Eukaryotic cell polarity and protein sorting

Andrea Gamba

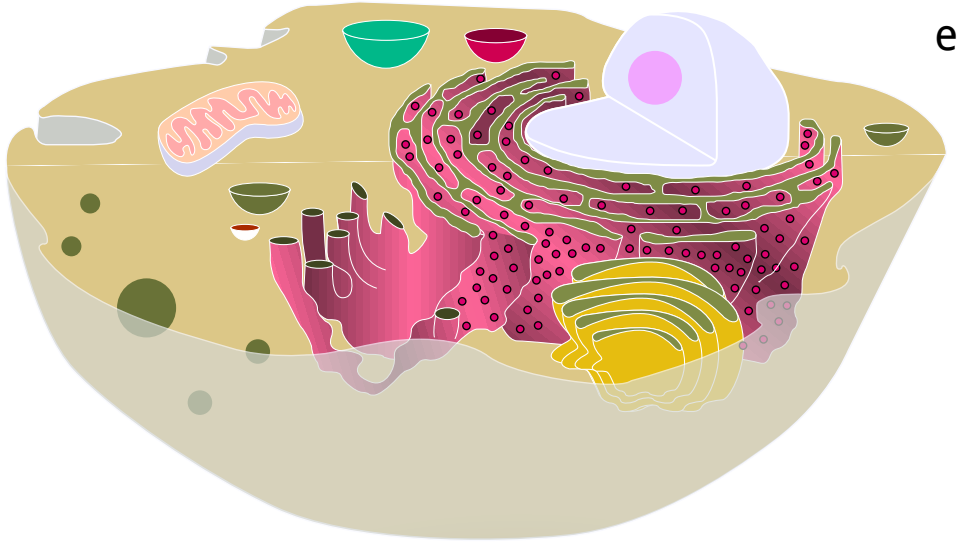
POLITECNICO
DI TORINO

Landau Institute, April 27, 2018

Plan of the talk

- Membrane identity in eukaryotic cells
- How membrane identity is created and maintained
- Molecular sorting
- Phenomenological theory
- Experimental validation

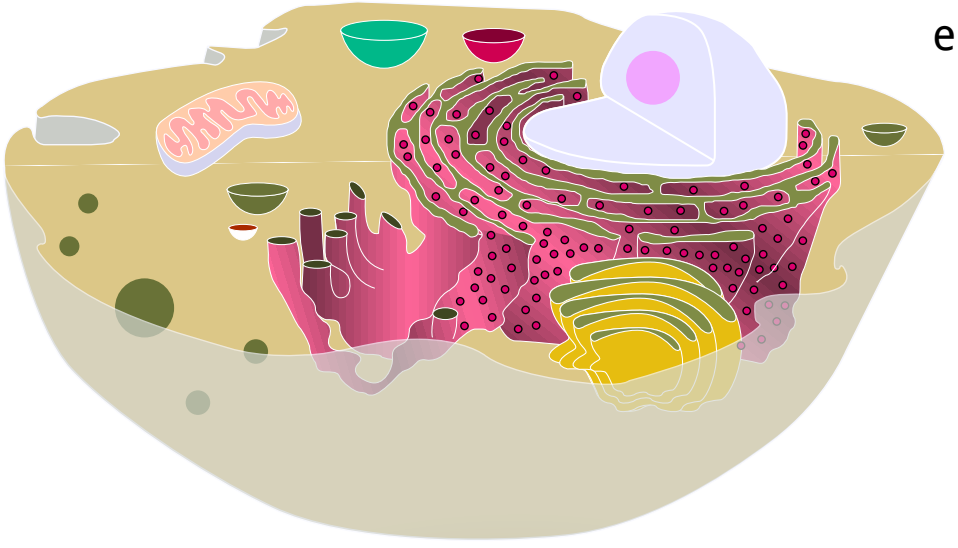
The eukaryotic cell



eukaryotic cell

R ≈ 10 μm

The eukaryotic cell

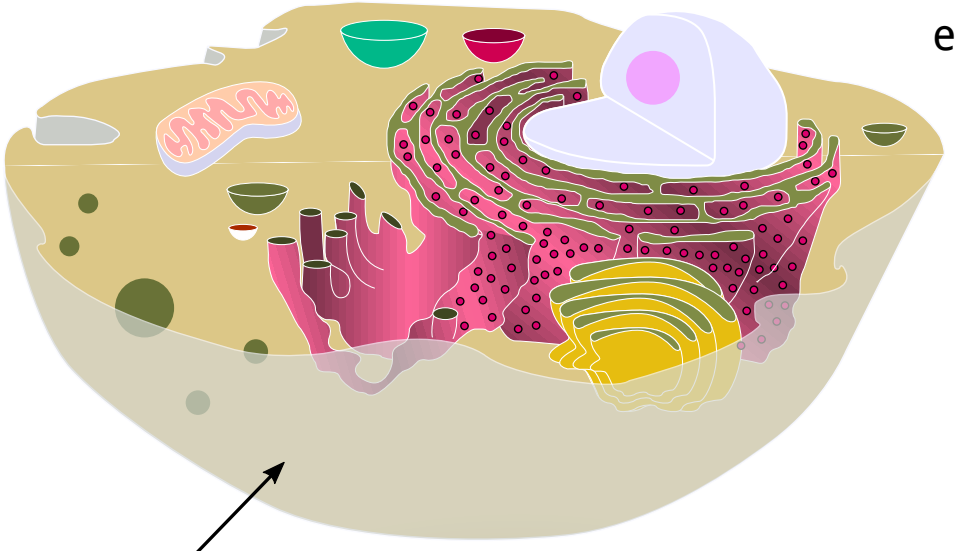


eukaryotic cell

prokaryotic cell (bacterium)

R ≈ 10 μm

The eukaryotic cell



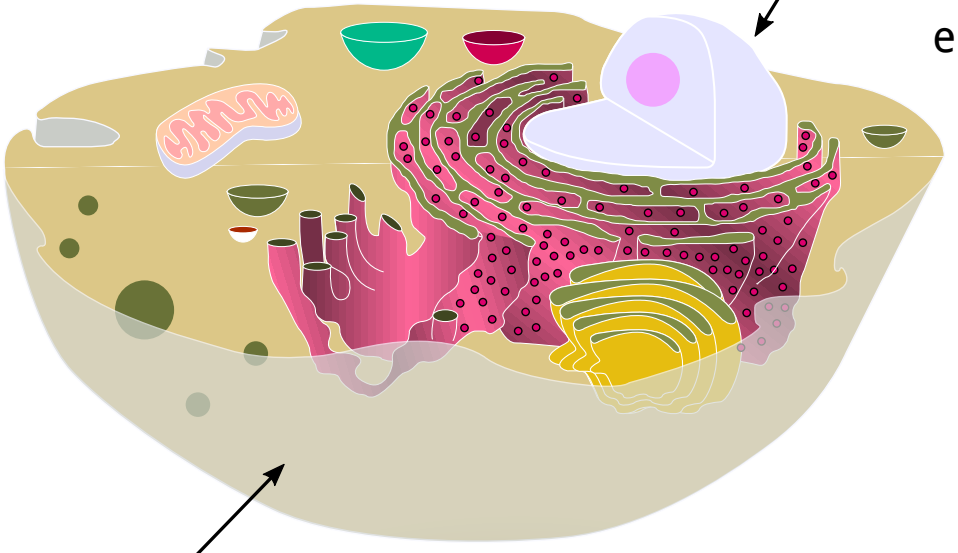
eukaryotic cell

plasmamembrane

prokaryotic cell (bacterium)

R ≃ 10 μm

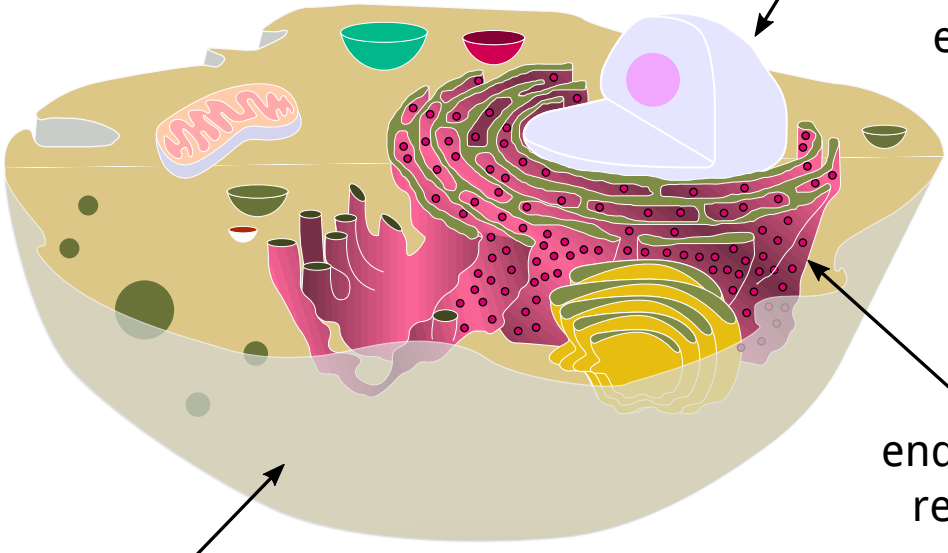
The eukaryotic cell



prokaryotic cell (bacterium)

R ≈ 10 μm

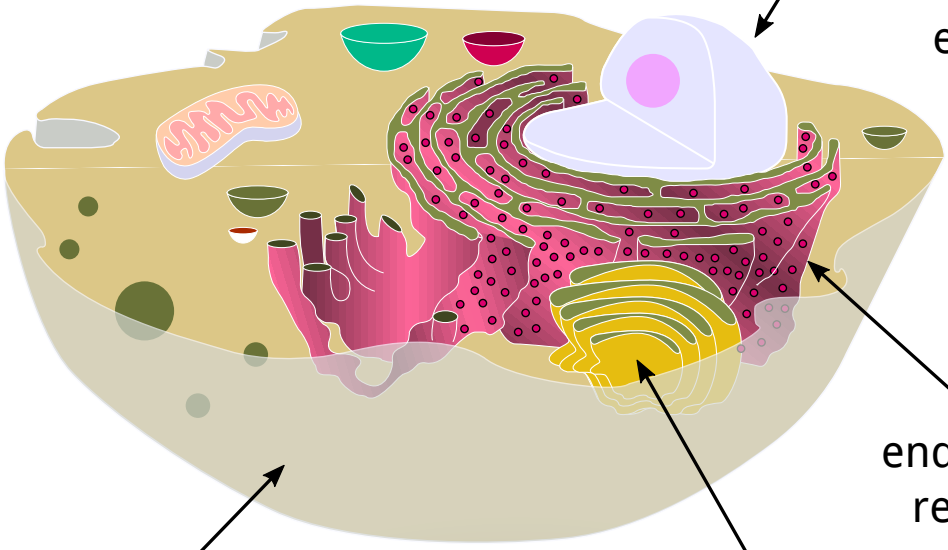
The eukaryotic cell



prokaryotic cell (bacterium)

R ≈ 10 μm

The eukaryotic cell



nuclear membrane

eukaryotic cell

endoplasmic reticulum

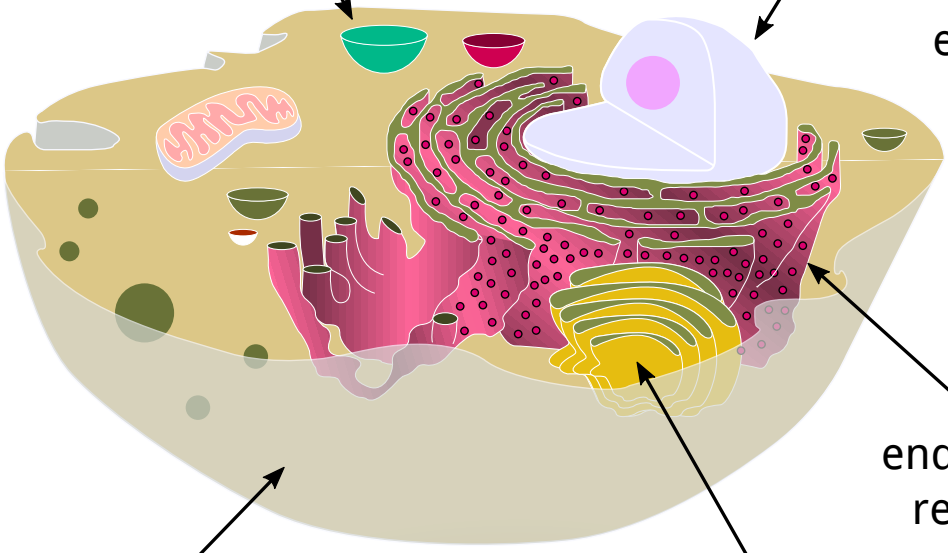
Golgi

plasmamembrane

prokaryotic cell (bacterium)

R ≈ 10 μm

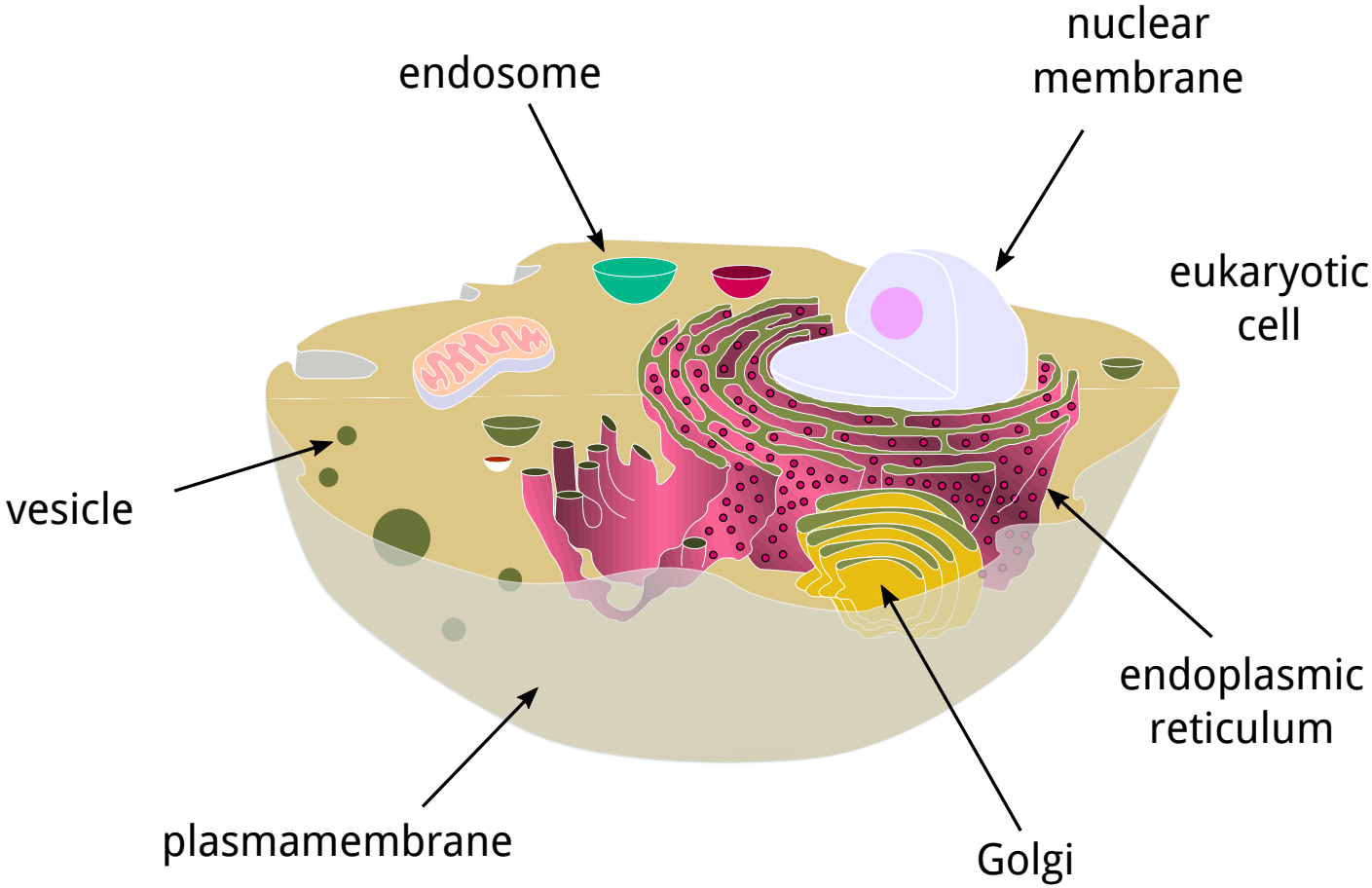
The eukaryotic cell



prokaryotic cell (bacterium)

R ≈ 10 μm

The eukaryotic cell

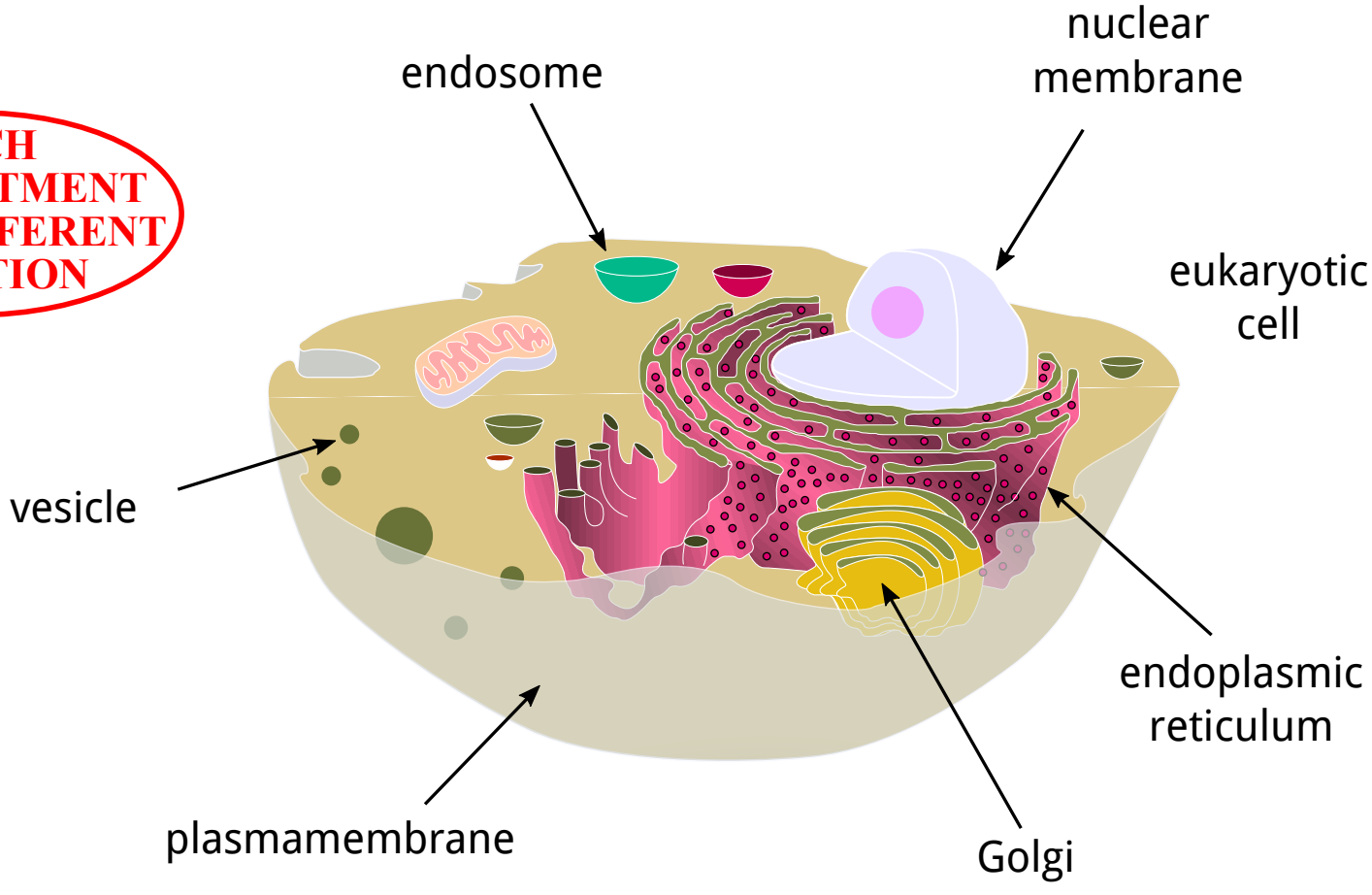


prokaryotic cell (bacterium)

R ≈ 10 μm

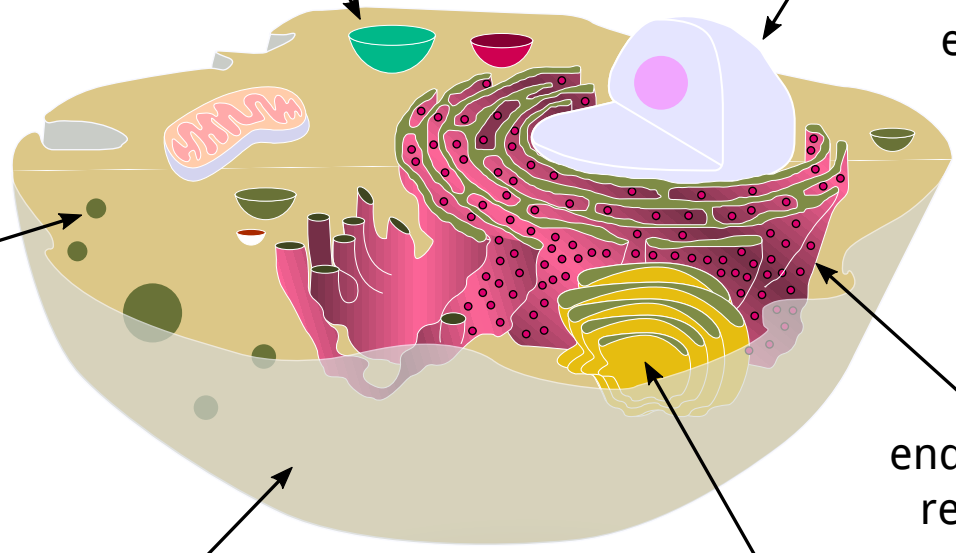
The eukaryotic cell

EACH COMPARTMENT HAS A DIFFERENT FUNCTION



The eukaryotic cell

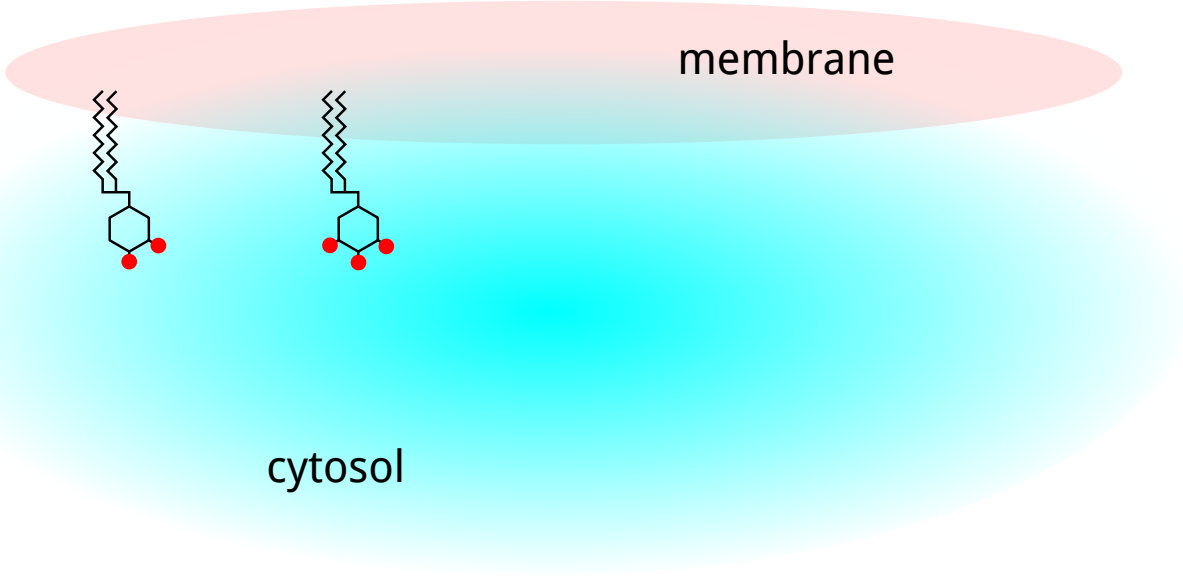
"MEMBRANE IDENTITY"



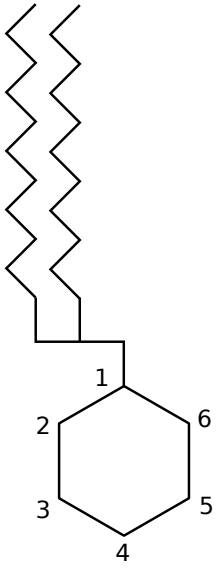
prokaryotic cell (bacterium)

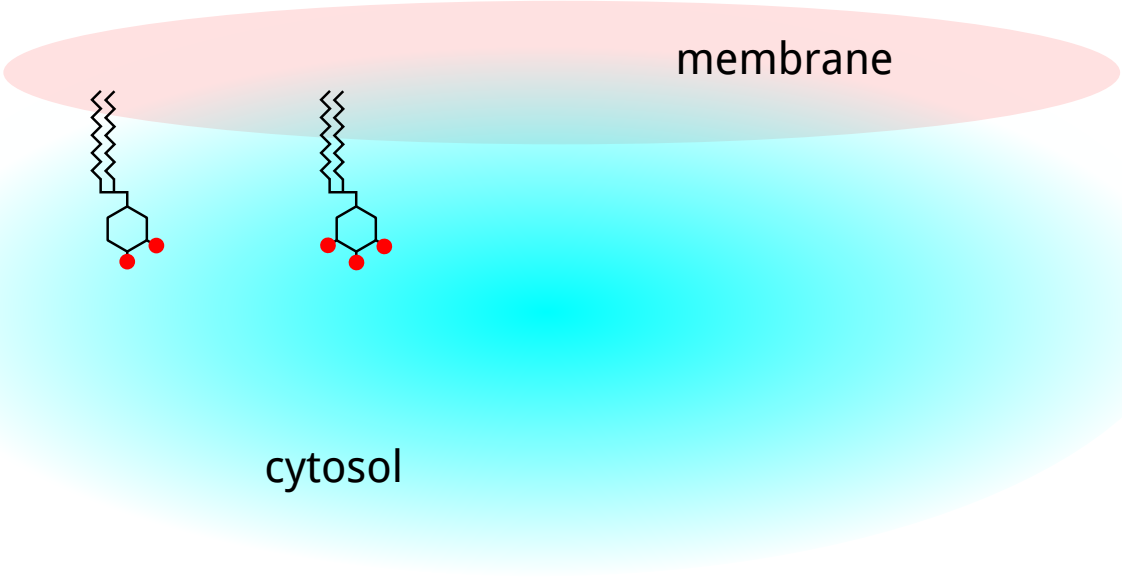
R ≈ 10 μm

Signaling molecules



Signaling molecules





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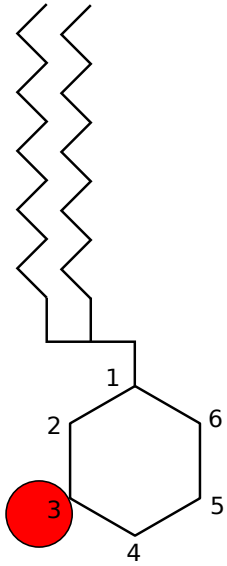
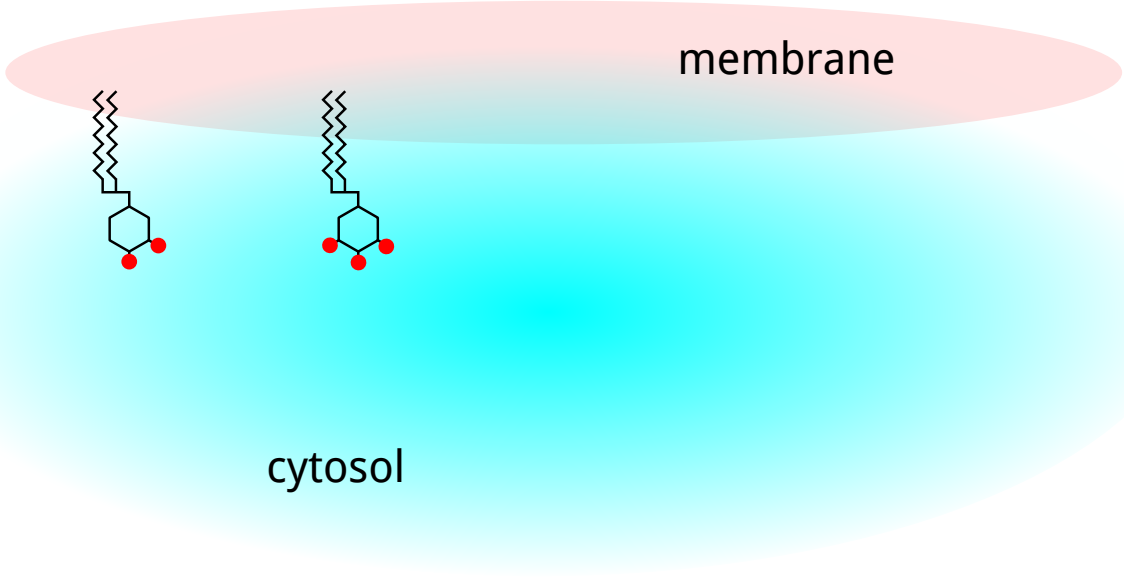
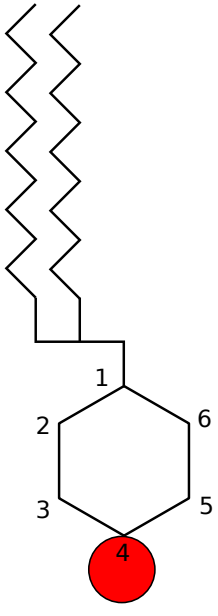
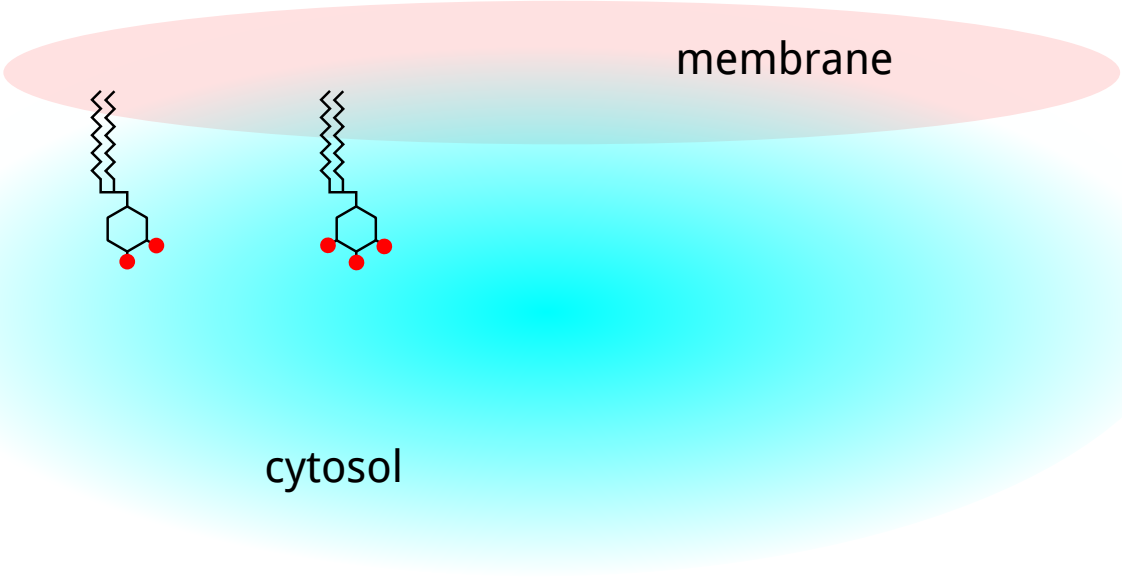


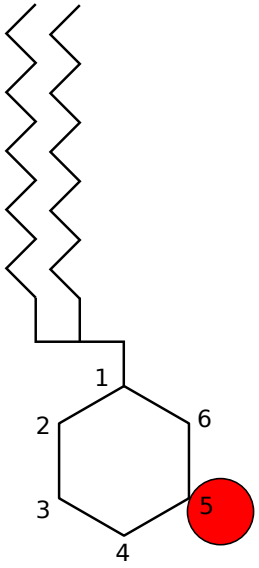


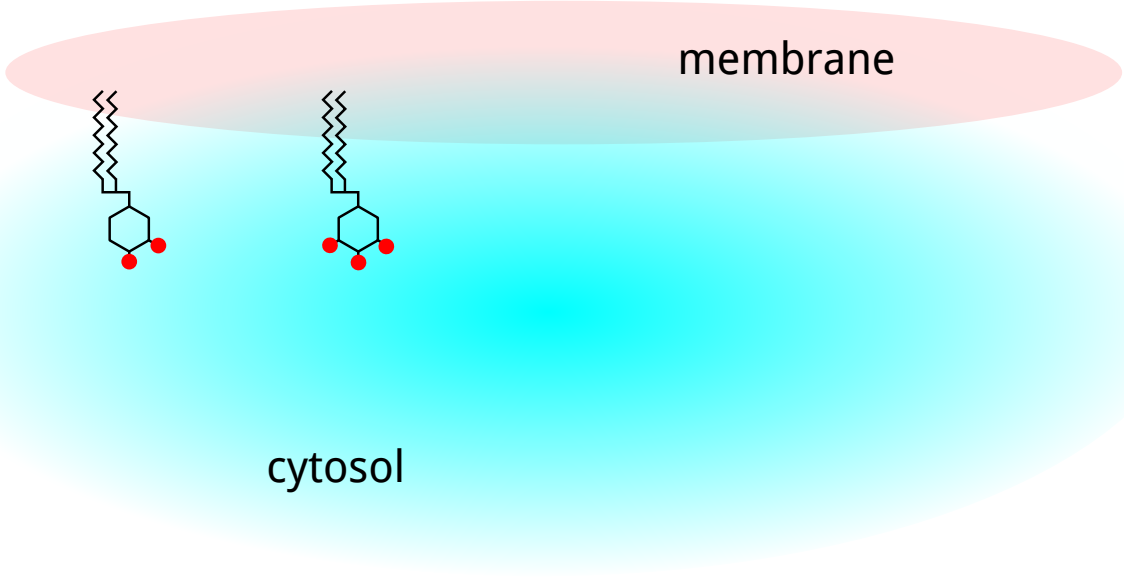
Signaling molecules



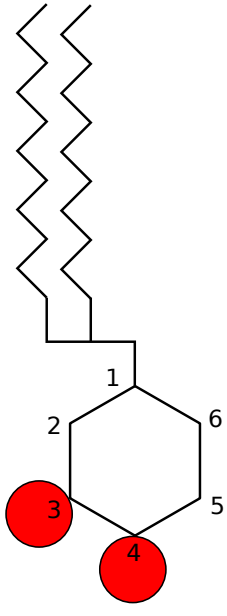


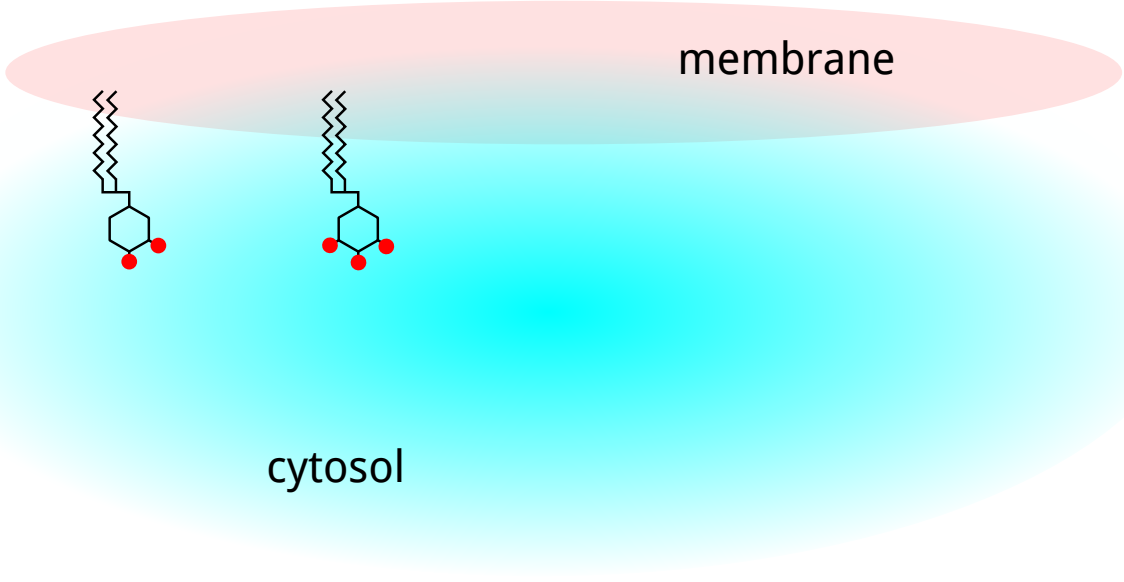
Signaling molecules





Signaling molecules





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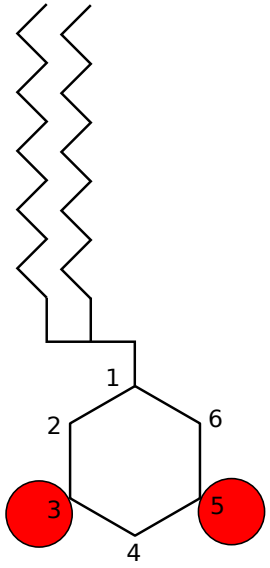

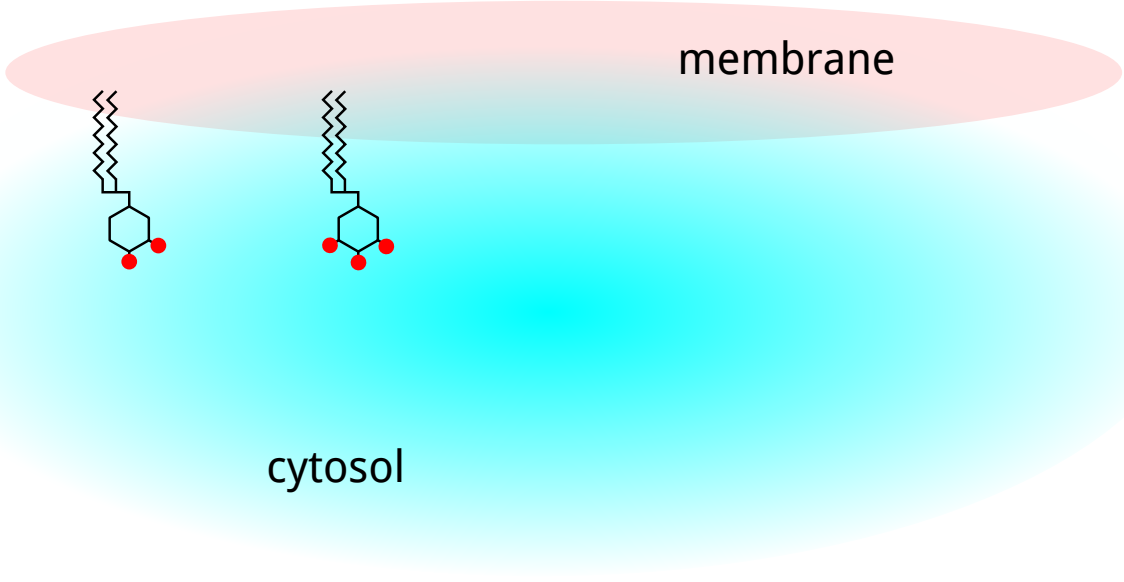

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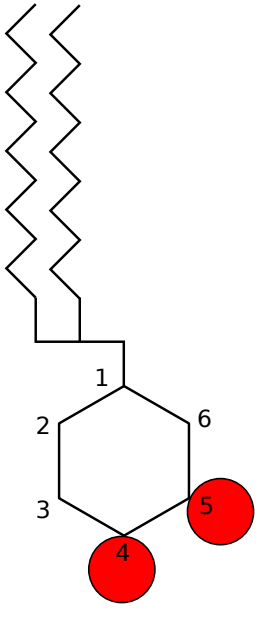

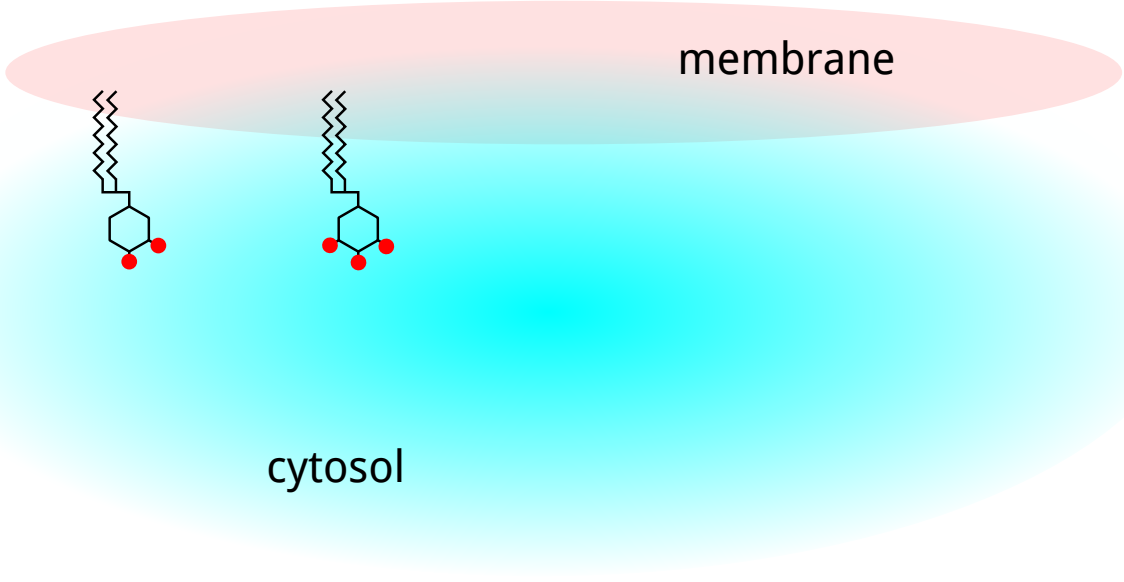

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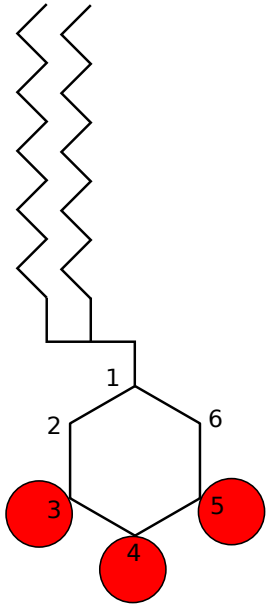

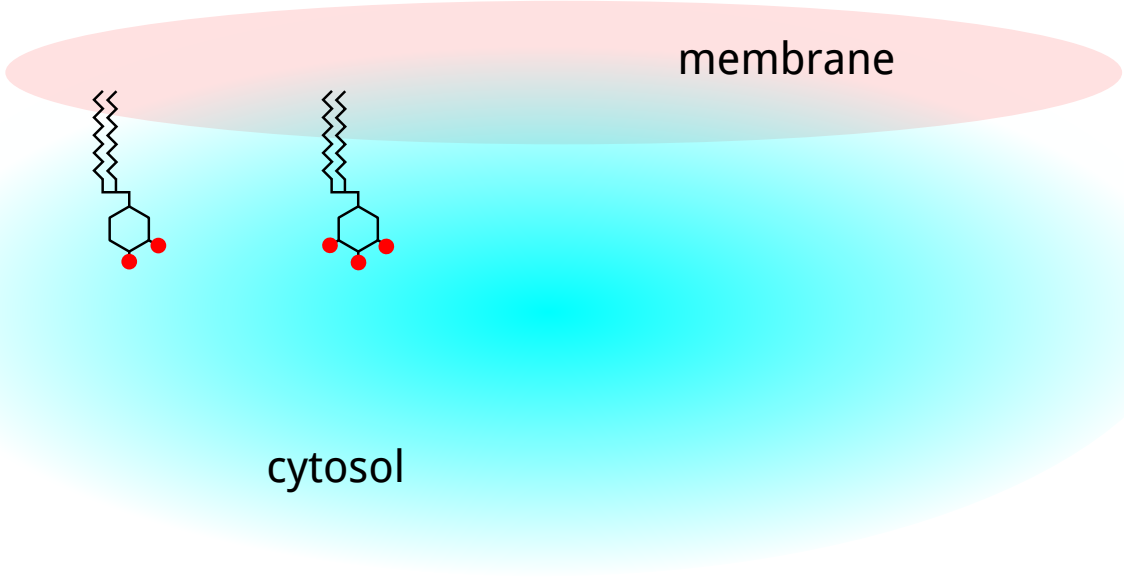

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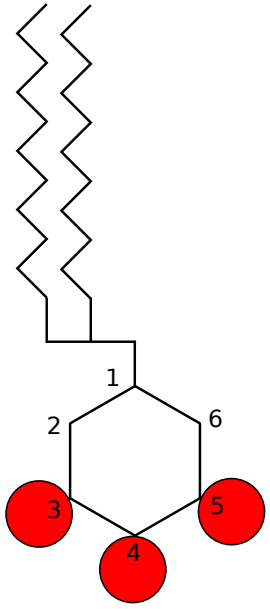

