Computación con GPUs: Aplicación a la simulación de membranas biológicas

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Molecular Dynamics (MD) simulations

One of the most widely used techniques for studying condensed systems (fluids, solids,…)

Access to equilibrium and dynamical properties

Some old and recent applications:

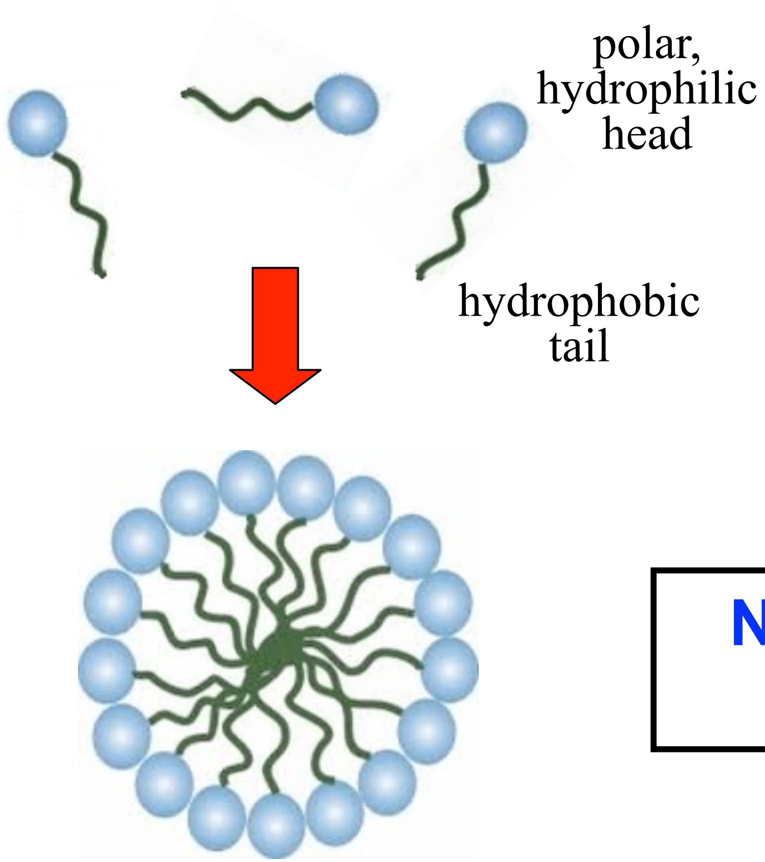
- Liquids (first applications ‘40, ‘60, …)
- Complex fluids (SOFT MATTER):

  liquid crystals, colloids, amphiphilic systems,…

→ Biological systems (macromolecules, proteins,…)

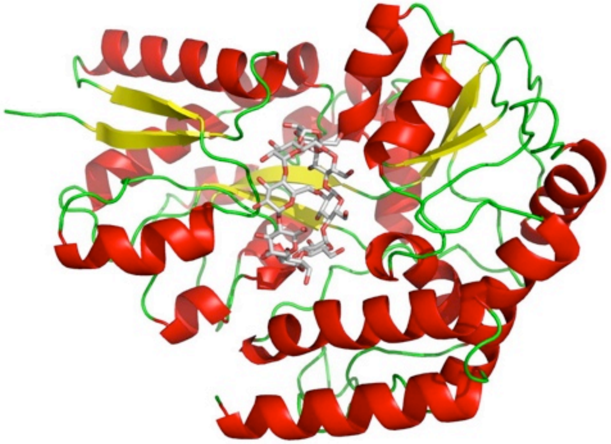
Limiting factors in complex fluid applications: mesoscales

- *Length* scales (not nm but 100 nm – 1 μm)
- *Time* scales (not ps but ns – μs)



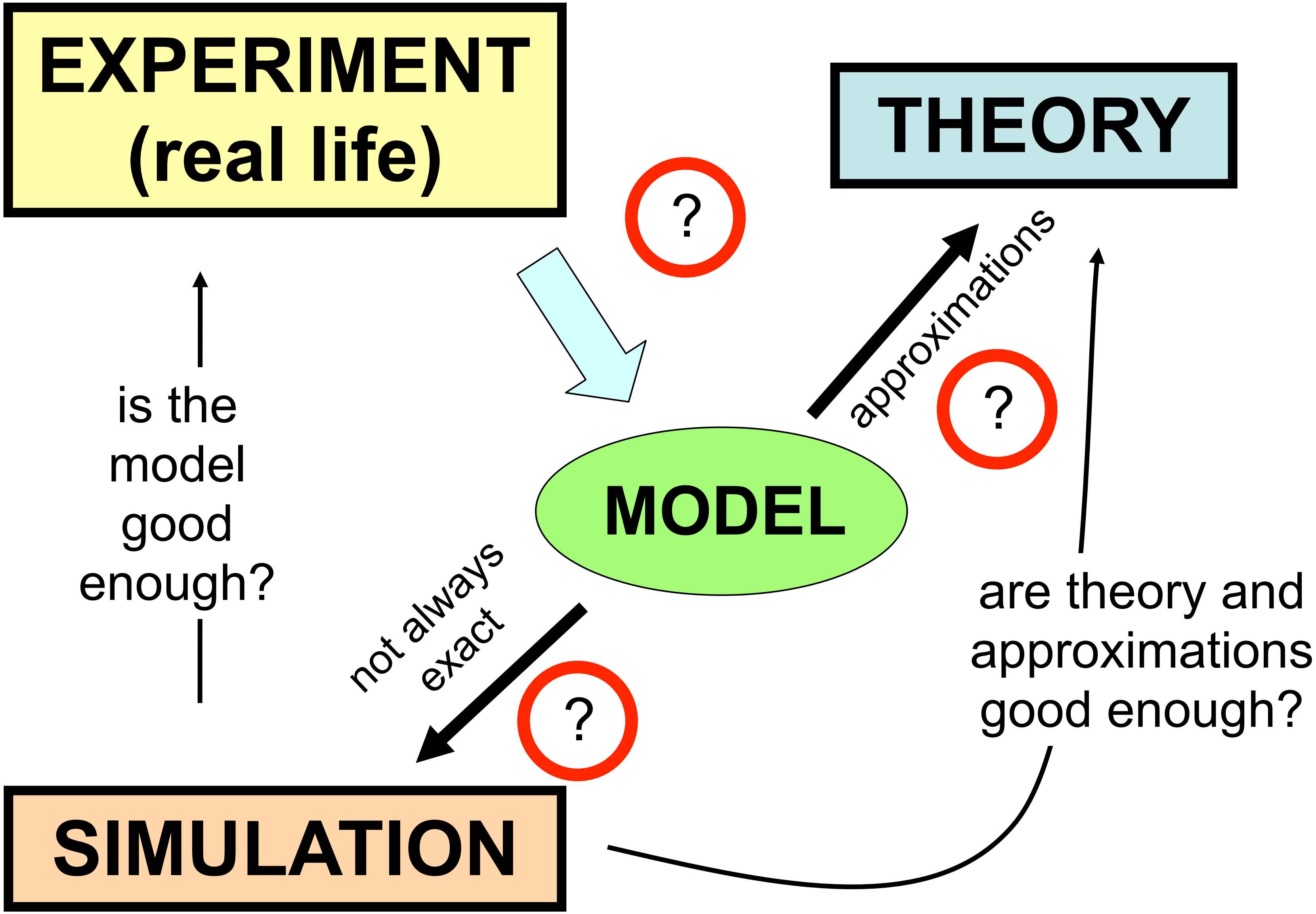
MICELLE FORMATION

PROTEIN DYNAMICS



NEED FOR COARSE GRAINING

MESOSCOPIC MODELS



EXPERIMENT (real life)

THEORY

?

approximations

?

is the model good enough?

MODEL

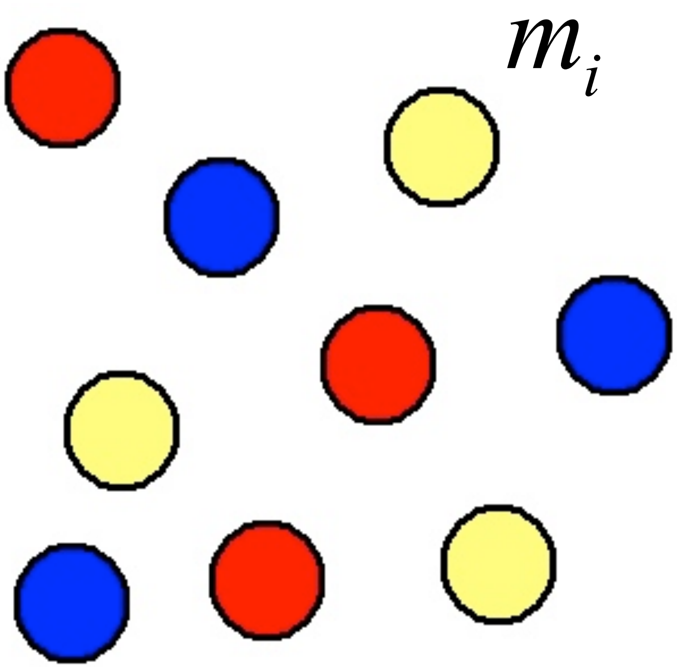
not always exact

?

are theory and approximations good enough?

SIMULATION

MD (classical) simulations: basic facts



We solve classical Newton's equations of motion and obtain dynamical trajectories from the forces:

Hamiltonian system (energy conserved)

$$\begin{cases} \dfrac{d\mathbf{r}_i}{dt} = \mathbf{v}_i, \\ m_i \dfrac{d\mathbf{v}_i}{dt} = \mathbf{F}_i, \end{cases}$$

$$i = 1, 2, \ldots, N$$

$$\mathbf{F}_i = -\nabla_i \Phi$$

potential energy function

- The potential energy Φ has to be specified
- A finite-difference scheme is used

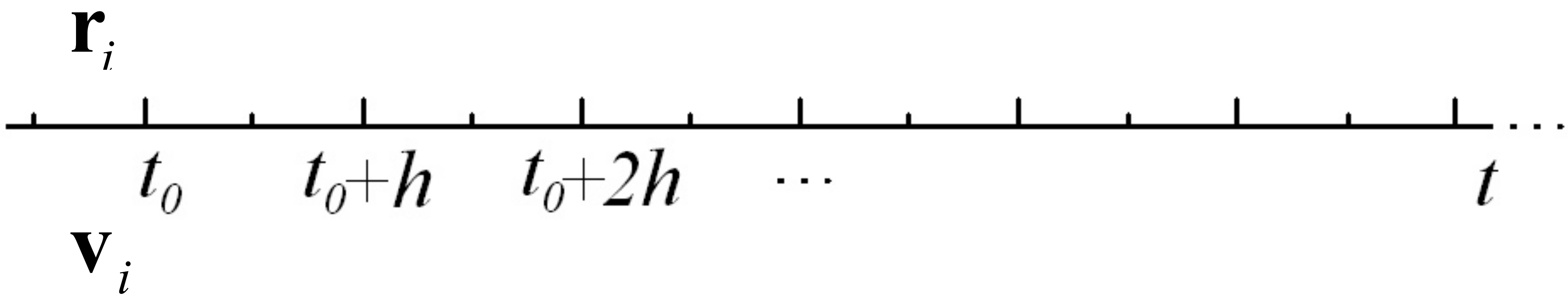
$$\Phi = \Phi\left(\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_N\right)$$

Finite-difference scheme: **Verlet (leap-frog) algorithm**

$$t \text{ ® } t_0, t_1, t_2, \ldots \quad t_n = nh, \;\; n = 0,1,2,\ldots$$

$$h: \text{ MD simulation step}$$

$$\begin{cases} \mathbf{v}_i\left(t_n + \dfrac{h}{2}\right) = \mathbf{v}_i\left(t_n - \dfrac{h}{2}\right) + \dfrac{h}{m_i}\mathbf{F}_i(t_n), \\ \\ \mathbf{r}_i(t_n + h) = \mathbf{r}_i(t_n) + h\mathbf{v}_i\left(t_n + \dfrac{h}{2}\right) \end{cases} \qquad i = 1, 2, \ldots, N$$



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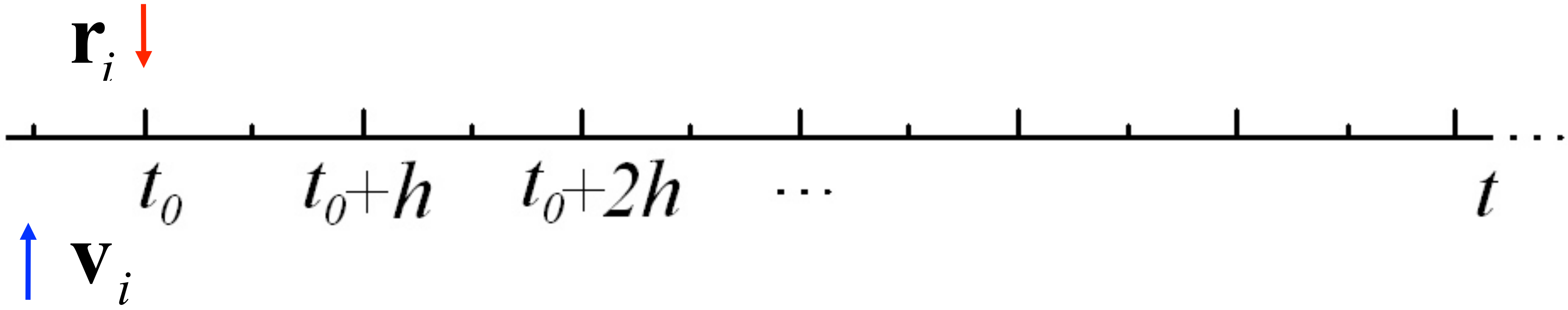

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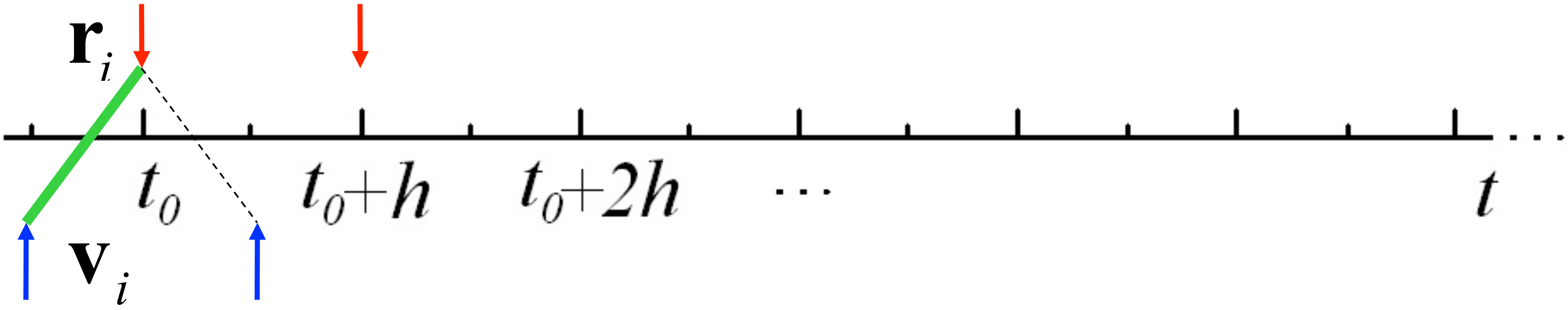

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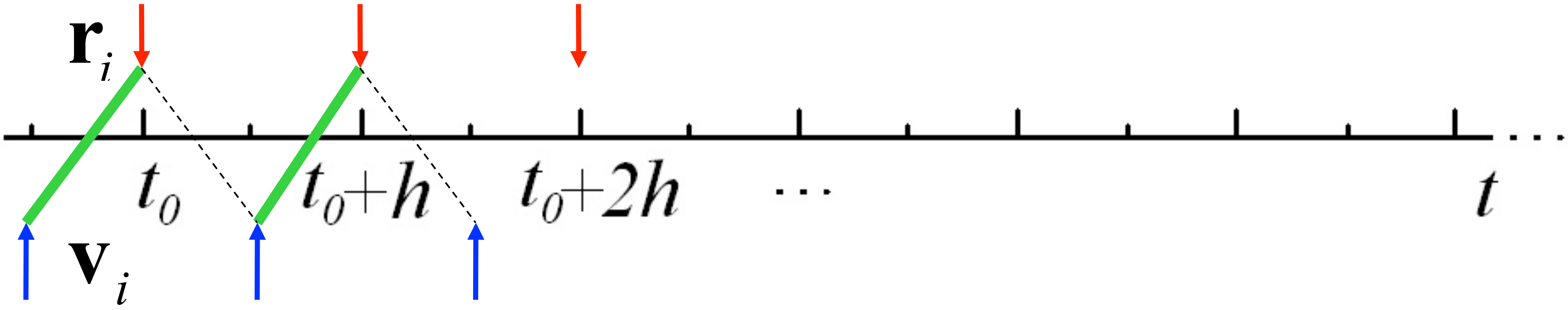

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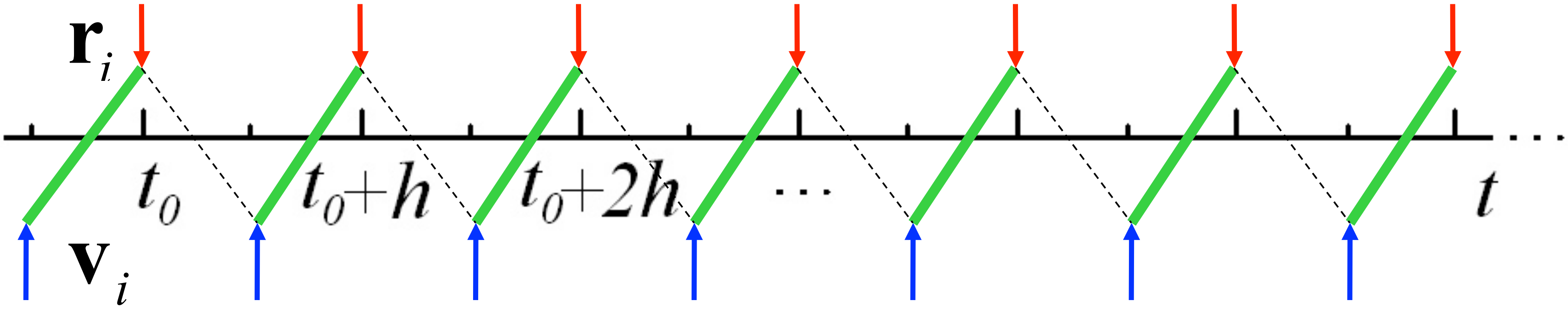

