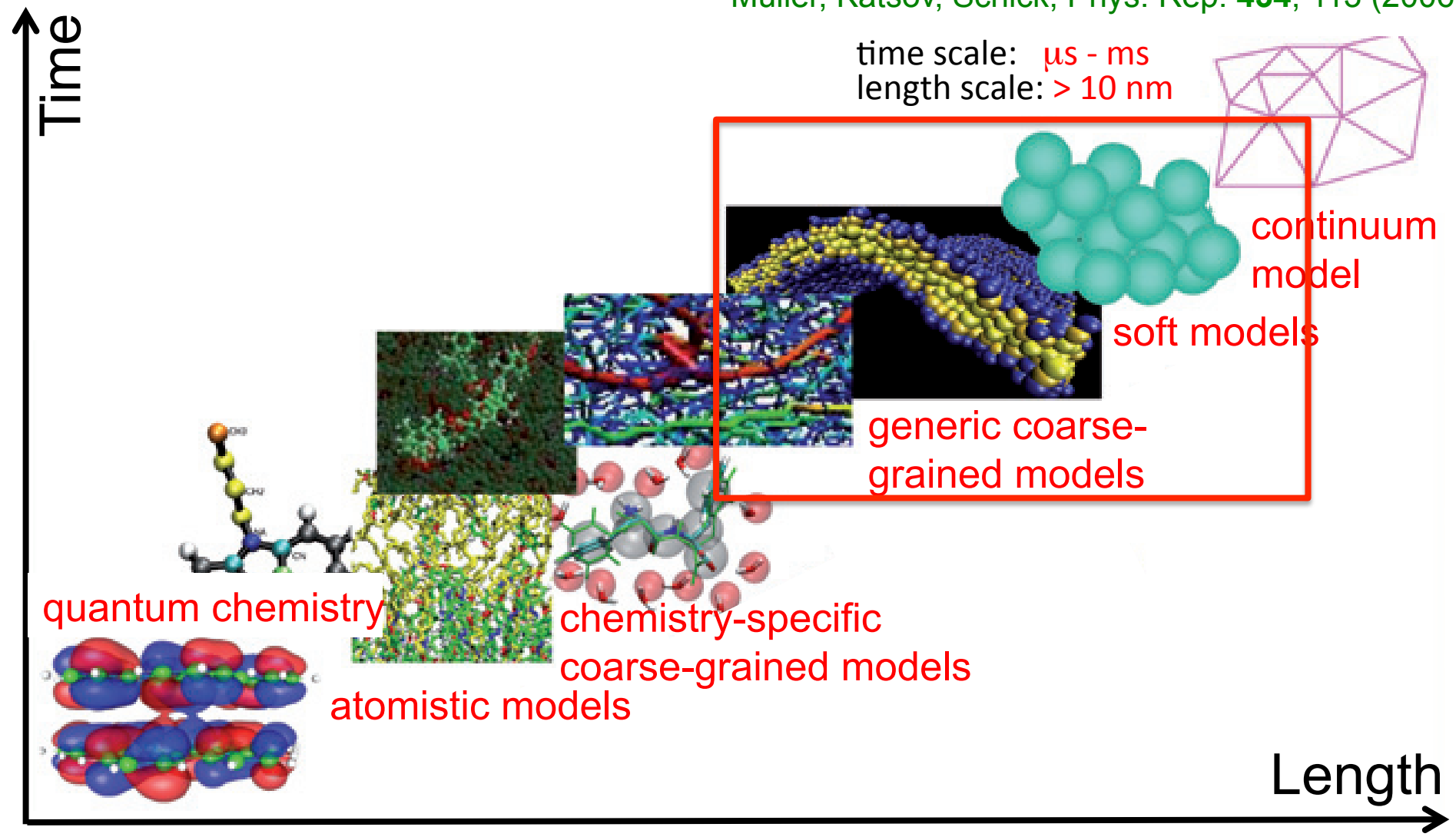
1. *Role* of dynamin's *constriction*.
2. Pathway and *free energy landscapes* of fission process.

Goals:

Study and understand dynamin's role in membrane fission via *computer simulation*.

Characteristic length and time scales in soft matter

Müller, Katsov, Schick, Phys. Rep. **434**, 113 (2006)



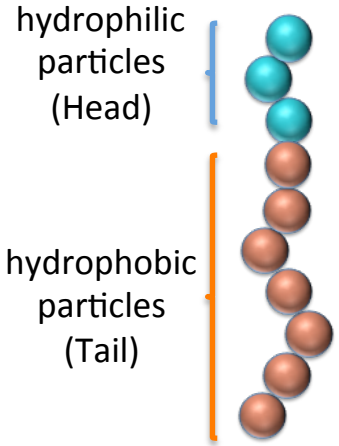
local chemical properties
energy dominance

⟺

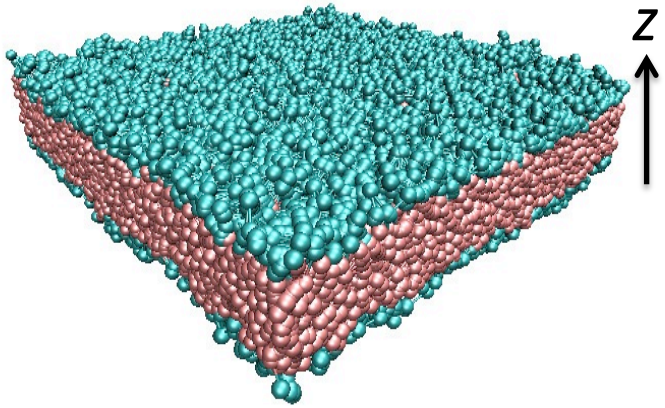
scaling behavior
entropy dominance

A soft, solvent-free model for lipid membrane

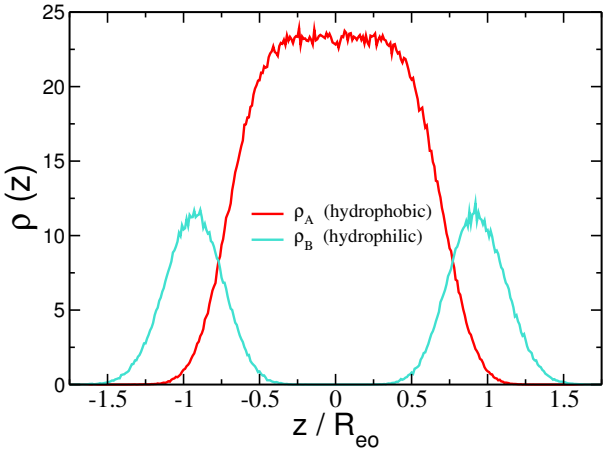
❑ Coarse-grained model for lipid membrane



lipid bilayer



density distribution



$$\mathcal{H} = \mathcal{H}_b + \mathcal{H}_{nb}$$

Hömberg and Müller, J. Chem. Phys. **132**, 155104 (2010)

- Harmonic springs and bending angle potentials

$$\frac{\mathcal{H}_b}{k_B T} = \sum_i \frac{k_s}{2}(\mathbf{r}_{i+1} - \mathbf{r}_i)^2 + \sum_i k_b(1 - \cos\theta_i)$$

- "density-functional theory"-based description for H_{nb}

$$\frac{\mathcal{H}_{nb}}{k_B T} = \int \frac{d\mathbf{r}}{R_{eo}^3} \hat{\rho}_\alpha(\mathbf{r}) \left[\frac{\upsilon_{\alpha\beta}}{2} \bar{\rho}_{2\beta}(\mathbf{r}) + \frac{\omega_{\alpha\beta\gamma}}{3} \bar{\rho}_{3\beta}(\mathbf{r}) \bar{\rho}_{3\gamma}(\mathbf{r}) \right]$$

$$\hat{\rho}_\alpha(\mathbf{r}) = \frac{R_{eo}^3}{N} \sum_i \delta(\mathbf{r}_i - \mathbf{r}) \delta_{\alpha t(i)}$$

$$\bar{\rho}_{m\alpha}(\mathbf{r}) = \frac{R_{eo}^3}{N} \sum_i w_m(|\mathbf{r}_i - \mathbf{r}|) \delta_{\alpha t(i)}$$

$\upsilon_{\alpha\beta}, \omega_{\alpha\beta\gamma}$: thermodynamic properties

w_m : local structures (packing)

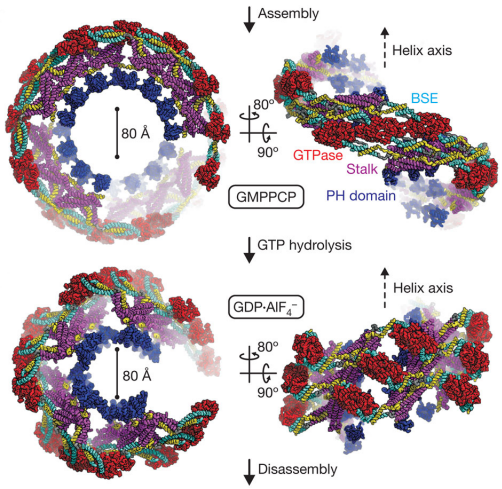
- Particle-based simulation Implementation: MD, MC, DPD, …

- Capabilities of the model
  - ✧ Self-assembly of lipids
  - ✧ Mechanical properties
  - ✧ Main phase transitions

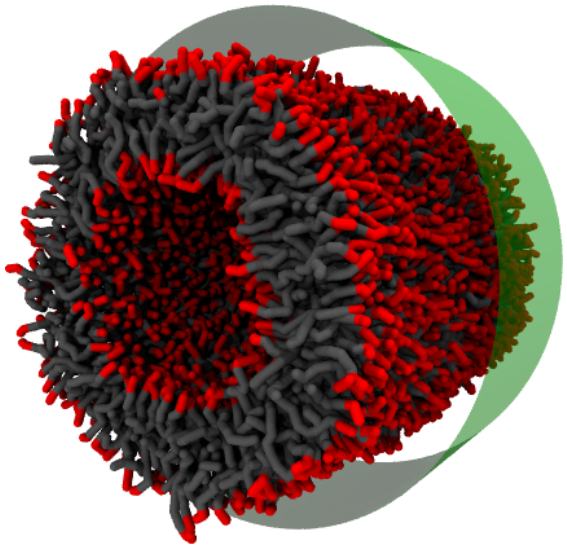
Two coarse-grained descriptions for dynamin