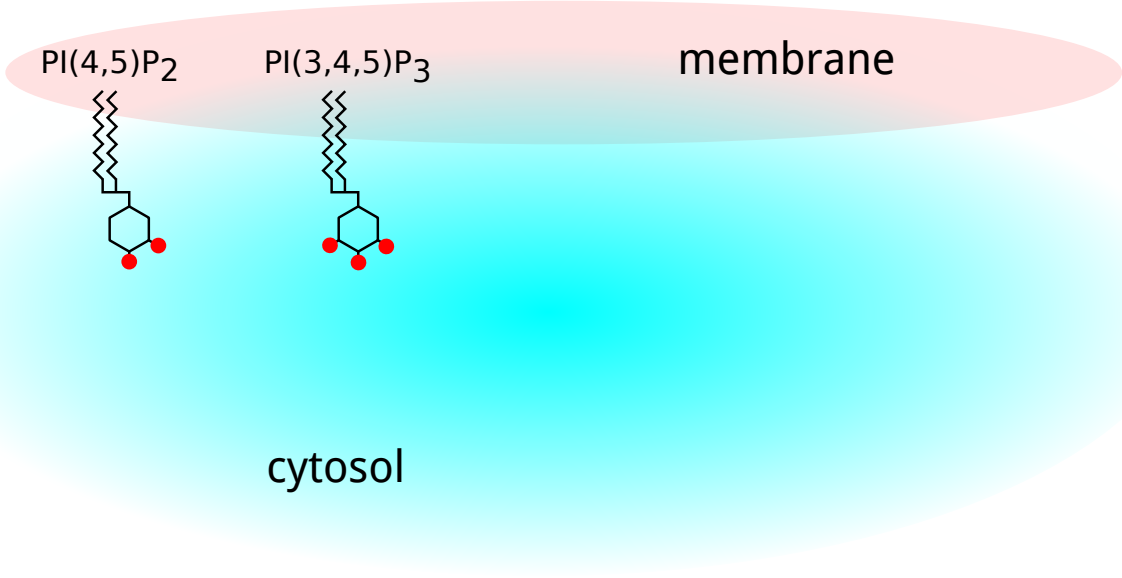

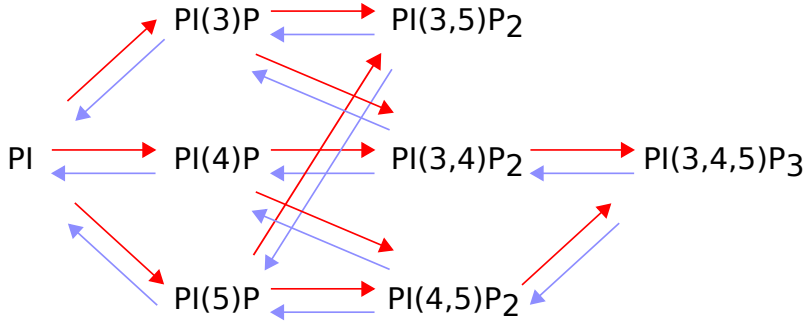

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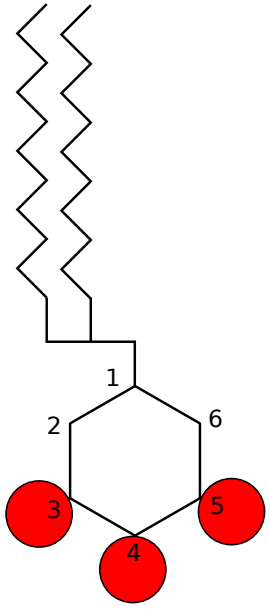

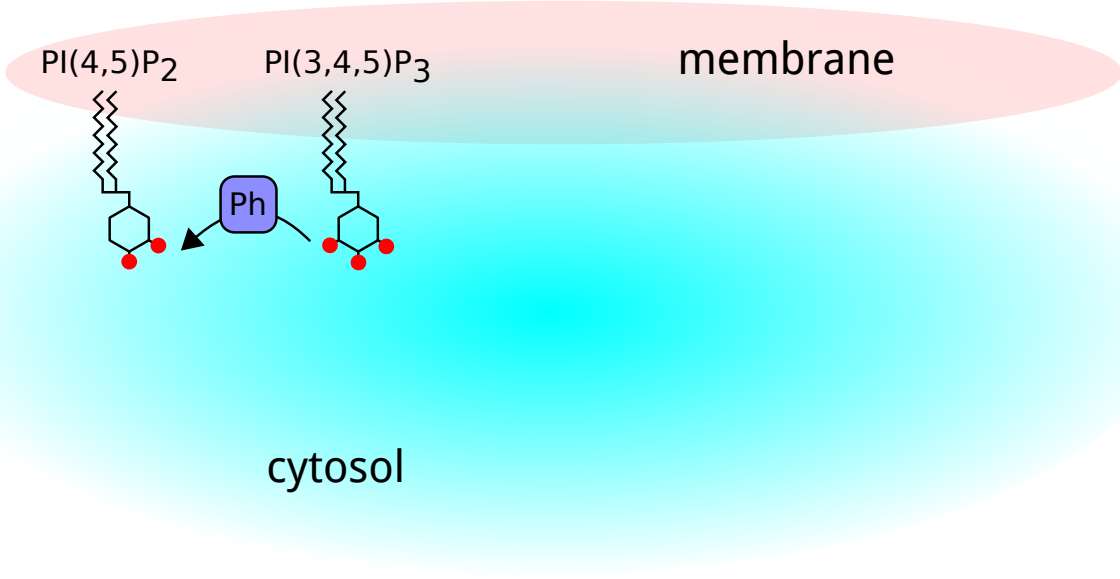

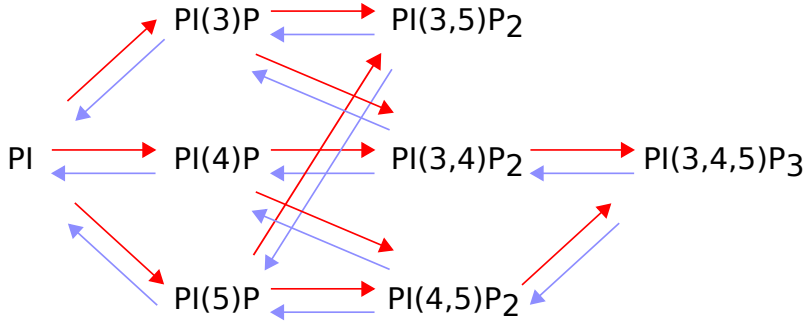

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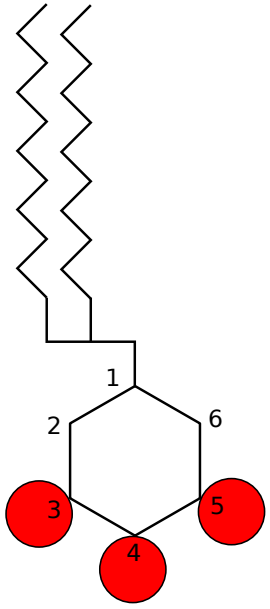

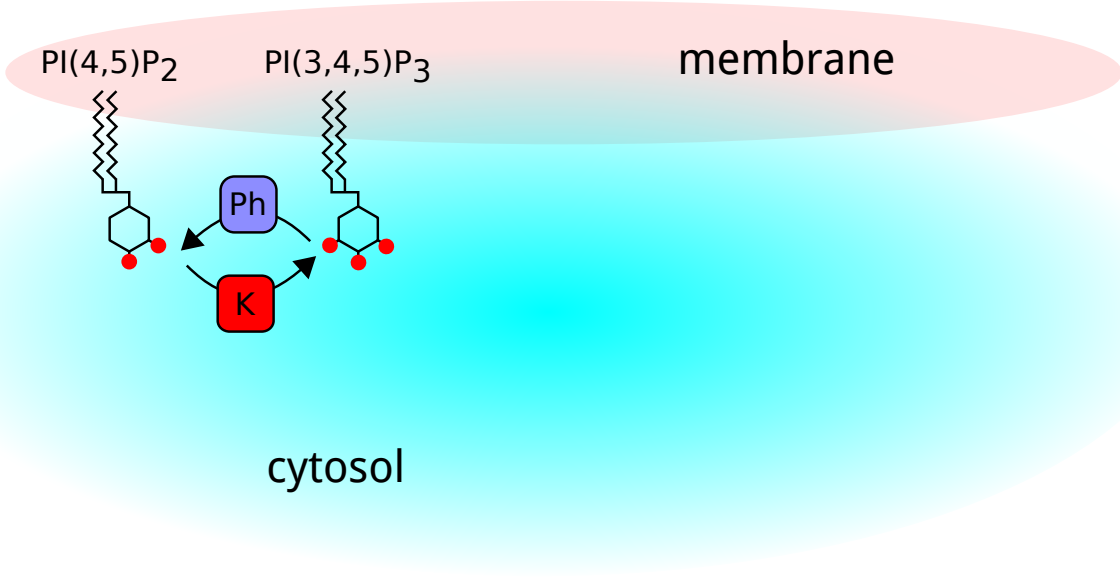

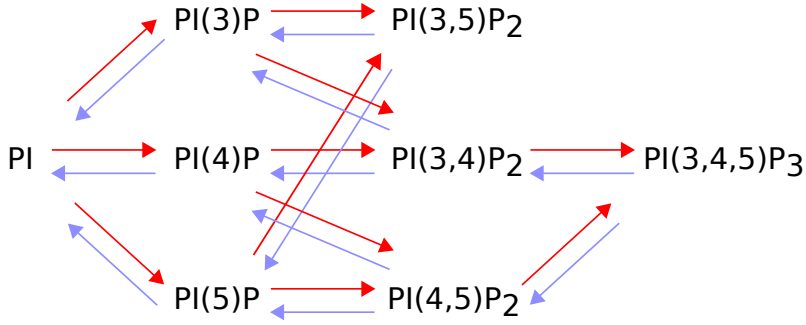

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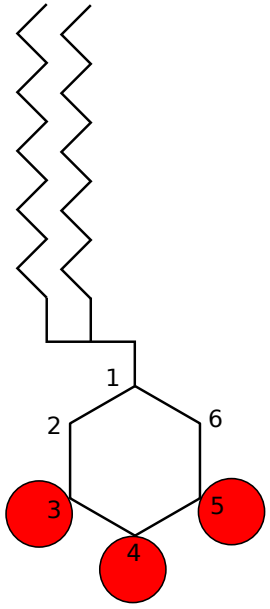

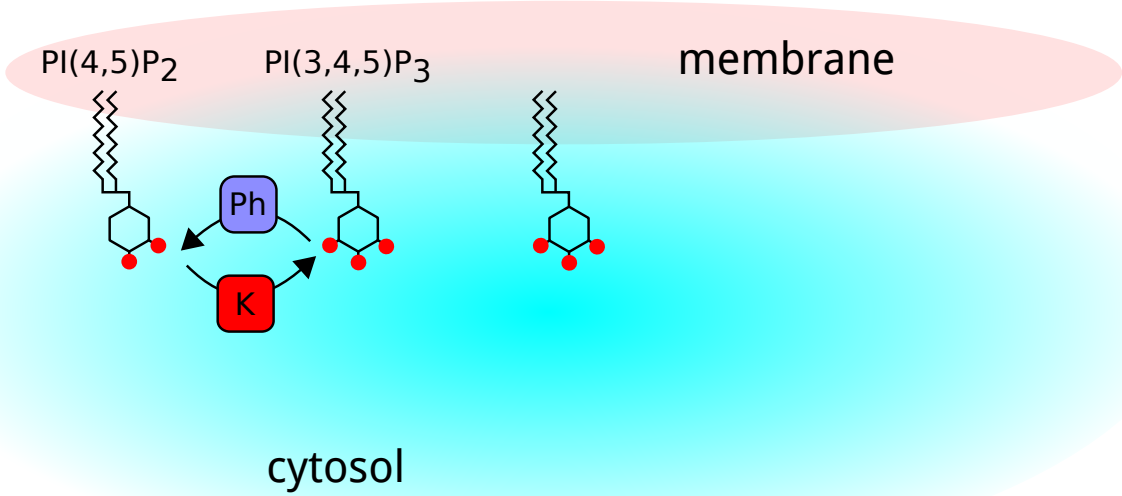

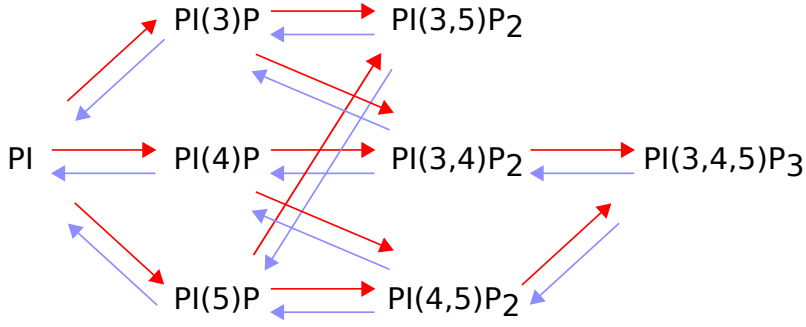

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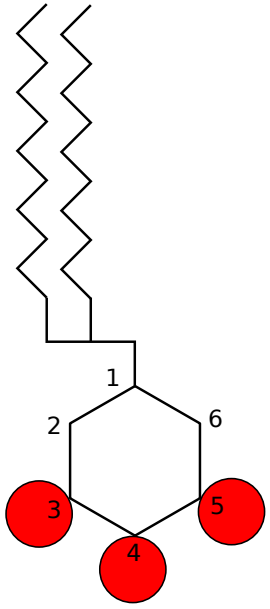

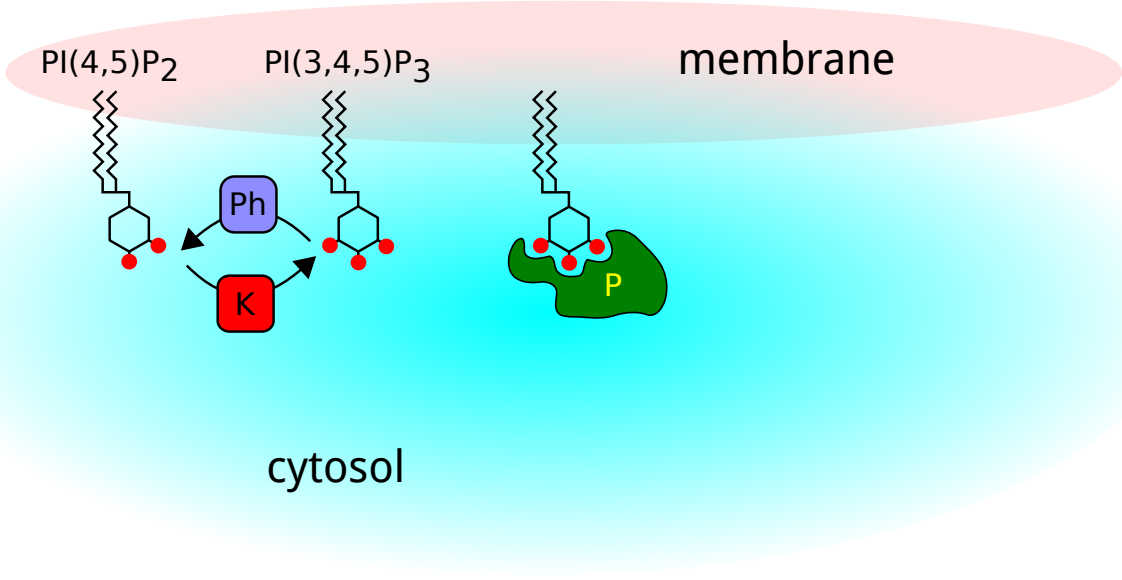

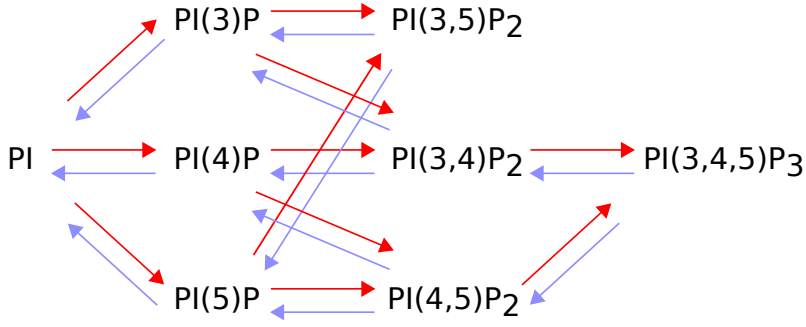

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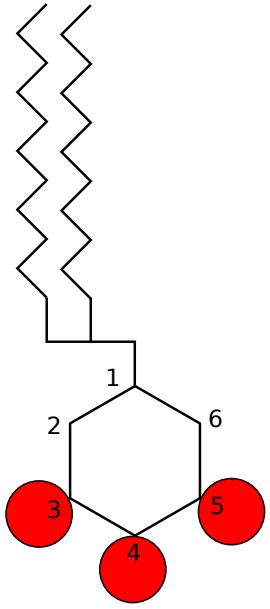

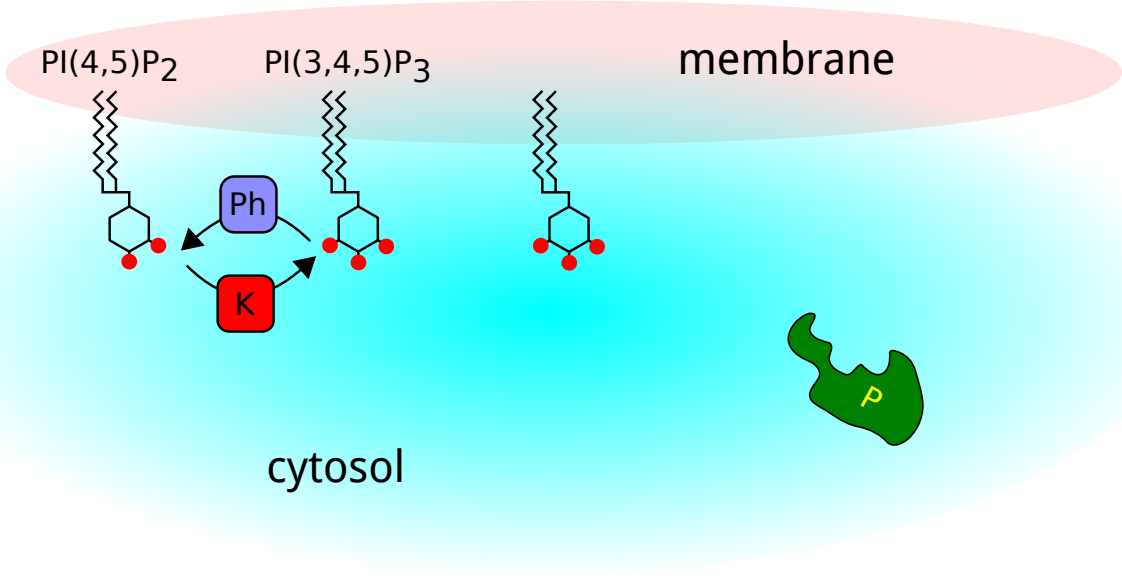

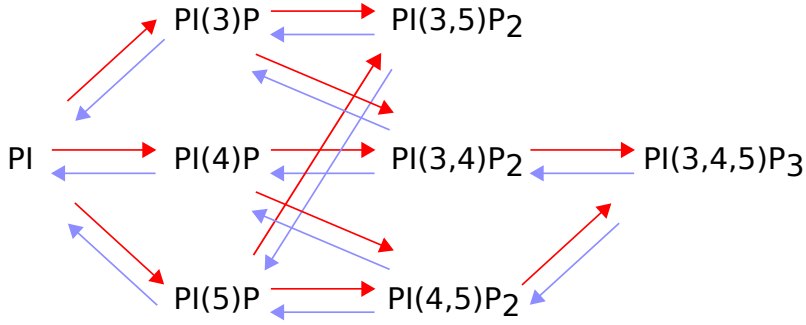

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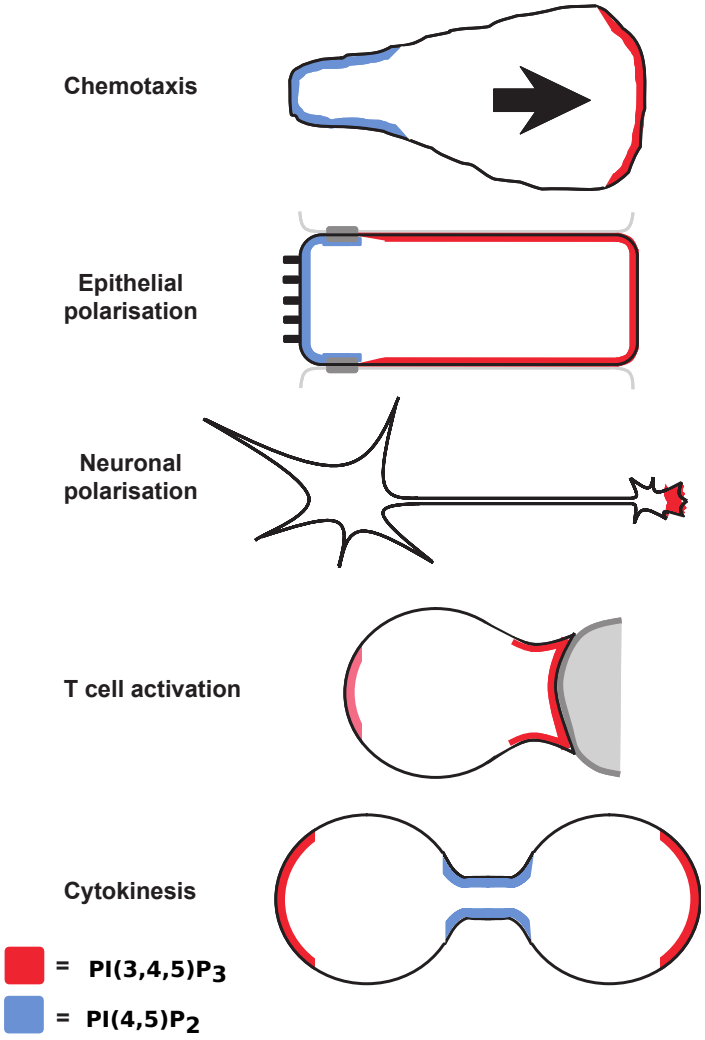
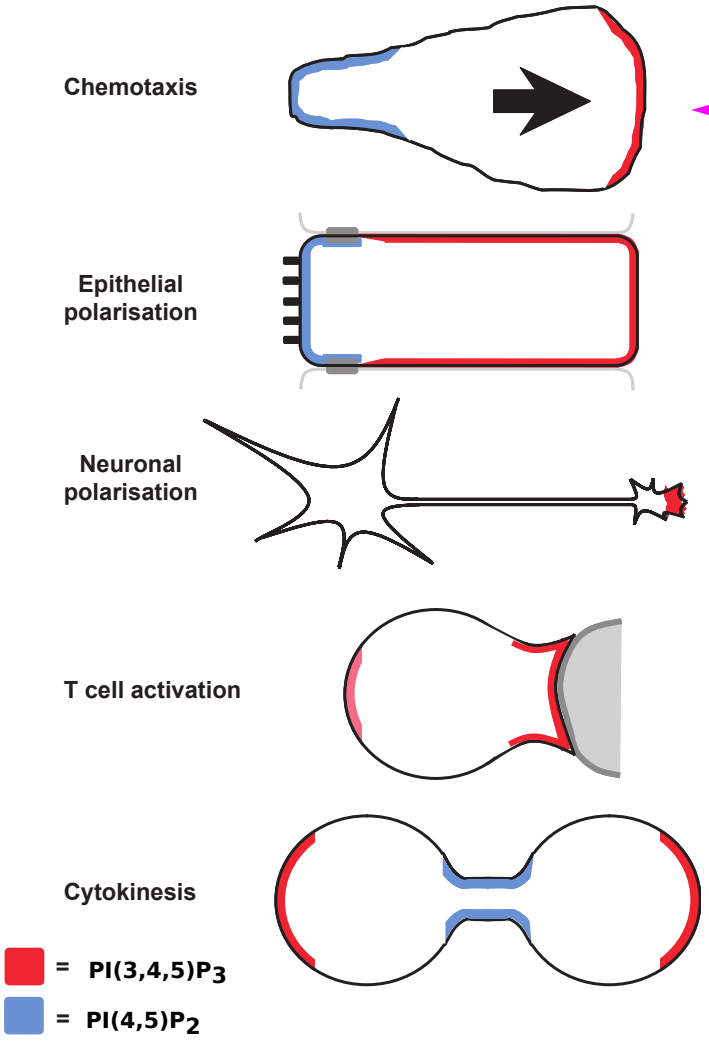


Leslie et al. Oncogene, 2008

Signaling domains



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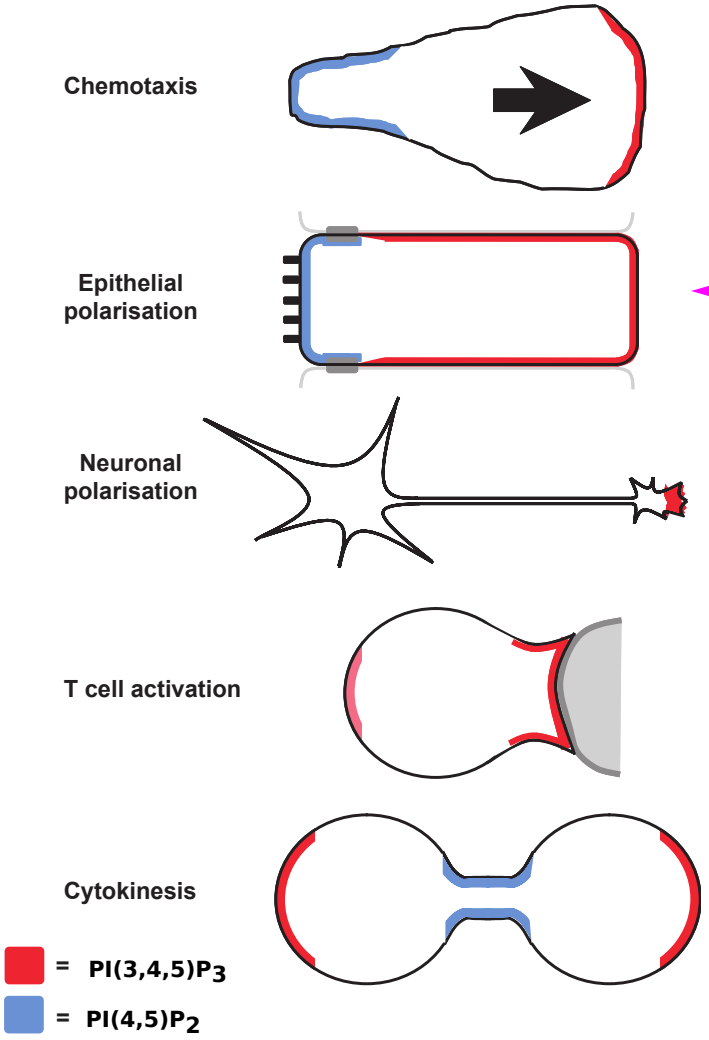
Devreotes, Janetopoulos
J. Biol. Chem. 2003.

Leslie et al. Oncogene, 2008

Signaling domains



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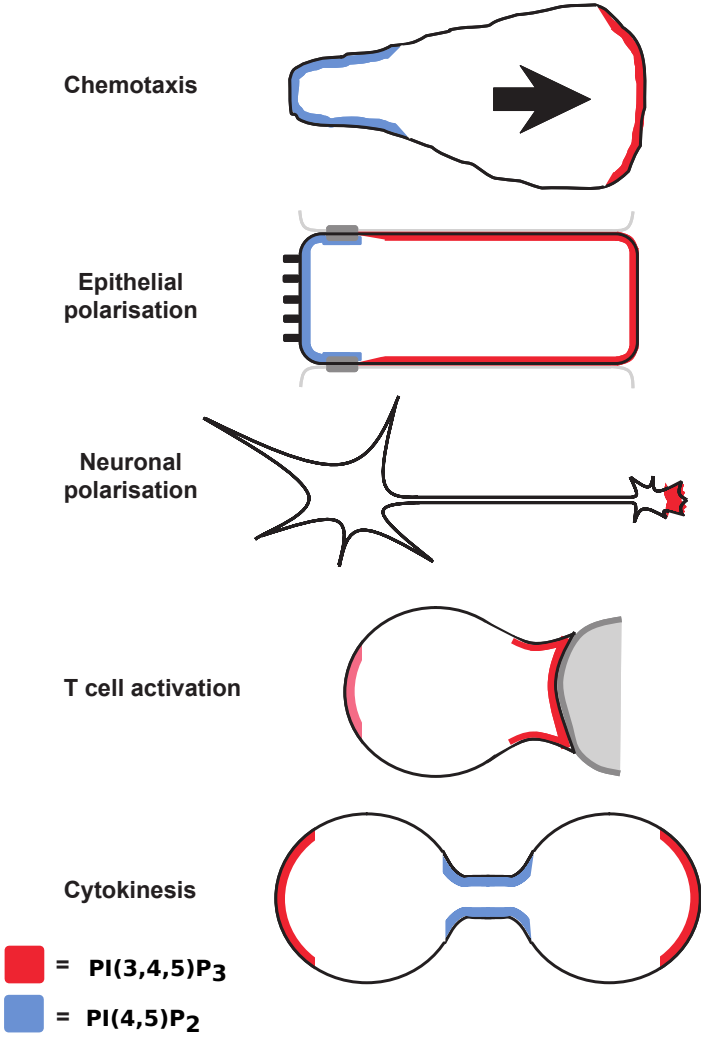
Martin-Belmonte et al.
Cell 2007

Leslie et al. Oncogene, 2008

Signaling domains



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Menager et al.
J. Neurochem. 2004.

Leslie et al. Oncogene, 2008

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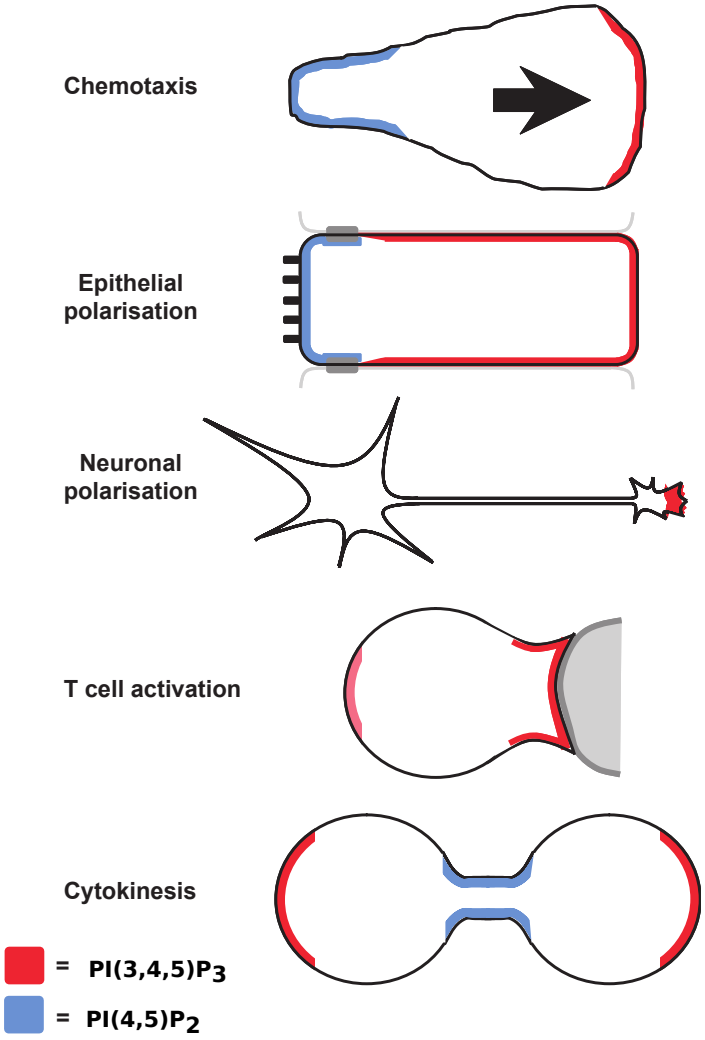
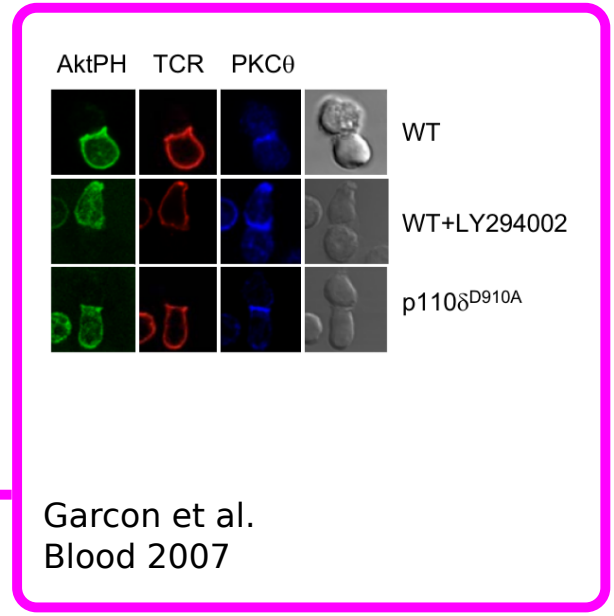
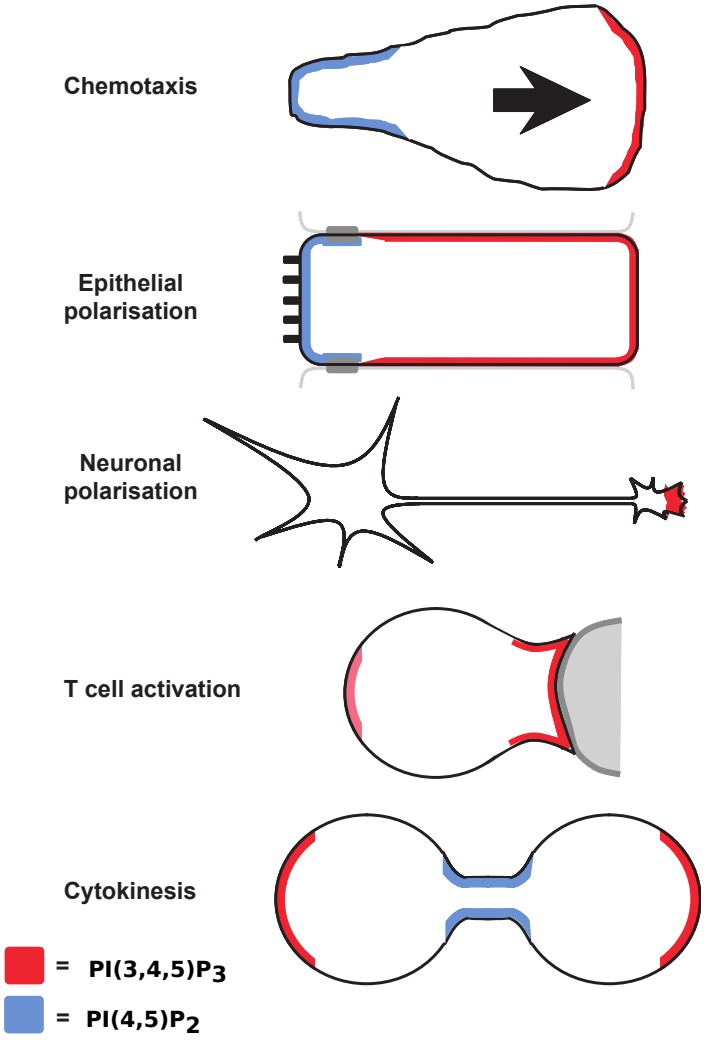
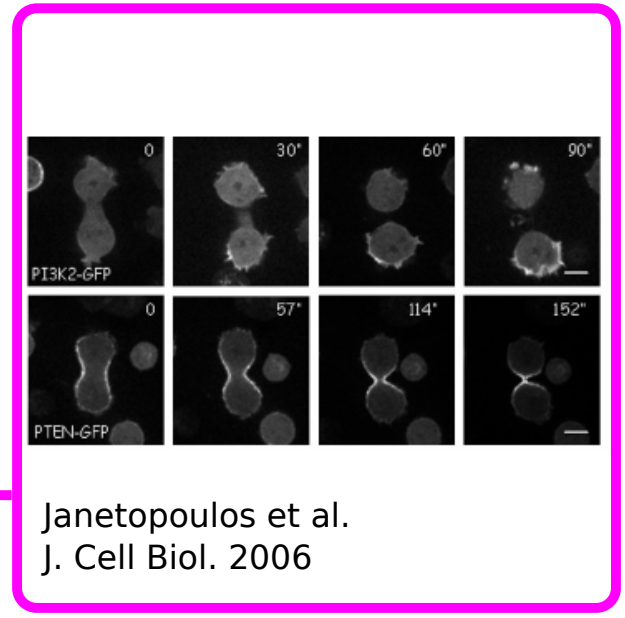




Leslie et al. Oncogene, 2008

Signaling domains

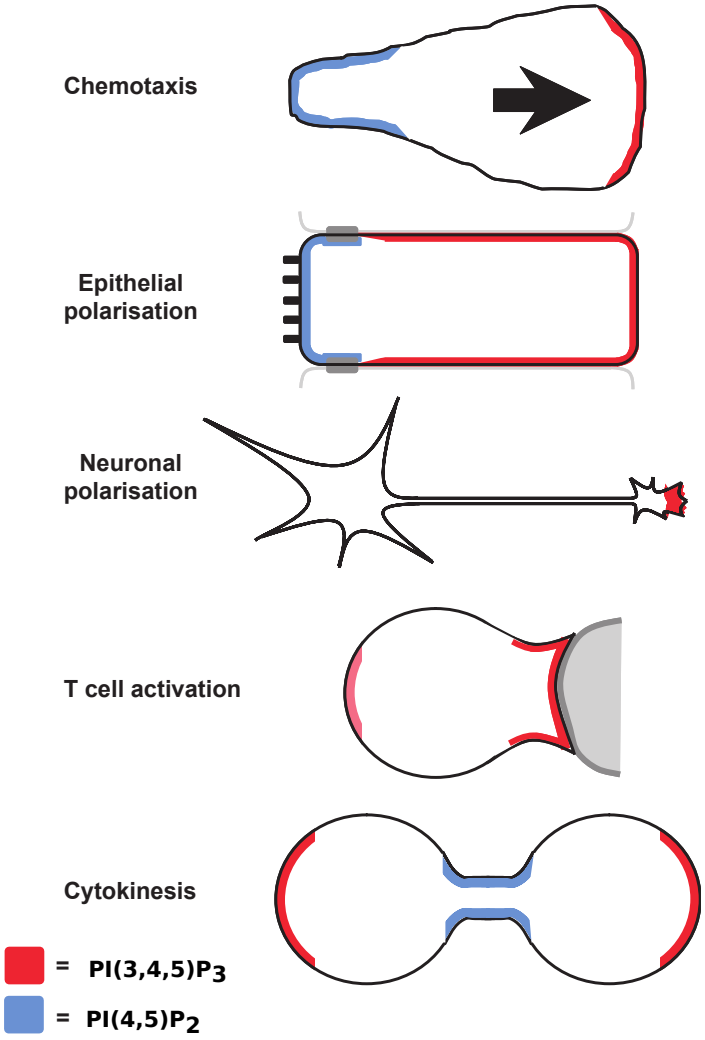




Janetopoulos et al.
J. Cell Biol. 2006

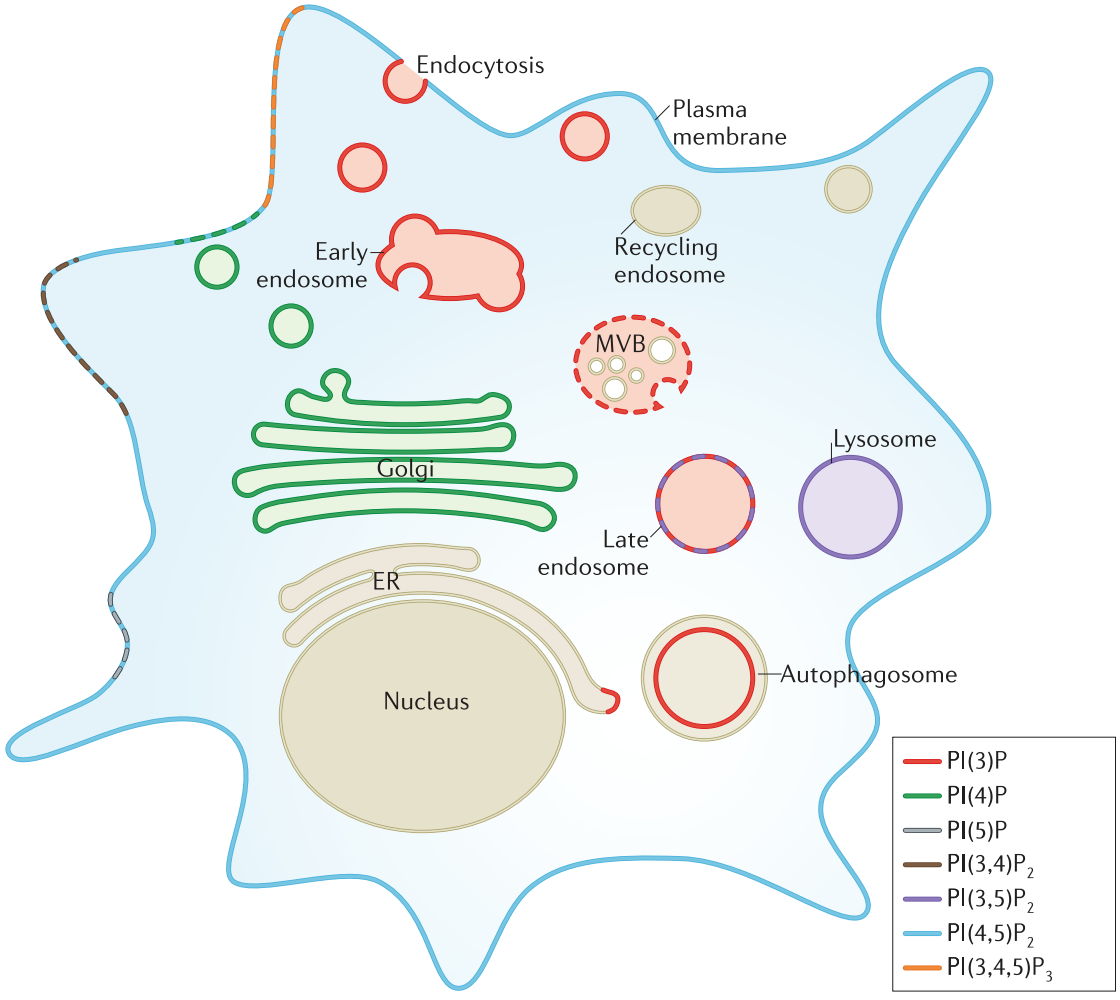
Leslie et al. Oncogene, 2008

Signaling domains



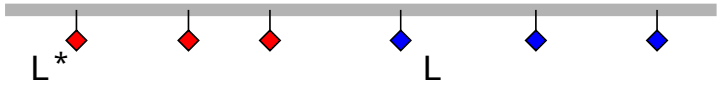
Leslie et al. Oncogene, 2008

Membrane identity



modified from Jean & Kiger
Nat Rev Mol Cell Biol 2012

Domain formation



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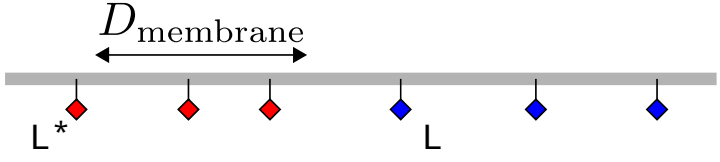