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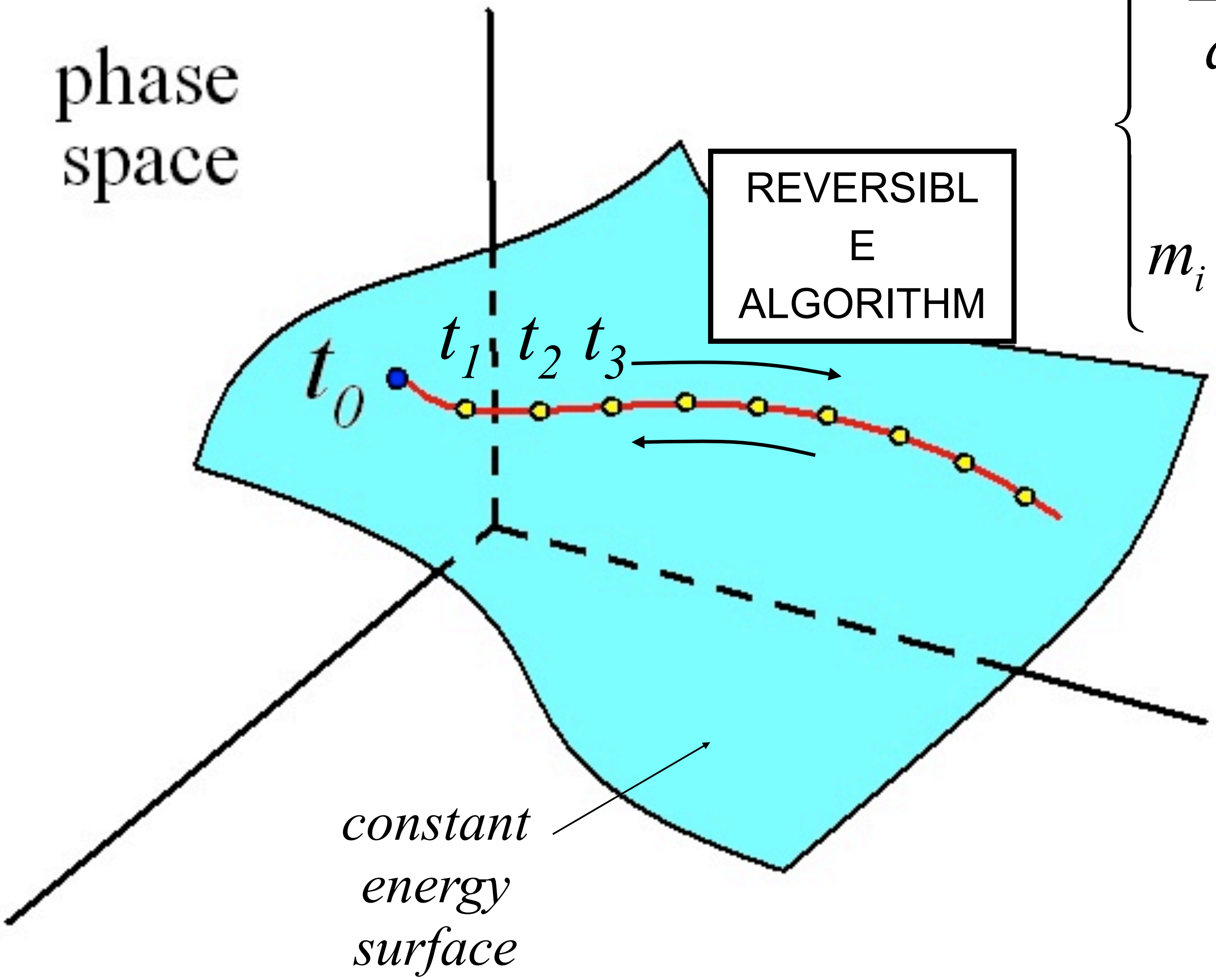


$$\begin{pmatrix} \mathbf{v}_i\left(t_n+\frac{h}{2}\right) \\ \\ \mathbf{r}_i\left(t_n+h\right) \end{pmatrix} = J \begin{pmatrix} \mathbf{v}_i\left(t_n-\frac{h}{2}\right) \\ \\ \mathbf{r}_i\left(t_n\right) \end{pmatrix}$$

$$\det J = 1$$

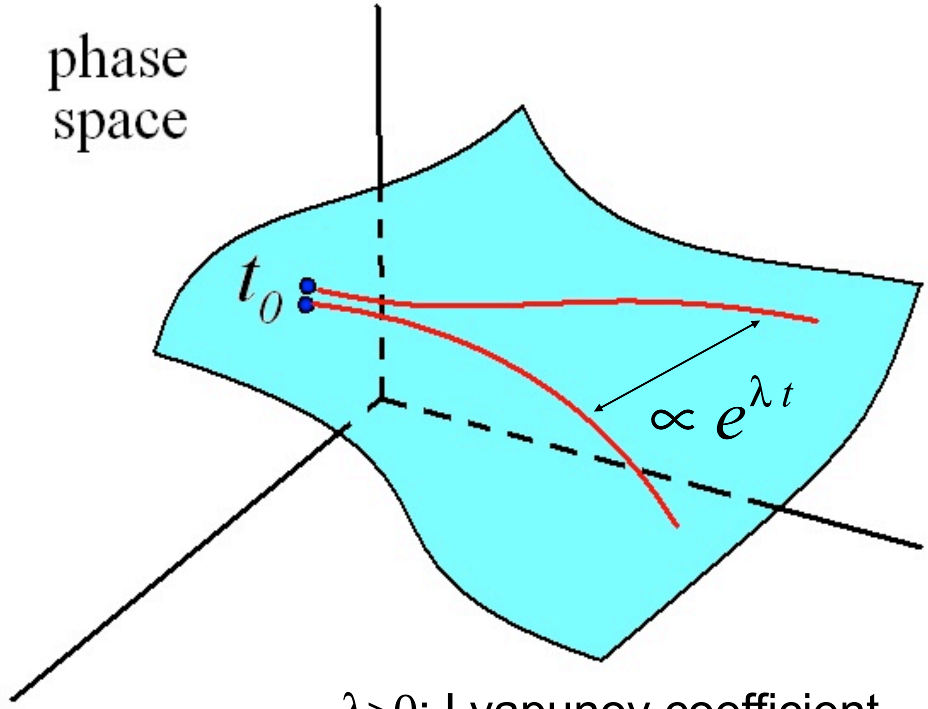
SYMPLECTIC
ALGORITHM

Space volume is conserved (as required by Liouville's theorem of Statistical Mechanics)

Classical many-body systems are intrinsically CHAOTIC

Therefore the algorithm cannot reproduce trajectories exactly

Only requirements are *reversibility* and *symplecticity*



$\lambda>0$: Lyapunov coefficient

Thermodynamic, dynamic, microscopic properties result as TIME AVERAGES over phase space trajectories. For example, the energy:

$$E = \langle H \rangle = \frac{1}{\tau} \sum_n H_n$$

Extensions of constant-energy MD:

- **Isothermal MD:**

the system is coupled to an external heat-bath (thermostat at specific temperature *T*), with which energy is exchanged to maintain a constant temperature

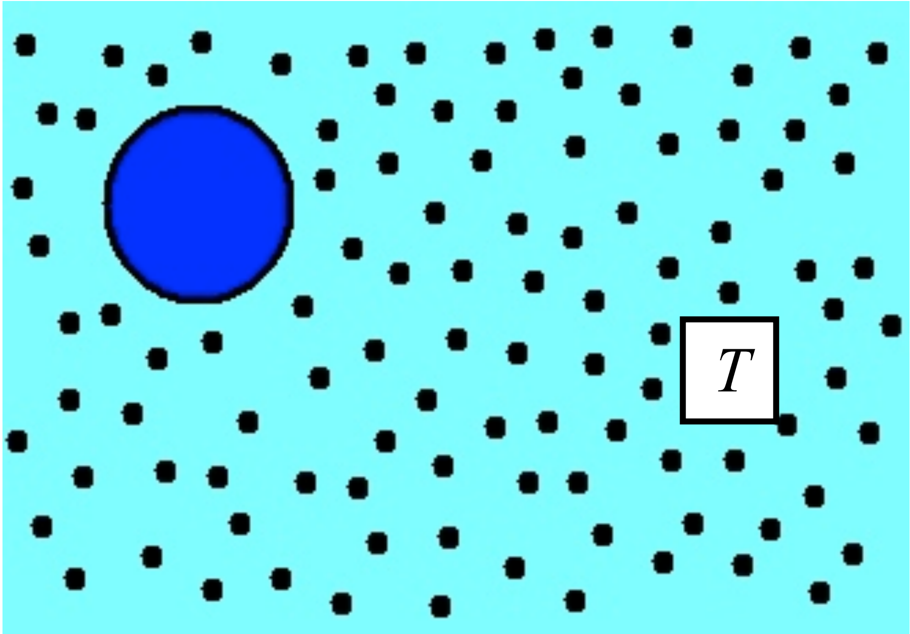
<u>Example</u>: Langevin thermostat

random force

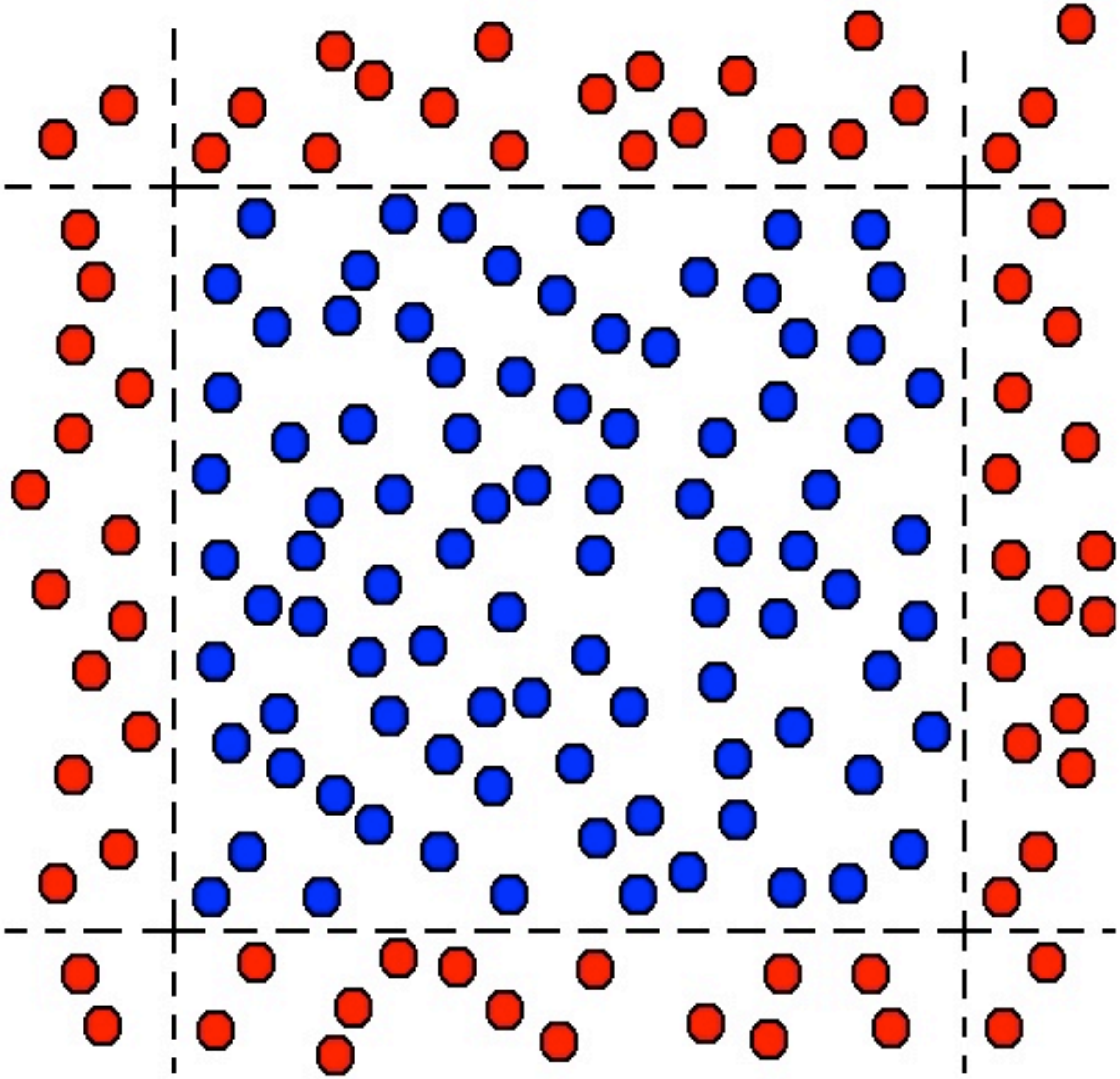
$$m_i \frac{d\mathbf{v}_i}{dt} = -\xi \, \mathbf{v}_i + \mathbf{g}_i + \mathbf{F}_i$$

friction term

deterministic force



periodic boundary conditions (2D)



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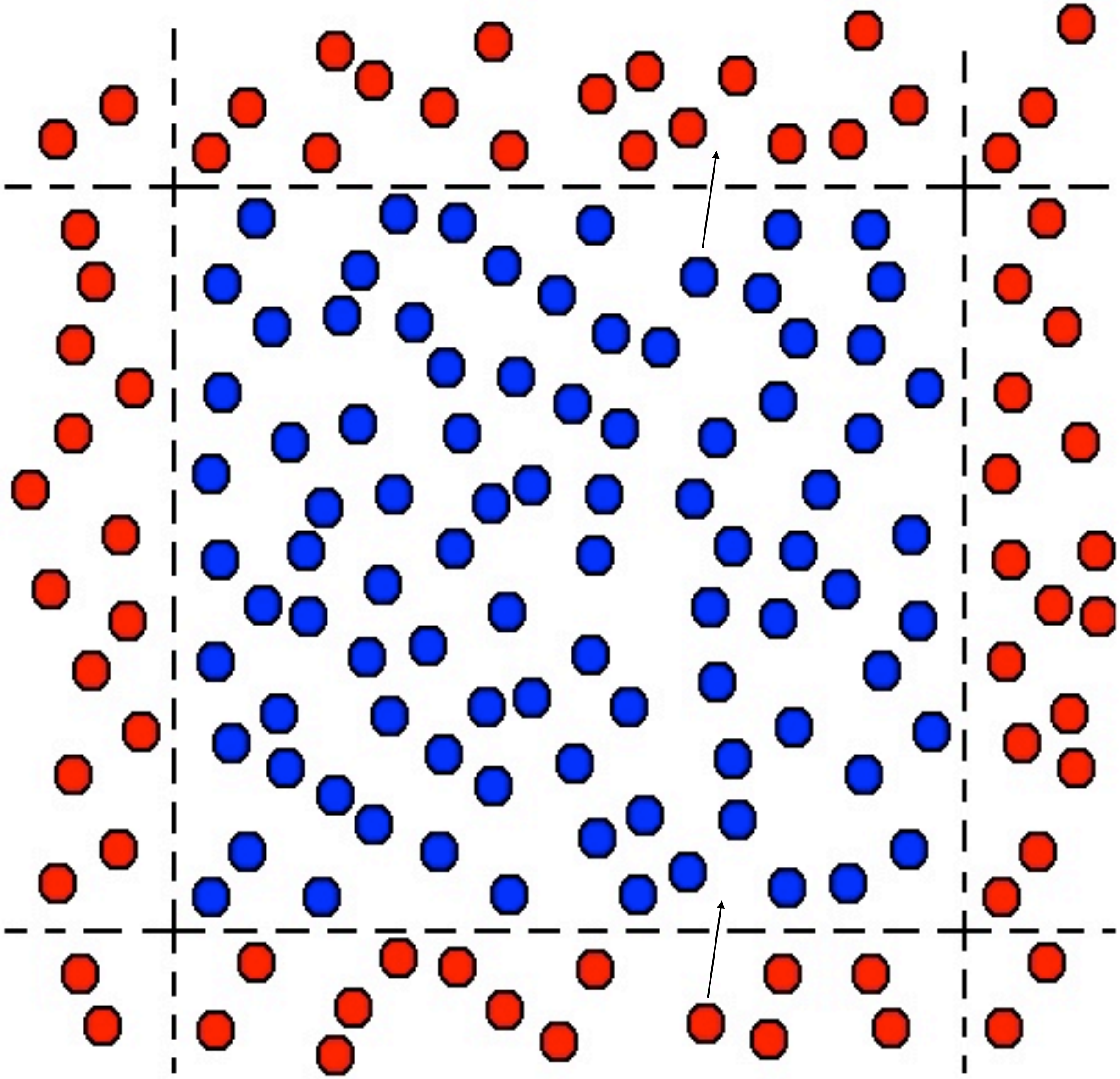

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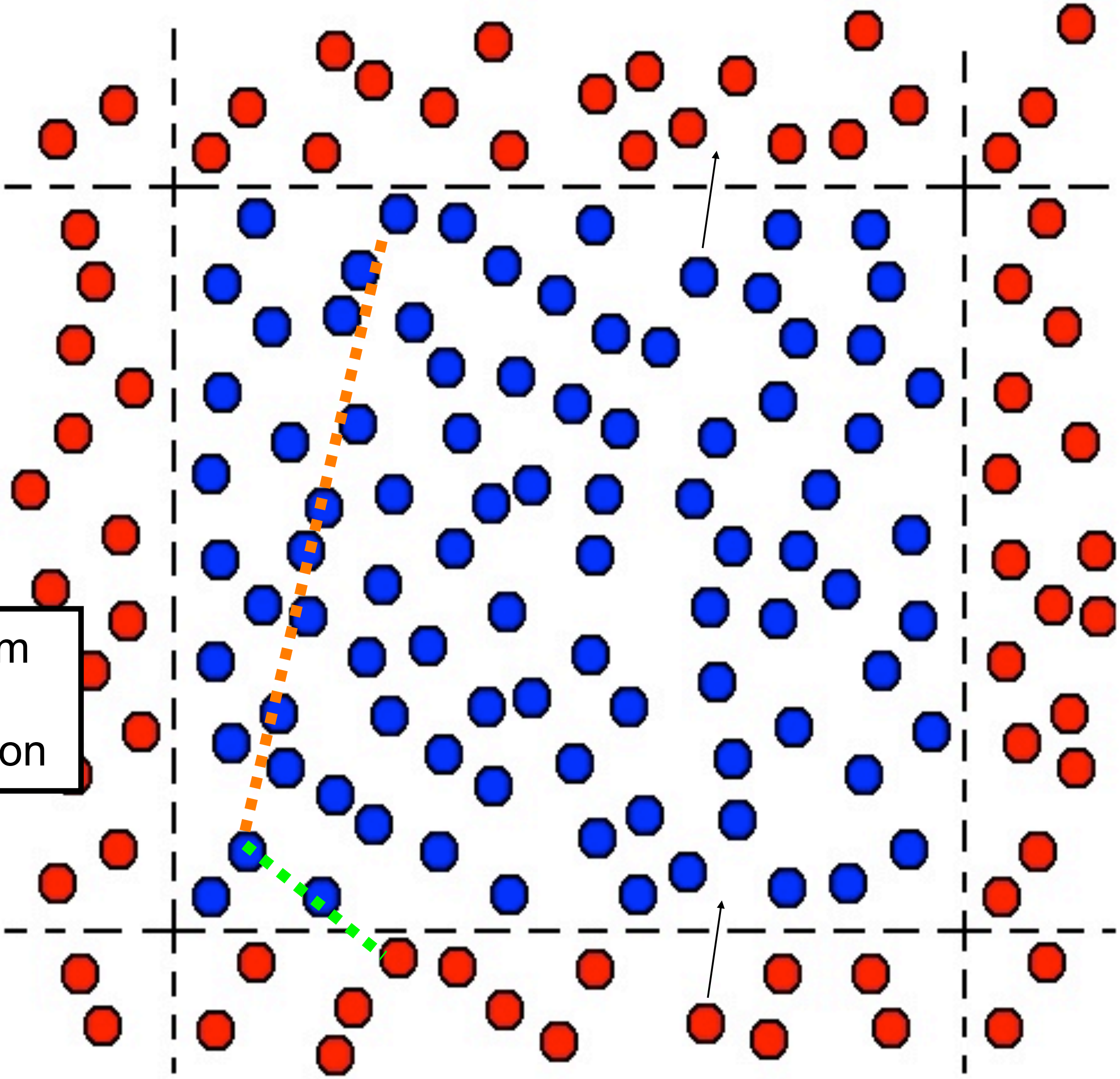


minimum image convention

The time-consuming part of the calculation is the force:

$$\mathbf{F}_{ij} = \mathbf{F}_{ji}$$

$$m_i \frac{d\mathbf{v}_i}{dt} = \mathbf{F}_i \xrightarrow{\text{assuming two-body forces}} \mathbf{F}_i = \sum_{j \neq i} \mathbf{F}_{ij}$$