❑ A very crude model for dynamin constriction

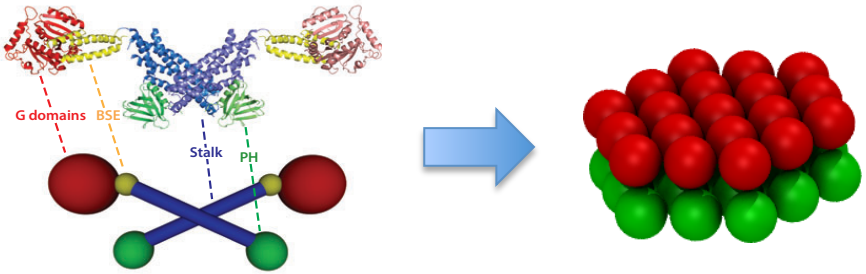
constriction by *dynamin coating* ⟹ constriction by *a cuff potential*

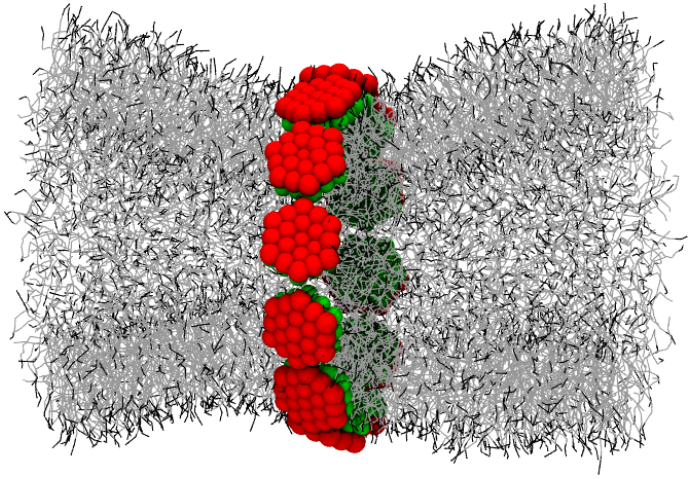


Ford et al., *Nature*, **477**, 561 (2011)



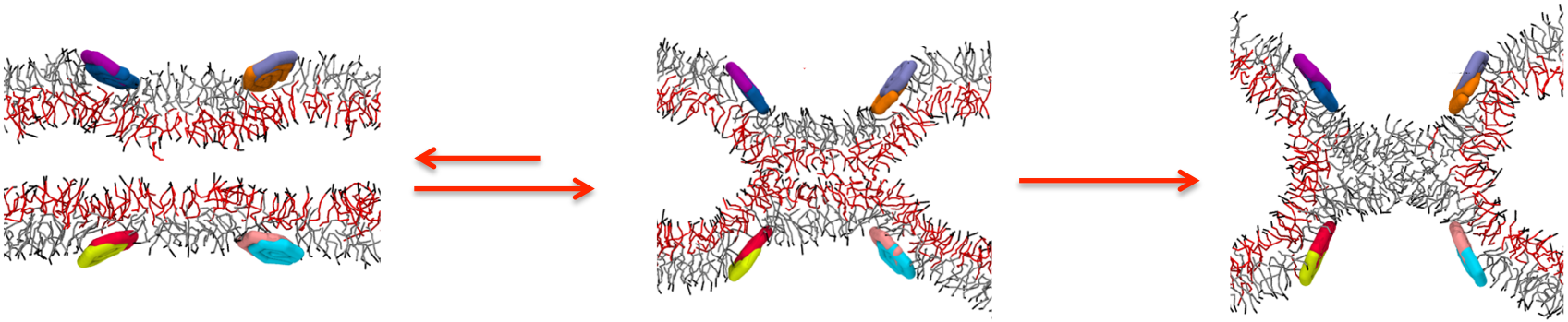
❑ A more realistic model of dynamin (constriction + PH domain insertion)





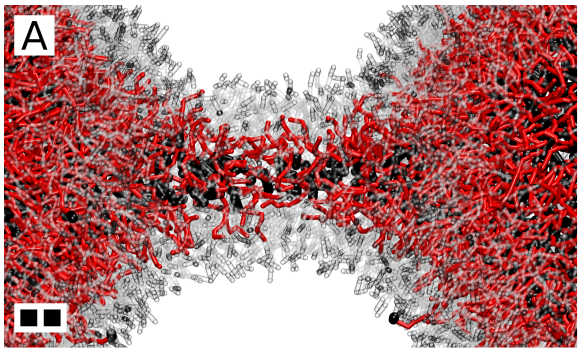
Fuhrmans and Müller, Soft Matter **11**, 1464 (2015)

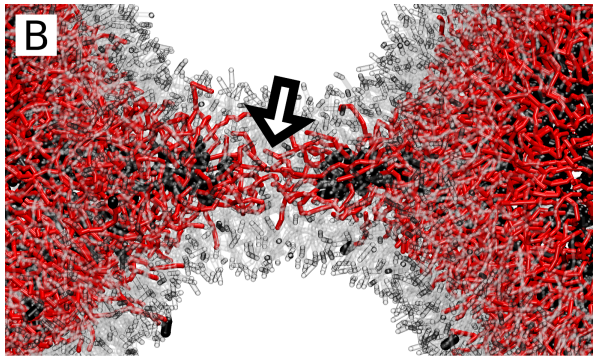
Part I: Role of dynamin's constriction

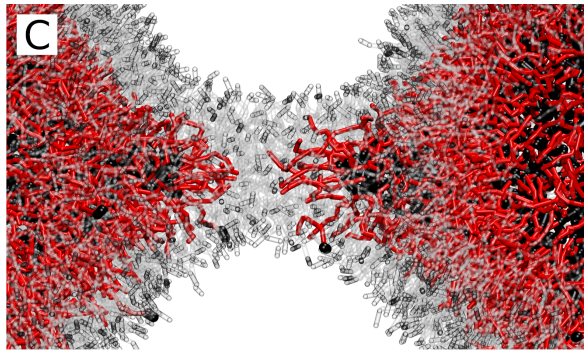


hemi-fission

Dynamin's constriction as a cuff potential







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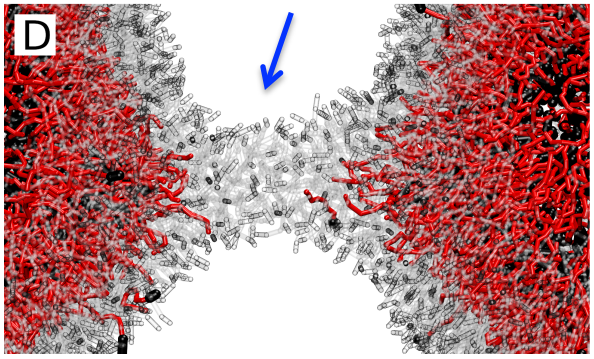
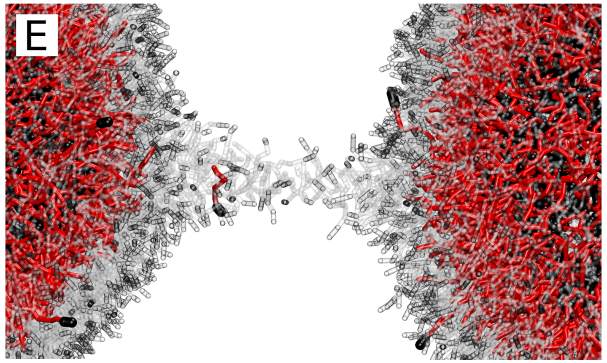
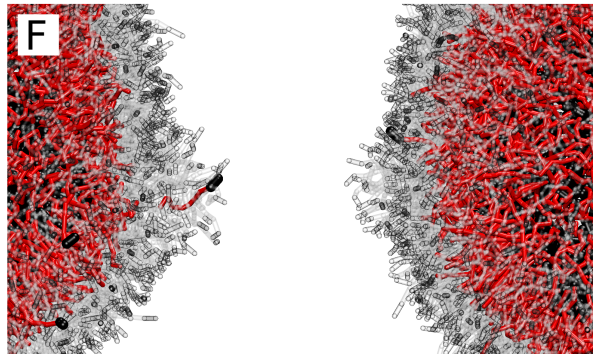
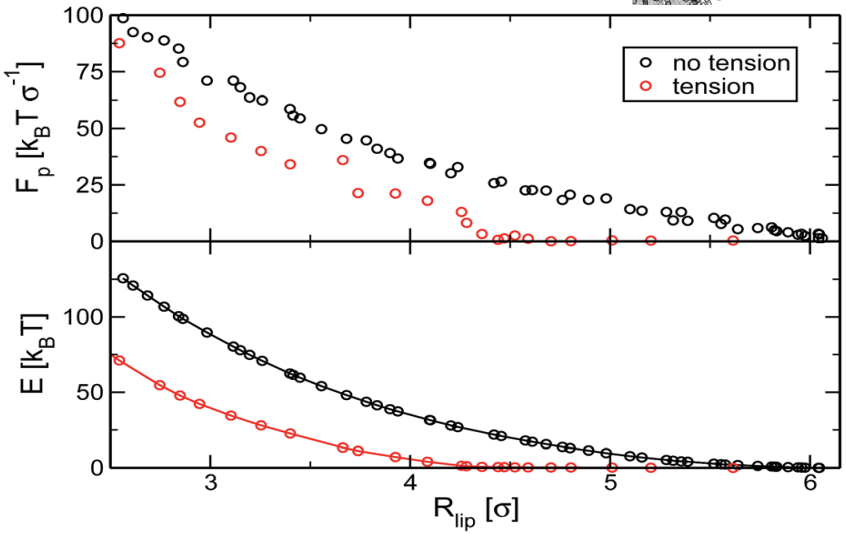




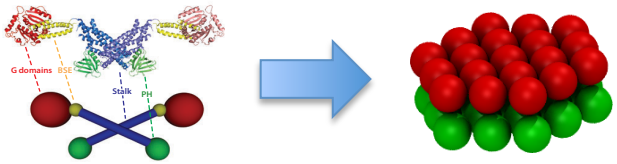




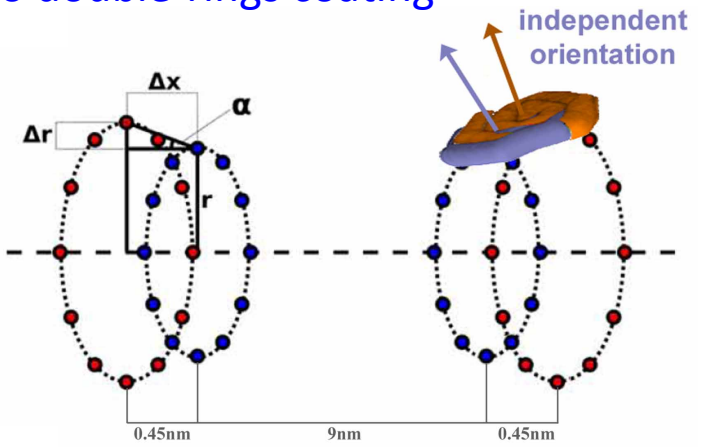
- non-leaky fission through formation of a worm-like micelle (*hemi-fission*) intermediate
- very *high* free-energy cost (about 150 $k_B T$) for the constriction.
- *two* free-energy barriers involved: (i) formation of the worm-like micelle; (ii) rupture of the micelle.