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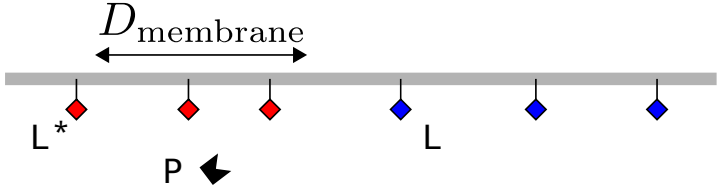
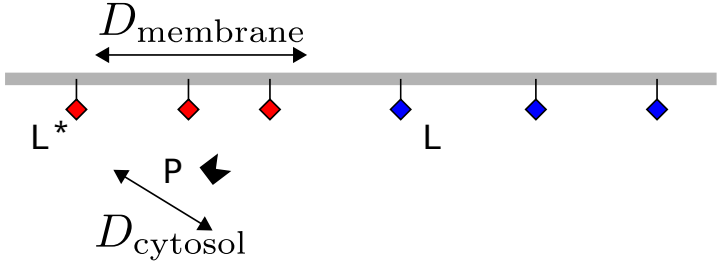
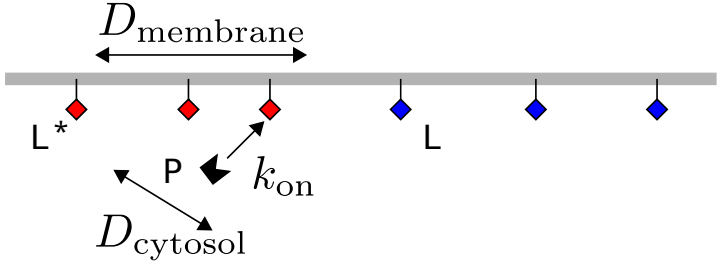


Domain formation



Domain formation



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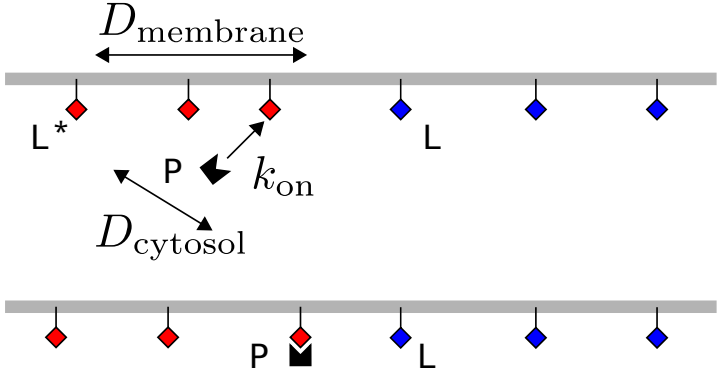

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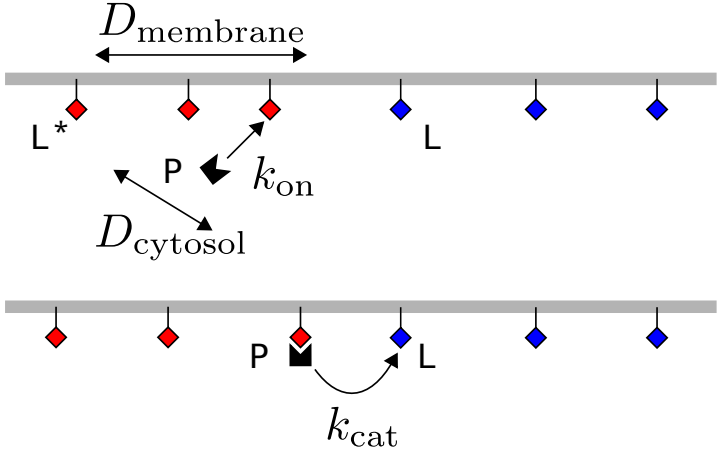

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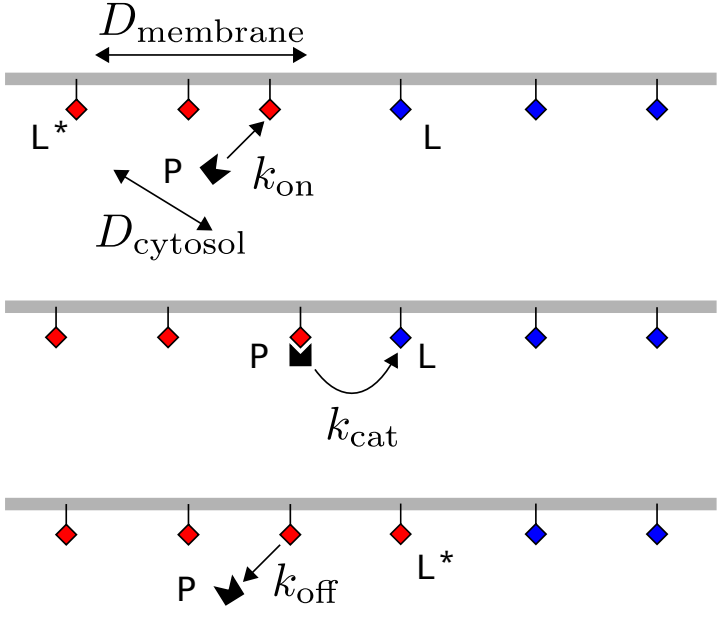

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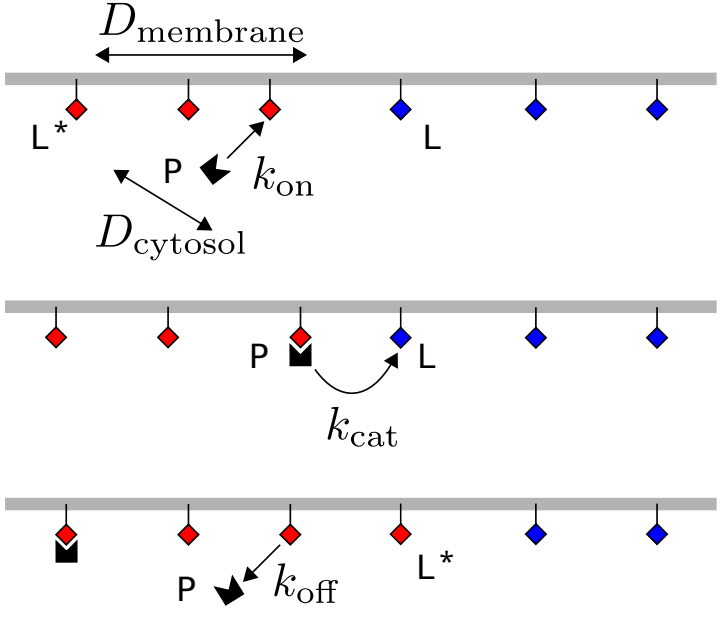

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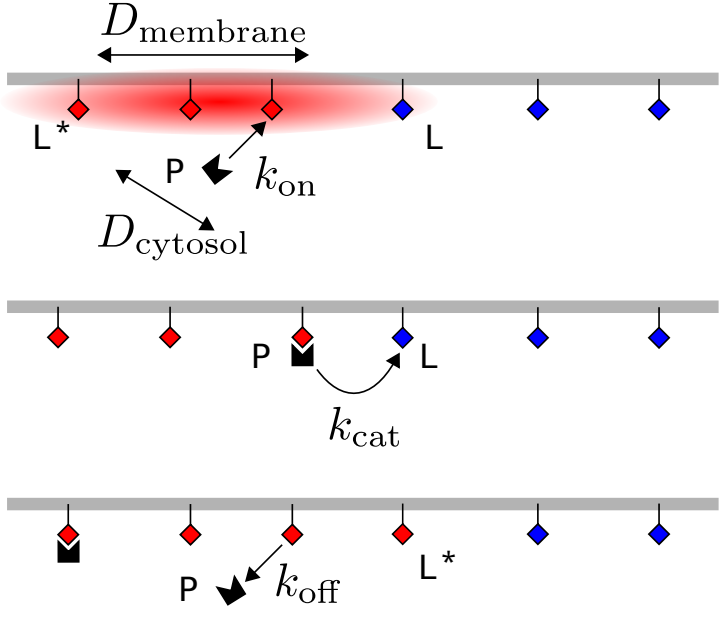

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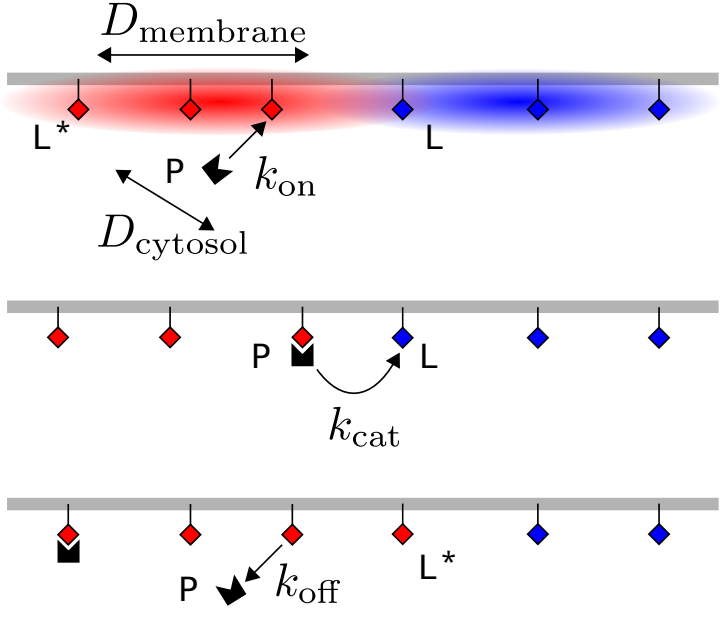

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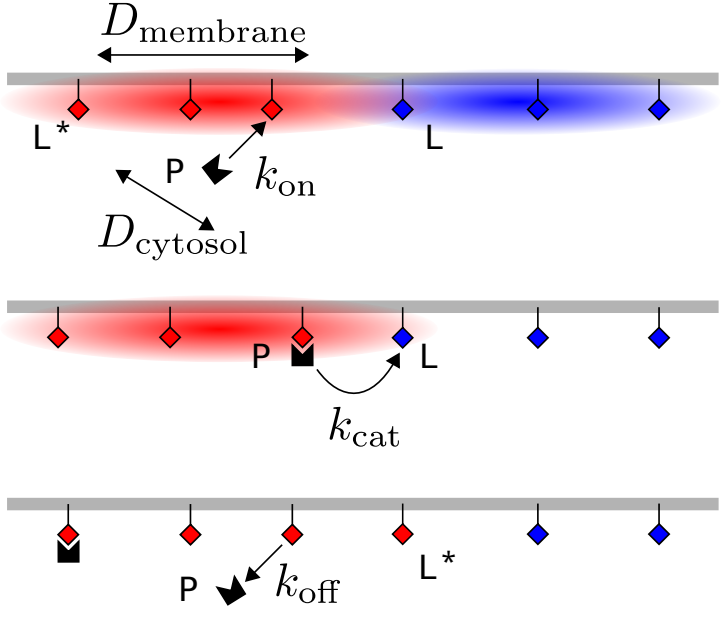

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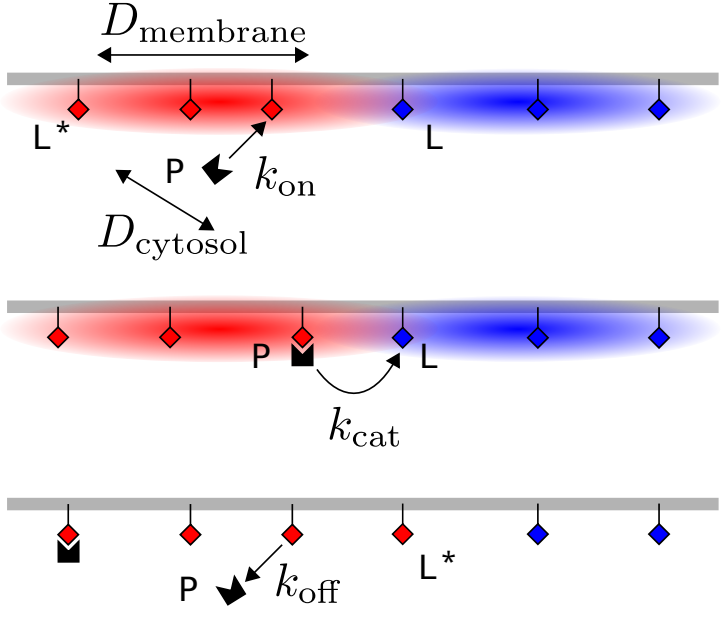

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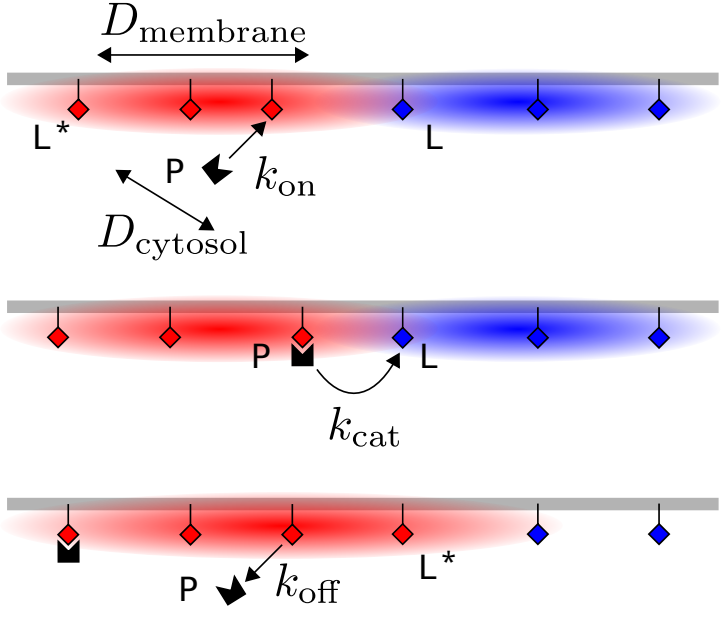

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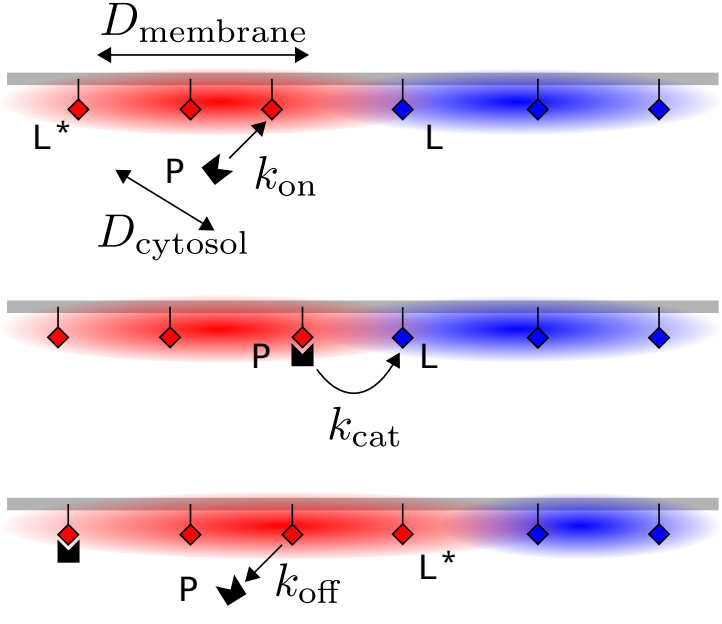

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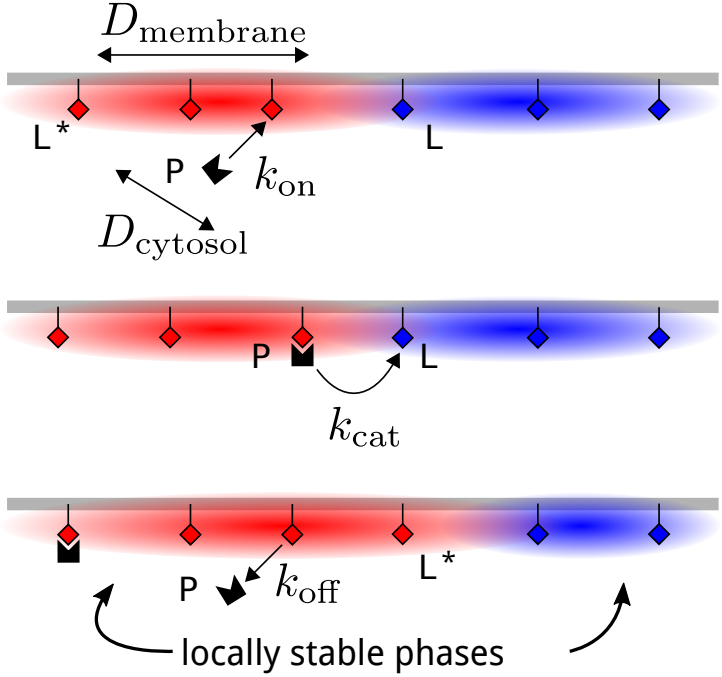

P depleted from cytosol as red phase grows

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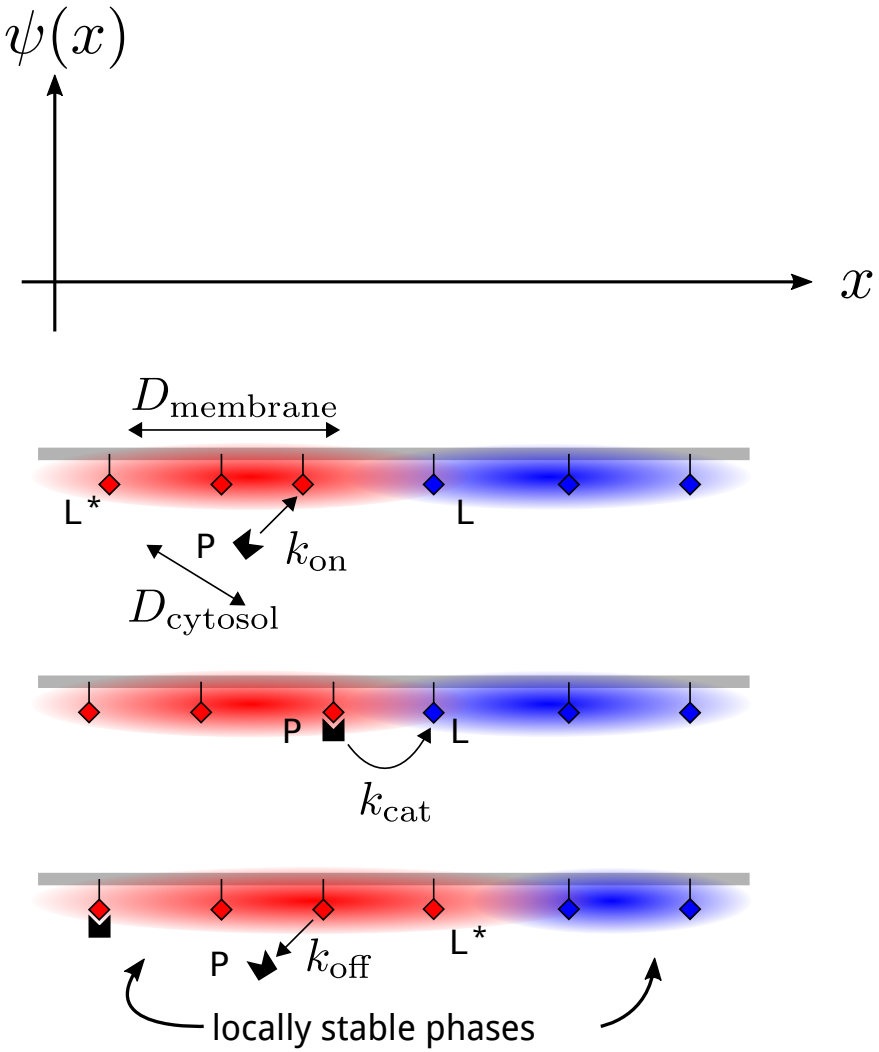

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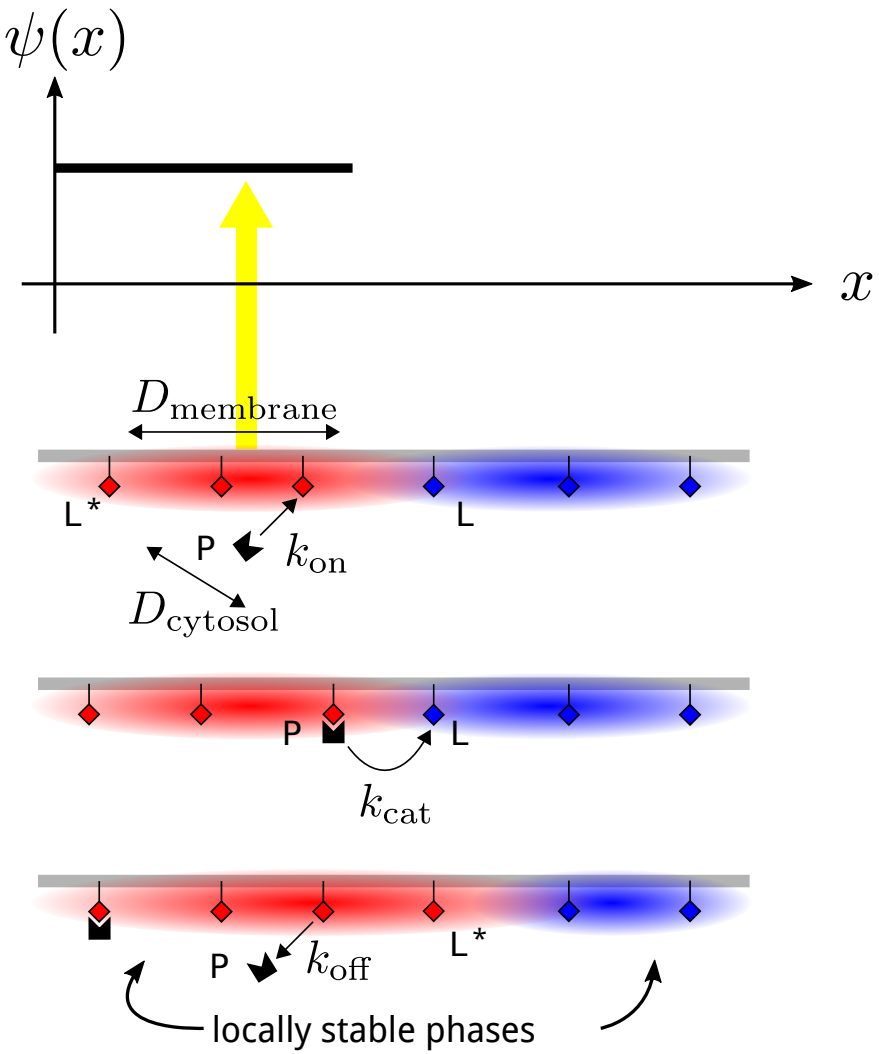

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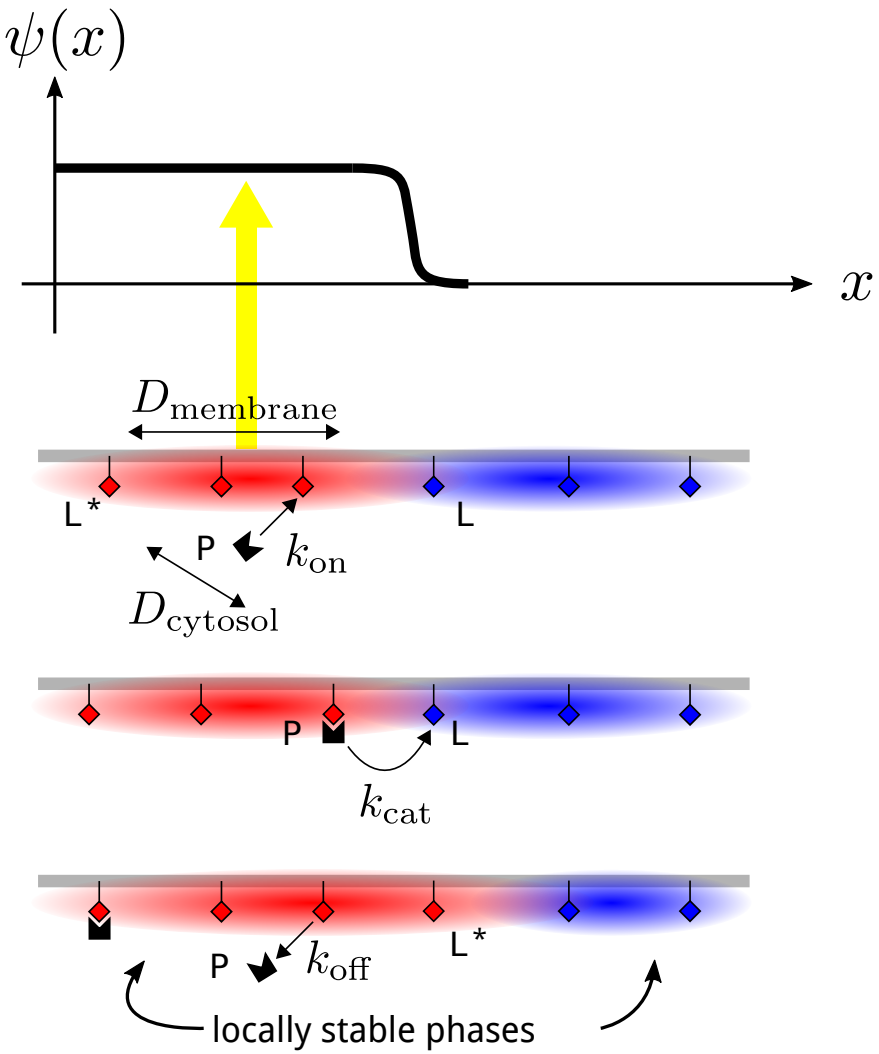

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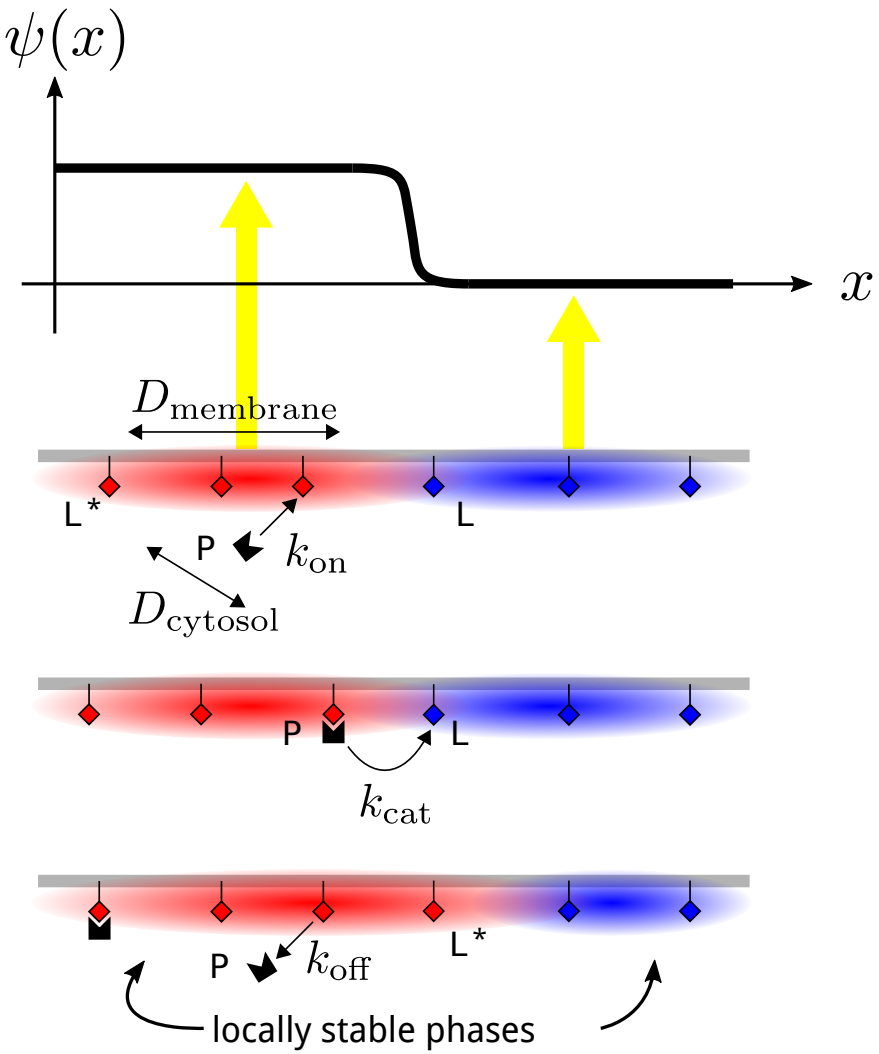

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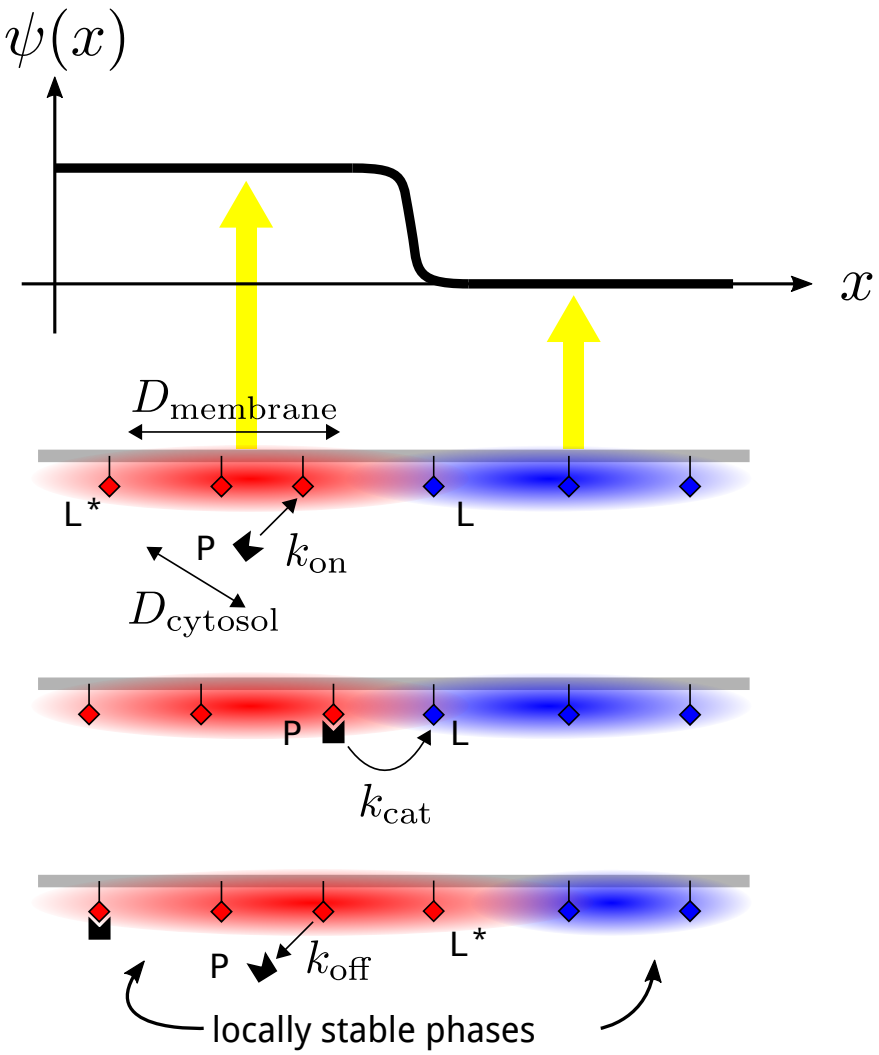

$$\frac{\partial \psi}{\partial t} = -D\nabla^2\psi + V'(\varepsilon, \psi) + \xi$$

P depleted from cytosol as red phase grows

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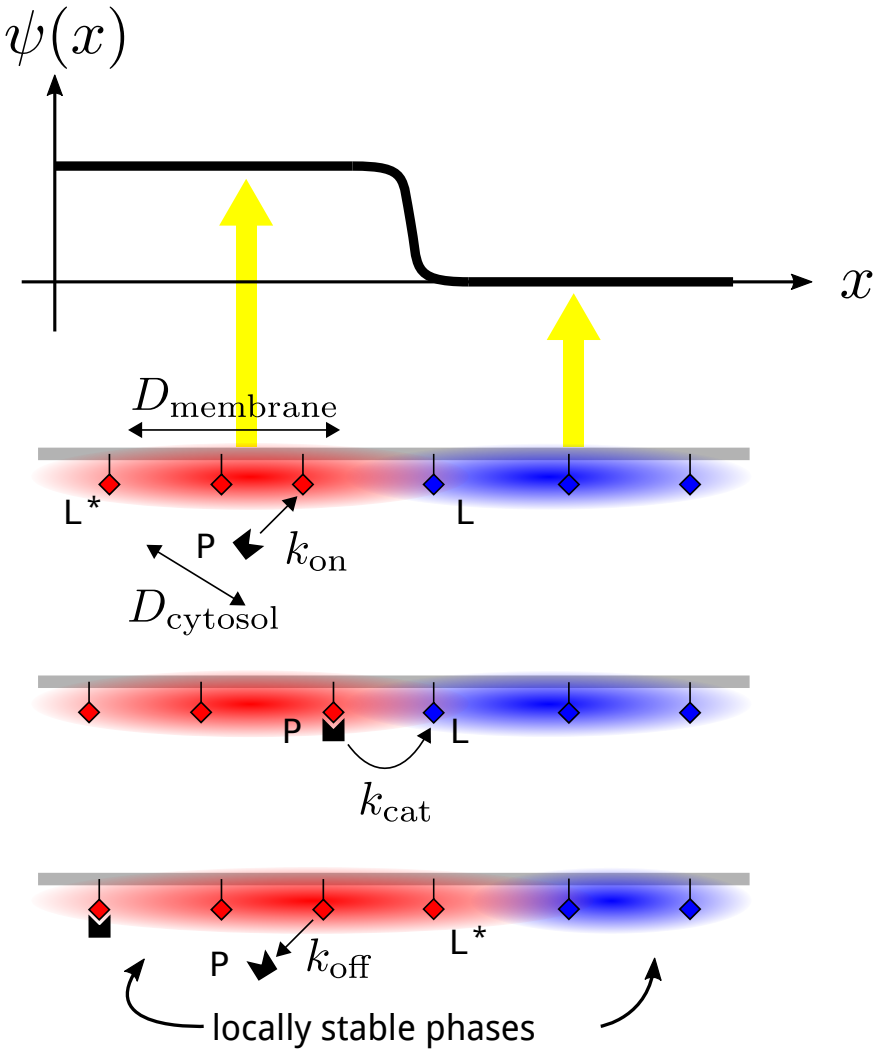

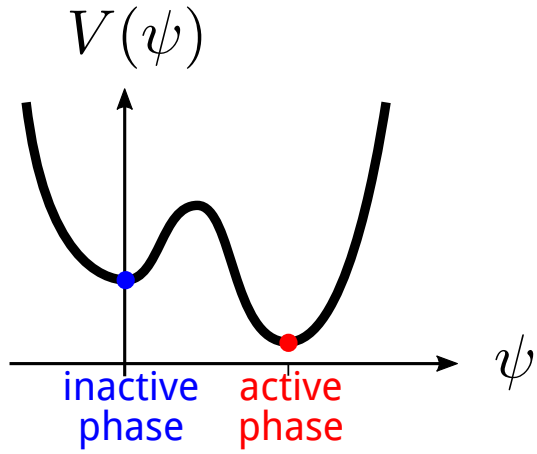

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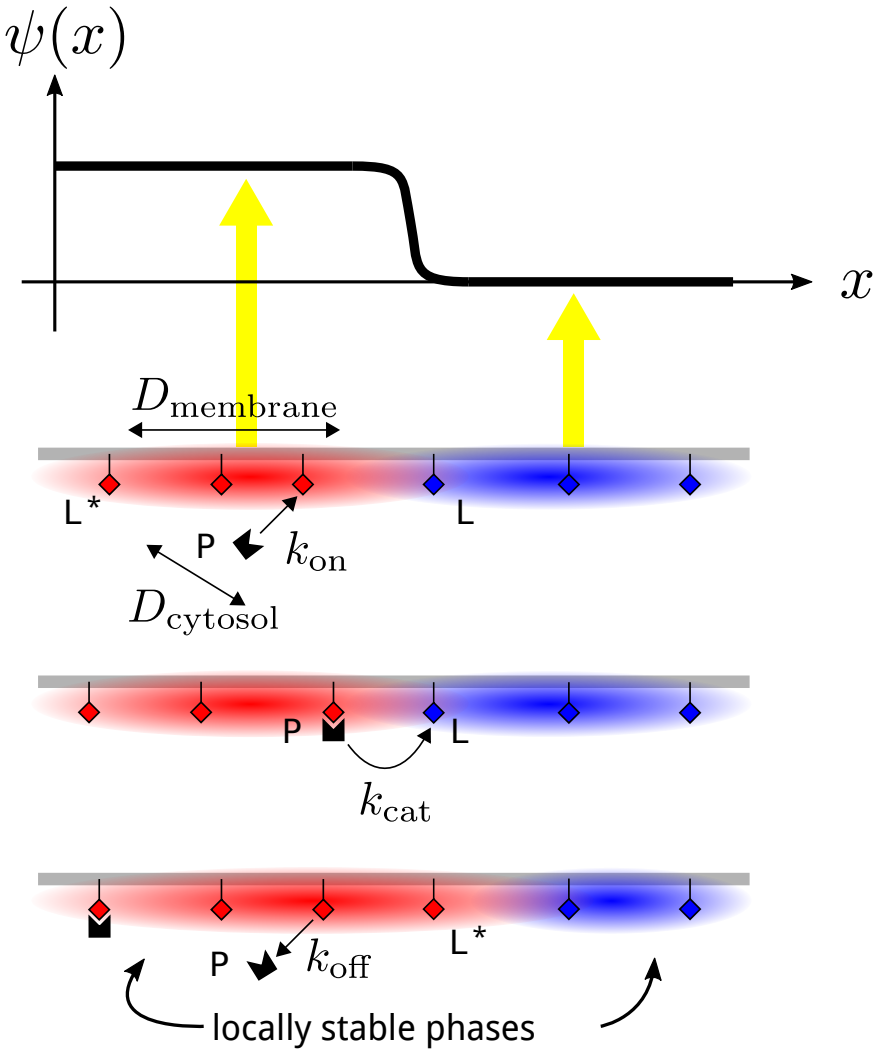

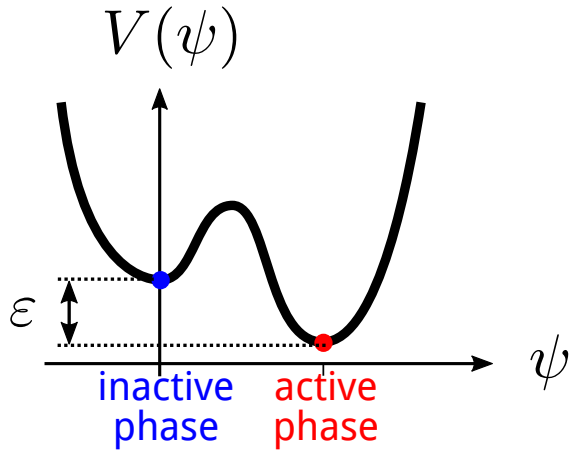

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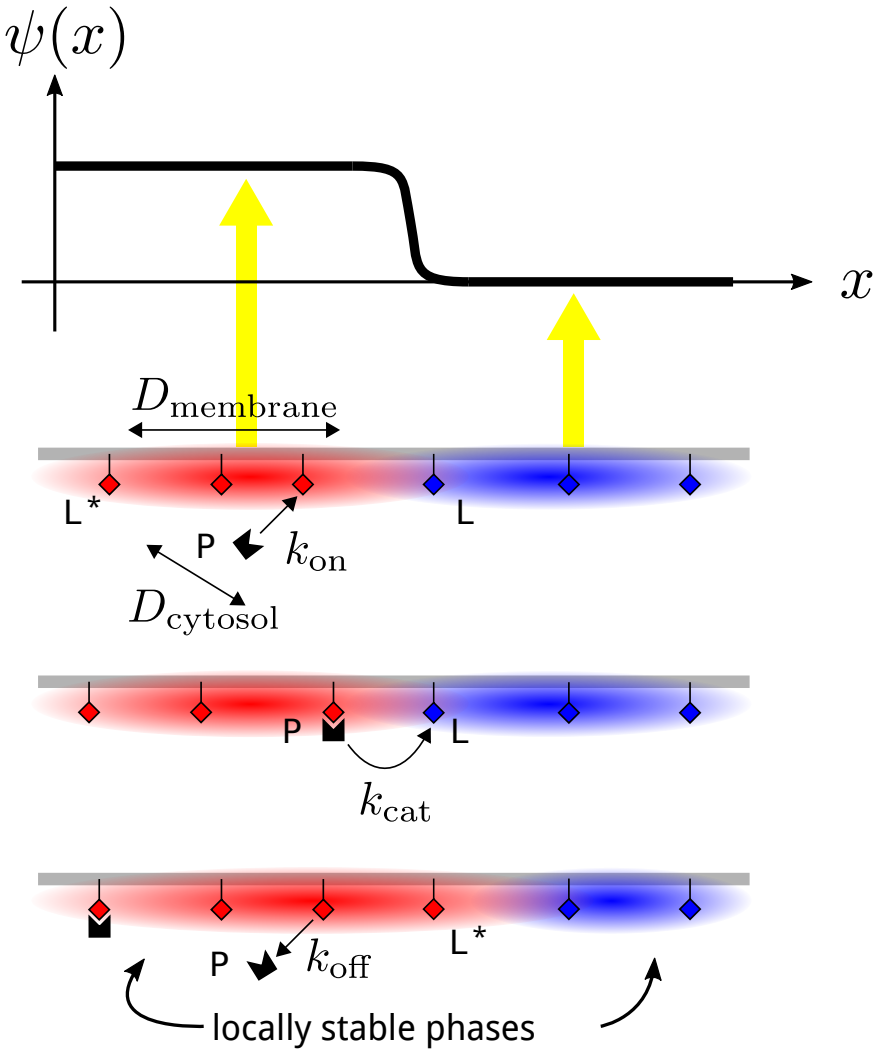