Force calculation amounts to up to 90% of CPU time required in whole calculation

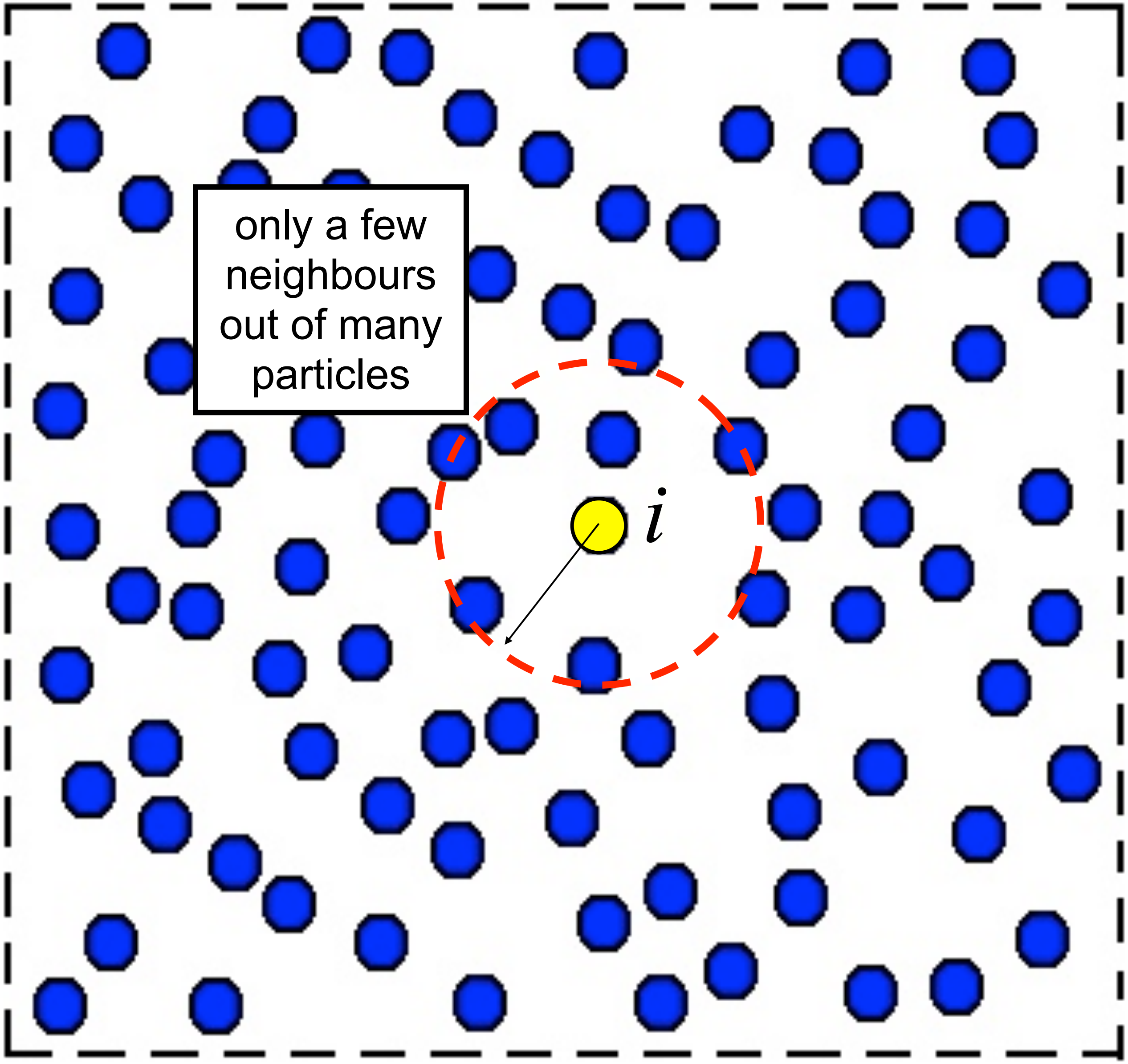
⇨ mayor barrier to large-scale simulations

need for new algorithms and techniques

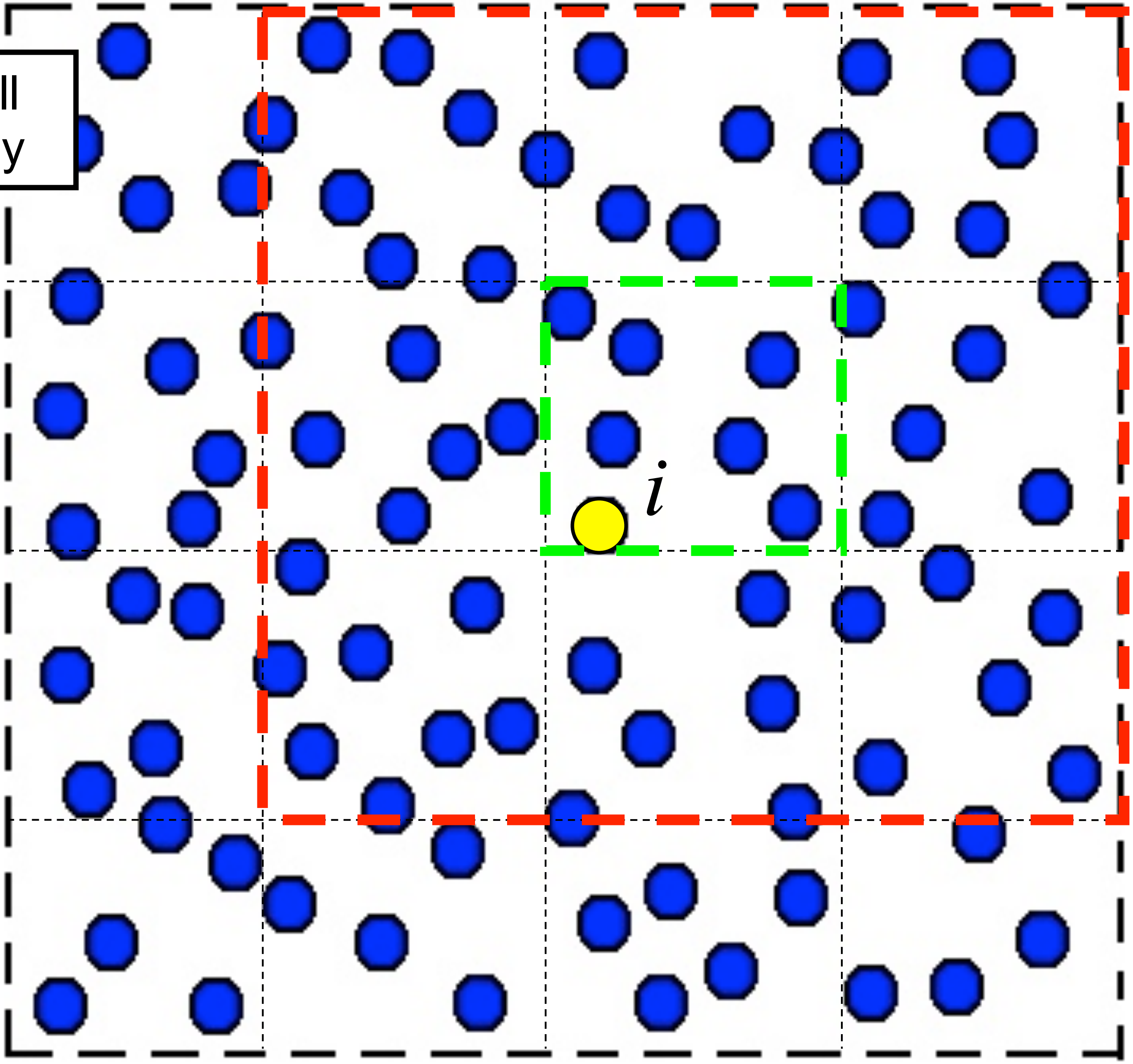
The sum is over all neighbours within the interaction distance. But, which are they?

⇩

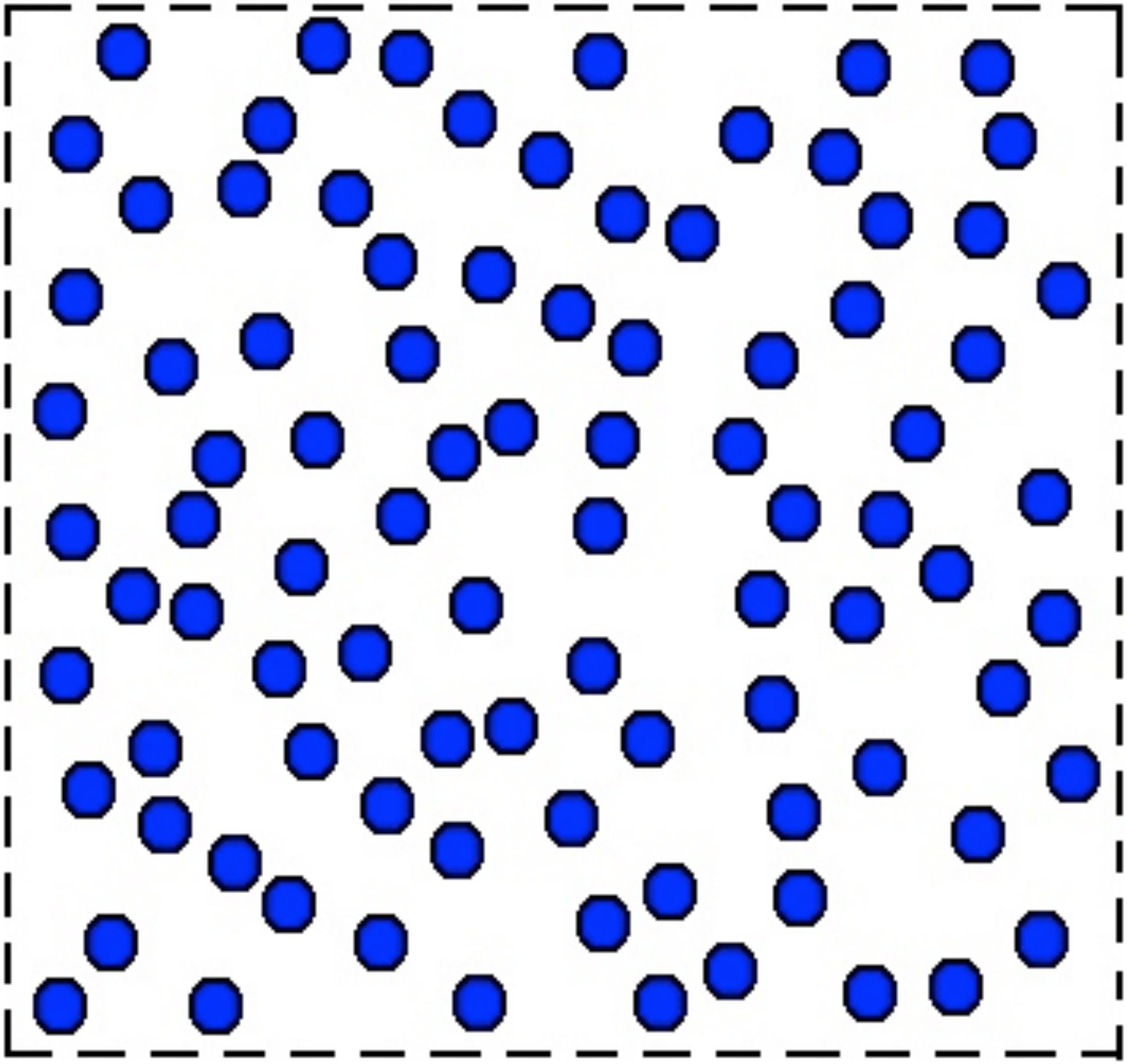
Identify all distinct pairs



only a few neighbours out of many particles link-cell strategy



parallelisation: domain decomposition



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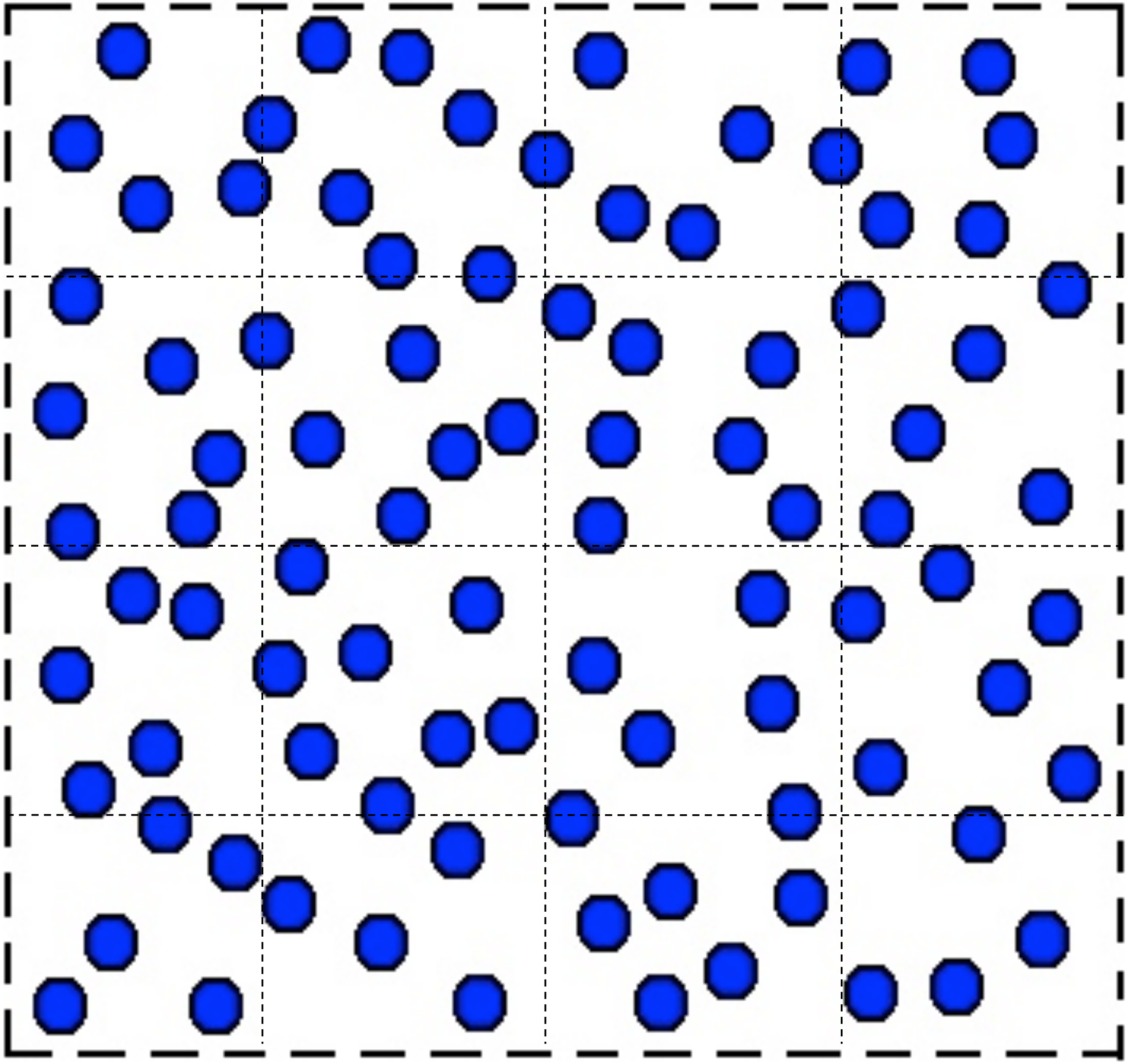

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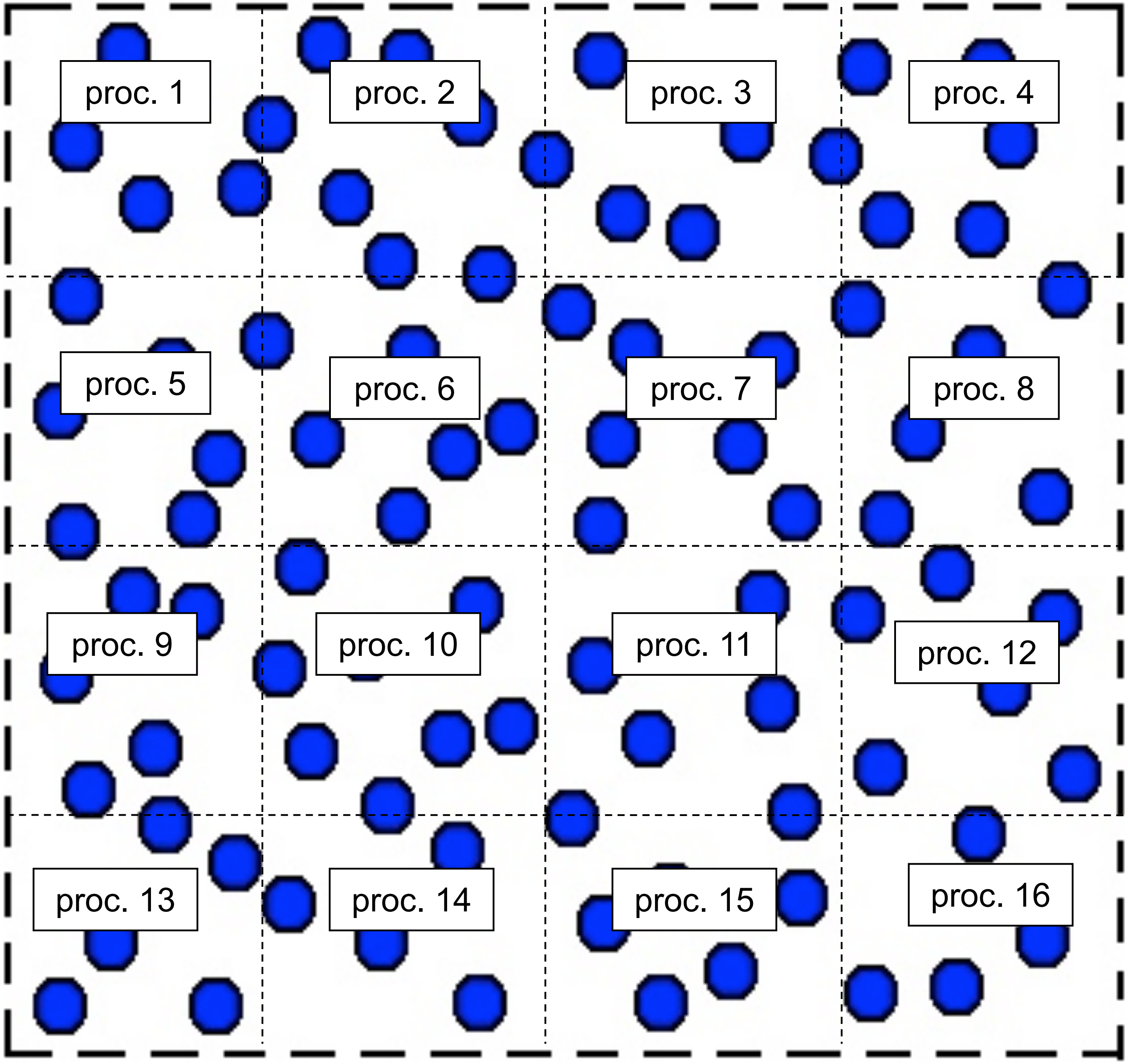