Hemi-fission from a model with two double-dynamin rings

- Model of dynamin

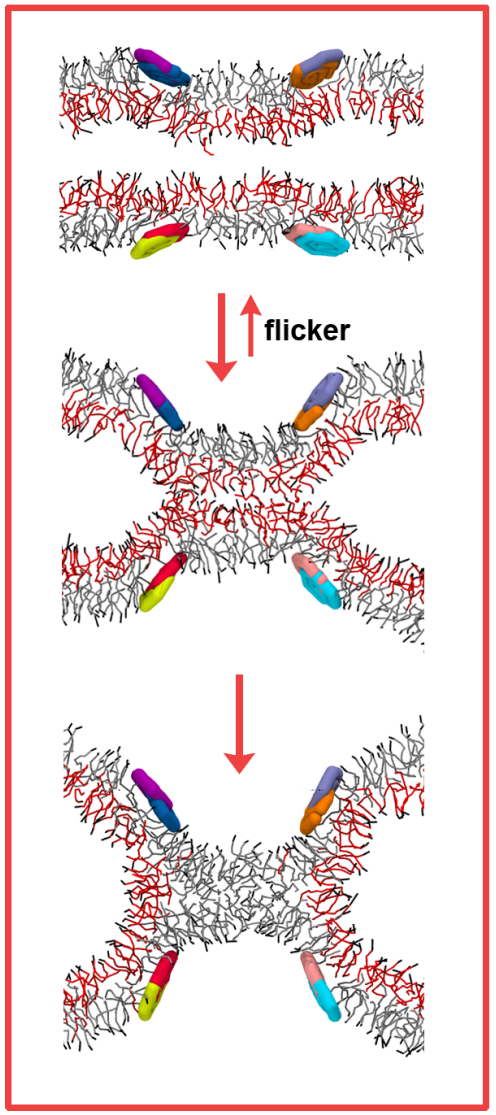


- Two double-rings coating



Δr ≠ 0

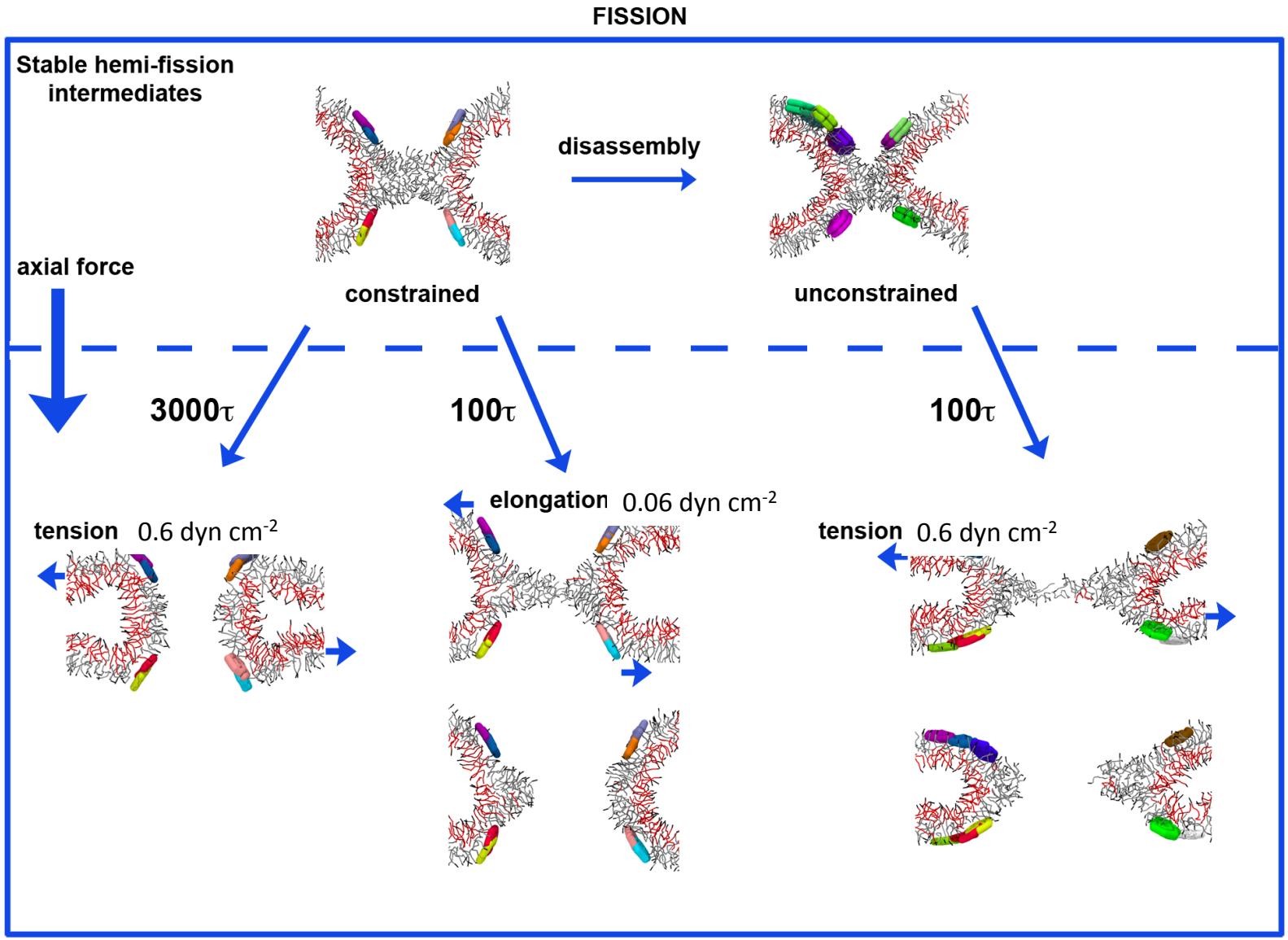
HEMI-FISSION



no hemi-fission intermediate formation
only thinning of membrane tube

Nature 524, 109 (2015)

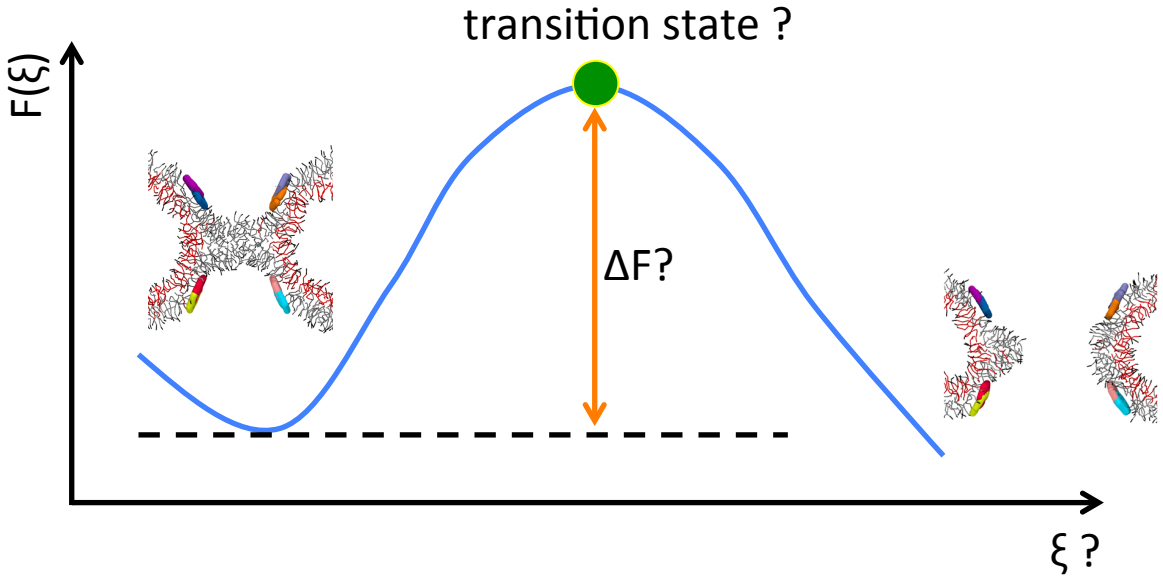
Completion of fission via rupture of the hemi-fission intermediate



The hemi-fission state is *(meta)stable*, i.e., rupture of hemi-fission state requires external effects.