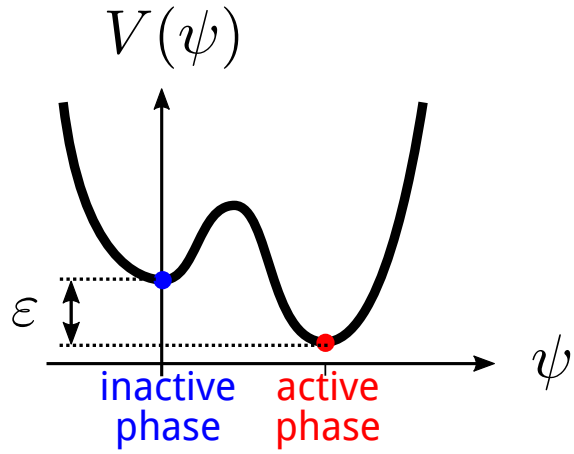

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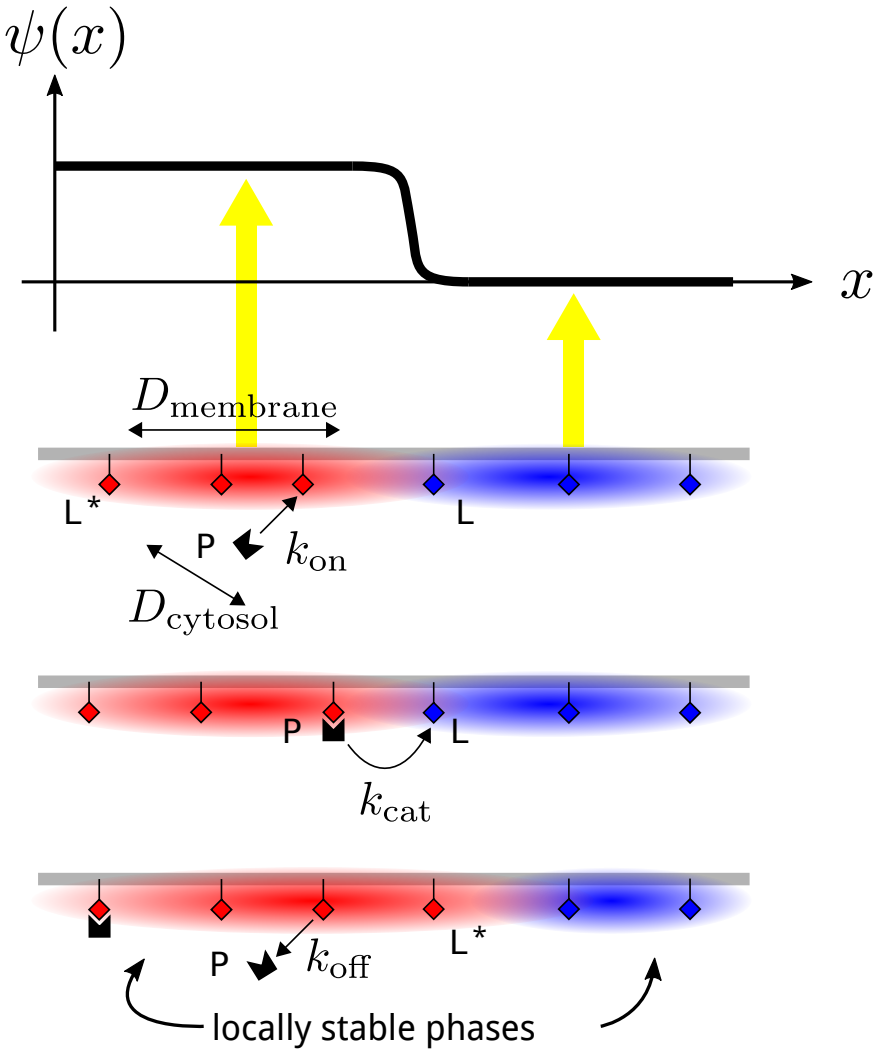

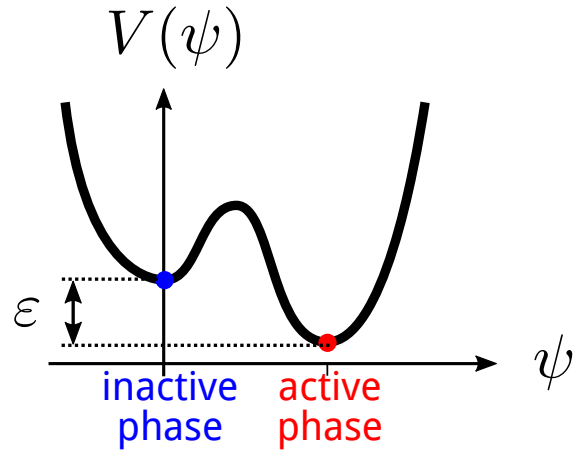

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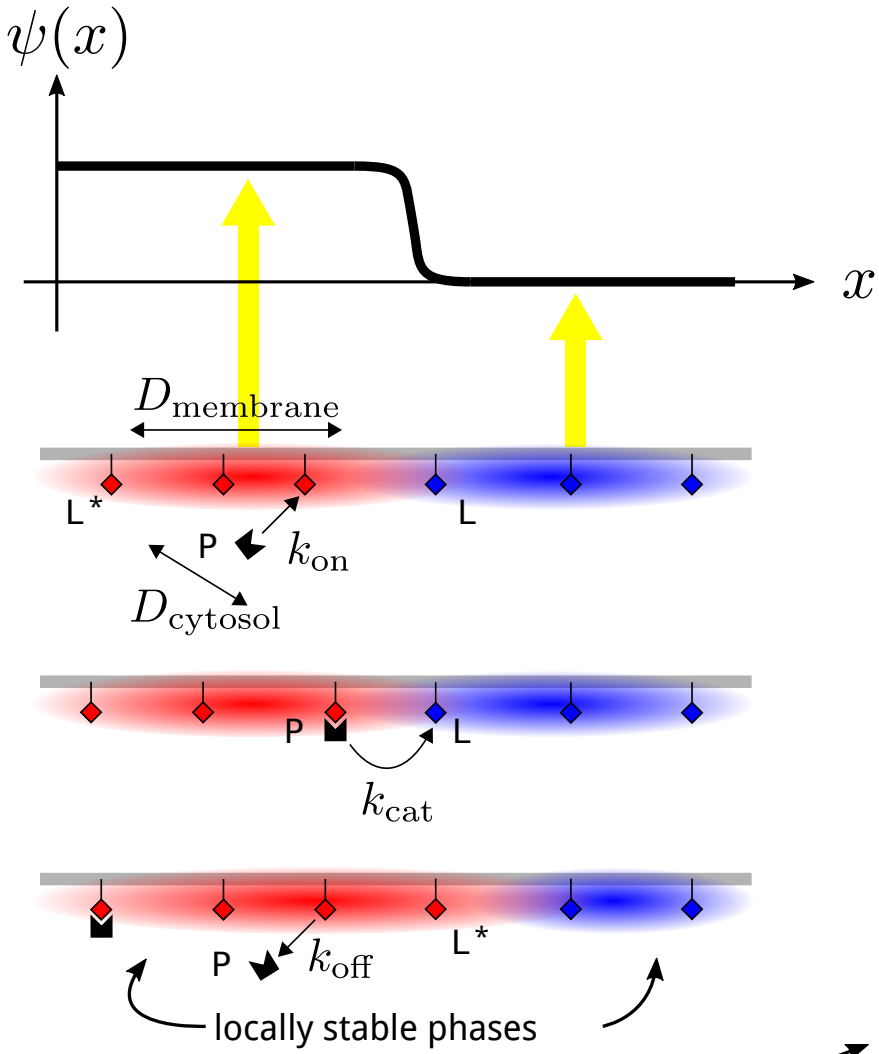

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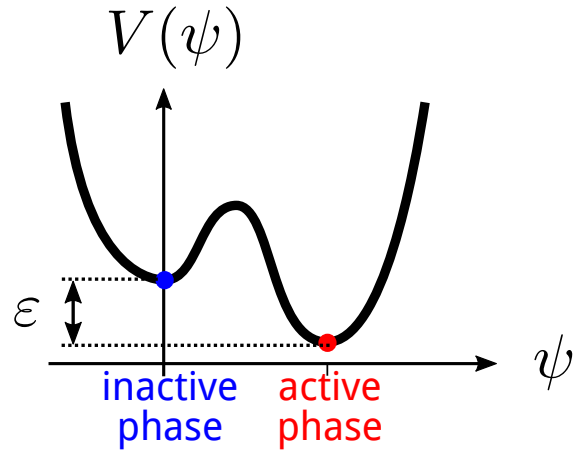

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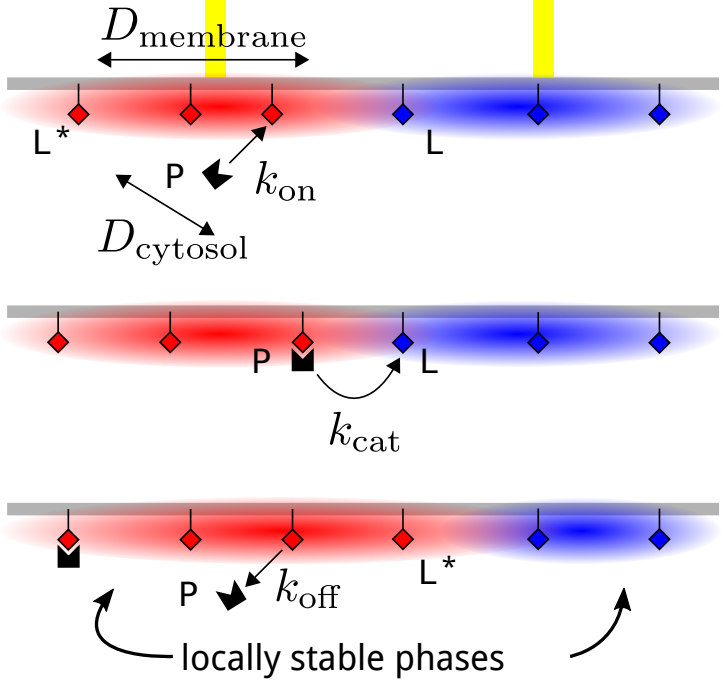

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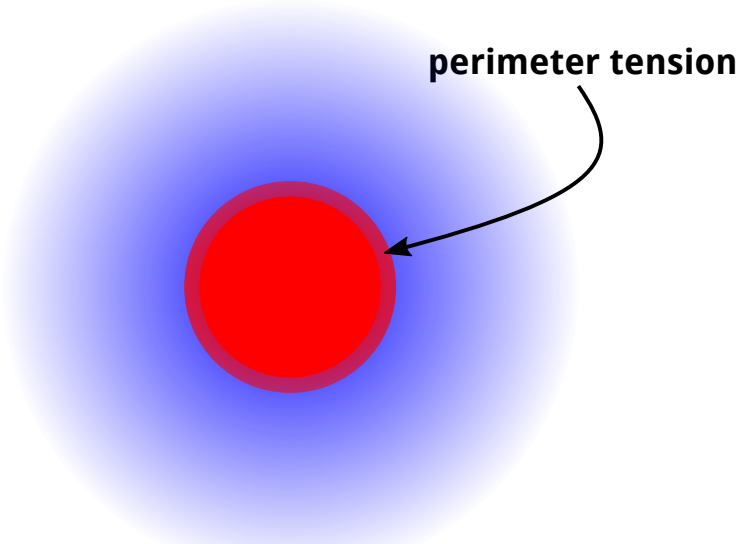

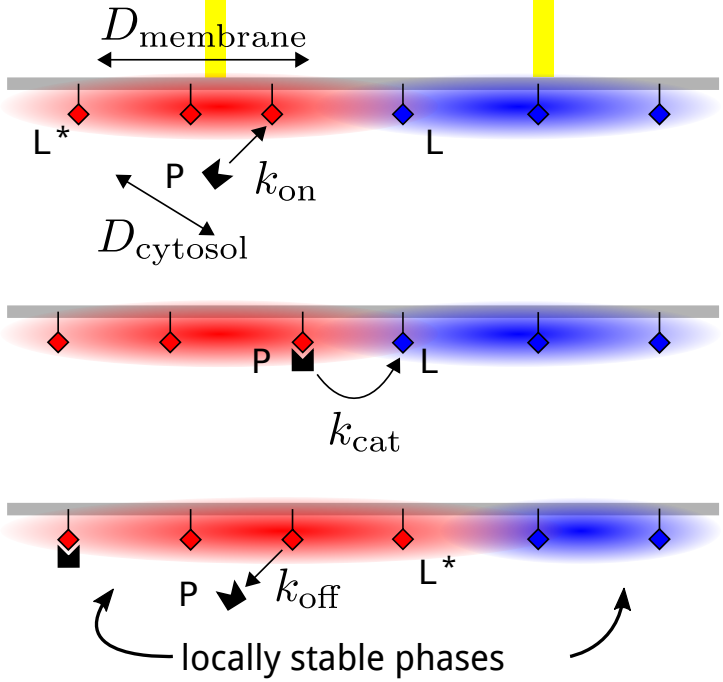

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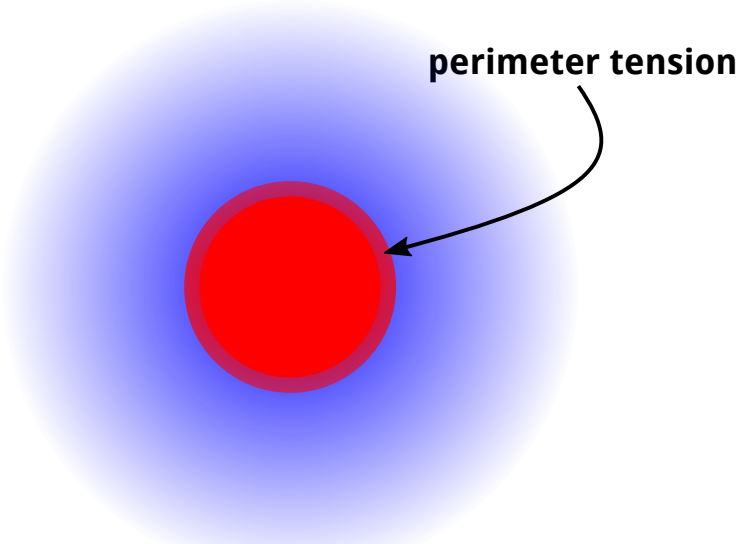

- **nucleation**
- **coarsening**
- **coalescence**

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V Lebedev, G Ortenzi
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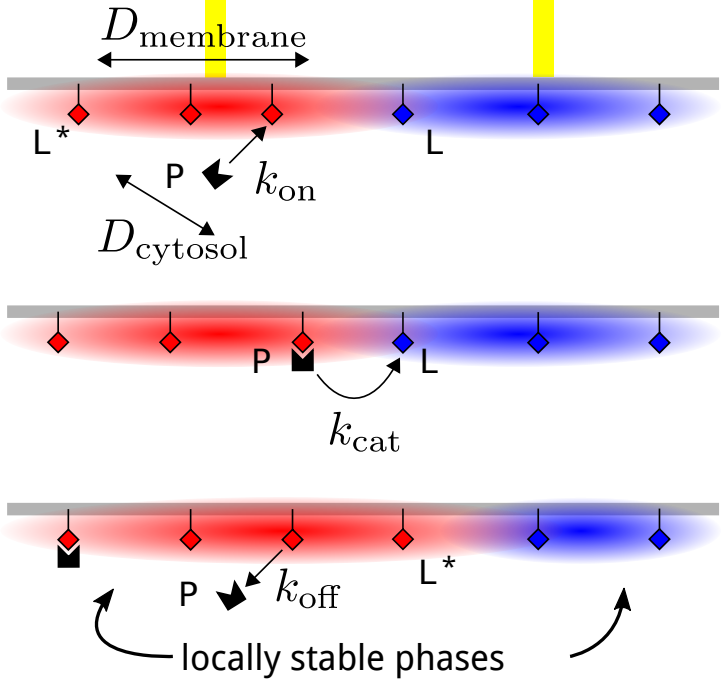

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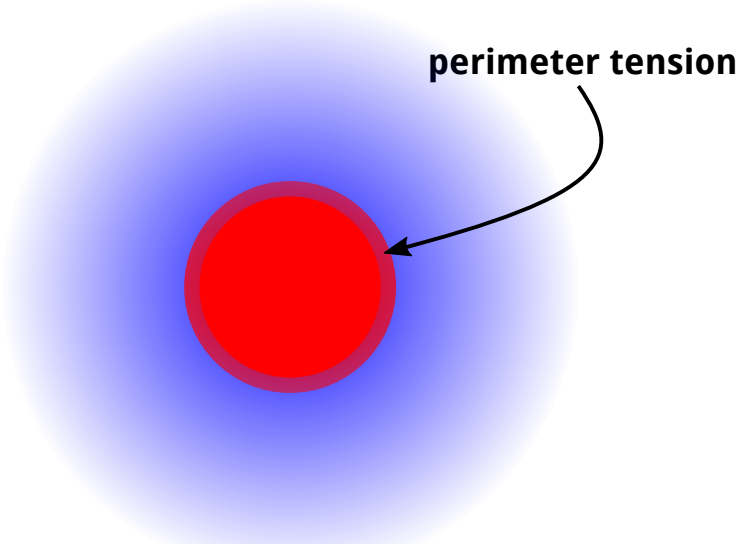

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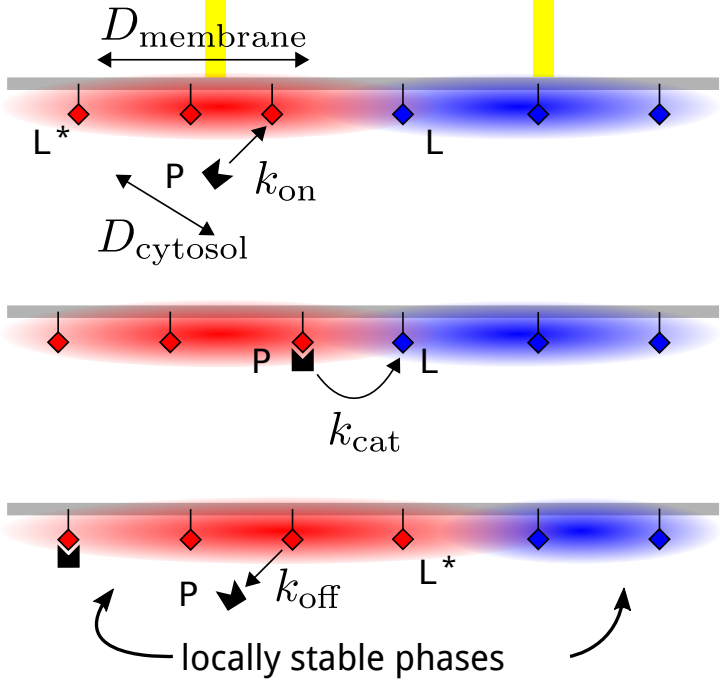
time



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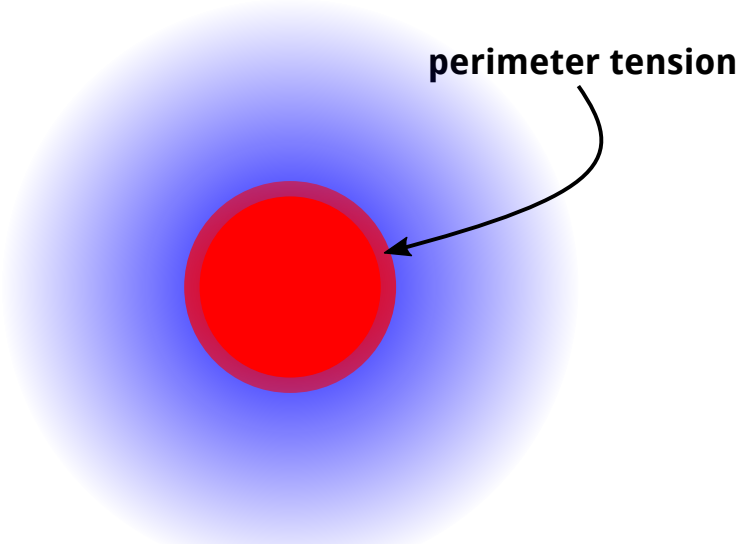

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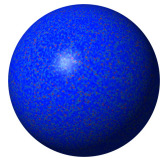

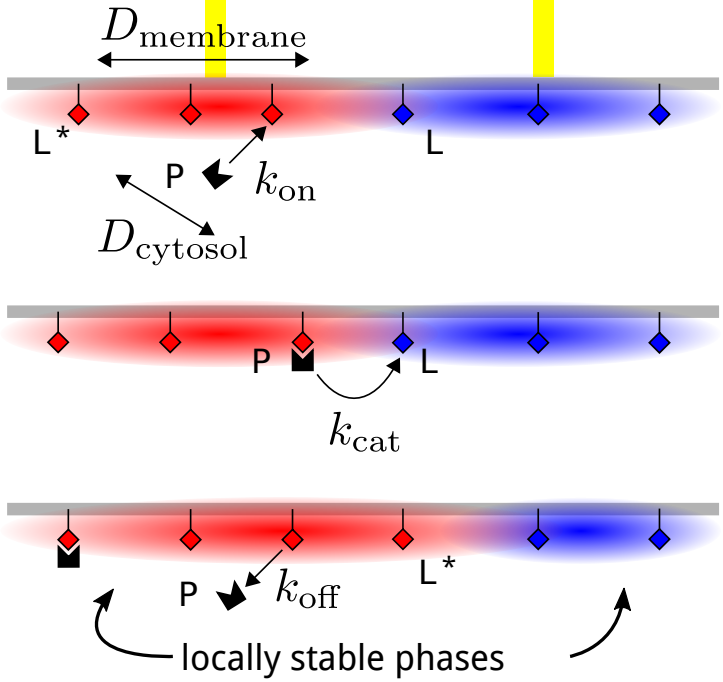

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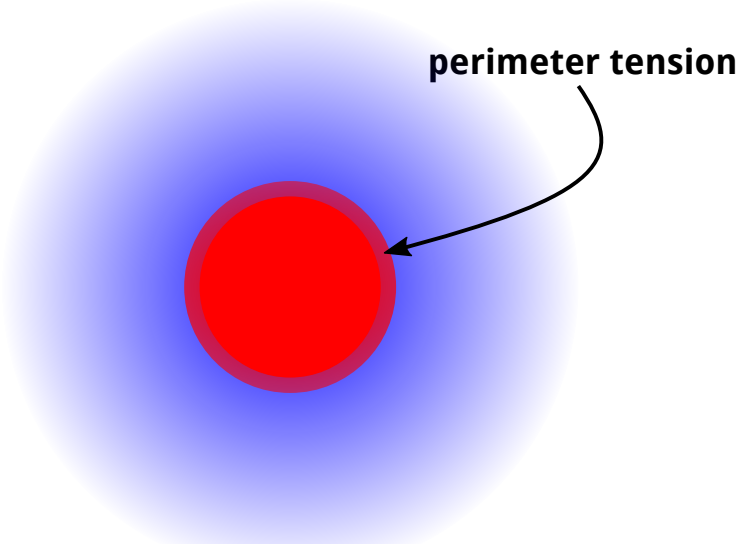

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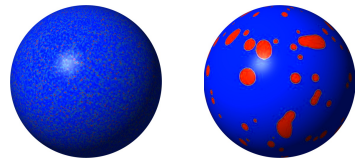

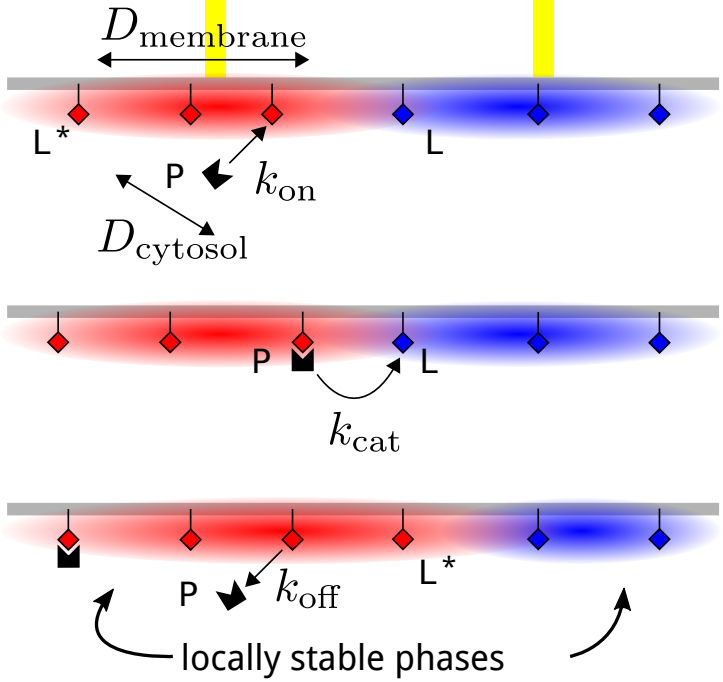

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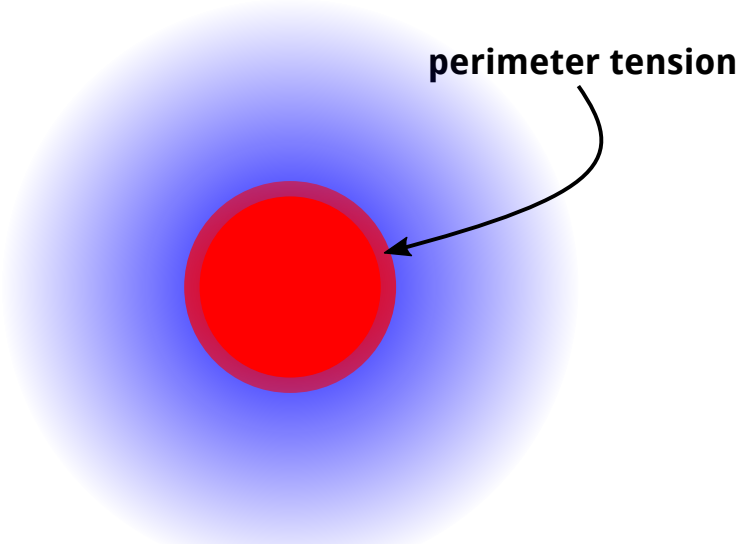

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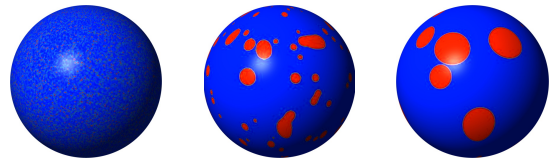

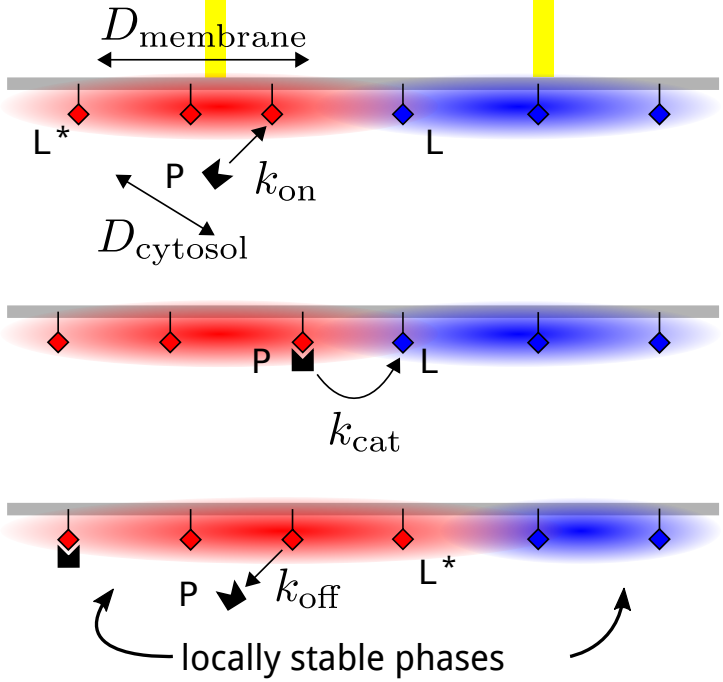

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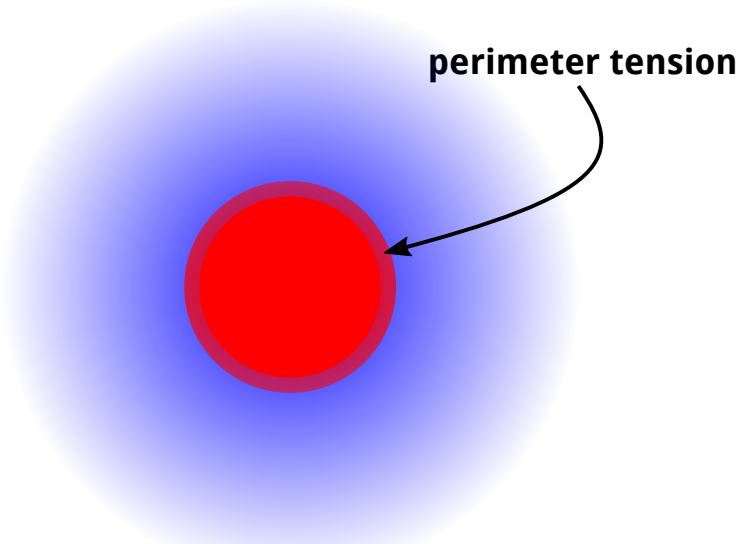

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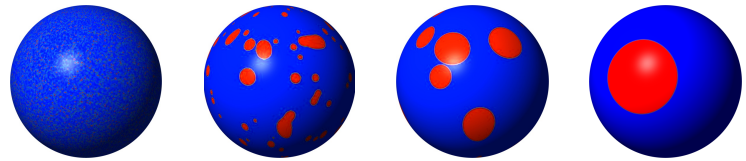

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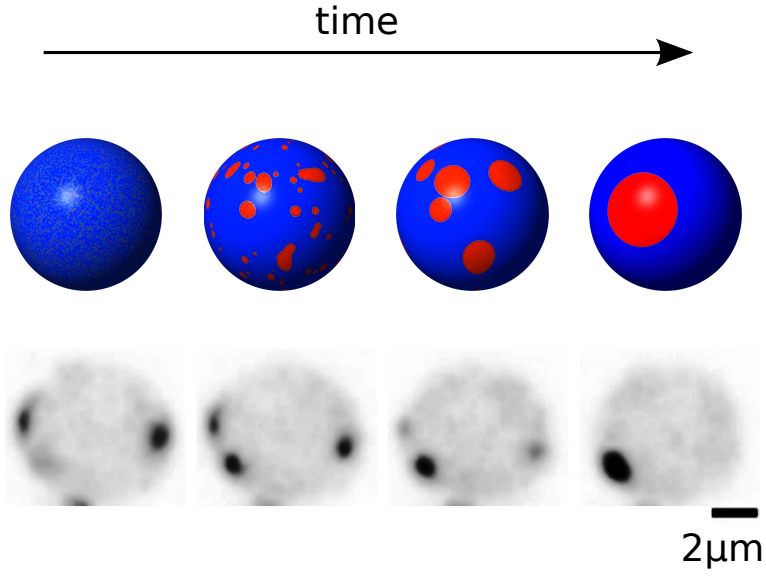
Domain coarsening

The competition hypothesis predicts that polarity establishment should frequently proceed via a transient intermediate stage with more than one polarity cluster, but there is limited experimental evidence for such intermediates, as only rare, fleeting two-cluster instances were identified in *rsr1*Δ cells (Howell et al., 2009). Thus, either competition occurs very rapidly, or some other mechanism ensures that only a single cluster develops. To distinguish between these possibilities, we developed higher-resolution filming conditions that circumvented the phototoxicity of previous protocols. We now document the frequent formation of more than one polarity cluster, and rapid competition between clusters, during symmetry-breaking polarization in *rsr1*Δ cells. Rapid filming of initial polarity



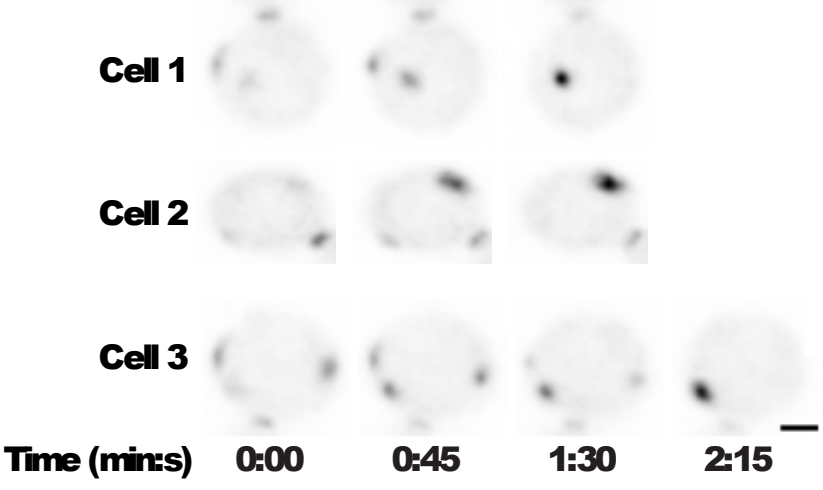


Figure 1. Dynamic Behaviors of Bem1p-GFP during Polarity Establishment

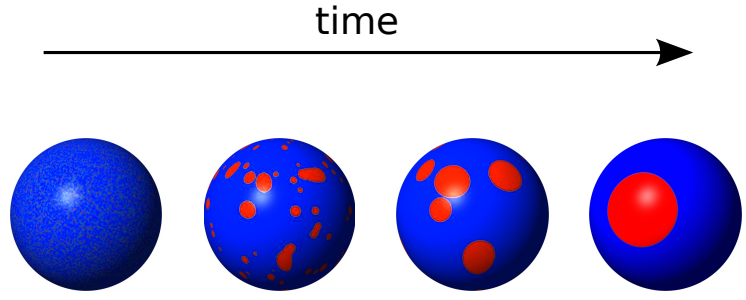
Inverted images (so dark spots represent concentrations of Bem1p-GFP) from movies of cells breaking symmetry. Time in min:s. Scale bar, 2 µm. (Neck) The "old" neck signal in the attached daughter cell.

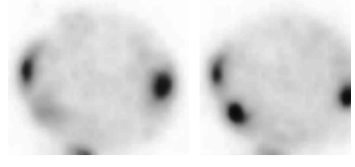
(A) Growth of multiple Bem1p clusters (numbered in the key at right) and resolution to a single cluster. t = 0 indicates the first detection of polarized signal.

Howell et al, *Cell* 2012

AG, I Kolokolov,
V Lebedev, G Ortenzi
PRL 2007

Domain coarsening





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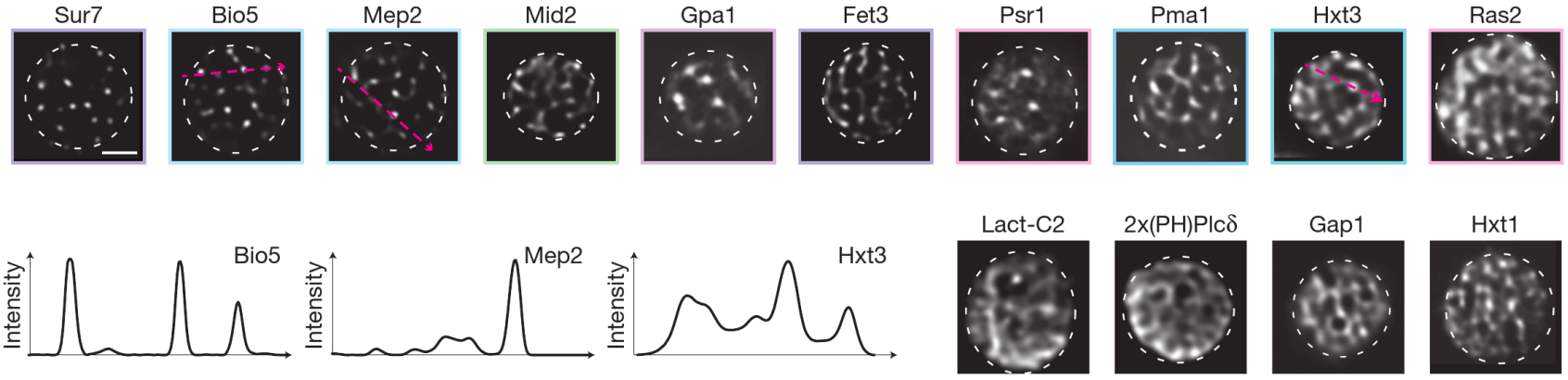
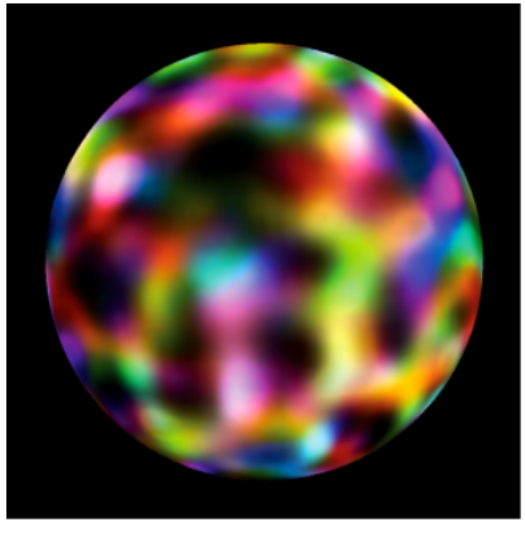
Howell et al, *Cell* 2012

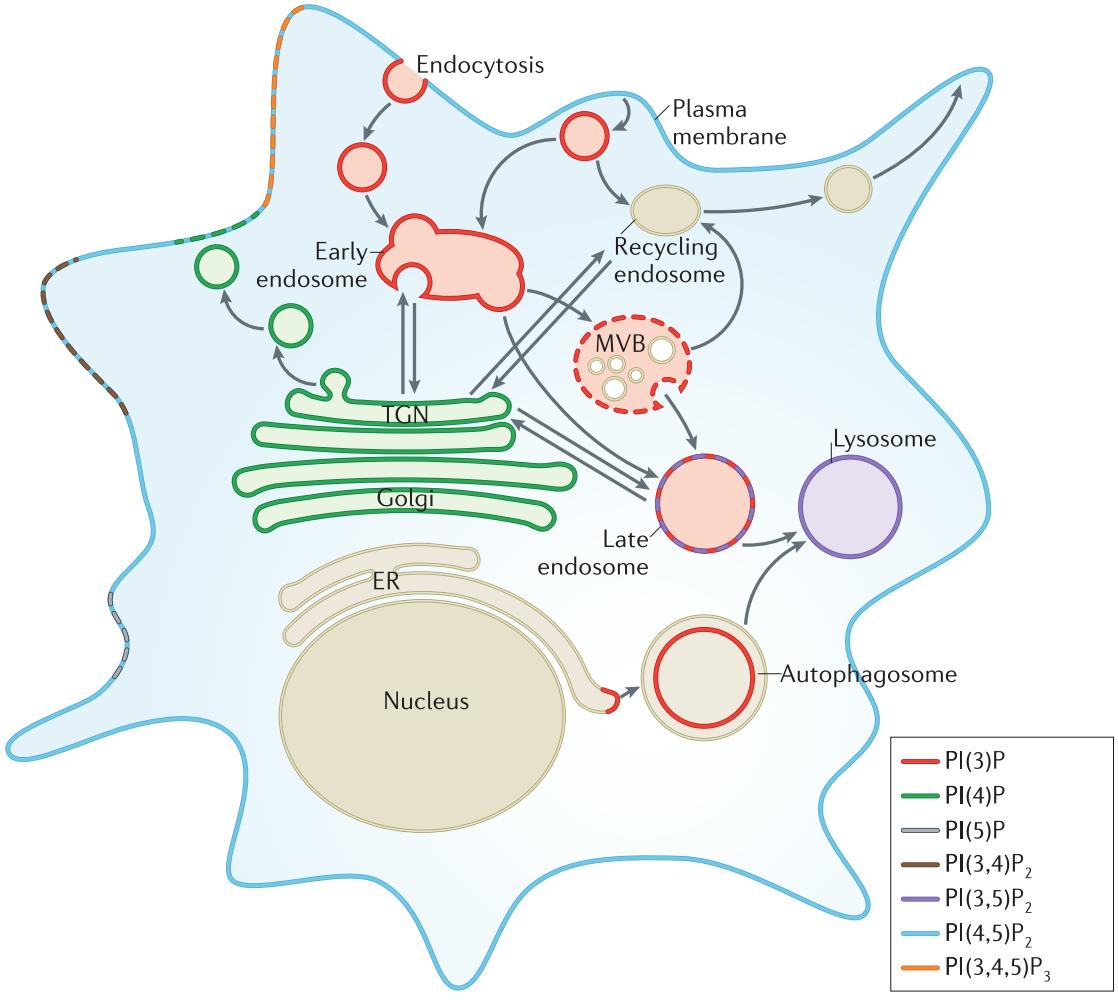
Microdomains



Spira et al. Pathwork organization of the yeast plasma membrane into numerous coexisting domains, Nat Cell Biol 14 (2012)

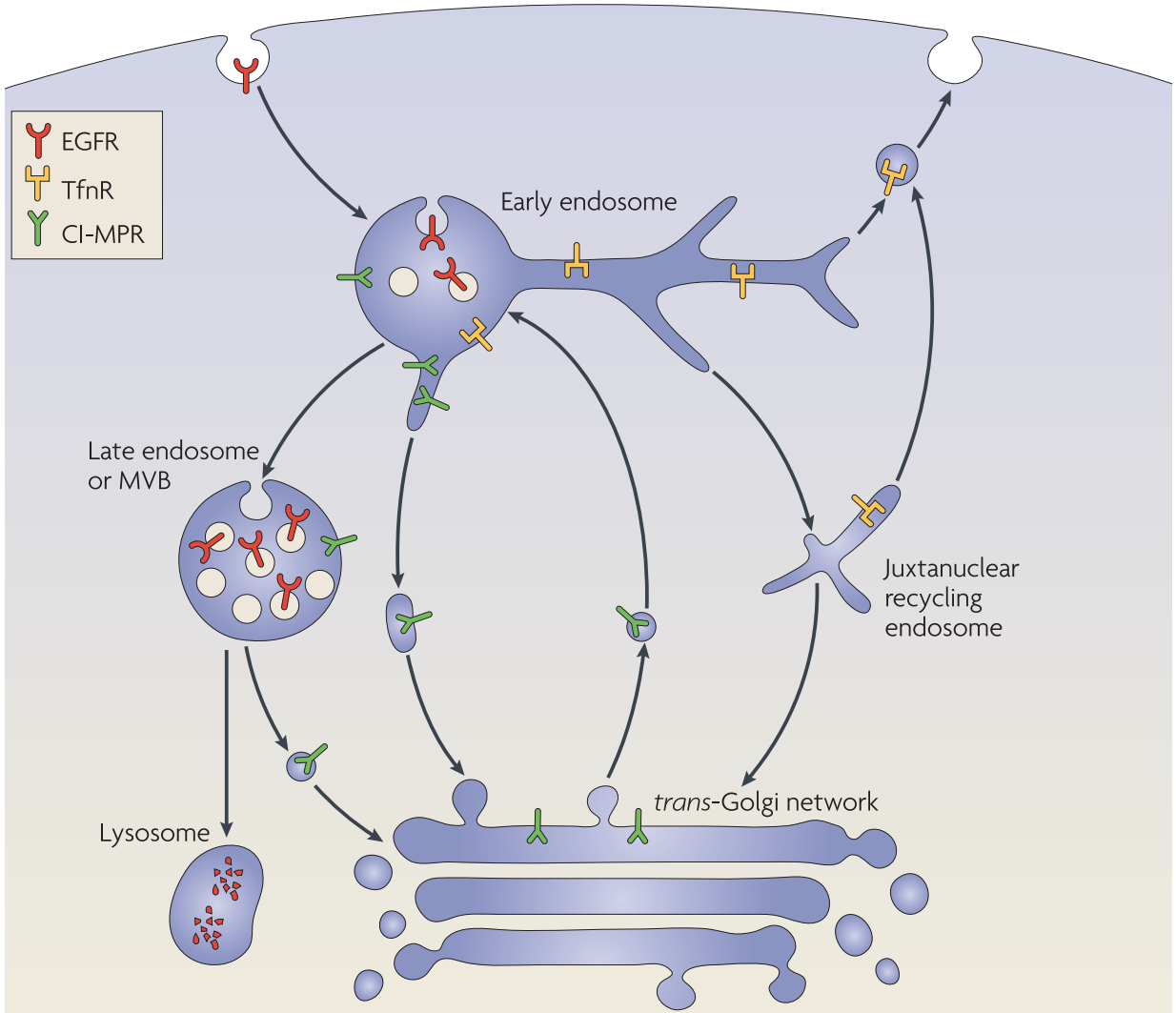


A dynamic picture



modified from Jean & Kiger
Nat Rev Mol Cell Biol 2012

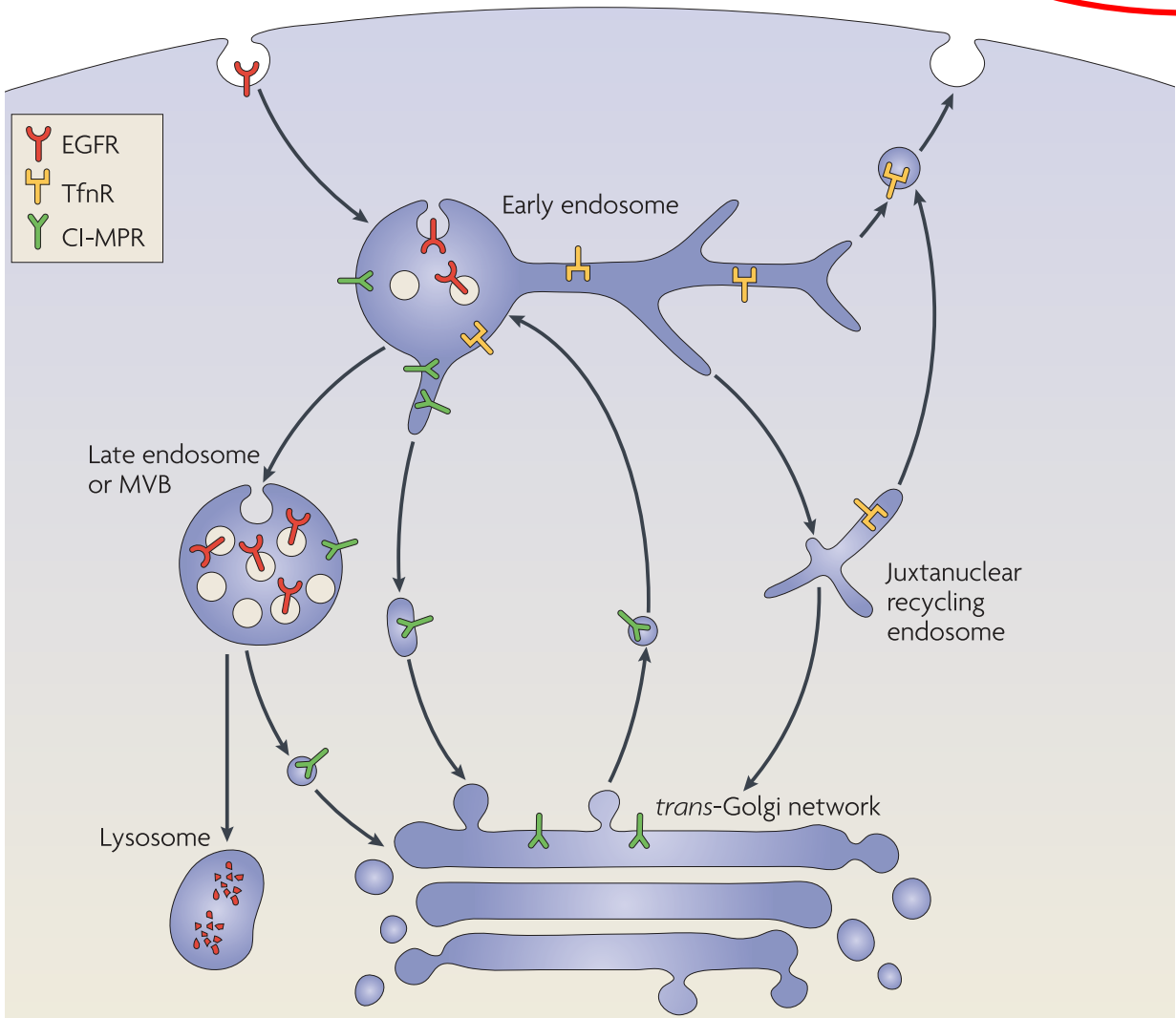
Molecular sorting



Cullen
Nat Rev
Mol Cell Biol
2008

Molecular sorting

SORTING COUNTERS DIFFUSION, ORDERS THE SYSTEM



Cullen
Nat Rev
Mol Cell Biol
2008

Molecular sorting

Underlying physical mechanism?

