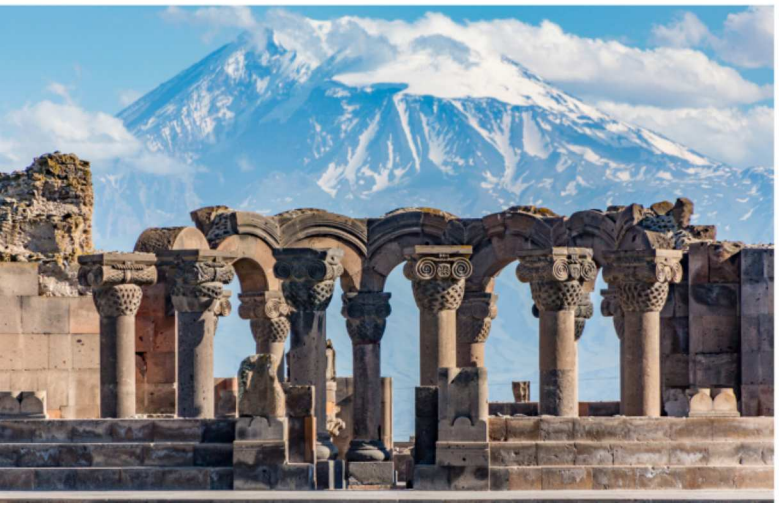
Phenomenological theory of self-organized molecular sorting

Marco Zamparo, Donatella Valdembri, Guido Serini,
Igor Kolokolov, Vladimir Lebedev, Luca Dall'Asta, Andrea Gamba

[Phys. Rev. Lett. 126, 088101 (2021)]

Politecnico di Torino

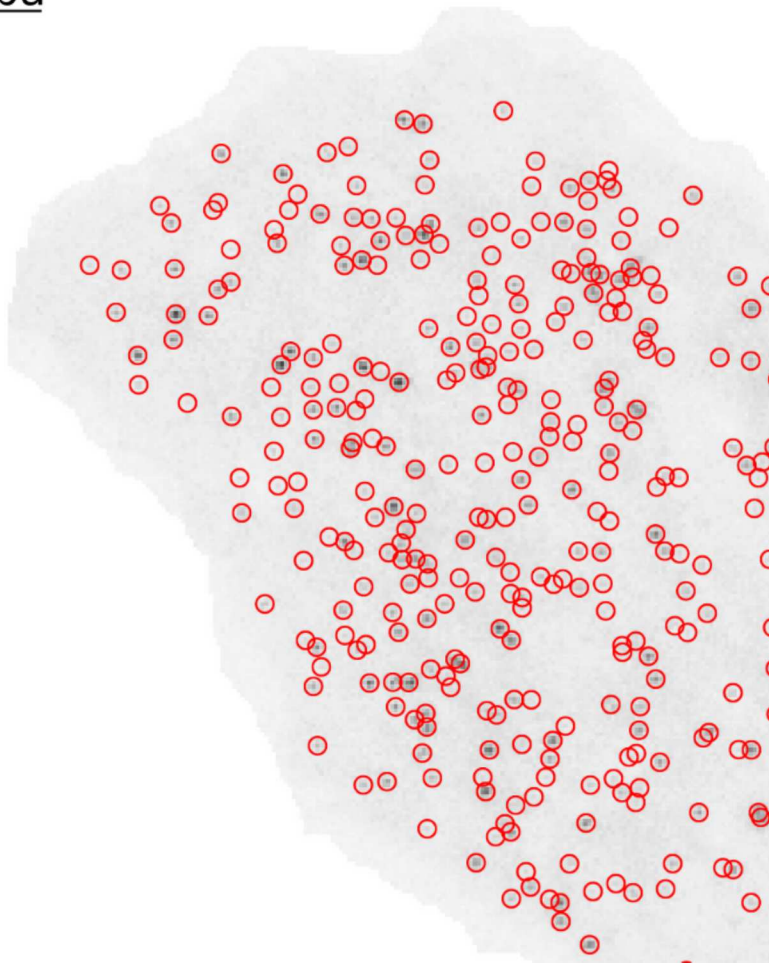
INFN
Istituto Nazionale di Fisica Nucleare



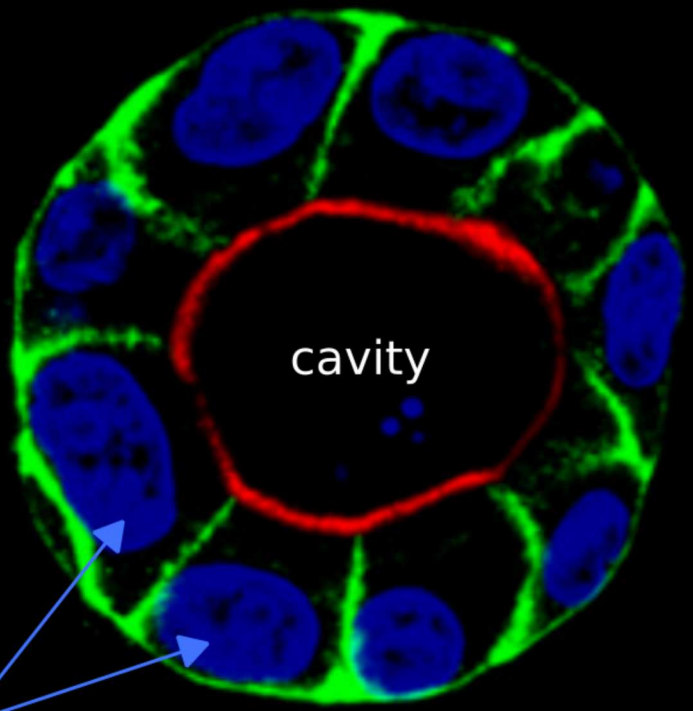
LANDAU WEEK 2023

Yerevan, Armenia

June, 22-29, 2023

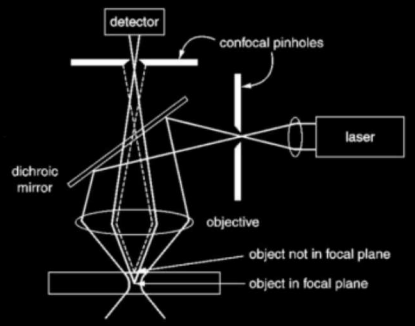


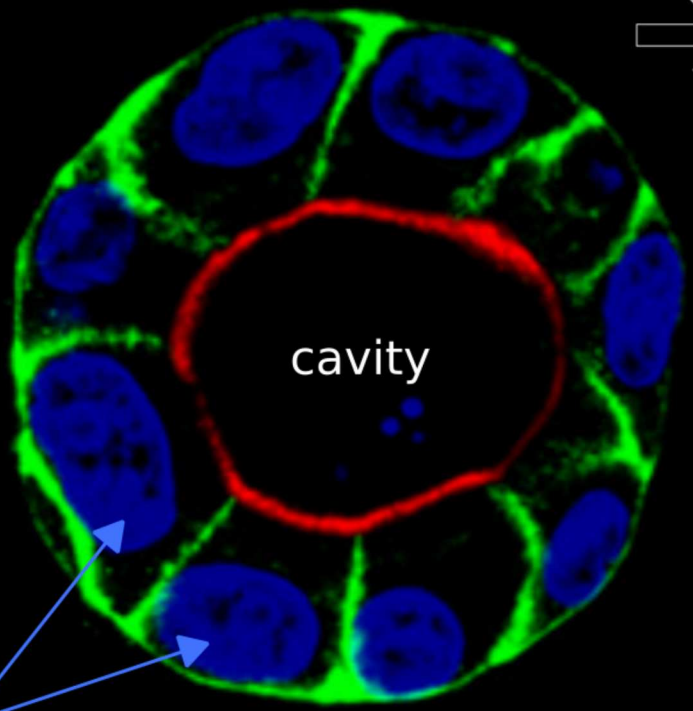
Multicellular structures



F Martin-Belmonte et al, Cell (2007)

Multicellular structures



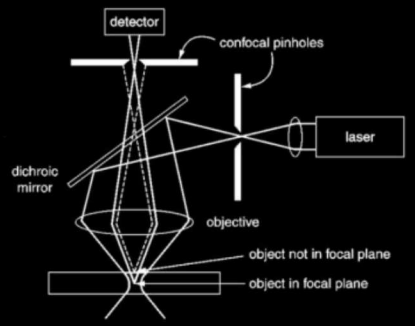


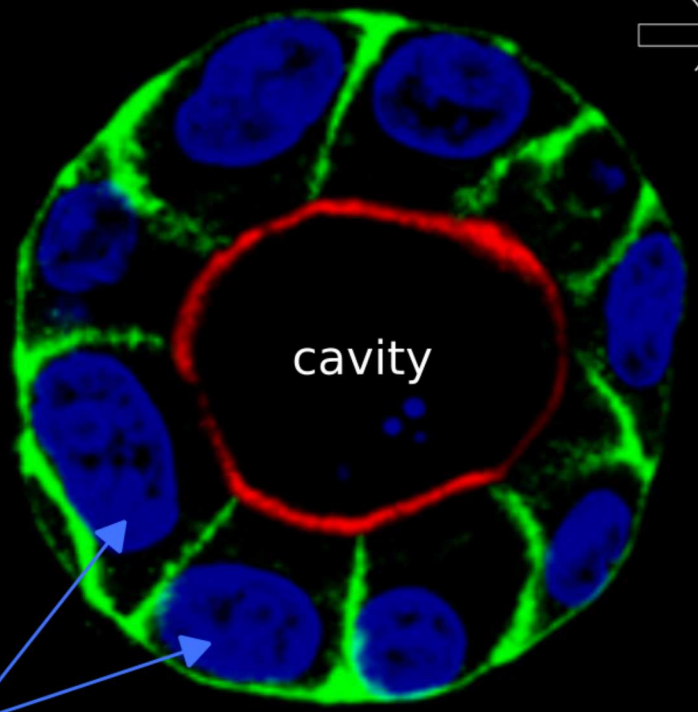
5 µm

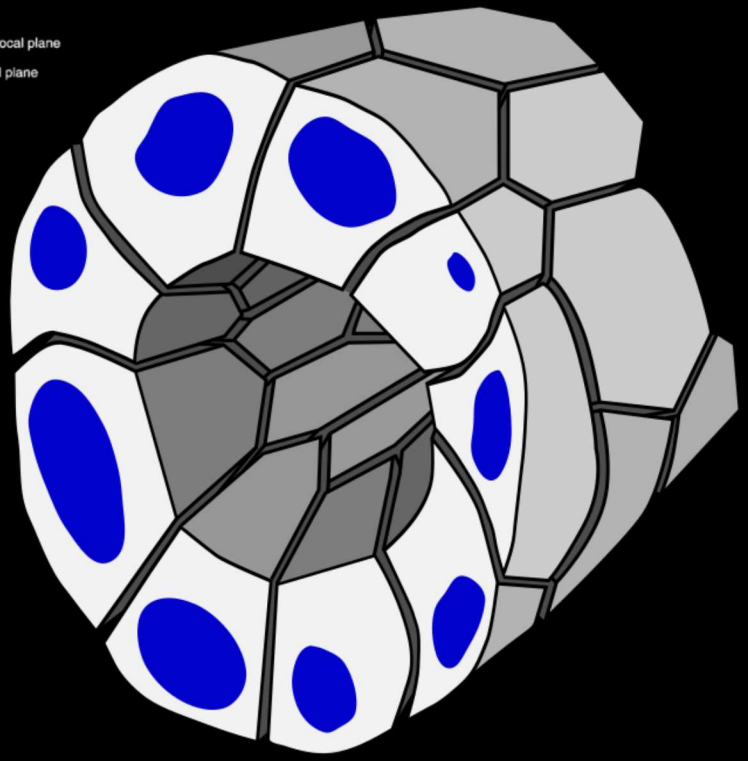
nuclei

F Martin-Belmonte et al, Cell (2007)

Multicellular structures





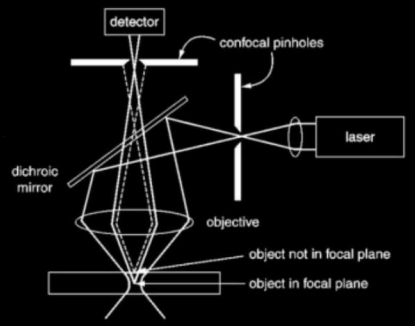


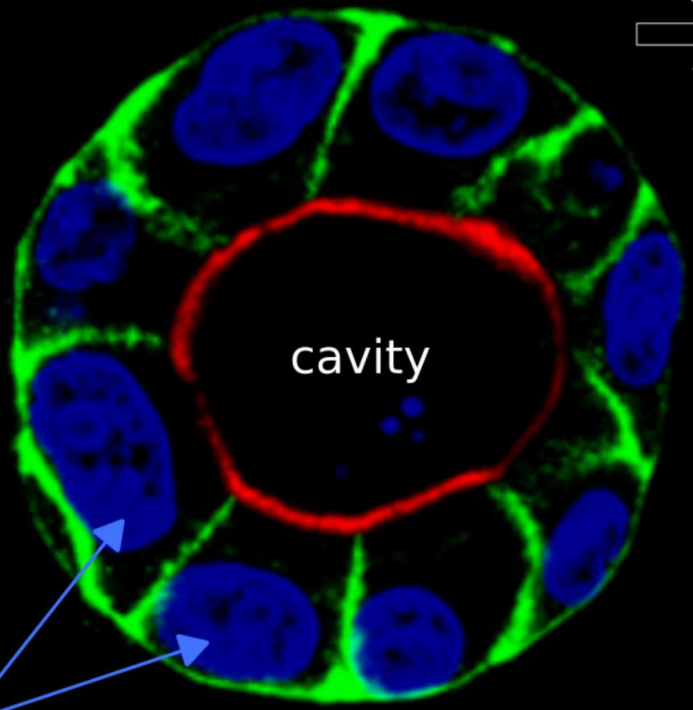
5 µm

nuclei

F Martin-Belmonte et al, Cell (2007)

Multicellular structures

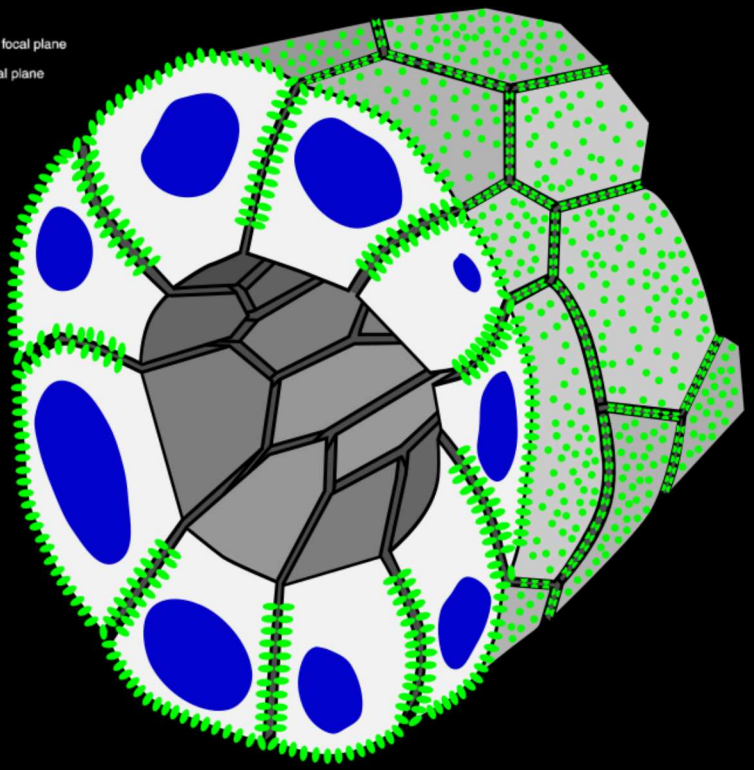




lateral proteins

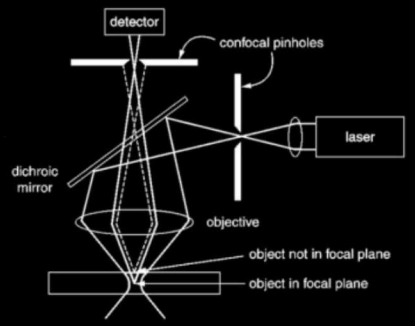
5 µm

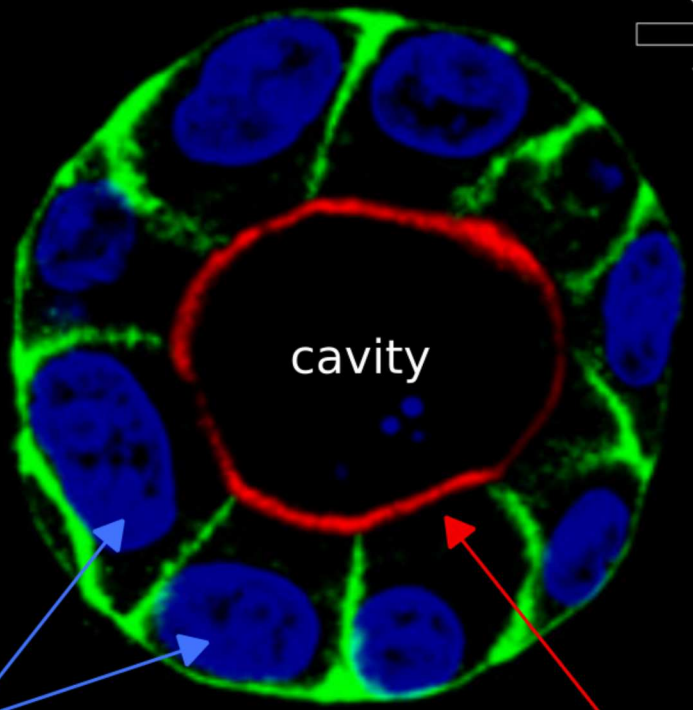
nuclei

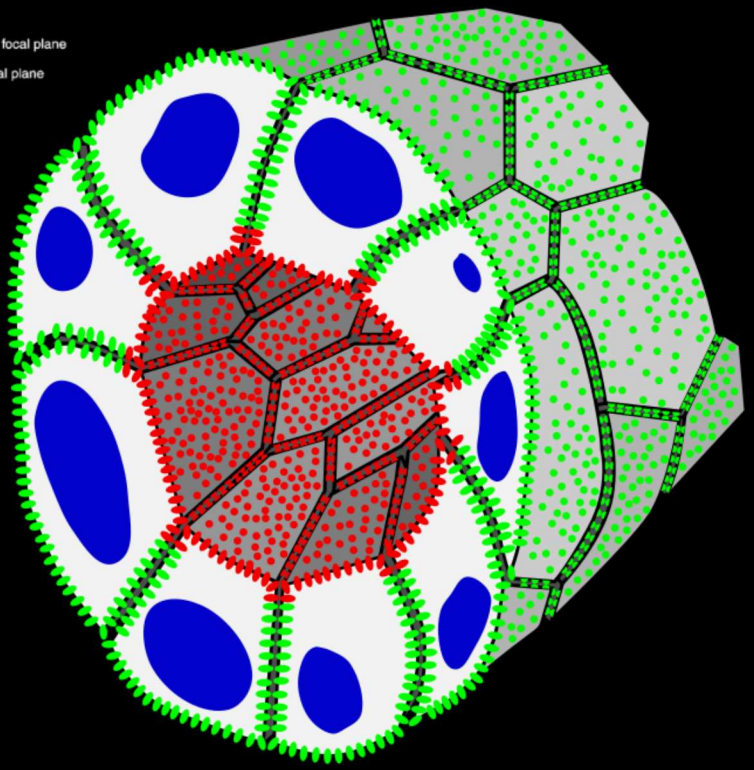


F Martin-Belmonte et al, Cell (2007)

Multicellular structures







lateral proteins

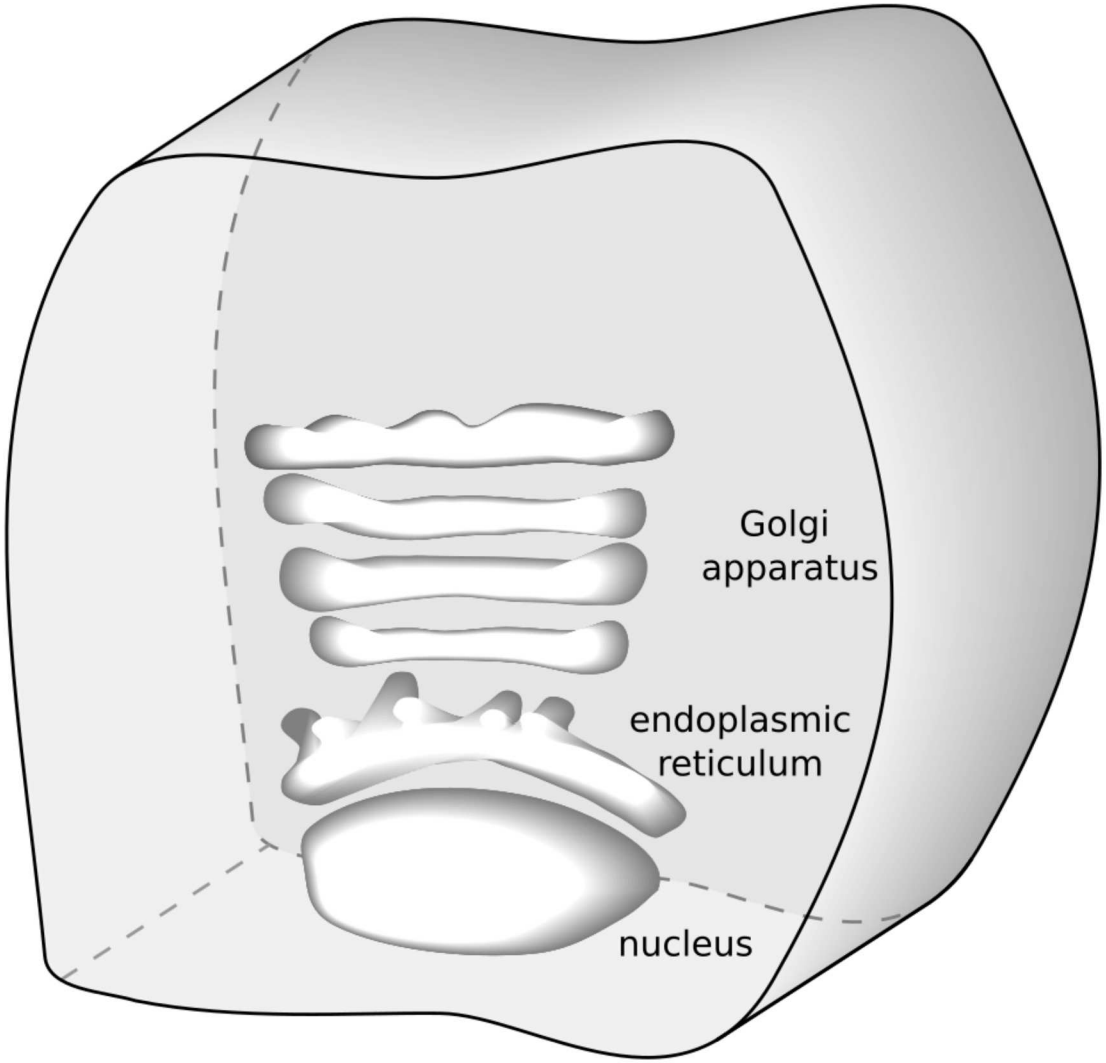
5 µm

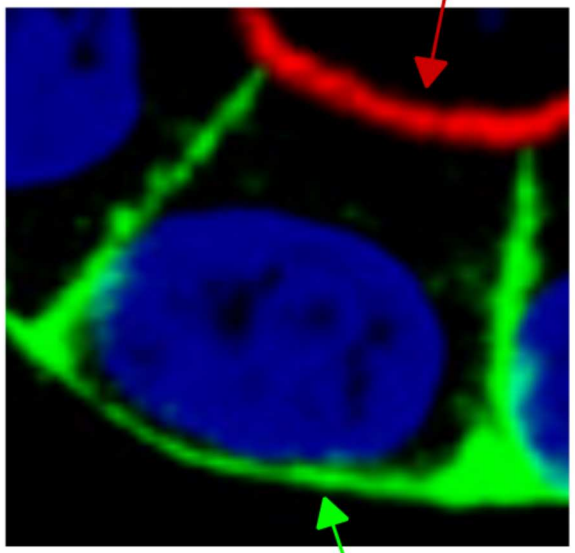
nuclei

apical proteins

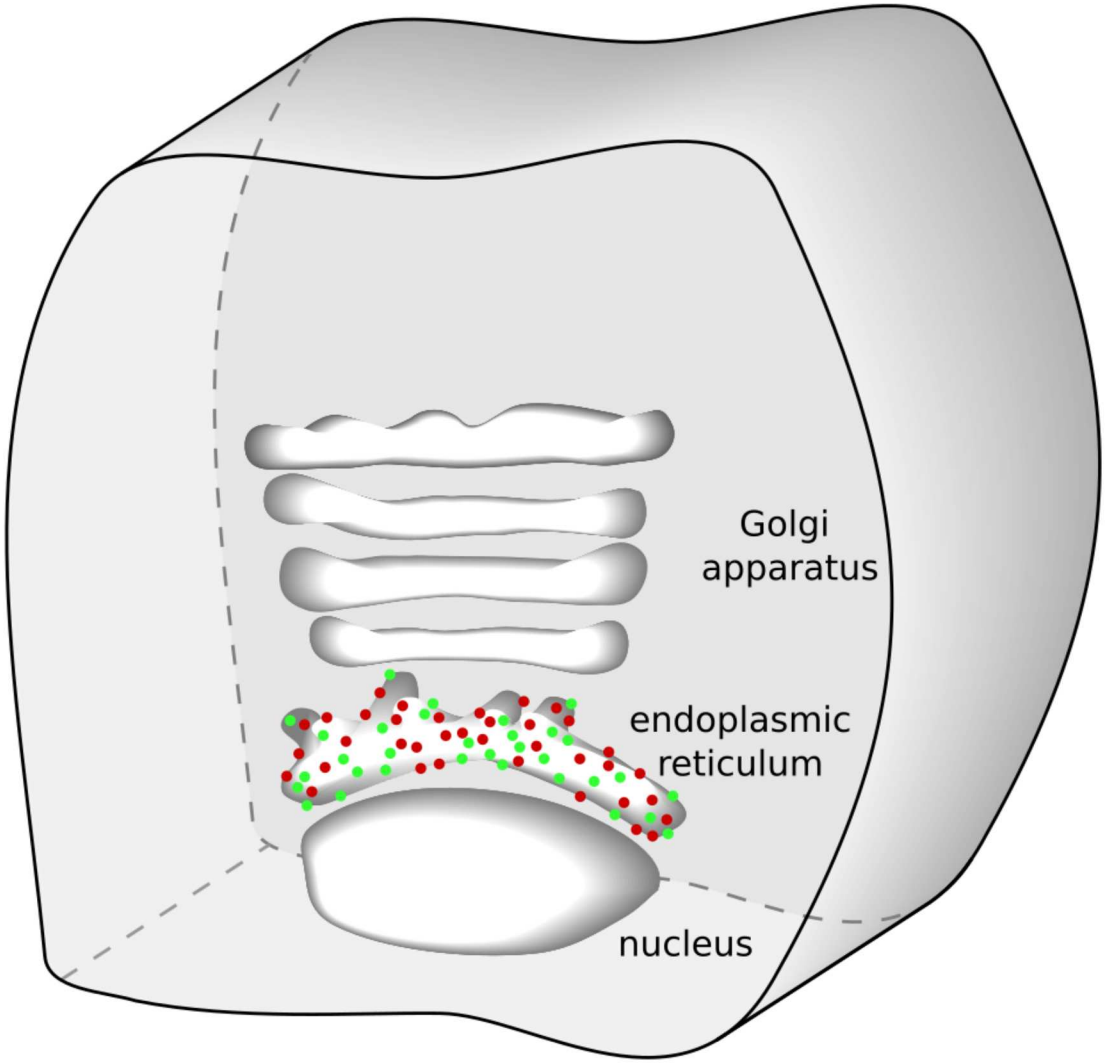
F Martin-Belmonte et al, Cell (2007)