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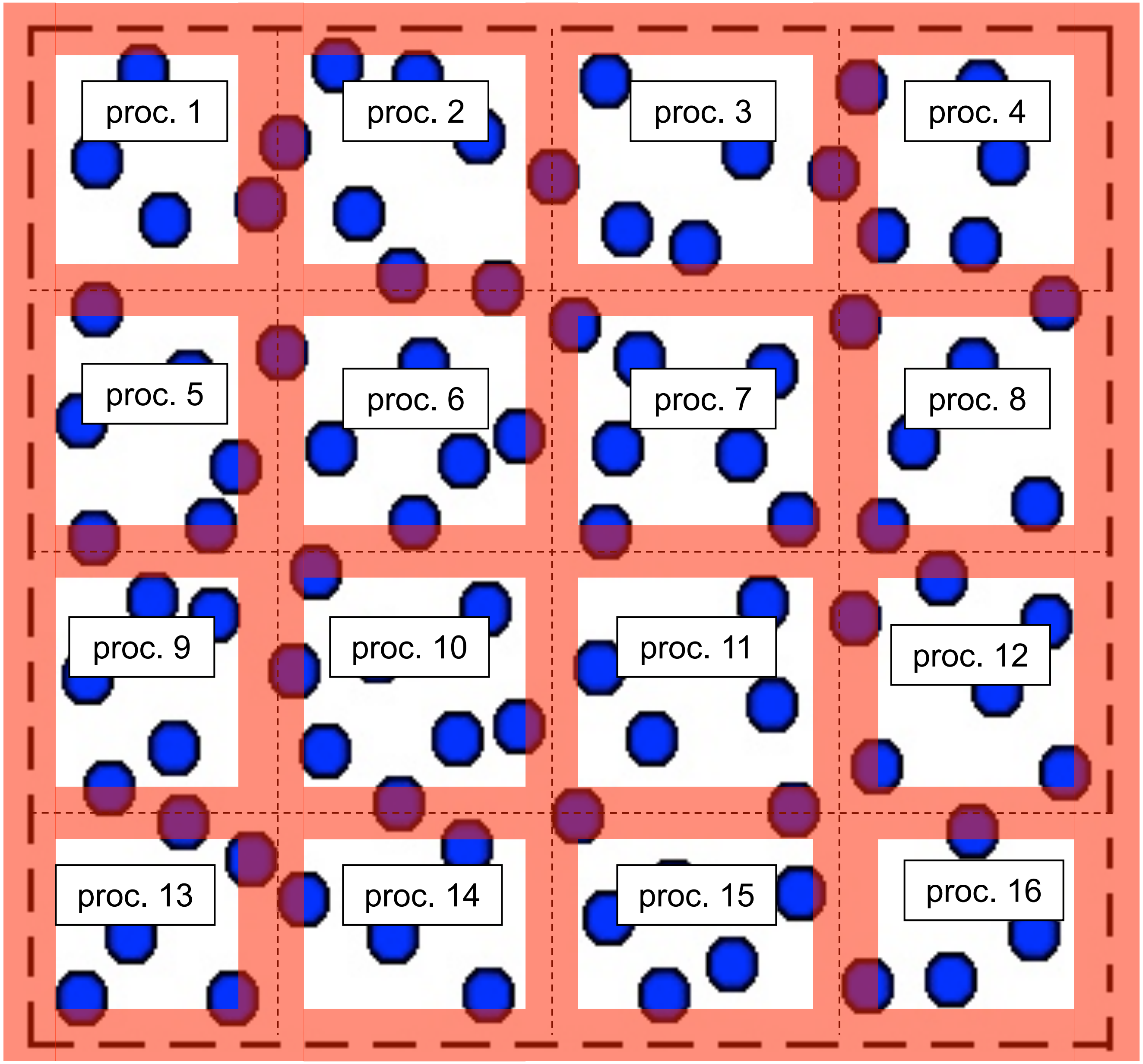


- **GPU (Graphics Processing Unit)**

Specialised processor for graphics rendering

(multithreaded, data parallel co-processor)

GPGPU: General purpose computing on GPU

GeForce 8800 GTX (128 cores)

Tesla C1060 (240 cores)

- **CUDA (Compute Unified Device Architecture)**

Arquitectura para la programación en paralelo de la empresa NVIDIA

Permite acceder a la GPU para calcular como si fuera una CPU

Programables inicialmente en OpenGL (orientado a gráficos)

CUDA C: lenguaje C extendido

Actualmente también admite códigos en C++, FORTRAN, Java…

Página web de CUDA en NVIDIA:

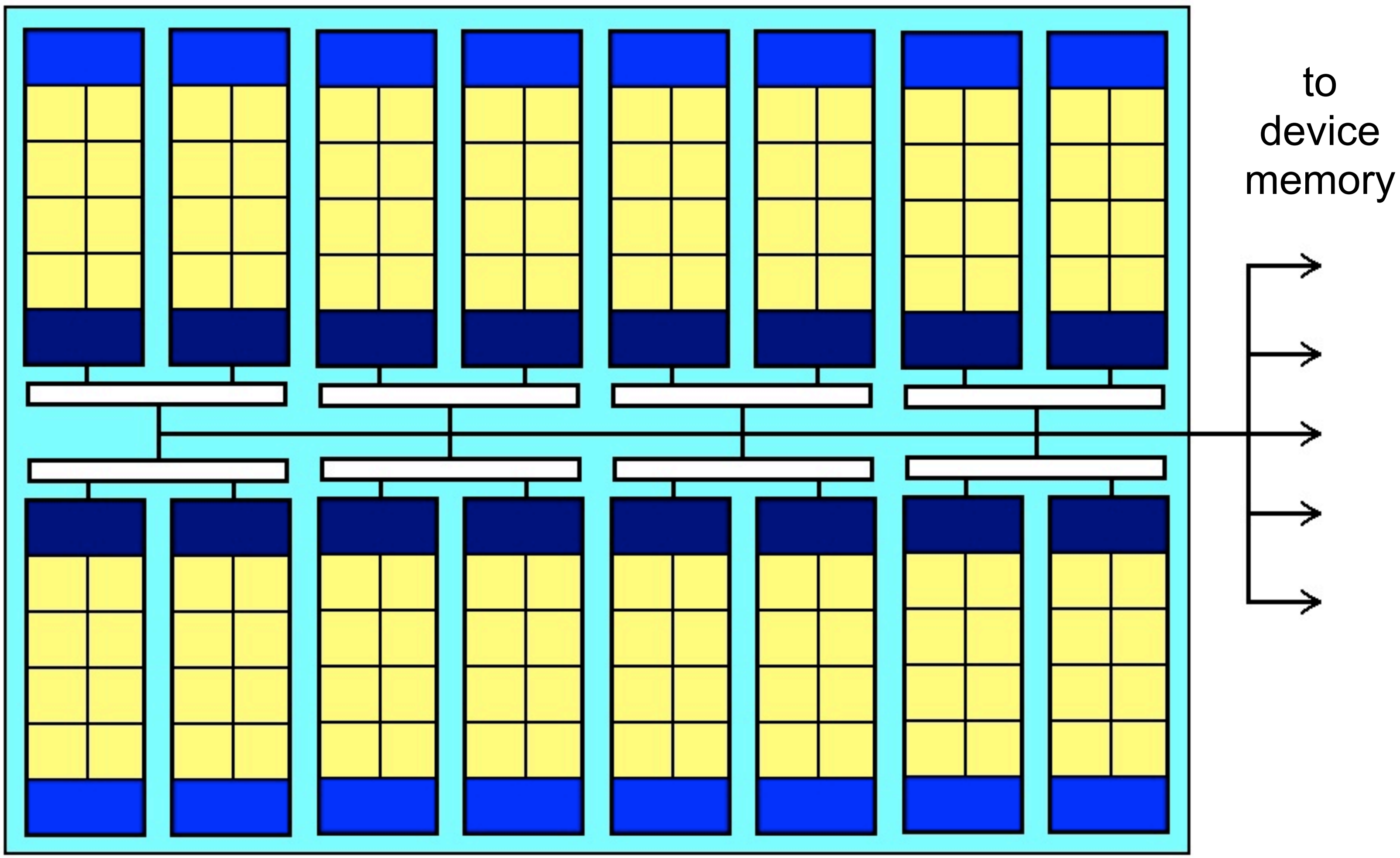
`http://www.nvidia/com/object/cuda_home.html`

Curso de programación en CUDA en UIUC:

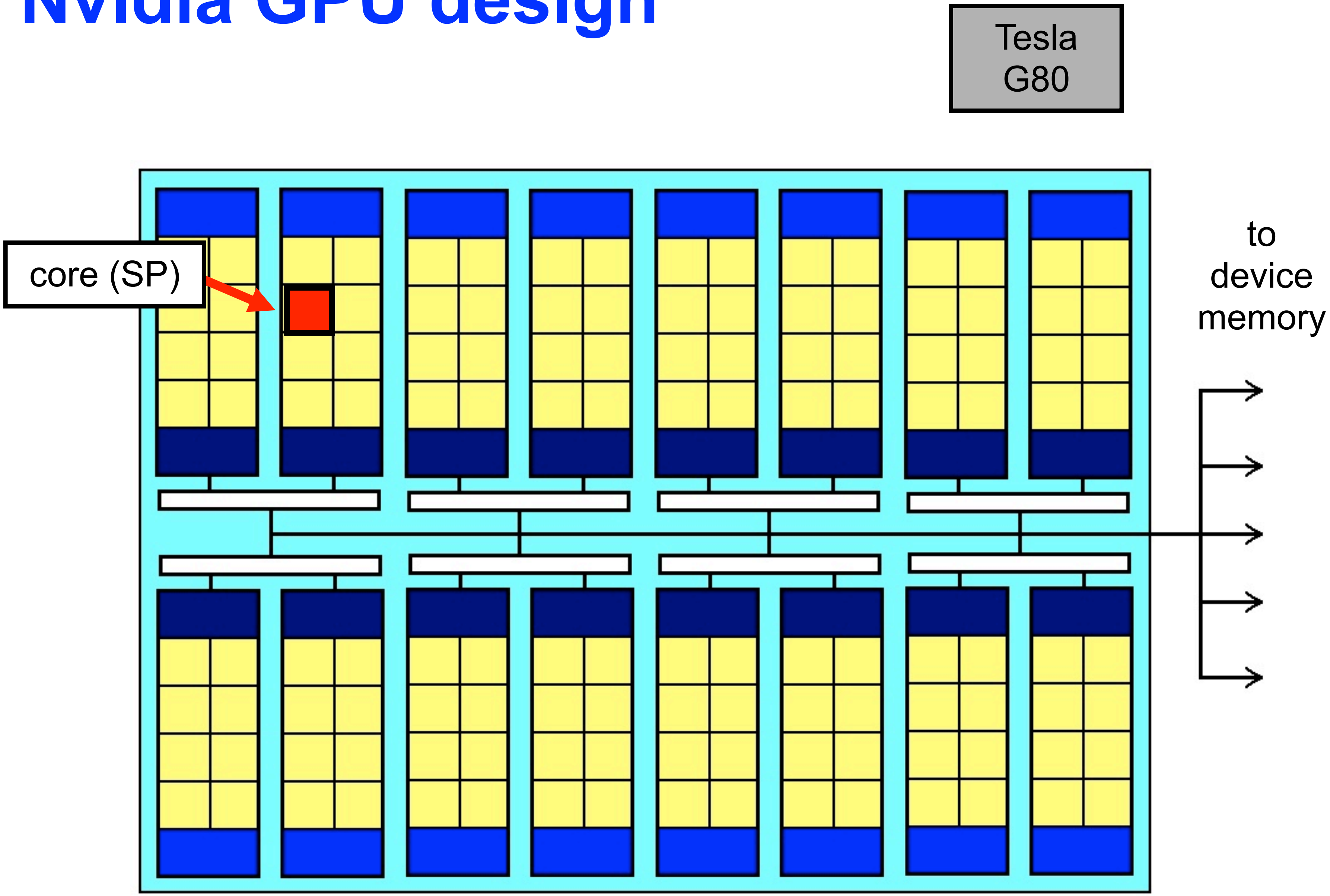
`http://courses.ece.illinois.edu/ece498/al`

Nvidia GPU design

Tesla
G80



Nvidia GPU design



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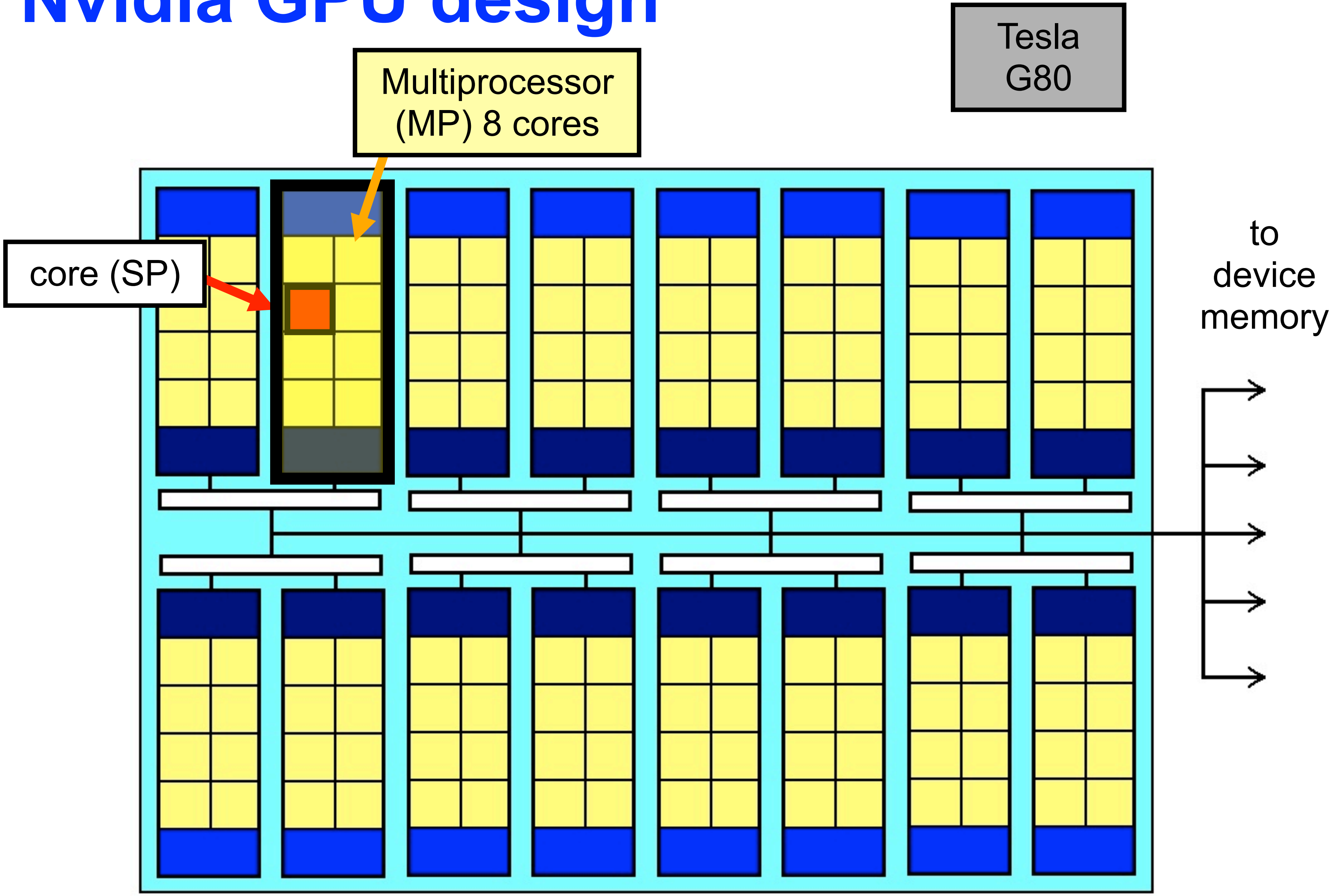
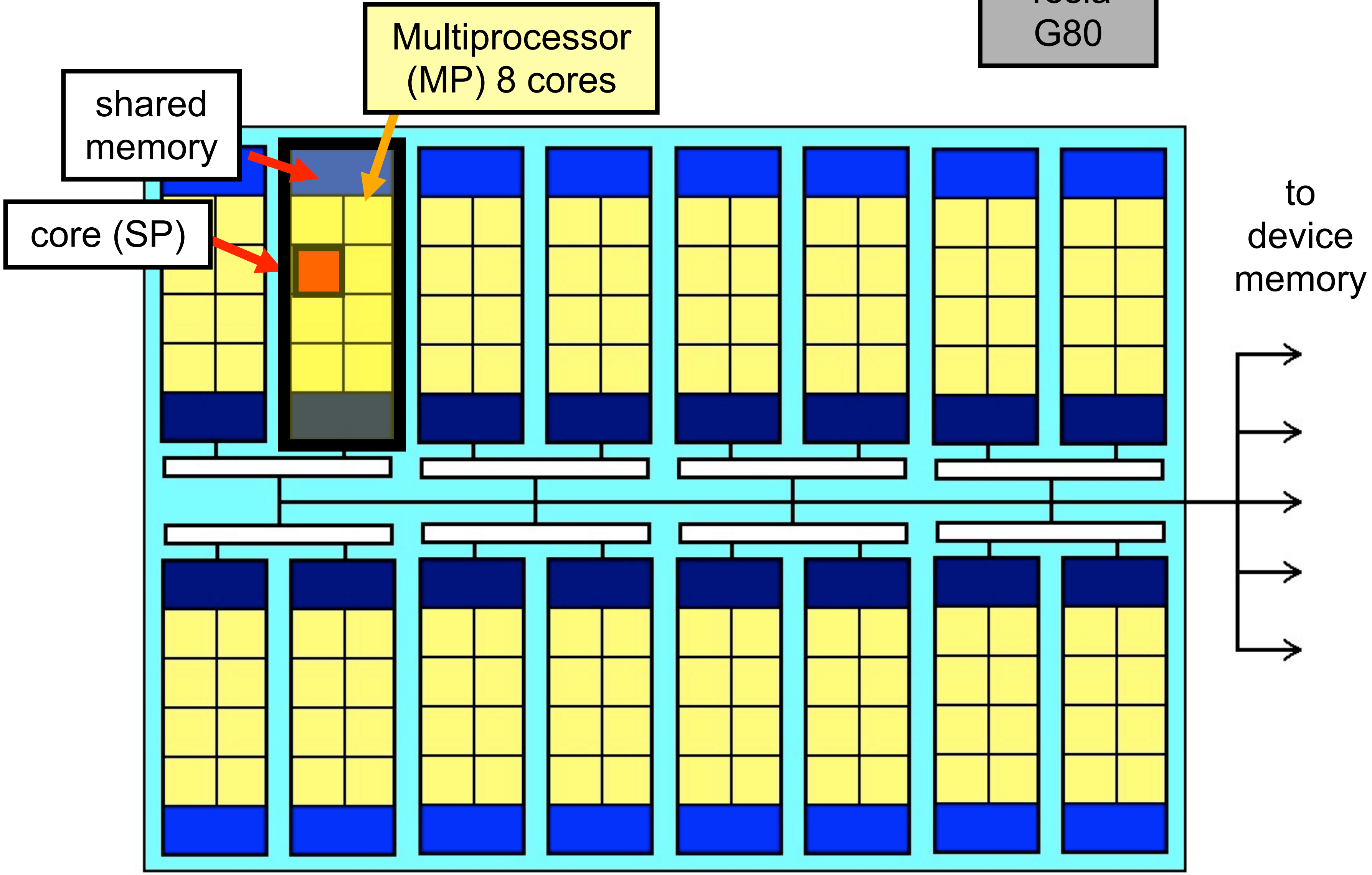