Molecular sorting

Underlying physical mechanism?

coupling:

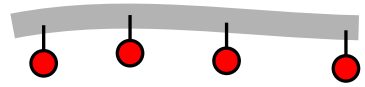
Molecular sorting

Underlying physical mechanism?

coupling:

affinity-driven aggregation

Molecular sorting



Underlying physical mechanism?

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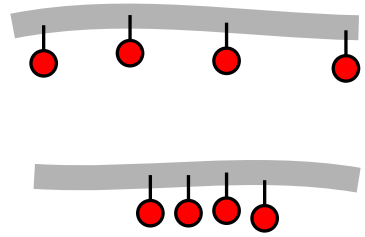
affinity-driven aggregation

Molecular sorting

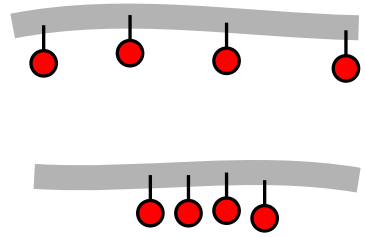


Underlying physical mechanism?

coupling:

affinity-driven aggregation

Molecular sorting

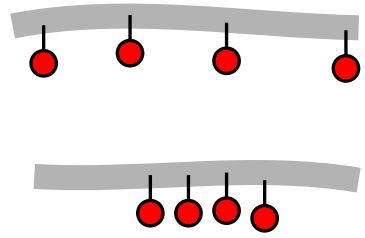


Underlying physical mechanism?

coupling:

affinity-driven aggregation **+**

Molecular sorting

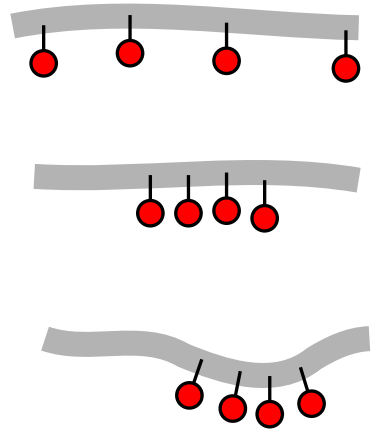


Underlying physical mechanism?

coupling:

affinity-driven aggregation + **vesicle nucleation**

Molecular sorting



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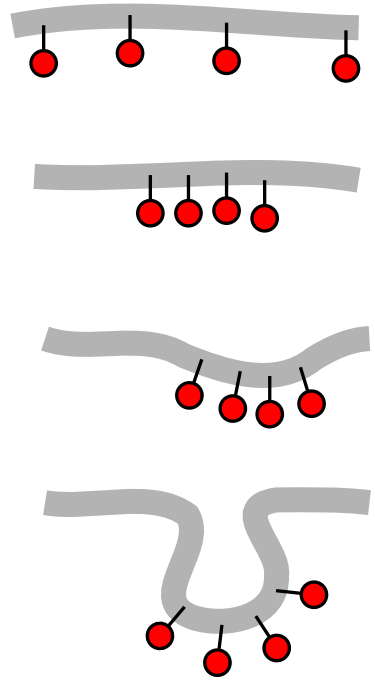
Molecular sorting



Underlying physical mechanism?

coupling:

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Molecular sorting

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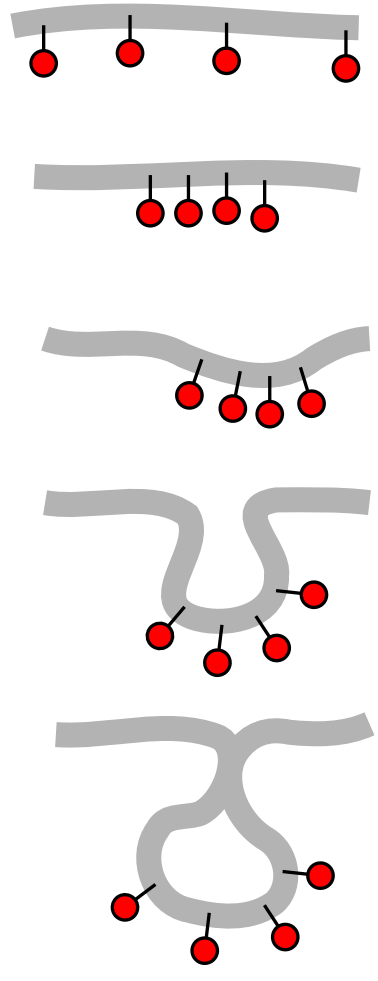


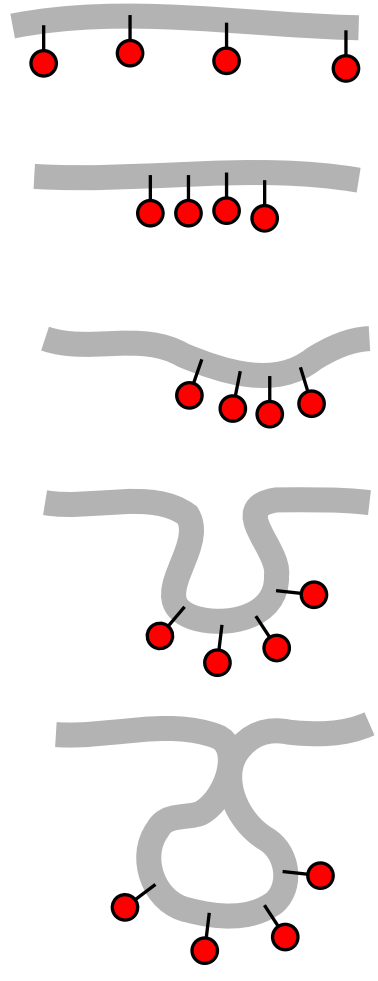
Molecular sorting

Underlying physical mechanism?

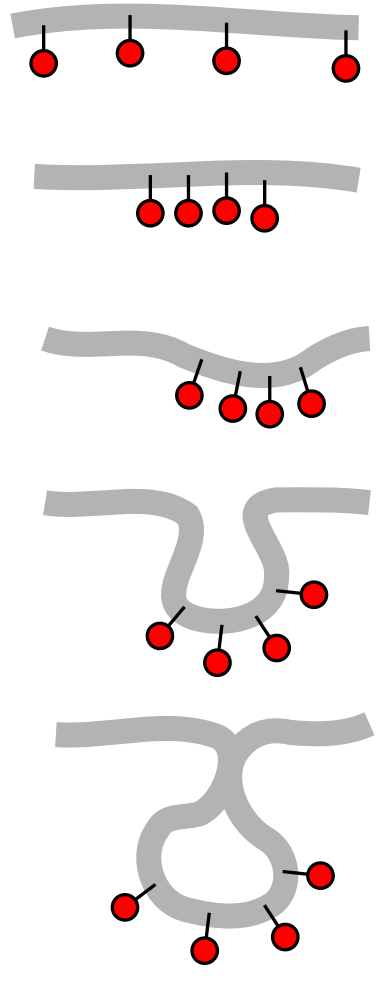
coupling:

affinity-driven aggregation + **vesicle nucleation**

should result in:



Molecular sorting



Underlying physical mechanism?

coupling:

affinity-driven aggregation + **vesicle nucleation**

should result in:

spontaneous distillation of molecular factors

Molecular sorting

Underlying physical mechanism?

coupling:

affinity-driven aggregation + **vesicle nucleation**

should result in:

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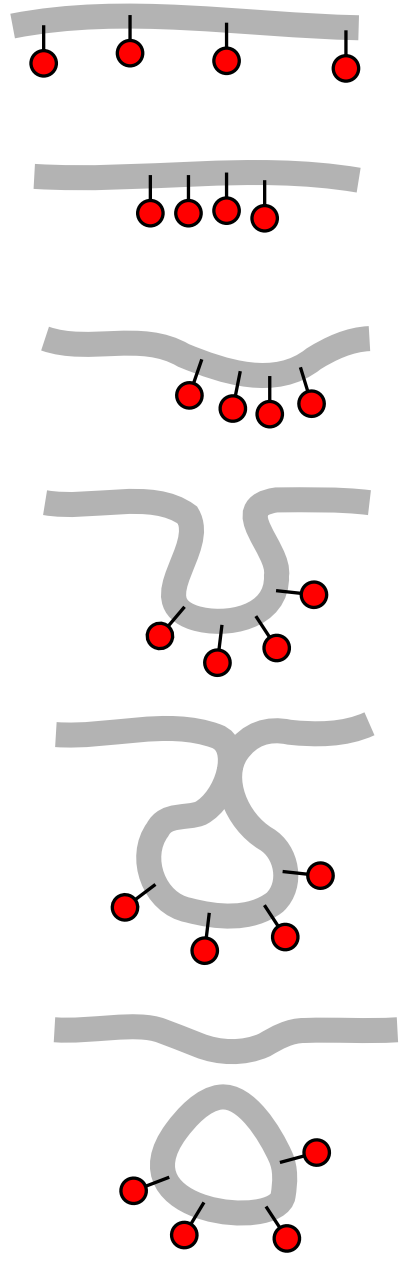
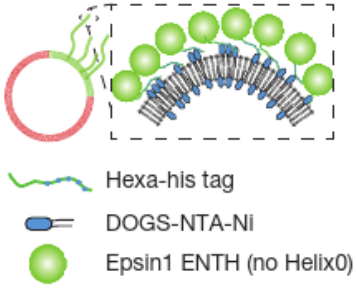
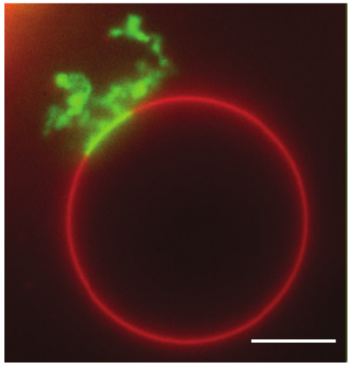
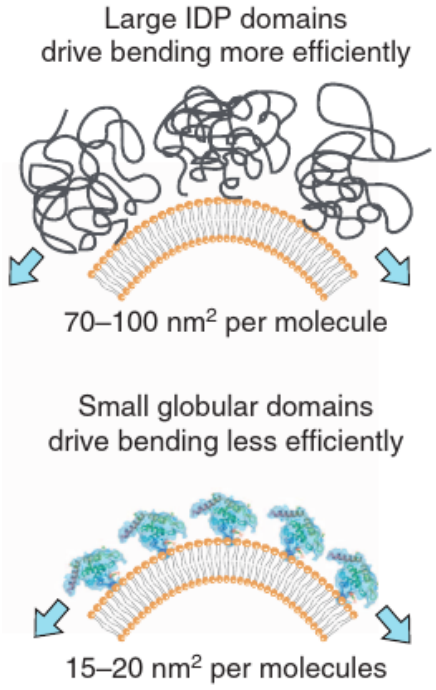


Molecular crowding induces membrane bending and vesicle nucleation



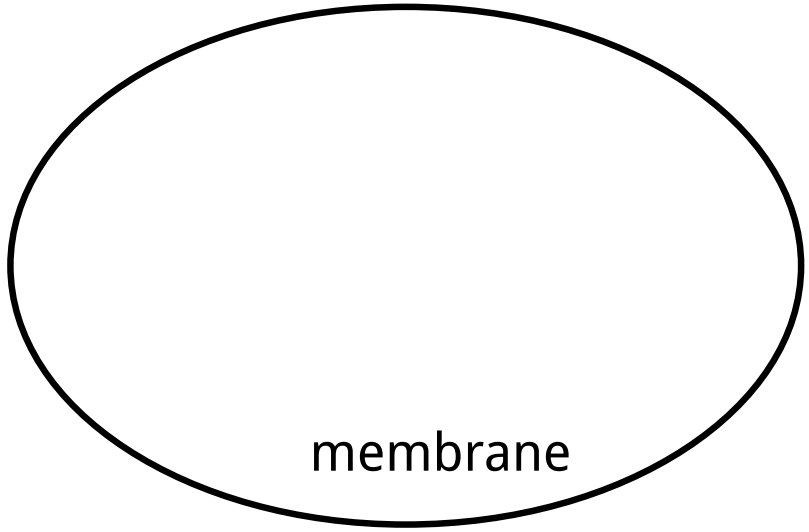




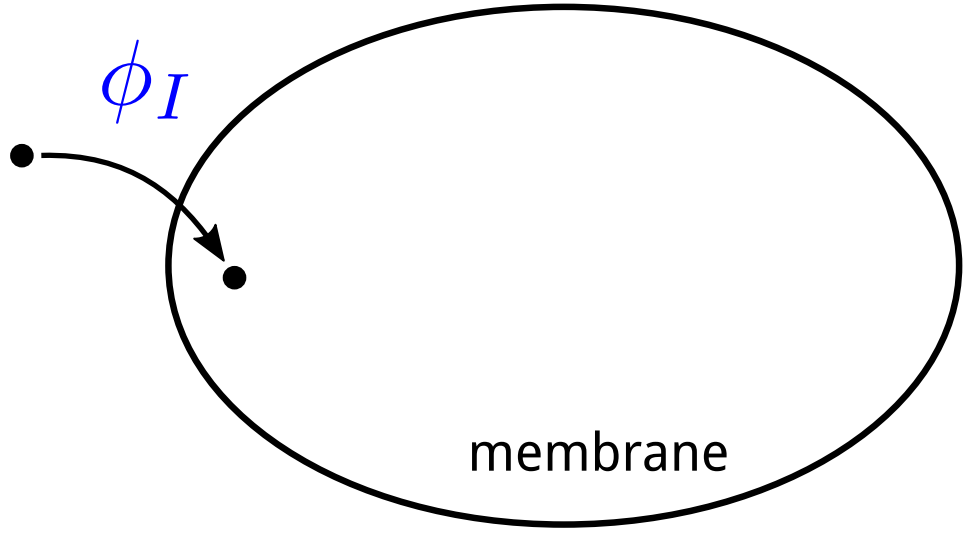
JC Stachowiak et al
Membrane bending
by protein-protein crowding
Nat Cell Biol 2012

DJ Busch et al
Intrinsically disordered proteins drive membrane curvature.
Nat Commun 2015

Minimal model of molecule sorting

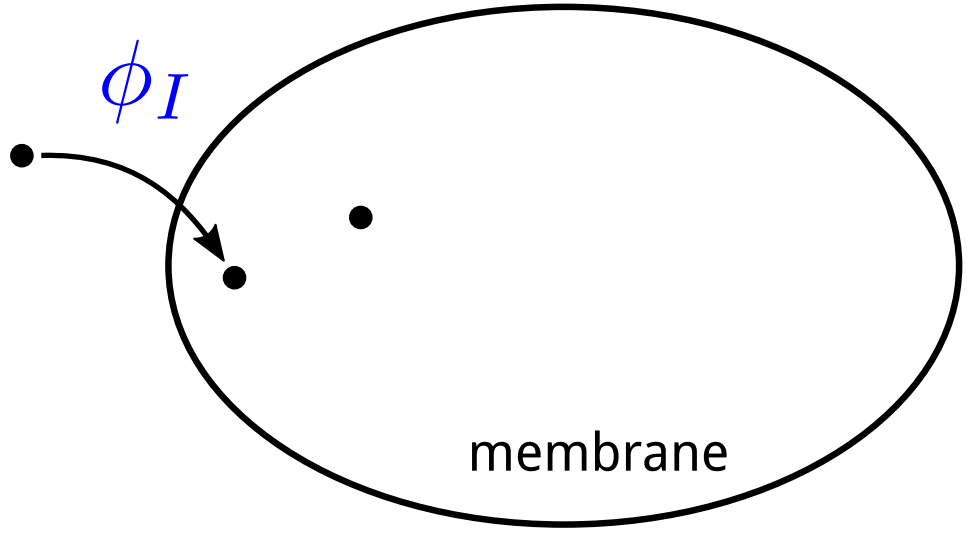


Minimal model of molecule sorting



ϕ_I : incoming molecule flux

Minimal model of molecule sorting



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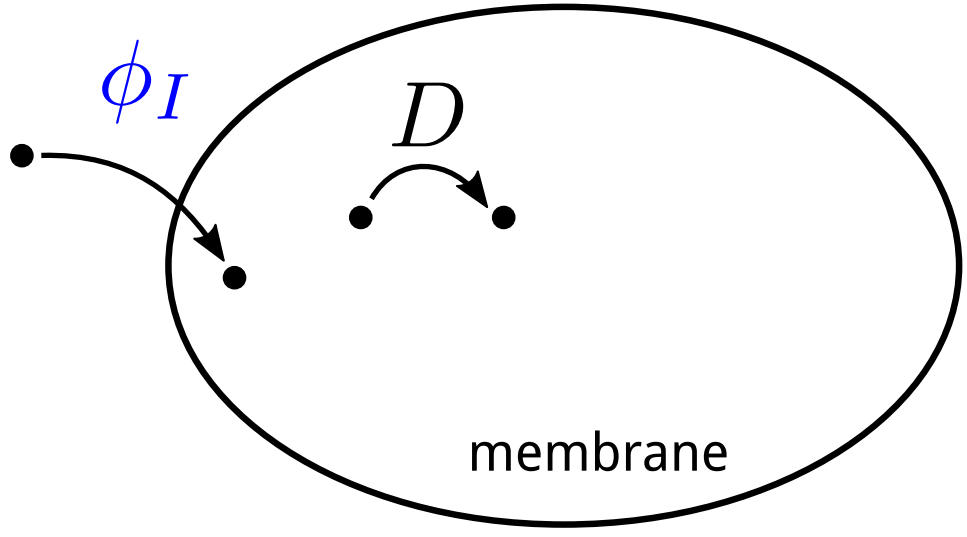
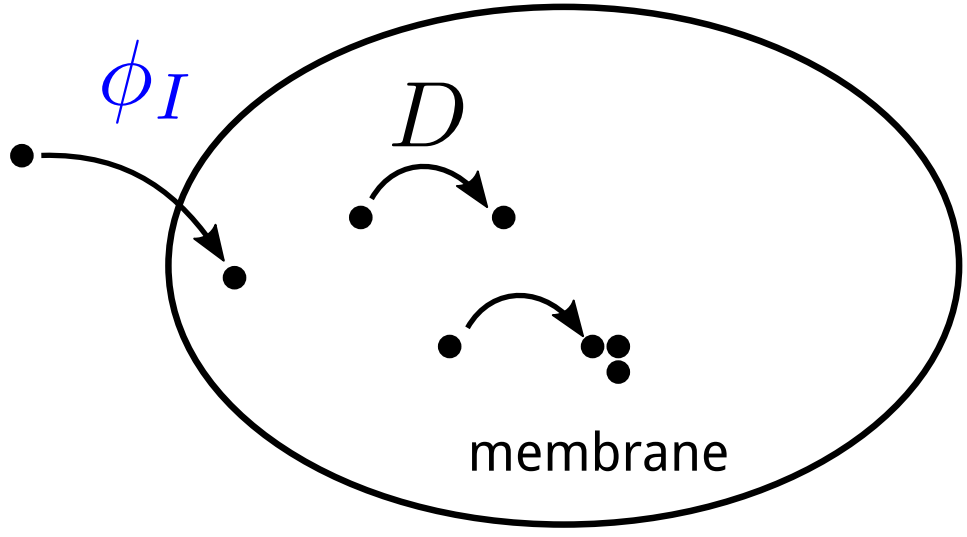
Minimal model of molecule sorting



ϕ_I : incoming molecule flux

D : diffusivity

Minimal model of molecule sorting



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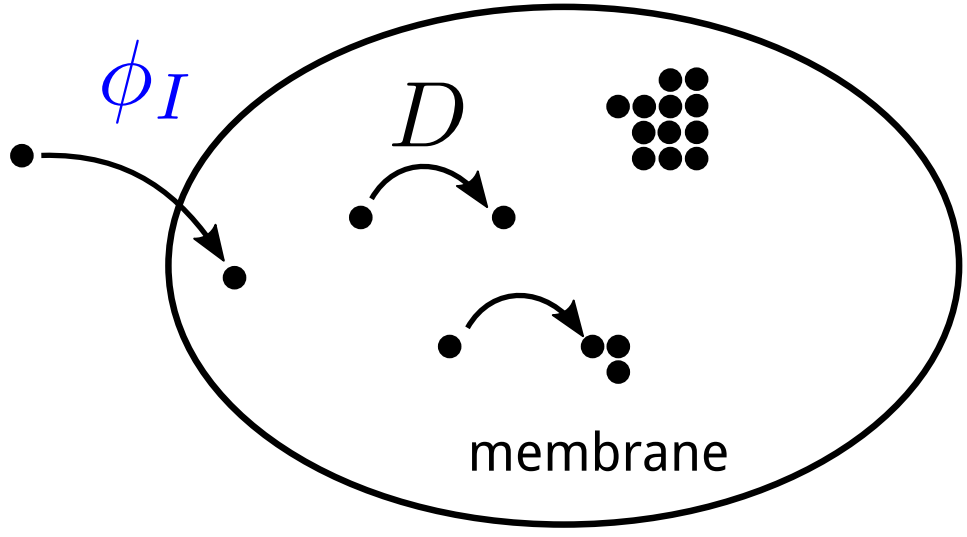
D : diffusivity

attractive interaction

Minimal model of molecule sorting



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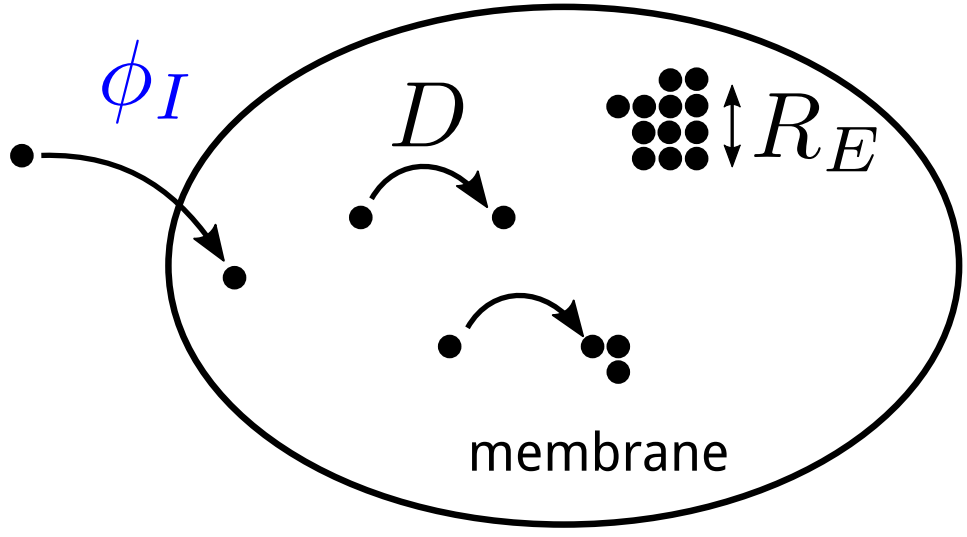


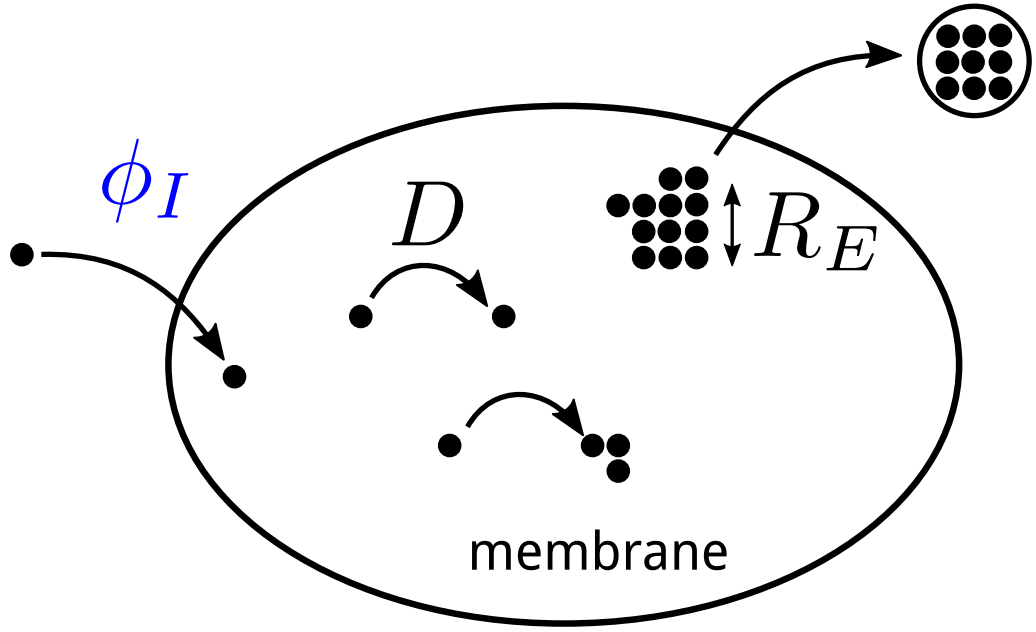
ϕ_I : incoming molecule flux

D : diffusivity

R_E : extraction size

attractive interaction

Minimal model of molecule sorting



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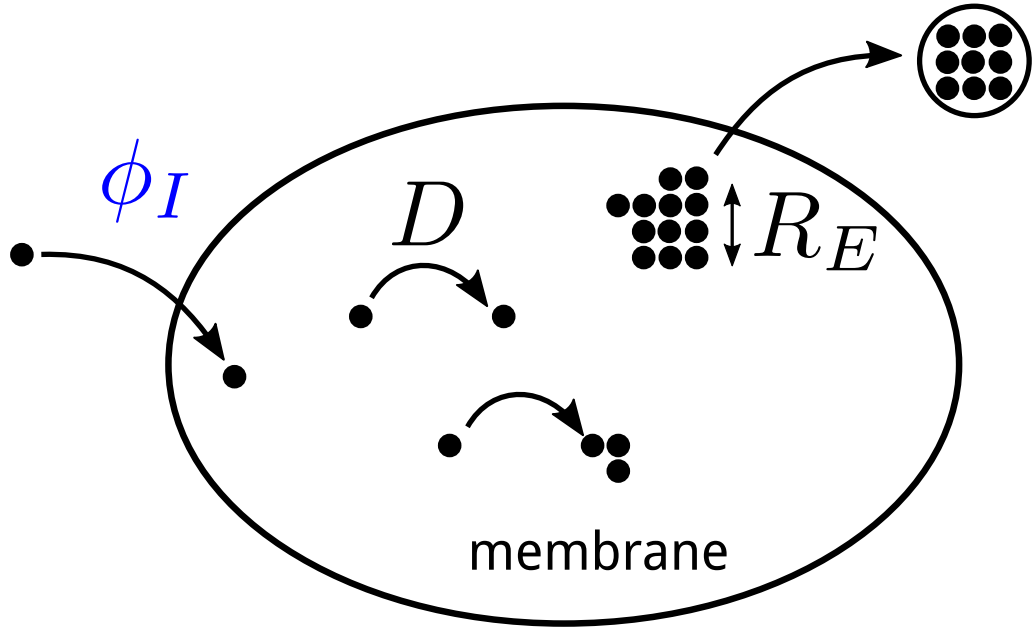

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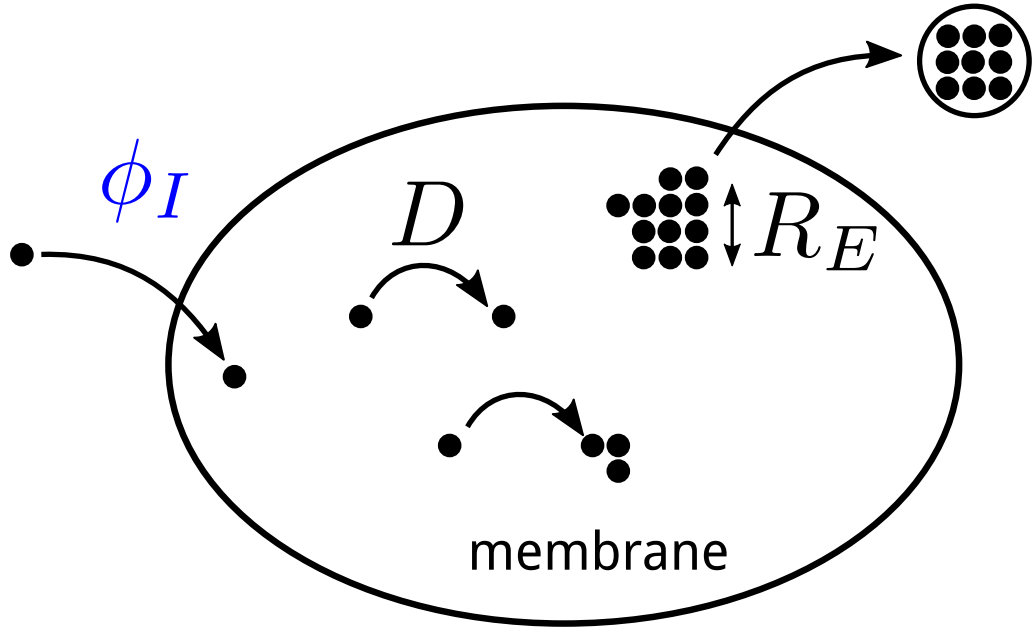


Sorting efficiency?

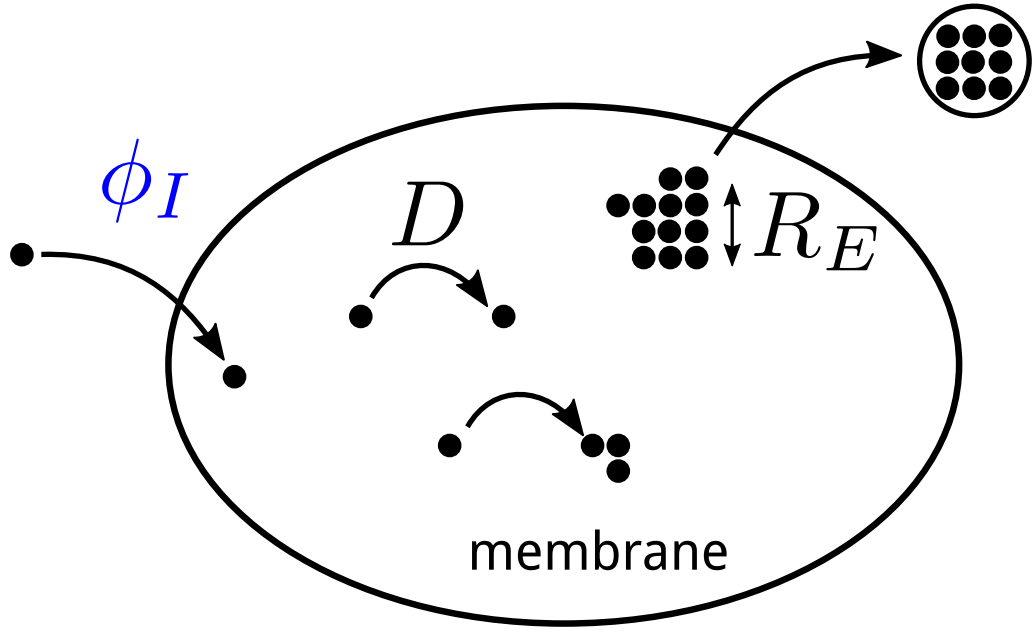
ϕ_I : incoming molecule flux

D : diffusivity

R_E : extraction size

attractive interaction

Minimal model of molecule sorting



Sorting efficiency?

$\bar{T}$: average time spent by a molecule in the system

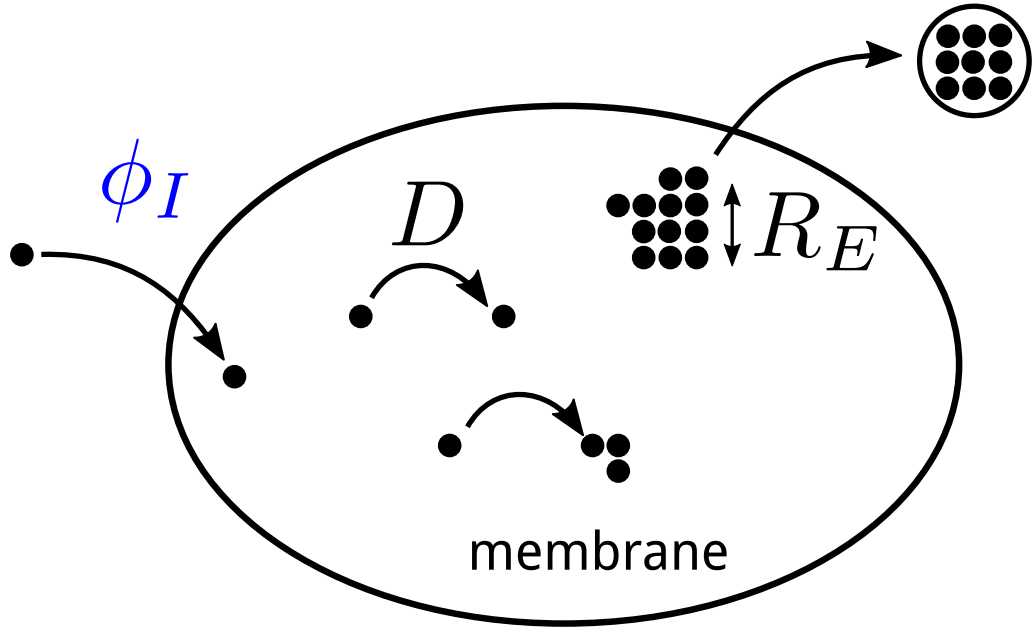
ϕ_I : incoming molecule flux

D : diffusivity

R_E : extraction size

attractive interaction

Minimal model of molecule sorting



ϕ_I : incoming molecule flux

D : diffusivity

R_E : extraction size

attractive interaction

Sorting efficiency?

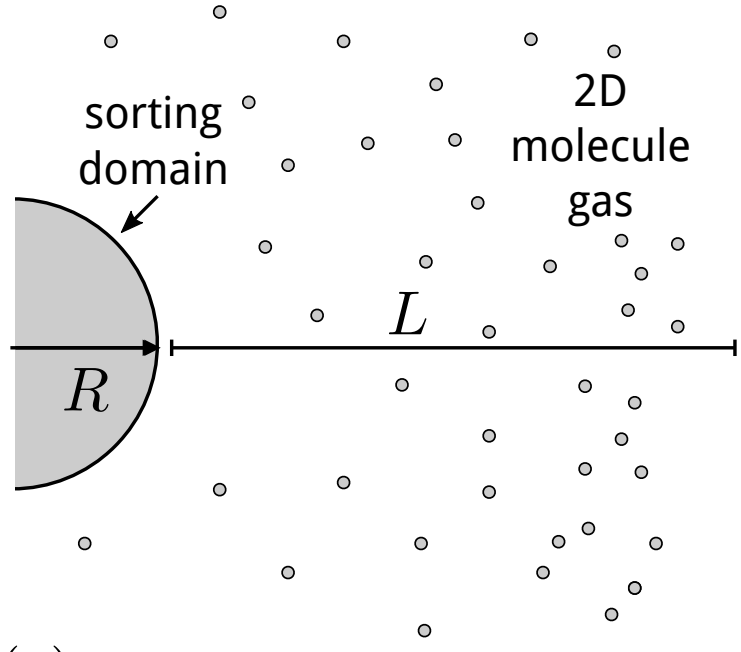
$\bar{T}$: average time spent by a molecule in the system

$S = \frac{1}{\bar{T}}$: sorting rate

Domain growth

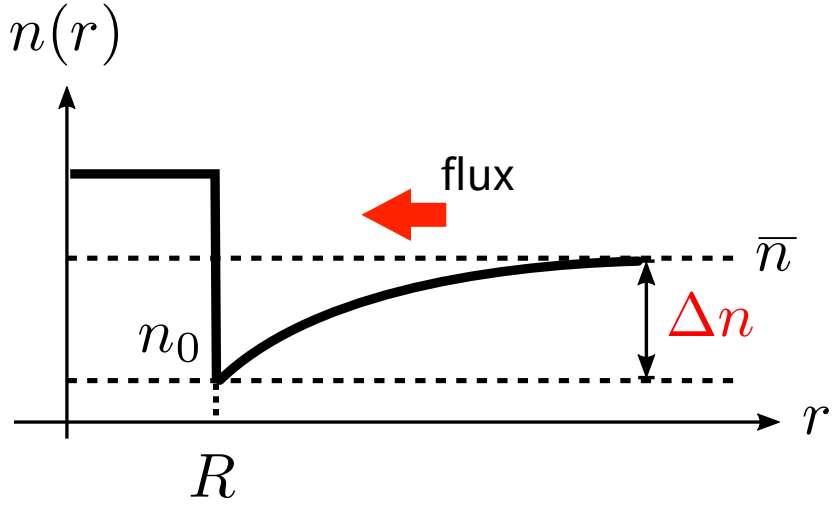
density profile of
freely diffusing molecules:

$$n(r) = n_0 + \frac{\log r/R}{\log L/R}\Delta n$$



flux of molecules
towards sorting domain:

$$\Phi_R = 2\pi r D \frac{\partial n}{\partial r}\bigg|_{r=R} = \frac{2\pi D \Delta n}{\ln L/R}$$



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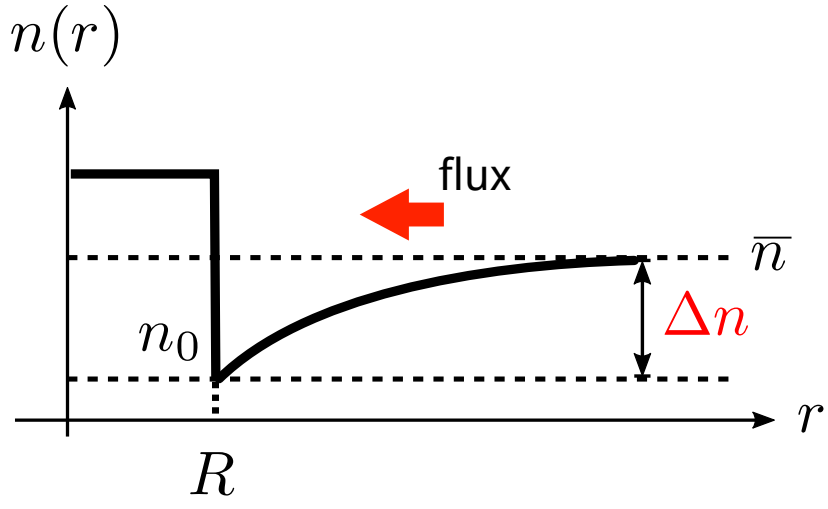
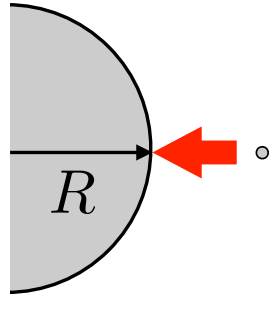


speed of accretion of
sorting domain:

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \frac{\Phi_R}{2\pi R}$$



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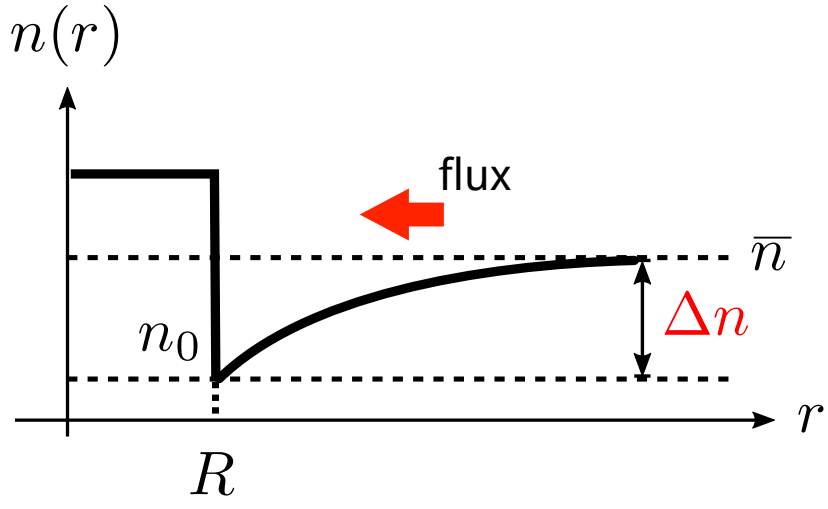

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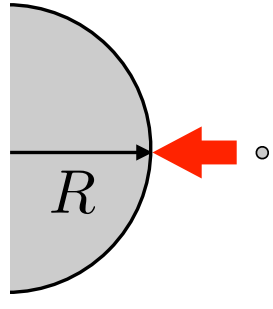

$N(R,t)$: number distribution of domains

flux of molecules
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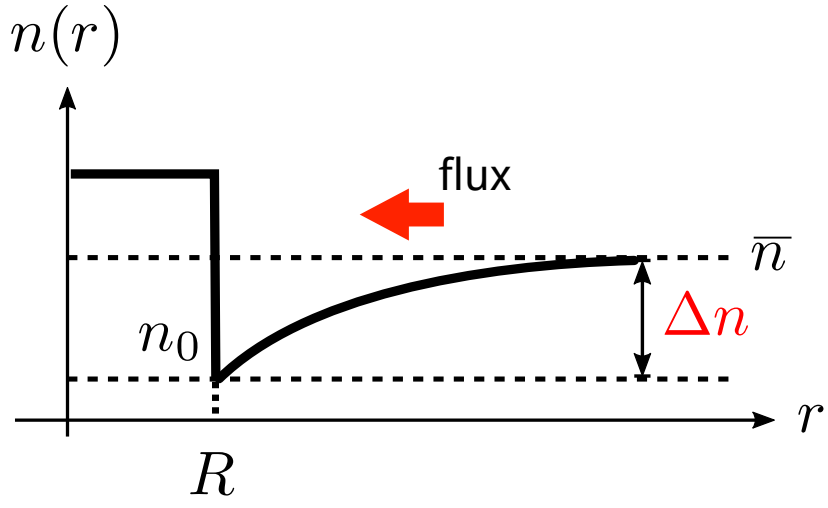