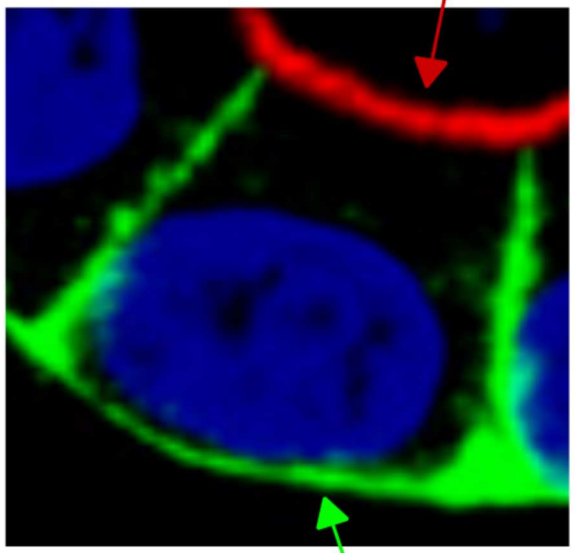
Molecular sorting



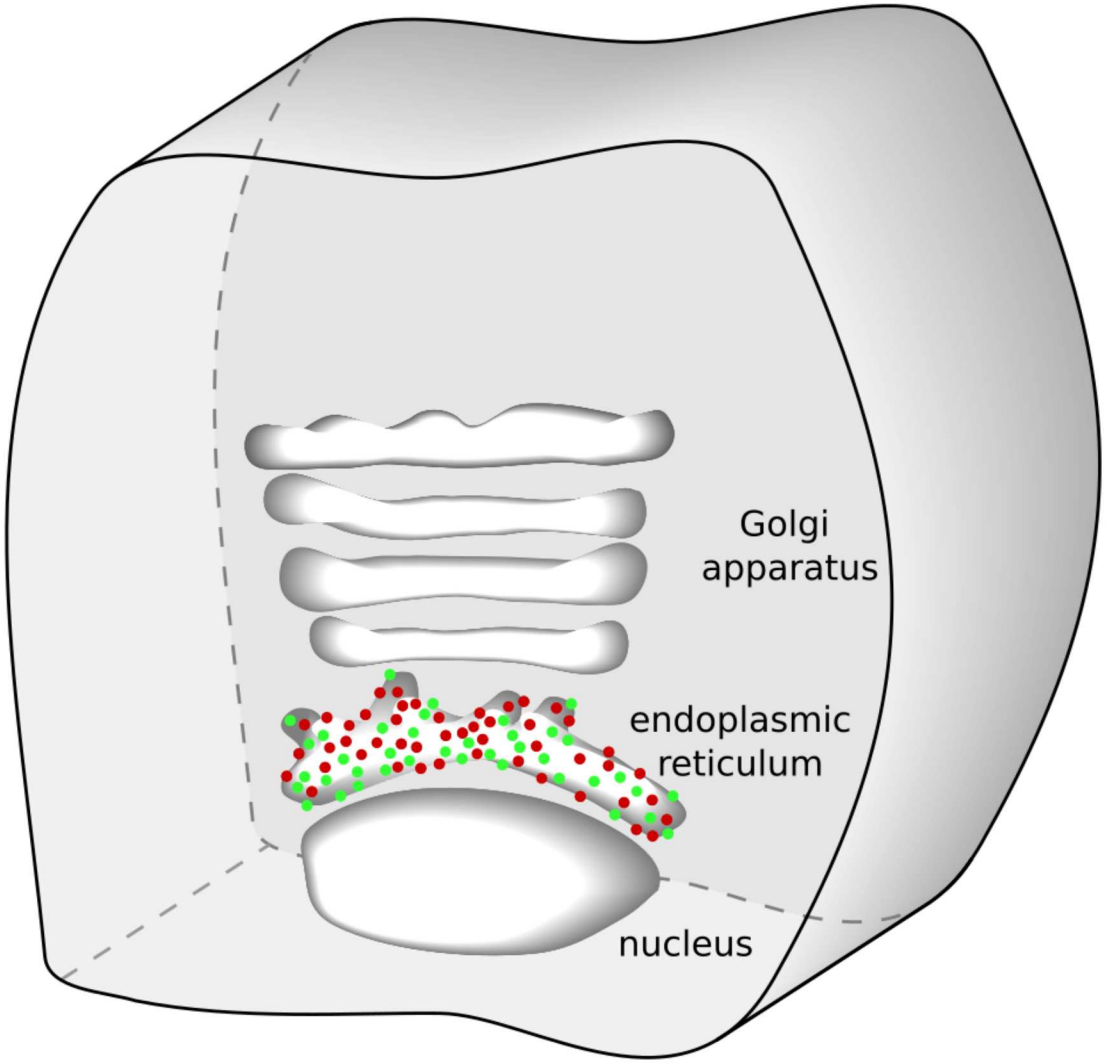


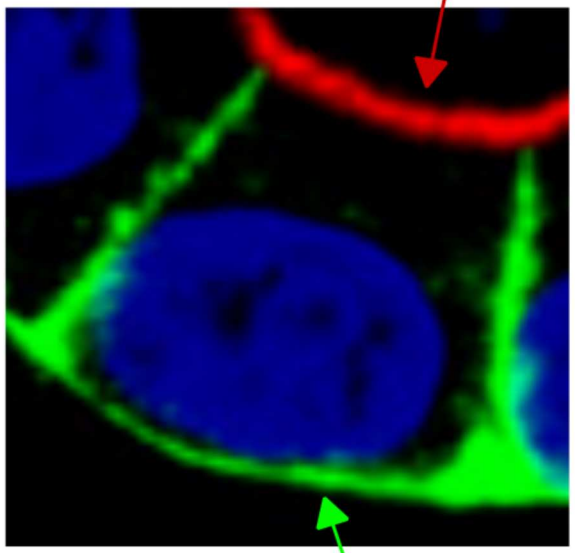
Molecular sorting



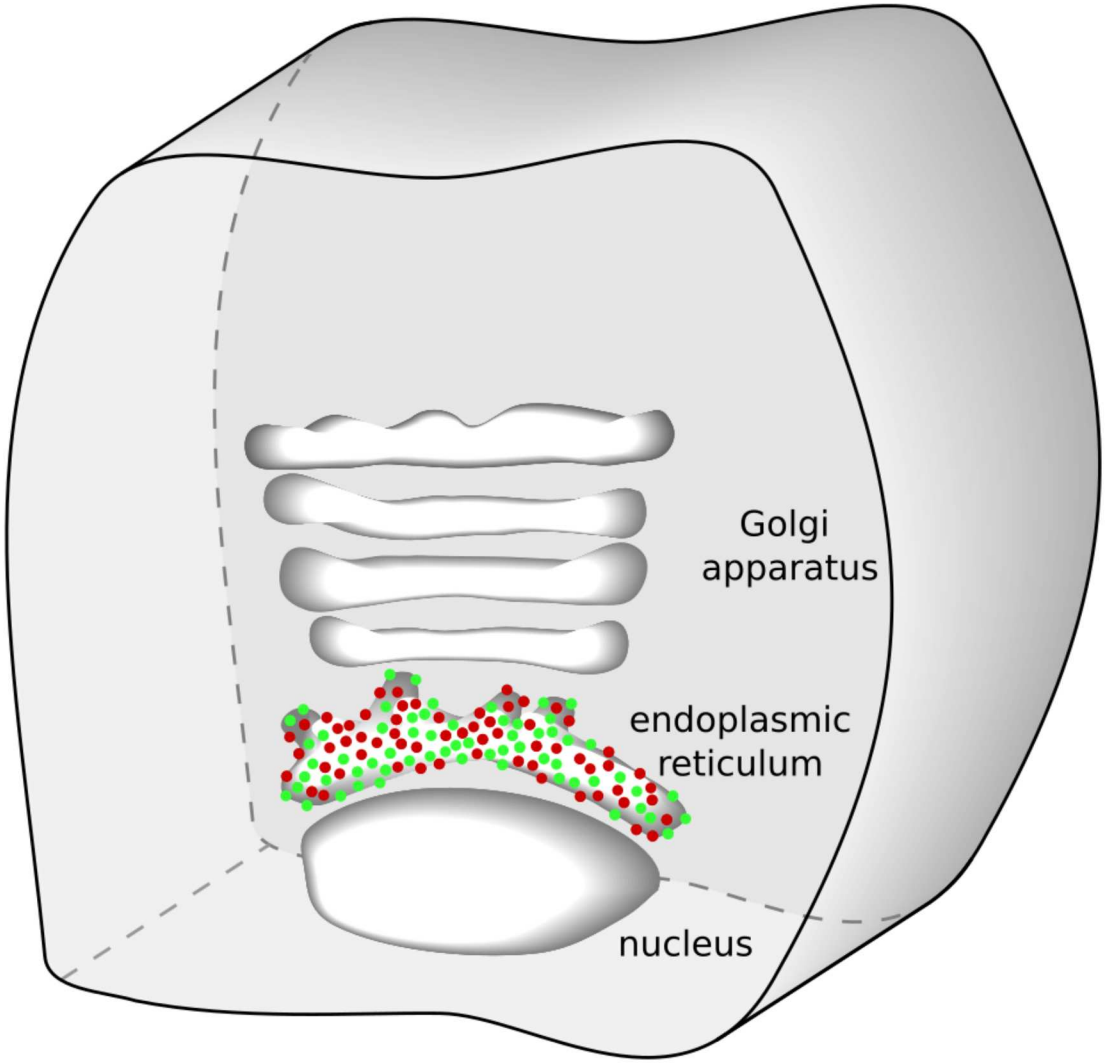


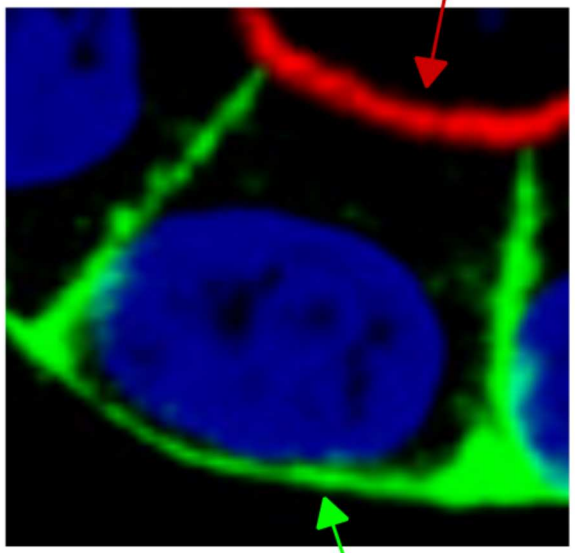
Molecular sorting



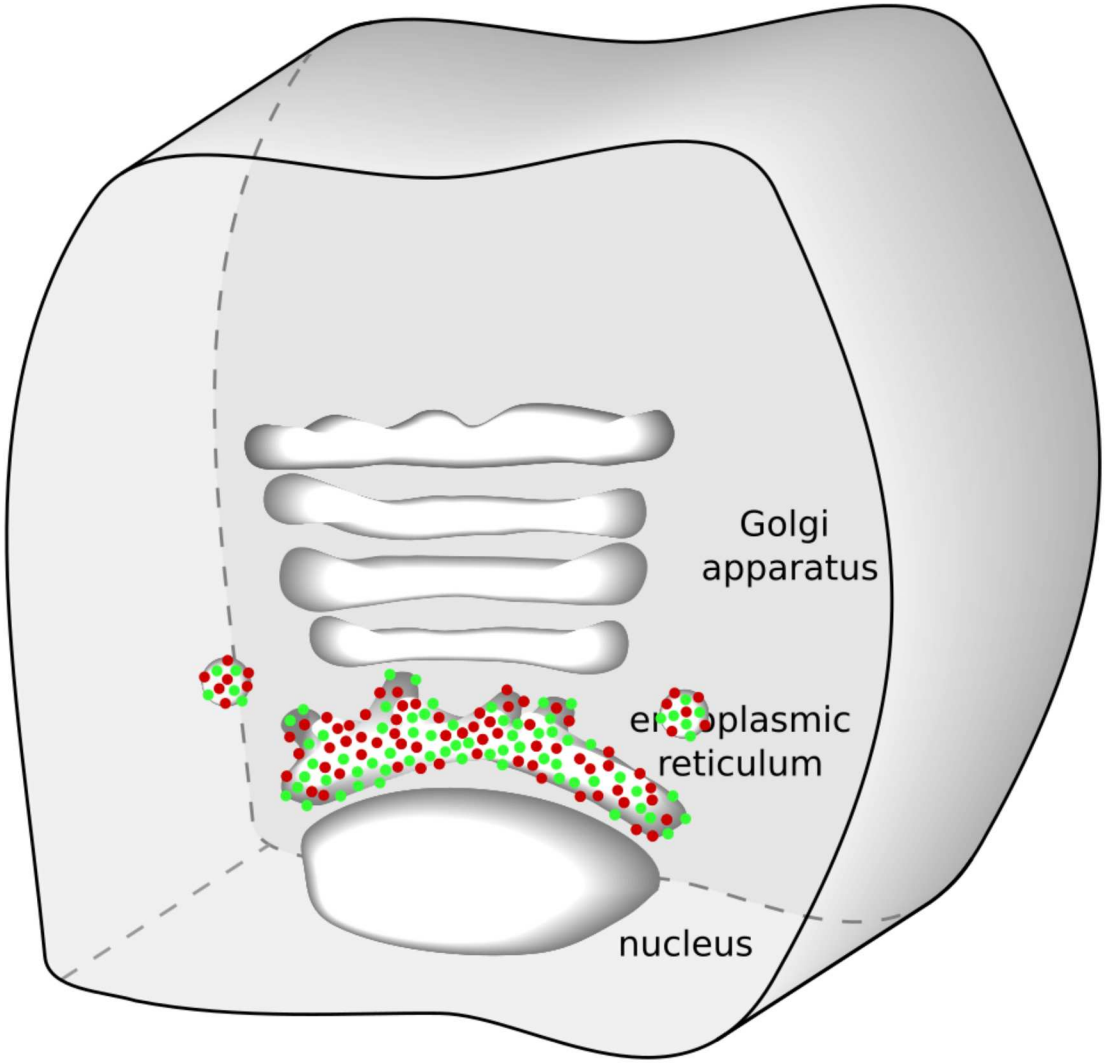


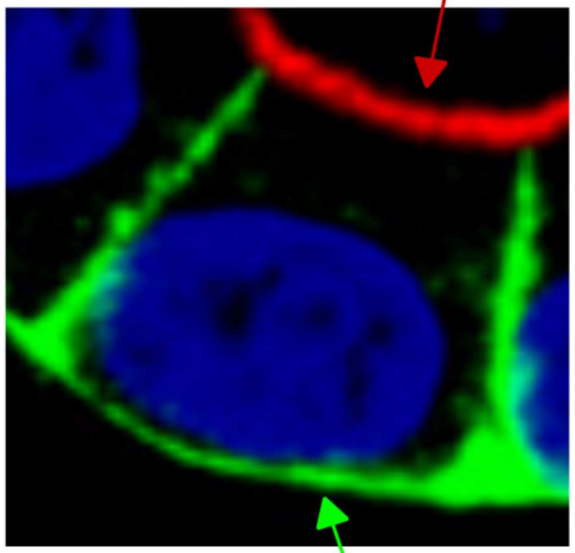
Molecular sorting



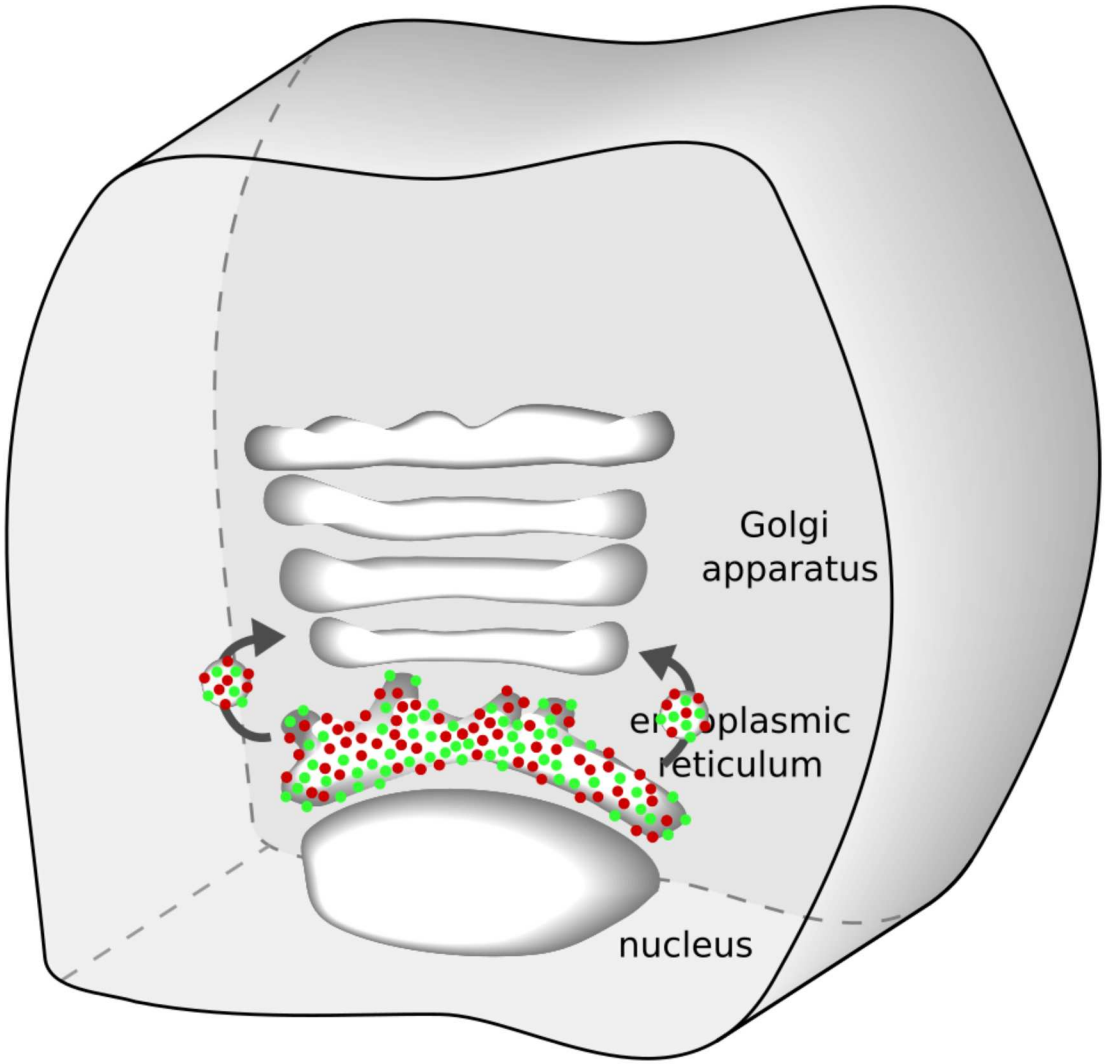


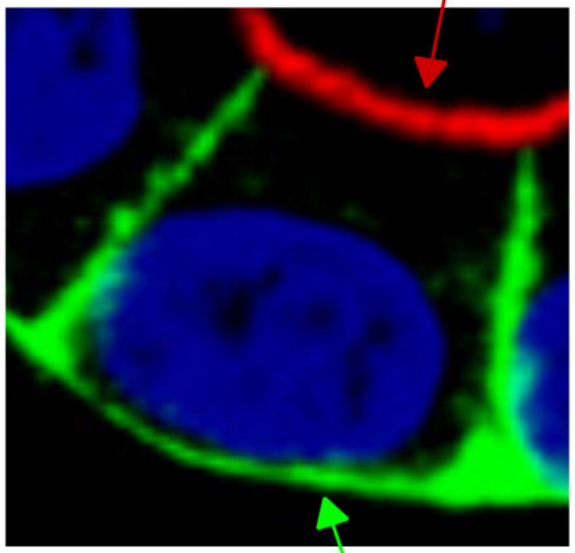
Molecular sorting



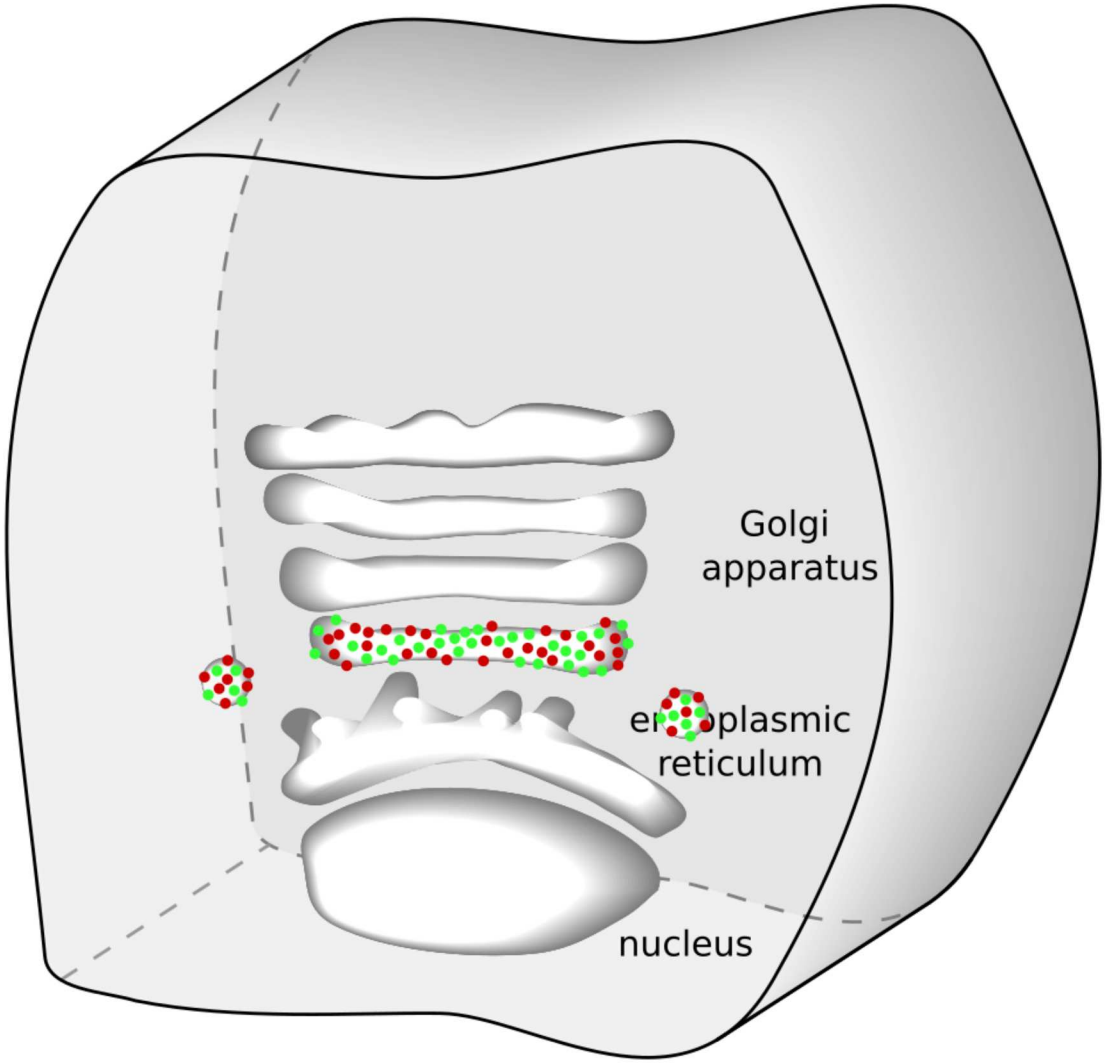


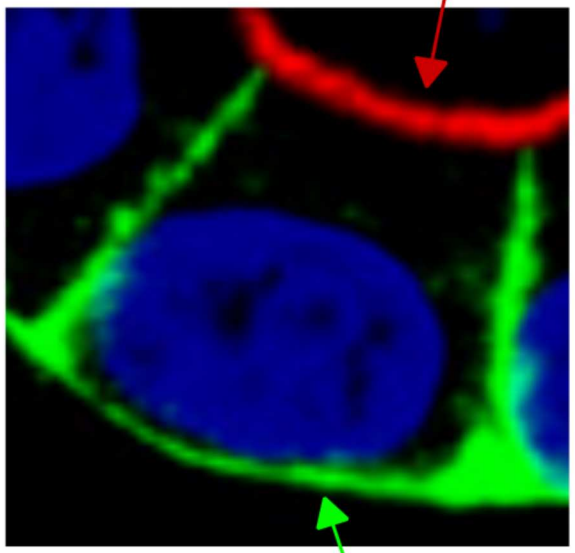
Molecular sorting



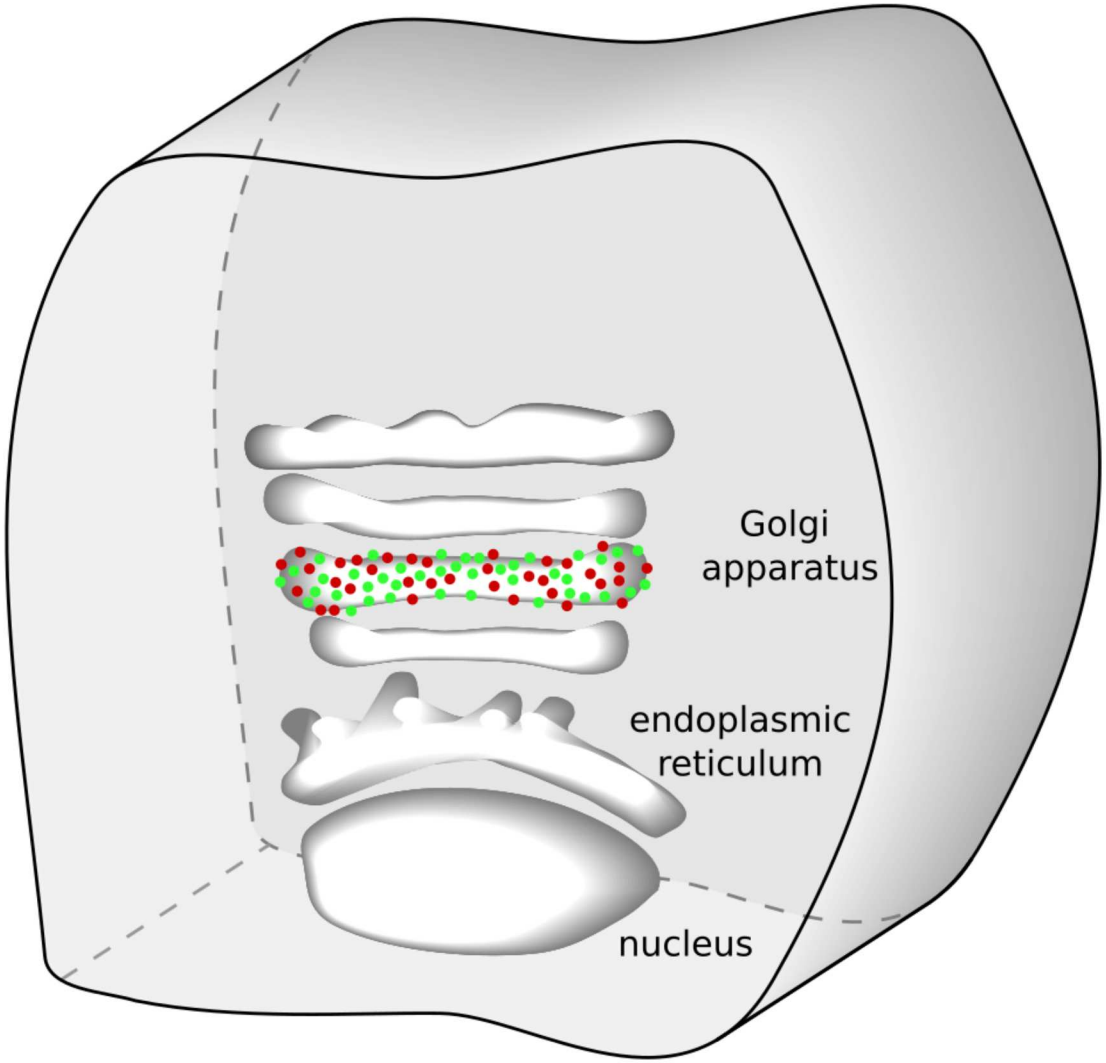


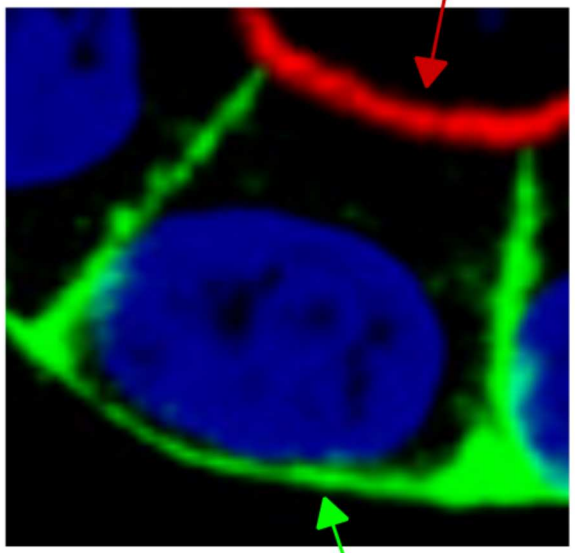
Molecular sorting



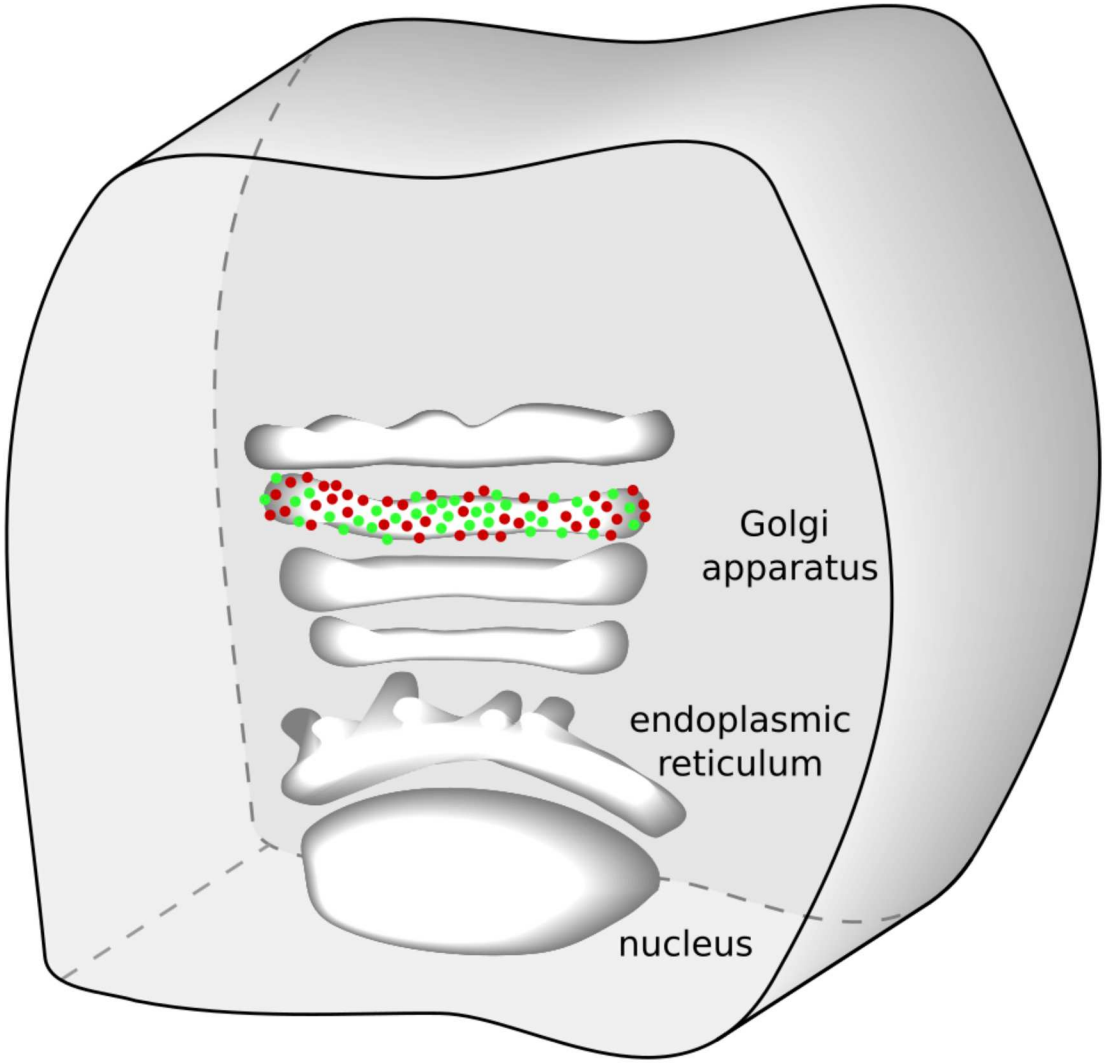


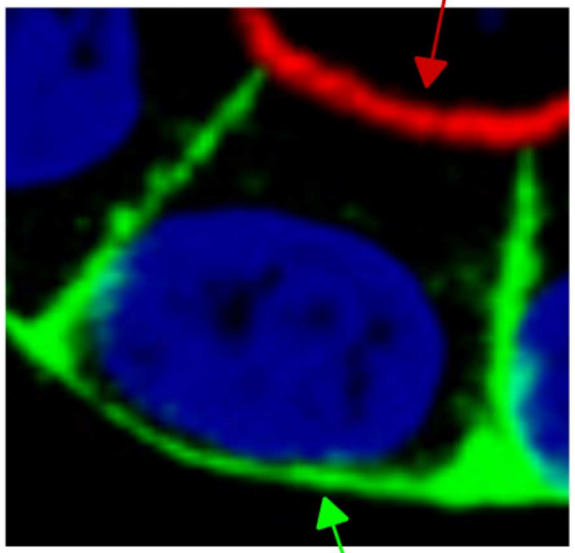
Molecular sorting



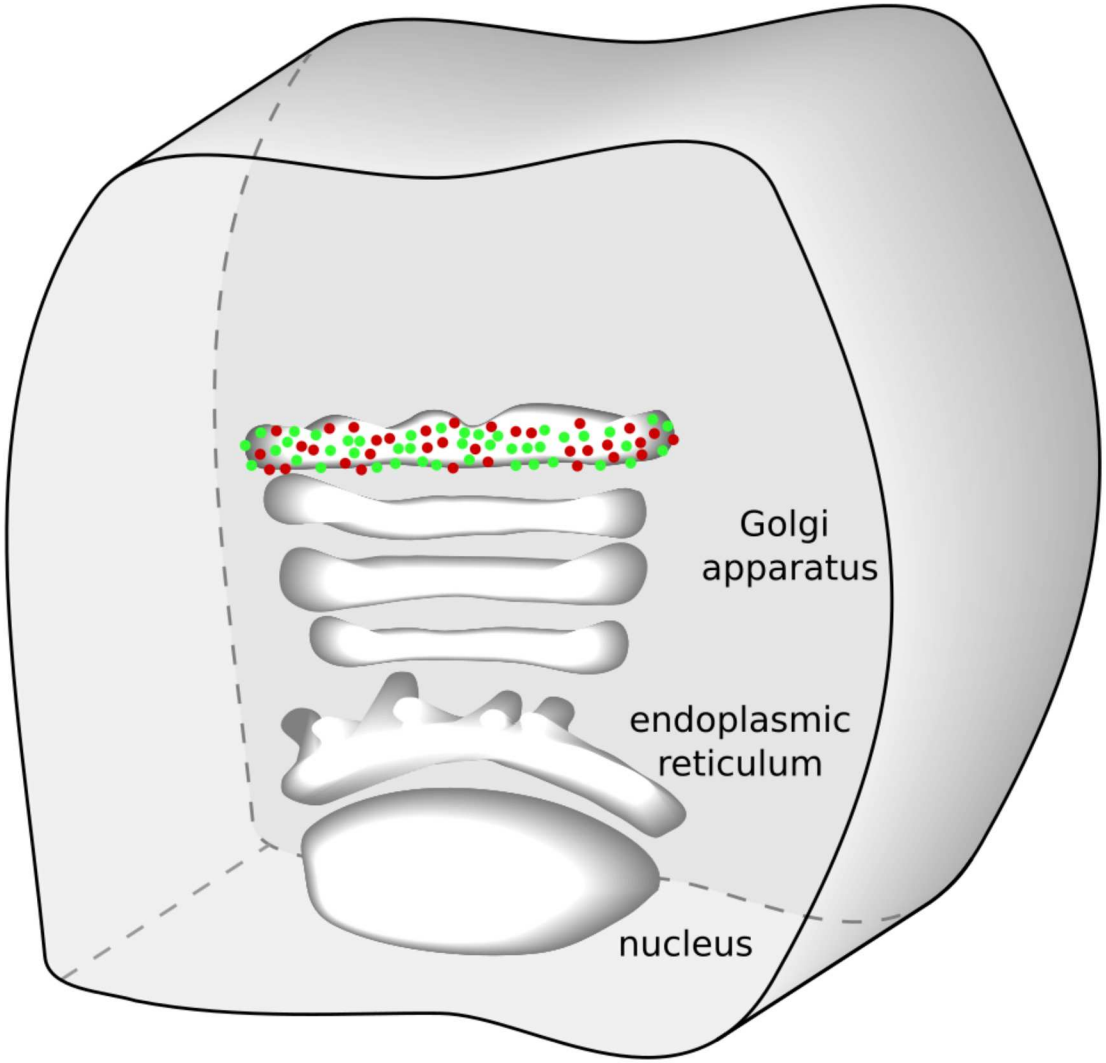


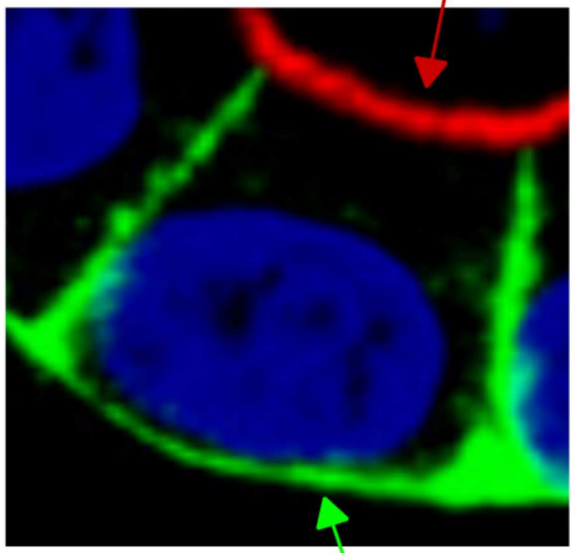
Molecular sorting

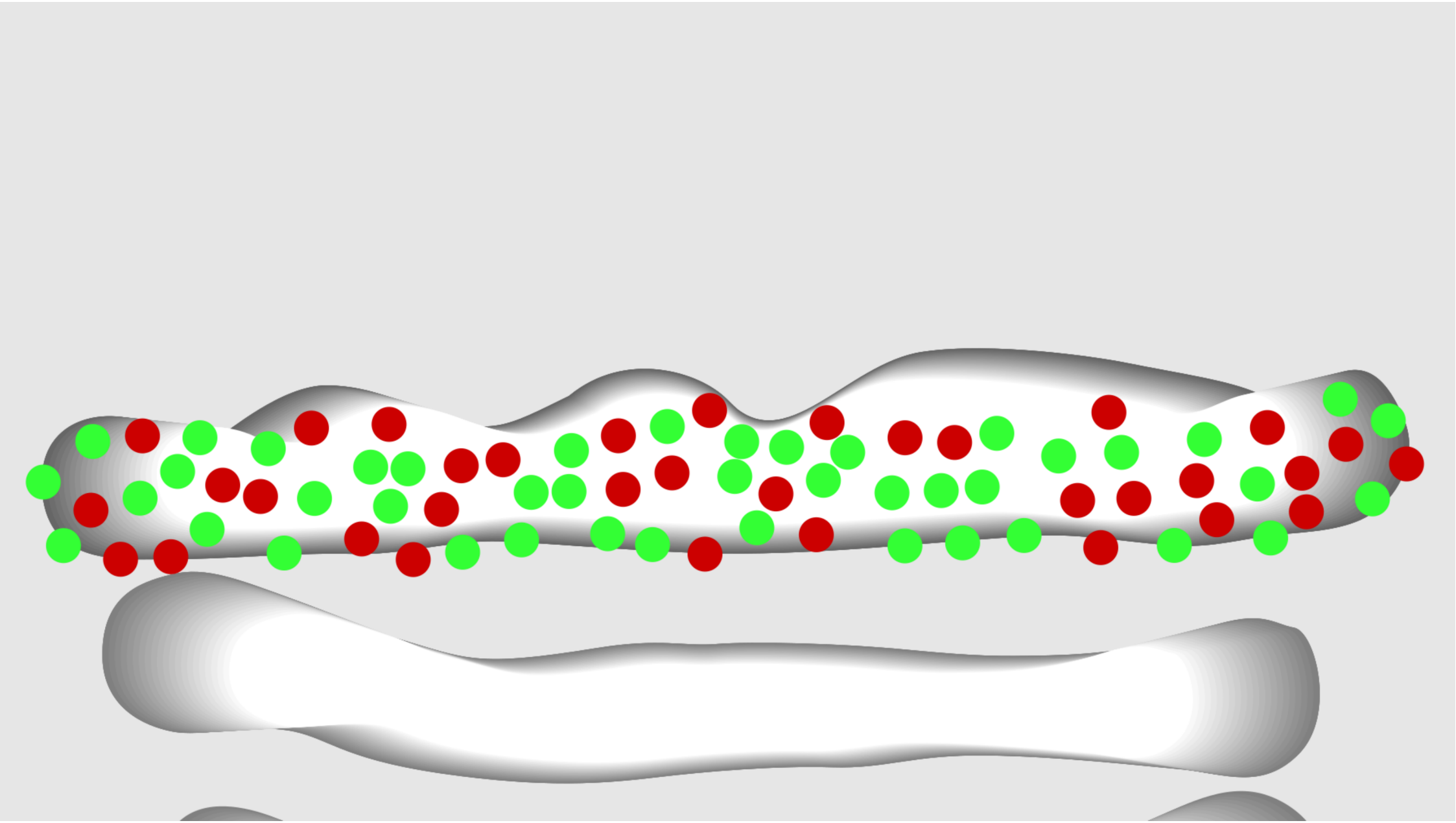


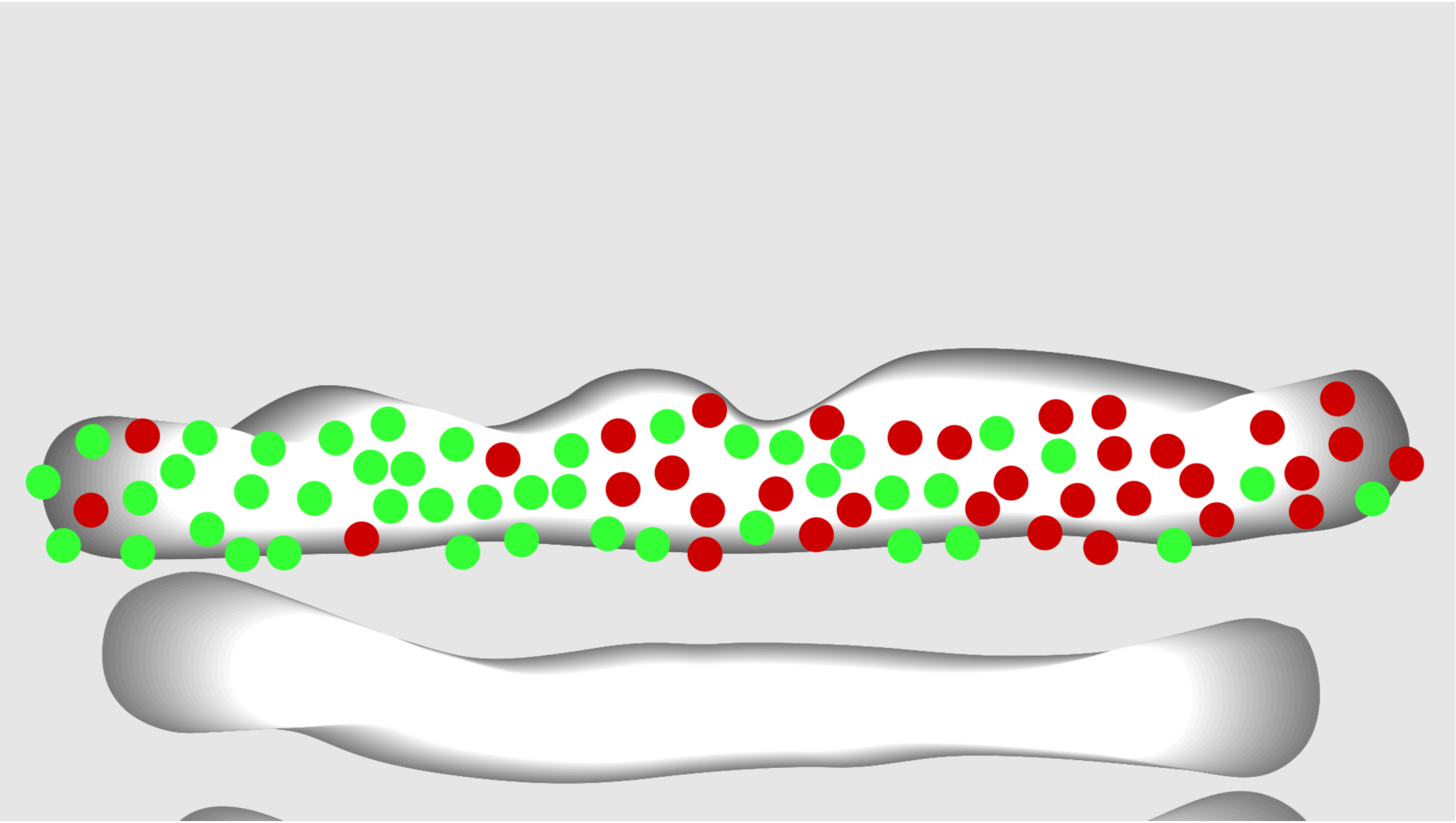


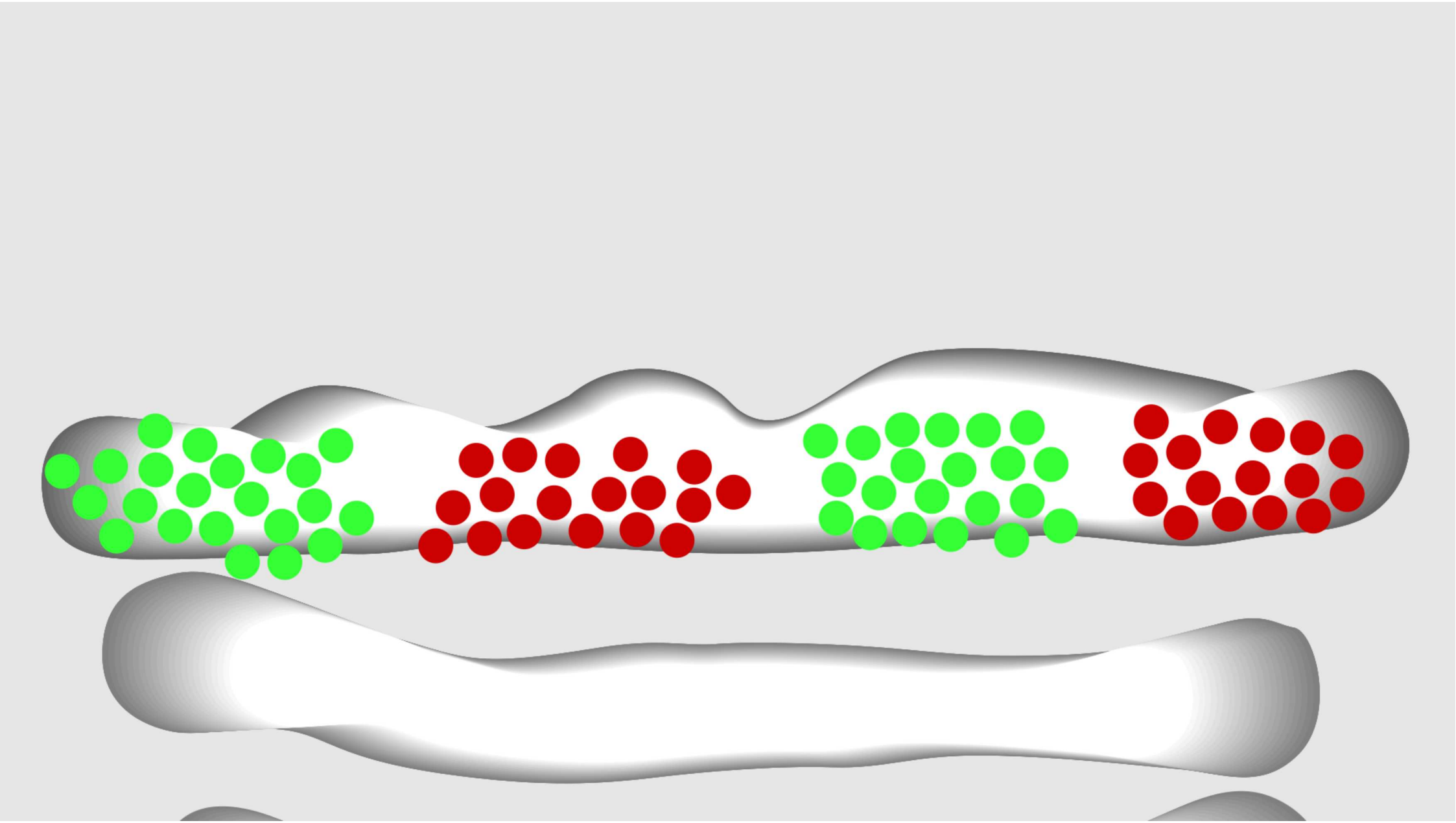
Molecular sorting

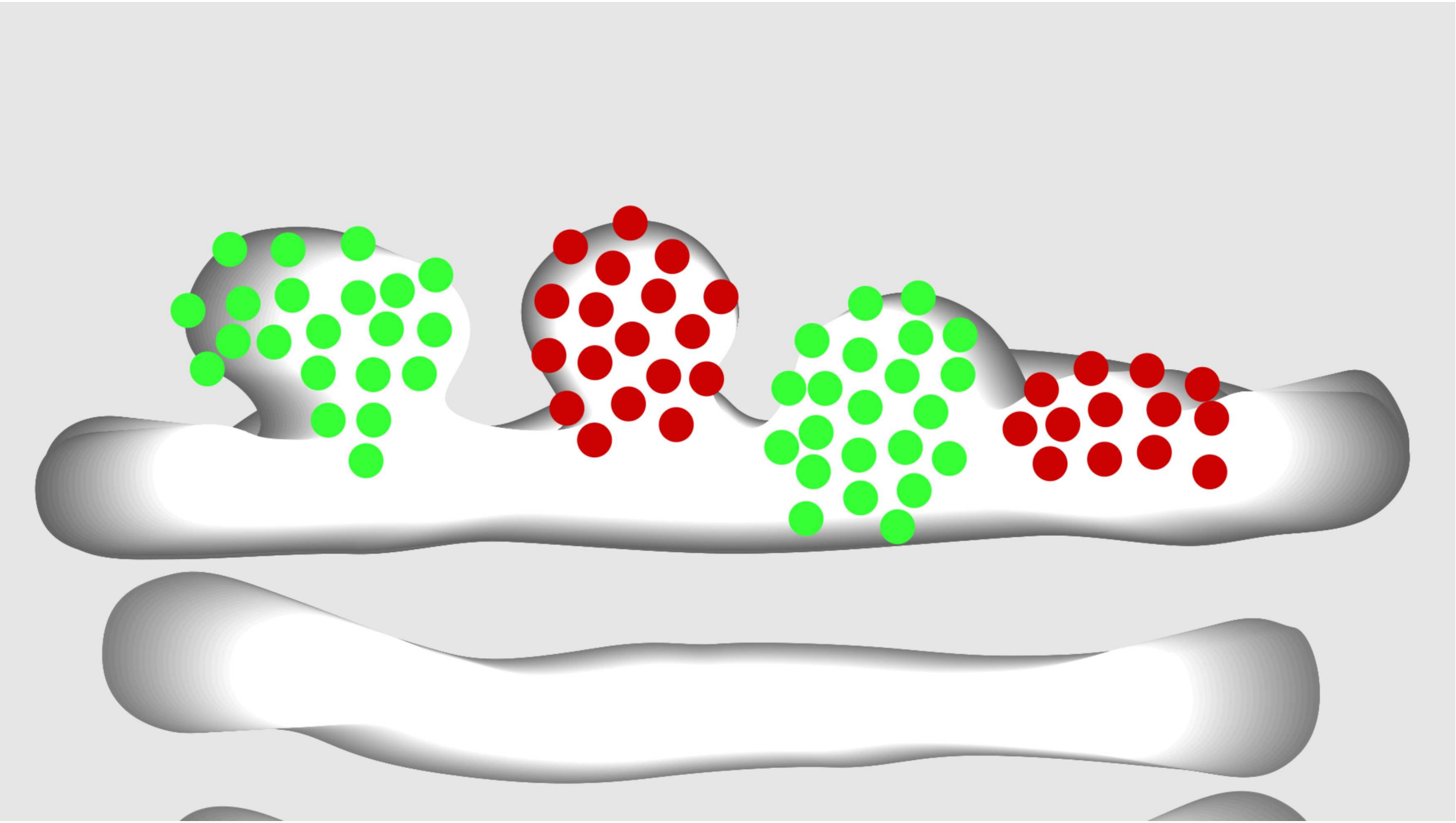


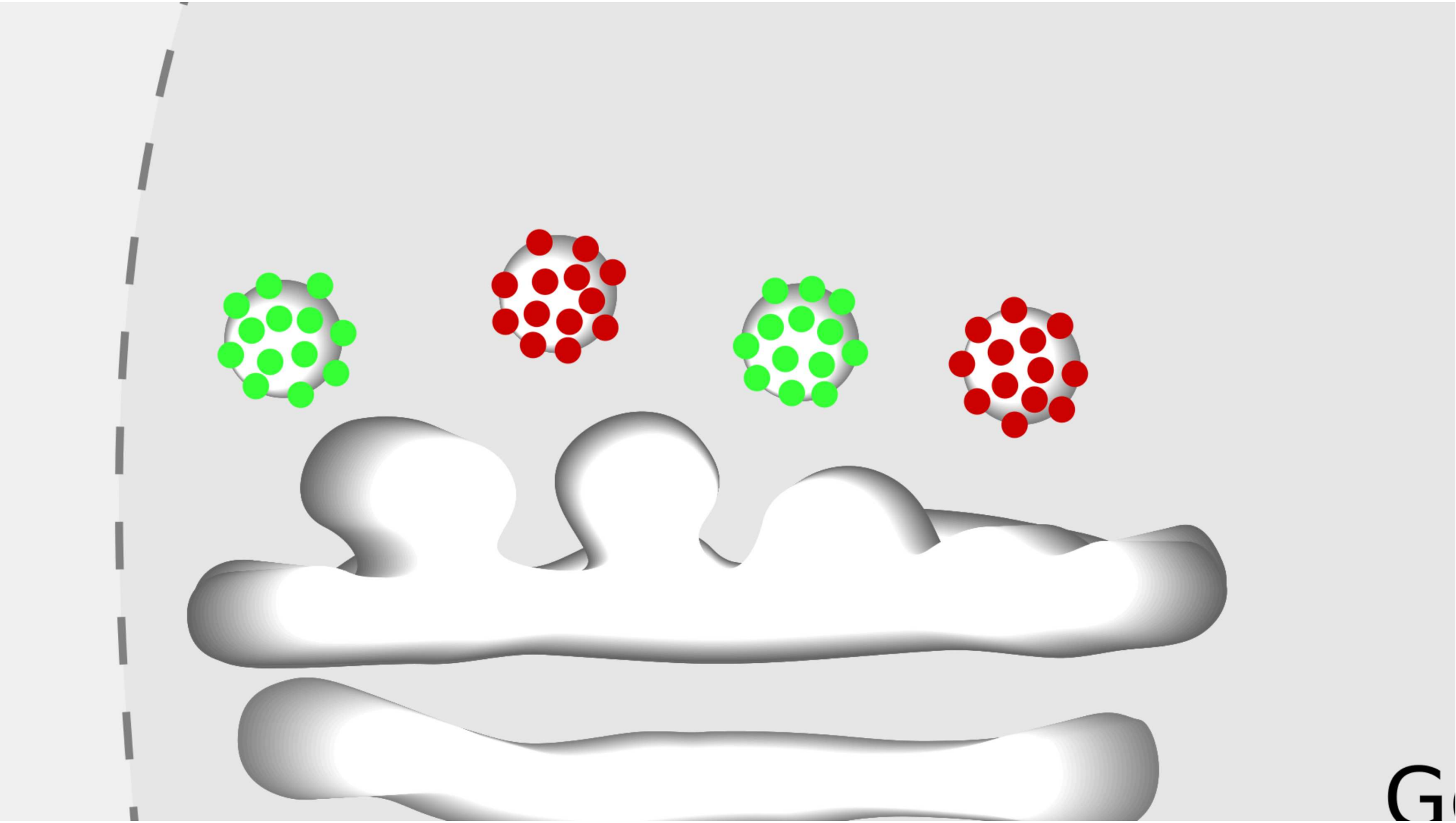


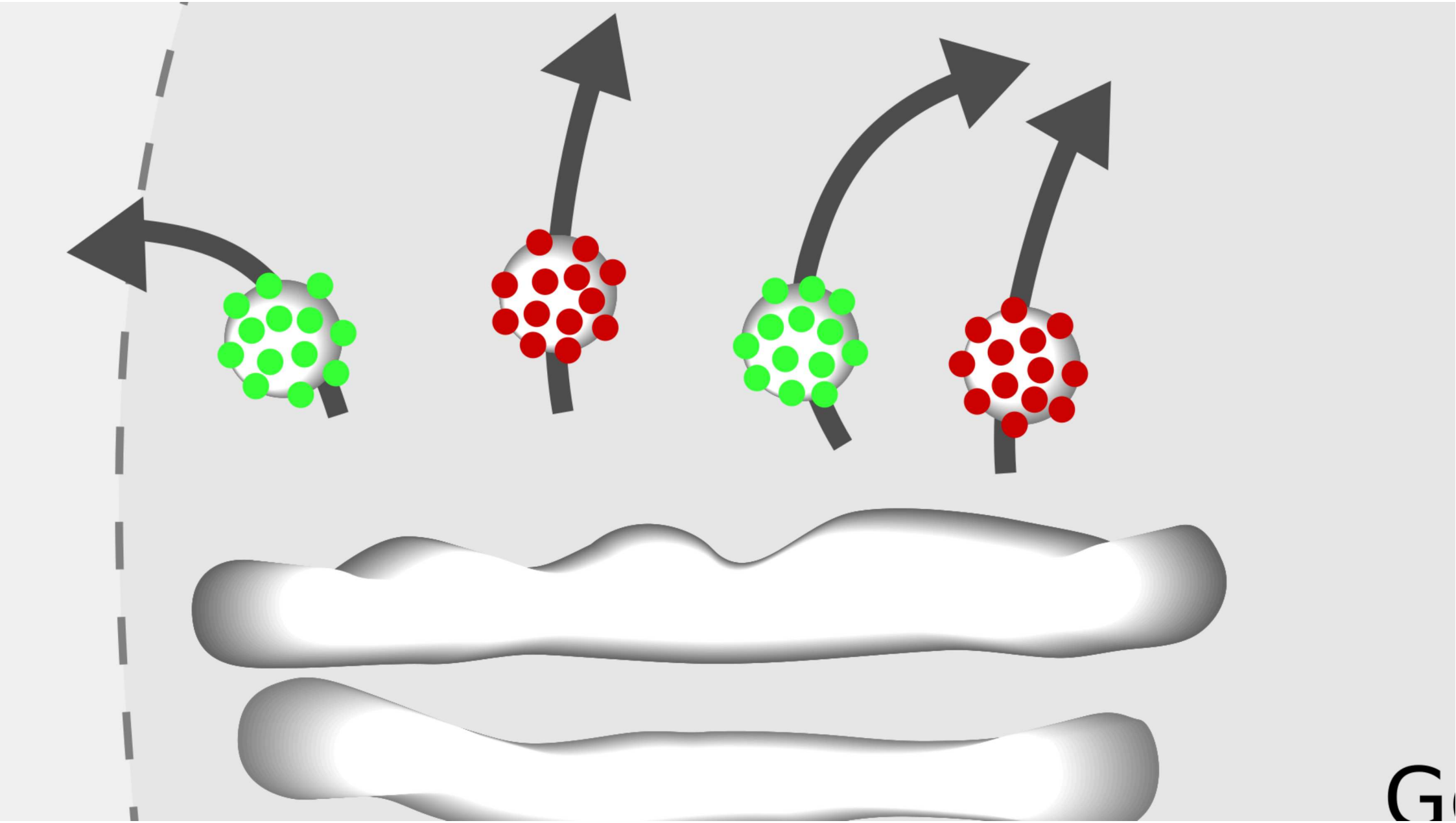


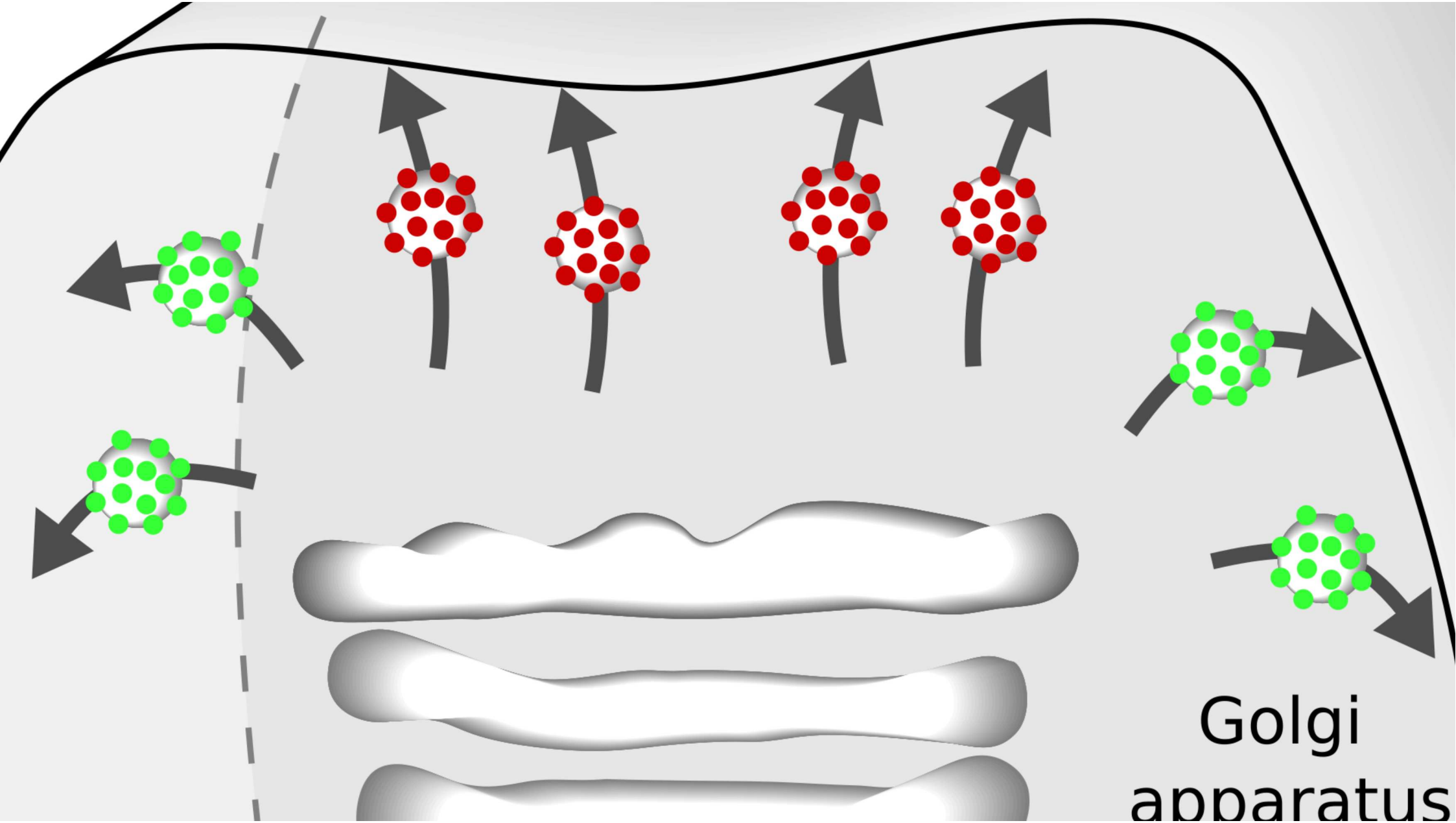


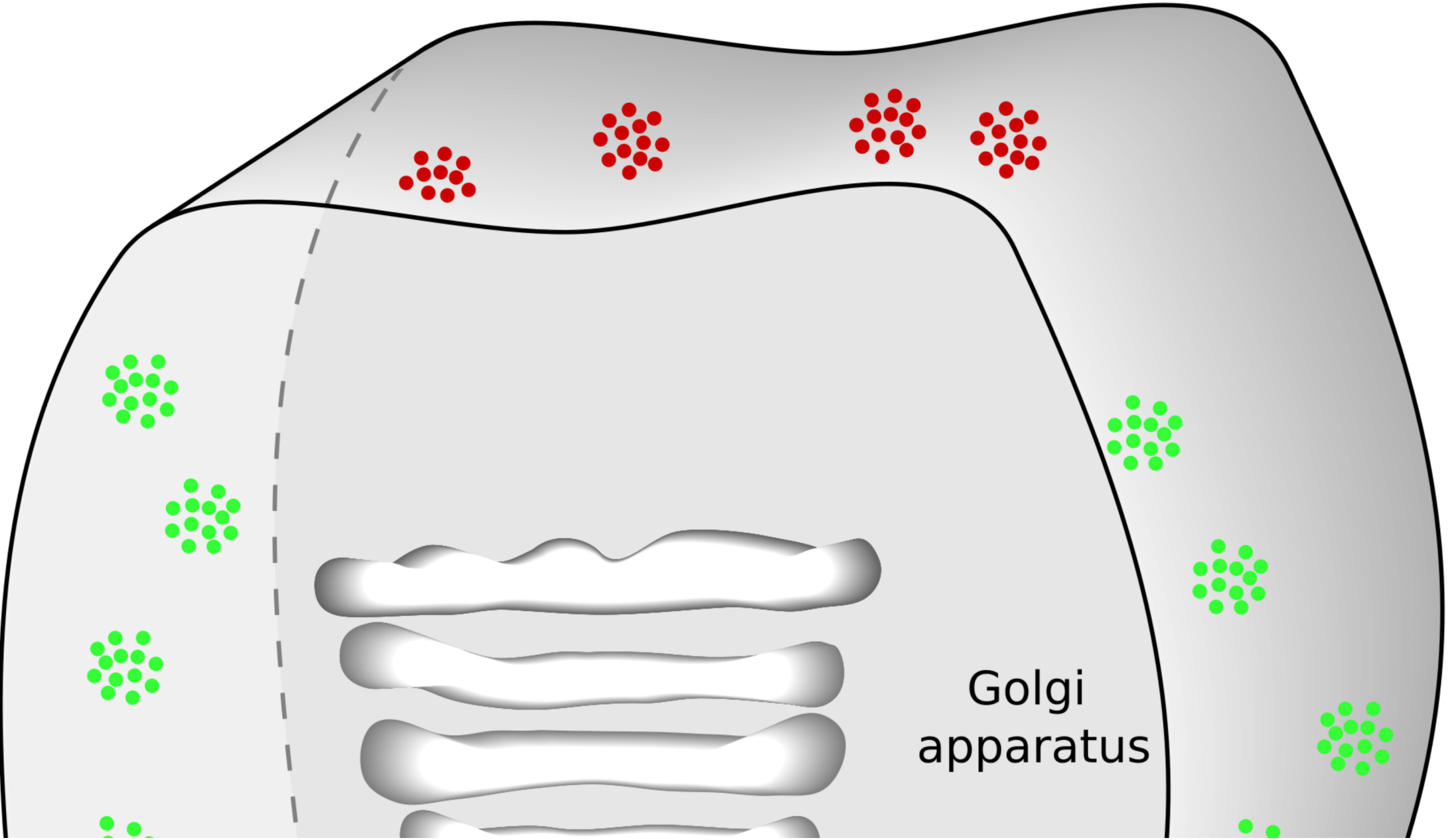


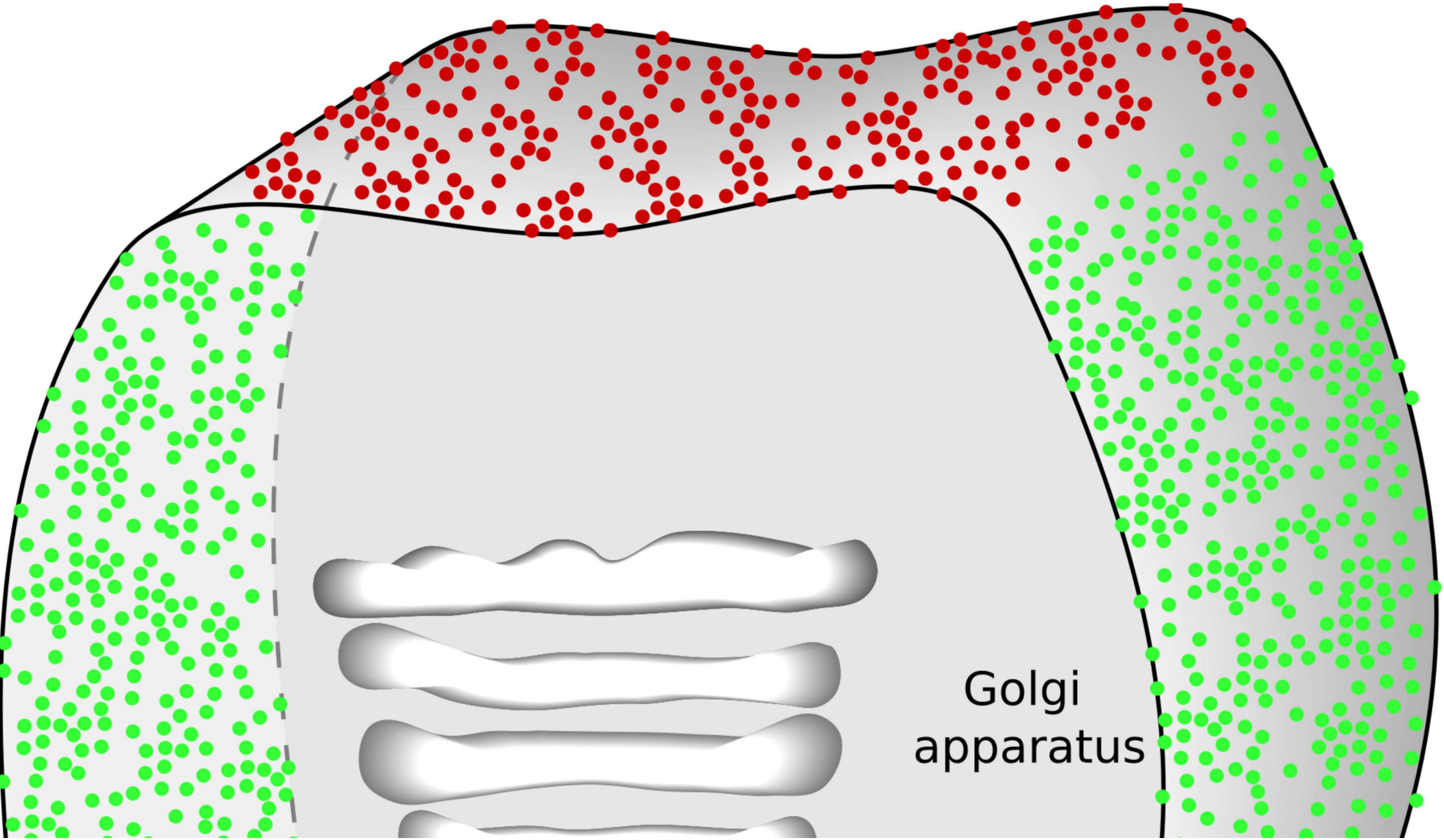




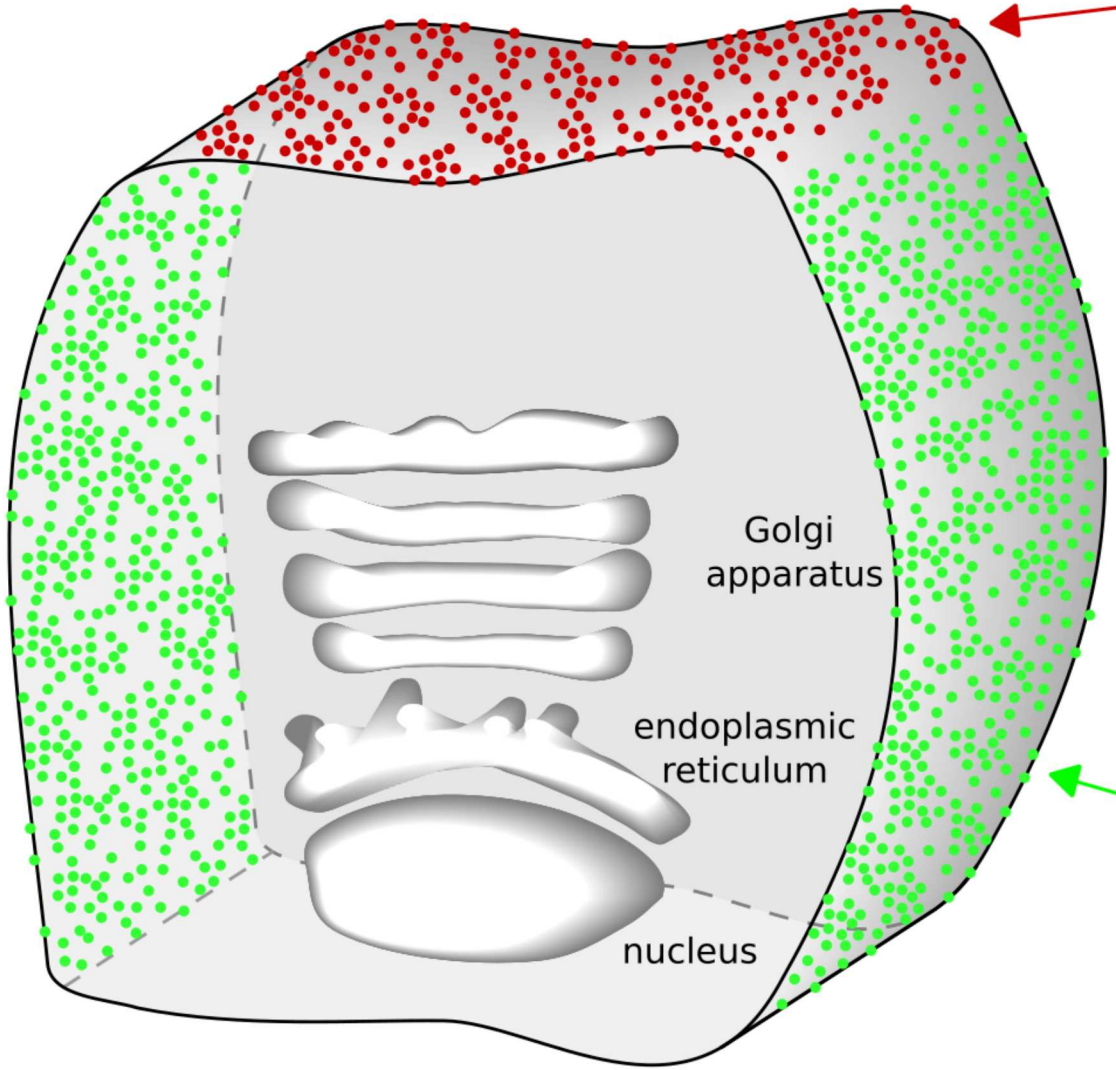



Golgi
apparatus

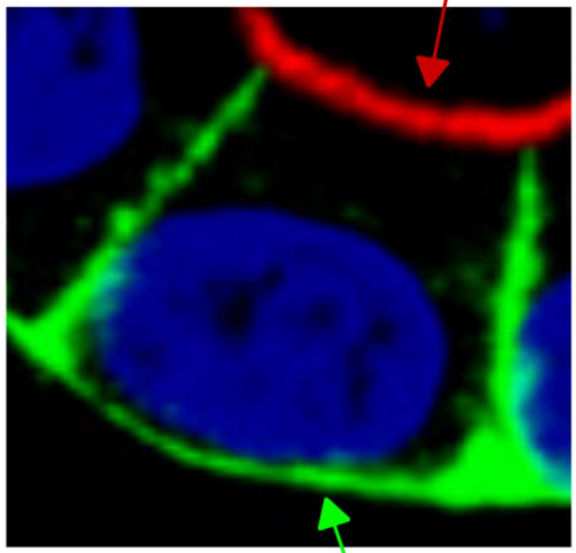

Golgi
apparatus


Golgi
apparatus

Molecular sorting

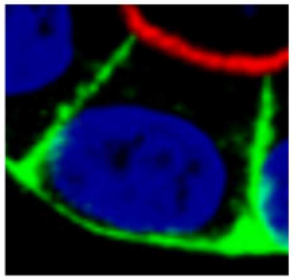


apical

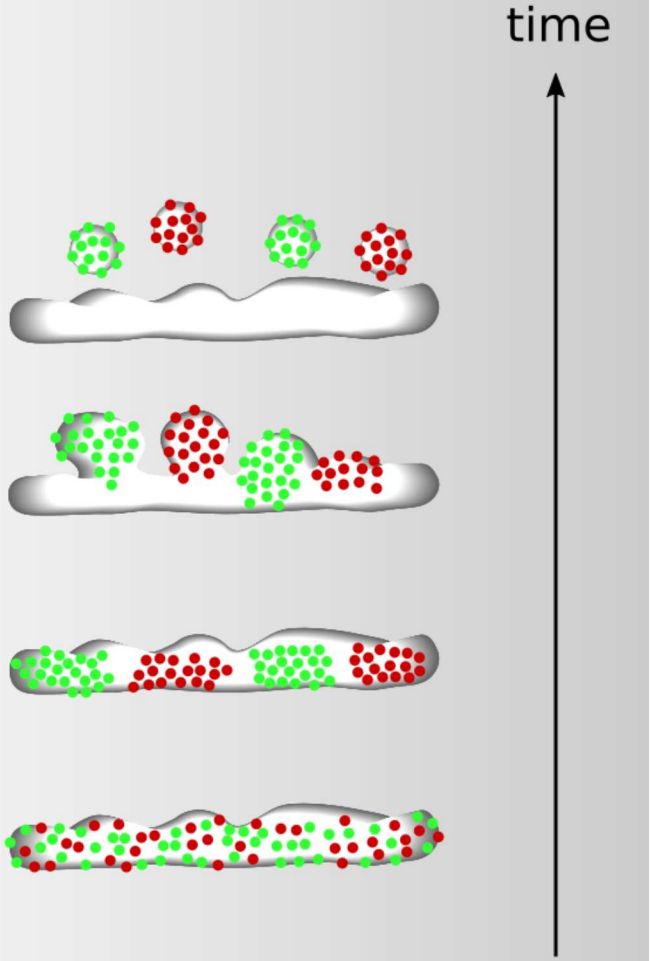


lateral

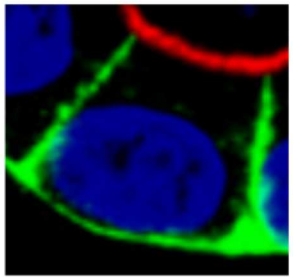
Molecular sorting



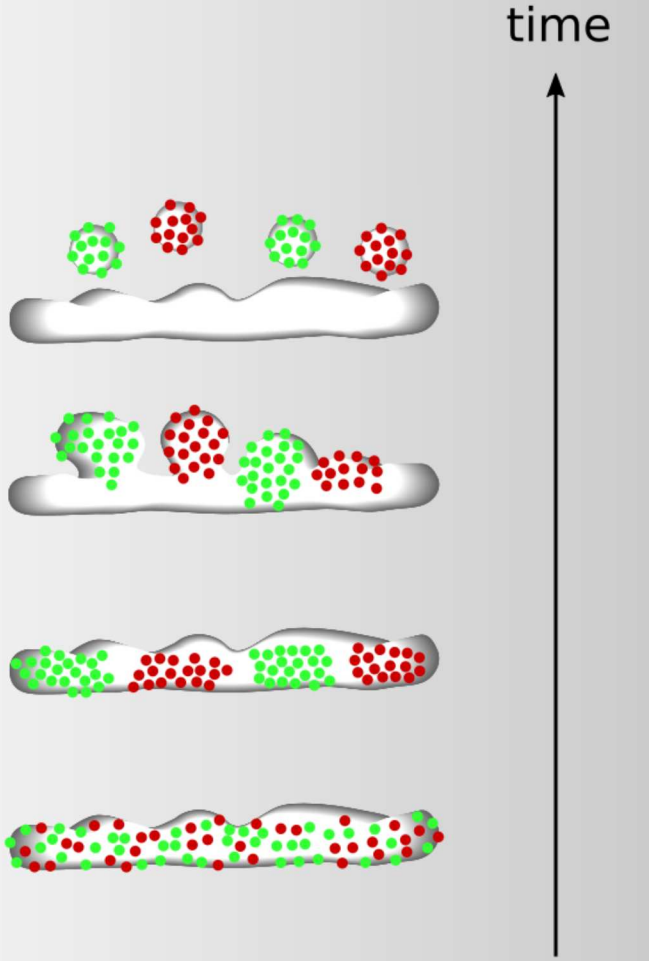
- ubiquitous!
- main ordering process
- continuous demixing
- specific molecules are distilled and packed in small lipid vesicles
- complicated microscopic details: hundreds of different protein species involved



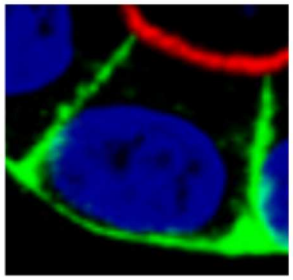
Molecular sorting



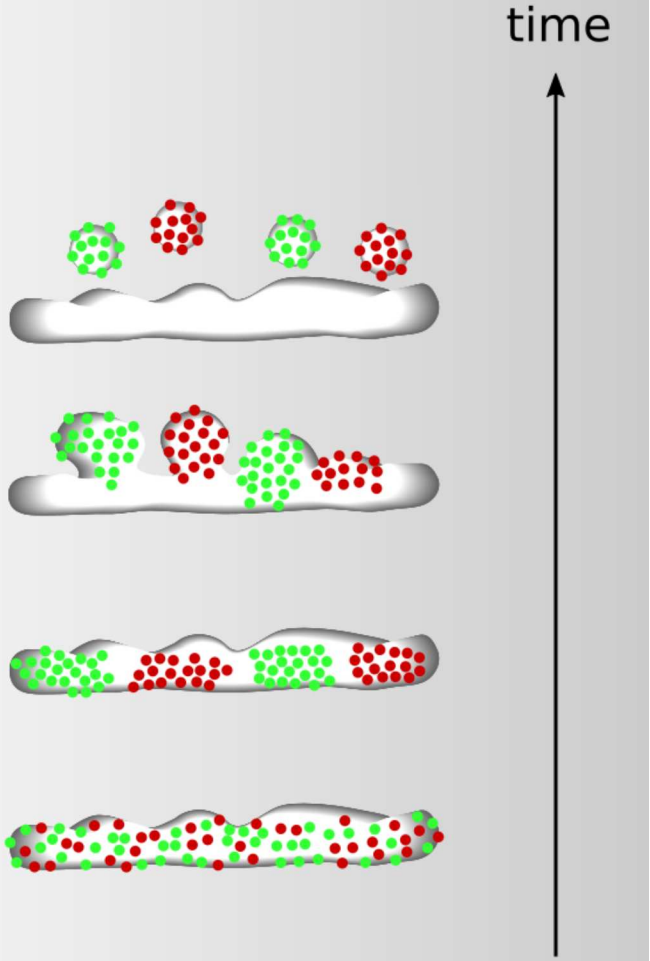
- ubiquitous!
- main ordering process
- continuous demixing