Nvidia GPU design

Tesla
G80



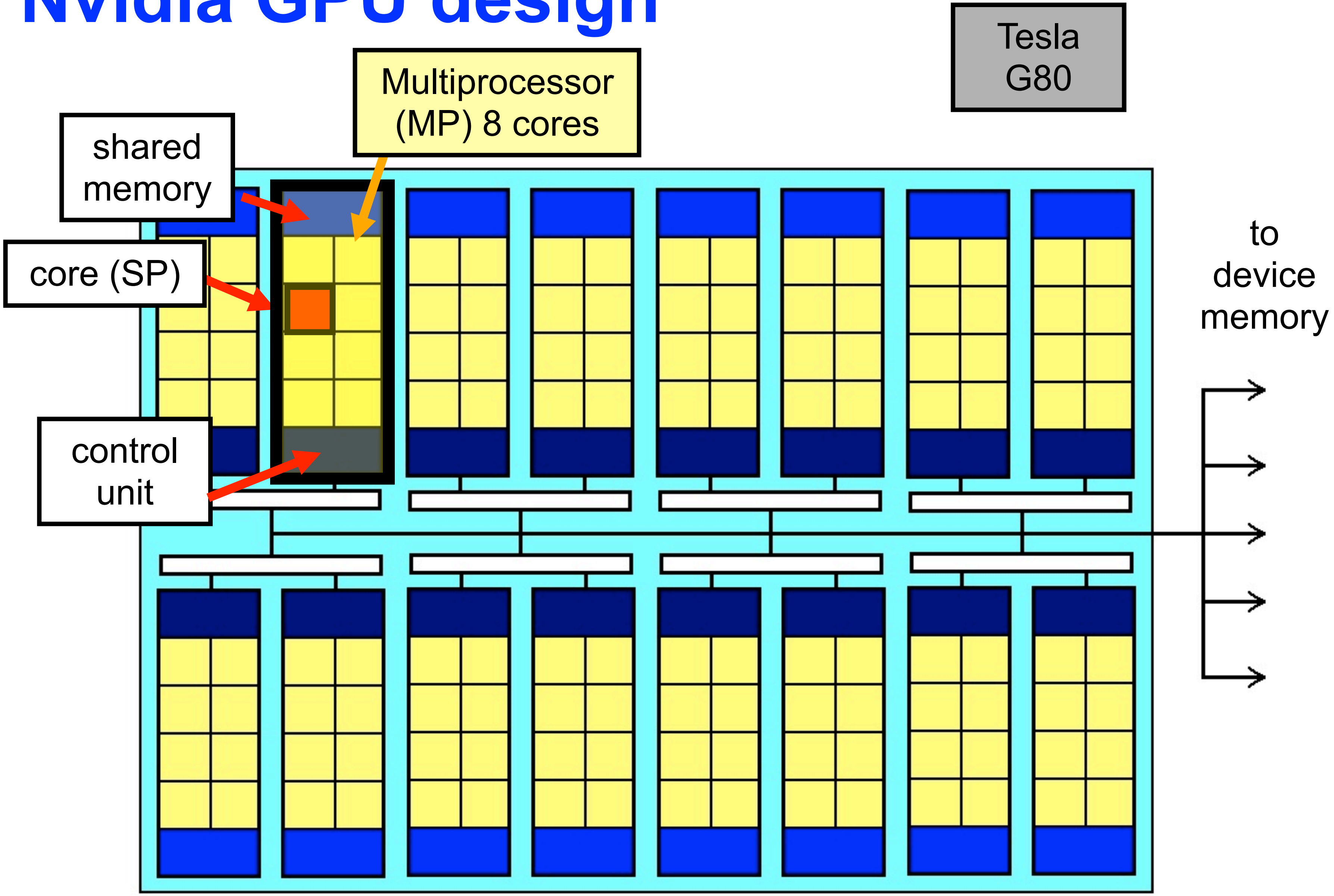
Multiprocessor
(MP) 8 cores

shared
memory

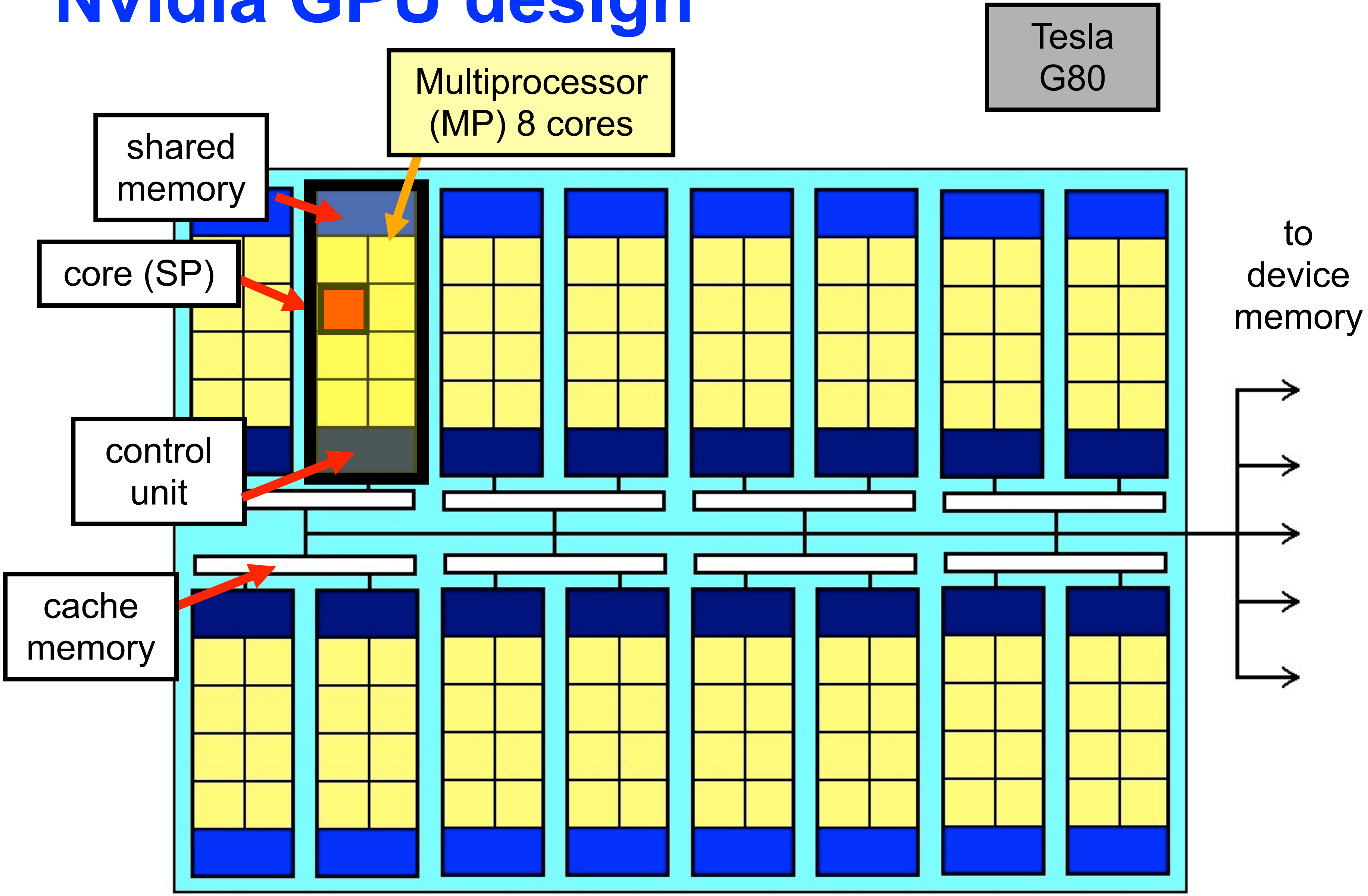
core (SP)

to
device
memory

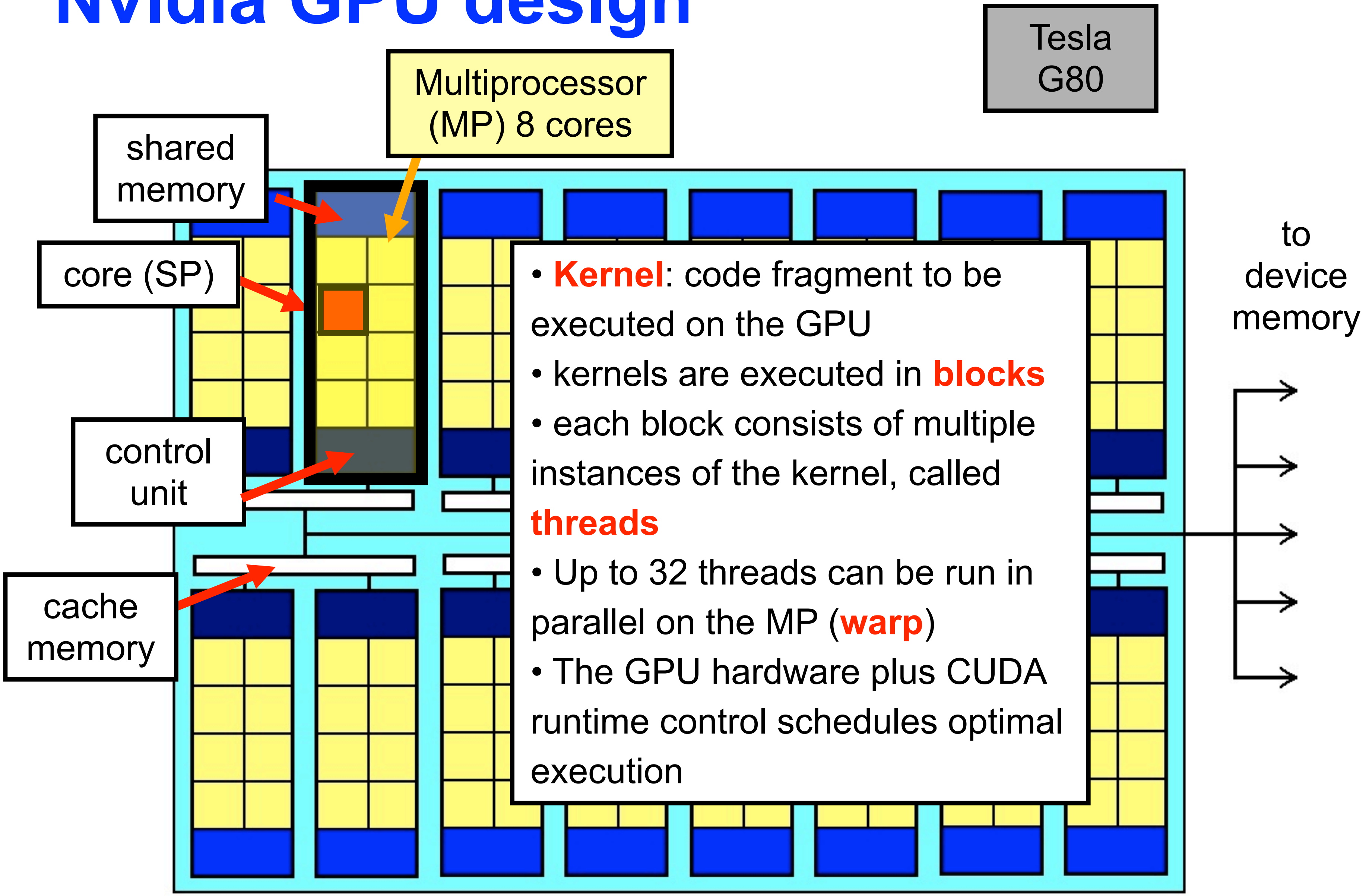
Nvidia GPU design



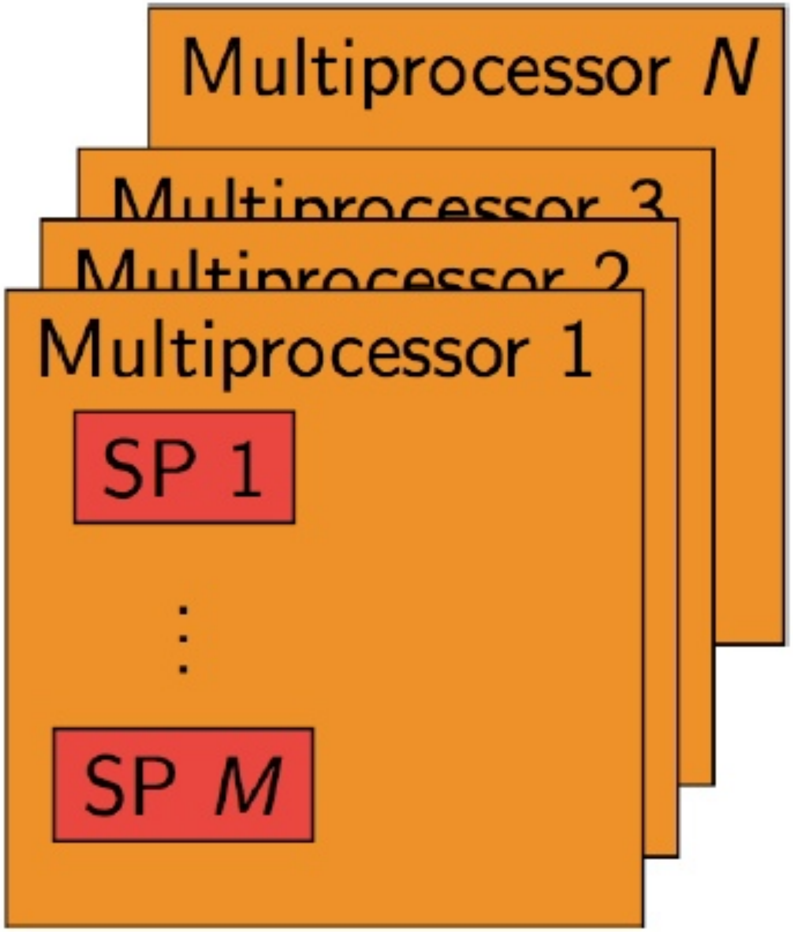
Nvidia GPU design



Nvidia GPU design



- **Kernel**: code fragment to be executed on the GPU
- kernels are executed in **blocks**
- each block consists of multiple instances of the kernel, called **threads**
- Up to 32 threads can be run in parallel on the MP (**warp**)
- The GPU hardware plus CUDA runtime control schedules optimal execution



GeForce GTX580

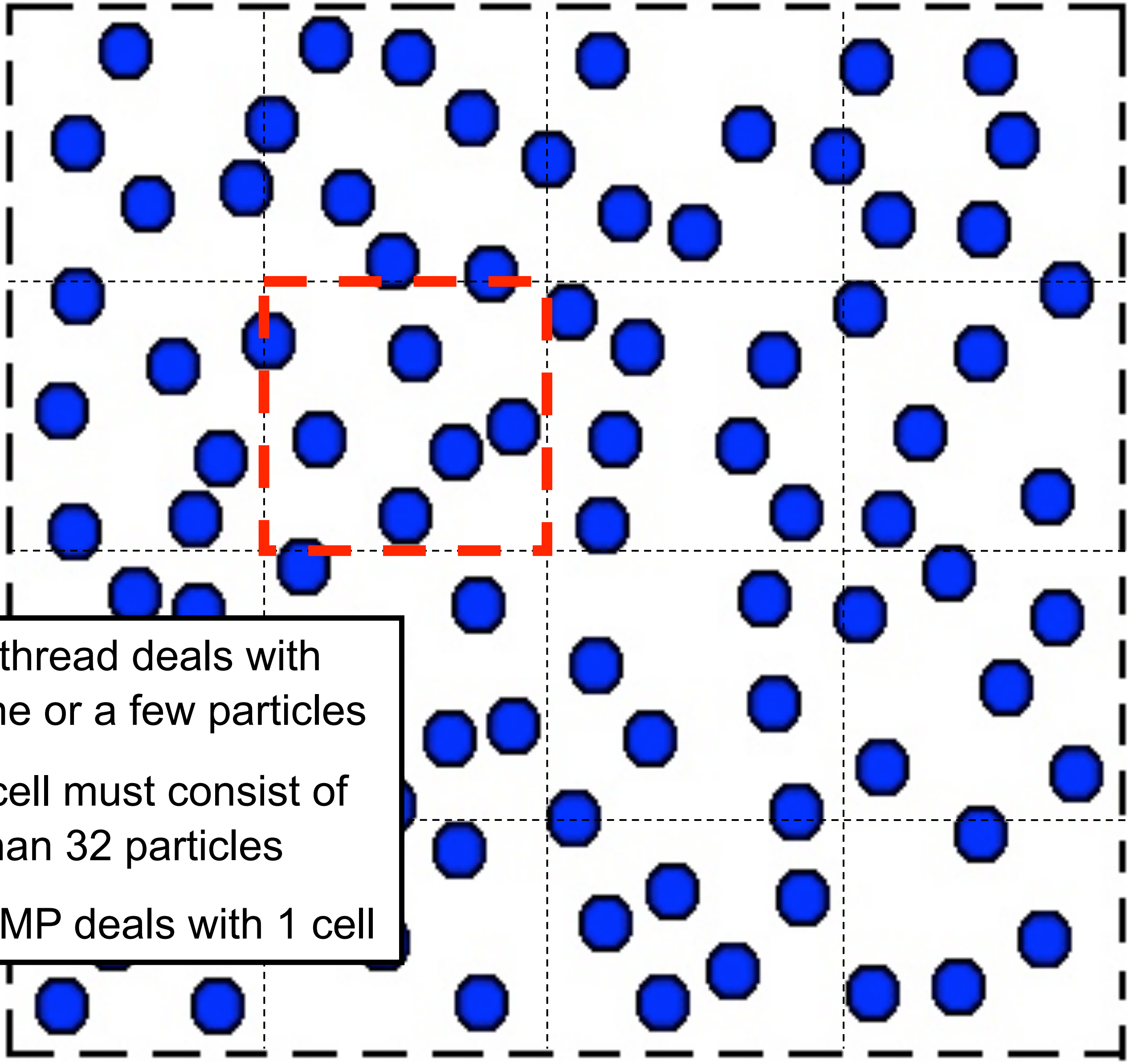
$N = 64$

$M = 8$

512 CUDA SP cores

64k shared memory

Teraflop performance (10^{12} floating point operations per second)