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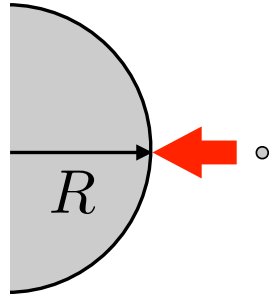
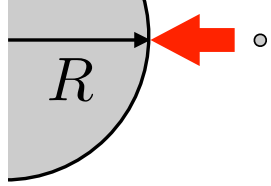


$N(R,t)$: number distribution of domains

$$\frac{\partial}{\partial t}N + \frac{\partial}{\partial R}\left(\frac{\Phi_R}{2\pi R}N\right) = \gamma(R)N$$

$\gamma(R)$: extraction rate

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \frac{\Phi_R}{2\pi R}$$



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$$\frac{\partial}{\partial t}N + \frac{\partial}{\partial R}\left(\frac{\Phi_R}{2\pi R}N\right) = \gamma(R)N$$

$\gamma(R)$: extraction rate

in a stationary condition:

$$N_{\mathrm{st}}(R) = \frac{JR\ln L/R}{D\Delta n}\exp\left[-\int_0^R \frac{r\ln L/r}{D\Delta n}\gamma(r)\mathrm{d}r\right]$$

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$$\frac{\partial}{\partial t}N + \frac{\partial}{\partial R}\left(\frac{\Phi_R}{2\pi R}N\right) = \gamma(R)N$$

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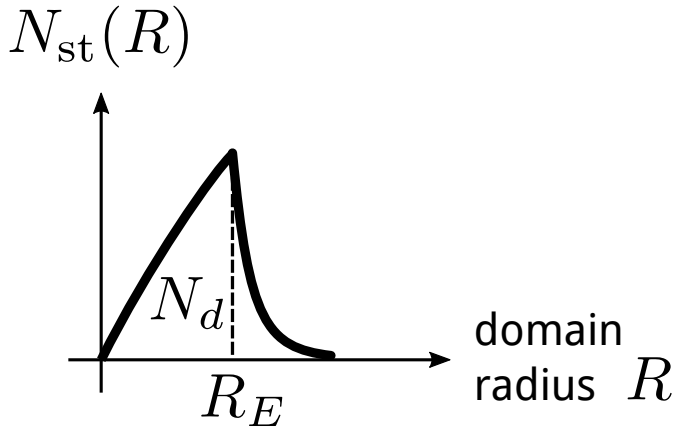
the total number of domains is found self-consistently:

$$\int \Phi_R N_{\mathrm{st}}(R)\mathrm{d}R = \phi_I \quad \Rightarrow \quad J \sim \frac{\phi_I}{R_E^2}$$

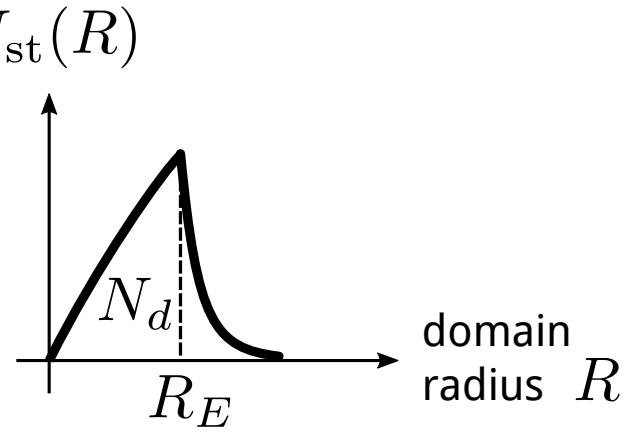


ϕ_I : incoming molecule flux

$$N_d = \int N_{\mathrm{st}}(R)\mathrm{d}R \sim \frac{\phi_I}{D\Delta n}$$

the total number of domains is found self-consistently:

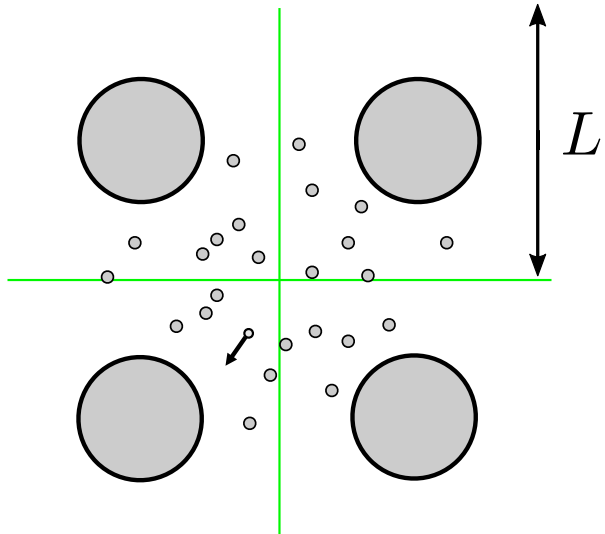
$$\int \Phi_R N_{\rm st}(R)\mathrm{d}R = \phi_I \quad \Rightarrow \quad J \sim \frac{\phi_I}{R_E^2}$$



ϕ_I : incoming molecule flux

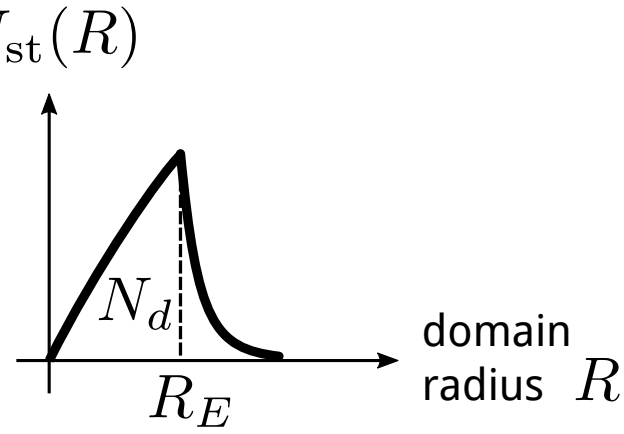
$$N_d = \int N_{\rm st}(R)\mathrm{d}R \sim \frac{\phi_I}{D\Delta n}$$

Average time spent on the membrane: $\bar{T} = \bar{T}_f + \bar{T}_d$



the total number of domains is found self-consistently:

$$\int \Phi_R N_{\rm st}(R)\mathrm{d}R = \phi_I \quad \Rightarrow \quad J \sim \frac{\phi_I}{R_E^2}$$

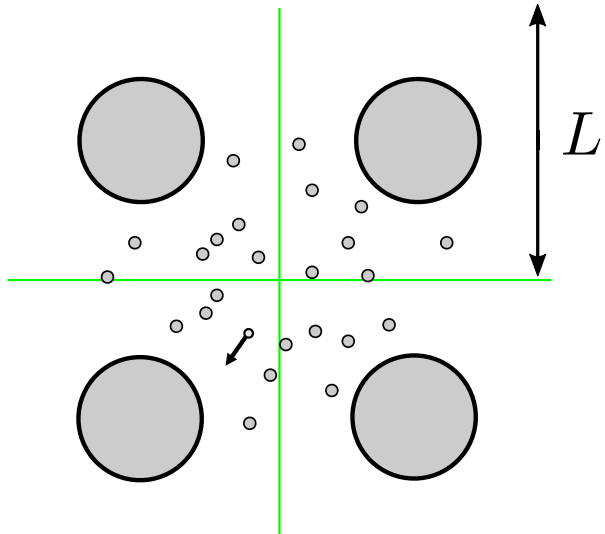


ϕ_I : incoming molecule flux

$$N_d = \int N_{\rm st}(R)\mathrm{d}R \sim \frac{\phi_I}{D\Delta n}$$

Average time spent on the membrane: $\bar{T} = \bar{T}_f + \bar{T}_d$

$$\bar{T}_f \sim \frac{L^2}{D}$$



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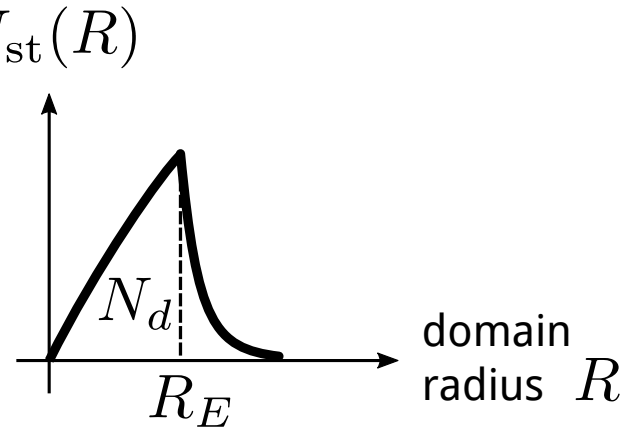

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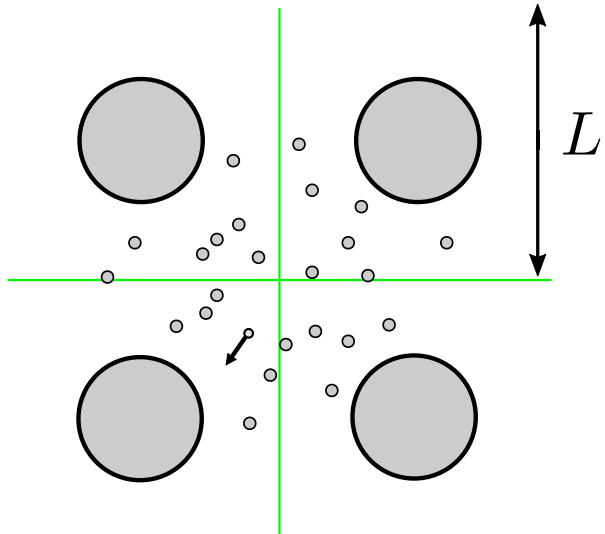
Average time spent on the membrane: $\bar{T} = \bar{T}_f + \bar{T}_d$

$$\bar{T}_f \sim \frac{L^2}{D} \sim \frac{1}{DN_d}$$



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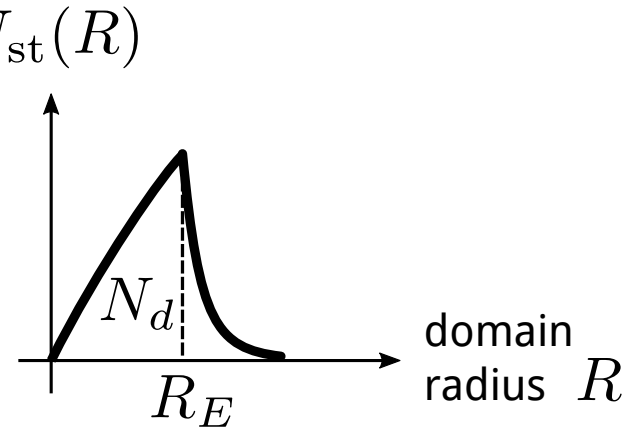

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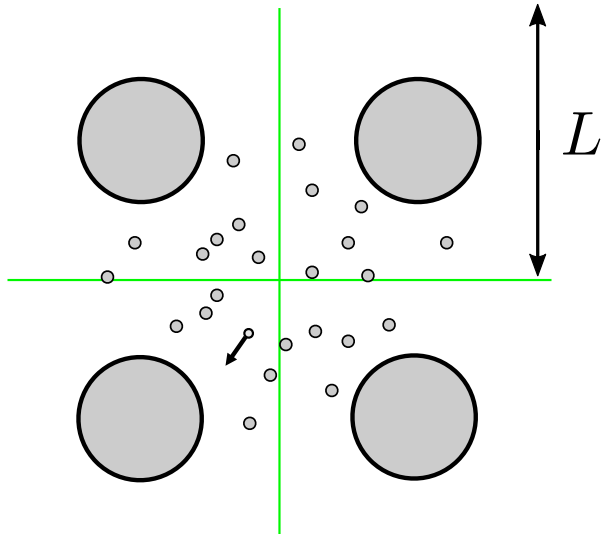

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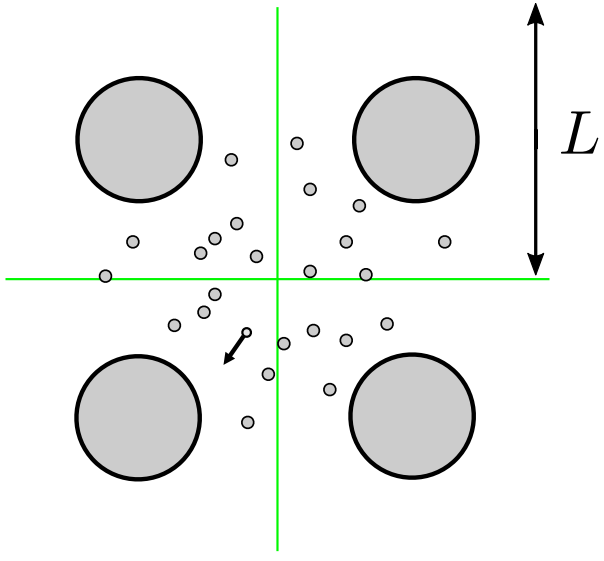

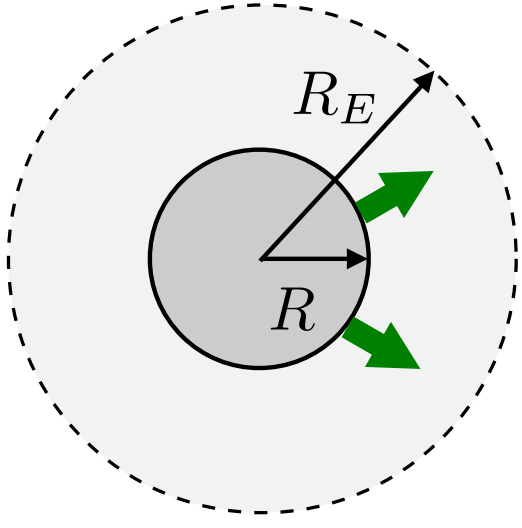

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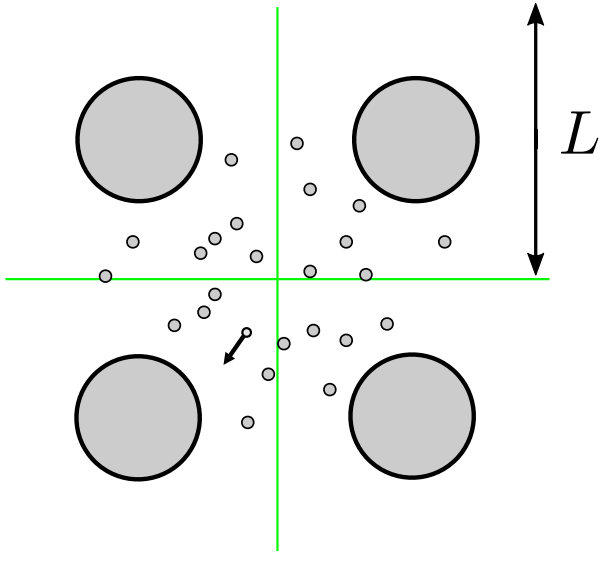
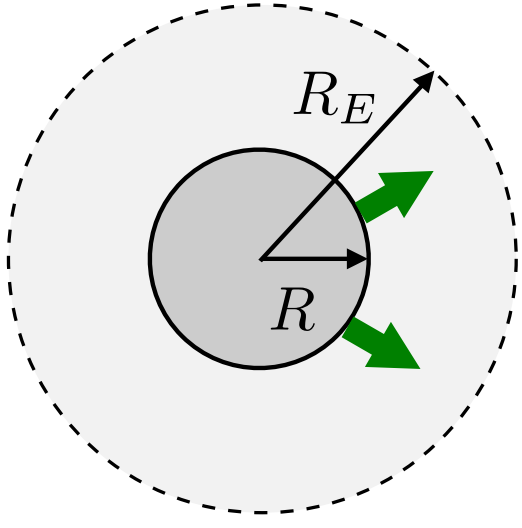
$$\bar{T}_f \sim \frac{L^2}{D} \sim \frac{1}{DN_d} \sim \frac{\Delta n}{\phi_I}$$



$$\bar{T}_d \sim \frac{R_E^2}{\Phi_R}$$



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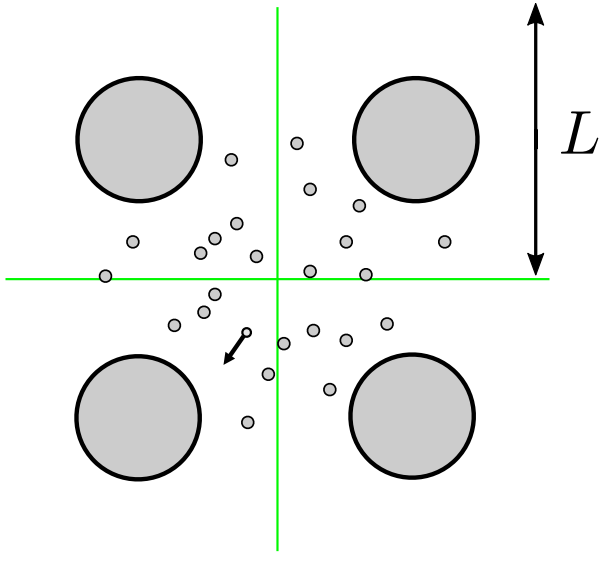

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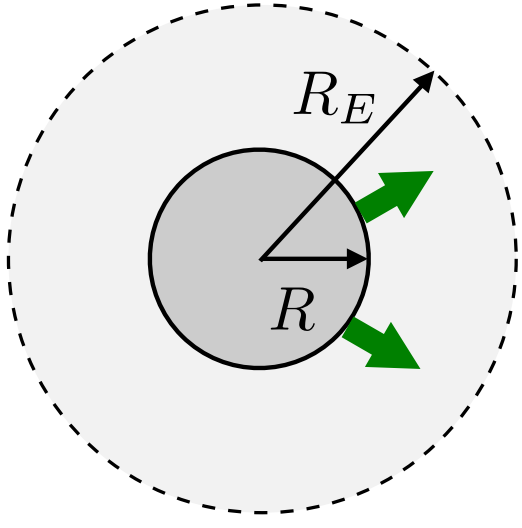

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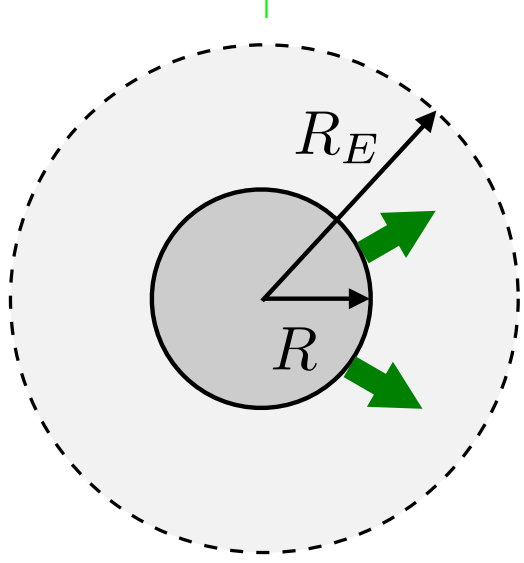
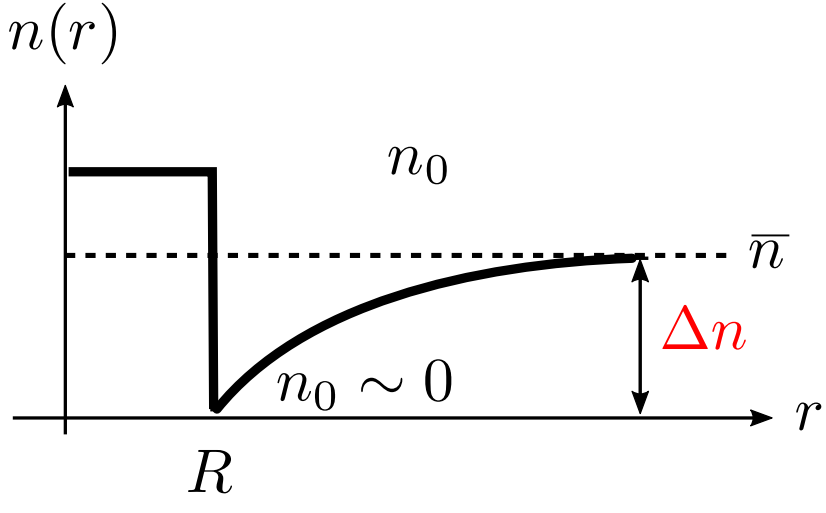


For absorbing domains $\Delta n \sim \bar{n}$



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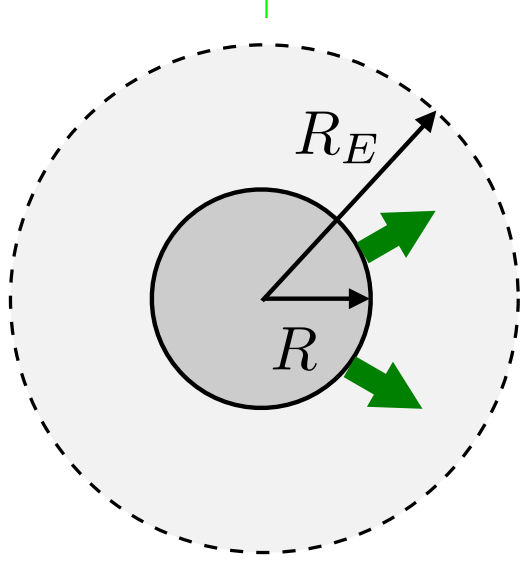
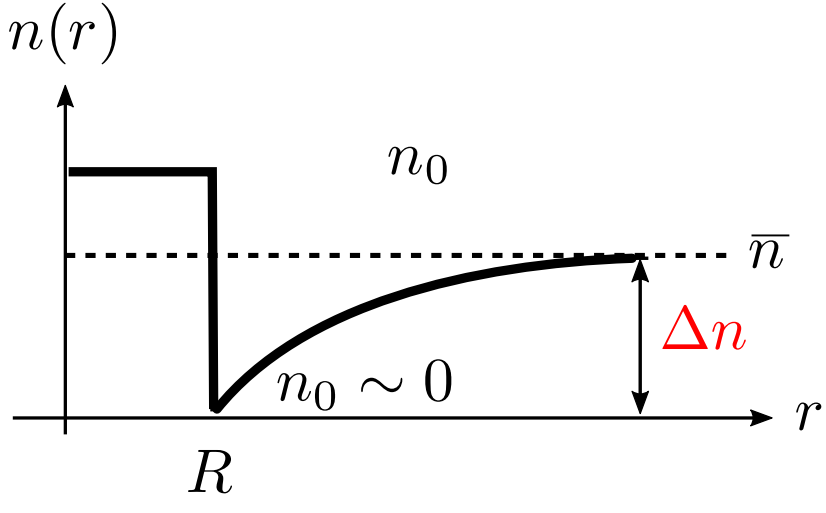


For absorbing domains $\Delta n \sim \bar{n}$

$$\frac{\mathrm{d}N_{d,\mathrm{new}}}{\mathrm{d}t}$$



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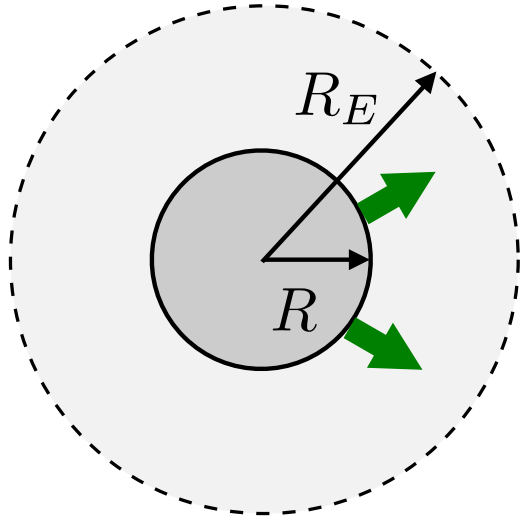

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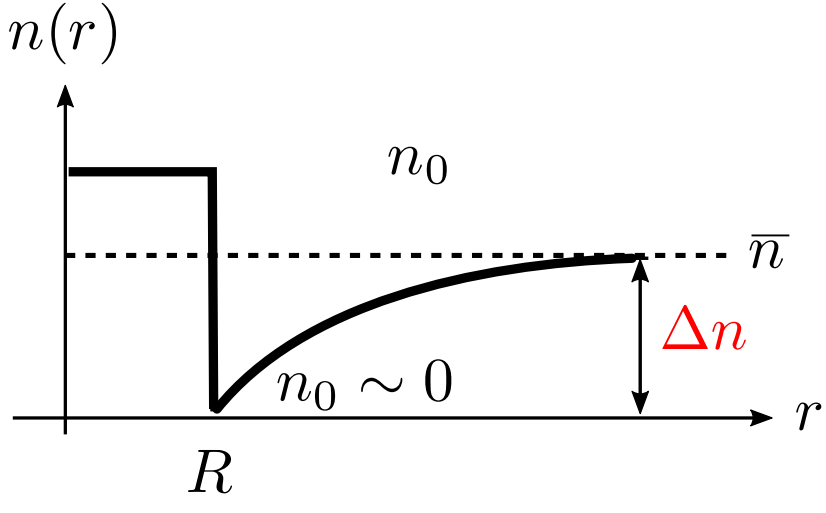
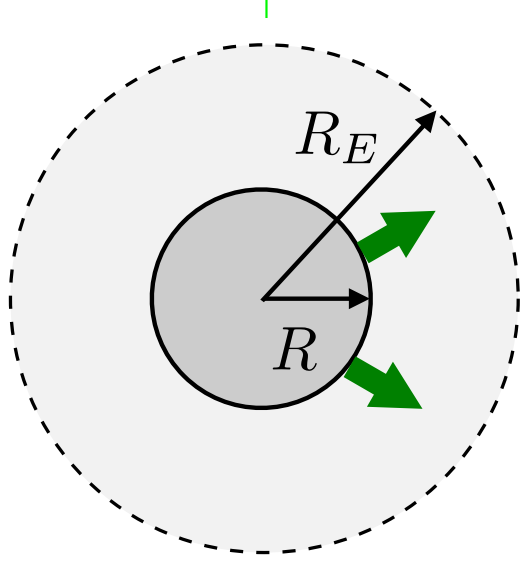
$$\frac{\mathrm{d}N_{d,\mathrm{new}}}{\mathrm{d}t} = CD\bar{n}^2$$



$$\bar{T}_d \sim \frac{R_E^2}{\Phi_R} \sim \frac{R_E^2}{D\Delta n}$$



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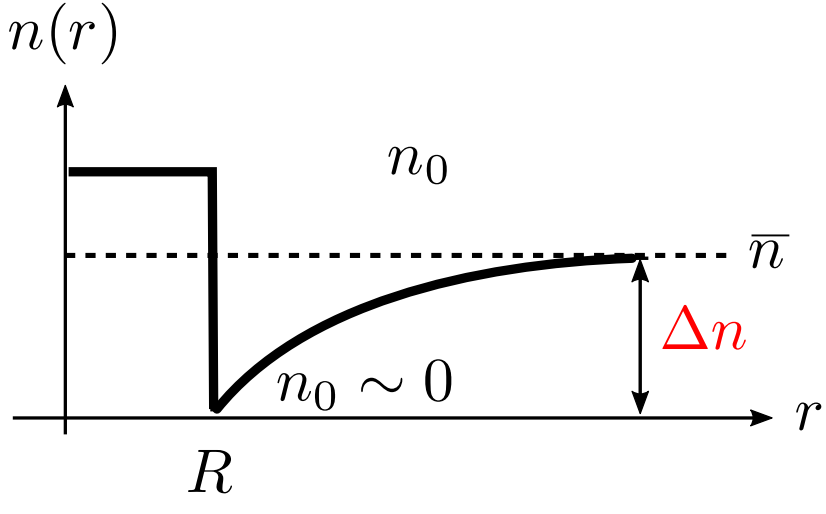

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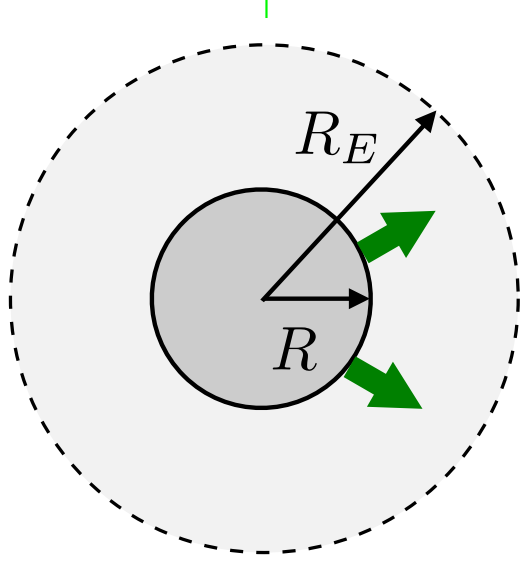

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$$\frac{\mathrm{d}N_{d,\mathrm{new}}}{\mathrm{d}t} = CD\bar{n}^2 = \frac{N_d}{\bar{T}_d}$$

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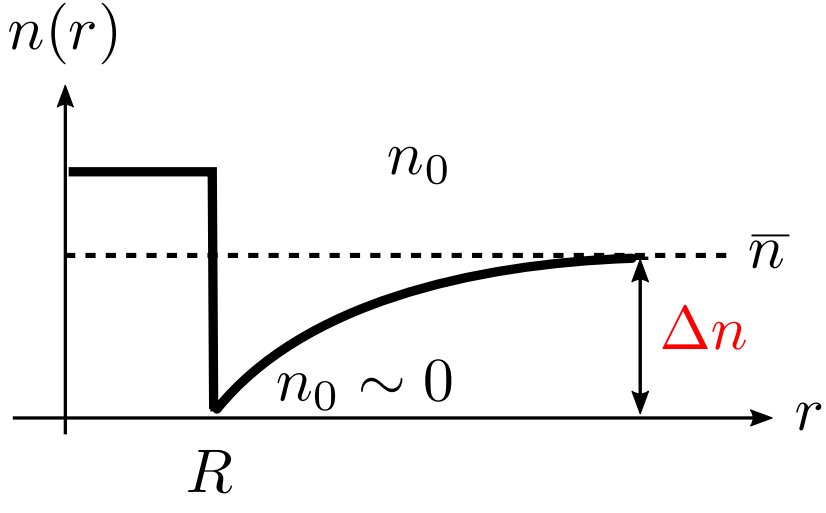

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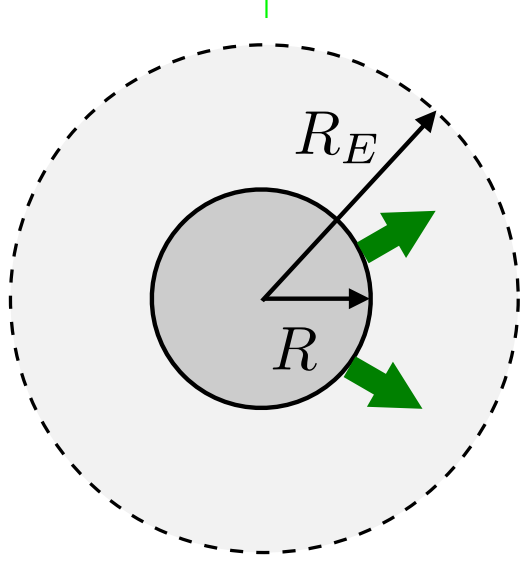

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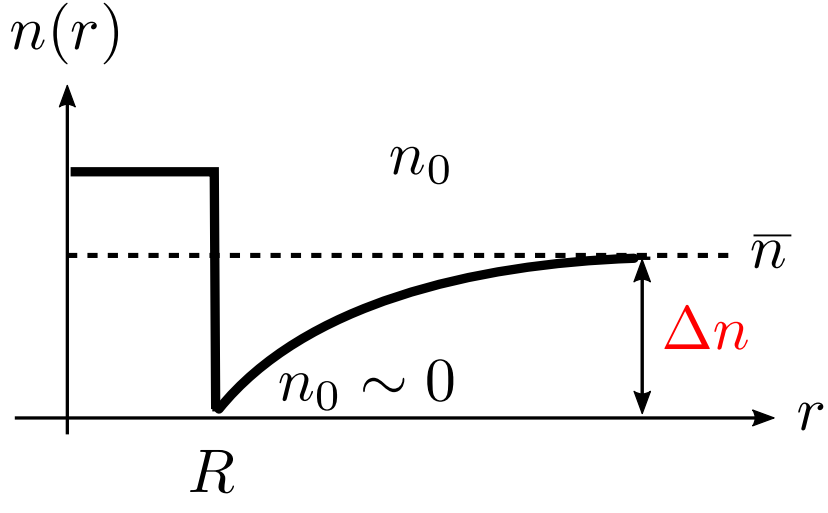

C ~ aggregation strength

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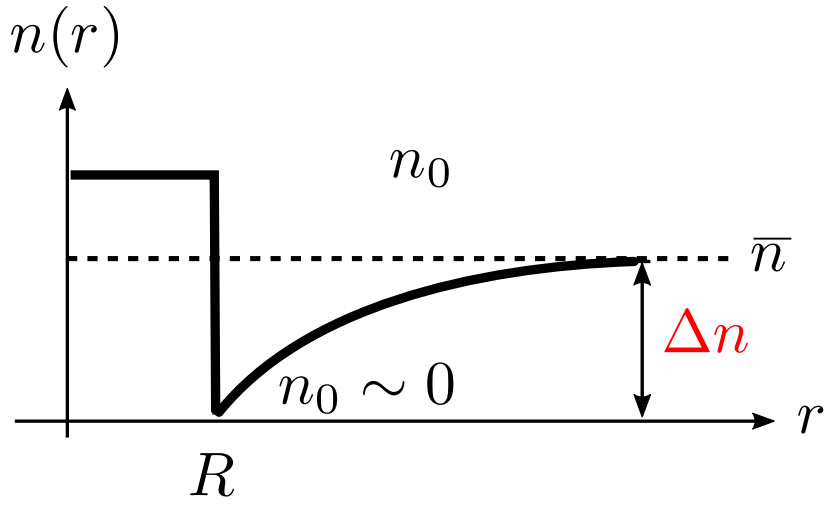

C ~ aggregation strength

$$\bar{T}_f \sim C^{-1/2} \frac{1}{(D\phi_I)^{1/2} R_E}$$

$$\bar{T}_d \sim C^{1/2} \frac{R_E^3}{(D\phi_I)^{1/2}}$$

For absorbing domains $\Delta n \sim \bar{n}$

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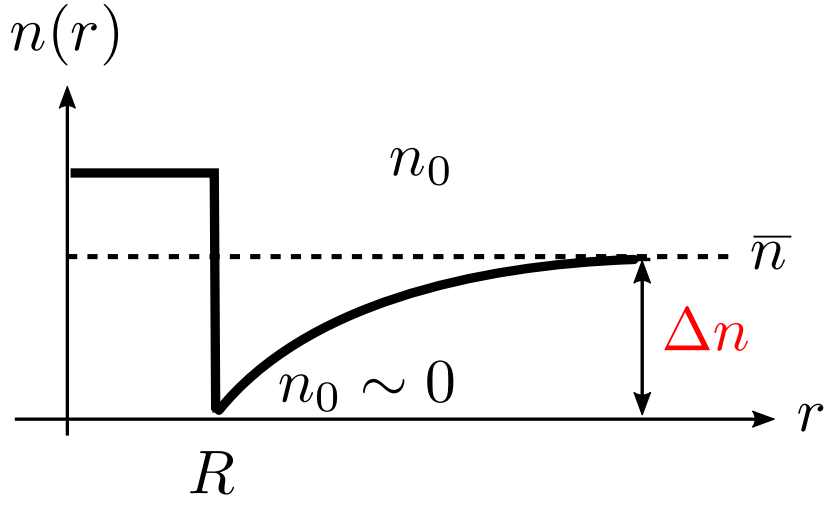

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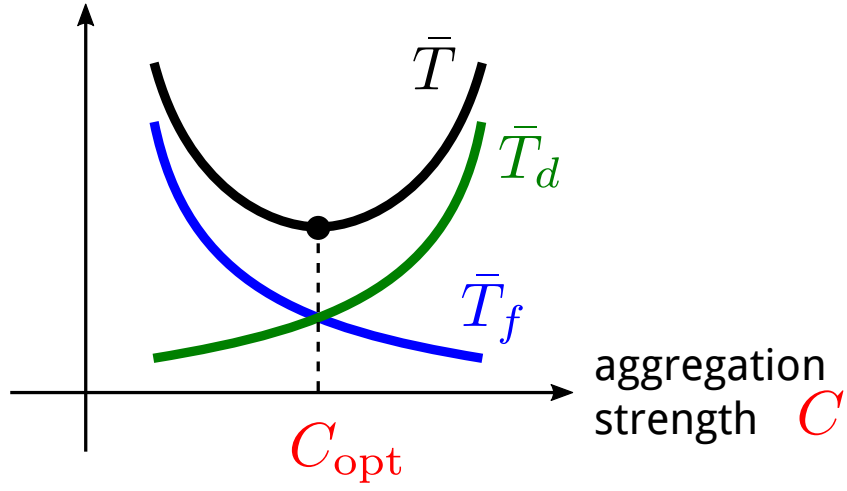
$$C_{\mathrm{opt}} \sim R_E^{-4}$$



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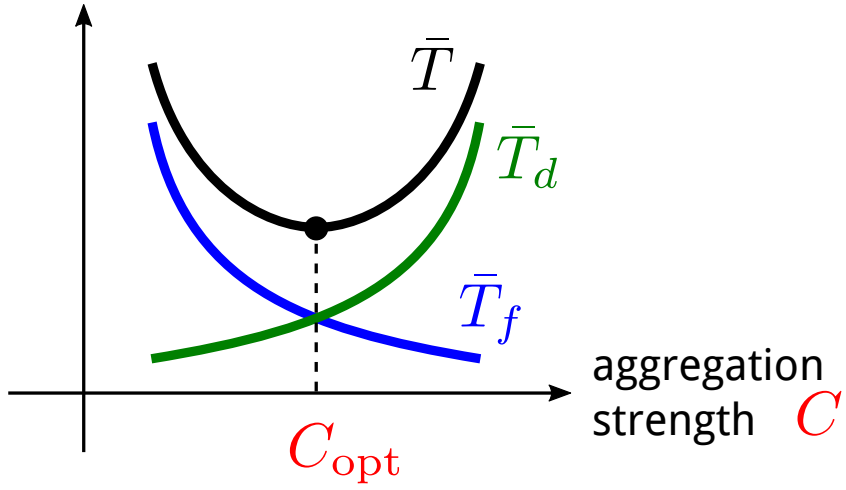


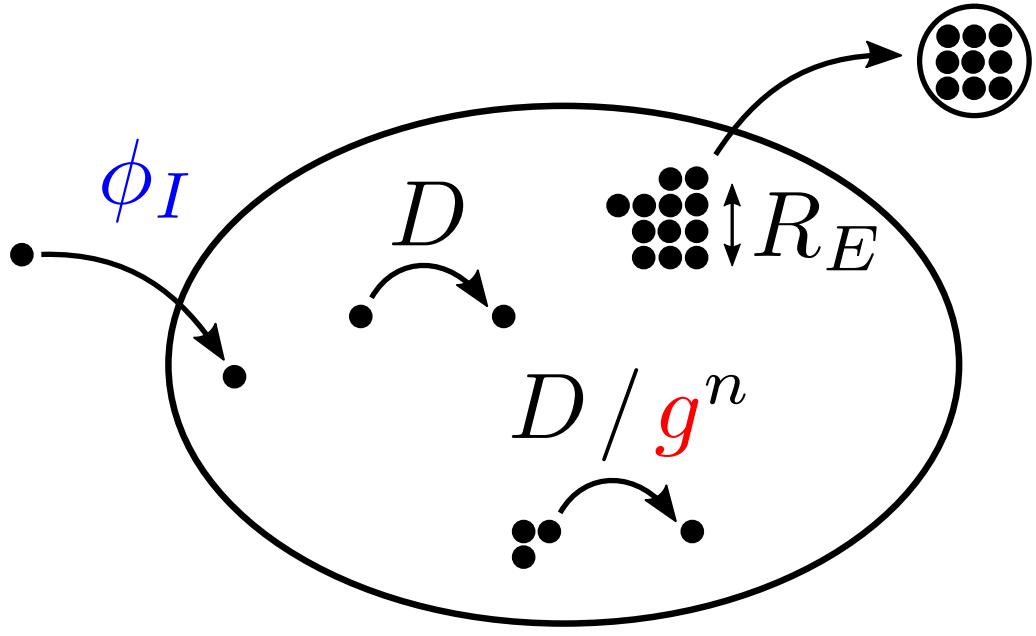
$$C_{\rm opt} \sim R_E^{-4}$$

$$\bar{T}_f^{\,\rm opt} \sim \bar{T}_d^{\,\rm opt} \sim \frac{R_E}{(D\phi_I)^{1/2}}$$

$$\bar{n}^{\,\rm opt} \sim \Delta n^{\,\rm opt} \sim \frac{\phi_I^{1/2} R_E}{D^{1/2}}$$

$\rho^{\,\rm opt} \sim \bar{n}^{\,\rm opt}$ is also minimal at fixed ϕ_I $\quad (\,\bar{T} = \rho\,\phi_I\,)$

Numerical simulations



ϕ_I : incoming molecule flux

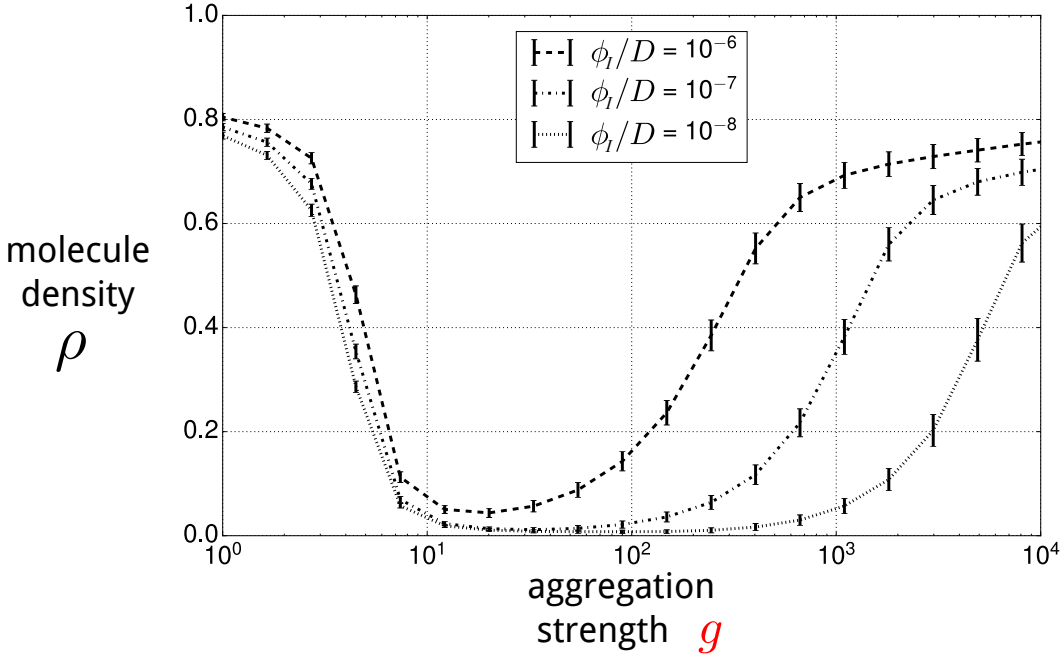
D : diffusivity

g : aggregation strength

n : number of neighbours

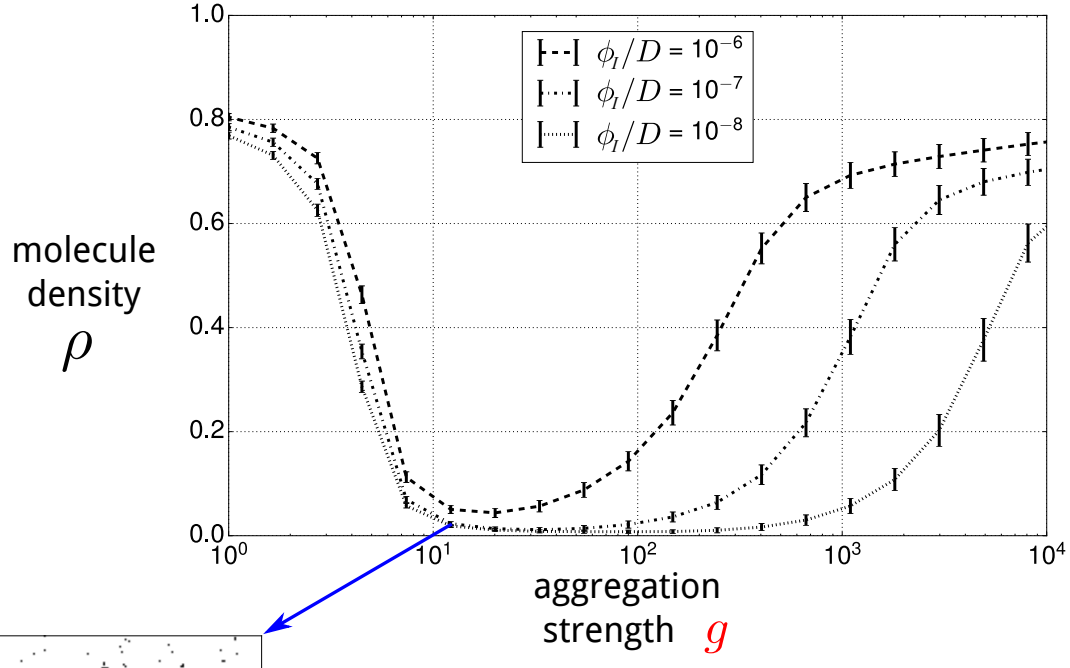
R_E : extraction size

Numerical simulations



$$\overline{T} = \rho\,\phi_I$$

Numerical simulations



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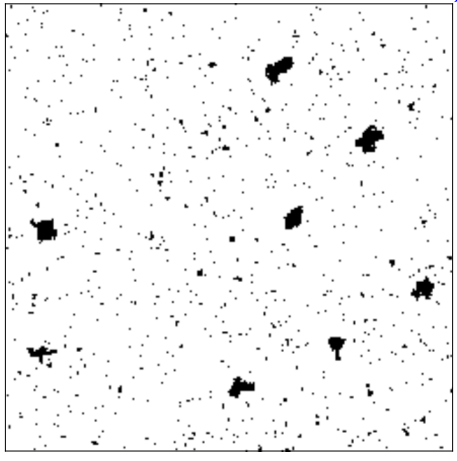