- specific molecules are distilled and packed in small lipid vesicles
- complicated microscopic details: hundreds of different protein species involved
- phenomenological theory?



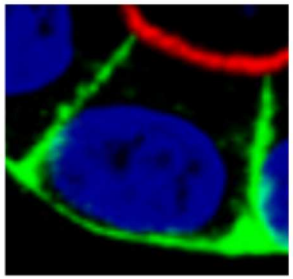
Molecular sorting



- ubiquitous!
- main ordering process
- continuous demixing
- specific molecules are distilled and packed in small lipid vesicles
- complicated microscopic details: hundreds of different protein species involved
- phenomenological theory?
- general features:

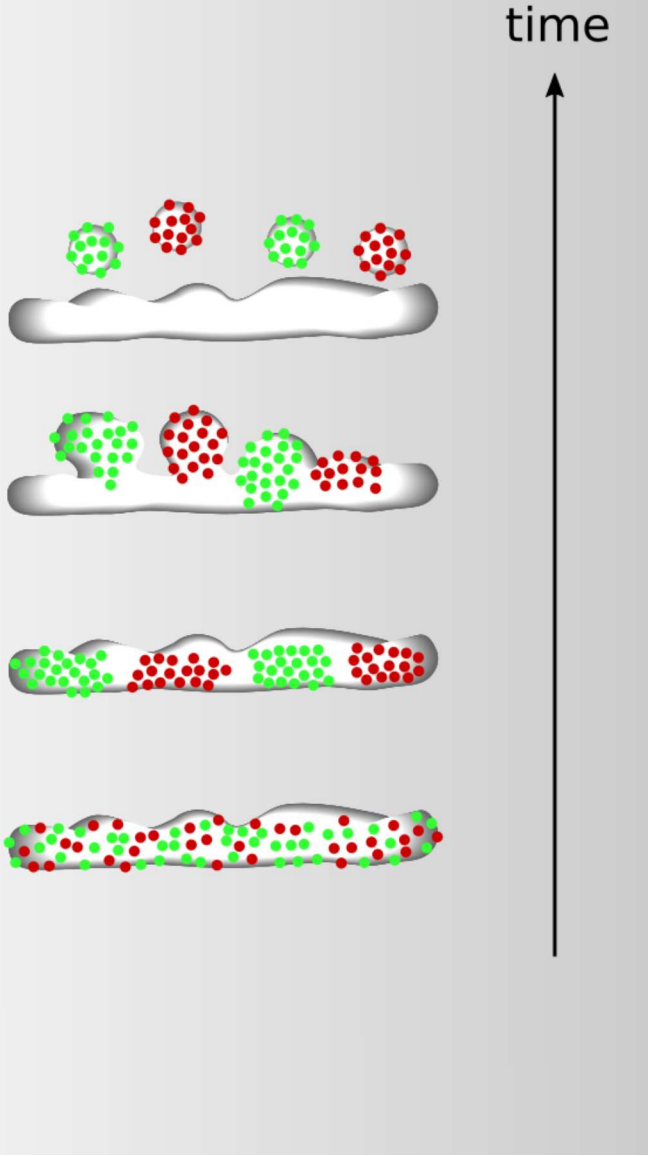


Molecular sorting

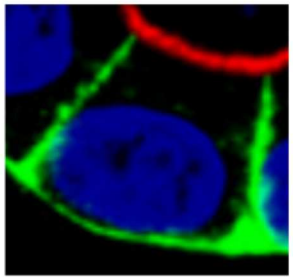


- ubiquitous!
- main ordering process
- continuous demixing
- specific molecules are distilled and packed in small lipid vesicles
- complicated microscopic details: hundreds of different protein species involved
- phenomenological theory?
- general features:

  → demixing



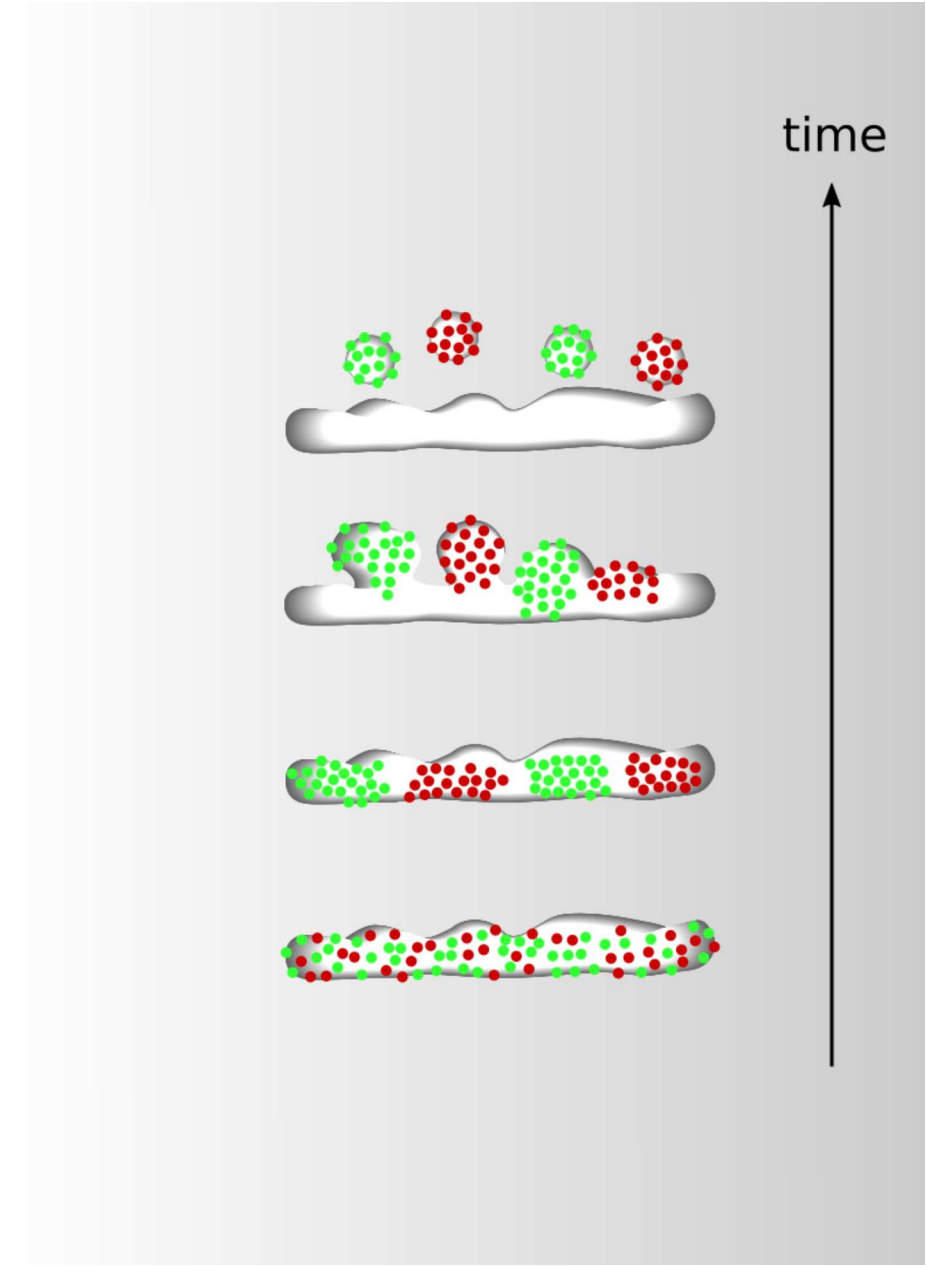
Molecular sorting



- ubiquitous!
- main ordering process
- continuous demixing
- specific molecules are distilled and packed in small lipid vesicles
- complicated microscopic details: hundreds of different protein species involved
- phenomenological theory?
- general features:

  → demixing

  → extraction



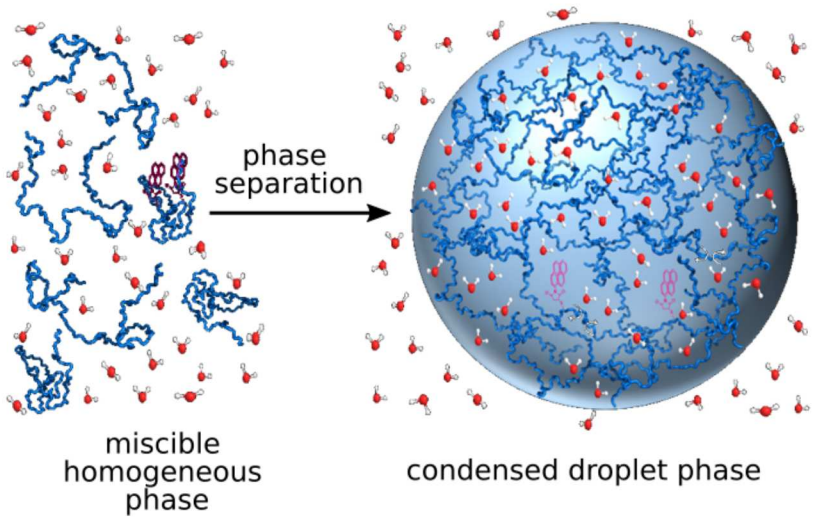
Biological phase separation

→ demixing

→ extraction

Biological phase separation

direct interactions



A Majumdar et al, J Phys Chem Lett (2019)

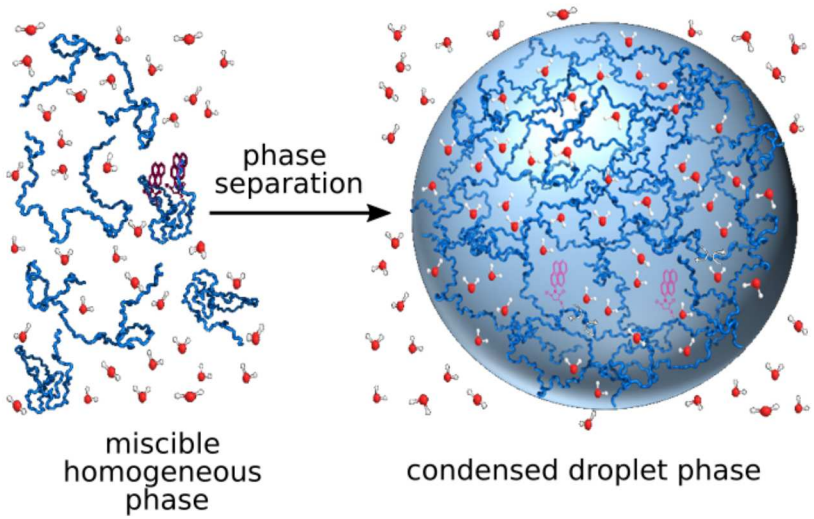
→ demixing

→ extraction

Biological phase separation

direct interactions

indirect interactions



A Majumdar et al, J Phys Chem Lett (2019)

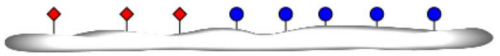
→ demixing

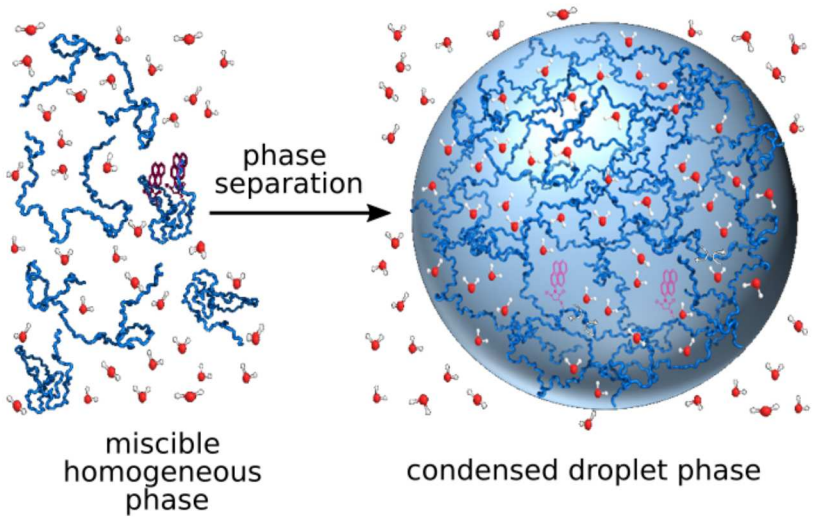
→ extraction

Biological phase separation

direct interactions

indirect interactions





A Majumdar et al, J Phys Chem Lett (2019)

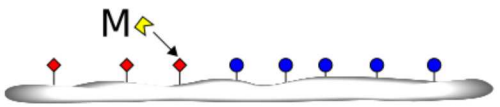
→ demixing

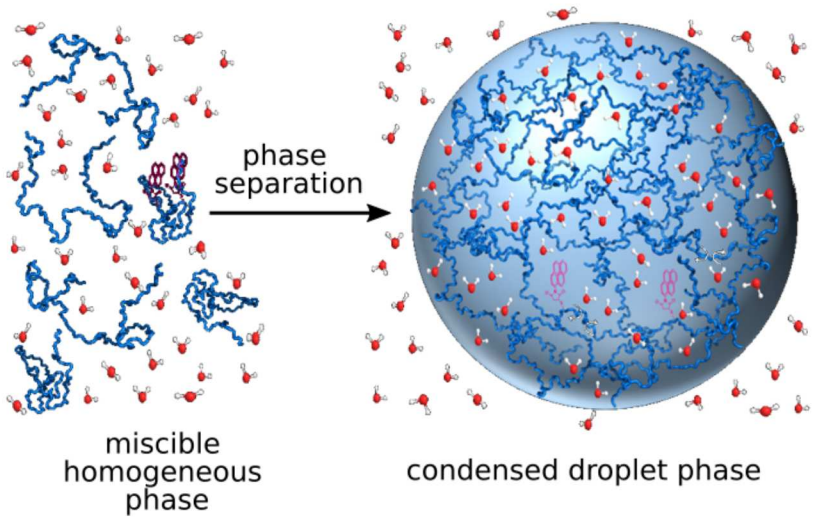
→ extraction

Biological phase separation

direct interactions

indirect interactions





A Majumdar et al, J Phys Chem Lett (2019)