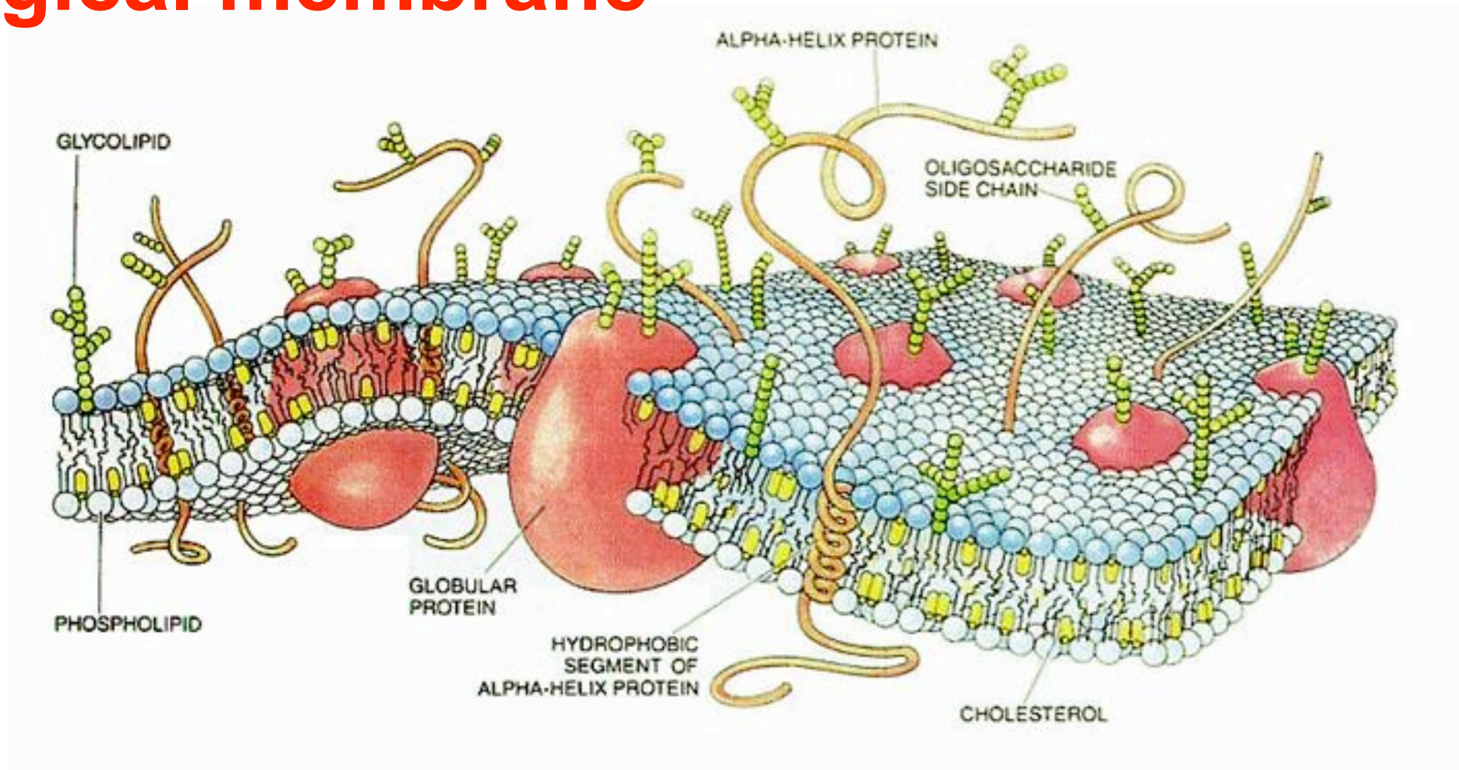


every thread deals with just one or a few particles

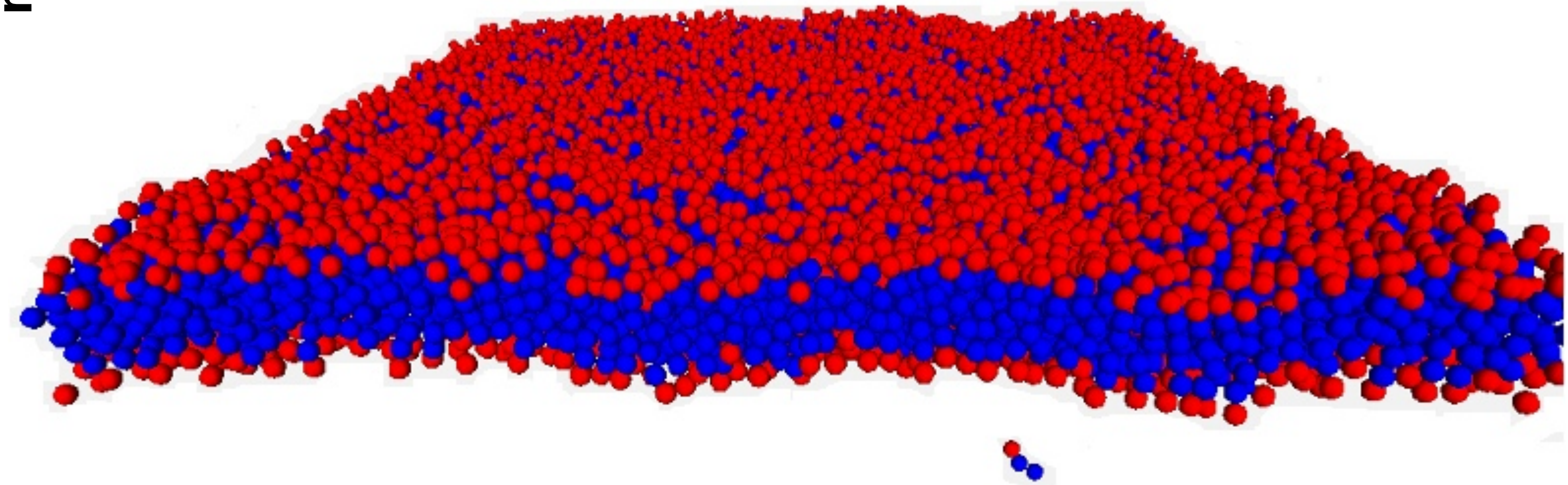
each cell must consist of less than 32 particles

every MP deals with 1 cell

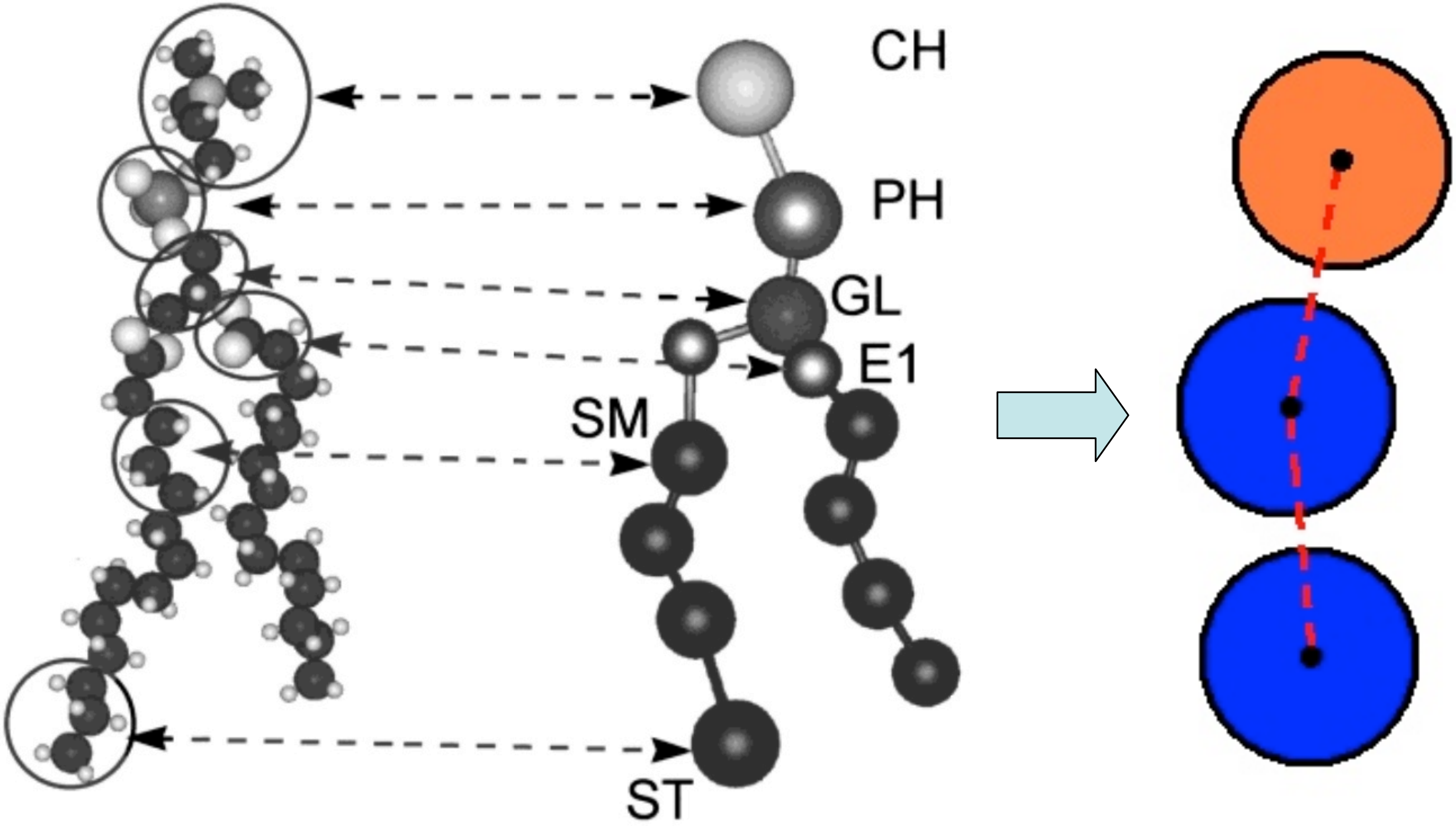
Biological membrane


ALPHA-HELIX PROTEIN
GLYCOLIPID
OLIGOSACCHARIDE SIDE CHAIN
GLOBULAR PROTEIN
PHOSPHOLIPID
HYDROPHOBIC SEGMENT OF ALPHA-HELIX PROTEIN
CHOLESTEROL

mesoscopic model

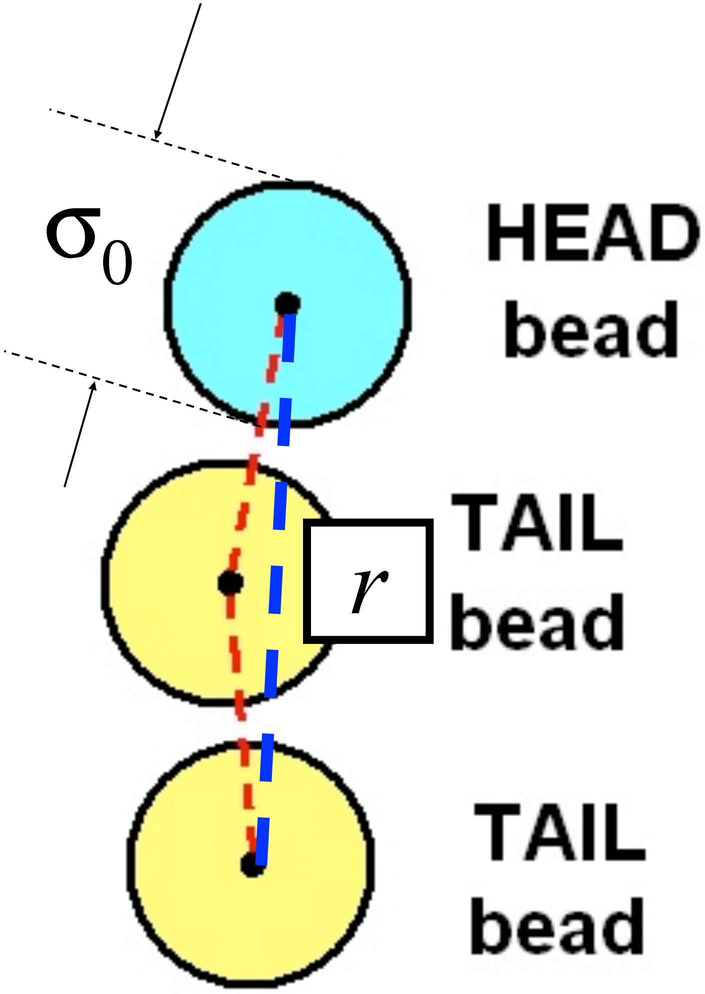


Coarse-grained molecular model



Molecular model

Three beads: one head, two tail, no solvent (water)



INTRAMOLECULAR:

- **bend**

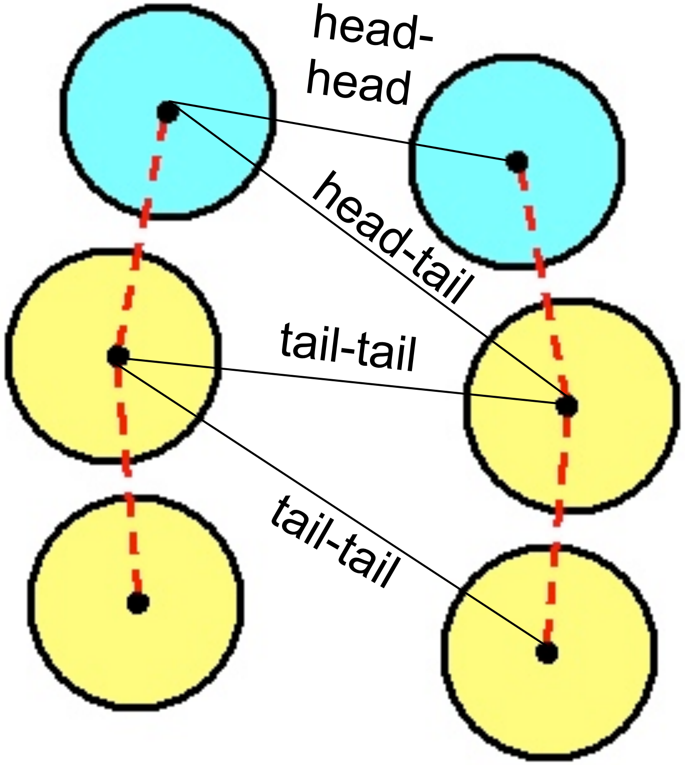
$$V_{bend}(r) = \frac{1}{2} k_{bend} (r - 3\sigma_0)^2$$

$$k_{bend}\sigma_0^2 = 10\varepsilon_0$$

- **bond**

$$V_{bond}(r) = -\frac{1}{2} k_{bond} r_\infty^2 \log\left[1 - (r / r_\infty)^2\right]$$

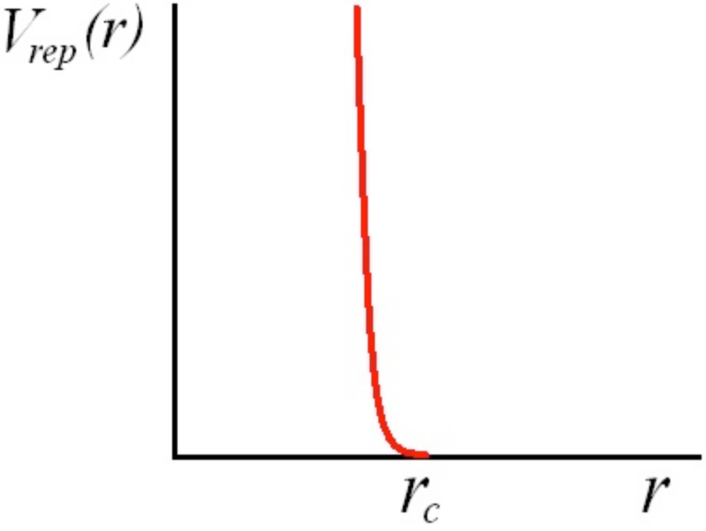
$$k_{bond}\sigma_0^2 = 30\varepsilon_0, \; r_\infty = 1.5\sigma_0$$



INTERMOLECULAR:

all beads of different molecules interact via the Weeks-Chandler-Andersen potential:

$$V_{rep}(r) = \begin{cases} 4\varepsilon_0\left[\left(\frac{b}{r}\right)^{12} - \left(\frac{b}{r}\right)^{6}\right] + \varepsilon_0, & r \le r_c, \\ 0, & r > r_{c.} \end{cases}$$



ε_0 is the unit of energy

$b_{head\text{-}head} = 0.95\ \sigma_0$

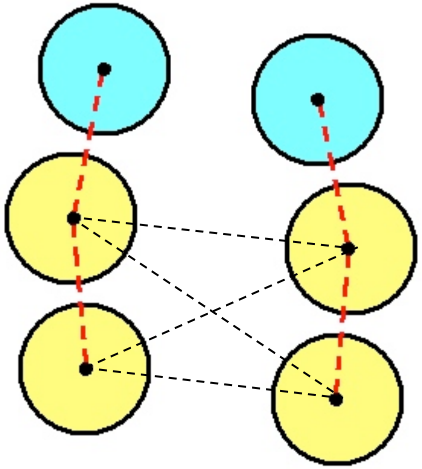
$b_{hear\text{-}tail} = 0.95\ \sigma_0$

$b_{tail\text{-}tail} = \sigma_0$

$$r_c = 2^{1/6}\sigma_0$$

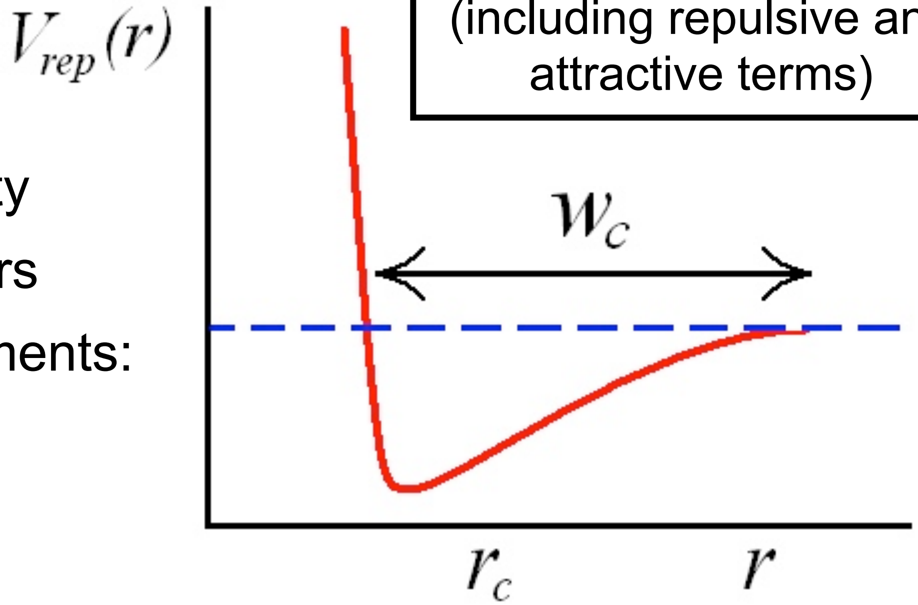
PLUS tail attraction (to mimic hydrophobic effect):

$$V_{attr}(r) = \begin{cases} -\varepsilon, & r < r_c, \\ -\varepsilon_0 \cos^2\left[\dfrac{\pi(r-r_c)}{2w_c}\right], & r_c \le r \le r_c + w_c, \\ 0, & r > r_c + w_c. \end{cases}$$