Nature 524, 109 (2015)

Part II: Pathway and free-energy landscape of rupturing the hemi-fission state (Stability of the hemi-fission state)



Free energy calculations: with explicit reaction coordinates

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$$F(\xi) = -k_{\mathrm{B}}T \ln \int d\mathbf{r}^n e^{-H(\{\mathbf{r}^n\})/k_B T} \delta[\hat{\xi} - \xi] = -k_{\mathrm{B}}T \ln P(\xi) - k_{\mathrm{B}}T \ln Z(n, V, T)$$

ξ: reaction coordinate

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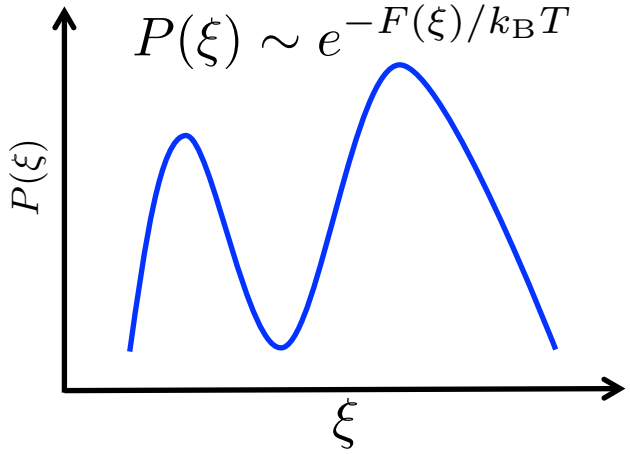
- Direct sampling in a *conventional* ensemble



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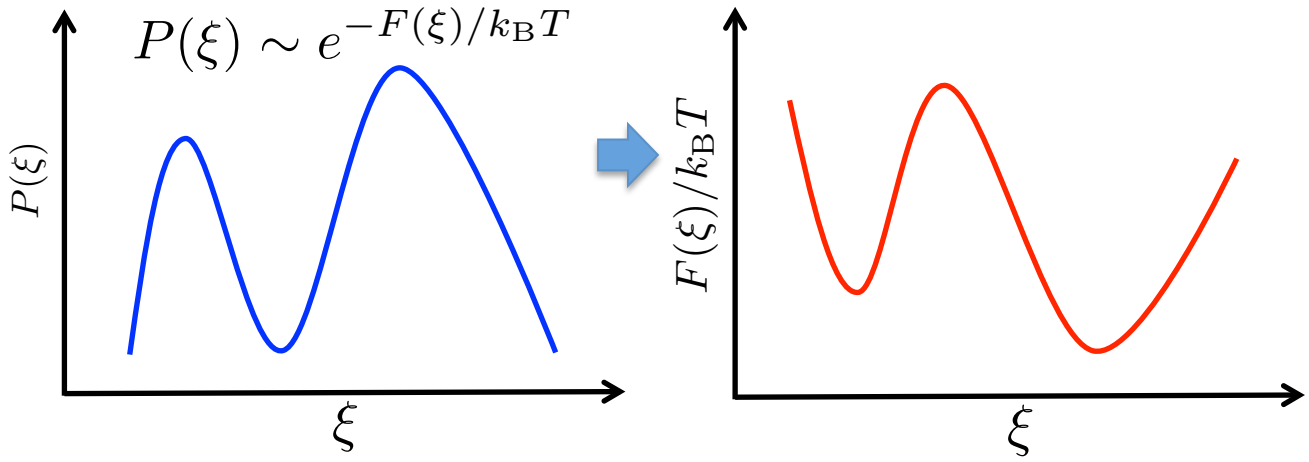

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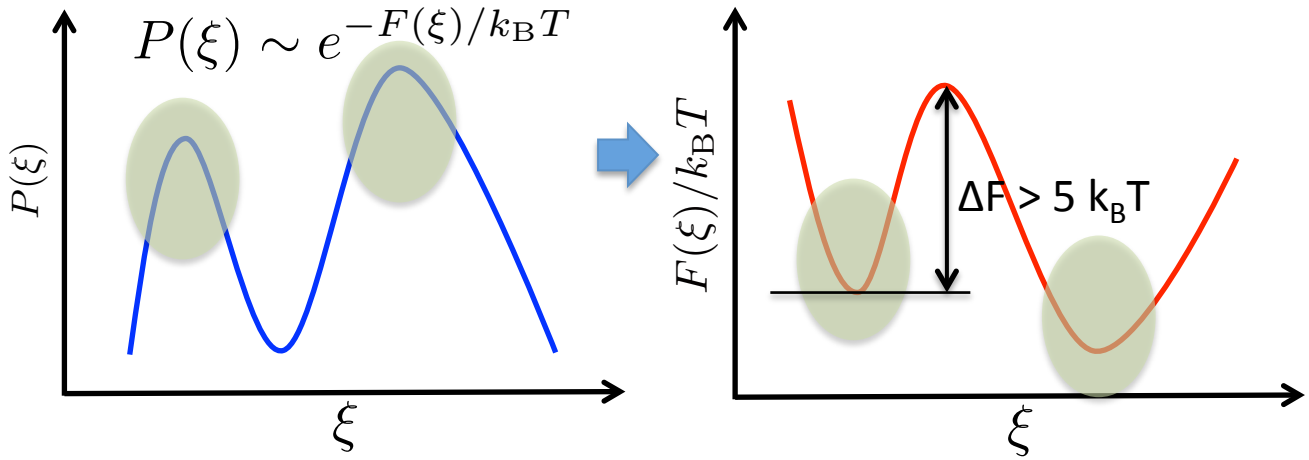

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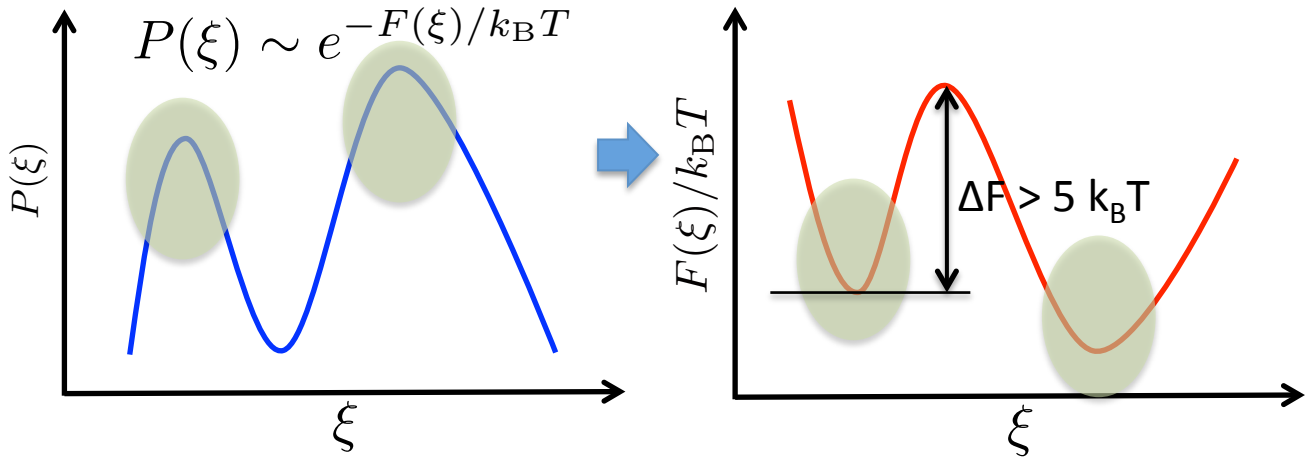

Sampling problem in rare event

non-ergodic in a case with *large* free energy barrier (> 5 k_BT).

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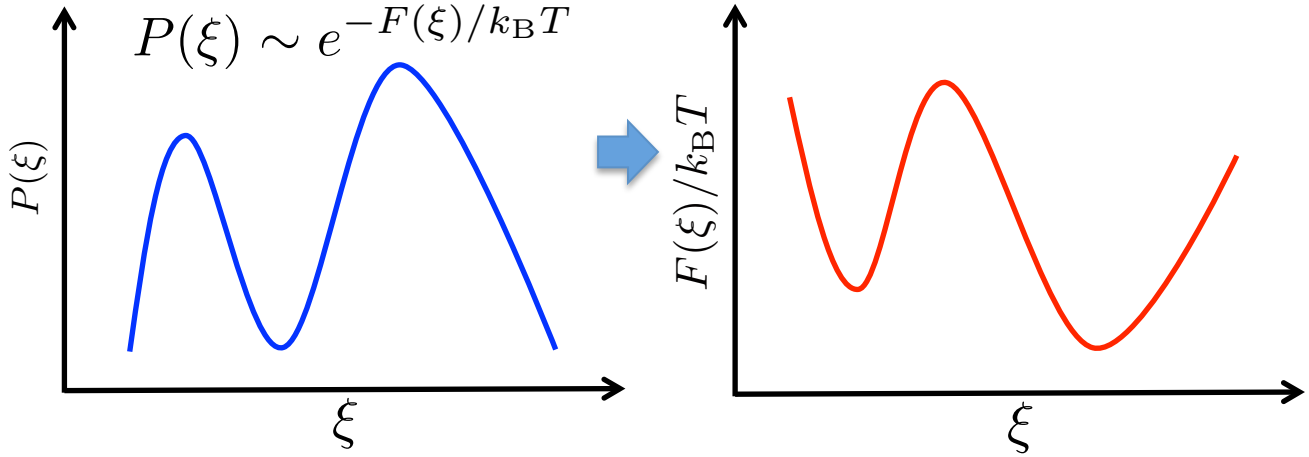

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- Biased sampling in an *extended* ensemble

➢ Umbrella sampling: enhancing sampling over the reaction coordinate by *biasing* the Hamiltonian

$$H_{\mathrm{us}}(\mathbf{r}^n) = H(\mathbf{r}^n) + W[\xi(\mathbf{r}^n)] \longrightarrow F(\xi) = -k_{\mathrm{B}}T \ln P_{\mathrm{us}}(\xi) - W(\xi) + const.$$

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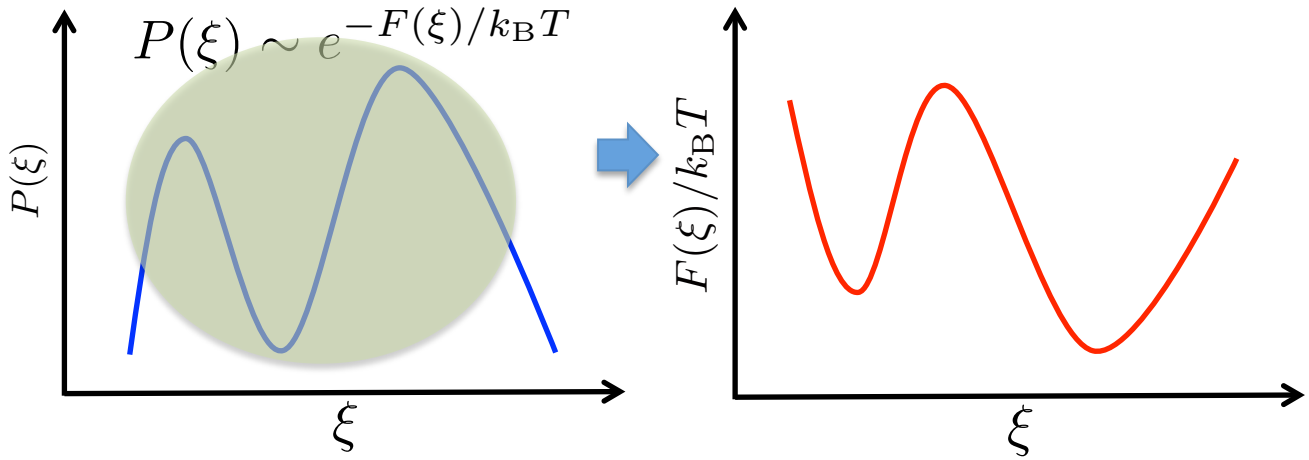