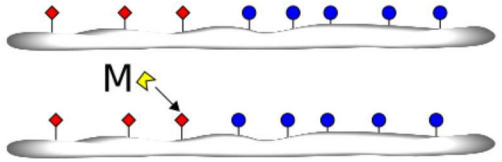
→ demixing

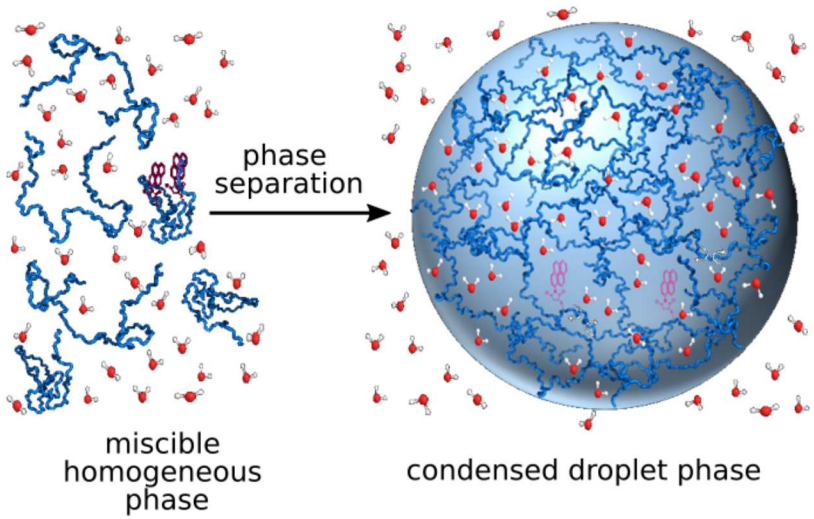
→ extraction

Biological phase separation

direct interactions

indirect interactions





A Majumdar et al, J Phys Chem Lett (2019)

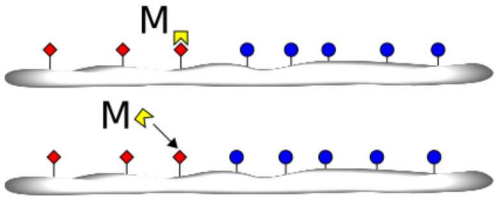
→ demixing

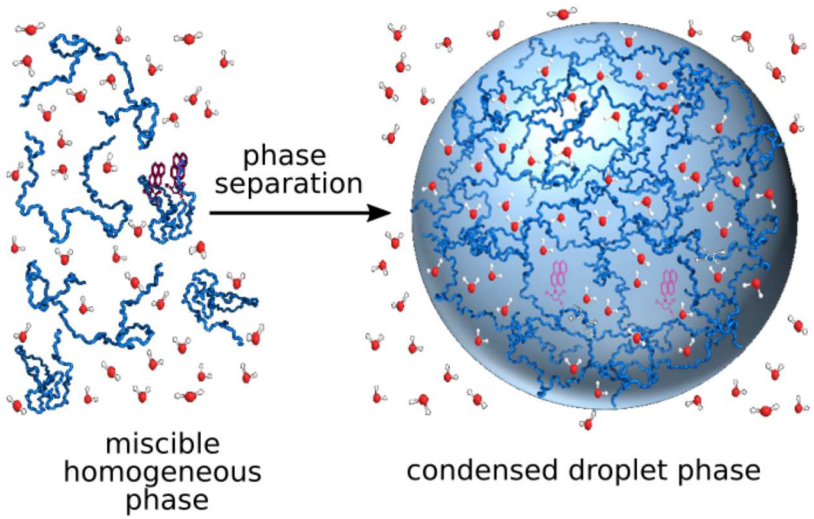
→ extraction

Biological phase separation

direct interactions

indirect interactions





A Majumdar et al, J Phys Chem Lett (2019)

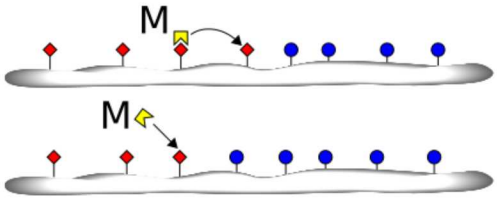
→ demixing

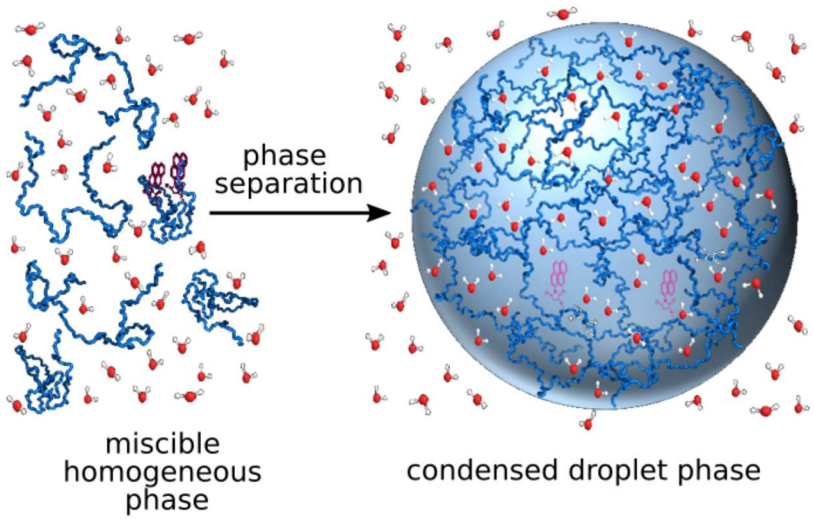
→ extraction

Biological phase separation

direct interactions

indirect interactions





A Majumdar et al, J Phys Chem Lett (2019)

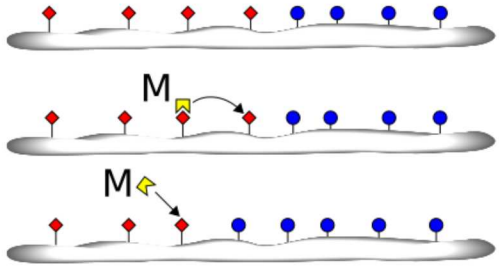
→ demixing

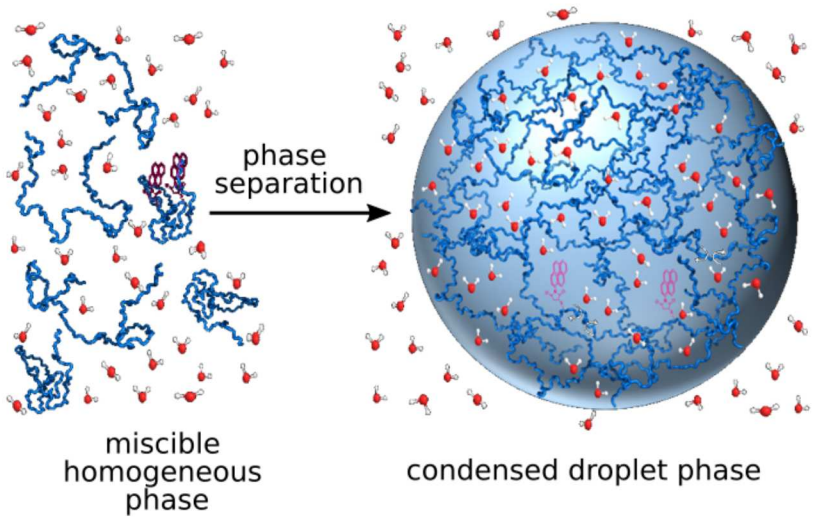
→ extraction

Biological phase separation

direct interactions

indirect interactions





A Majumdar et al, J Phys Chem Lett (2019)

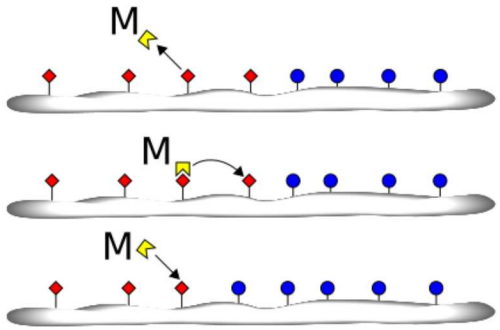
→ demixing

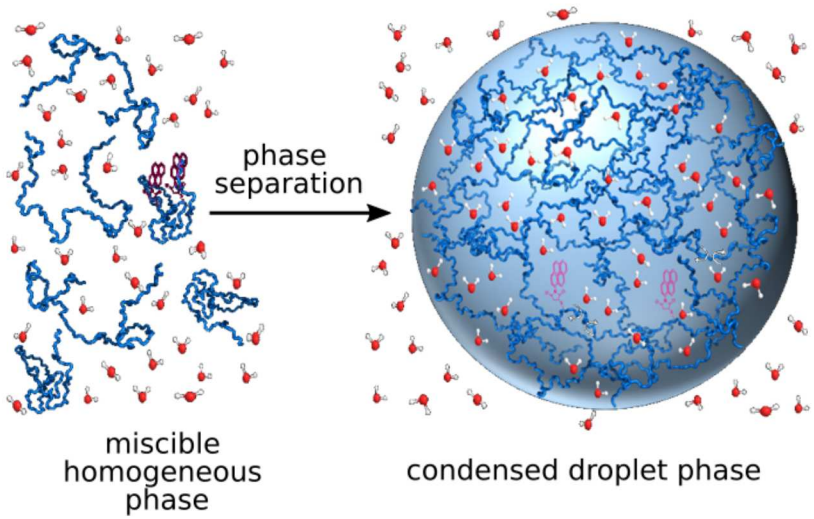
→ extraction

Biological phase separation

direct interactions

indirect interactions





A Majumdar et al, J Phys Chem Lett (2019)

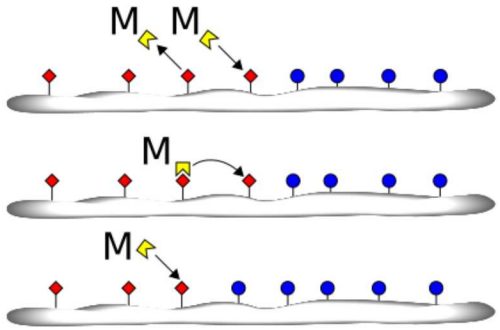
→ demixing

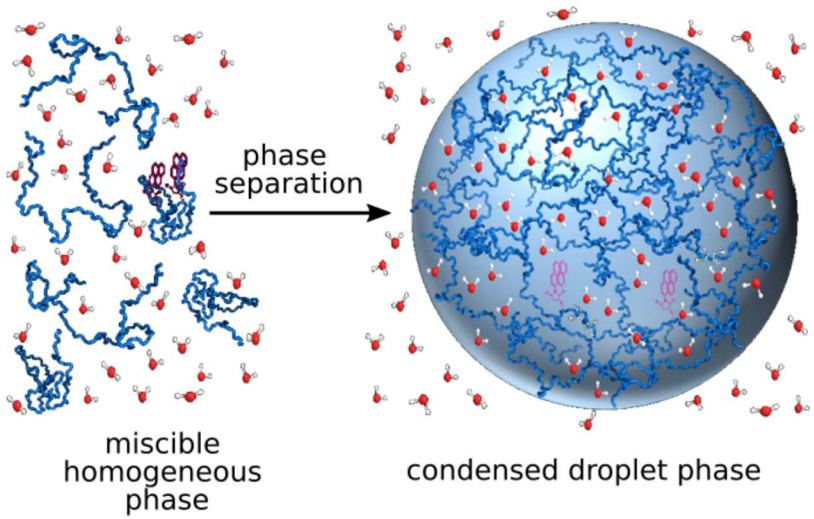
→ extraction

Biological phase separation

direct interactions

indirect interactions





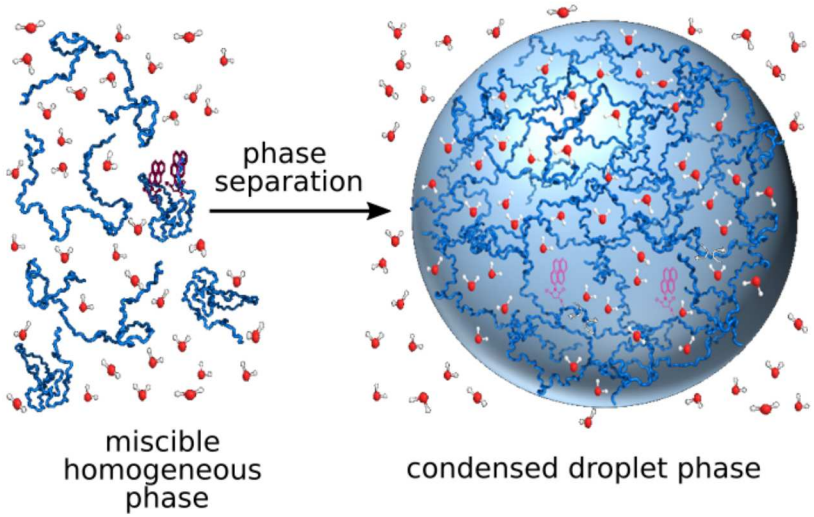
A Majumdar et al, J Phys Chem Lett (2019)

→ demixing

→ extraction

Biological phase separation

direct interactions

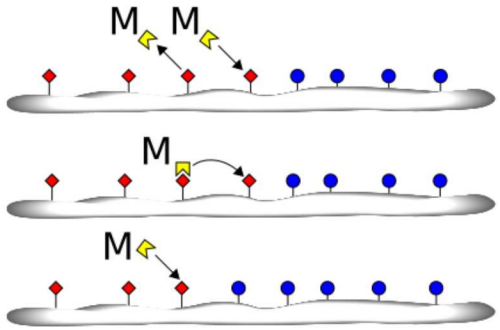


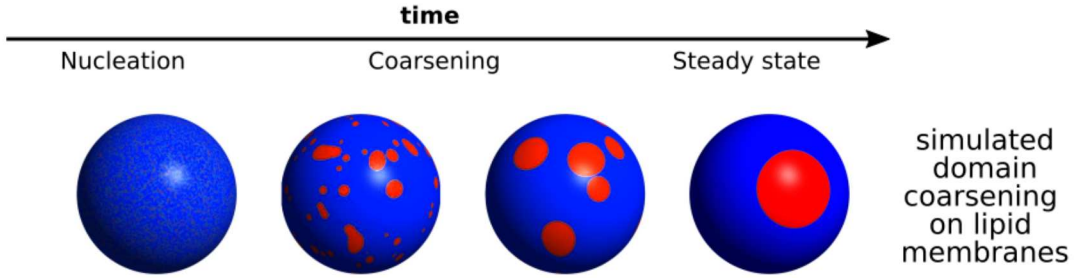
A Majumdar et al, J Phys Chem Lett (2019)

→ demixing

→ extraction

indirect interactions



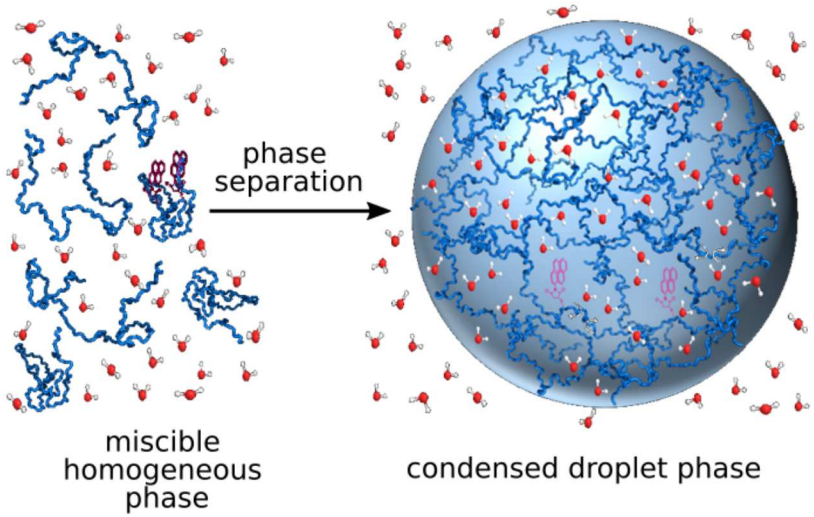


AG, A de Candia, S Di Talia, A Coniglio, F Bussolino, G Serini, PNAS (2005)

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

Biological phase separation

direct interactions

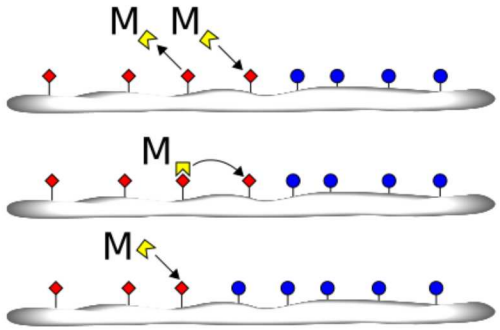


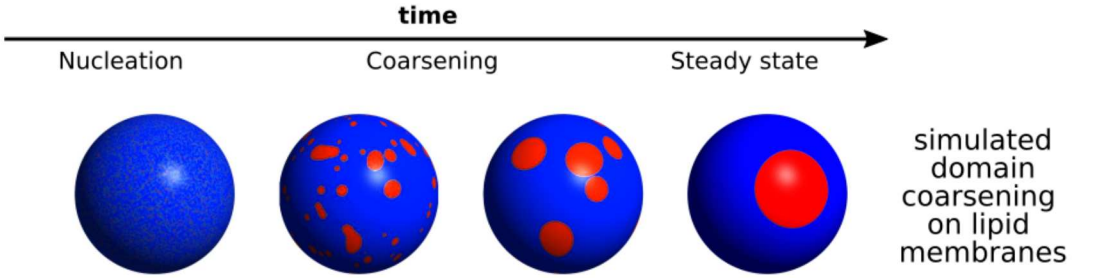
A Majumdar et al, J Phys Chem Lett (2019)

→ demixing

→ extraction

indirect interactions

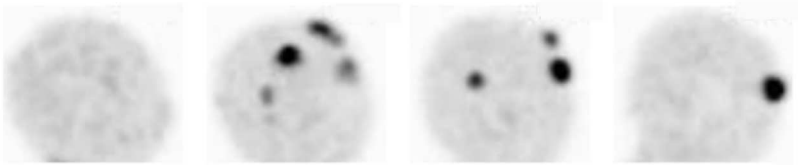




simulated domain coarsening on lipid membranes

AG, A de Candia, S Di Talia, A Coniglio, F Bussolino, G Serini, PNAS (2005)

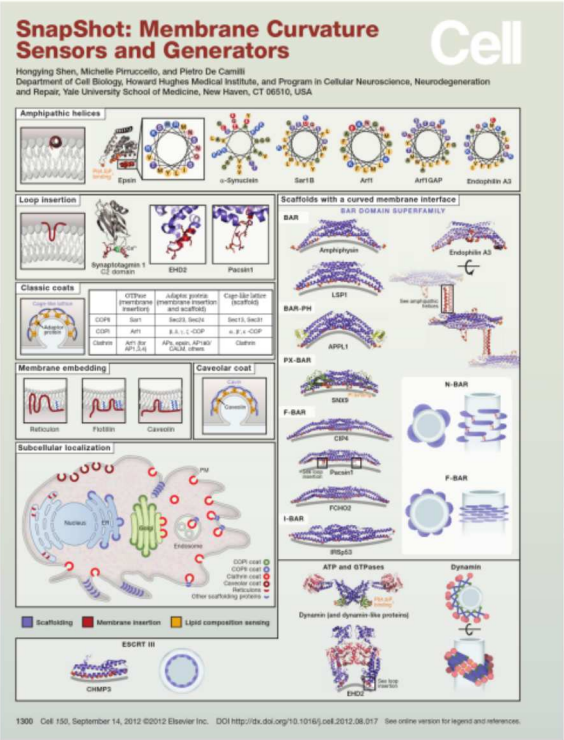
AG, I Kolokolov, V Lebedev, G Ortenzi, PRL (2007)

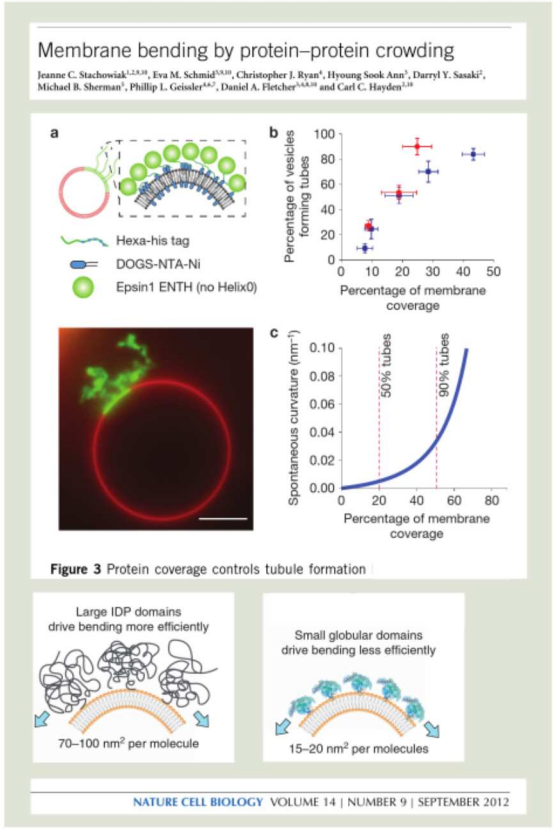


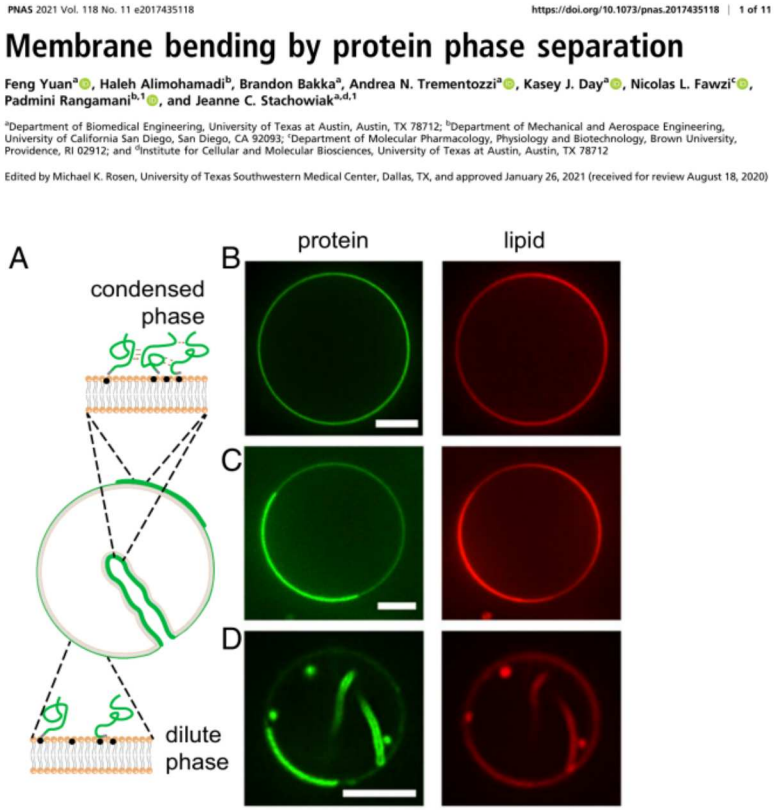
coarsening of polarity domains in yeast cells

A Howell, M Jin, CF Wu, TR Zyla, TC Elston, D Lew, Cell (2012)