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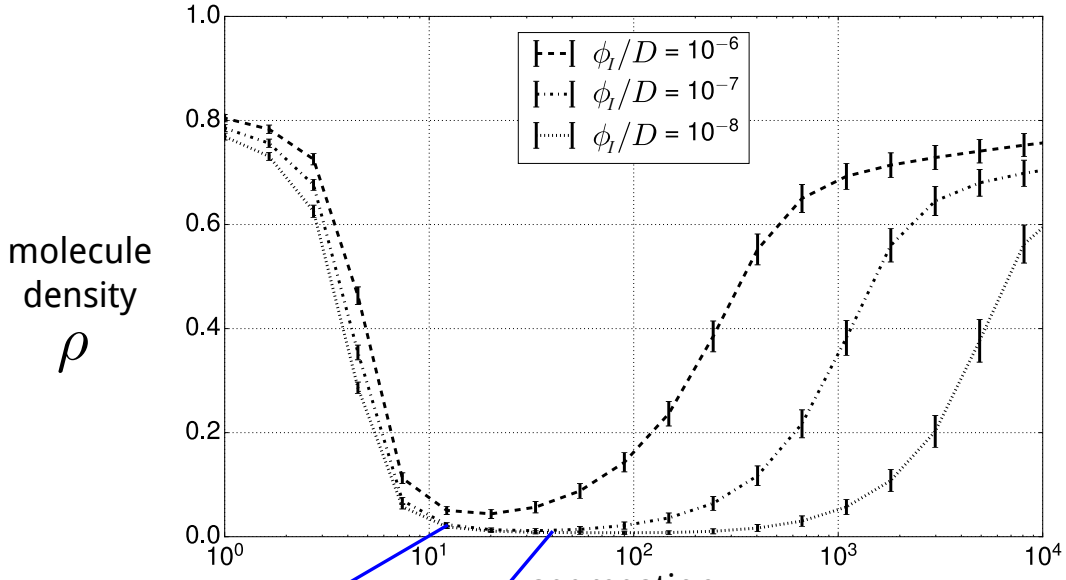

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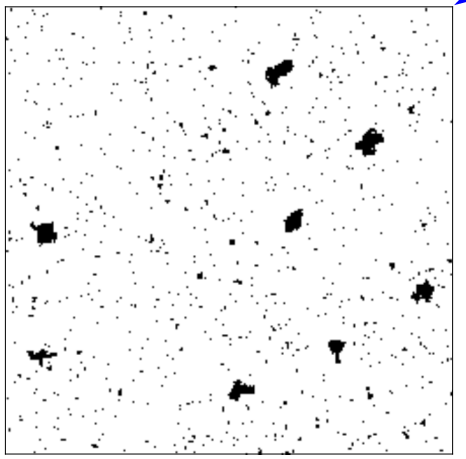
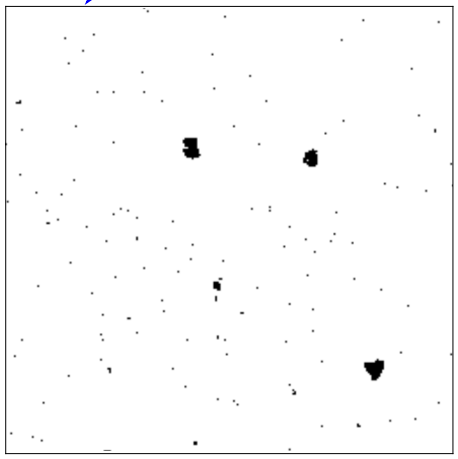
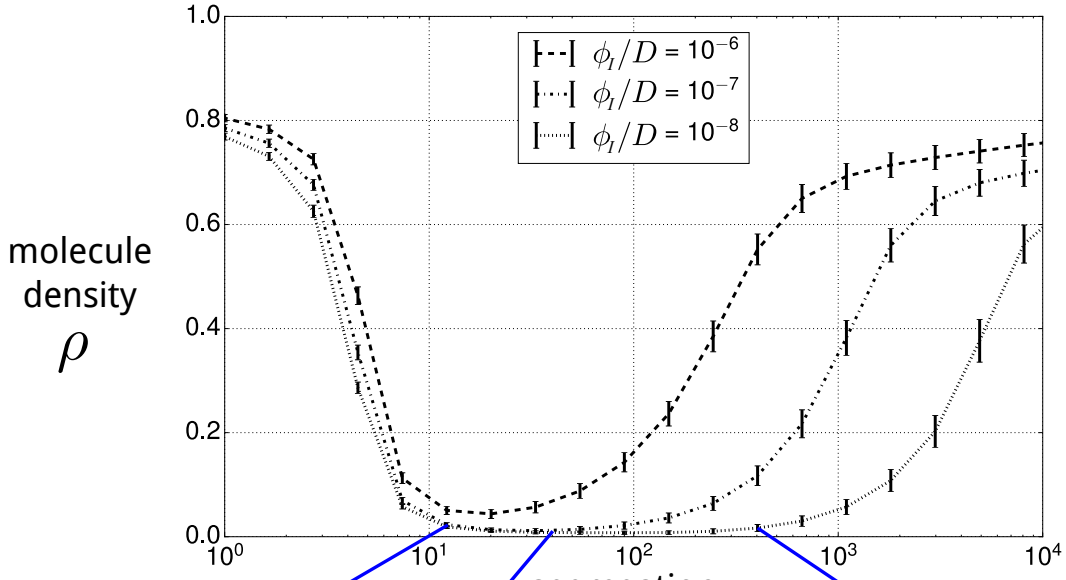
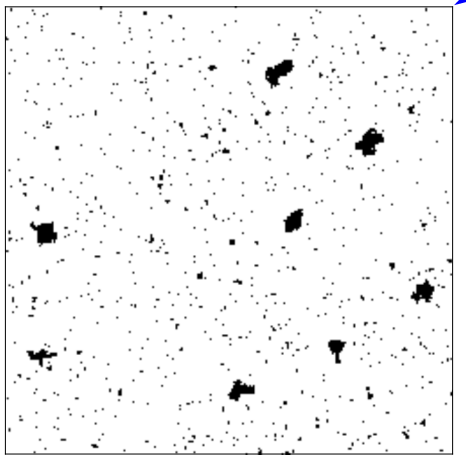


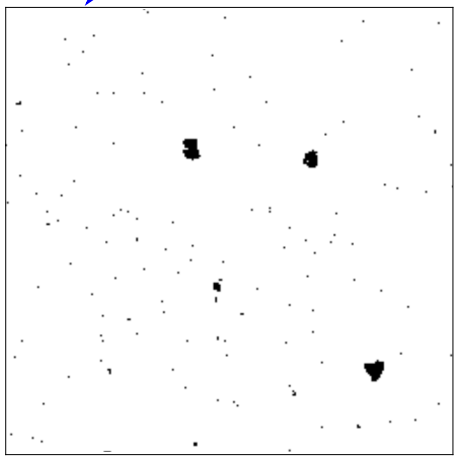


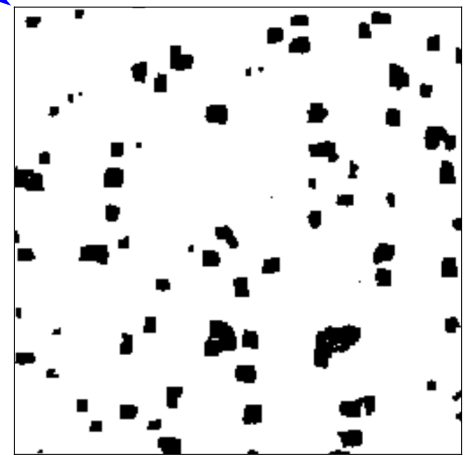
Numerical simulations



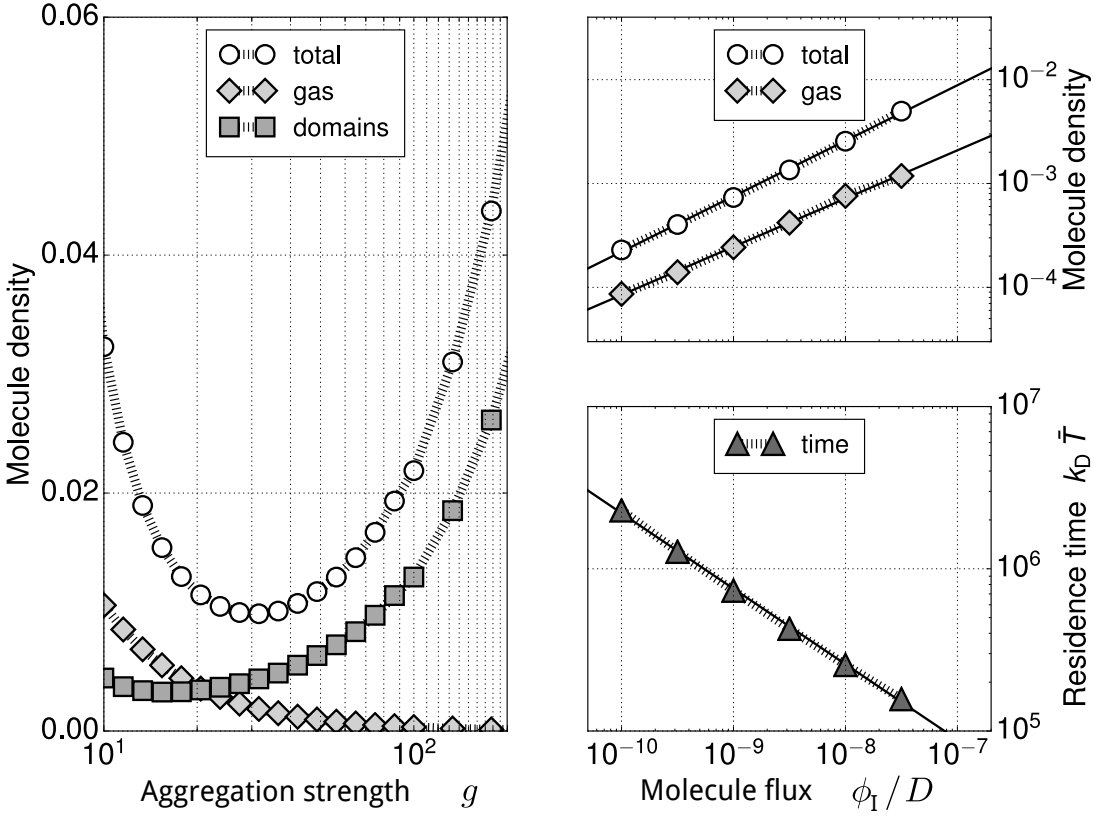
$$\overline{T} = \rho\,\phi_I$$







Numerical simulations

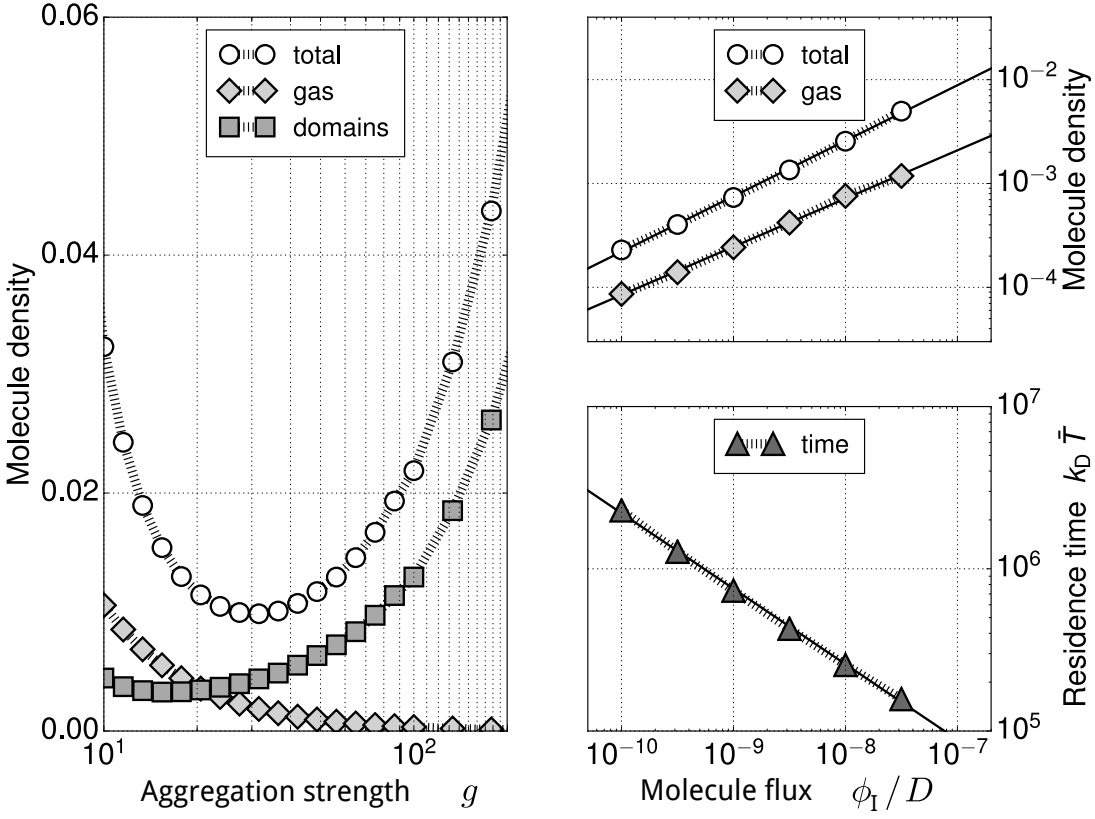


$$\rho \propto \phi_I^{0.53}$$

$$\bar{n} \propto \phi_I^{0.46}$$

$$\bar{T} \propto \phi_I^{-0.47}$$

Numerical simulations



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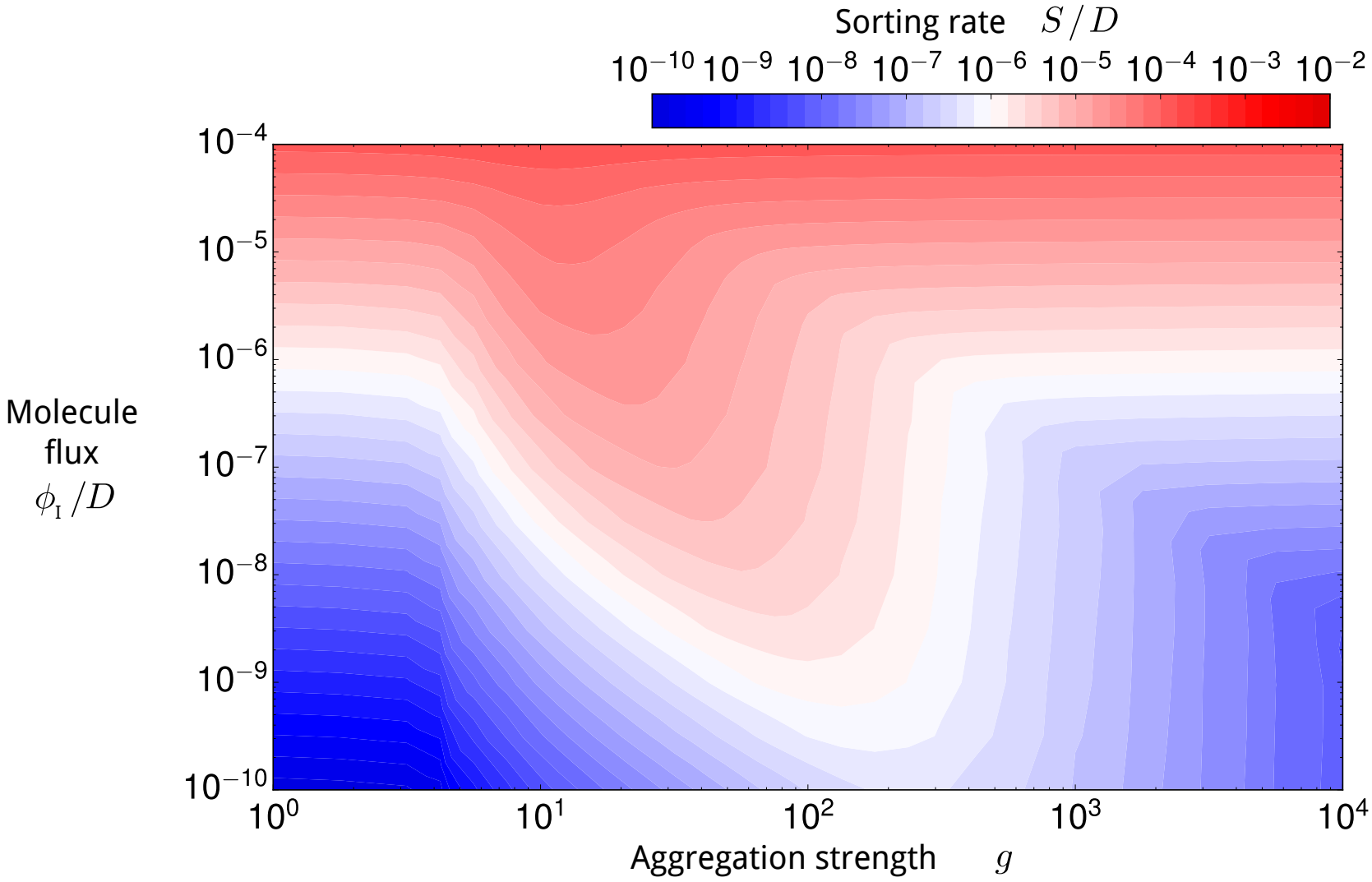
A phase diagram of sorting



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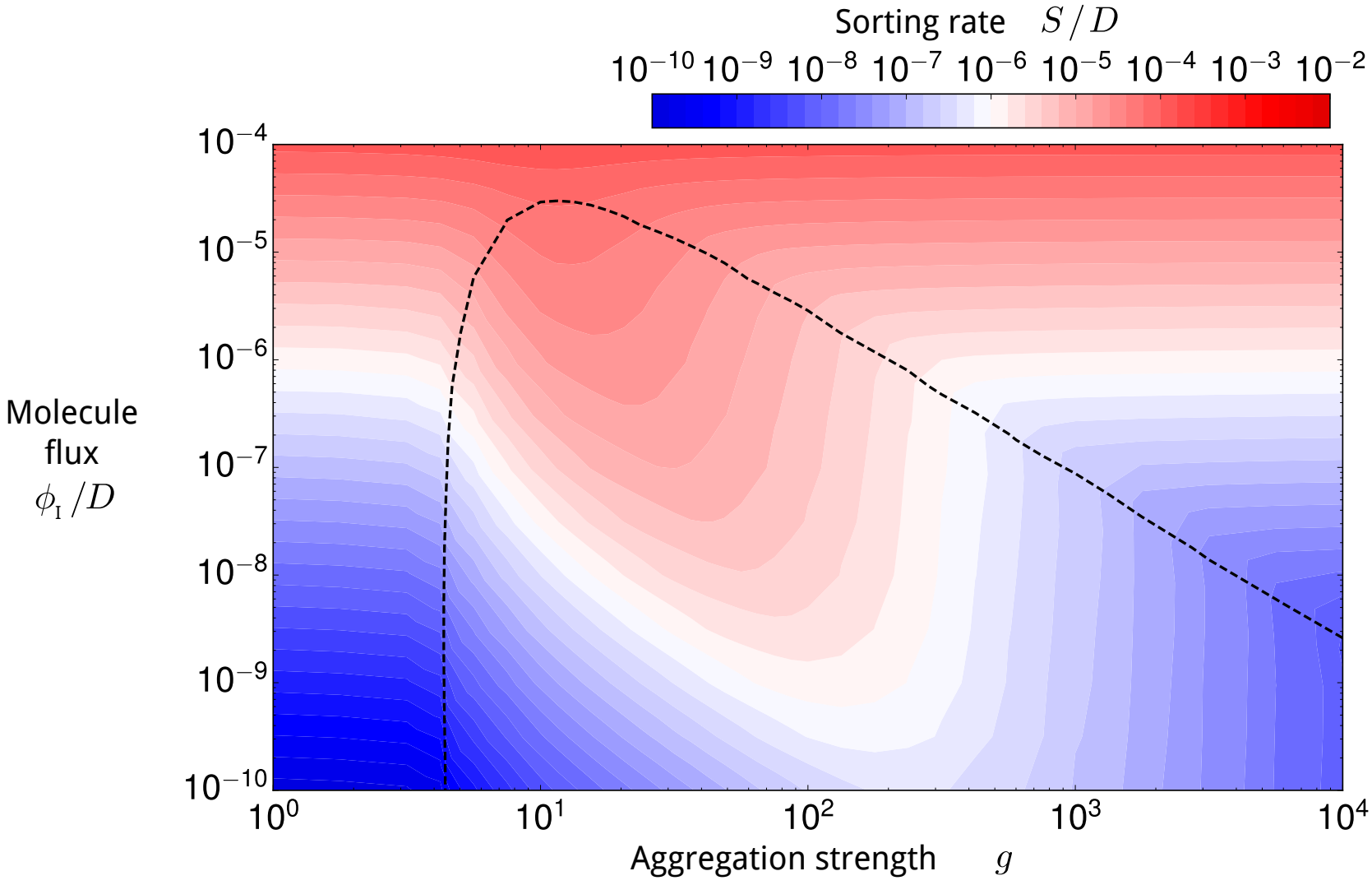

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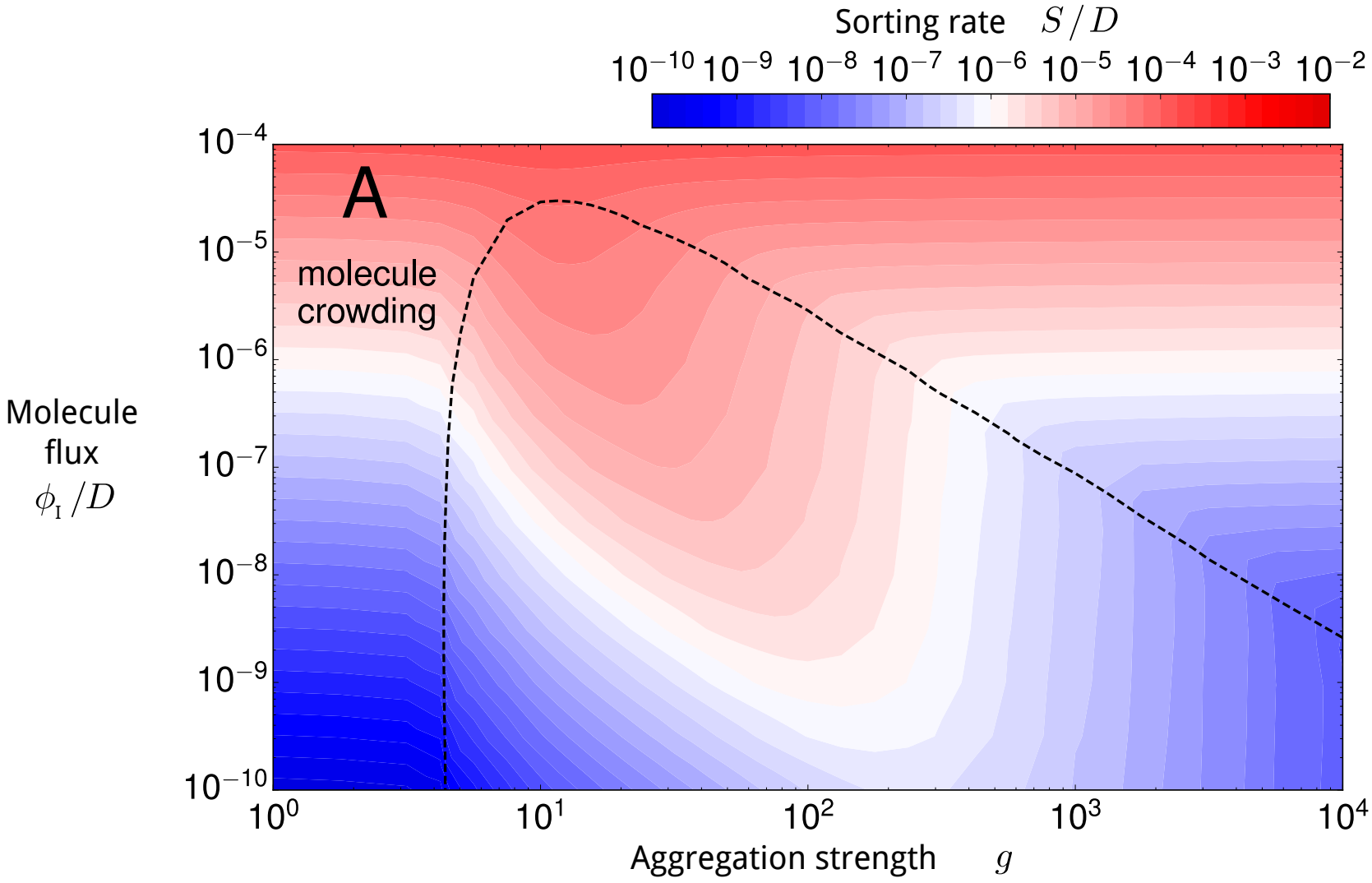

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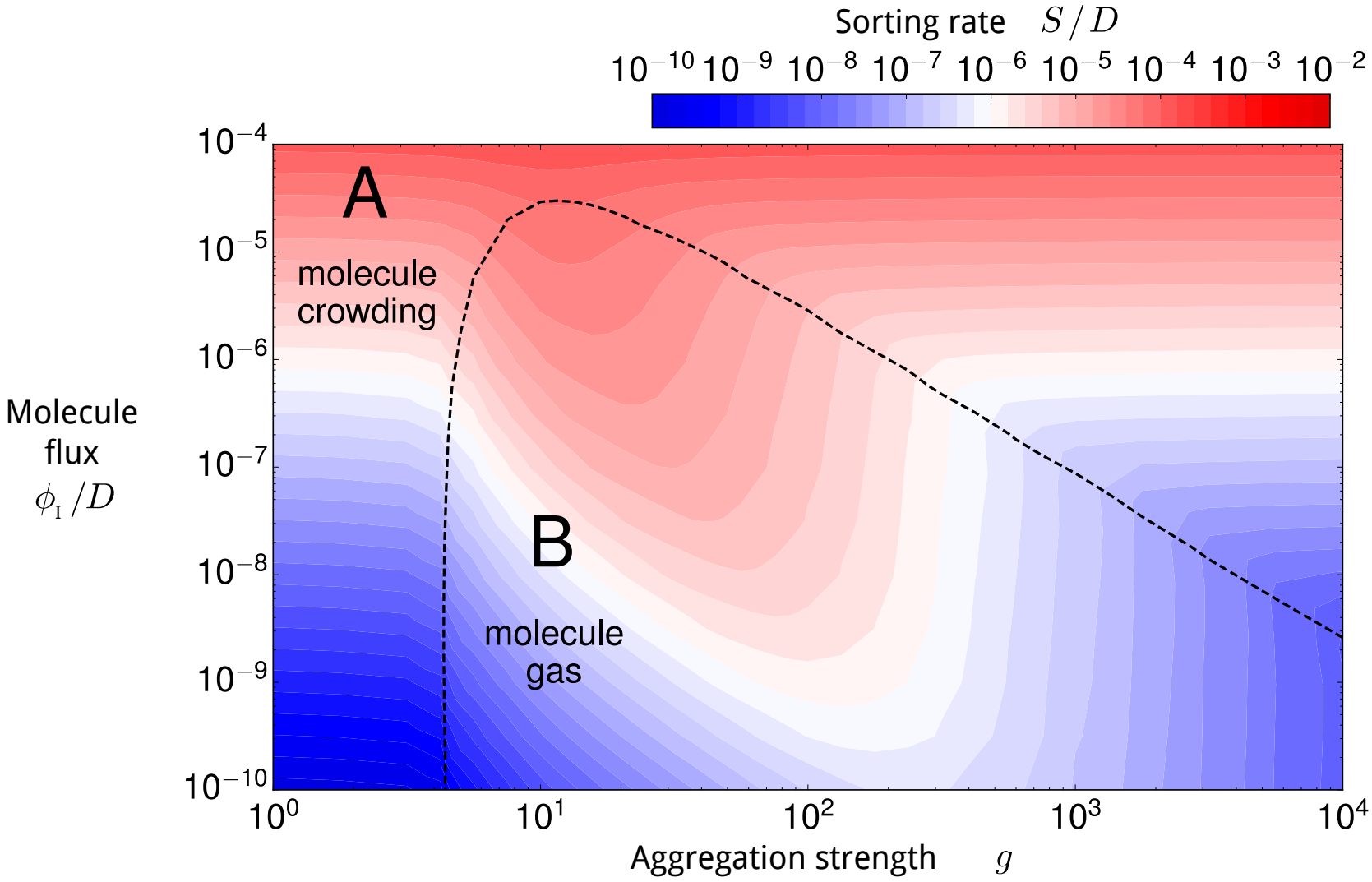
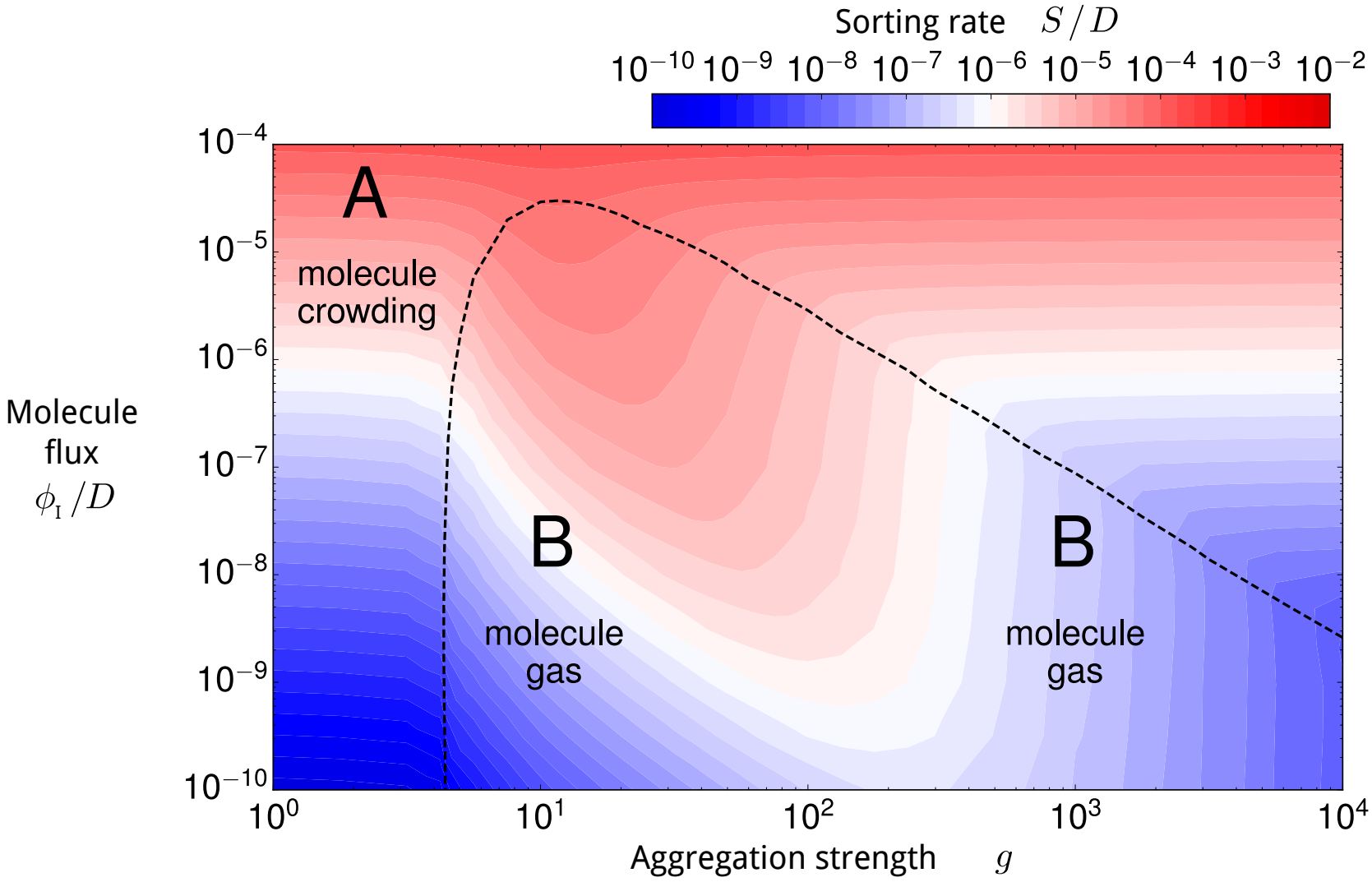


A phase diagram of sorting



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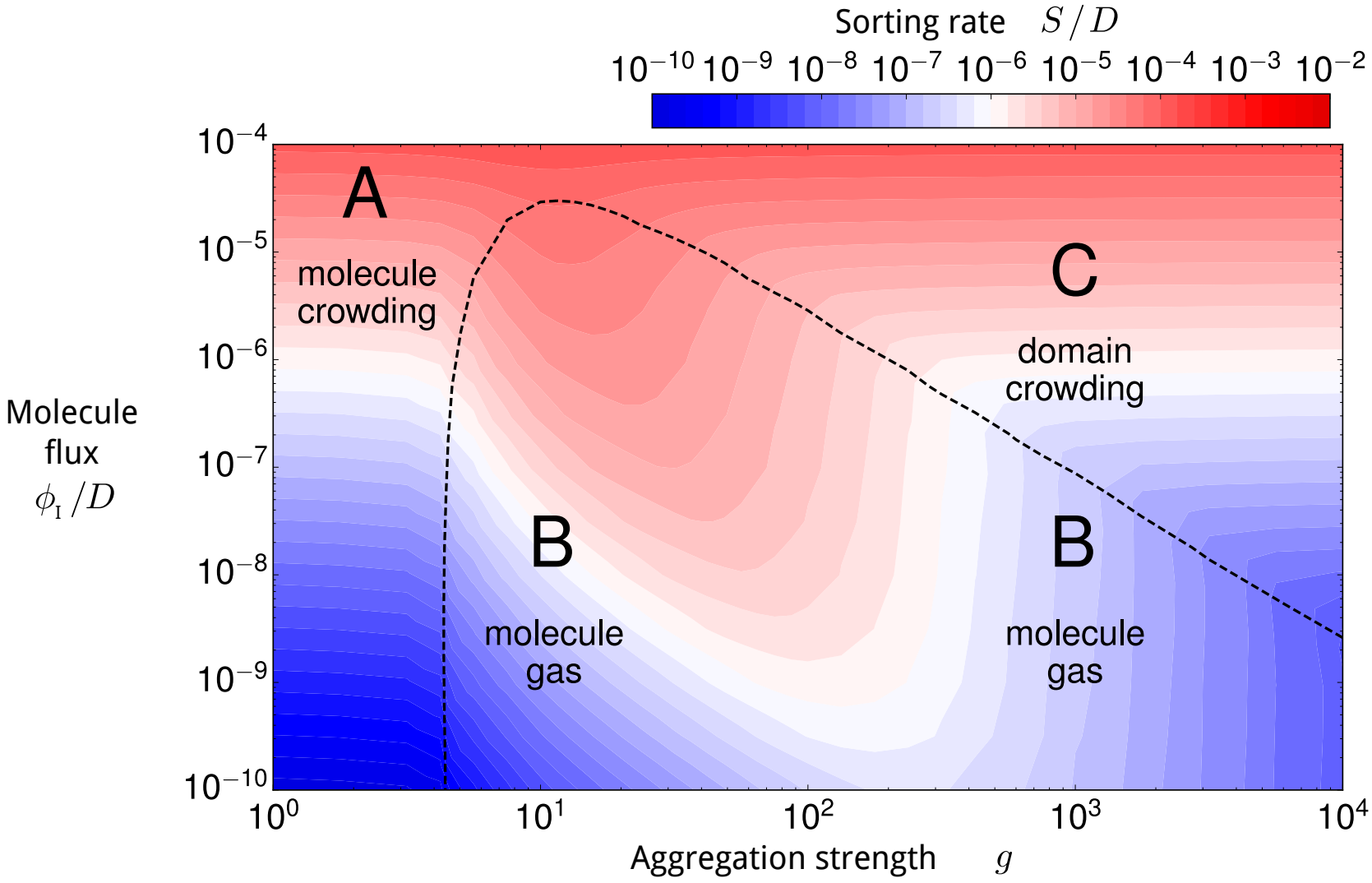

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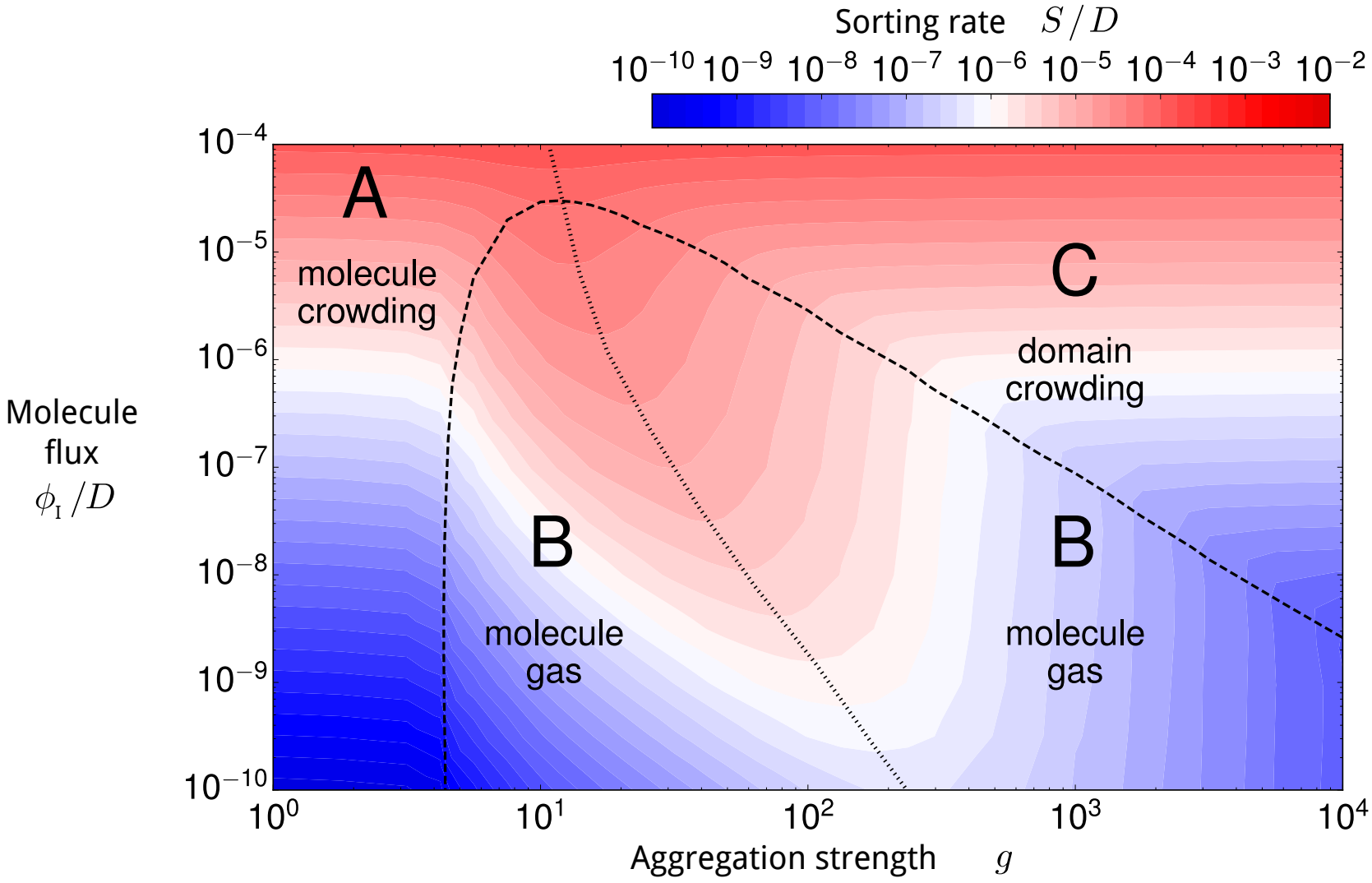