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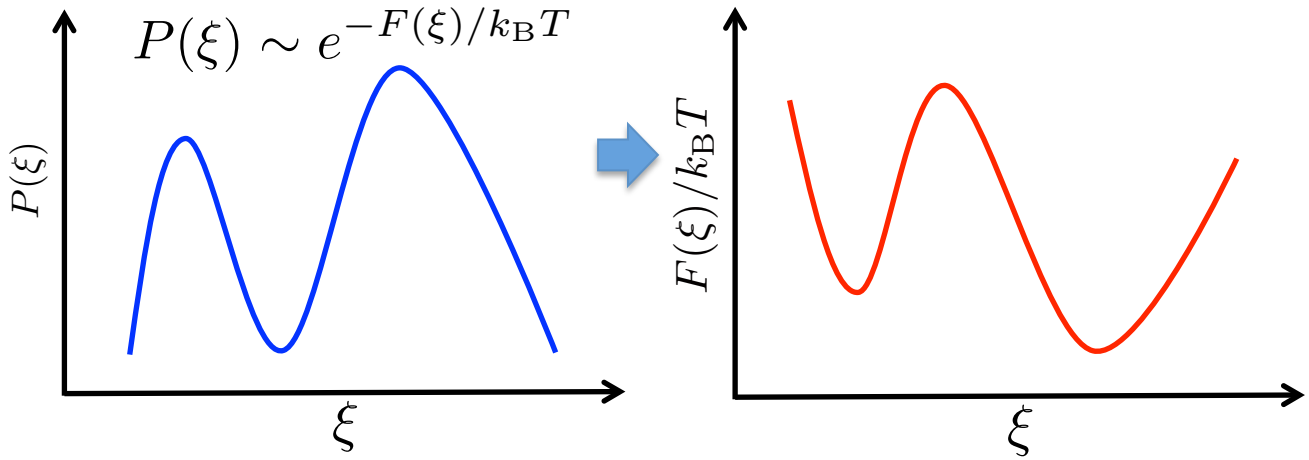

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$$P_{\mathrm{fh}}(\xi) \sim \int d\mathbf{r}^n e^{[-H(\mathbf{r}^n)+F(\hat{\xi})]/k_{\mathrm{B}}T} \delta[\hat{\xi} - \xi]$$
$$\sim e^{-F(\xi)/k_{\mathrm{B}}T} e^{F(\xi)/k_{\mathrm{B}}T} = O(\xi^0)$$

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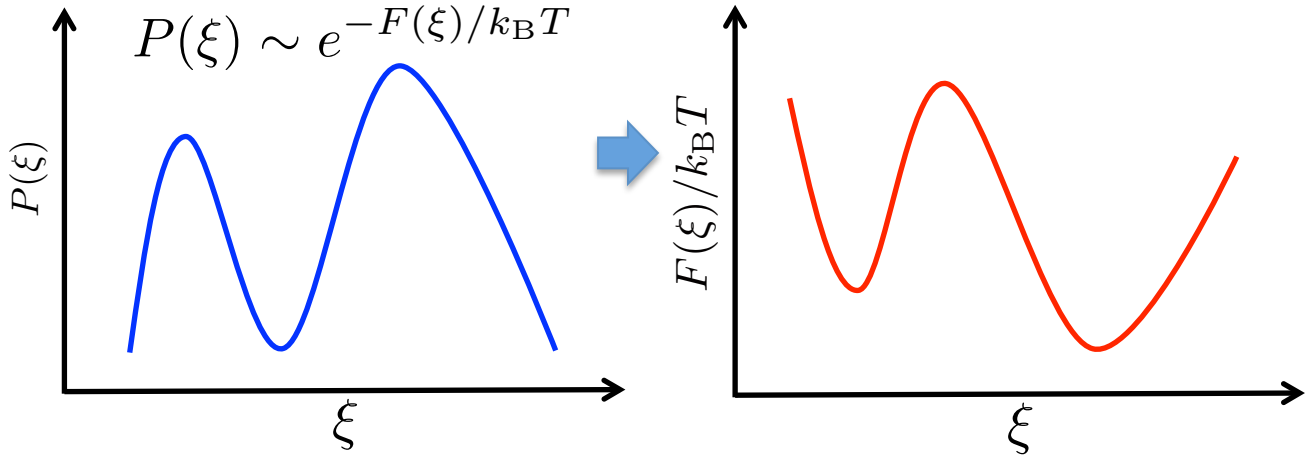

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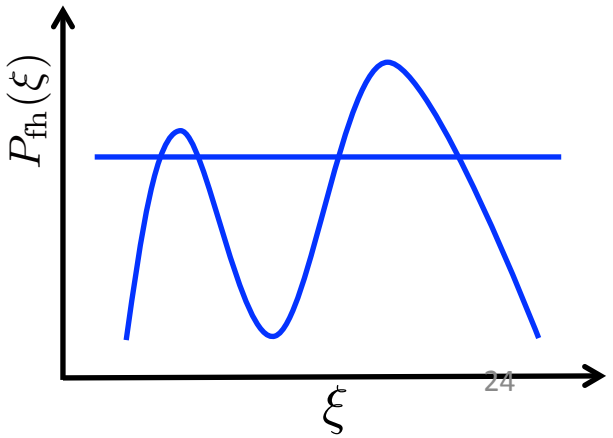
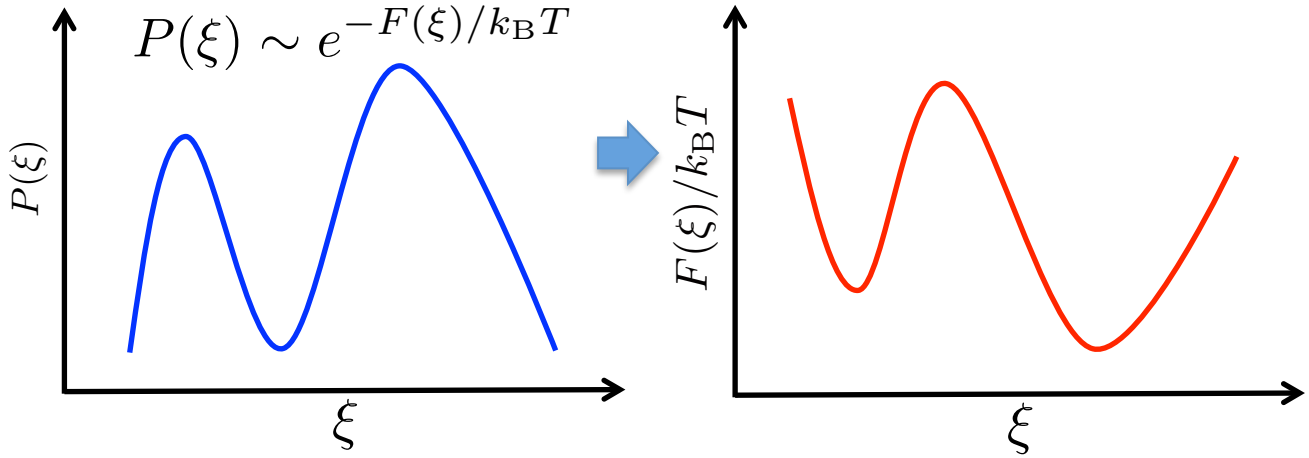


Free energy calculations: with explicit reaction coordinates

$$F(\xi) = -k_{\mathrm{B}}T \ln \int d\mathbf{r}^n e^{-H(\{\mathbf{r}^n\})/k_B T} \delta[\hat{\xi} - \xi] = -k_{\mathrm{B}}T \ln P(\xi) - k_{\mathrm{B}}T \ln Z(n, V, T)$$

ξ: reaction coordinate

- Direct sampling in a *conventional* ensemble



Sampling problem in rare event

non-ergodic in a case with *large* free energy barrier (e.g. > 5 k_BT).

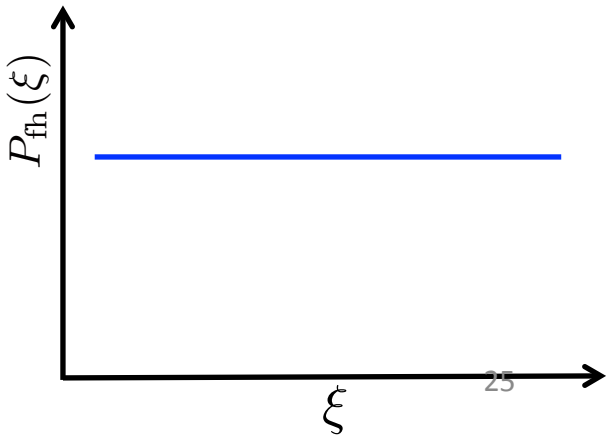
- Biased sampling in an *extended* ensemble

- Umbrella sampling: enhancing sampling over the reaction coordinate by *biasing* the Hamiltonian

$$H_{\mathrm{us}}(\mathbf{r}^n) = H(\mathbf{r}^n) + W[\xi(\mathbf{r}^n)] \longrightarrow F(\xi) = -k_{\mathrm{B}}T \ln P_{\mathrm{us}}(\xi) - W(\xi) + const.$$

- Flat-histogram method: when the biased potential is the free energy

$$P_{\mathrm{fh}}(\xi) \sim \int d\mathbf{r}^n e^{[-H(\mathbf{r}^n)+F(\hat{\xi})]/k_{\mathrm{B}}T} \delta[\hat{\xi} - \xi]$$
$$\sim e^{-F(\xi)/k_{\mathrm{B}}T} e^{F(\xi)/k_{\mathrm{B}}T} = O(\xi^0)$$



- Goal of the method is to obtain F(ξ) by realizing a flat-histogram of P(ξ).