Membrane bending



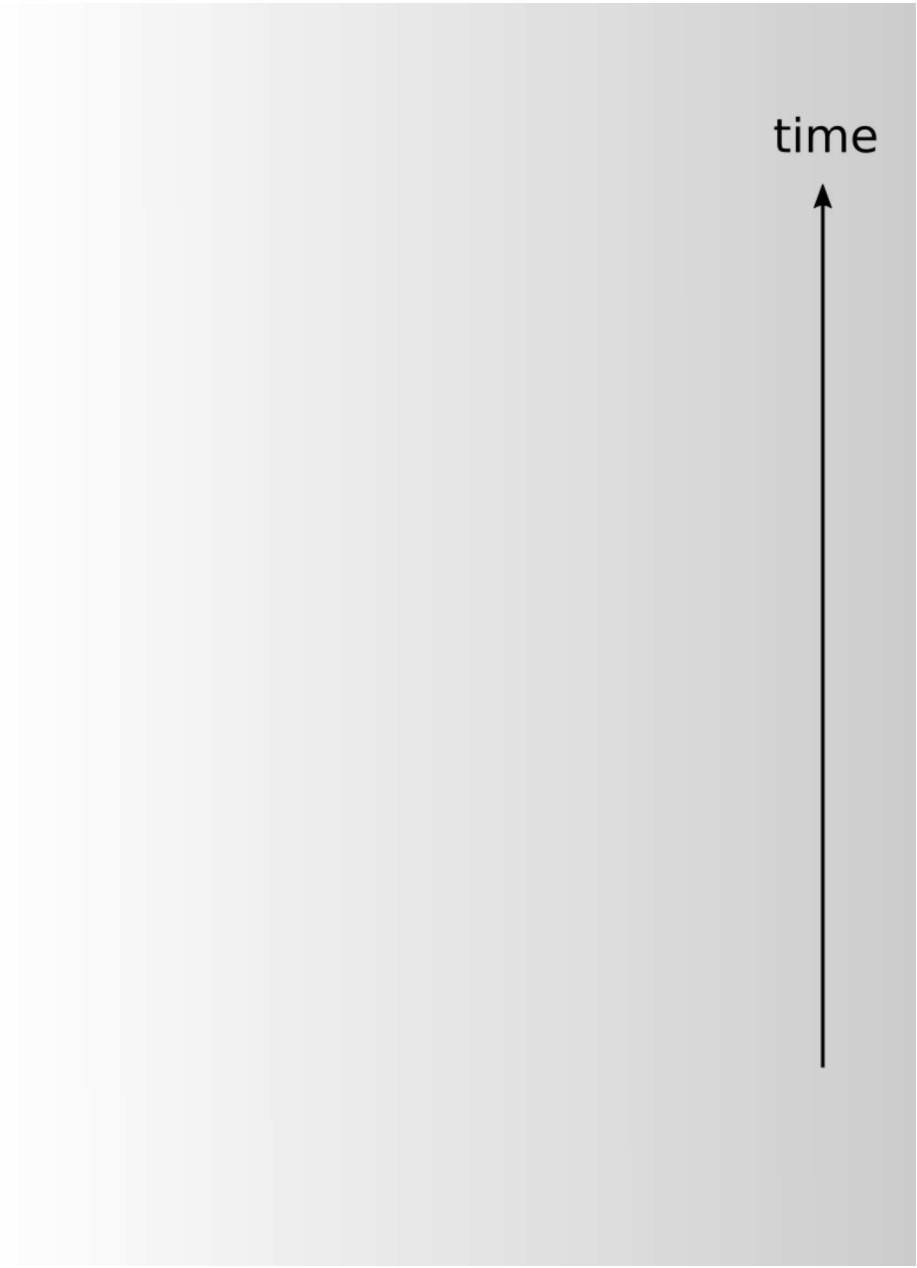




→ demixing

→ extraction

Minimal model of molecular sorting

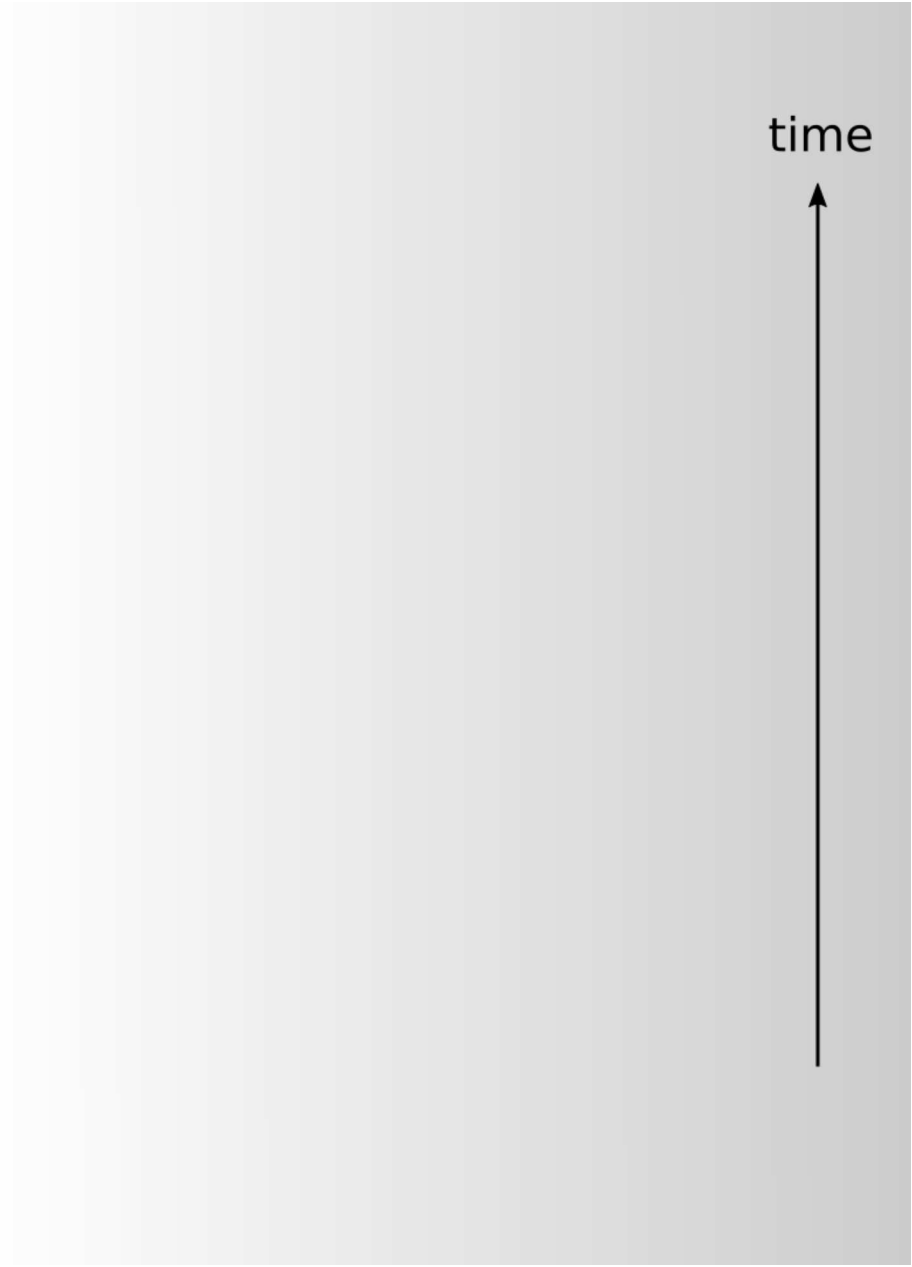


→ demixing

→ extraction

Minimal model of molecular sorting

phase separation on lipid membranes



→ demixing

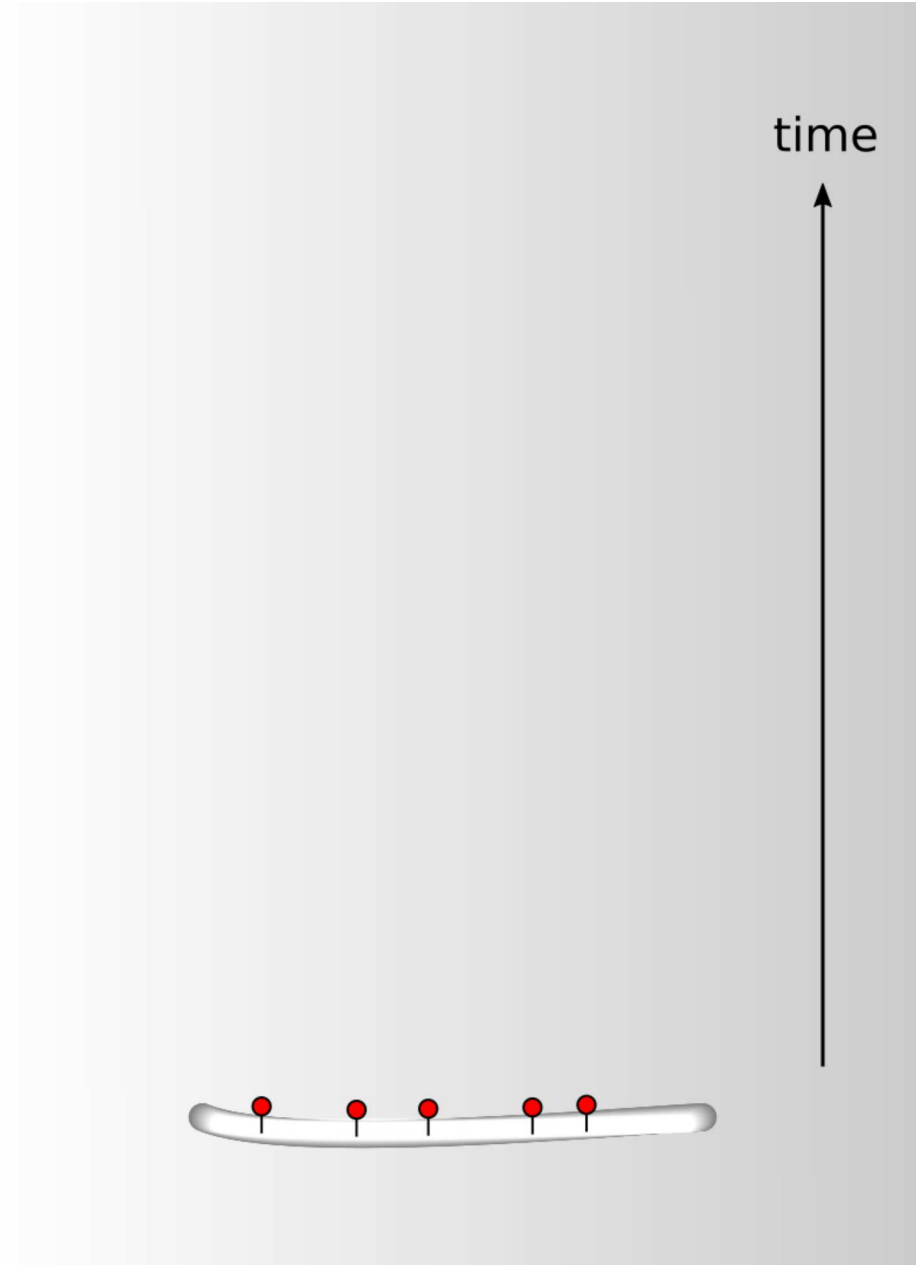
→ extraction

Minimal model of molecular sorting

phase separation on lipid membranes

→ demixing

→ extraction

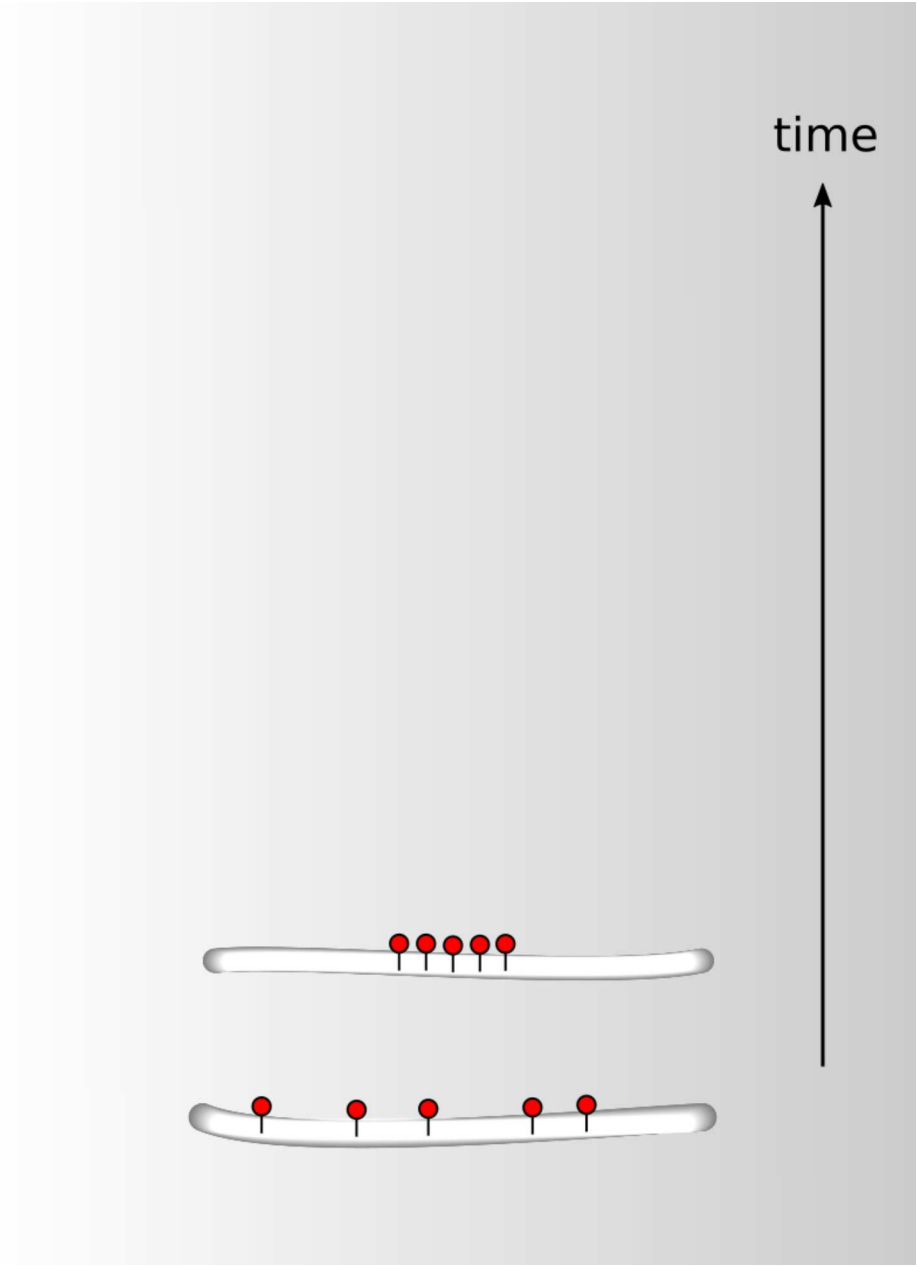


Minimal model of molecular sorting

phase separation on lipid membranes

→ demixing

→ extraction

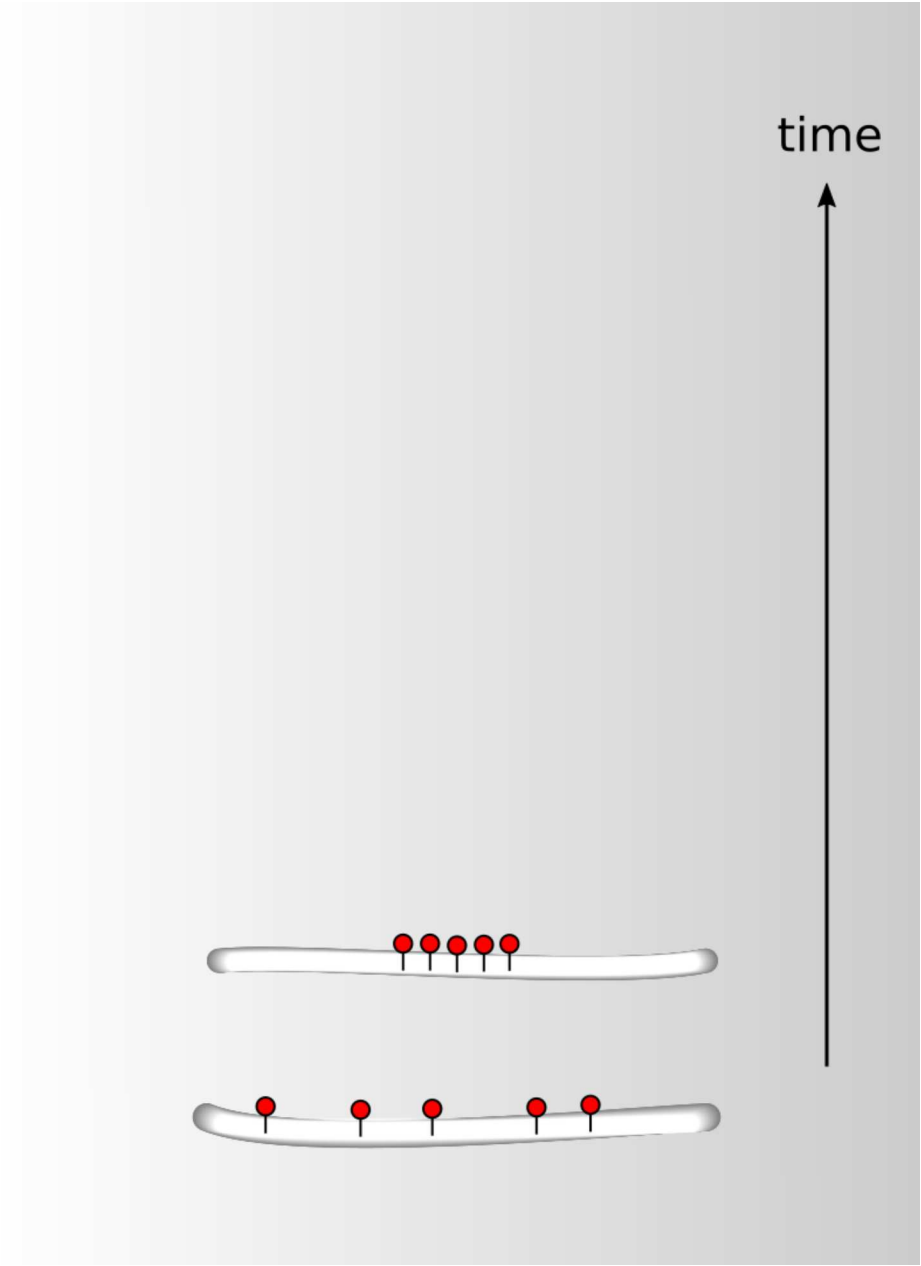


Minimal model of molecular sorting

phase separation on lipid membranes

→ demixing

→ extraction

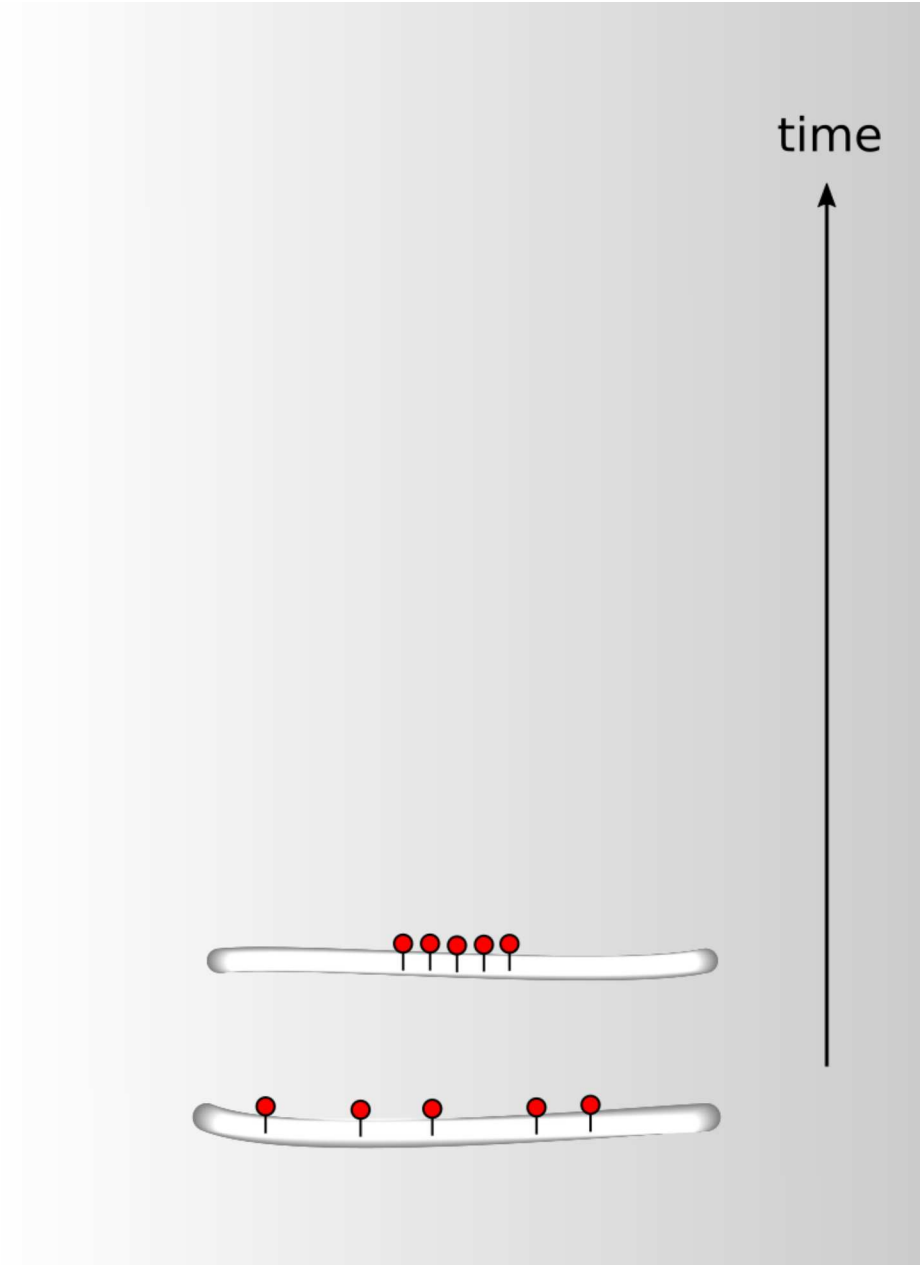


Minimal model of molecular sorting

phase separation on lipid membranes +

→ demixing

→ extraction

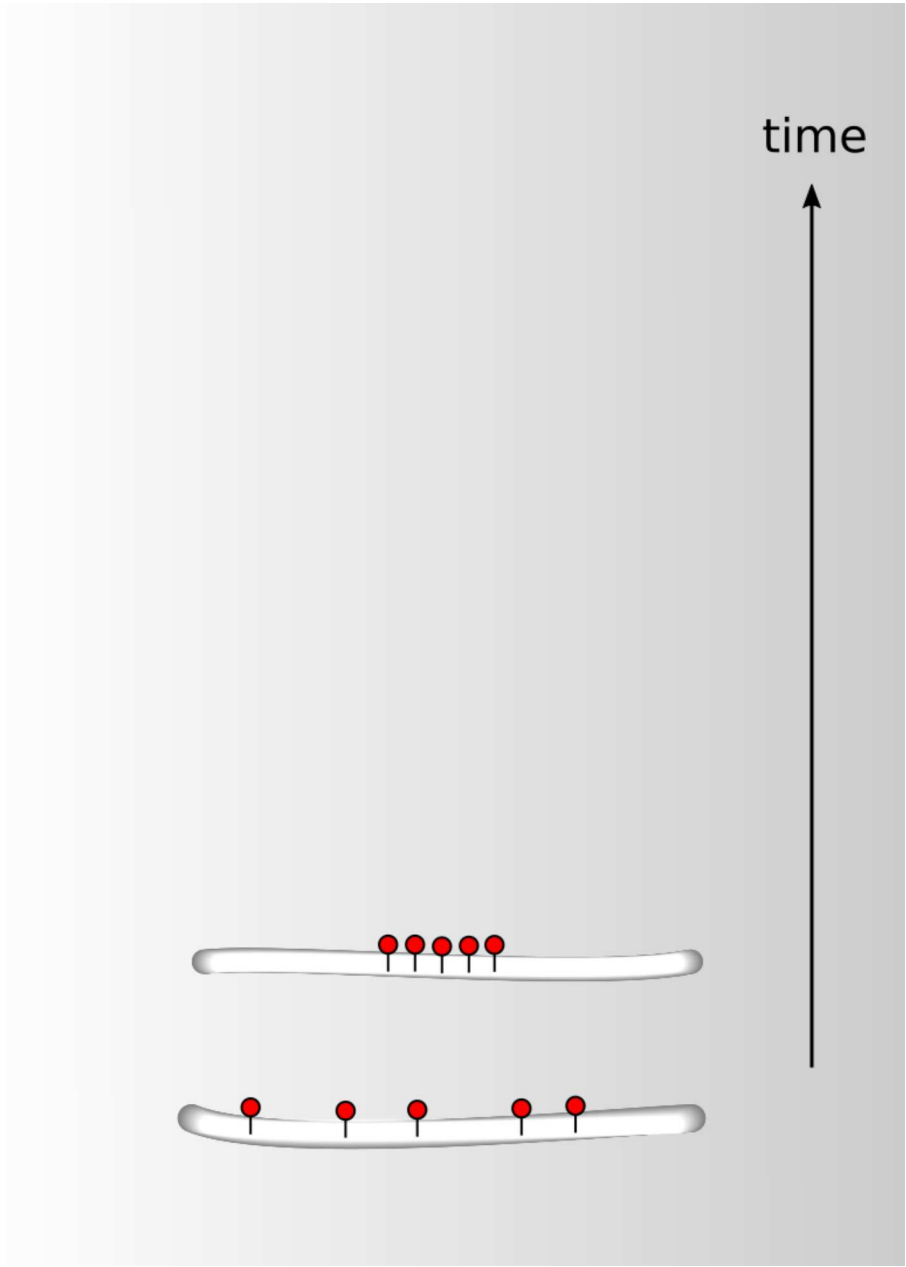


Minimal model of molecular sorting

phase separation on lipid membranes + **domain-induced membrane bending**

→ demixing

→ extraction

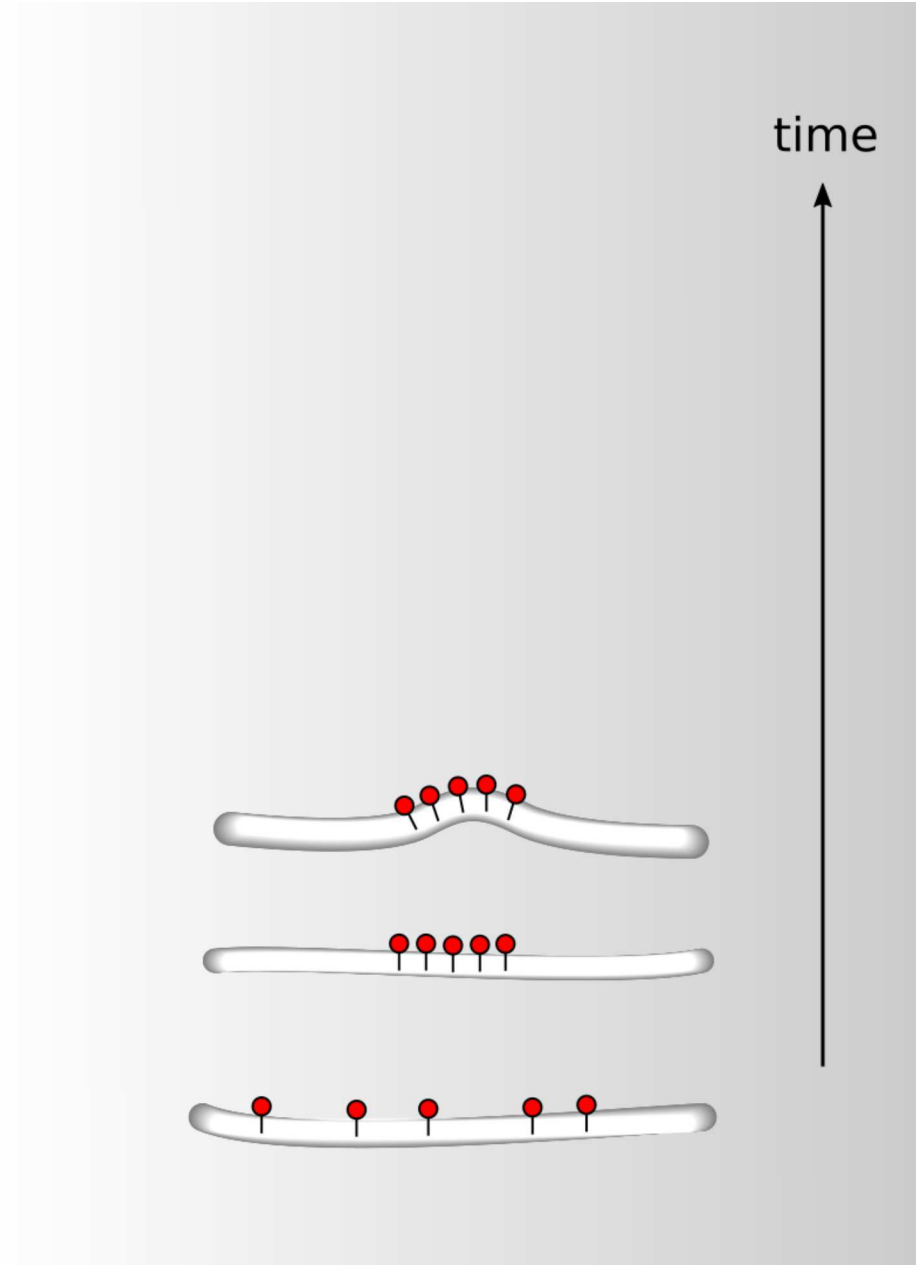


Minimal model of molecular sorting

phase separation on lipid membranes + **domain-induced membrane bending**

→ demixing

→ extraction

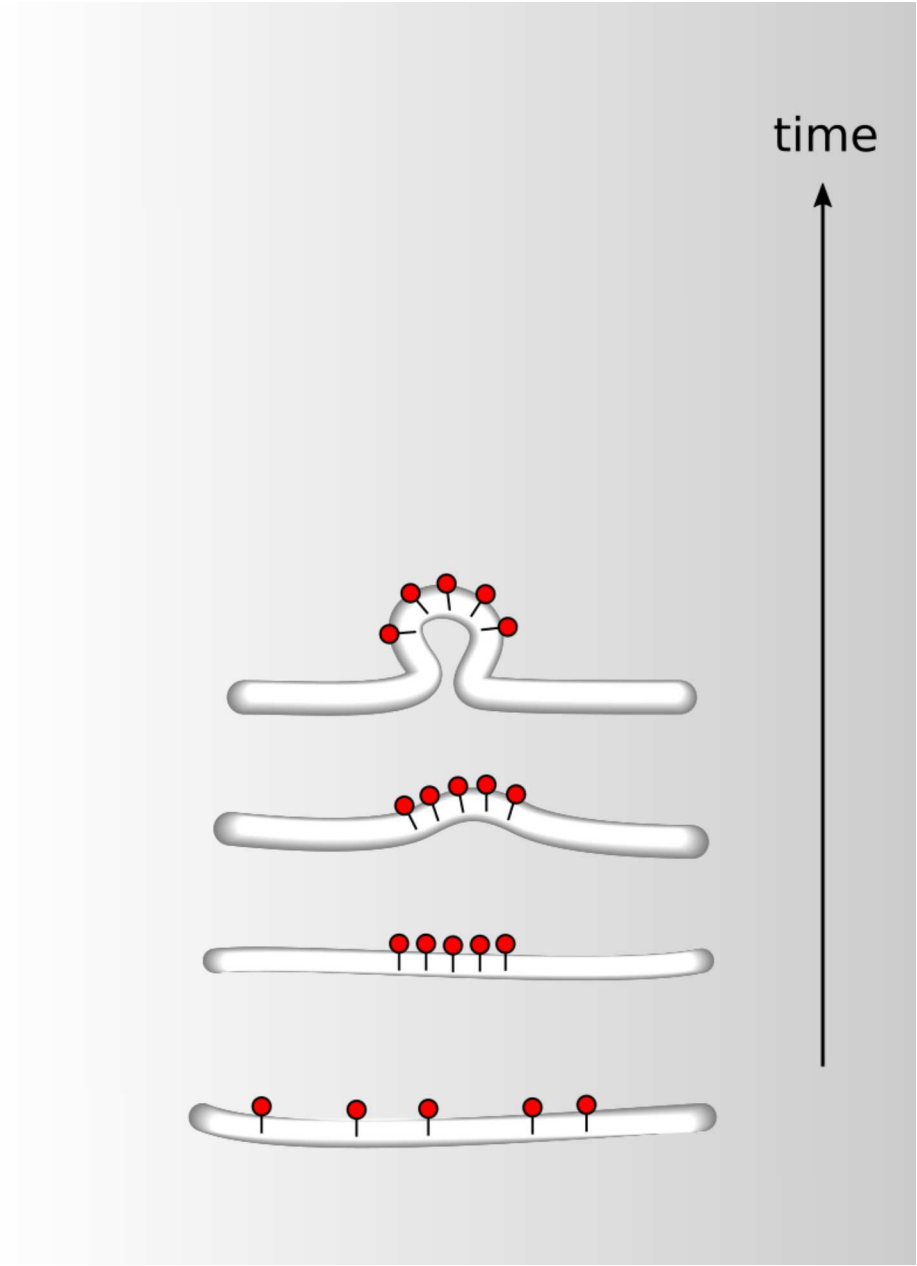


Minimal model of molecular sorting

phase separation on lipid membranes + **domain-induced membrane bending**

→ demixing

→ extraction

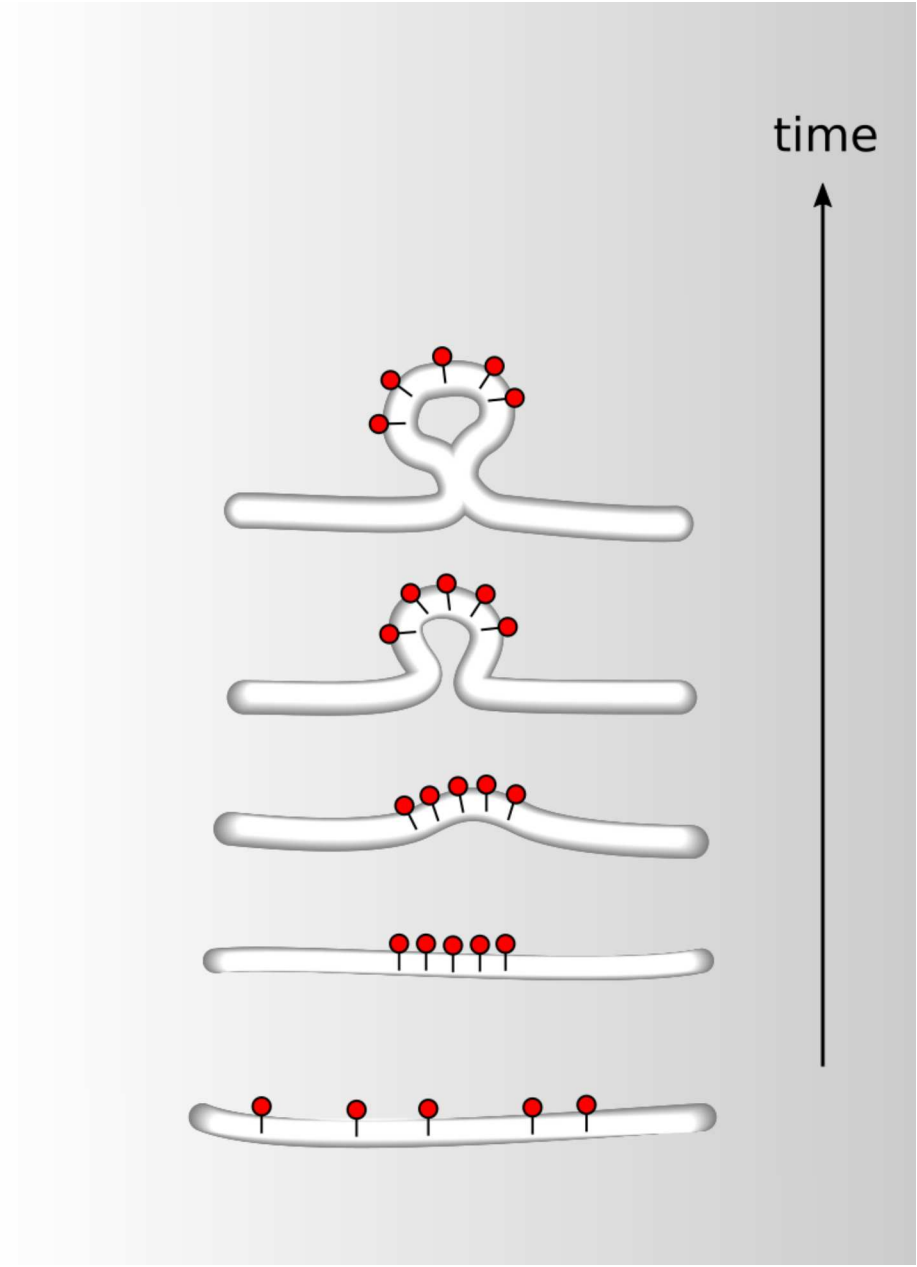


Minimal model of molecular sorting

phase separation on lipid membranes + **domain-induced membrane bending**

→ demixing

→ extraction



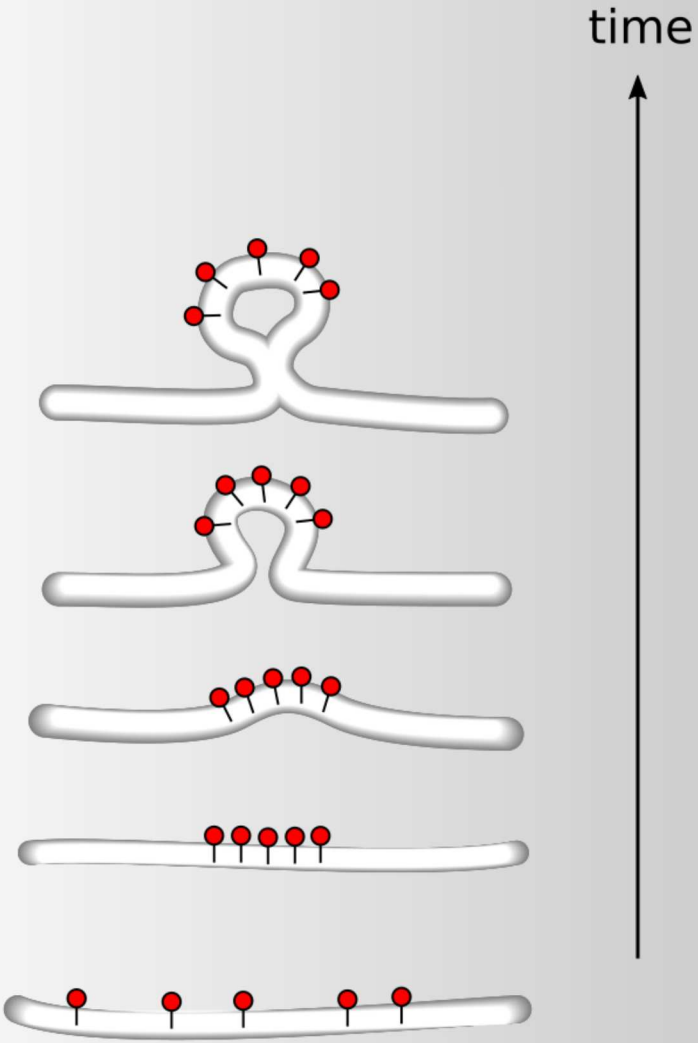
Minimal model of molecular sorting

phase separation on lipid membranes + **domain-induced membrane bending**

⇩

→ demixing

→ extraction



Minimal model of molecular sorting

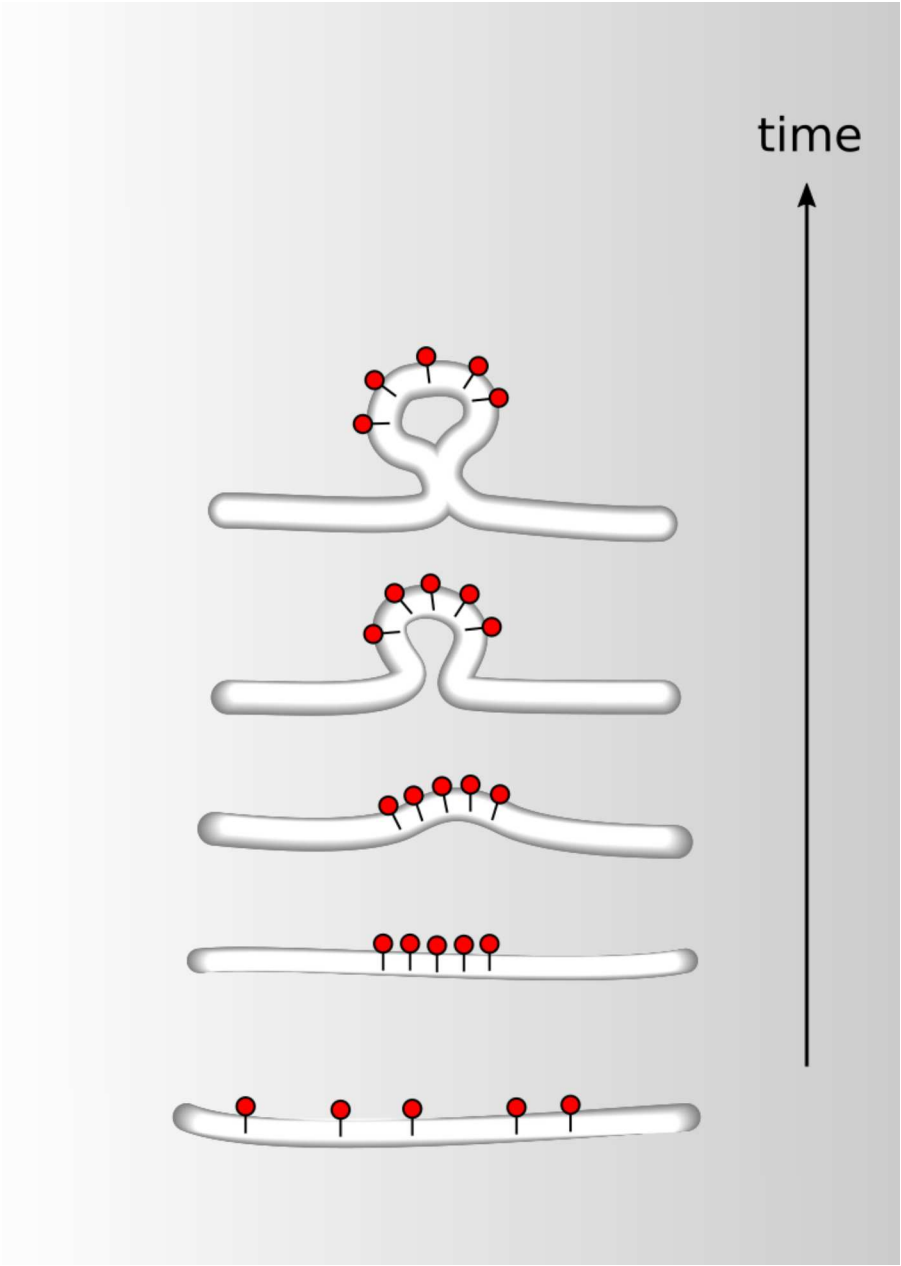
phase separation on lipid membranes + **domain-induced membrane bending**

⇩

spontaneous distillation of molecular factors

→ demixing

→ extraction



Minimal model of molecular sorting

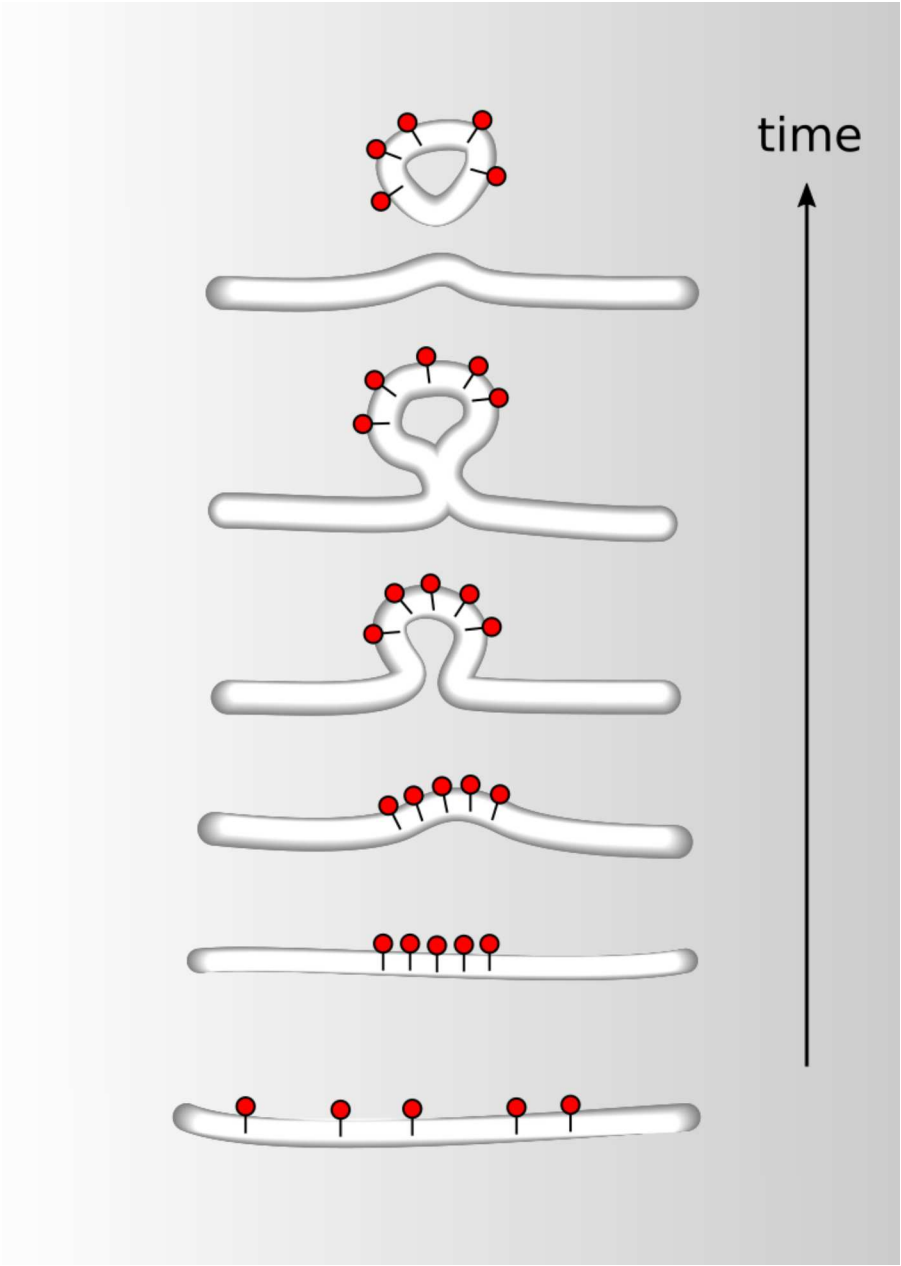
phase separation on lipid membranes + **domain-induced membrane bending**

⇩

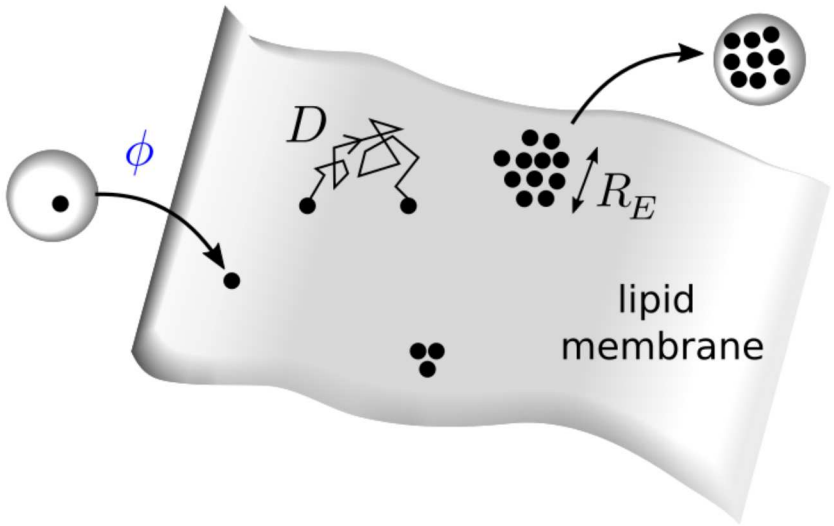
spontaneous distillation of molecular factors

→ demixing

→ extraction



Minimal model of molecular sorting



D : diffusivity

R_E : extraction size

Steady state

Observables:

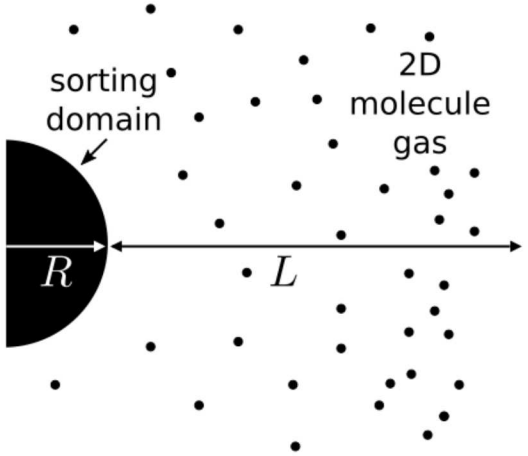
- ϕ : molecule flux
- ρ : molecule density
- T : residence time

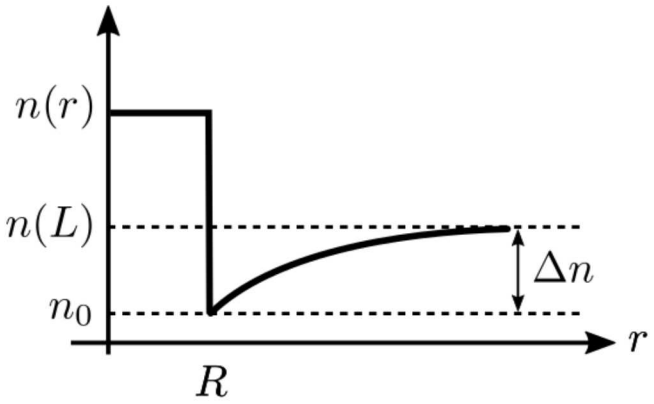
$$\rho = \phi\, T$$

Phenomenological theory

density profile of 2D gas:

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





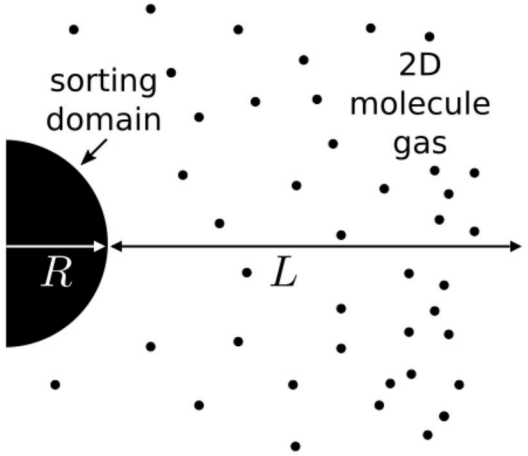
for absorbing domains:

$\Delta n \sim \bar{n}$

Phenomenological theory

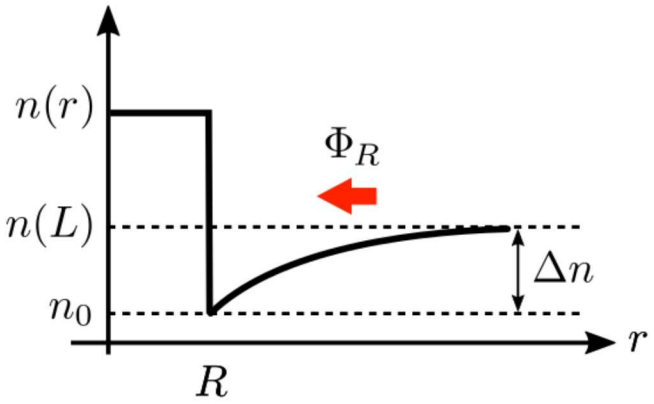
density profile of 2D gas:

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



flux towards a sorting domain:

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

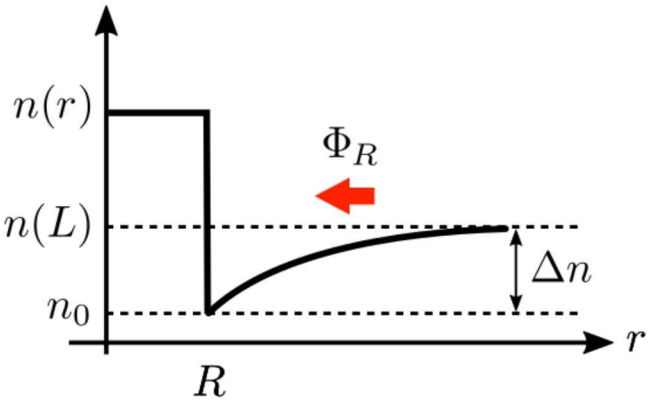


for absorbing domains:

$$\Delta n \sim \bar{n}$$

flux towards a sorting domain:

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

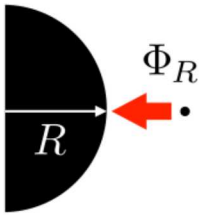


for absorbing domains:

$$\Delta n \sim \bar{n}$$

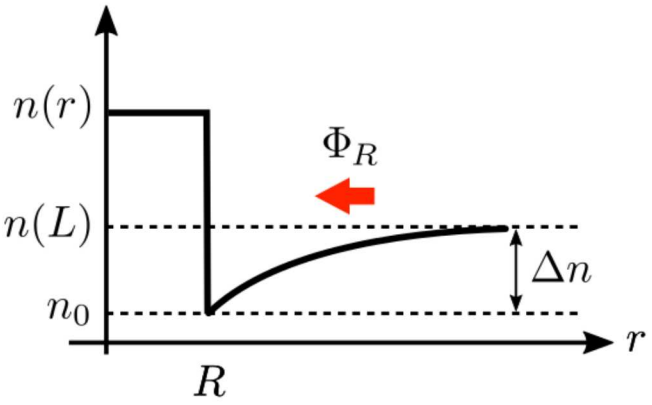
speed of accretion of a sorting domain:

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \frac{\Phi_R}{2\pi R} = \frac{D\Delta n}{R \ln L/R}$$



flux towards a sorting domain:

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

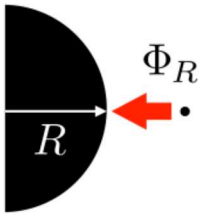


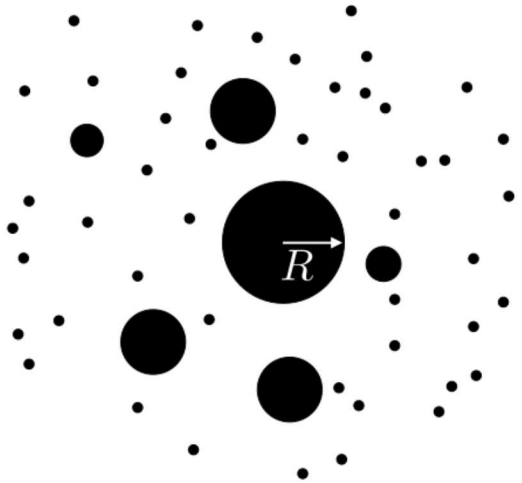
for absorbing domains:

$$\Delta n \sim \bar{n}$$

speed of accretion of a sorting domain:

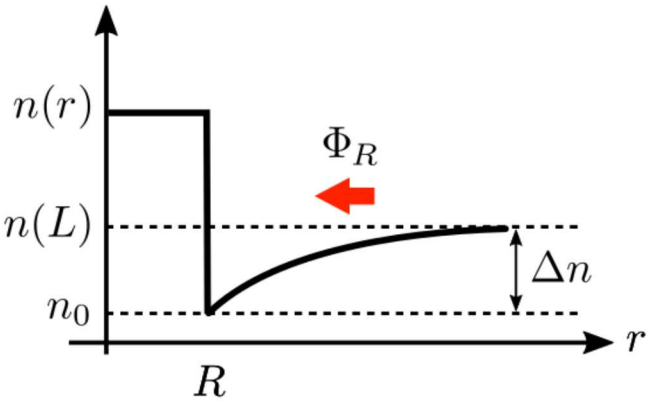
$$\frac{\mathrm{d}R}{\mathrm{d}t} = \frac{\Phi_R}{2\pi R} = \frac{D\Delta n}{R \ln L/R}$$





flux towards a sorting domain:

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

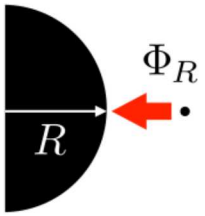


for absorbing domains:

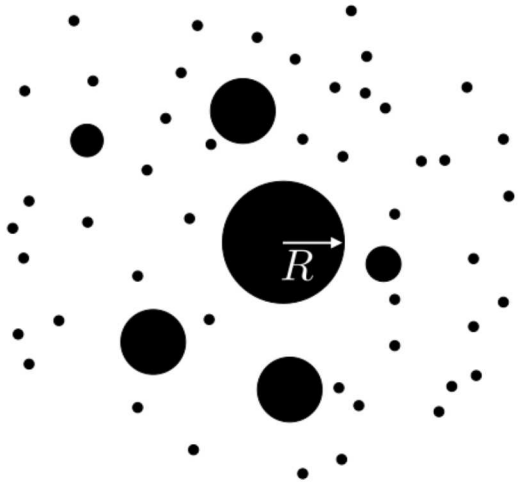
$\Delta n \sim \bar{n}$

speed of accretion of a sorting domain:

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \frac{\Phi_R}{2\pi R} = \frac{D\Delta n}{R \ln L/R}$$

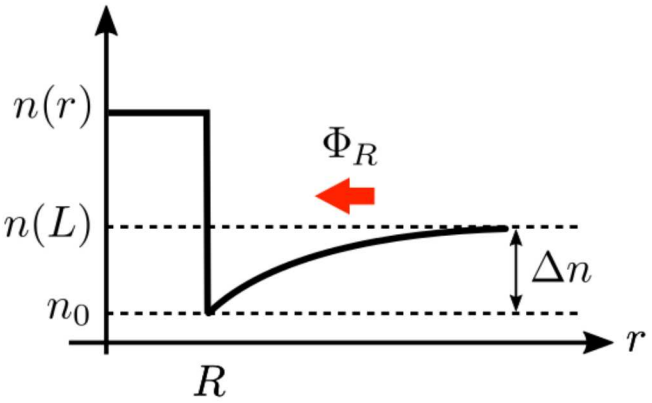


$N(R,t)\,\mathrm{d}R$: domains with $R <$ size $< R + \mathrm{d}R$



flux towards a sorting domain:

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

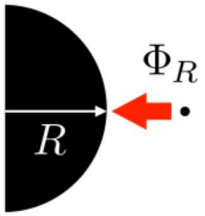


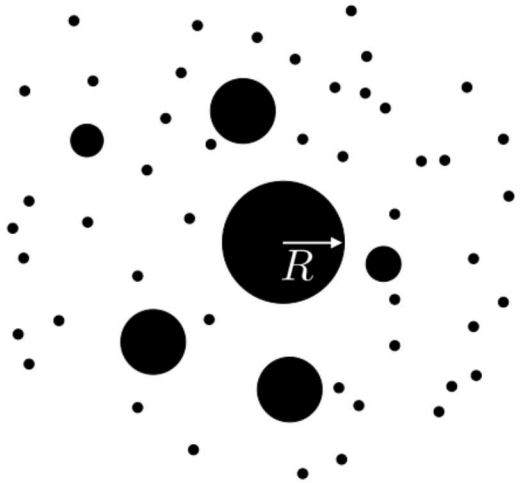
for absorbing domains:

$\Delta n \sim \bar{n}$

speed of accretion of a sorting domain:

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \frac{\Phi_R}{2\pi R} = \frac{D\Delta n}{R \ln L/R}$$