Advantages of model:

- Broad range of membrane fluidity
- Easily tunable via few parameters
- Good agreement with measurements: rigidity, diffusion, density



Total tail-tail potential (including repulsive and attractive terms)

Features of our simulations

- $N = 7164 - 28800$ molecules (x 3 beads)

- $\tau = 2 - 3$ ns

- NPT ensemble (constant pressure = constant $\gamma = 0$)
(fluctuating system volume)

- Langevin thermostat

- To model typical phospholipid:

$d = 10$ nm (membrane thickness) $\longrightarrow$ $\sigma_0 = 1.7$ nm

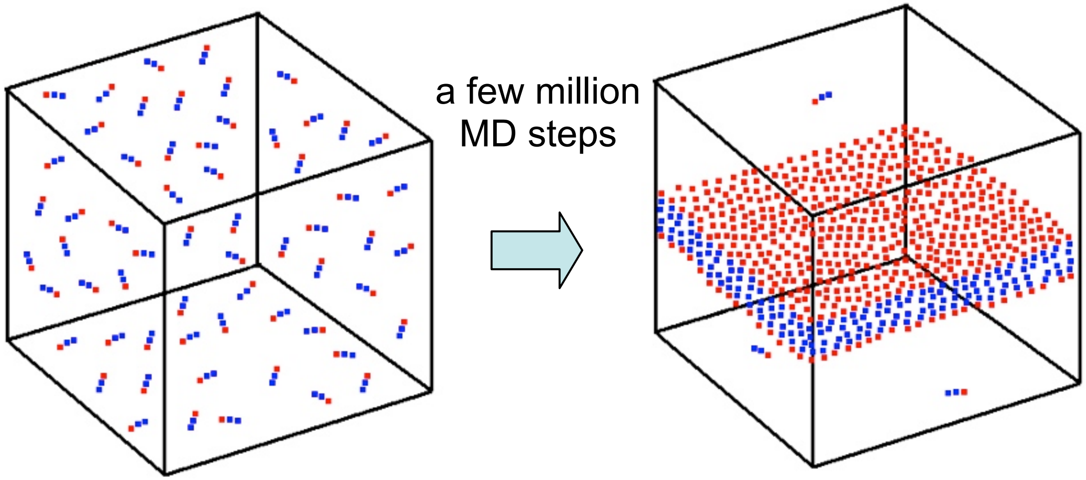
$\varepsilon_0 = 3.72 \times 10^{-21}$ J

$m_0 = 220$ g/mol

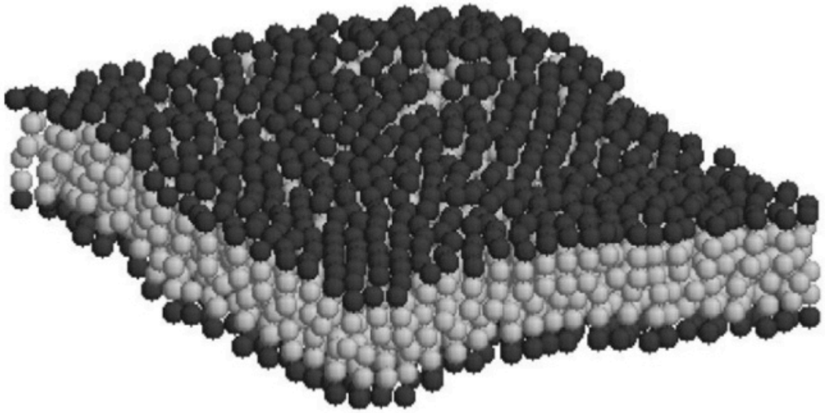
$\rightarrow$ $\tau_0 = \sigma_0 \sqrt{\dfrac{m_0}{\varepsilon_0}} = 9.85$ ps (time scale of MD simulation)

molecules self-assemble spontaneously into planar membranes

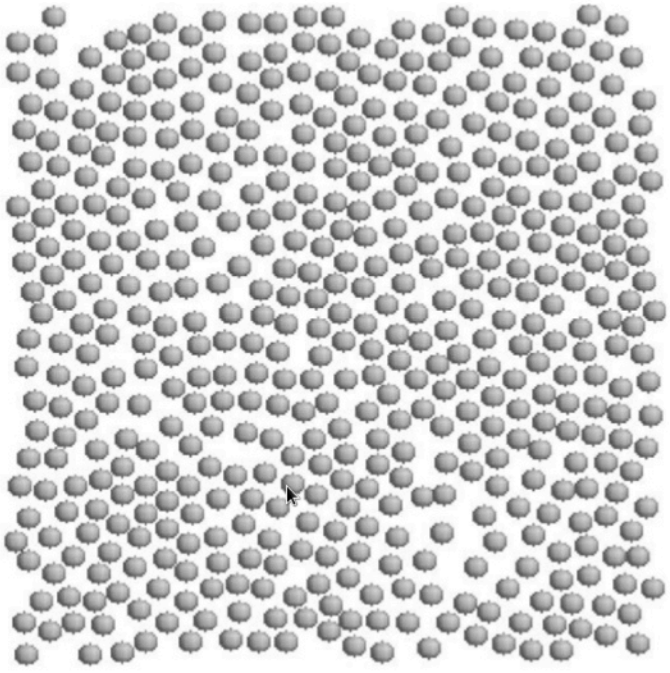
special MD techniques (ensuring $\gamma=0$) are needed (fluctuating box)



side view



top view



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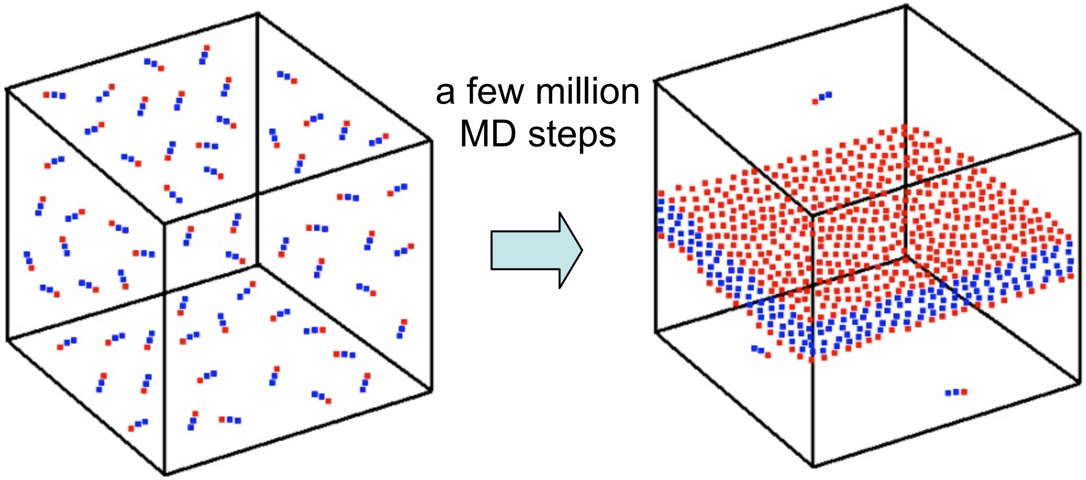

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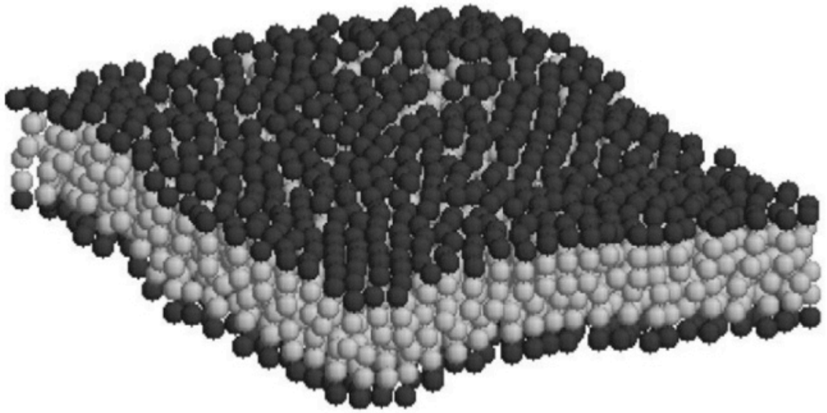

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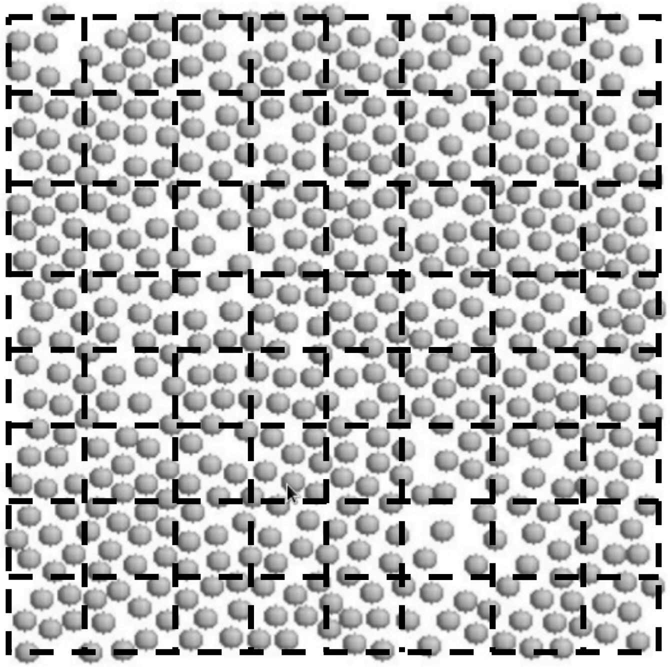
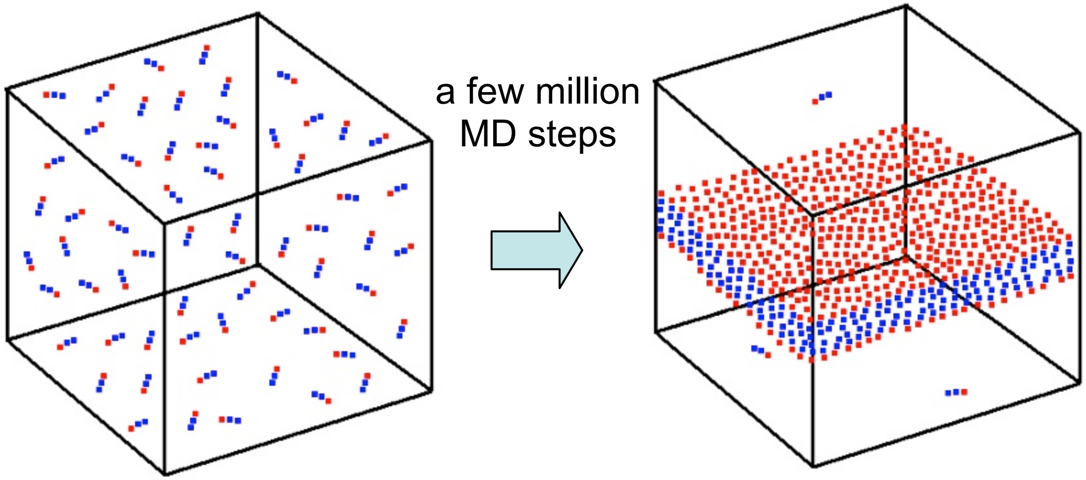
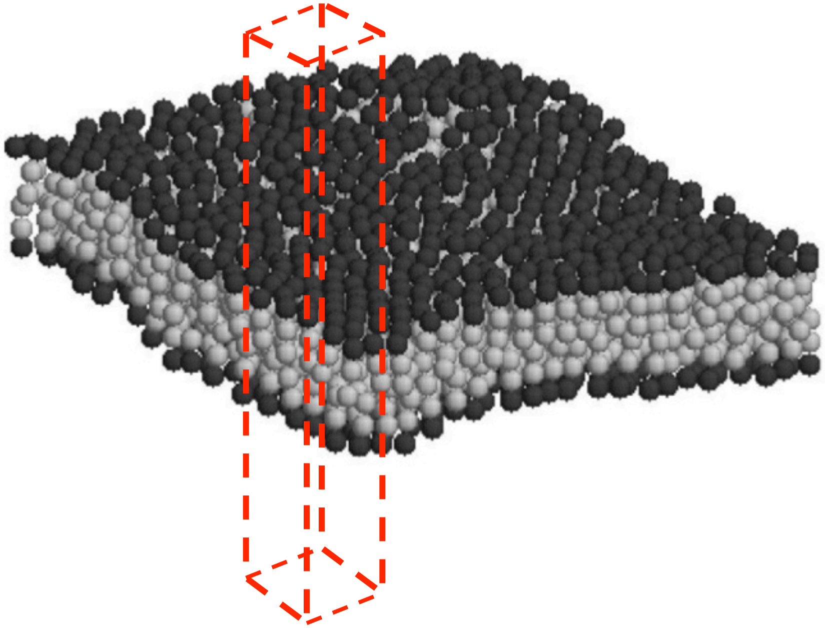


molecules self-assemble spontaneously into planar membranes

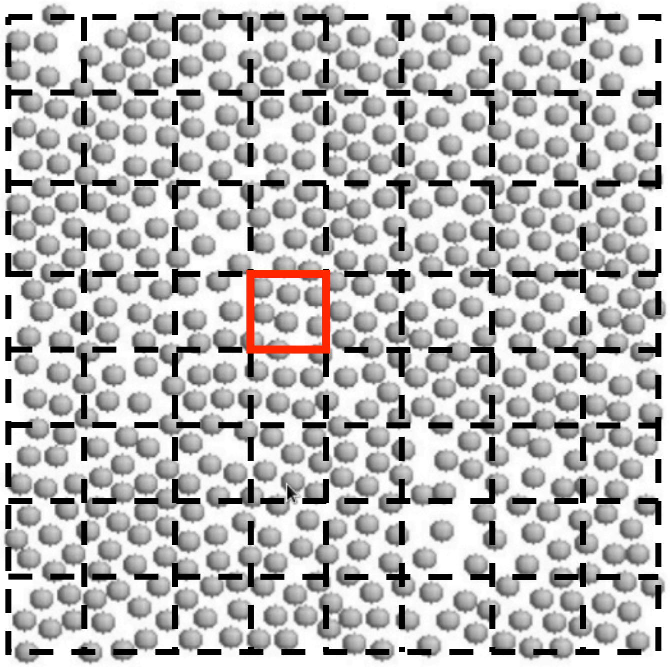
special MD techniques (ensuring $\gamma=0$) are needed (fluctuating box)



side view



top view



Properties of a mathematical membrane

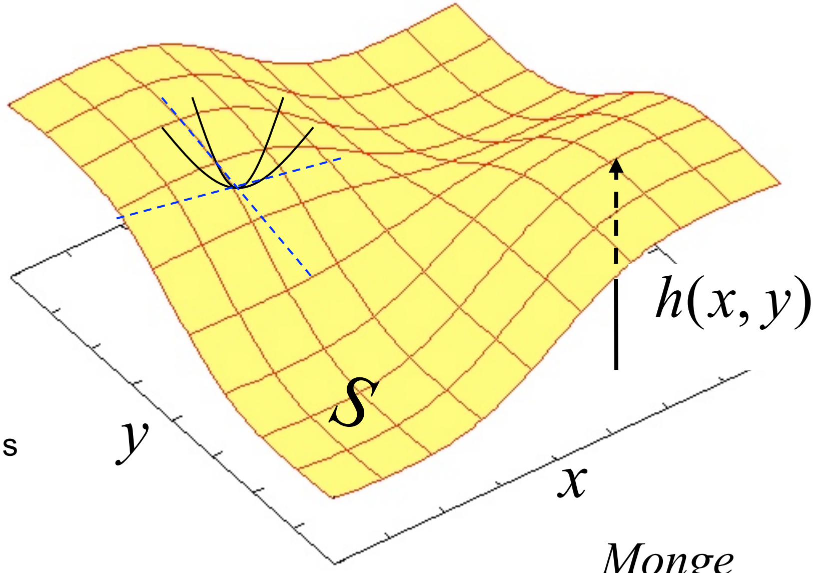
Fluctuating sheet of zero thickness

Described by Helfrich free energy:

$$F = \int_S dA \left[\gamma + \frac{\kappa}{2} \big(\underbrace{c_1 + c_2} - 2c_0 \big)^2 \right]$$

spontaneous curvature

mean curvature $H = \dfrac{c_1 + c_2}{2}$



Monge representation

For our membranes c_0=0 and

$$F = \int_S dA \left(\gamma + 2\kappa H^2 \right) \longrightarrow \frac{1}{2} \iint dxdy \left[\gamma \left| \nabla_\perp h \right|^2 + \kappa \left(\nabla^2 h \right)^2 \right]$$

Properties of a mathematical membrane

Fluctuating sheet of zero thickness

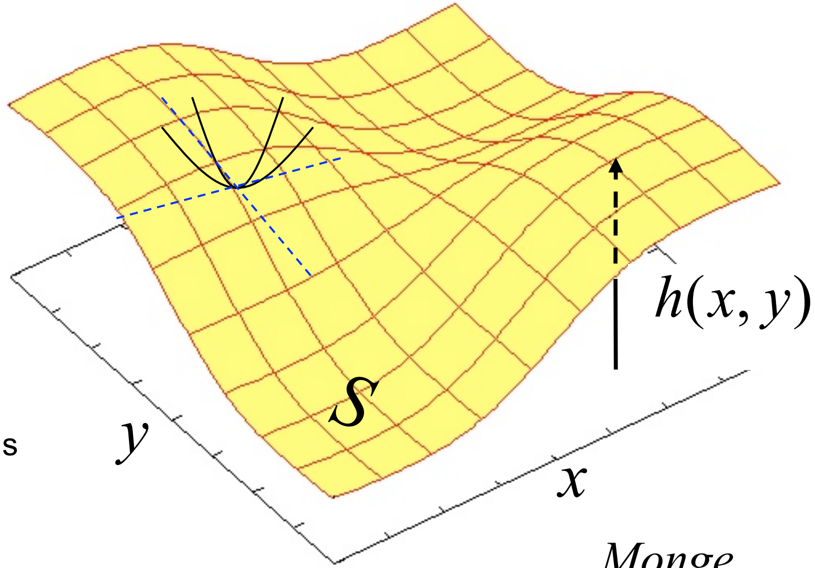
Described by Helfrich free energy:

$$F = \int_S dA\left[\gamma + \frac{\kappa}{2}\underbrace{\left(c_1 + c_2\right.}_{}\left. - 2c_0\right)^2\right]$$

surface tension

mean curvature $H = \frac{c_1 + c_2}{2}$

spontaneous curvature



Monge representation

For our membranes c_0=0 and

$$F = \int_S dA\left(\gamma + 2\kappa H^2\right) \longrightarrow \frac{1}{2}\iint dxdy\left[\gamma\left|\nabla_\perp h\right|^2 + \kappa\left(\nabla^2 h\right)^2\right]$$