Free energy calculations: with explicit reaction coordinates

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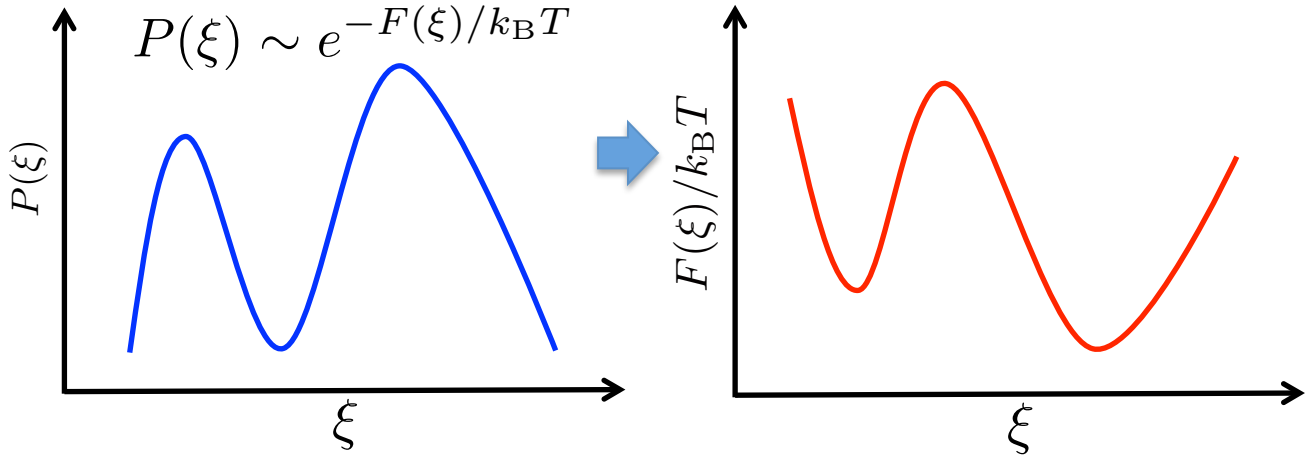

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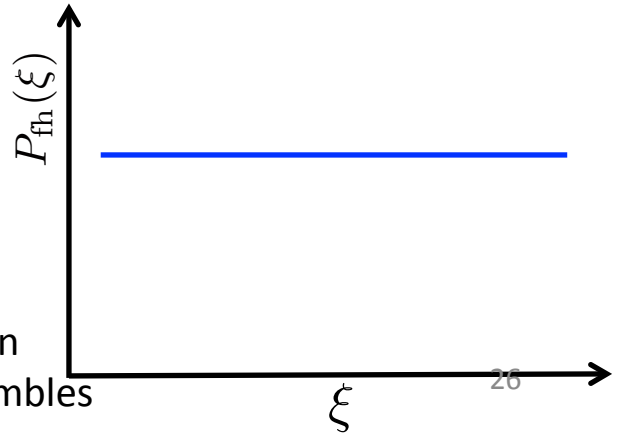


Wang-Landau (WL) sampling

Monte Carlo simulation
convenient for any ensembles

Metadynamics

molecular dynamics simulation
not easy for grand-canonical ensembles

A practical recipe for Wang-Landau sampling

Goal: to derive a Metropolis acceptance criterion in Wang-Landau sampling in a general sense.

Methodology:

Wang and Landau, Phys. Rev. Lett. 86, 2050 (2001)
Ganzenmueller and Camp, J. Chem. Phys. 127, 154594 (2007)

(1) The microscopic state distribution in Wang-Landau sampling

$$1 = p_{WL}(\xi) = \int p_{WL}(\Gamma,\xi)d\Gamma \quad ?$$

Γ: microstate ξ: reaction coordinate

$$p_{WL}(\Gamma,\xi) = \frac{p_0(\Gamma,\xi)}{p(\xi)} \Rightarrow p_{WL}(\xi) = \int p_{WL}(\Gamma,\xi)d\Gamma = \int \frac{p_0(\Gamma,\xi)}{p(\xi)}d\Gamma = 1$$

(2) The acceptance criterion from detailed balance

$$p_{WL}(\Gamma_o,\xi_o)acc(o\to n) = p_{WL}(\Gamma_n,\xi_n)acc(n\to o)$$

$$acc(o\to n) = \min\left[1, \frac{p_{WL}(\Gamma_n,\xi_n)}{p_{WL}(\Gamma_o,\xi_o)}\right]$$

Example: $\xi = E$ in canonical ensemble

$$p_0(\Gamma_o,E_o) = \frac{V^N e^{-\beta E_o}}{N!\Lambda^{3N}Q_{NVT}}$$

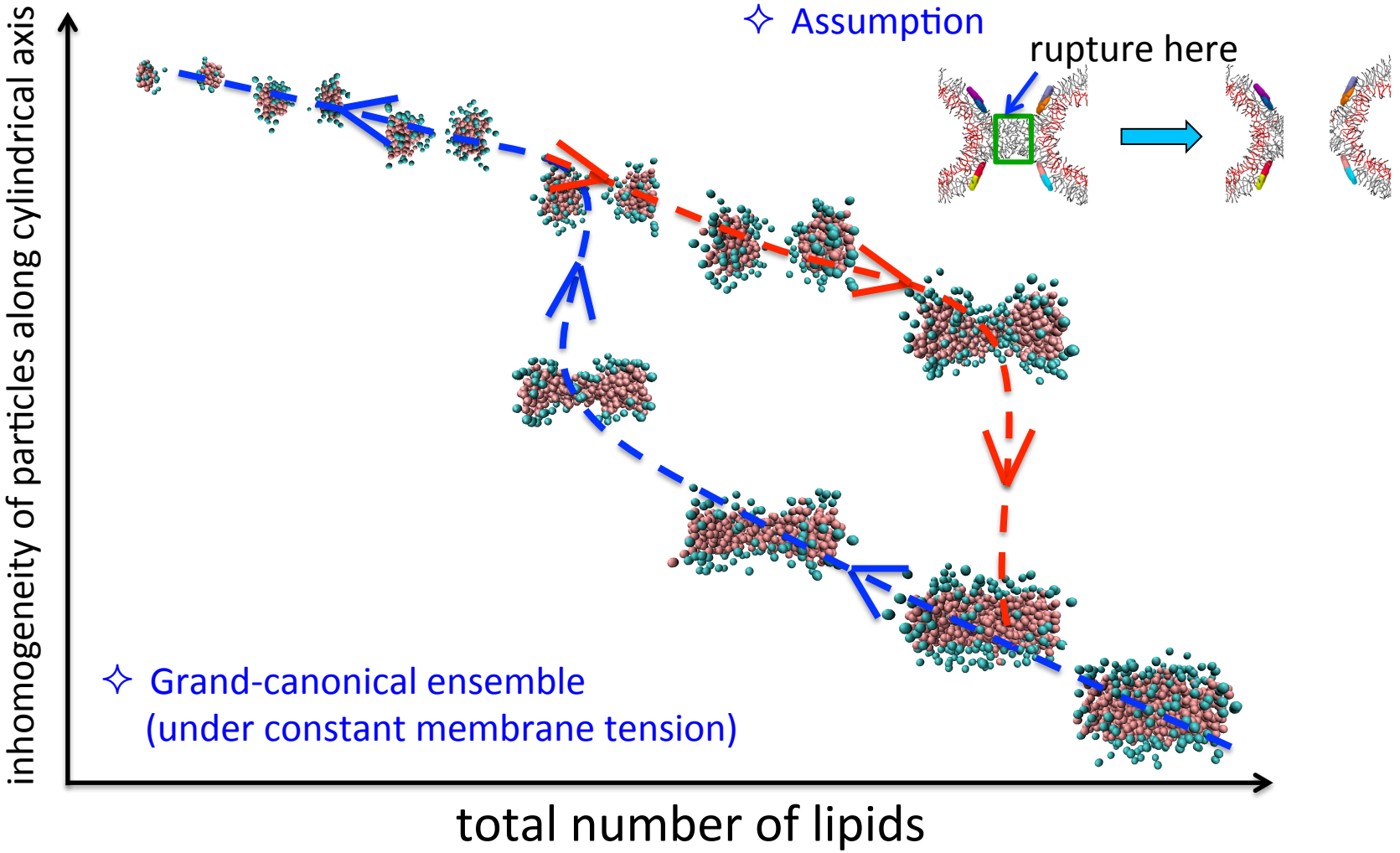
$$p(E_o) = \frac{V^N e^{-\beta E_o}\Omega(N,V,E_o)}{N!\Lambda^{3N}Q_{VNT}}$$

$$\Rightarrow p_{WL}(\Gamma_o,E_o) = \frac{p_0(\Gamma_o,E_o)}{p(E_o)} = \frac{1}{\Omega(N,V,E_o)}$$

$$acc(o\to n) = \min\left[1, \frac{\Omega(N,V,E_o)}{\Omega(N,V,E_n)}\right]$$

Microcanonical ensemble partition function is obtained from WL sampling in *canonical* ensemble.