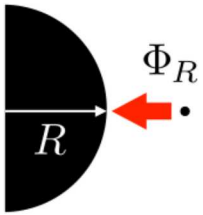


$N(R,t)\,\mathrm{d}R$: domains with $R <$ size $< R + \mathrm{d}R$

$$\frac{\partial}{\partial t}N + \frac{\partial}{\partial R}\left(\frac{D\Delta n}{R \ln L/R} N\right) = -\gamma(R) N$$

extraction rate

speed of accretion of a sorting domain:



$$\frac{\mathrm{d}R}{\mathrm{d}t} = \frac{\Phi_R}{2\pi R} = \frac{D\Delta n}{R \ln L/R}$$

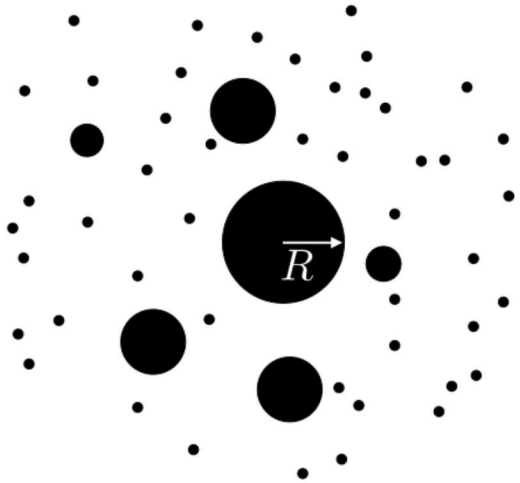
$N(R,t)\,\mathrm{d}R$: domains with $R <$ size $< R + \mathrm{d}R$

$$\frac{\partial}{\partial t}N + \frac{\partial}{\partial R}\left(\frac{D\Delta n}{R \ln L/R}N\right) = -\gamma(R)N$$

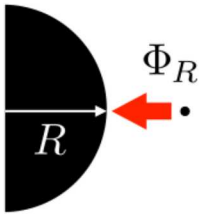
extraction rate

in the stationary state:

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

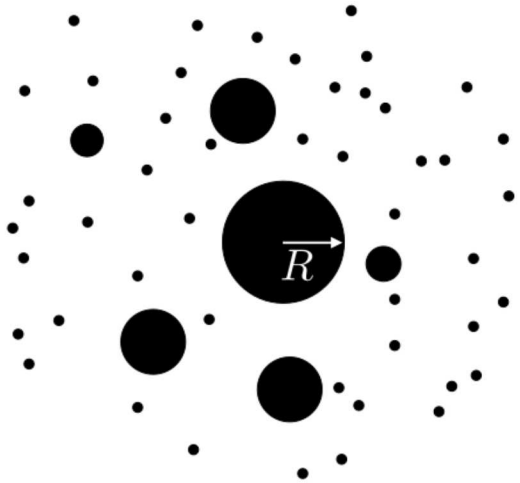


speed of accretion of a sorting domain:



$$\frac{\mathrm{d}R}{\mathrm{d}t} = \frac{\Phi_R}{2\pi R} = \frac{D\Delta n}{R \ln L/R}$$

$N(R,t)\,\mathrm{d}R$: domains with $R <$ size $< R + \mathrm{d}R$



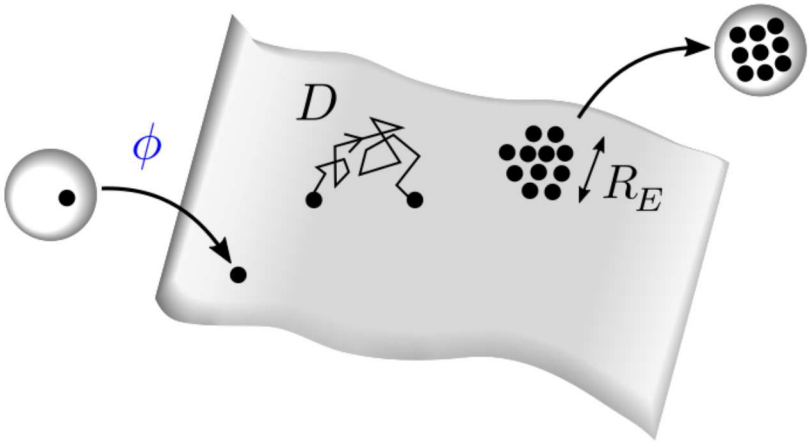
$$\frac{\partial}{\partial t}N + \frac{\partial}{\partial R}\left(\frac{D\Delta n}{R \ln L/R}N\right) = -\gamma(R)N$$

extraction rate

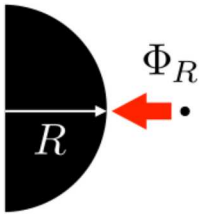
in the stationary state:

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

but the extraction flux must be equal to the incoming flux:

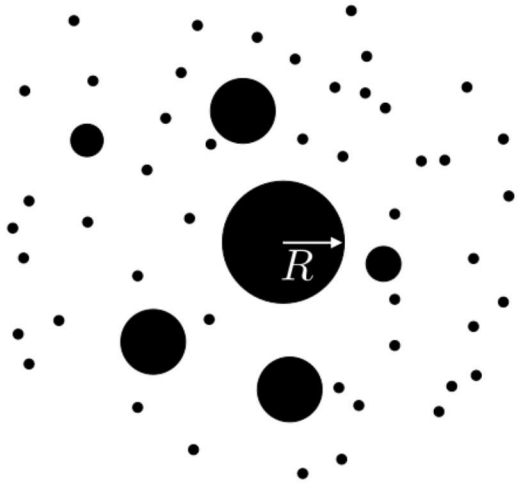


speed of accretion of a sorting domain:



$$\frac{\mathrm{d}R}{\mathrm{d}t} = \frac{\Phi_R}{2\pi R} = \frac{D\Delta n}{R \ln L/R}$$

$N(R,t)\,\mathrm{d}R$: domains with $R <$ size $< R + \mathrm{d}R$



$$\frac{\partial}{\partial t}N + \frac{\partial}{\partial R}\left(\frac{D\Delta n}{R \ln L/R}N\right) = -\gamma(R)N$$

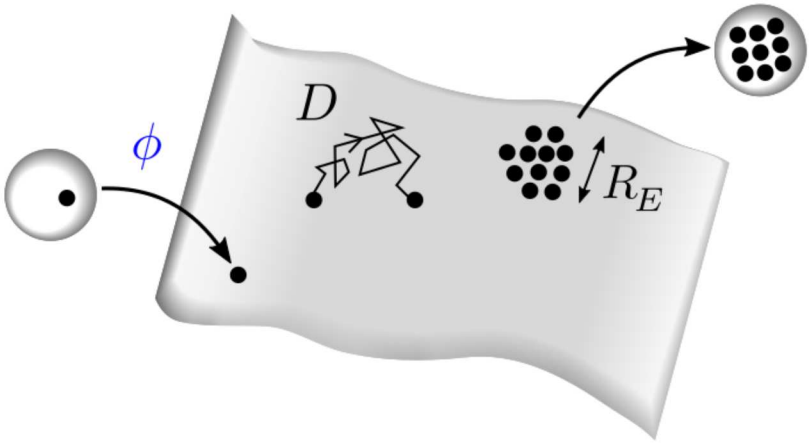
extraction rate

in the stationary state:

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

but the extraction flux must be equal to the incoming flux:

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

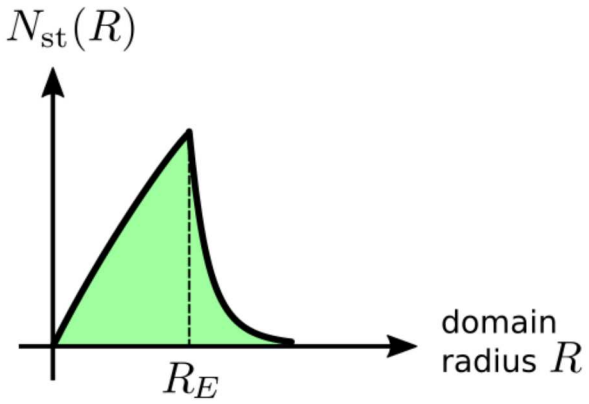


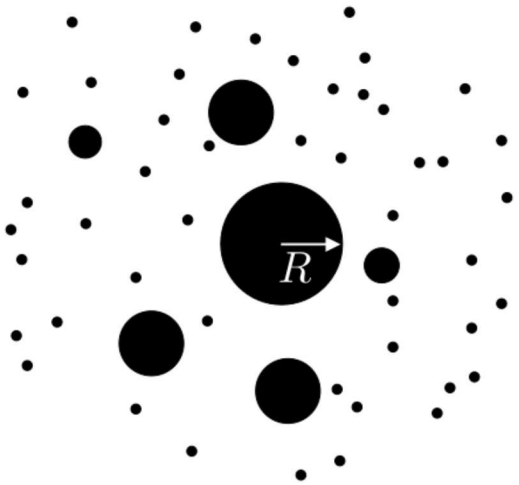
in the stationary state:

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

but the extraction flux must be equal to the incoming flux:

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





in the stationary state:

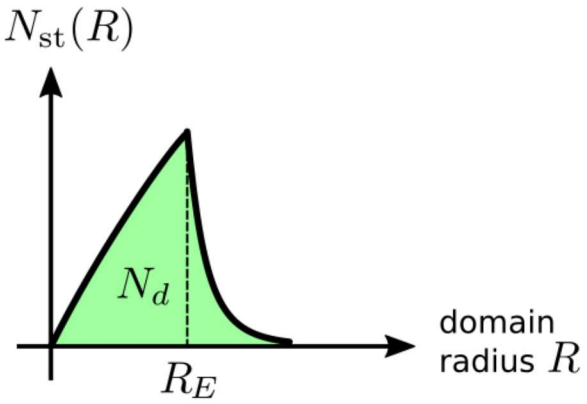
$$N_{\rm st}(R) = \frac{JR\ln L/R}{D\Delta n}\exp\left[-\int_0^R \frac{r\ln L/r}{D\Delta n}\gamma(r)\mathrm{d}r\right]$$

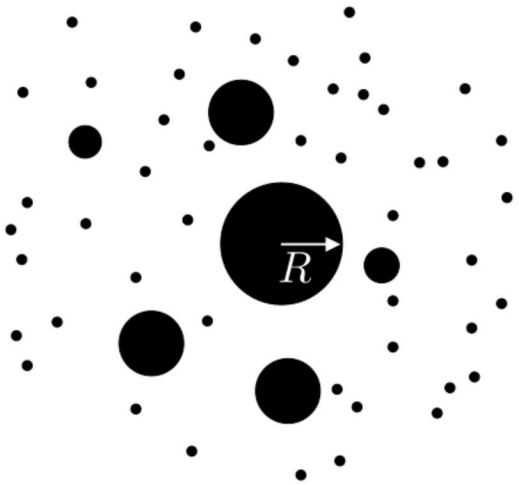
but the extraction flux must be equal to the incoming flux:

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

the number of domains is:

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





in the stationary state:

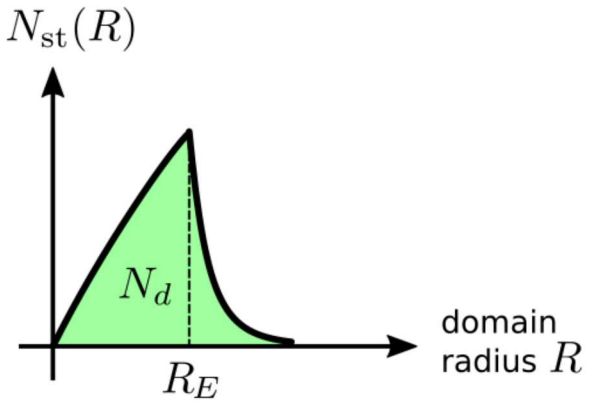
$$N_{\rm st}(R) = \frac{JR\ln L/R}{D\Delta n}\exp\left[-\int_0^R \frac{r\ln L/r}{D\Delta n}\gamma(r)\mathrm{d}r\right]$$

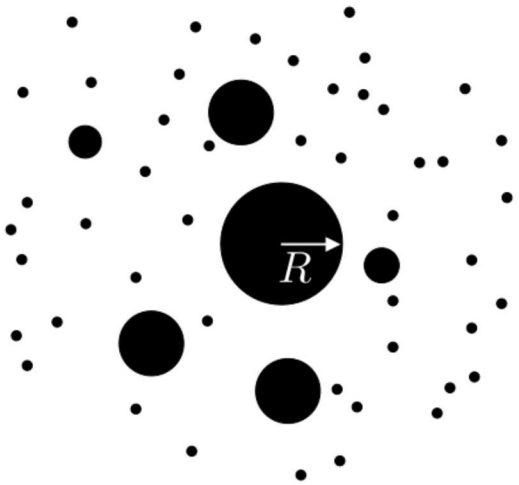
but the extraction flux must be equal to the incoming flux:

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

the number of domains is:

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





Average residence time:

in the stationary state:

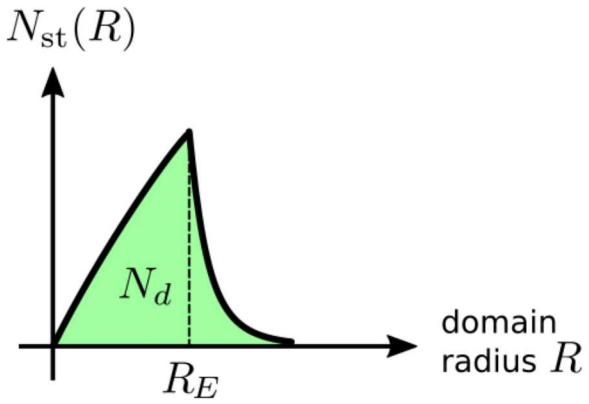
$$N_{\rm st}(R) = \frac{JR\ln L/R}{D\Delta n}\exp\left[-\int_0^R \frac{r\ln L/r}{D\Delta n}\gamma(r)\mathrm{d}r\right]$$

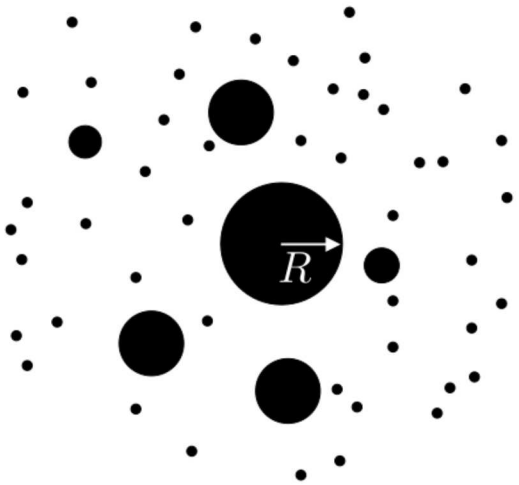
but the extraction flux must be equal to the incoming flux:

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

the number of domains is:

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





Average residence time: $T = T_f + T_d$

in the stationary state:

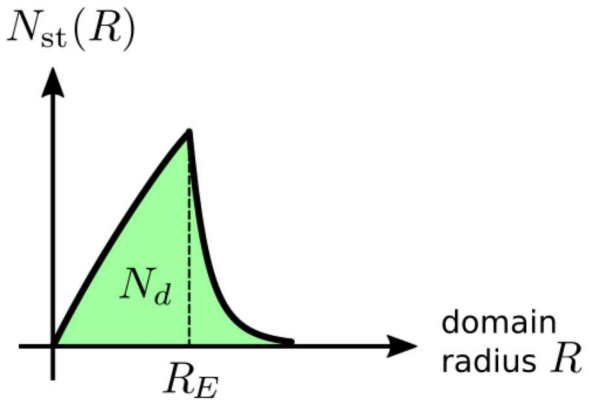
$$N_{\rm st}(R) = \frac{JR\ln L/R}{D\Delta n}\exp\left[-\int_0^R \frac{r\ln L/r}{D\Delta n}\gamma(r)\mathrm{d}r\right]$$

but the extraction flux must be equal to the incoming flux:

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

the number of domains is:

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

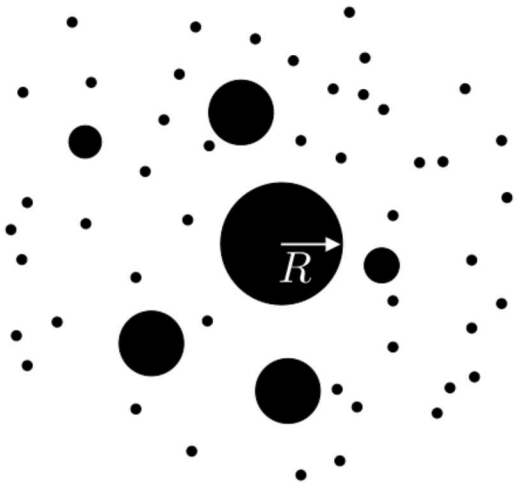


Average residence time:

$$T = T_f + T_d$$

T_d: in domains

T_f: freely diffusing



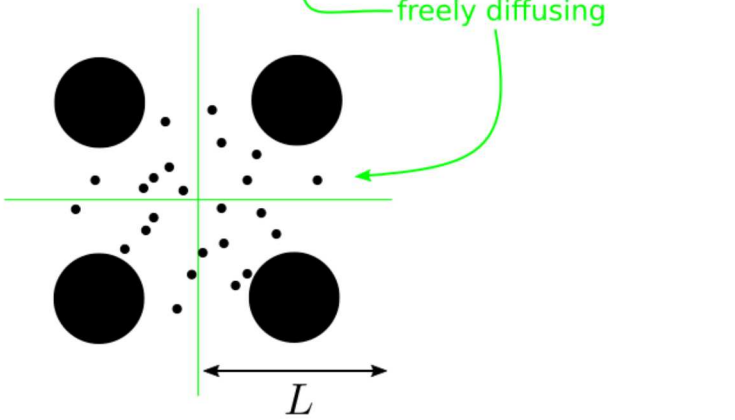
Average residence time:

$$T = T_f + T_d$$

in domains

freely diffusing

$$T_f \sim \frac{L^2}{D} \sim \frac{1}{DN_d} \sim \frac{\Delta n}{\phi}$$



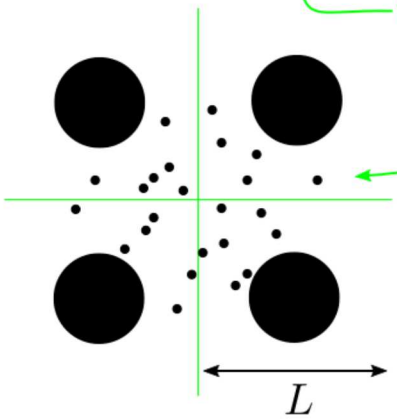
Average residence time:

$$T = T_f + T_d$$

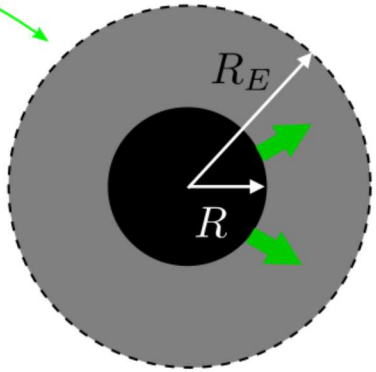
in domains

freely diffusing

$$T_f \sim \frac{L^2}{D} \sim \frac{1}{DN_d} \sim \frac{\Delta n}{\phi}$$



$$T_d \sim \frac{R_E^2}{\Phi_R} \sim \frac{R_E^2}{D\Delta n}$$



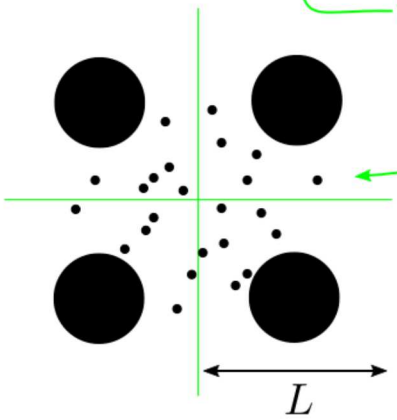
Average residence time:

$$T = T_f + T_d$$

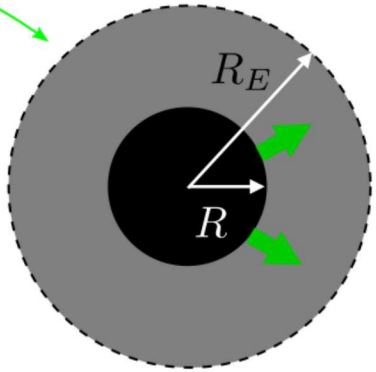
in domains

freely diffusing

$$T_f \sim \frac{L^2}{D} \sim \frac{1}{DN_d} \sim \frac{\Delta n}{\phi}$$



$$T_d \sim \frac{R_E^2}{\Phi_R} \sim \frac{R_E^2}{D\Delta n}$$



nucleation of new domains:

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

C : aggregation strength

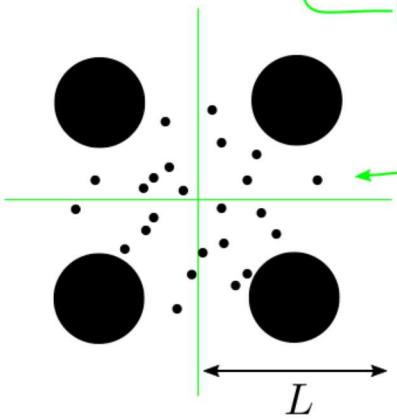
Average residence time:

$$T = T_f + T_d$$

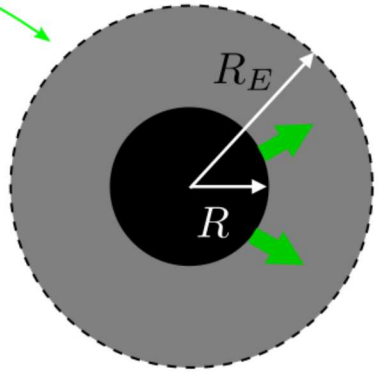
in domains

freely diffusing

$$T_f \sim \frac{L^2}{D} \sim \frac{1}{DN_d} \sim \frac{\Delta n}{\phi}$$



$$T_d \sim \frac{R_E^2}{\Phi_R} \sim \frac{R_E^2}{D\Delta n}$$



nucleation of new domains:

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

C : aggregation strength

$$\Rightarrow \quad \Delta n \sim \boxed{\bar{n} \sim \left(\frac{\phi}{CDR_E^2}\right)^{1/2}}$$

nucleation of new domains:

$$\frac{\mathrm{d}N_{d,\mathrm{new}}}{\mathrm{d}t} = C D \bar{n}^2 = \frac{N_d}{T_d}$$

C : aggregation strength

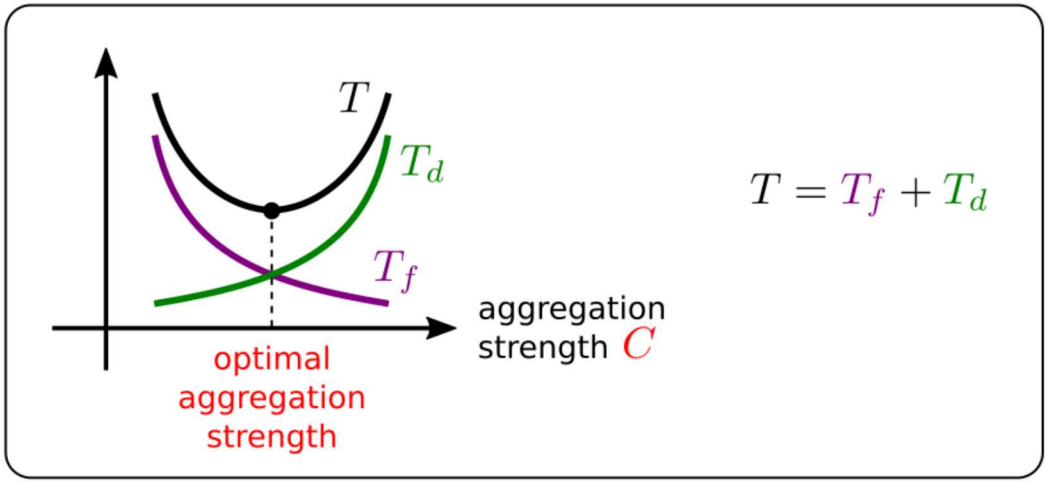
$$\Rightarrow \quad \Delta n \sim \boxed{\bar{n} \sim \left(\frac{\phi}{C D R_E^2} \right)^{1/2}}$$

$$T_f \sim C^{-1/2} \frac{1}{(D\,\phi\,)^{1/2} R_E}$$

$$T_d \sim C^{1/2} \frac{R_E^3}{(D\,\phi\,)^{1/2}}$$

for optimal aggregation strength:

$$T^{\mathrm{opt}} \sim \; T_f^{\mathrm{opt}} \sim T_d^{\mathrm{opt}} \sim \frac{R_E}{(D\,\phi\,)^{1/2}}$$



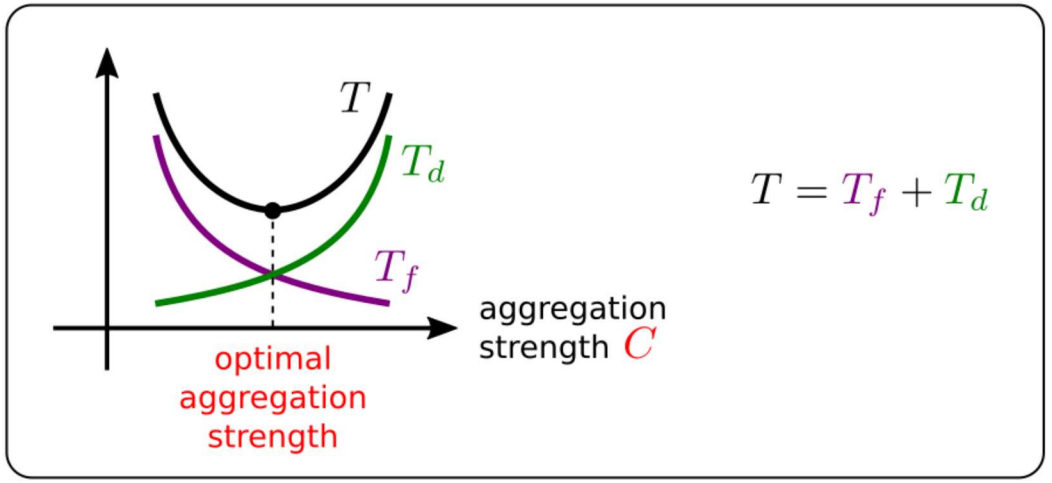
$$T_f \sim C^{-1/2} \frac{1}{(D\,\phi\,)^{1/2} R_E}$$

$$T_d \sim C^{1/2} \frac{R_E^3}{(D\,\phi\,)^{1/2}}$$

for optimal aggregation strength:

$$T^{\mathrm{opt}} \sim T_f^{\mathrm{opt}} \sim T_d^{\mathrm{opt}} \sim \frac{R_E}{(D\,\phi\,)^{1/2}}$$

$$\rho^{\mathrm{opt}} \sim \bar{n}^{\mathrm{opt}} \sim \frac{\phi^{1/2} R_E}{D^{1/2}}$$

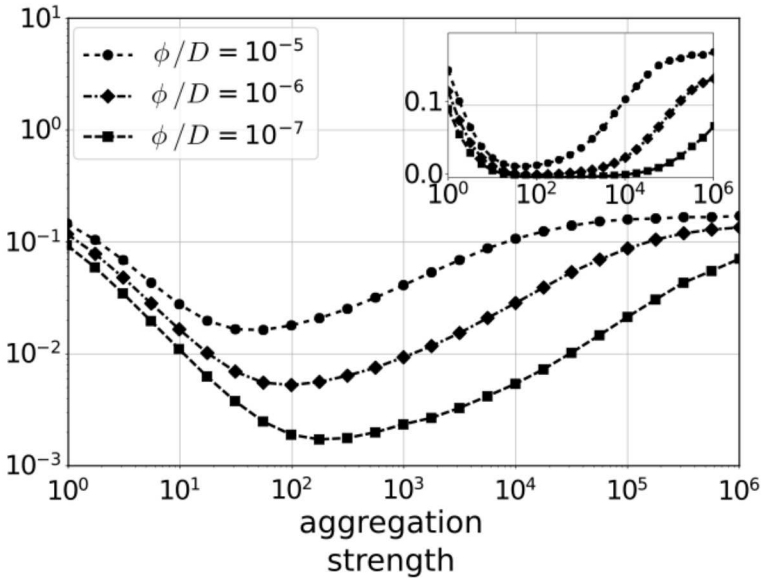


$$T = \rho/\phi$$

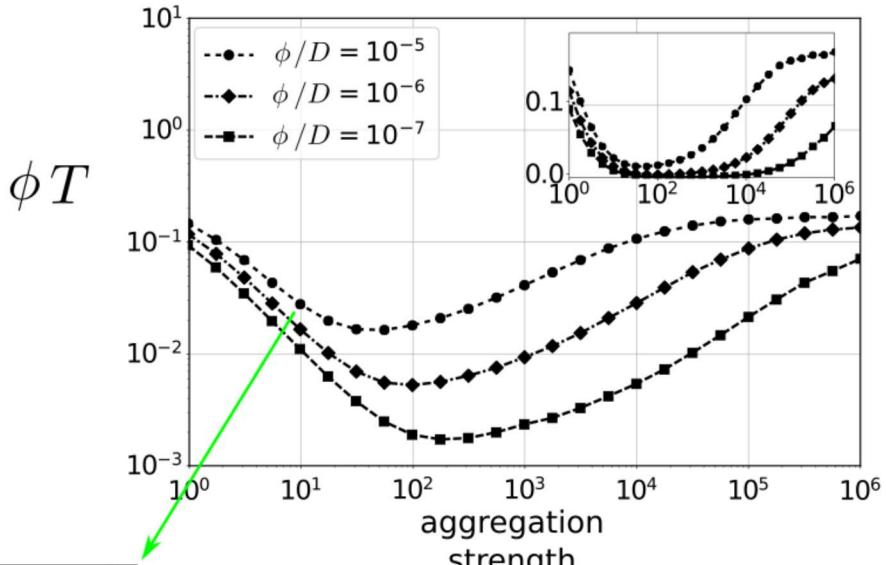
- sorting is most efficient at intermediate aggregation strength
- scaling laws for residence time, molecule density, number of domains
- molecule density is minimal in the optimal regime

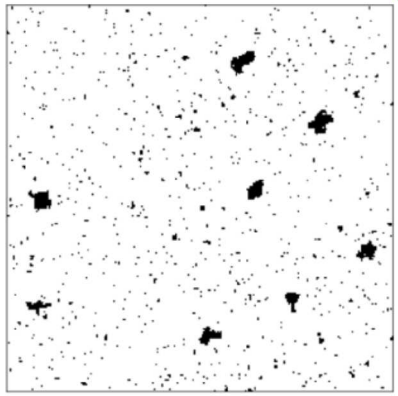
Numerical results

ϕT



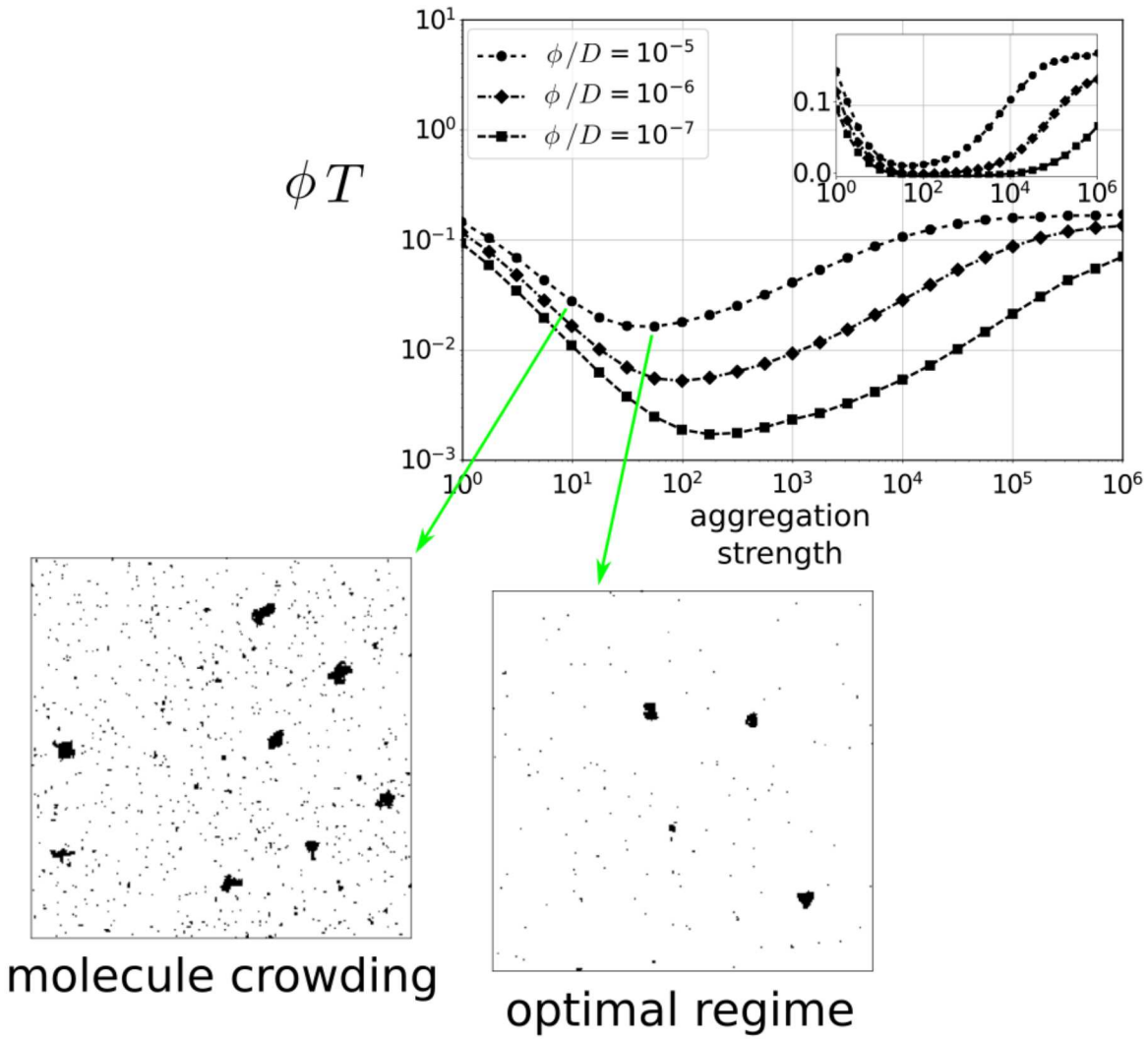
Numerical results



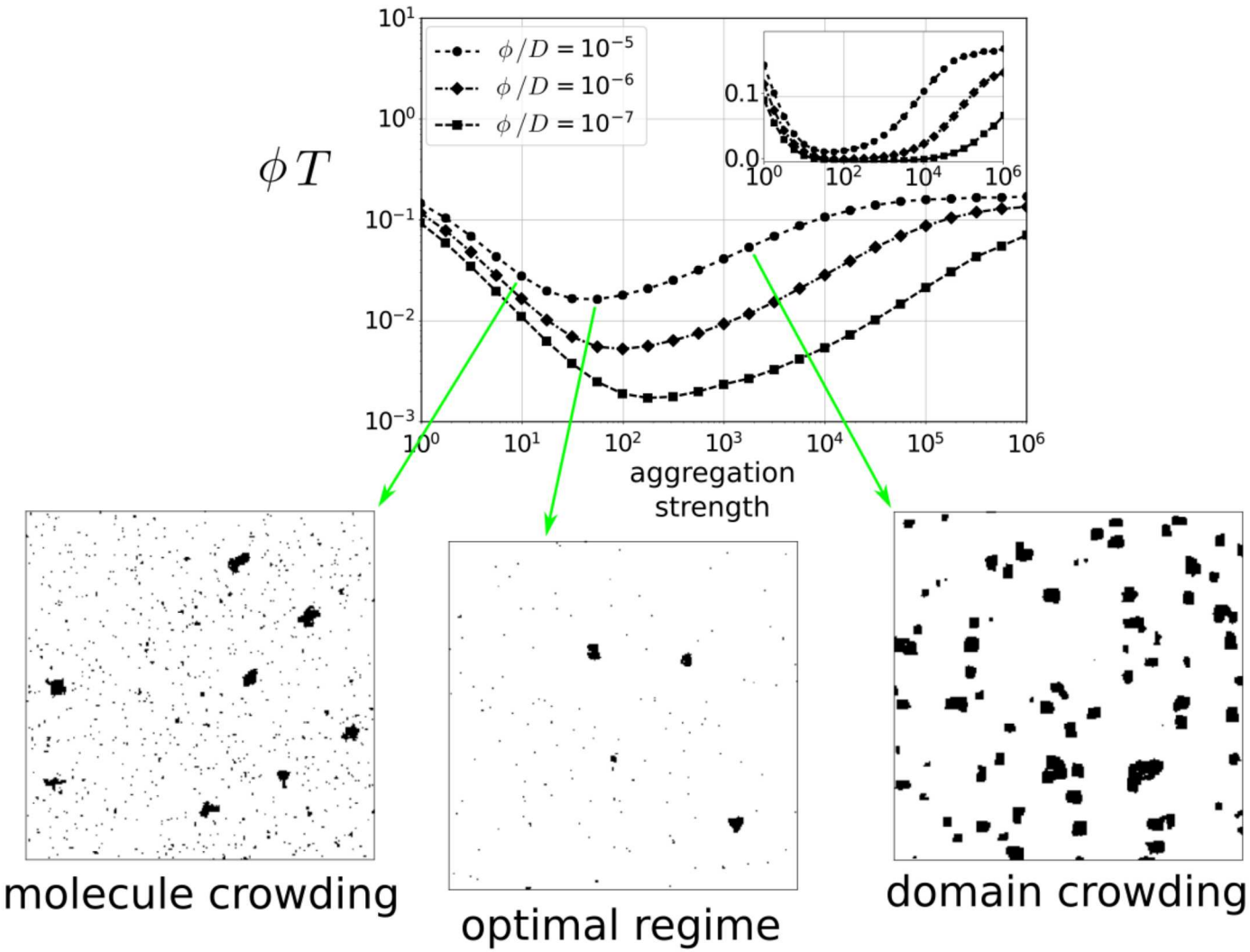


molecule crowding

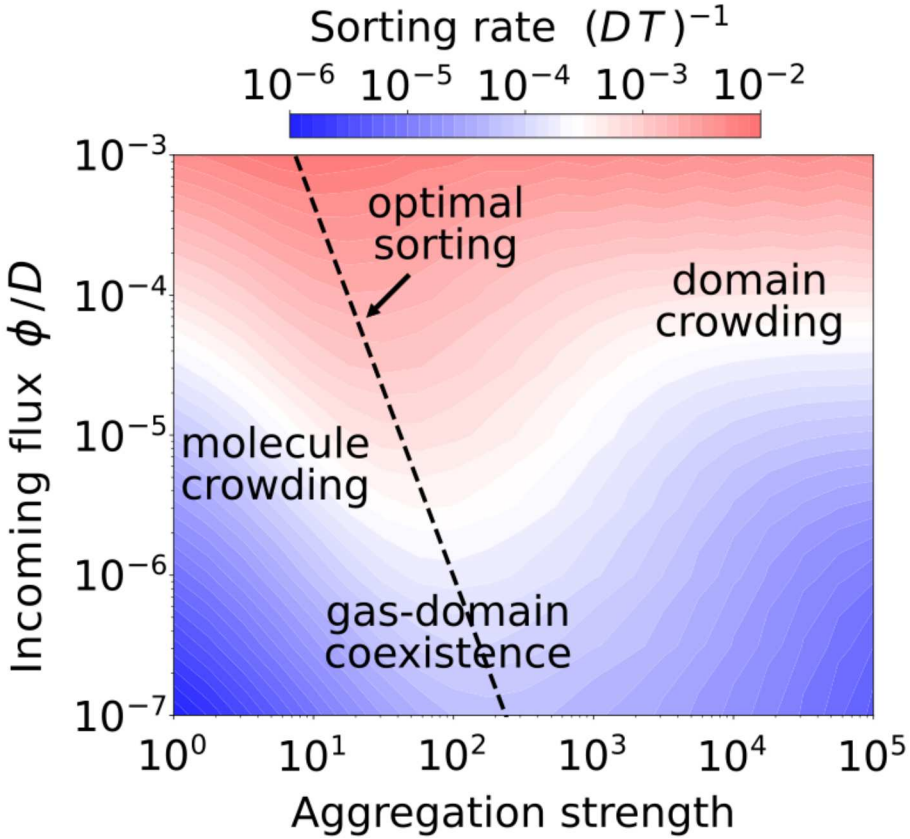
Numerical results



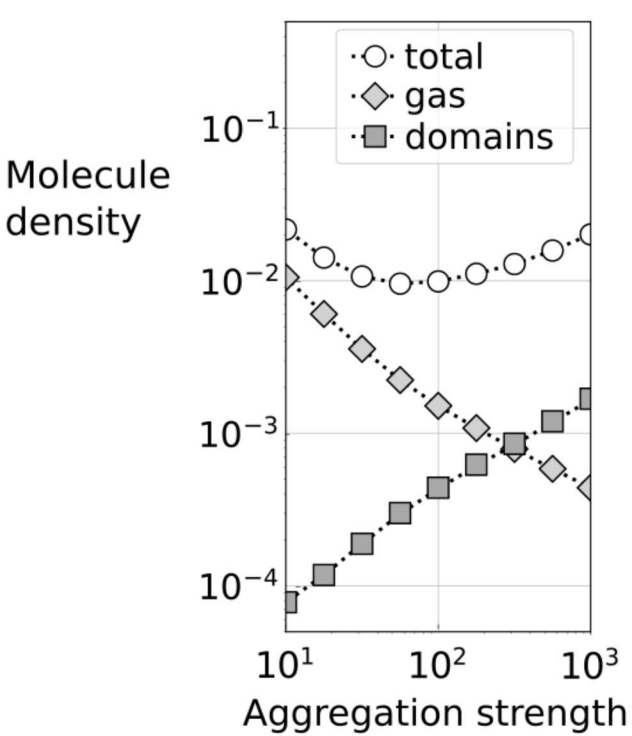
Numerical results

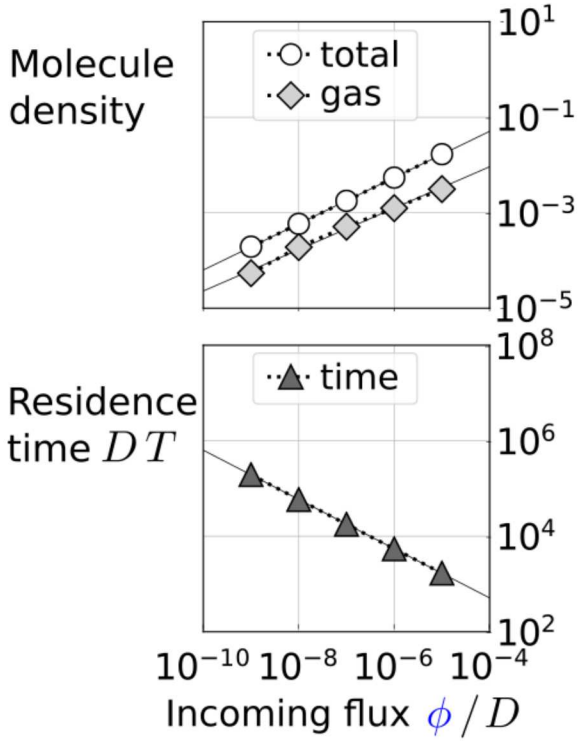


Phase diagram



Numerical results



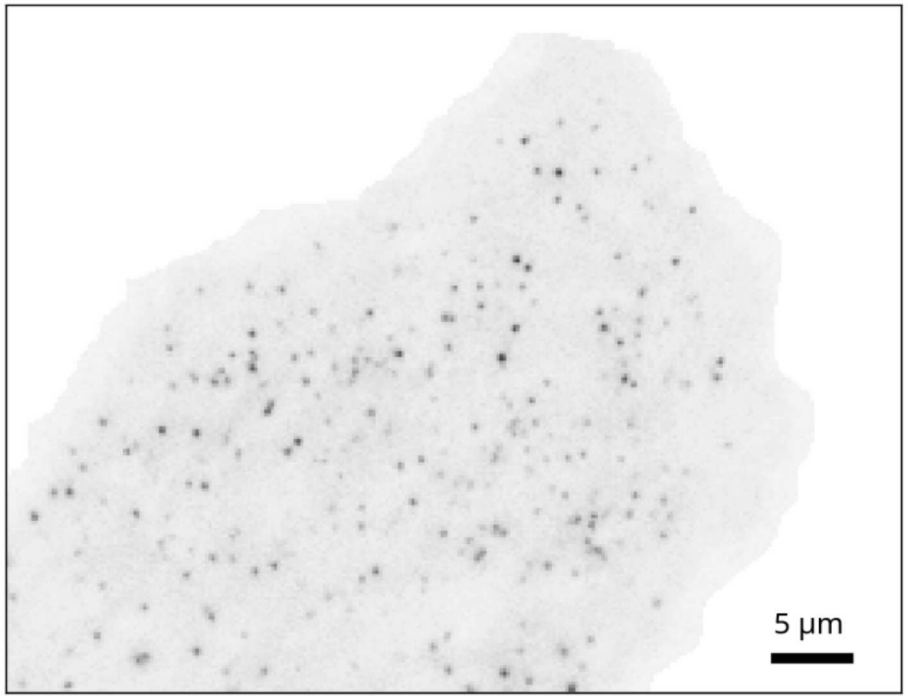


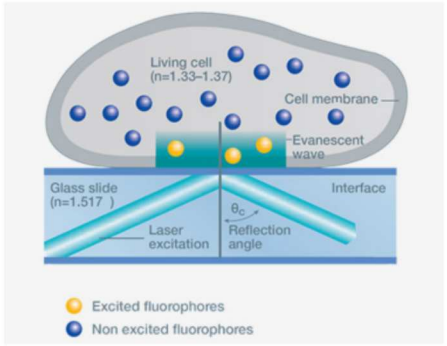
$\rho^{\mathrm{opt}} \sim \phi^{0.48}$ (total)