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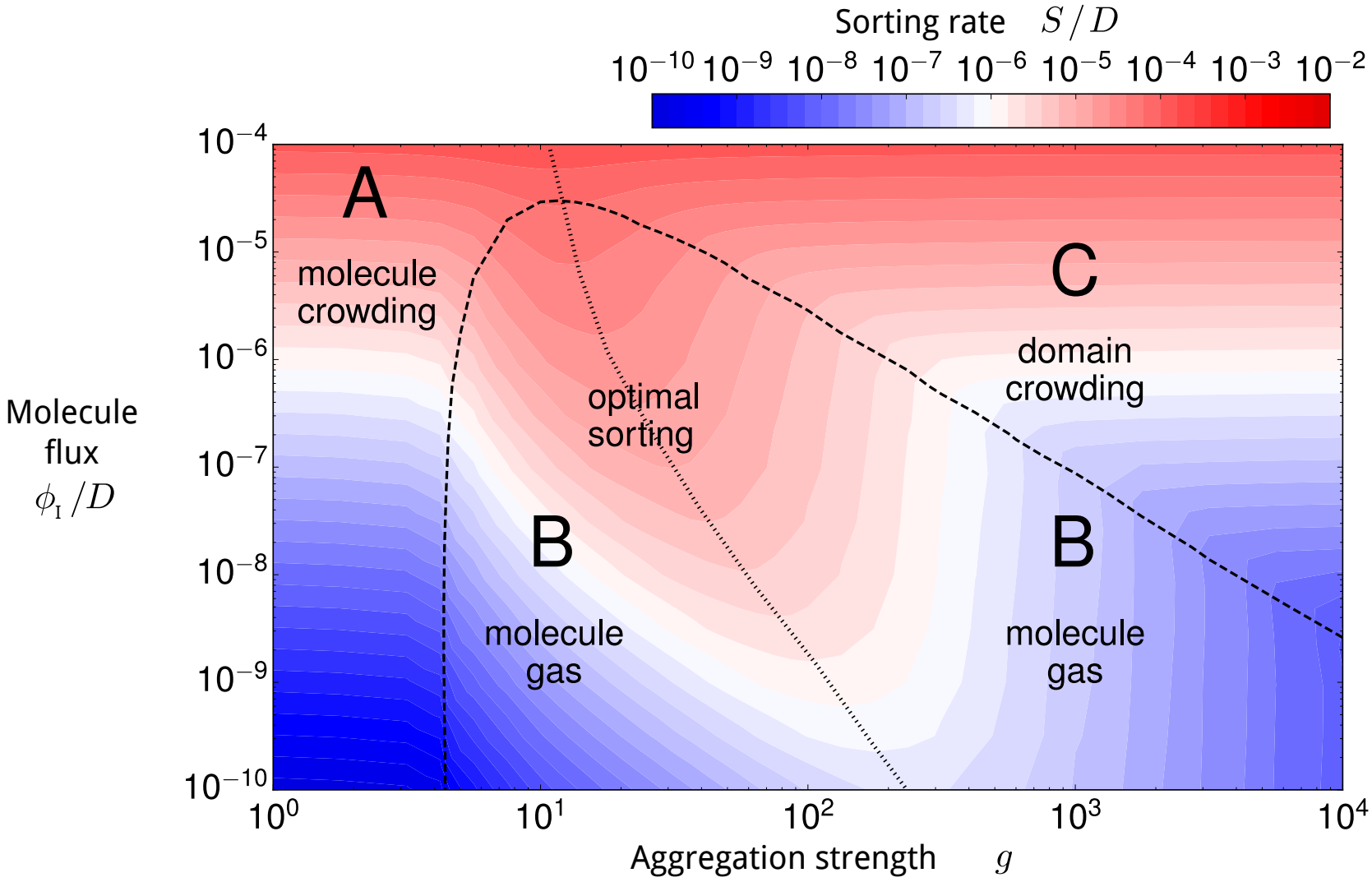
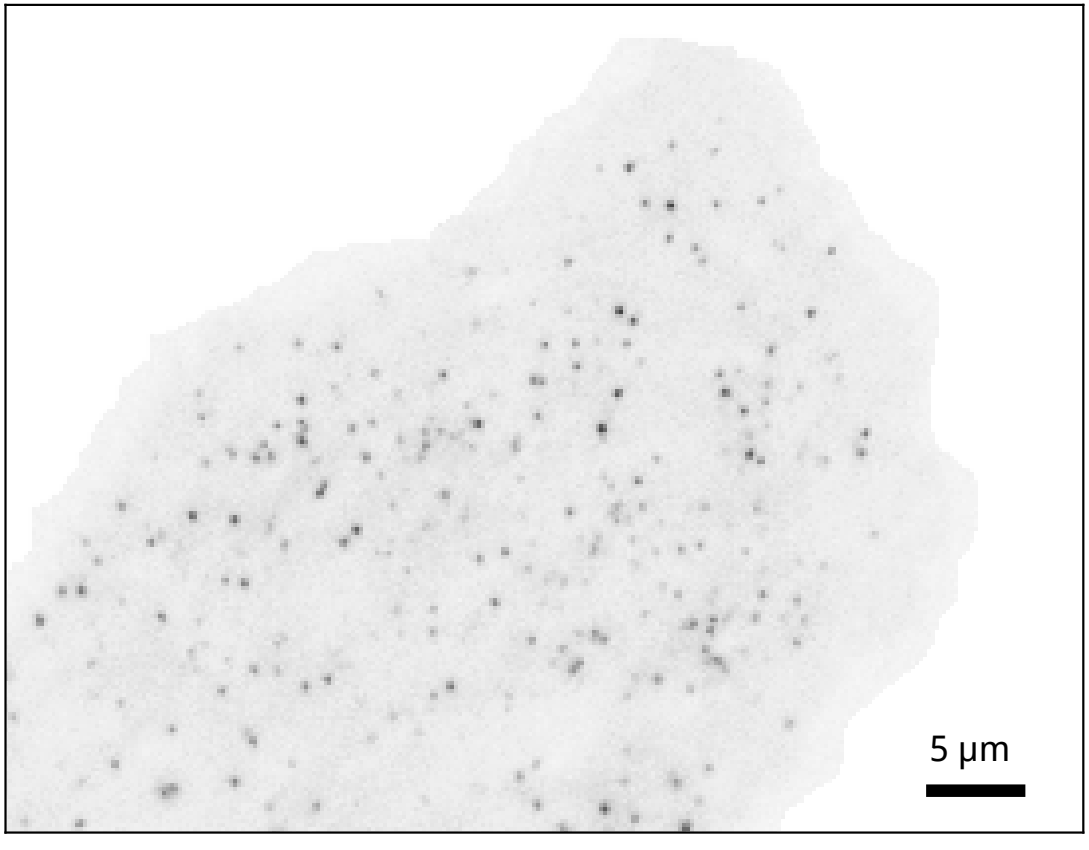


Endocytic sorting



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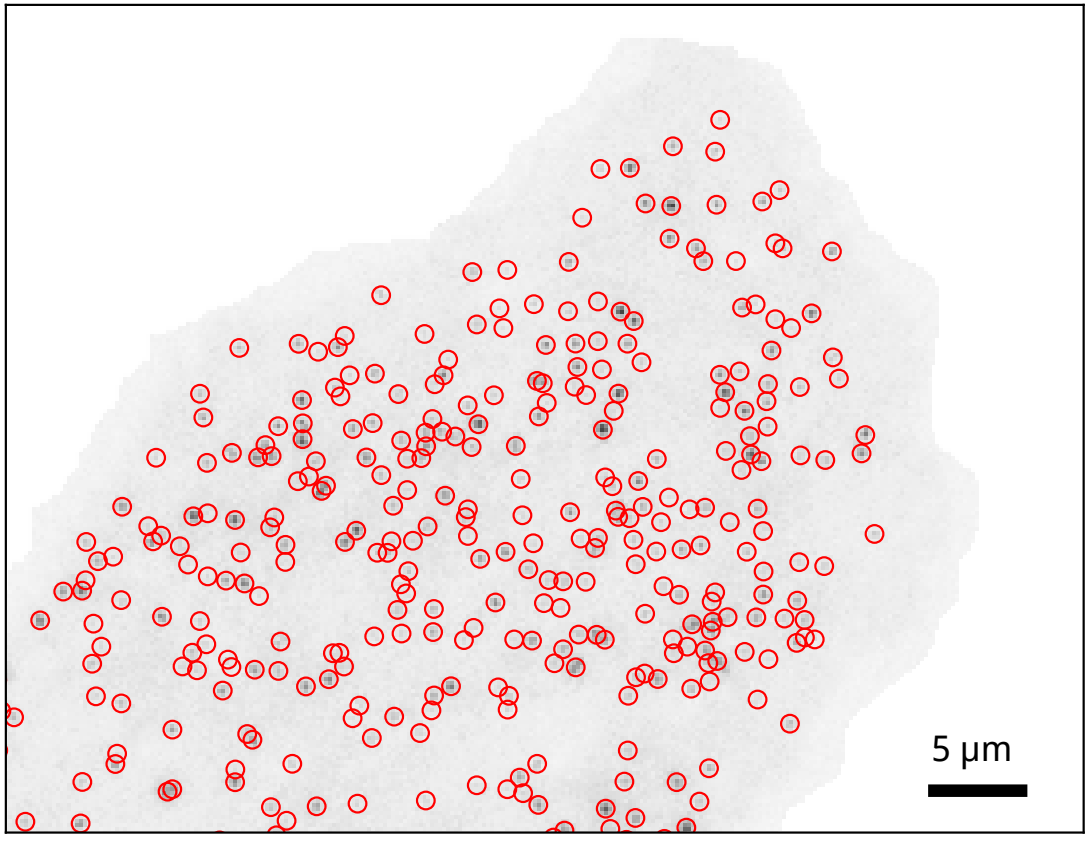

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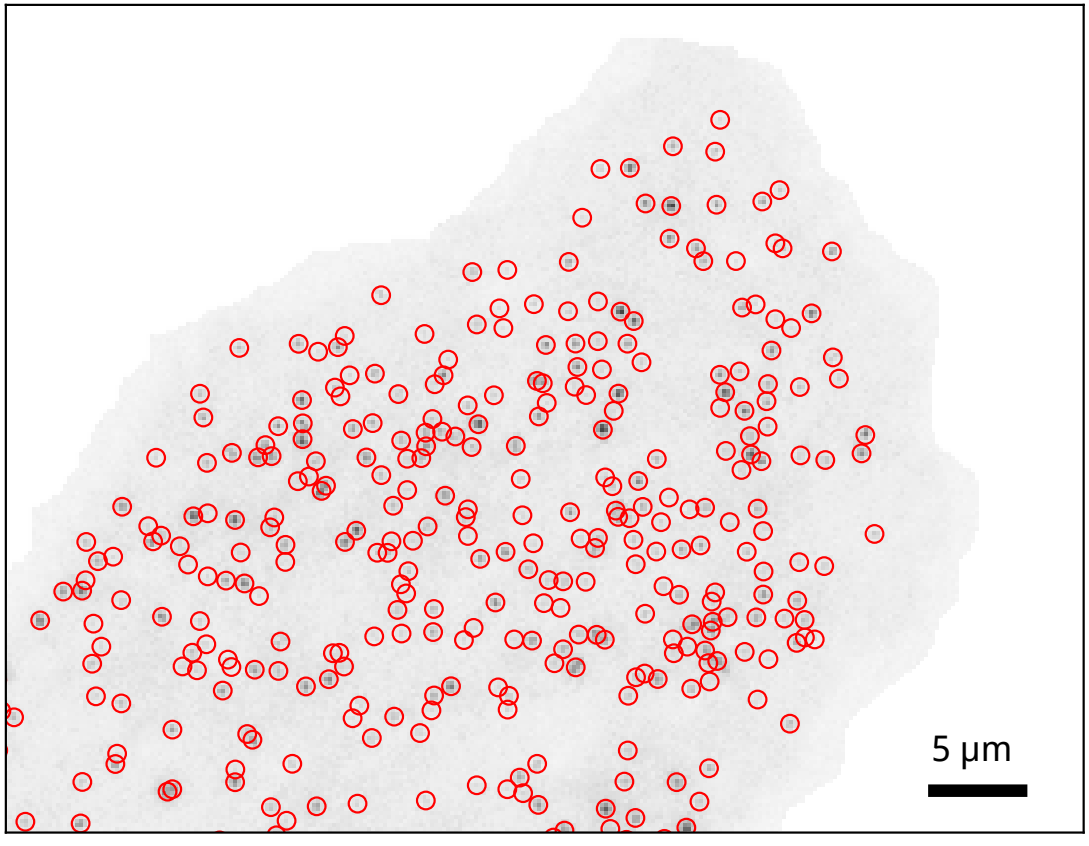

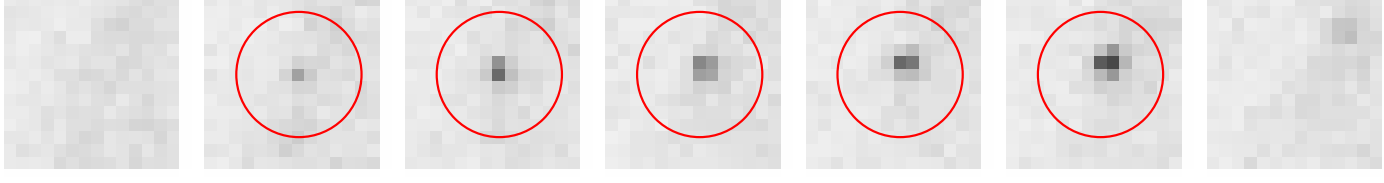

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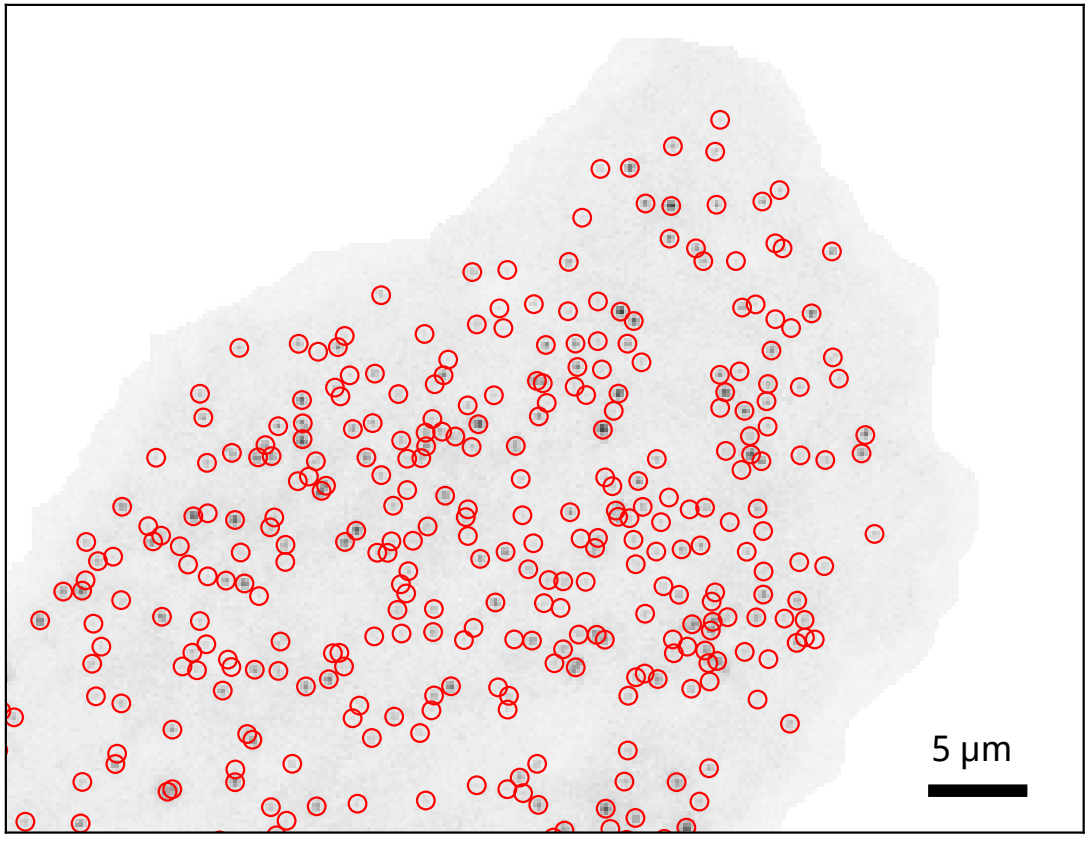

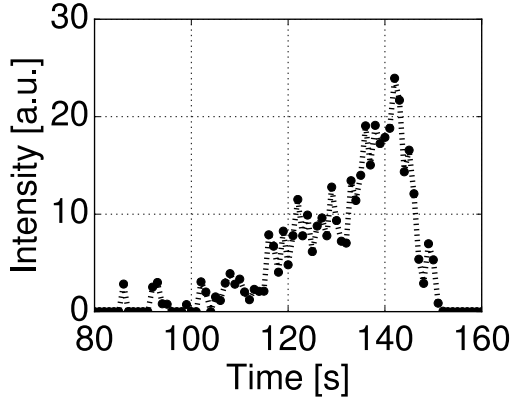

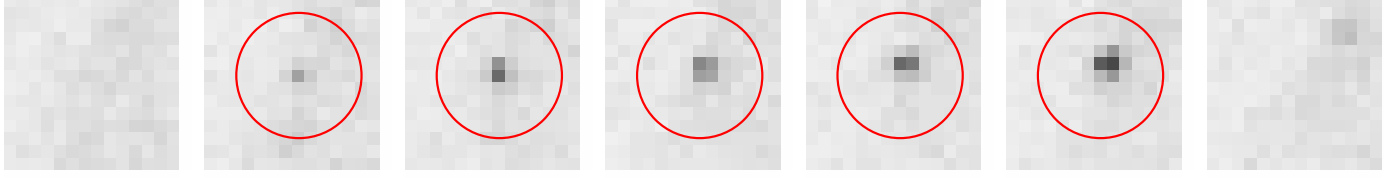

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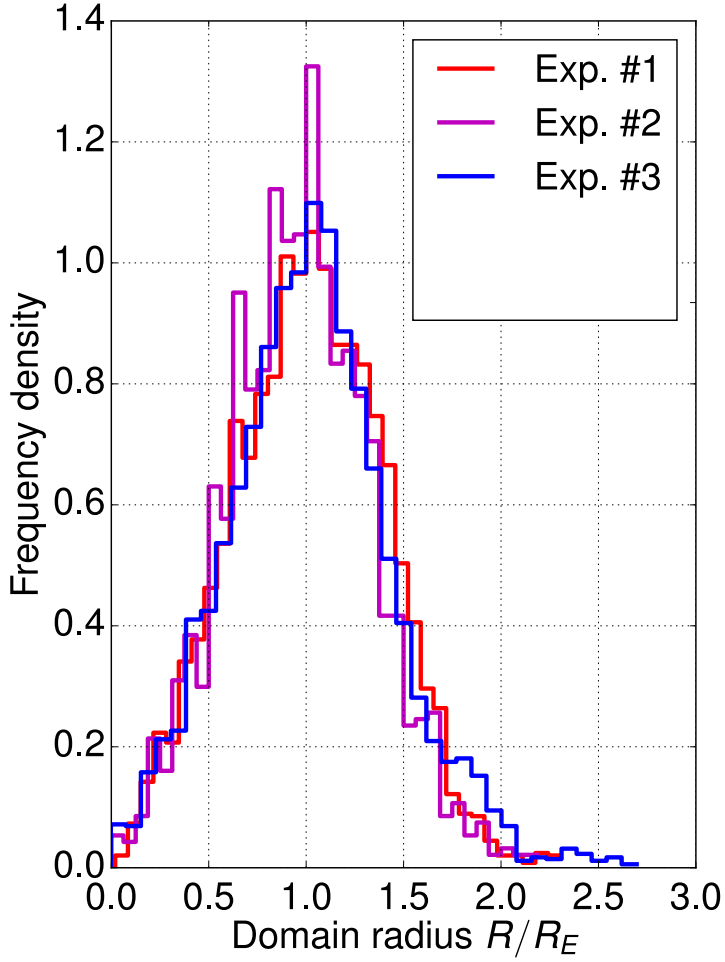

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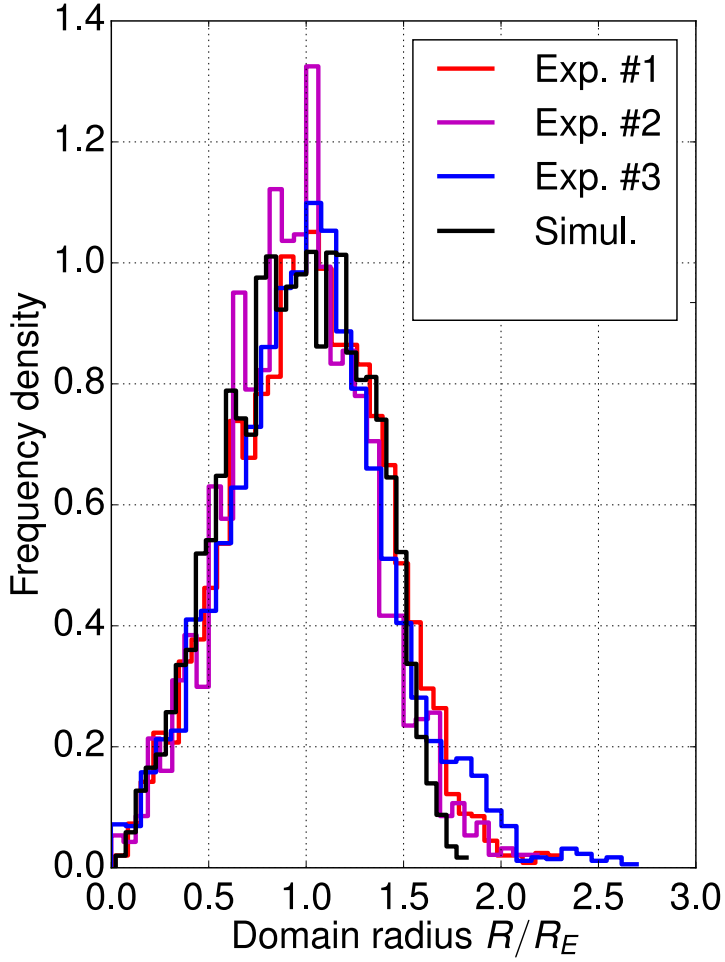

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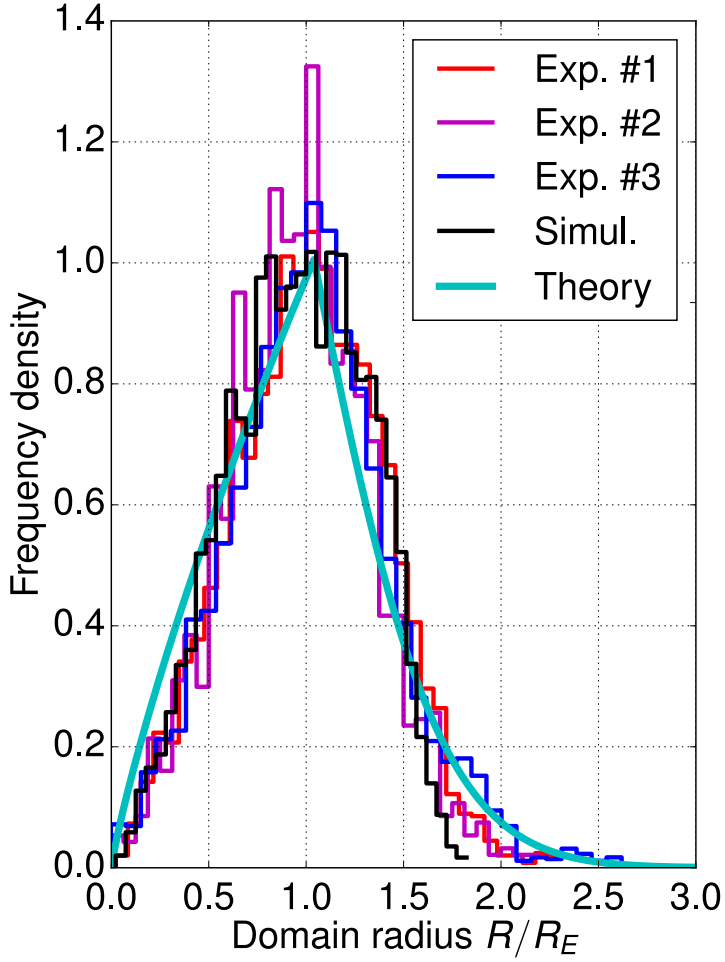
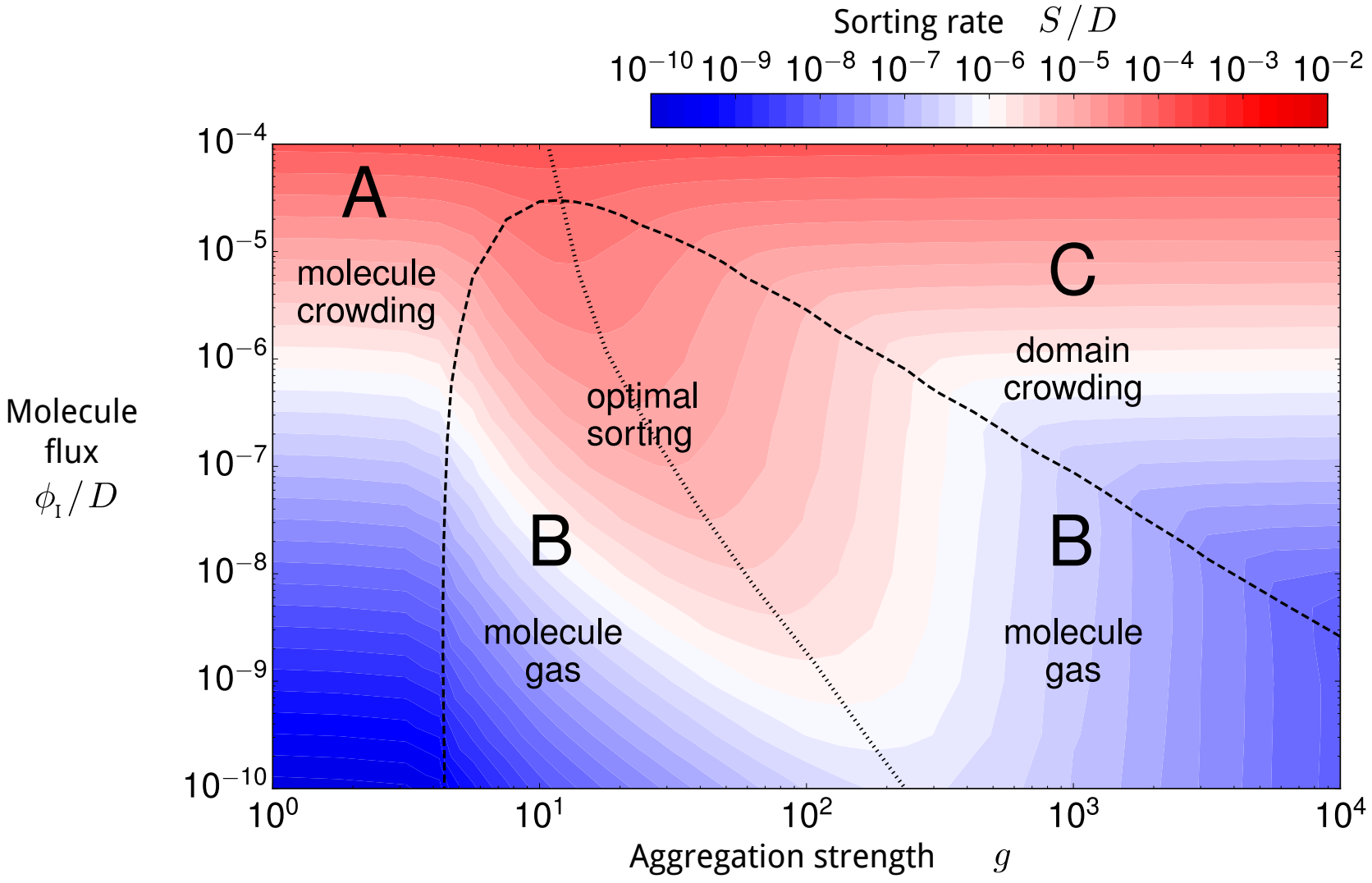


M Zamparo, D Valdembri,
G Serini, I Kolokolov,
V Lebedev, L Dall'Asta, AG
(submitted)

Do cells live close to the optimal regime?



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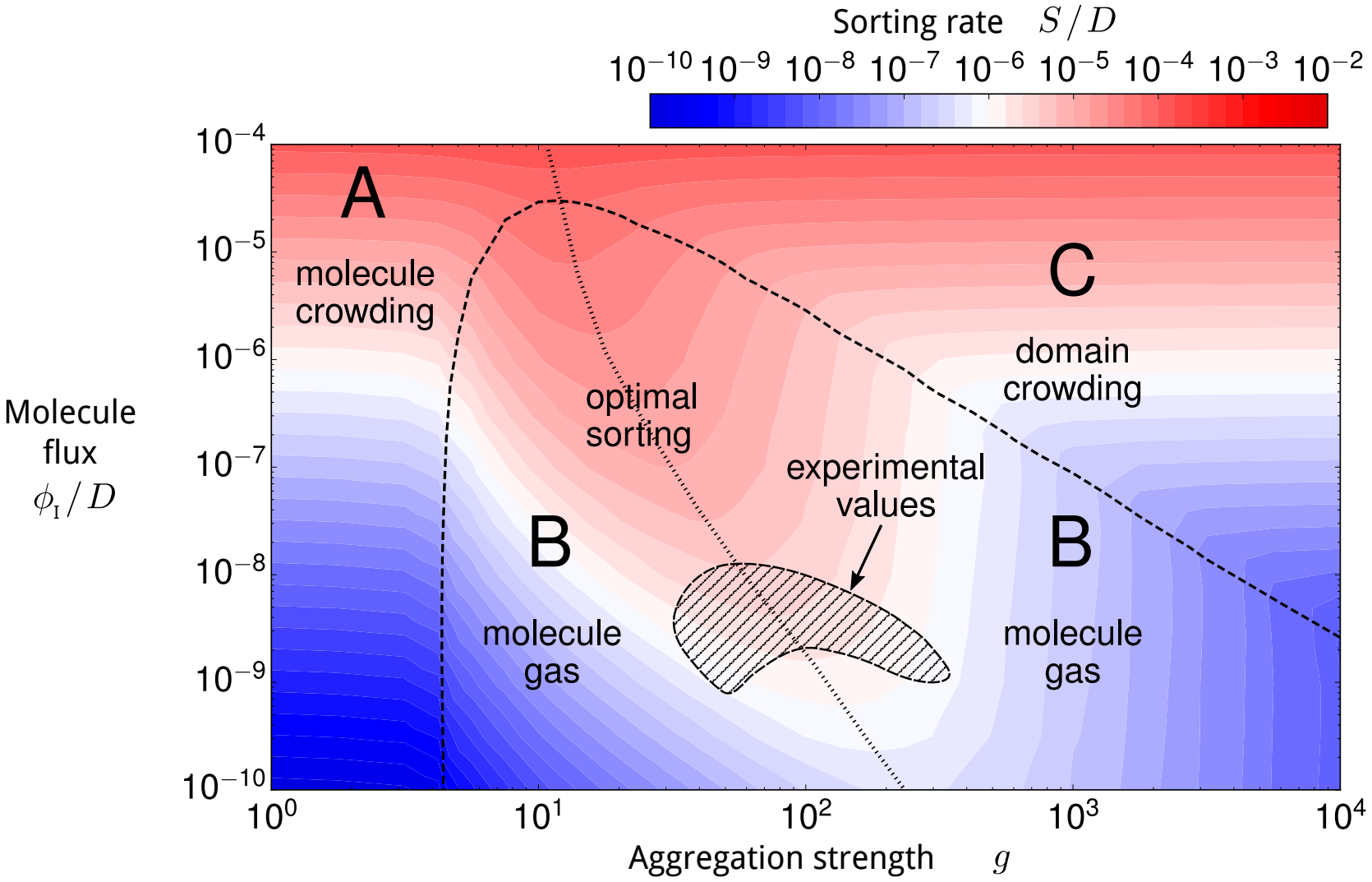

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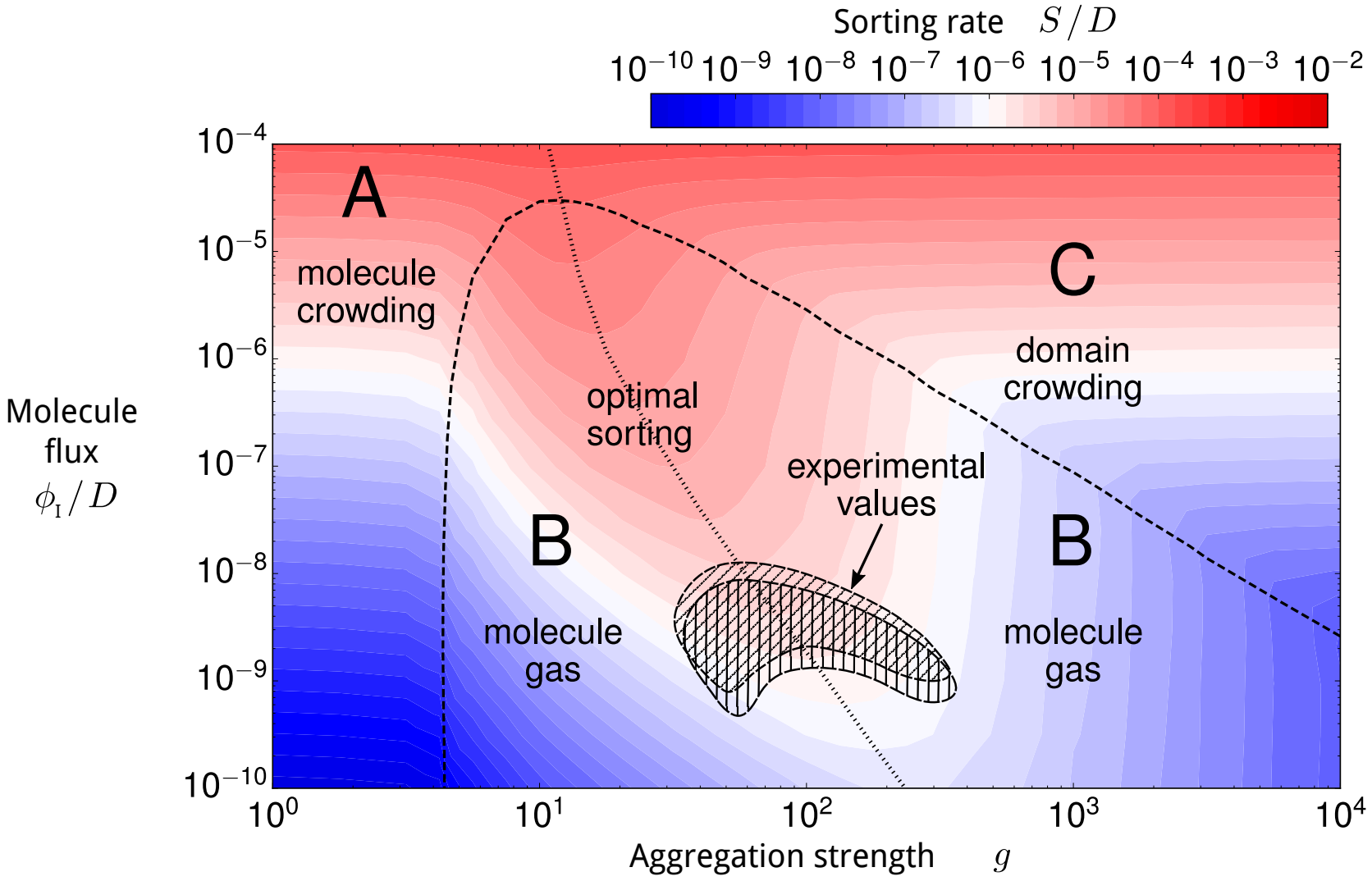

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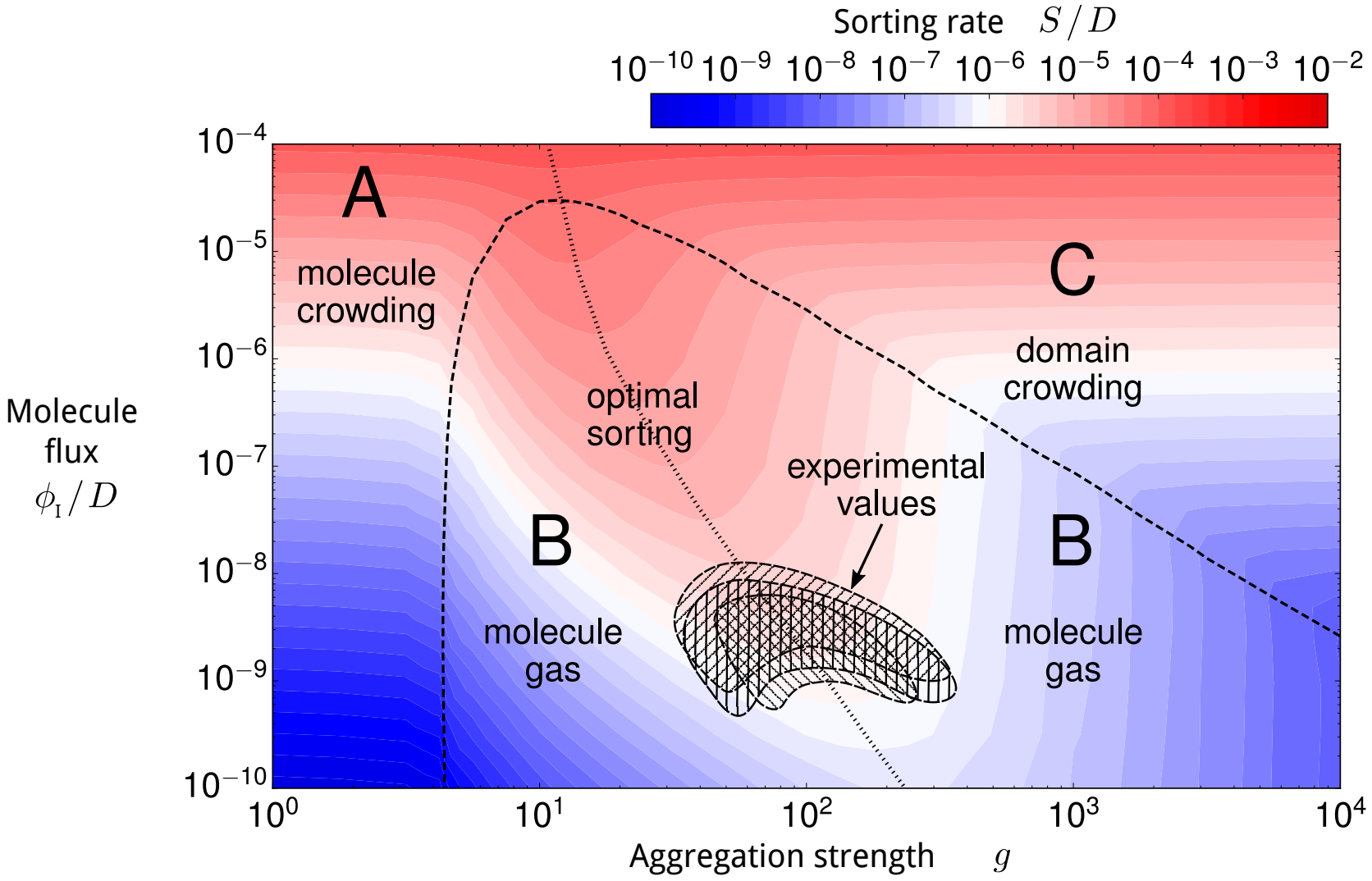

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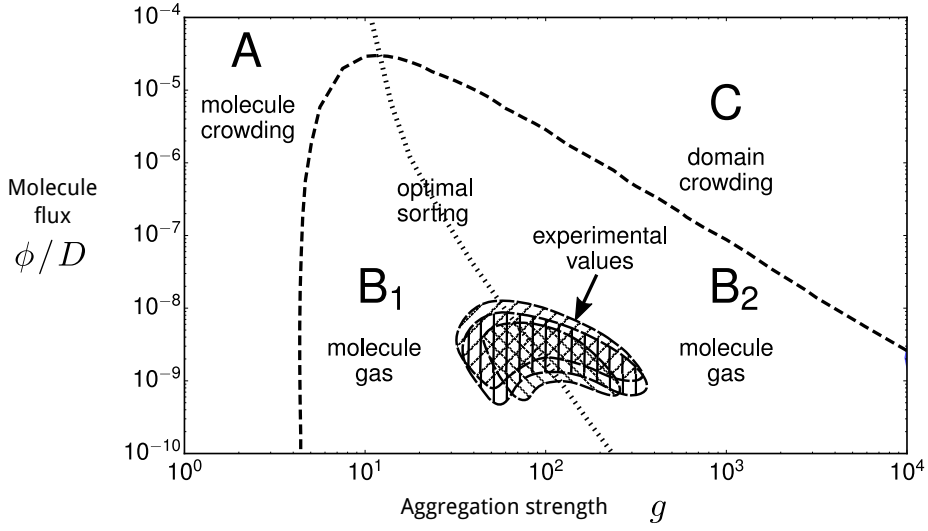

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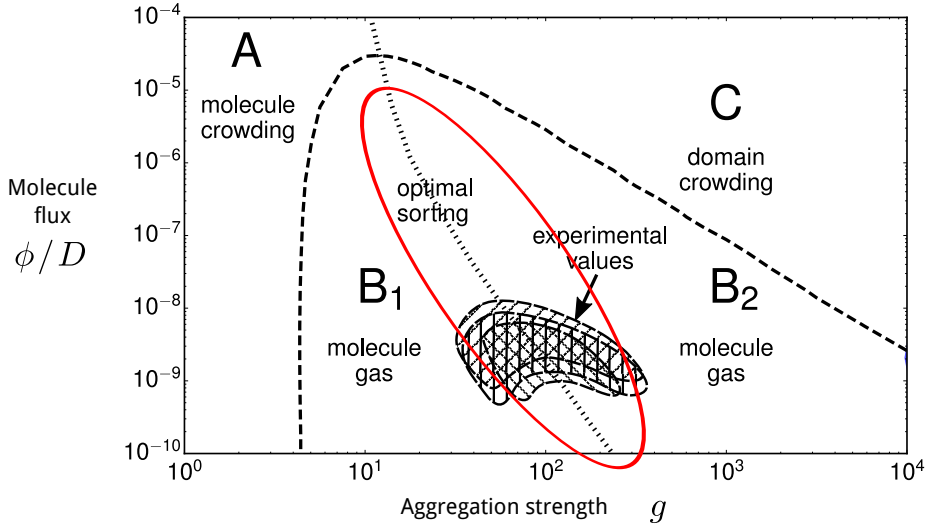

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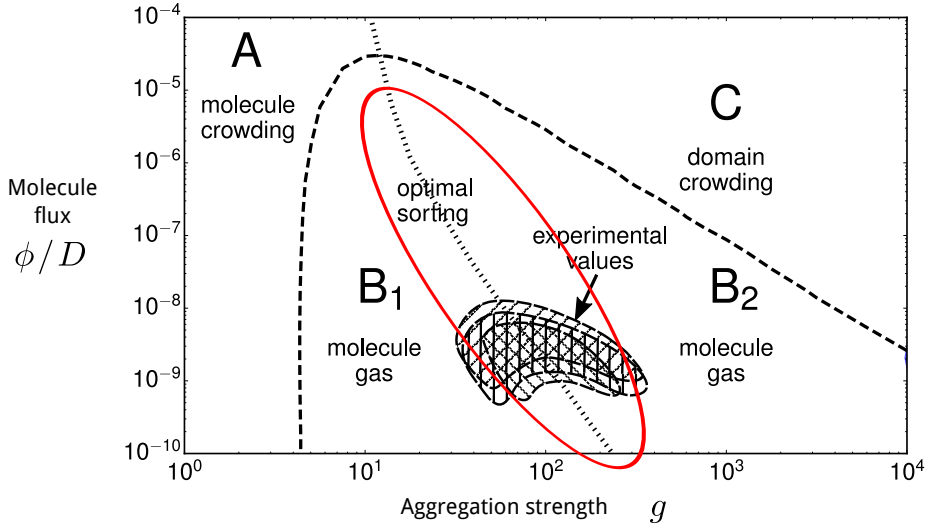

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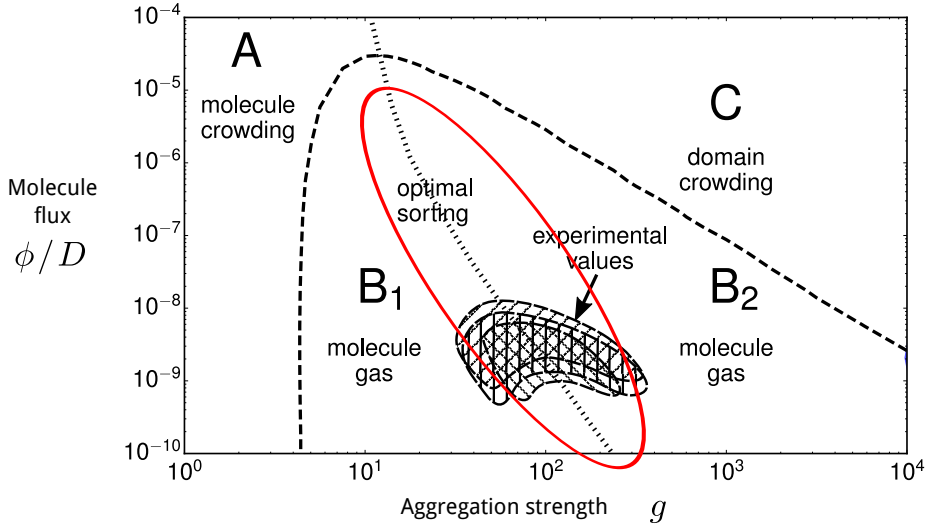
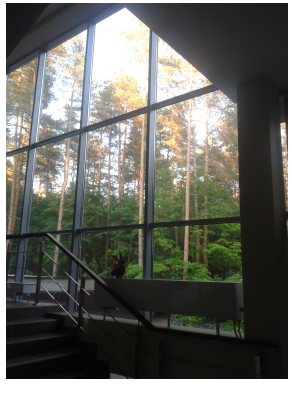


Collaboration

- Candiolo Cancer Institute
  - Guido Serini
  - Donatella Valdembri

- Landau Institute for Theoretical Physics, Moscow
  - Igor Kolokolov
  - Vladimir Lebedev



- Politecnico di Torino
  - Marco Zamparo
  - Luca Dall'Asta