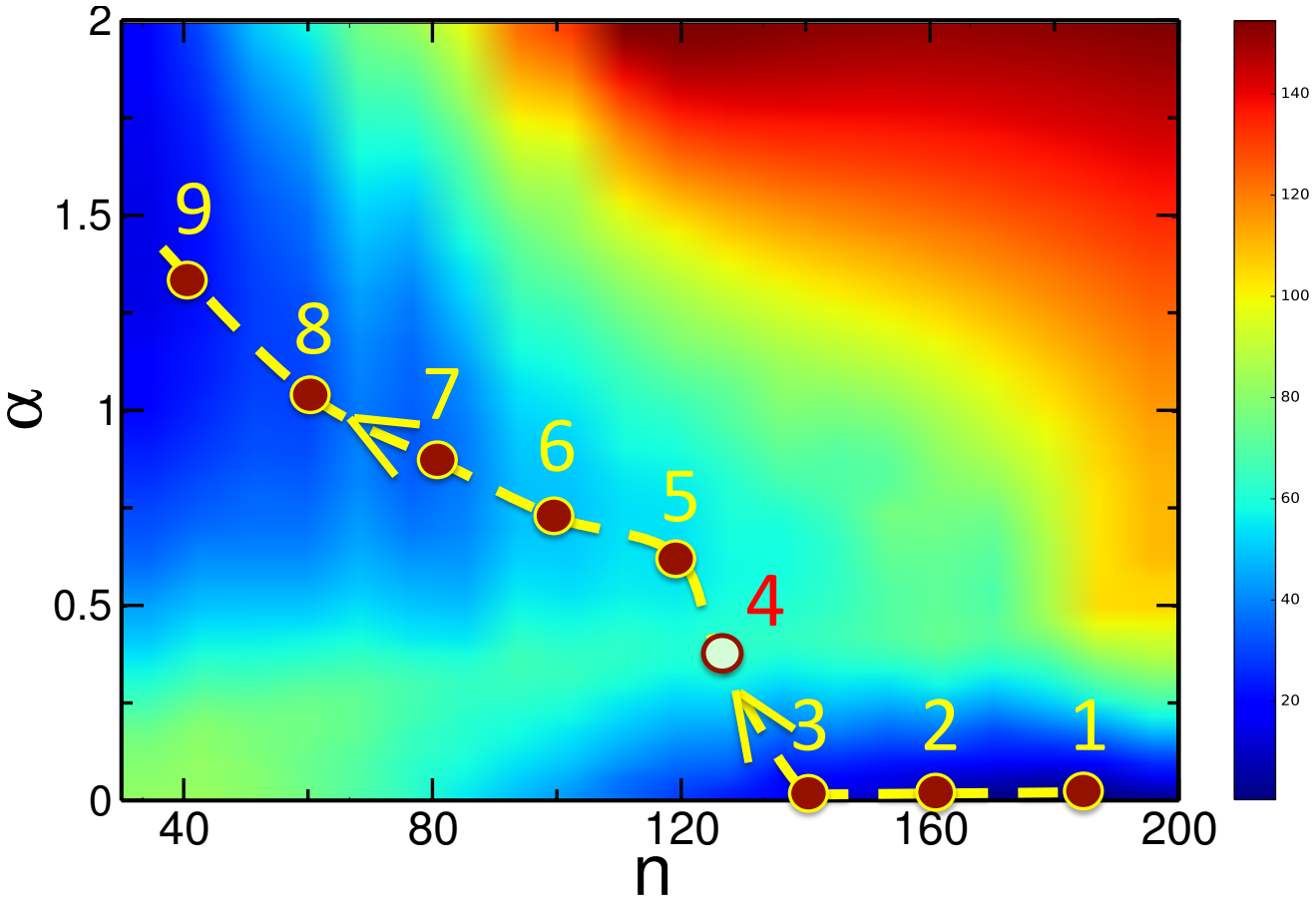
Identification of suitable reaction coordinates



- *Hysteresis* occurs if only one order parameter is used.
- One order parameter *isn't* sufficient.
- A *second* order parameter is identified as the inhomogeneity of particles along the cylindrical axis.

Free-energy landscape and transition path

- Projection of an intrinsic *high-dimensional* free-energy landscape to a *two-dimensional* one.

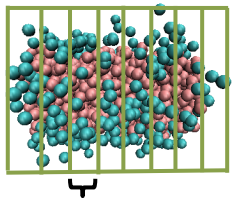


Reaction coordinates

n : total number of lipids

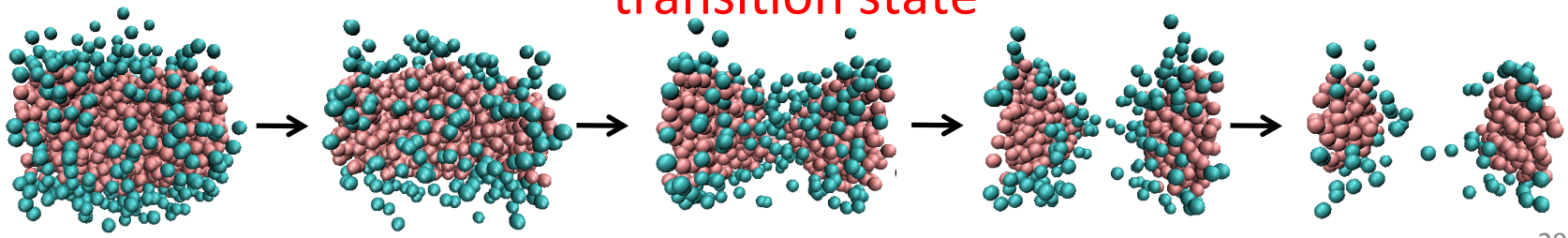
α : inhomogeneity of particles along cylinder axis, which is defined as:

$$\alpha = \frac{\langle N_i^2 \rangle - \langle N_i \rangle^2}{\langle N_i \rangle^2}$$

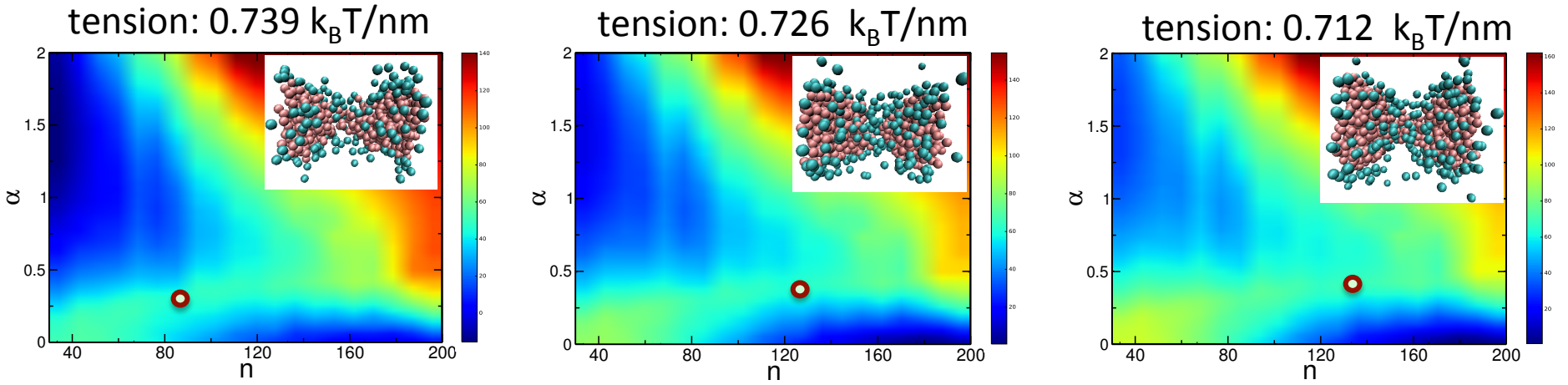


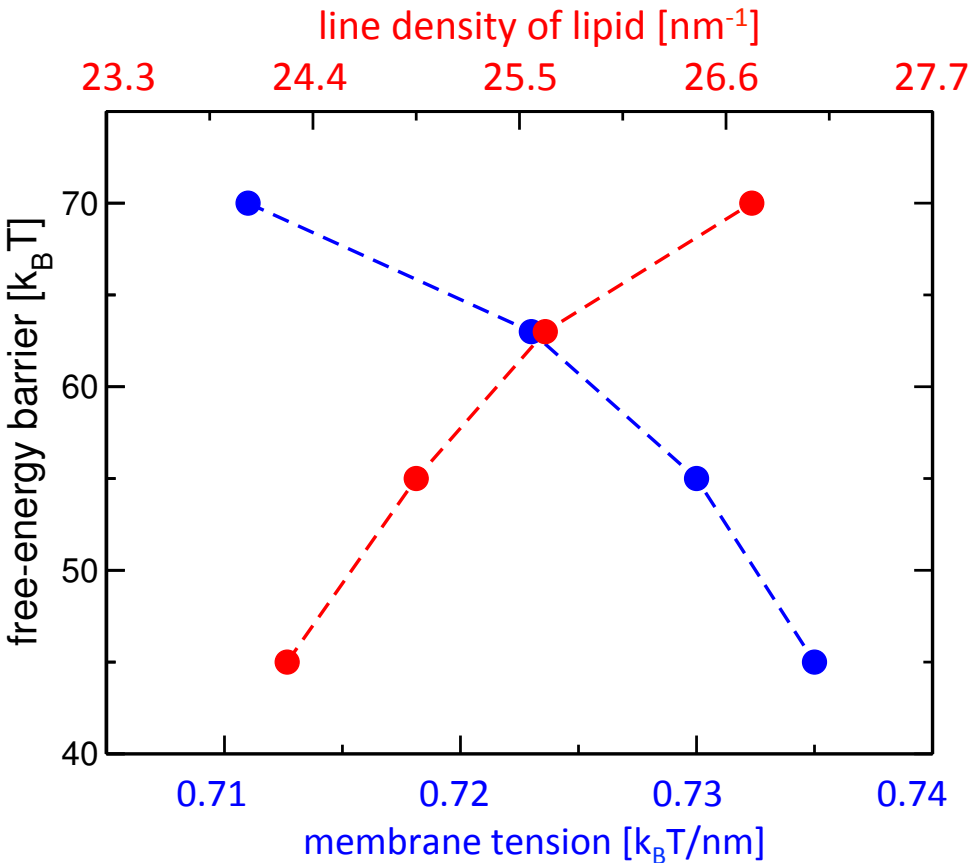
N_i particles in the i-th slab

transition state



Effect of tension on free-energy barriers





- The free-energy barrier of rupturing a hemi-fission intermediate is on order of tens of k_BT, dependent on tension.
- Increasing tension reduces the free-energy barrier of rupturing the hemi-fission state.

Free energy calculations: without explicit reaction coordinates

In general, identifying suitable reaction coordinates is very challenging.