$\bar{n}^{\mathrm{opt}} \sim \phi^{0.46}$ (gas)

$T^{\mathrm{opt}} \sim \phi^{-0.52}$

Endocytic sorting

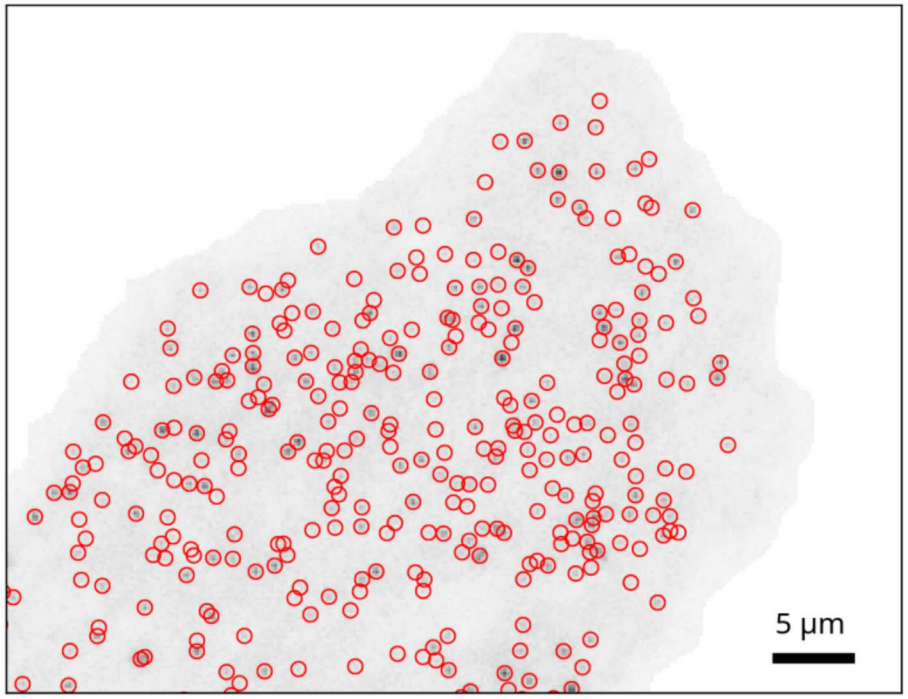


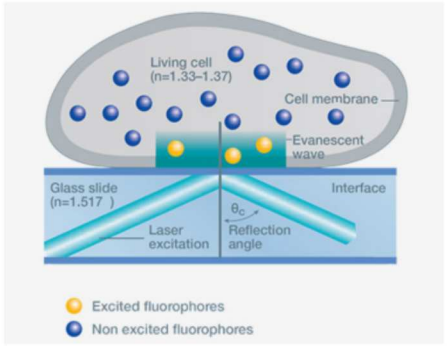


TIRF microscopy

M Zamparo, D Valdembri, G Serini, I Kolokolov, V Lebedev, L Dall'Asta, AG, PRL (2021)

Endocytic sorting



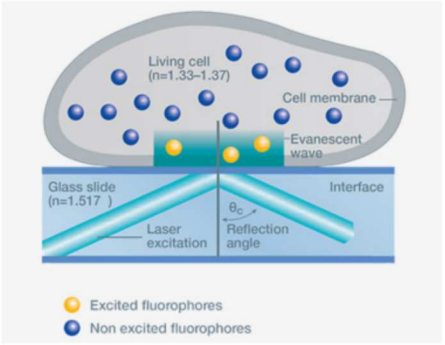


TIRF microscopy

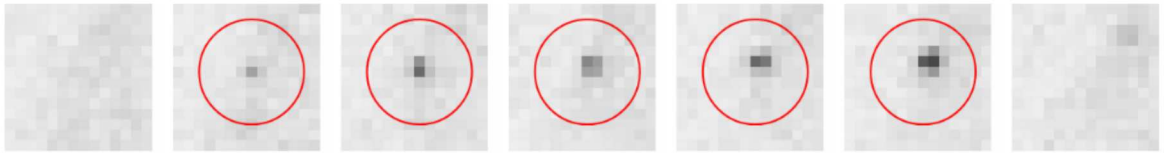
M Zamparo, D Valdembri, G Serini, I Kolokolov, V Lebedev, L Dall'Asta, AG, PRL (2021)

Endocytic sorting





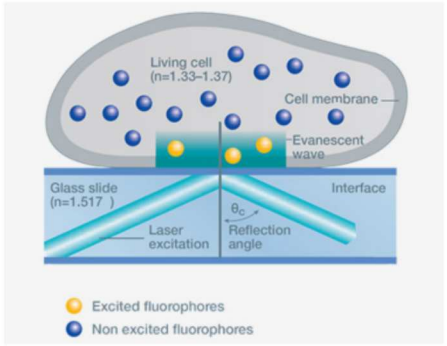
TIRF microscopy



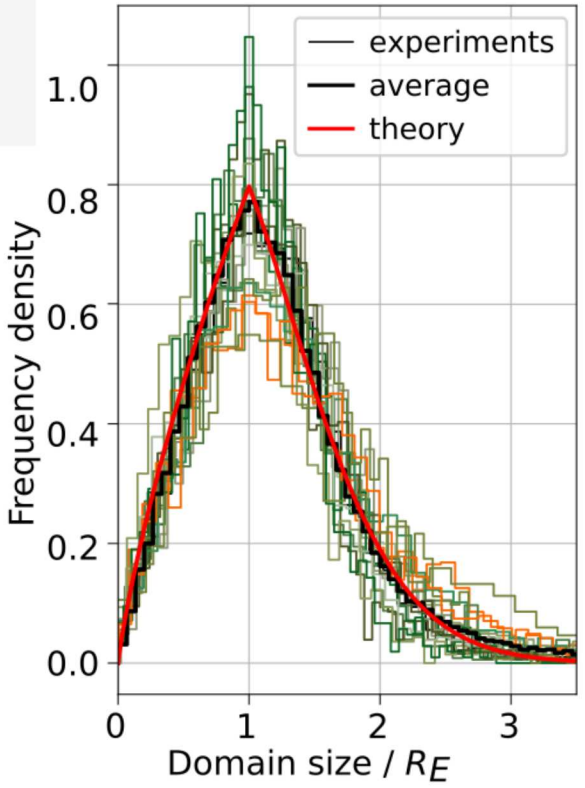
M Zamparo, D Valdembri, G Serini, I Kolokolov, V Lebedev, L Dall'Asta, AG, PRL (2021)

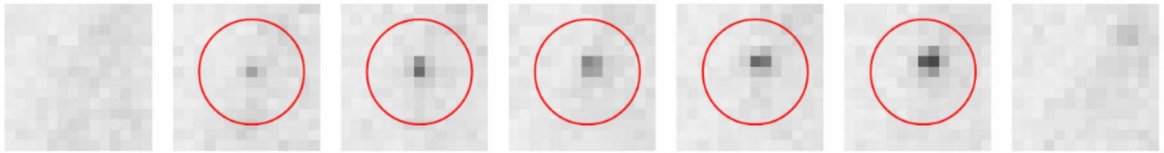
Endocytic sorting





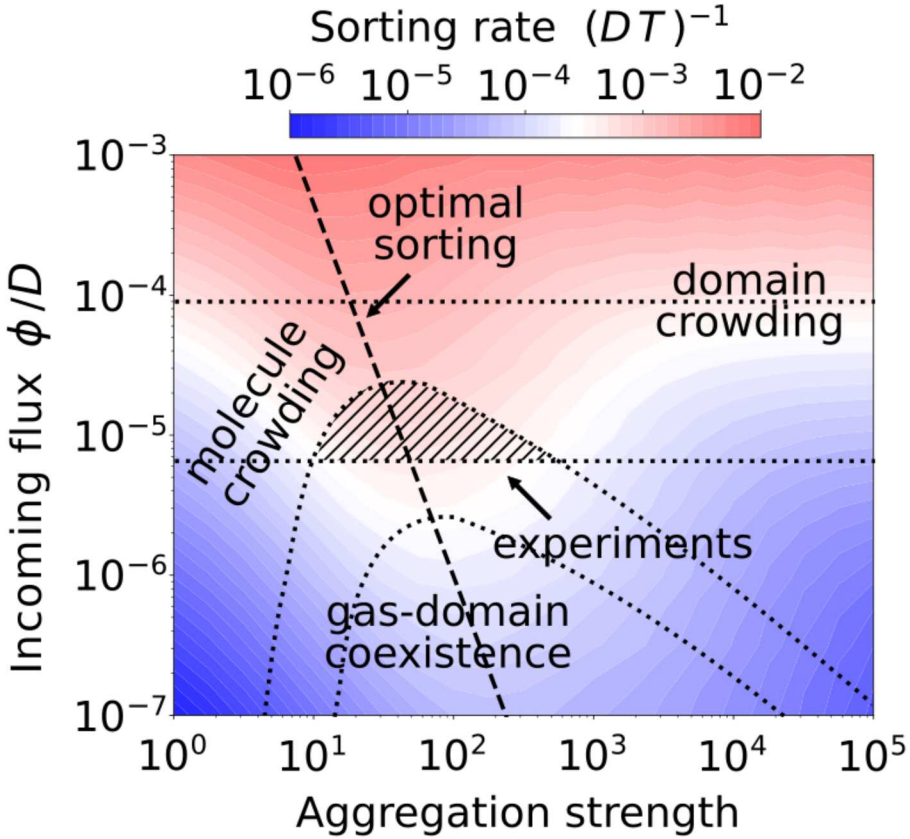
TIRF microscopy





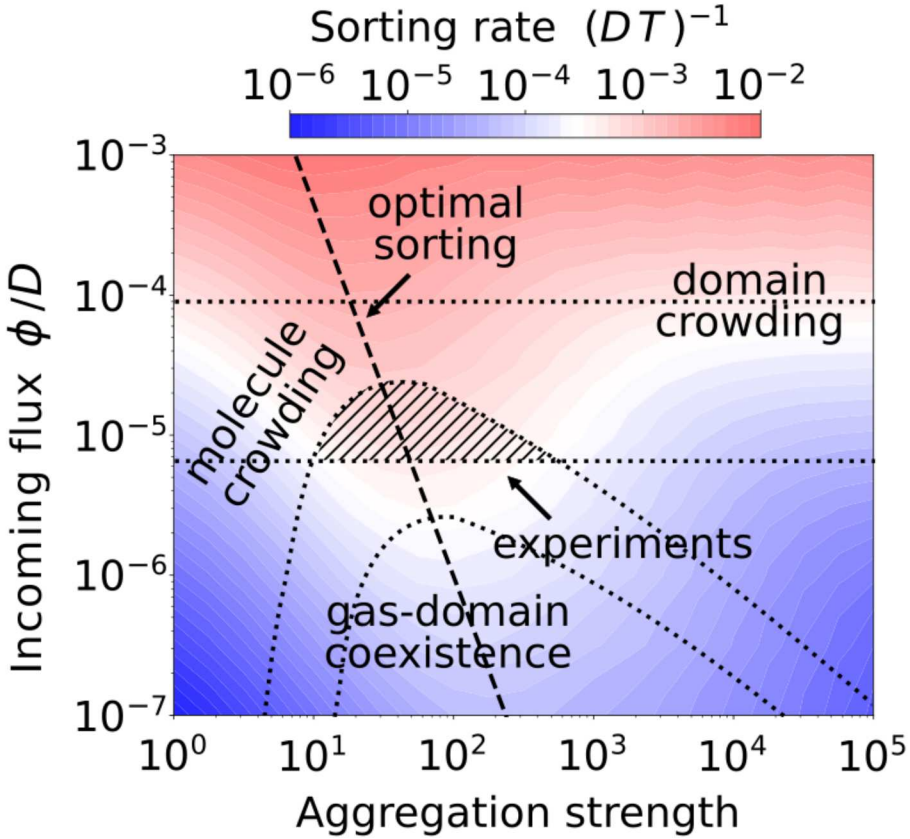
M Zamparo, D Valdembri, G Serini, I Kolokolov, V Lebedev, L Dall'Asta, AG, PRL (2021)

Endocytic sorting



M Zamparo, D Valdembri, G Serini, I Kolokolov, V Lebedev, L Dall'Asta, AG, PRL (2021)

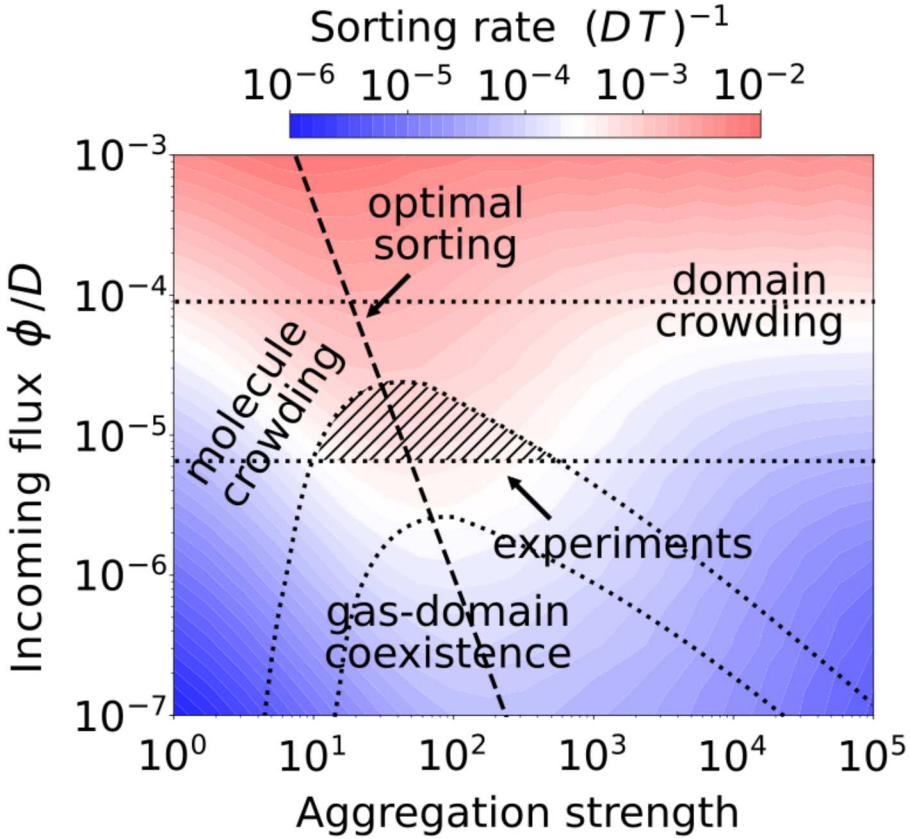
Endocytic sorting



- optimal sorting is predicted for *intermediate* levels of aggregation strength

M Zamparo, D Valdembri, G Serini, I Kolokolov, V Lebedev, L Dall'Asta, AG, PRL (2021)

Endocytic sorting



- optimal sorting is predicted for *intermediate* levels of aggregation strength
- experimental data are consistent with the hypothesis that the optimal regime is realized in living cells

M Zamparo, D Valdembri, G Serini, I Kolokolov, V Lebedev, L Dall'Asta, AG, PRL (2021)

Endocytic sorting

nature cell biology

ARTICLES

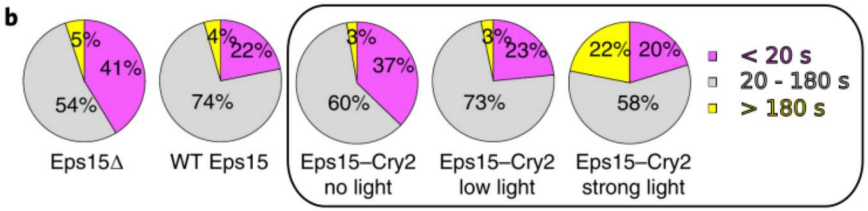
https://doi.org/10.1038/s41556-021-00646-5

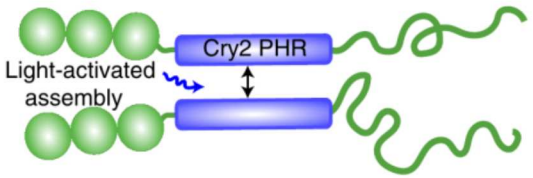
Check for updates

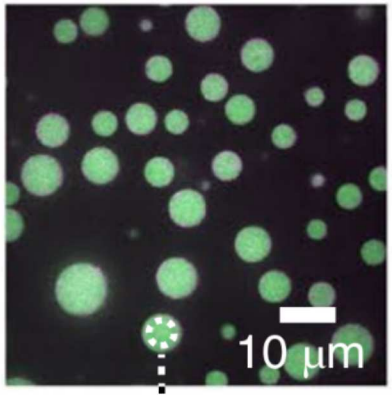
Liquid-like protein interactions catalyse assembly of endocytic vesicles

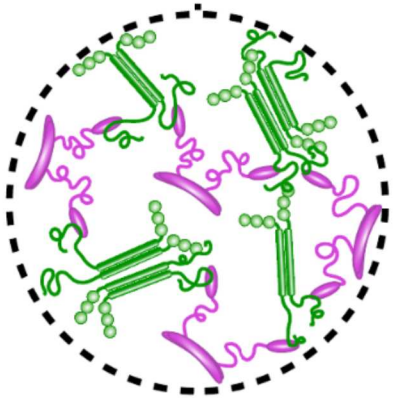
Kasey J. Day[1], Grace Kago[2], Liping Wang[3], J. Blair Richter[3], Carl C. Hayden[1], Eileen M. Lafer[3] and Jeanne C. Stachowiak[1,2]

During clathrin-mediated endocytosis, dozens of proteins assemble into an interconnected network at the plasma membrane. As initiators of endocytosis, Eps15 and Fcho1/2 concentrate downstream components, while permitting dynamic rearrangement within the budding vesicle. How do initiator proteins meet these competing demands? Here we show that Eps15 and Fcho1/2 rely on weak, liquid-like interactions to catalyse endocytosis. In vitro, these weak interactions promote the assembly of protein droplets with liquid-like properties. To probe the physiological role of these liquid-like networks, we tuned the strength of initiator protein assembly in real time using light-inducible oligomerization of Eps15. Low light levels drove liquid-like assemblies, restoring normal rates of endocytosis in mammalian Eps15-knockout cells. By contrast, initiator proteins formed solid-like assemblies upon exposure to higher light levels, which stalled vesicle budding, probably owing to insufficient molecular rearrangement. These findings suggest that liquid-like assembly of initiator proteins provides an optimal catalytic platform for endocytosis.



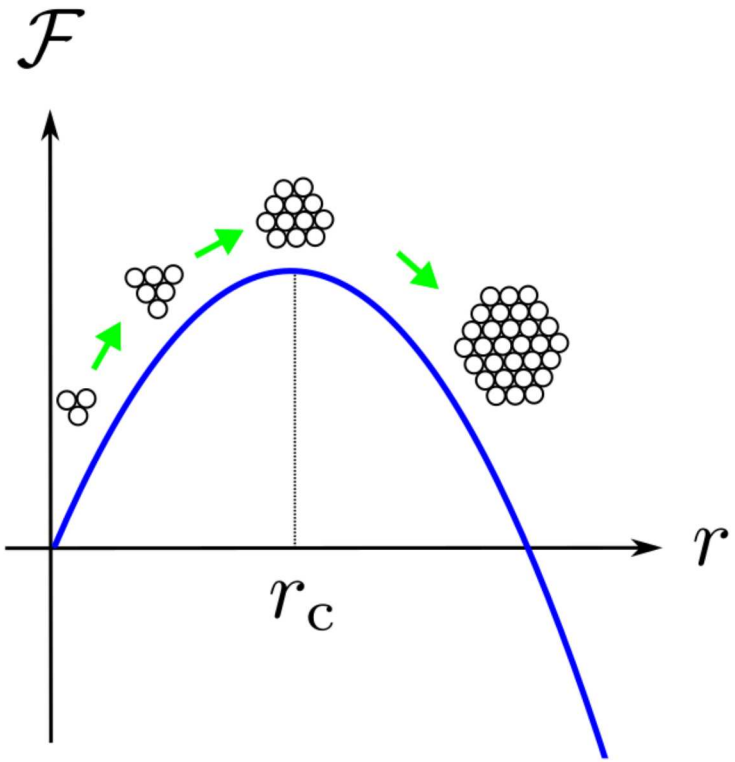




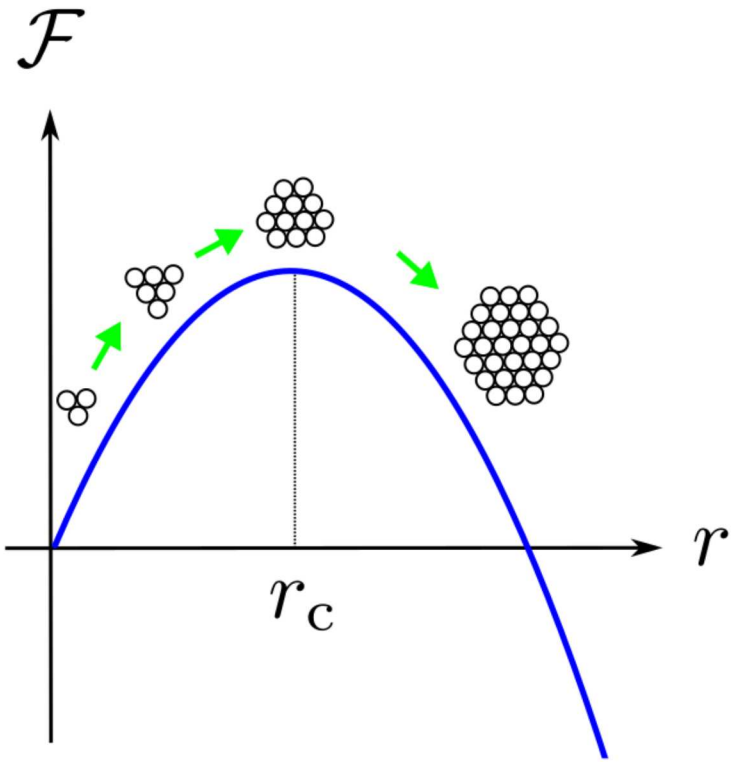


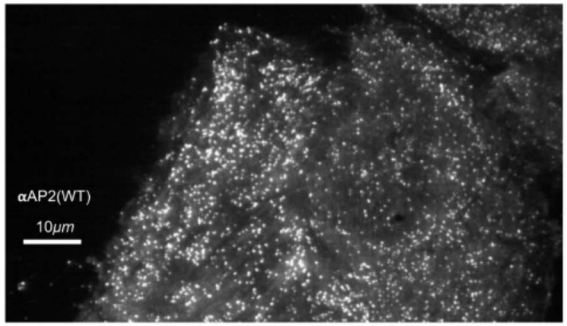
Critical size

Critical size



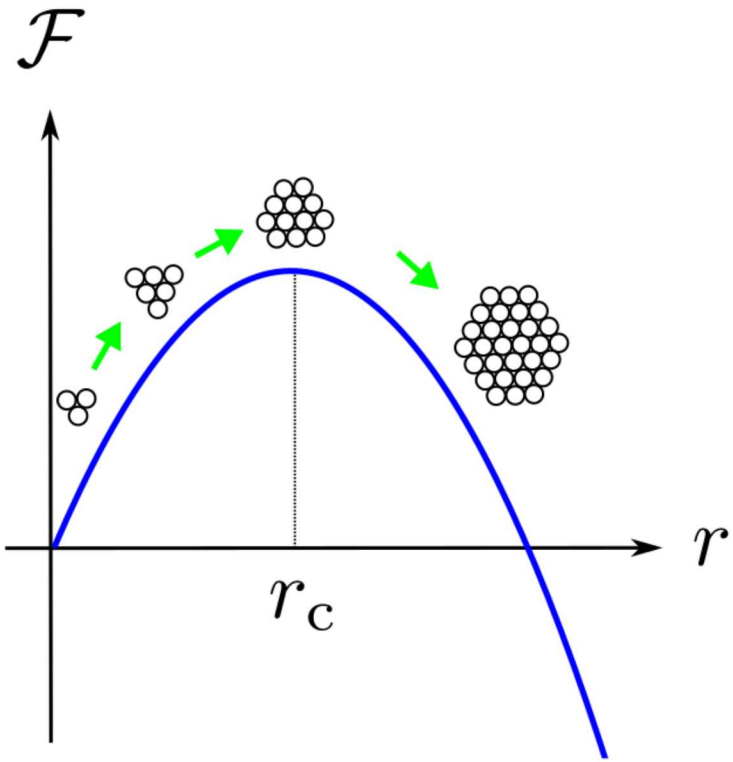
Critical size

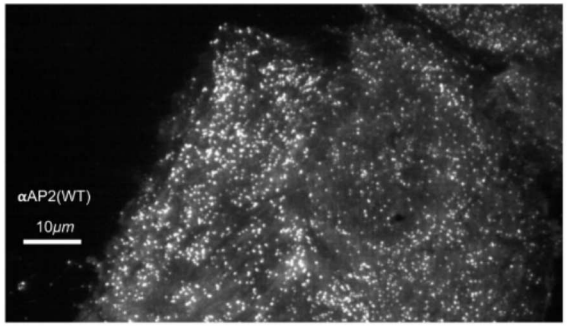


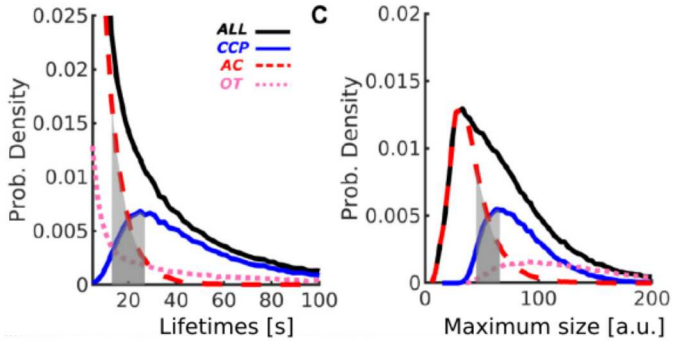


X Wang, Z Chen, M Mettlen, J Noh, S Schmid, G Danuser, eLife (2020)

Critical size

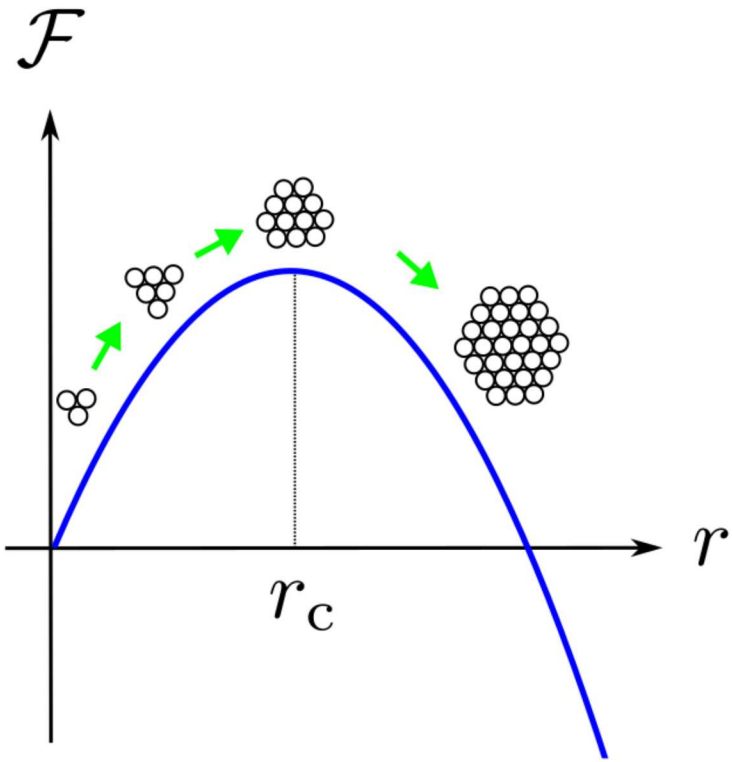


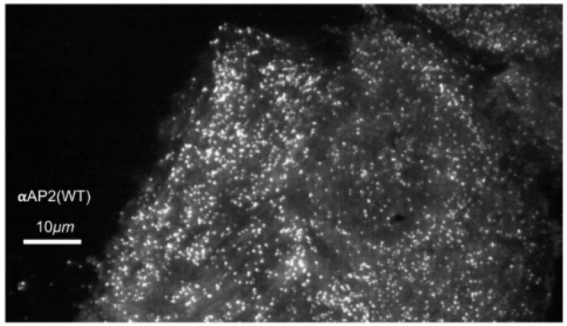


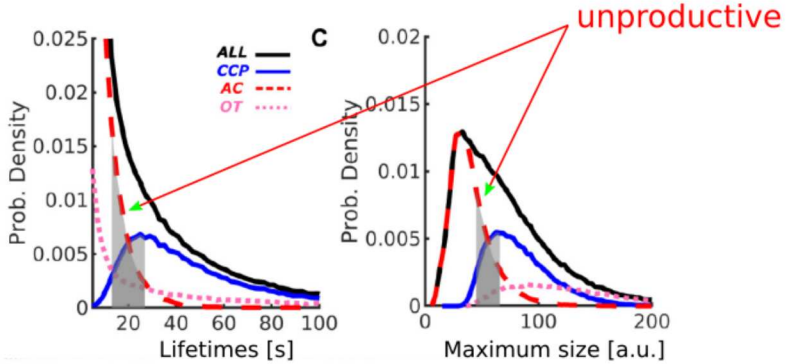


X Wang, Z Chen, M Mettlen, J Noh, S Schmid, G Danuser, eLife (2020)

Critical size

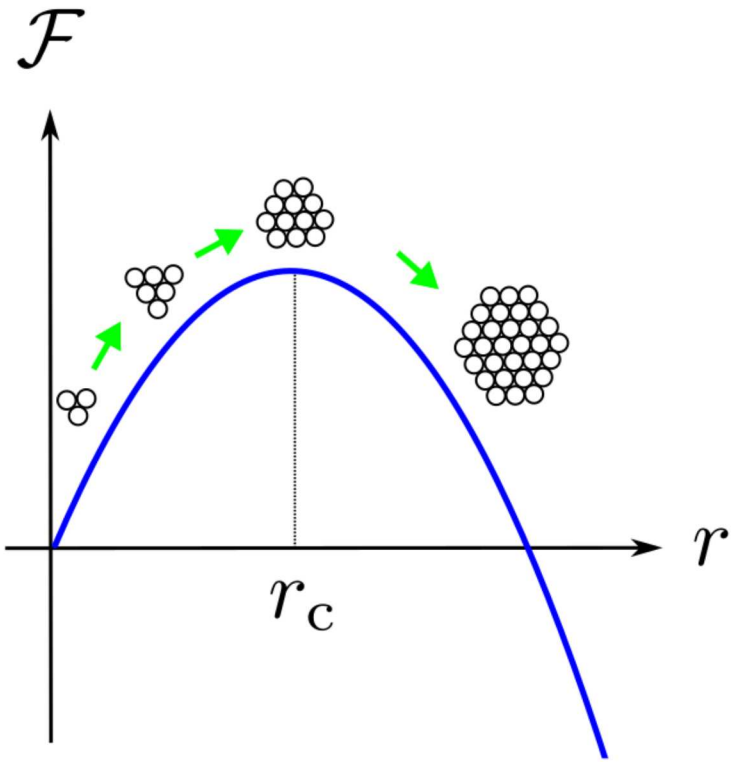


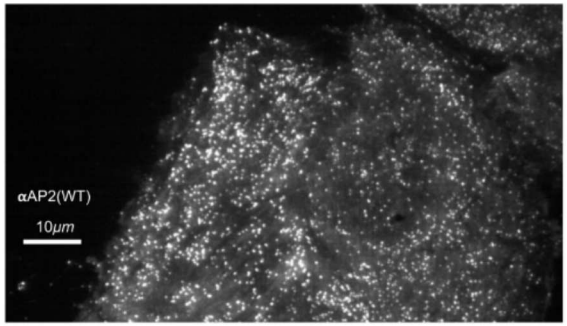


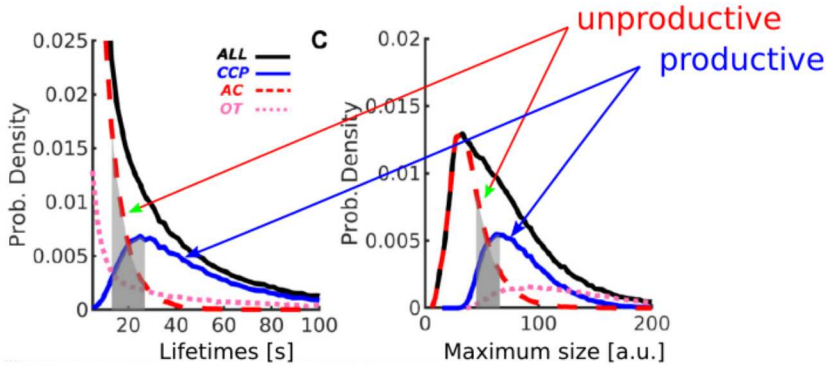


X Wang, Z Chen, M Mettlen, J Noh, S Schmid, G Danuser, eLife (2020)

Critical size

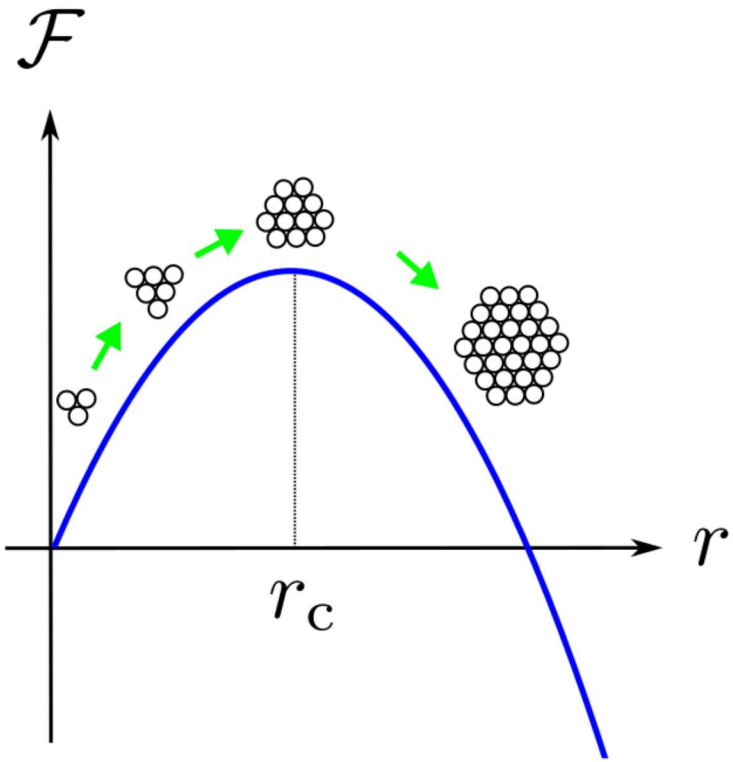


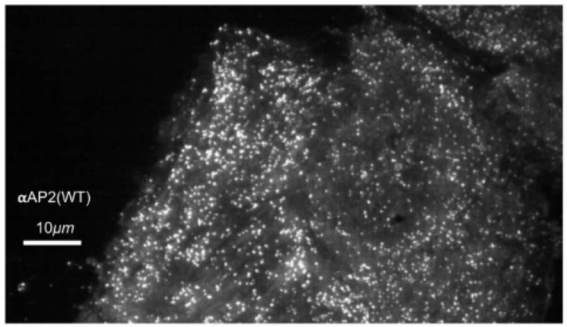


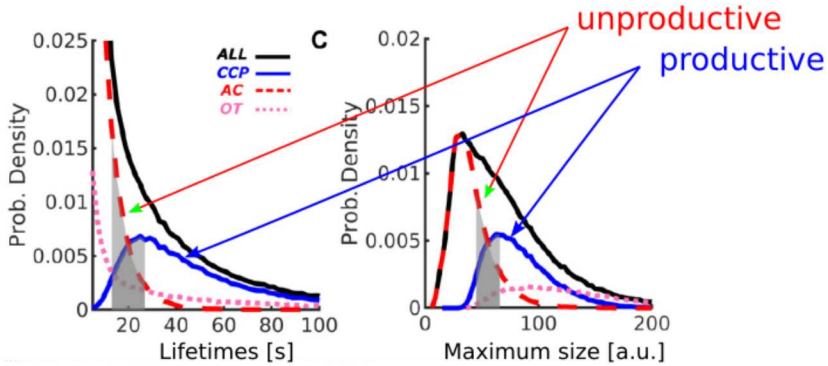


X Wang, Z Chen, M Mettlen, J Noh, S Schmid, G Danuser, eLife (2020)

Critical size







X Wang, Z Chen, M Mettlen, J Noh, S Schmid, G Danuser, eLife (2020)

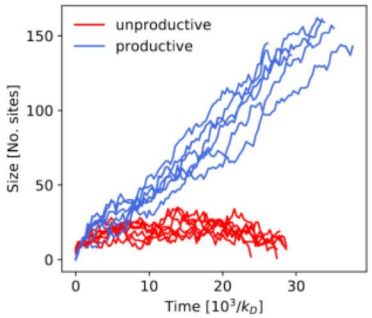
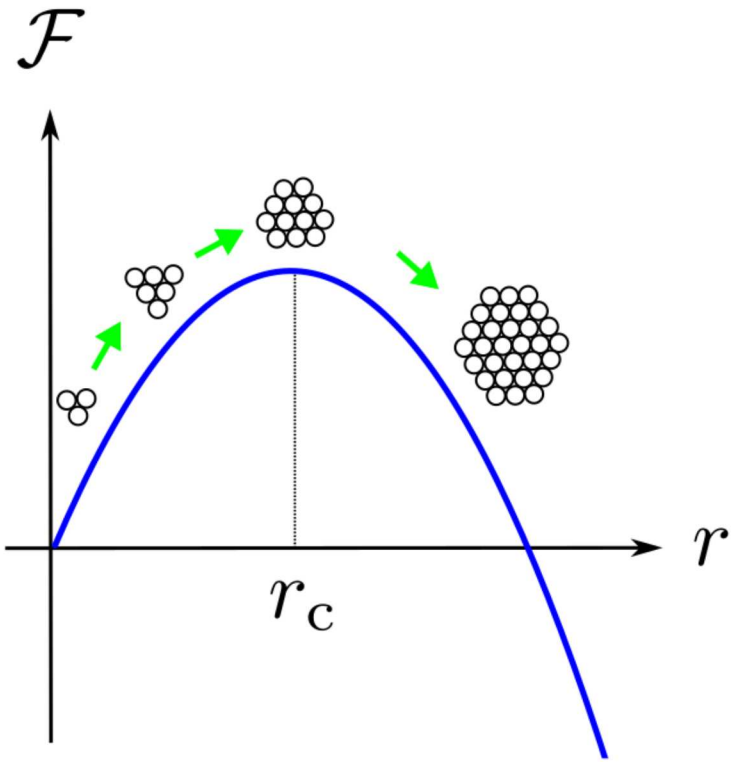
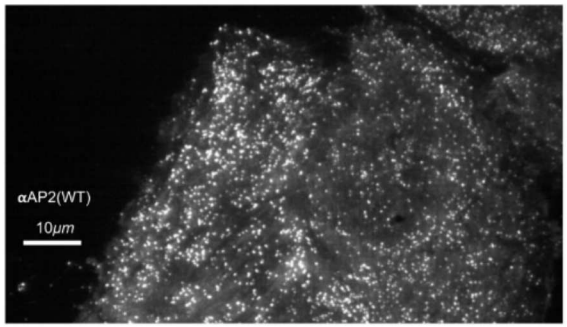


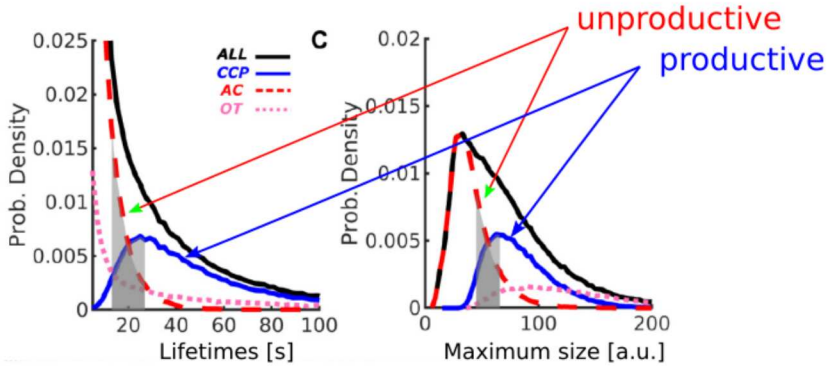
Figure 5. Time evolution of the size of productive (blue) and unproductive (red) sorting domains, from numerical simulation of the lattice-gas model ($\phi/k_D = 10^{-6}$, $g = 20$).