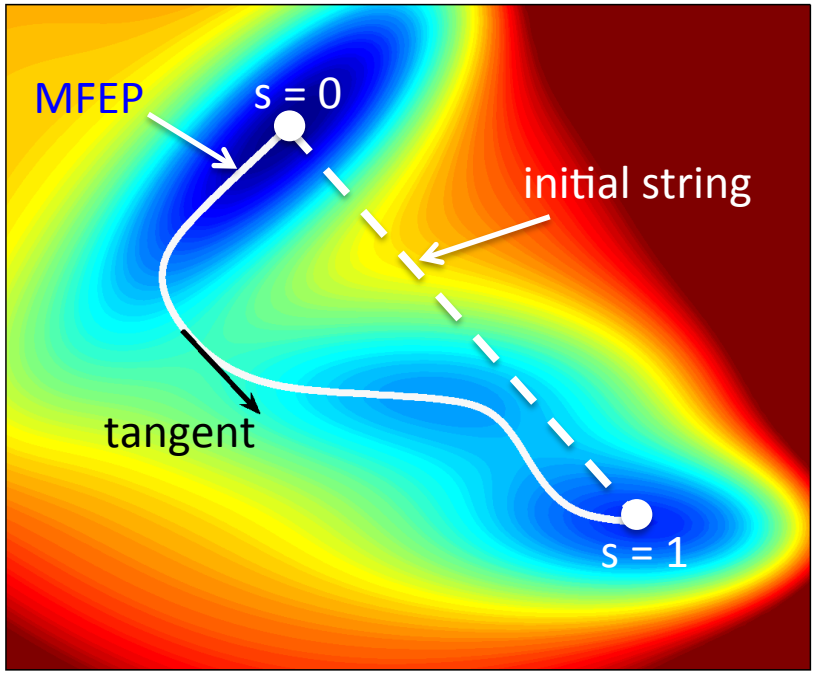
❑ String method for minimum free-energy path (MFEP)

(1) Theory

✧ The MFEP is defined by condition that the derivative *perpendicular* to the path *vanishes*.

$$\nabla_\perp \mathcal{F}[m] = \frac{\delta \mathcal{F}}{\delta m_s(\mathbf{r})} - \frac{\mathrm{d}m_s(\mathbf{r})}{ds} \frac{\int \mathrm{d}\mathbf{r} \frac{\delta \mathcal{F}}{\delta m_s(\mathbf{r})} \frac{\mathrm{d}m_s(\mathbf{r})}{\mathrm{d}s}}{\int \mathrm{d}\mathbf{r} \left(\frac{\mathrm{d}m_s(\mathbf{r})}{\mathrm{d}s} \right)^2} \overset{!}{=} 0$$

tangent term along the path



✧ A path: $m_s(\mathbf{r}), 0 < s < 1.$

✧ Free energy: $\mathcal{F}[m_s] = \int_0^s \mathrm{d}s \int \mathrm{d}\mathbf{r} \frac{\mathrm{d}m_s(\mathbf{r})}{\mathrm{d}s} \frac{\partial \mathcal{F}[m_s]}{\partial m_s(\mathbf{r})}$

✧ Transition state: $\mathrm{d}\mathcal{F}[m_s]/\mathrm{d}s = 0$

(2) Numerical implementation

✧ **Step 1:** $\Delta m_s(\mathbf{r}) = -\mu(\mathbf{r}|m_s)\Delta\varepsilon$

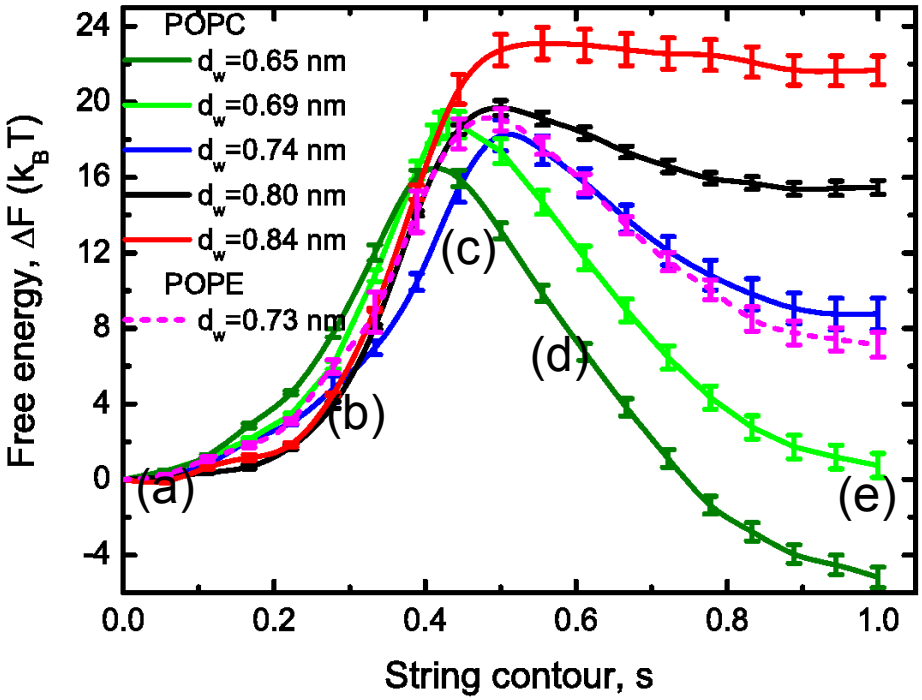
$$\mu(\mathbf{r}) = \frac{\delta \mathcal{F}}{\delta m_s(\mathbf{r})} \approx k_\mathrm{B}T\lambda \Big\langle m(\mathbf{r}) - \hat{m}(\mathbf{r}|\{\mathbf{r}\}) \Big\rangle_{\text{umbrella}}$$

✧ **Step 2:** re-parameterization of morphologies such that they are distributed *evenly* along the string.

E, Ren, Vanden-Eijnden, J. Chem. Phys. 126, 164103 (2007).
Müller, Smirnova, Marelli, Fuhrmans, Shi, Phy. Rev. Lett. 108, 228103 (2012).

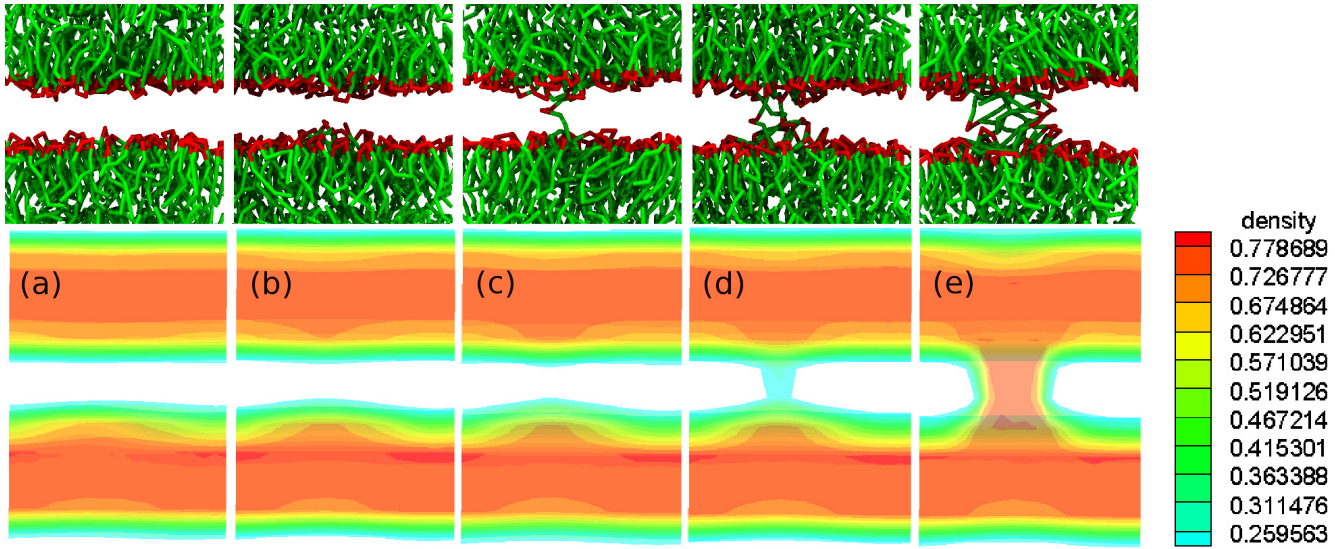
Application of string method to membrane fusion

- Model for lipid membrane: MARTINI model



- ✧ Degree of dehydration (thickness of bilayers) slightly modifies the free-energy barriers.
- ✧ It significantly affects the stability of the stalk morphology, higher dehyration favors formation of the stalk state.

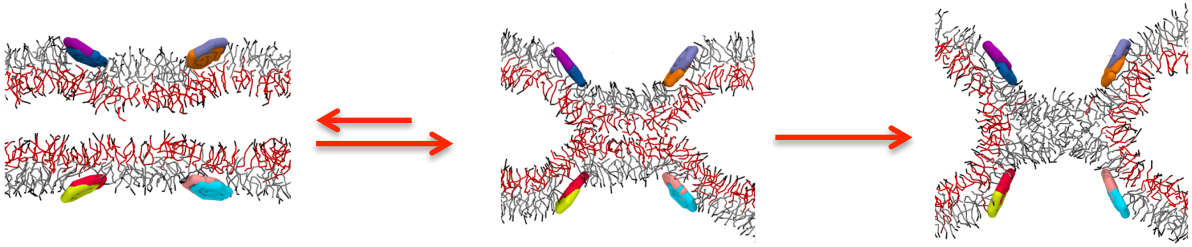
Smirnova, Müller, manuscript in preparation.



Summary

❑ Role of dynamin's constriction in fission

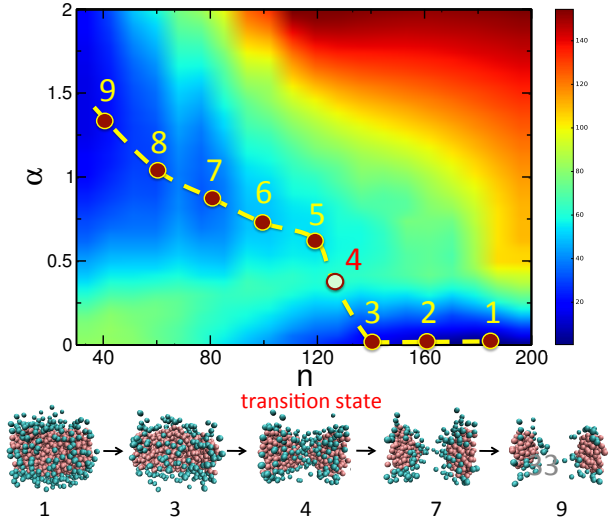
- ✓ The constriction model using a *cuff potential* gives rise to quite *large free energy cost* for constriction even before a topological change occurs.
- ✓ The more "realistic" model using *double-dynamin rings* leads to a formation of the (meta)stable *hemi-fission intermediate*.



Nature 524, 109 (2015)

❑ Free energy landscape of rupturing a hemi-fission state

- ✓ Two suitable *order parameters* has been identified.
- ✓ Two-dimensional free-energy landscape is calculated.
- ✓ Increasing membrane tension lowers the free-energy barrier.



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Thanks for your attention!