E Floris, A Piras, F Pezzicoli, M Zamparo, L Dall'Asta, AG, PRE (2022)

Critical size







X Wang, Z Chen, M Mettlen, J Noh, S Schmid, G Danuser, eLife (2020)

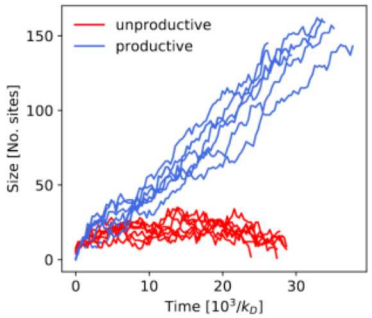


Figure 5. Time evolution of the size of productive (blue) and unproductive (red) sorting domains, from numerical simulation of the lattice-gas model ($\phi/k_D = 10^{-6}$, $g = 20$).

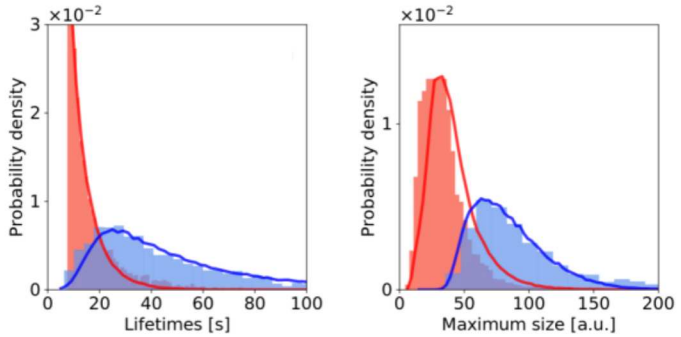
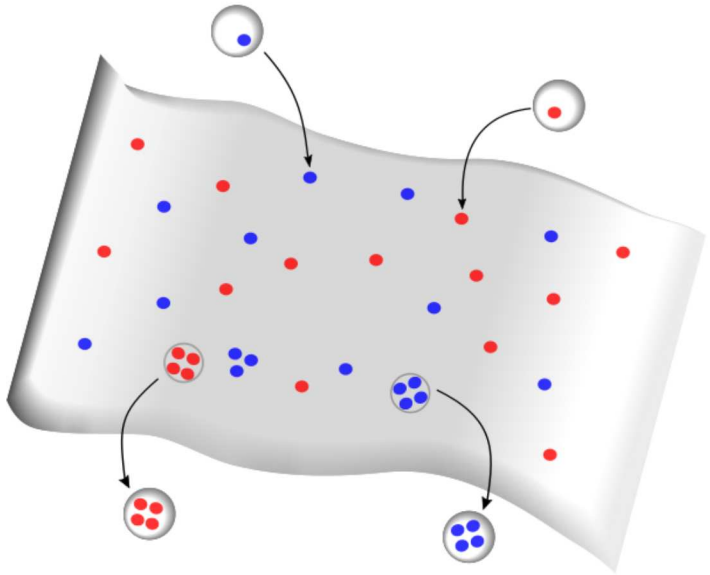


Figure 10. Comparison between the experimental distributions of lifetimes (left) and maximum sizes (right) of unproductive (red lines) and productive (blue lines) domains from Ref. [21] Fig. 2B,C (kindly shared by Dr. Xinxin Wang), and corresponding distributions obtained from simulations of the lattice-gas model (red and blue histograms, respectively) with fitted values of the model parameters ($g = 6.5$, $\phi/k_D = 10^{-6}$)

E Floris, A Piras, F Pezzicoli, M Zamparo, L Dall'Asta, AG, PRE (2022)

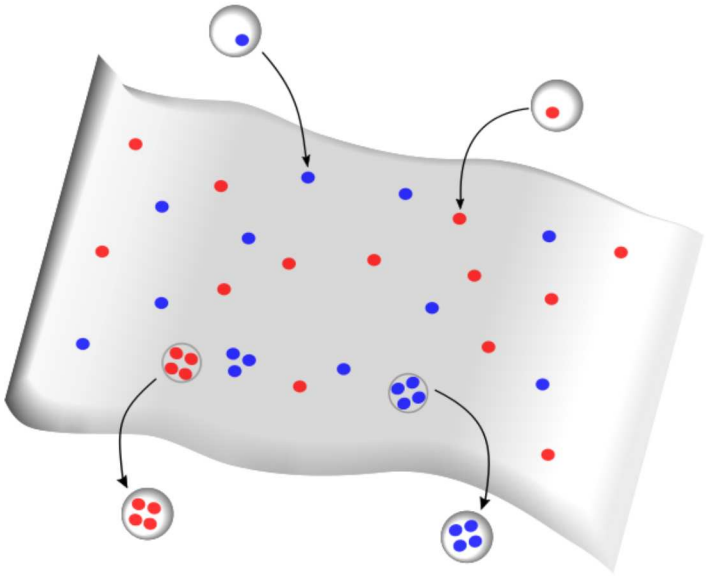
Many species

Many species



A Piras, E Floris, L Dall'Asta, AG, PRE (2023)

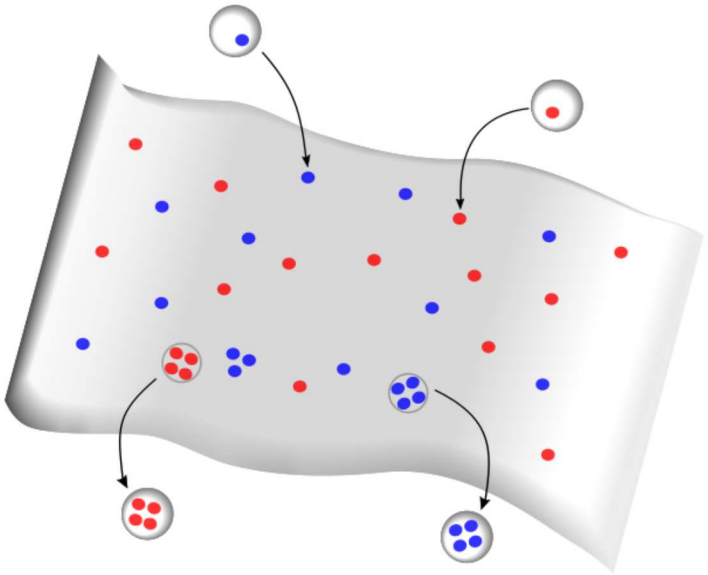
Many species



$$T = \phi^{-1}\rho \sim \left(\frac{A_E N}{A_0 D\,\phi}\right)^{1/2}$$

A Piras, E Floris, L Dall'Asta, AG, PRE (2023)

Many species



$$T = \phi^{-1}\rho \sim \left(\frac{A_E N}{A_0 D\,\phi}\right)^{1/2}$$

vesicle area

number of species

residence time

molecule density

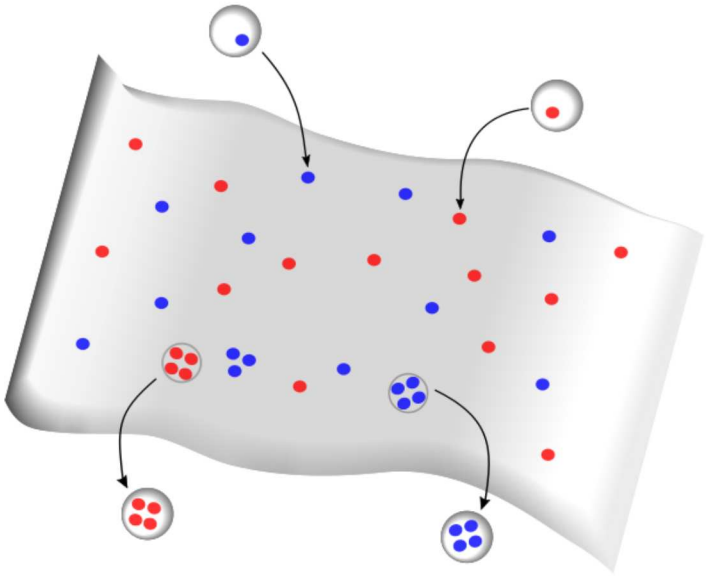
molecule area

diffusivity

total molecule flux

A Piras, E Floris, L Dall'Asta, AG, PRE (2023)

Many species



$$T = \phi^{-1}\rho \sim \left(\frac{A_E N}{A_0 D\,\phi}\right)^{1/2}$$

residence time

molecule density

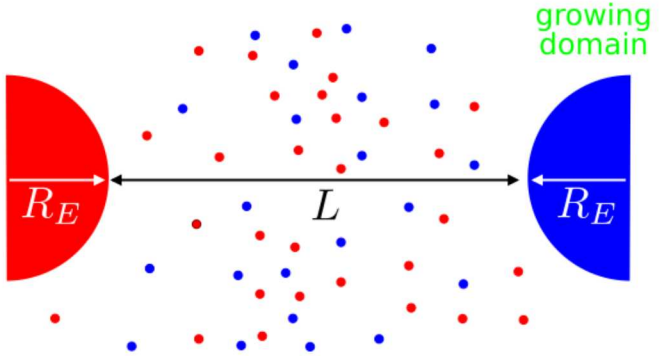
molecule area

diffusivity

vesicle area

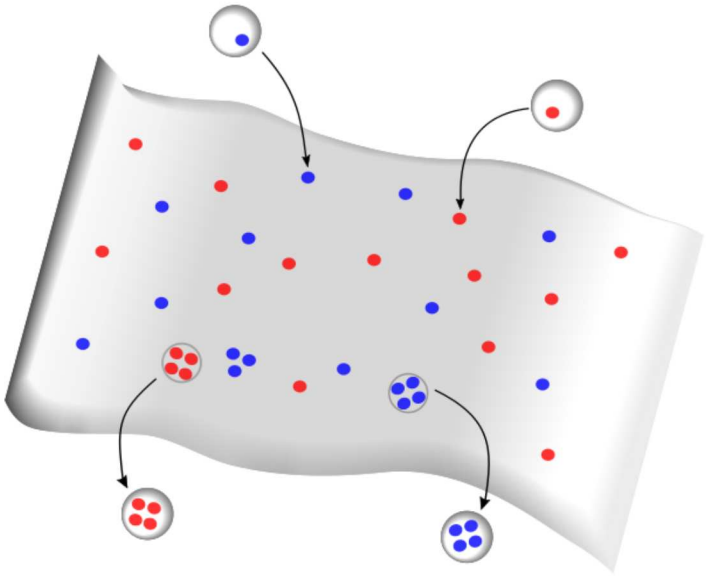
number of species

total molecule flux



A Piras, E Floris, L Dall'Asta, AG, PRE (2023)

Many species



$$T = \phi^{-1}\rho \sim \left(\frac{A_E N}{A_0 D\,\phi}\right)^{1/2}$$

residence time

molecule density

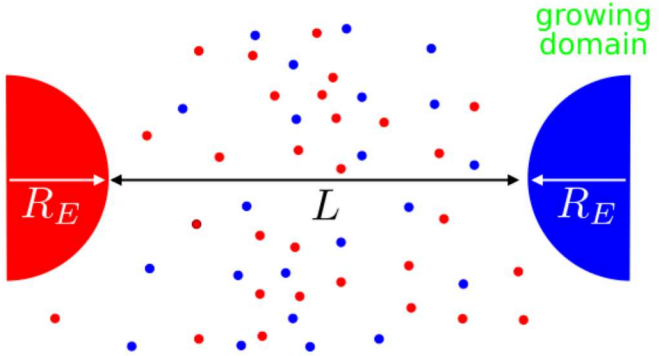
molecule area

diffusivity

total molecule flux

vesicle area

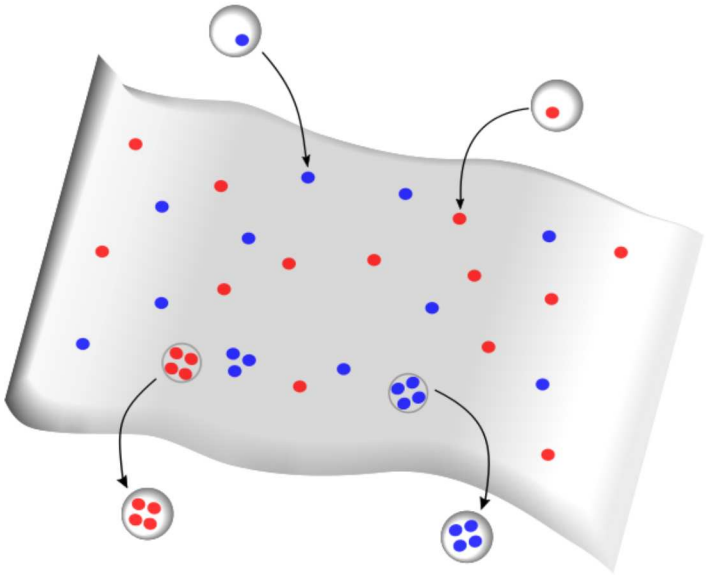
number of species



$$R_E \ll L$$

A Piras, E Floris, L Dall'Asta, AG, PRE (2023)

Many species



$$T = \phi^{-1}\rho \sim \left(\frac{A_E N}{A_0 D\,\phi}\right)^{1/2}$$

residence time

molecule density

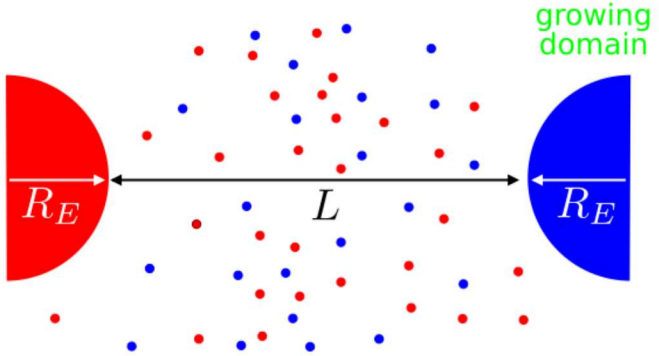
molecule area

diffusivity

total molecule flux

vesicle area

number of species

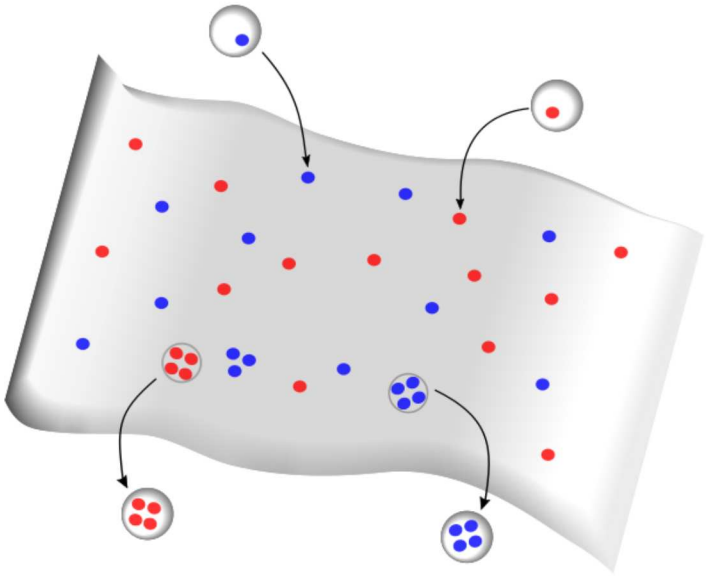


$$R_E \ll L$$

low-density regime

A Piras, E Floris, L Dall'Asta, AG, PRE (2023)

Many species



$$T = \phi^{-1}\rho \sim \left(\frac{A_E N}{A_0 D\,\phi}\right)^{1/2}$$

residence time

molecule density

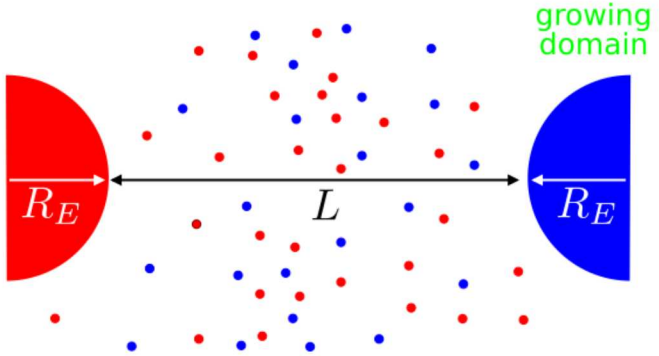
molecule area

diffusivity

total molecule flux

vesicle area

number of species

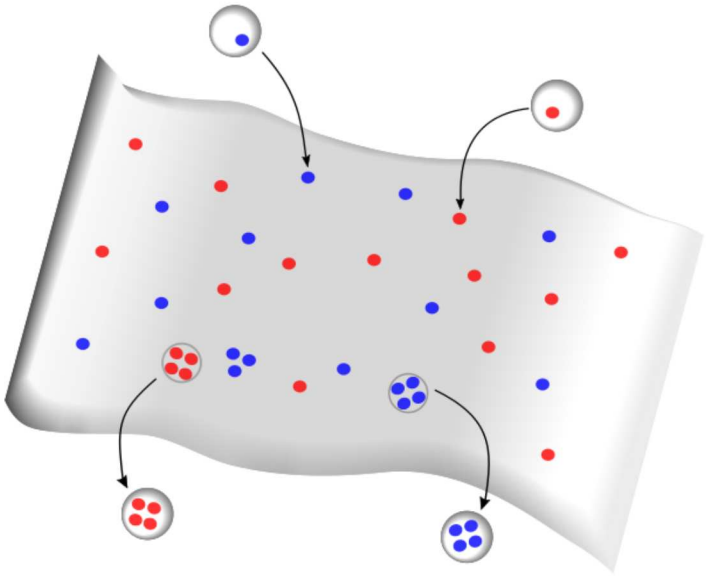


$$R_E \ll L \implies$$

low-density regime

A Piras, E Floris, L Dall'Asta, AG, PRE (2023)

Many species



$$T = \phi^{-1}\rho \sim \left(\frac{A_E N}{A_0 D\,\phi}\right)^{1/2}$$

residence time

molecule density

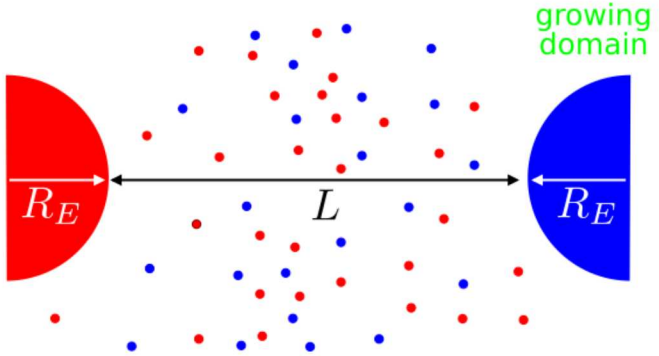
molecule area

diffusivity

total molecule flux

vesicle area

number of species

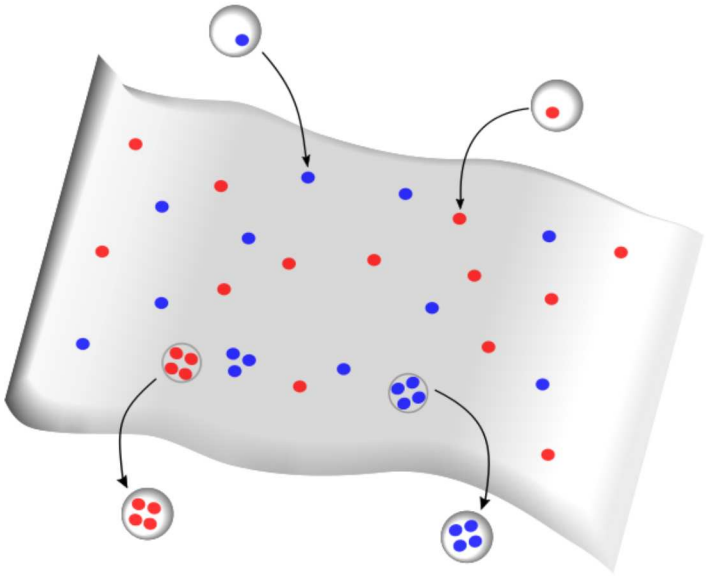


$$R_E \ll L \quad \Longrightarrow \quad N \ll \frac{D}{A_0 A_E \phi}$$

low-density regime

A Piras, E Floris, L Dall'Asta, AG, PRE (2023)

Many species



$$T = \phi^{-1}\rho \sim \left(\frac{A_E N}{A_0 D\,\phi}\right)^{1/2}$$

residence time

molecule density

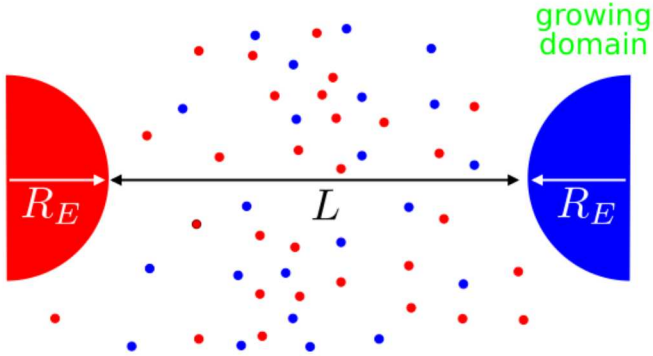
molecule area

diffusivity

total molecule flux

vesicle area

number of species

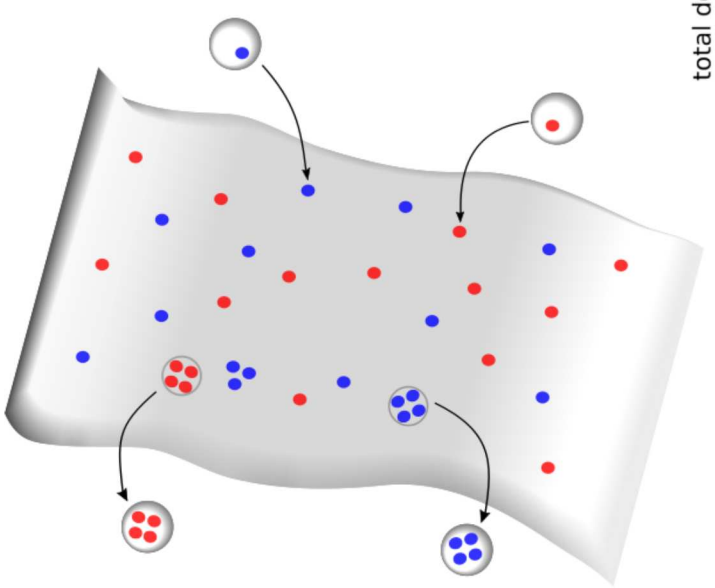


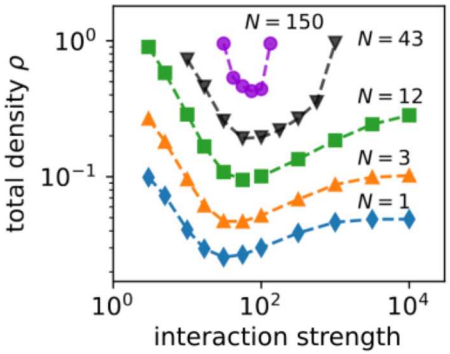
$$R_E \ll L \implies N \ll \frac{D}{A_0 A_E \phi}$$

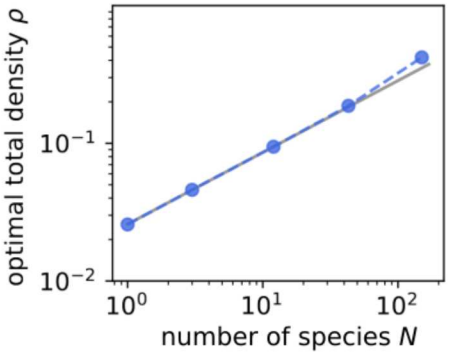
low-density regime

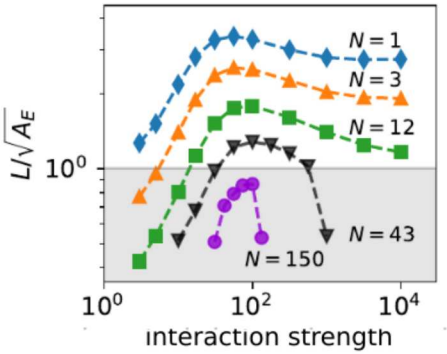
A Piras, E Floris, L Dall'Asta, AG, PRE (2023)

Many species





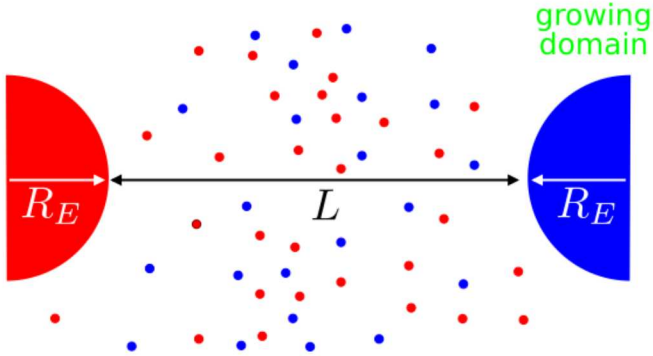




$$\rho^{\mathrm{opt}} \sim N^{0.51}$$

$$T = \phi^{-1}\rho \sim \left(\frac{A_E N}{A_0 D\,\phi}\right)^{1/2}$$

residence time · molecule density · molecule area · diffusivity · total molecule flux · vesicle area · number of species

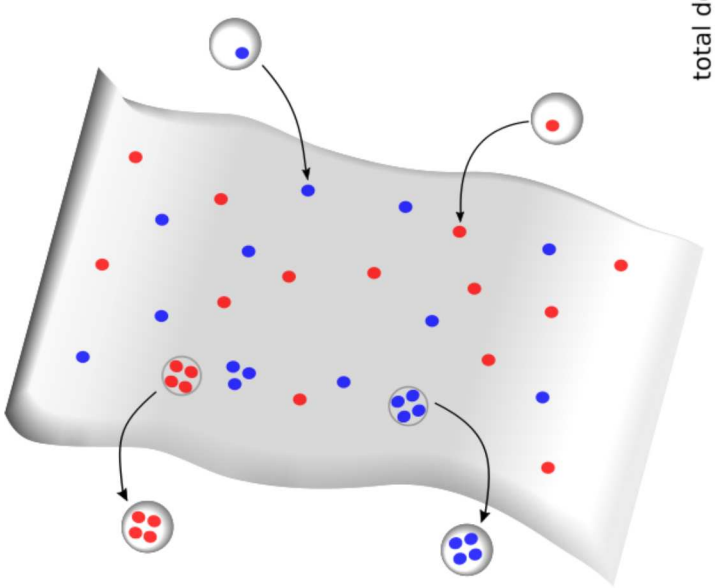


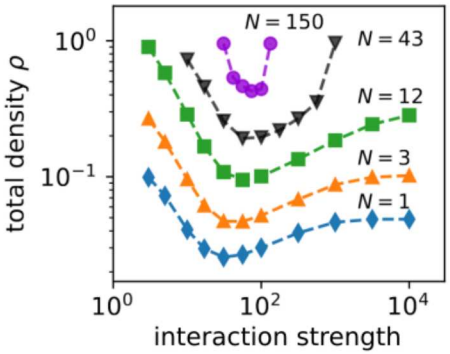
$$R_E \ll L \implies N \ll \frac{D}{A_0 A_E \phi}$$

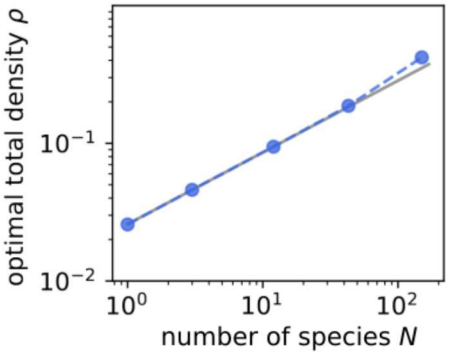
low-density regime

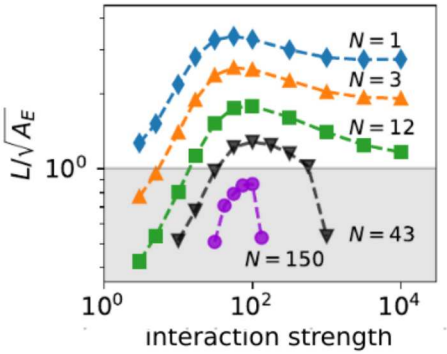
A Piras, E Floris, L Dall'Asta, AG, PRE (2023)

Many species







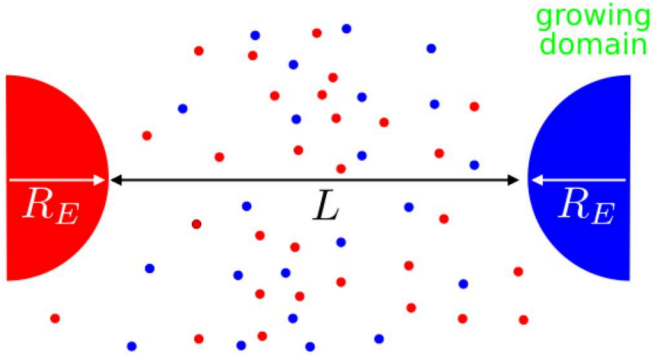


$$\rho^{\mathrm{opt}} \sim N^{0.51}$$

- Estimates suggest that *many distinct molecular species* may be sorted in parallel on lipid membranes

$$T = \phi^{-1}\rho \sim \left(\frac{A_E N}{A_0 D\,\phi}\right)^{1/2}$$

residence time; molecule density; molecule area; diffusivity; total molecule flux; vesicle area; number of species

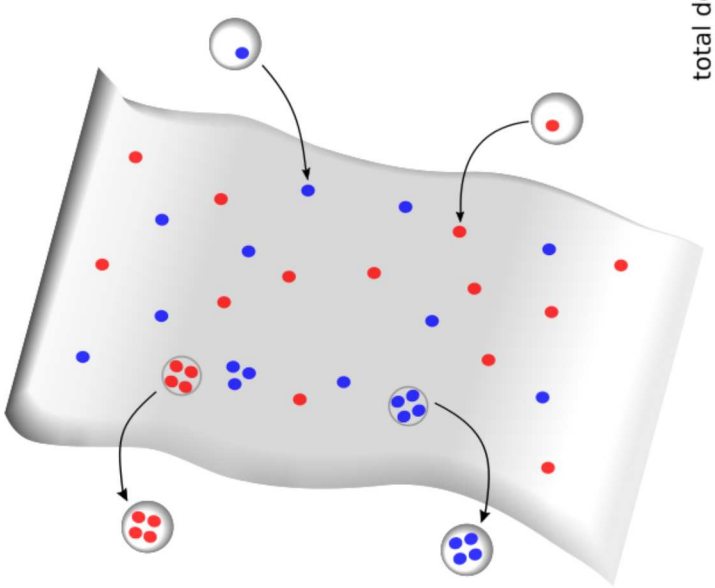


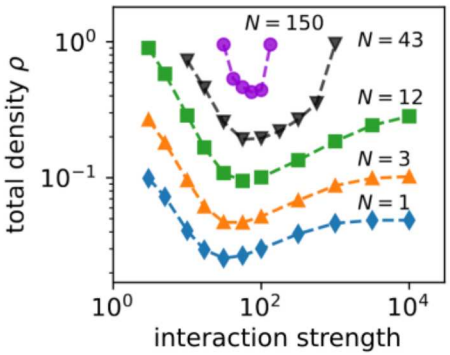
$$R_E \ll L \implies N \ll \frac{D}{A_0 A_E \phi}$$

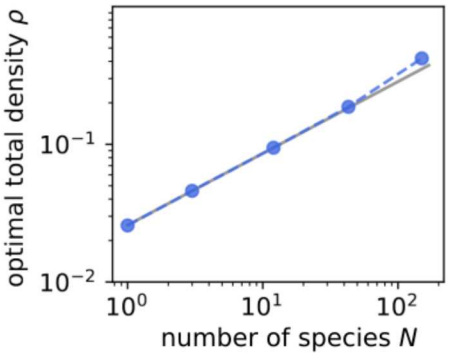
low-density regime

A Piras, E Floris, L Dall'Asta, AG, PRE (2023)

Many species

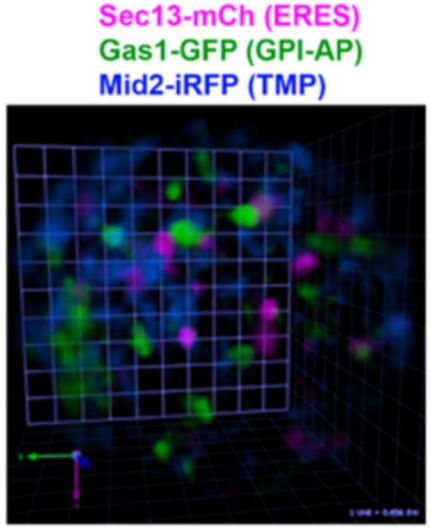




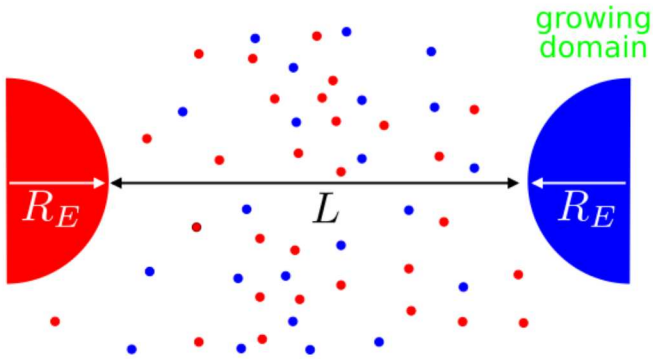


$$\rho^{\mathrm{opt}} \sim N^{0.51}$$

- Estimates suggest that *many distinct molecular species* may be sorted in parallel on lipid membranes



S Rodriguez-Gallardo et al, Sci Adv (2020)



$$R_E \ll L \implies N \ll \frac{D}{A_0 A_E \phi}$$

low-density regime

$$T = \phi^{-1}\rho \sim \left(\frac{A_E N}{A_0 D\,\phi}\right)^{1/2}$$

residence time; molecule density; molecule area; diffusivity; total molecule flux; vesicle area; number of species

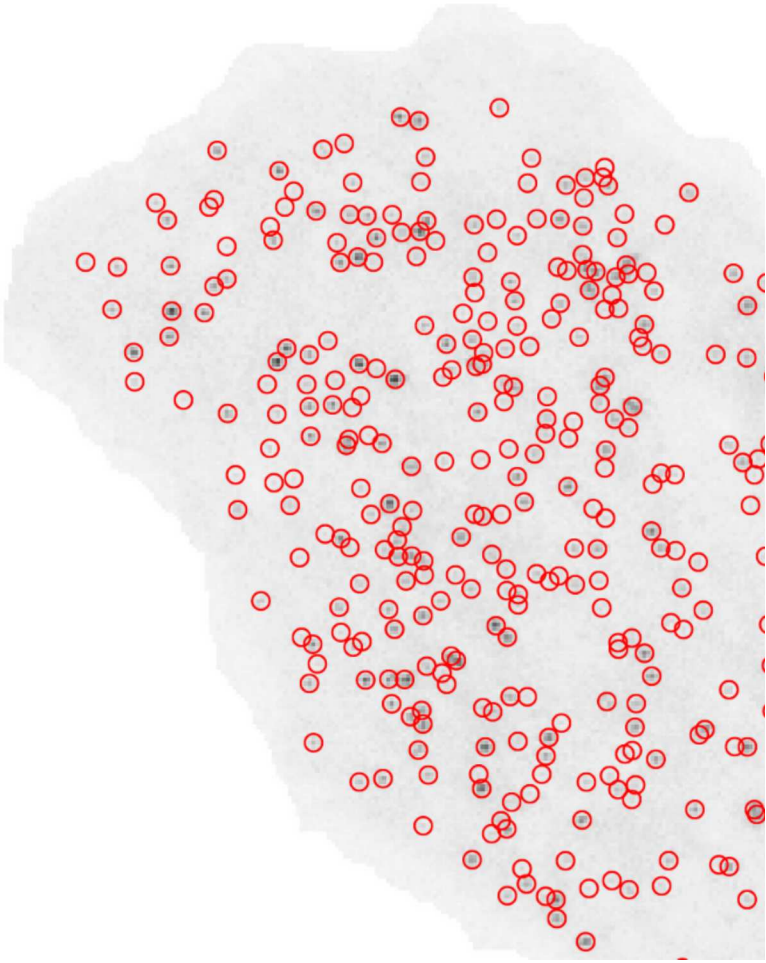
A Piras, E Floris, L Dall'Asta, AG, PRE (2023)

Summary

- Phenomenological theory of molecular sorting

  phase separation on cell membranes + domain-induced vesicle nucleation

- Approximately solvable, scaling laws
- Optimal regime for intermediate values of aggregation strength
- Experiments suggest that living cells work close to the optimal regime
- Evidence that molecular sorting is driven by a phase separation process
- A typical membrane may sort in parallel a large number of distinct species

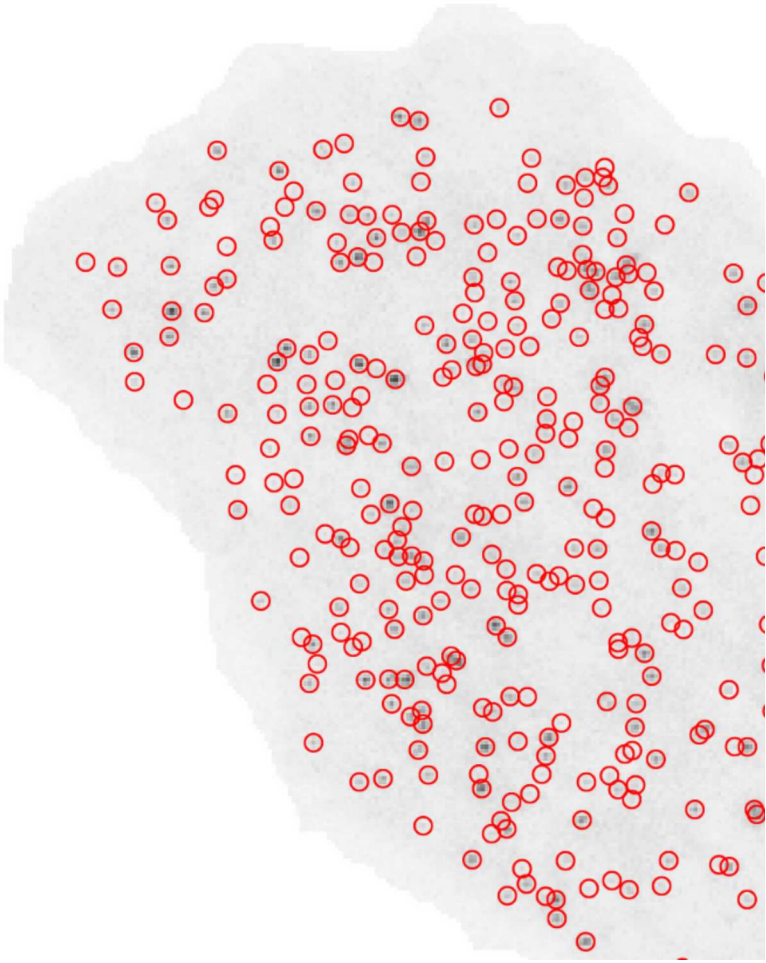


Summary

- Phenomenological theory of molecular sorting

  phase separation on cell membranes + domain-induced vesicle nucleation

- Approximately solvable, scaling laws
- Optimal regime for intermediate values of aggregation strength
- Experiments suggest that living cells work close to the optimal regime
- Evidence that molecular sorting is driven by a phase separation process
- A typical membrane may sort in parallel a large number of distinct species



Outlook

- Curvature
- Fluctuations
- Tuning aggregation strength with light, drugs, gene editing
- Misregulation of molecular sorting in genetic diseases