Properties of a mathematical membrane

Fluctuating sheet of zero thickness

Described by Helfrich free energy:

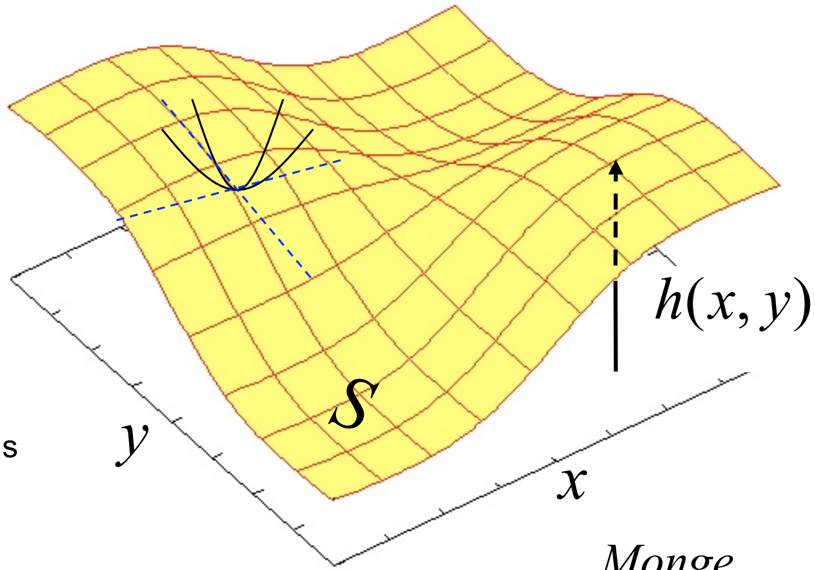
$$F = \int_S dA \left[\gamma + \frac{\kappa}{2} \left(\underbrace{c_1 + c_2}_{} - 2c_0 \right)^2 \right]$$

bending constant

surface tension

mean curvature $H = \frac{c_1 + c_2}{2}$

spontaneous curvature



Monge representation

For our membranes c_0=0 and

$$F = \int_S dA\left(\gamma + 2\kappa H^2\right) \longrightarrow \frac{1}{2}\iint dxdy\left[\gamma\left|\nabla_\perp h\right|^2 + \kappa\left(\nabla^2 h\right)^2\right]$$

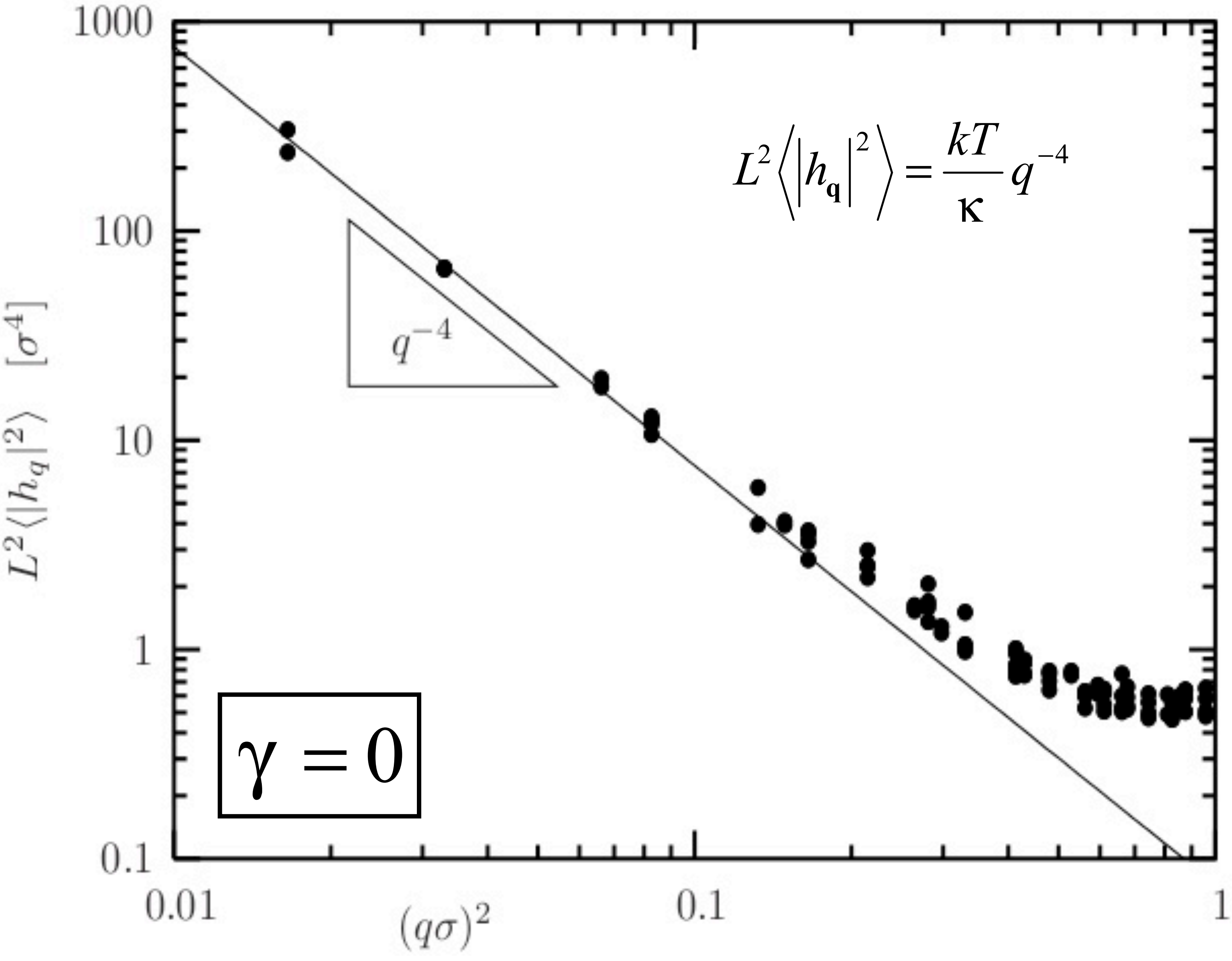
How can γ and κ be computed from a MD simulation?

Taking Fourier transform:

$$F = \frac{L^2}{2}\sum_{\mathbf{q}}\left(\gamma|\mathbf{q}|^2 + \kappa|\mathbf{q}|^4\right)|h_{\mathbf{q}}|^2$$

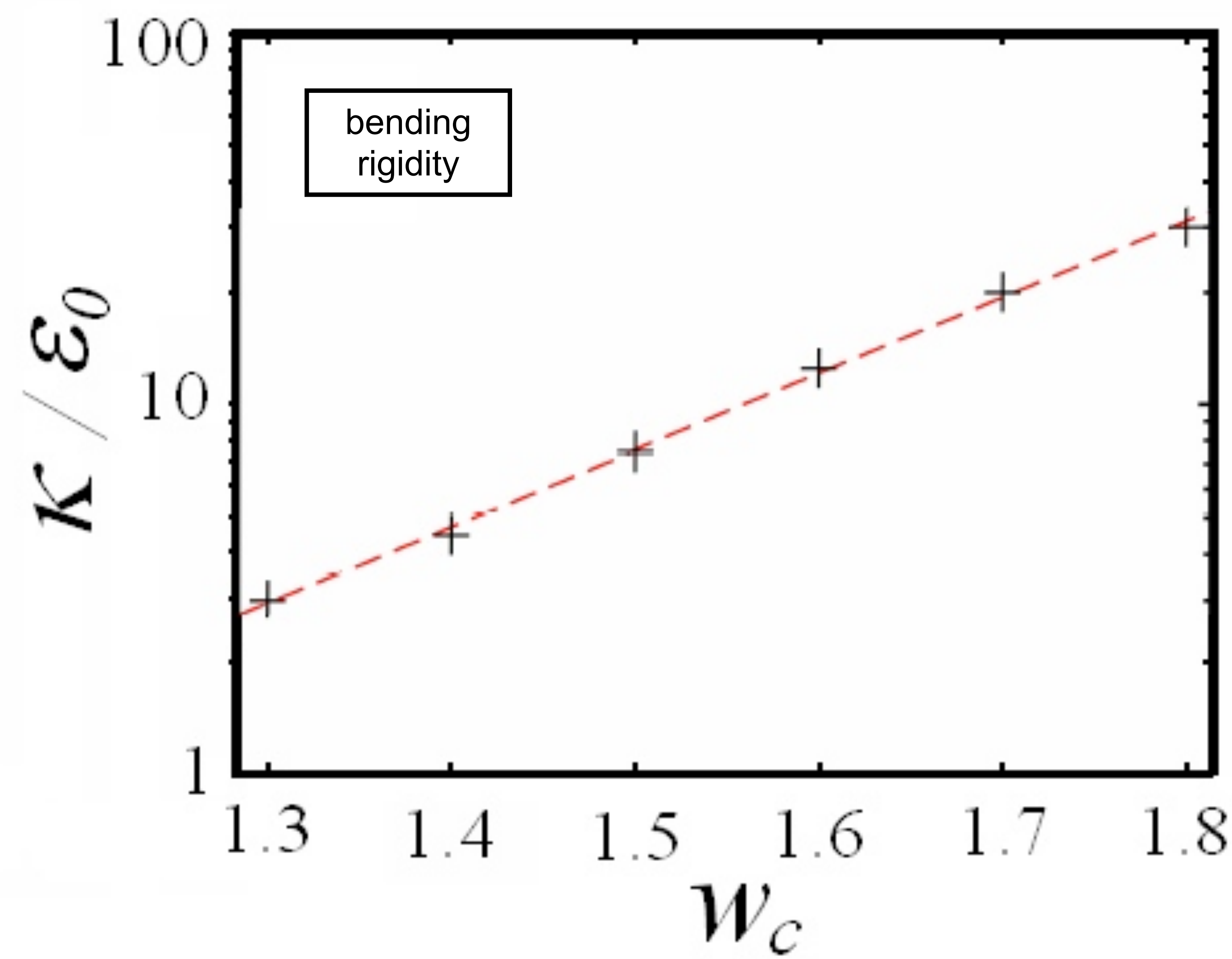
Equipartition theorem:

$$\frac{L^2}{2}\left(\gamma|\mathbf{q}|^2 + \kappa|\mathbf{q}|^4\right)\left\langle|h_{\mathbf{q}}|^2\right\rangle = \frac{kT}{2} \quad \Rightarrow \quad \boxed{L^2\left\langle|h_{\mathbf{q}}|^2\right\rangle = \frac{kT}{\gamma|\mathbf{q}|^2 + \kappa|\mathbf{q}|^4}}$$



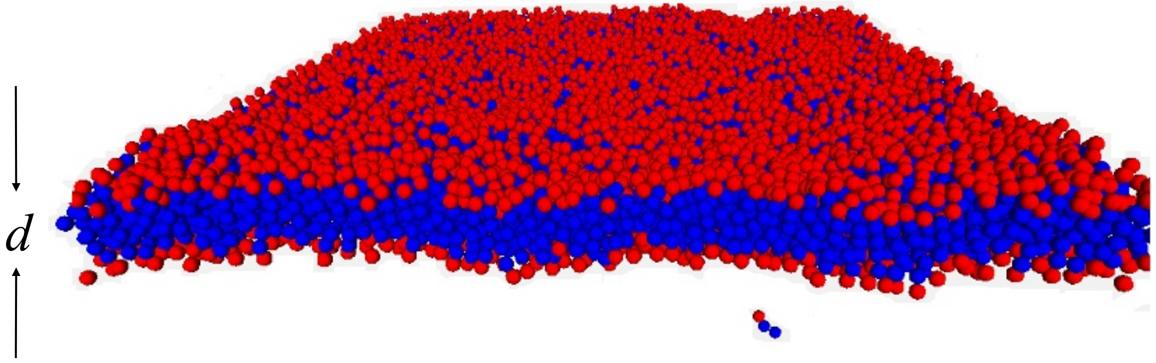
$$L^2\left\langle\left|h_{\mathbf{q}}\right|^2\right\rangle = \frac{kT}{\kappa}q^{-4}$$

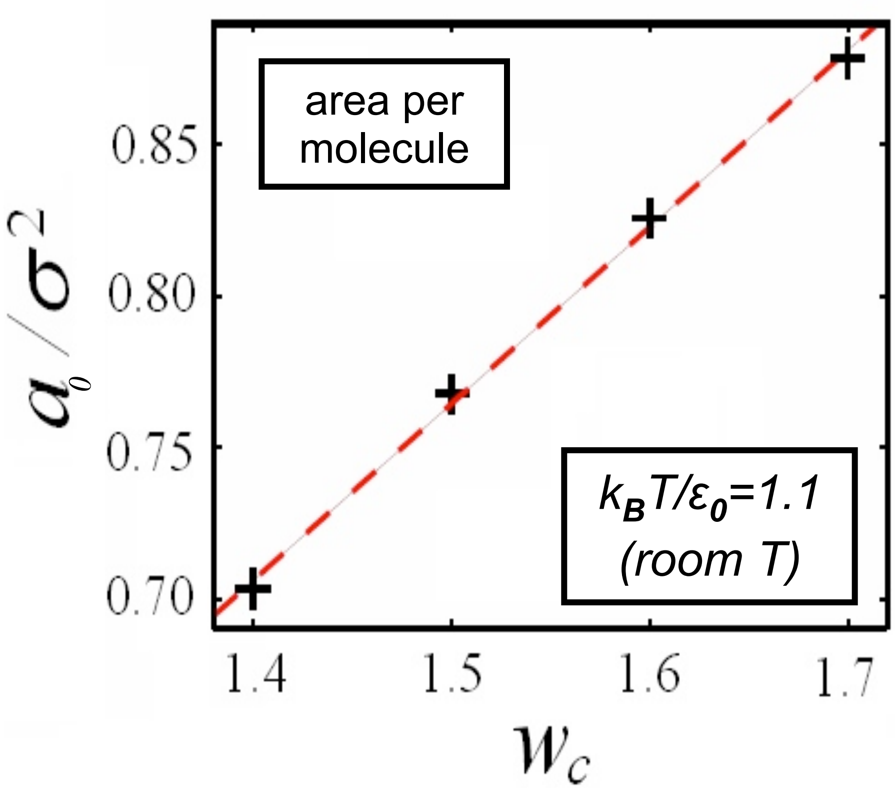
$\gamma = 0$

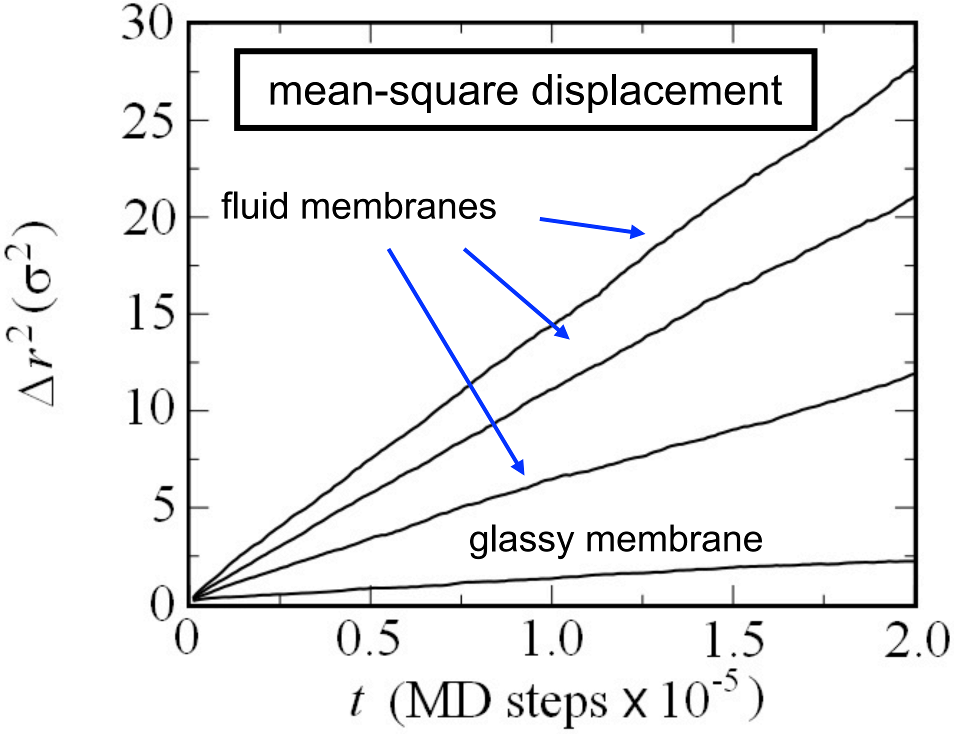

bending
rigidity
$\kappa\ /\ \varepsilon_0$
100
10
1
1.3
1.4
1.5
1.6
1.7
1.8
w_c

Properties of a physical membrane

- membrane thickness
- two-dimensional density
- molecular diffusion
- lateral compressibility







Properties of a physical membrane

- membrane thickness
- two-dimensional density
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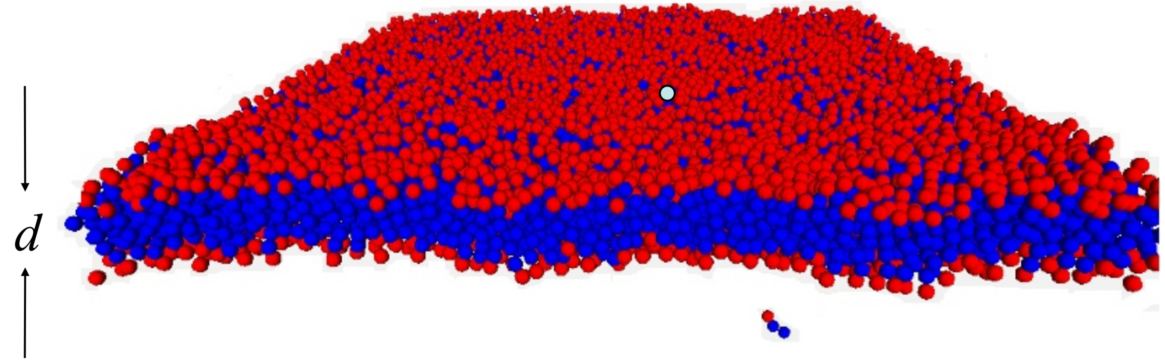

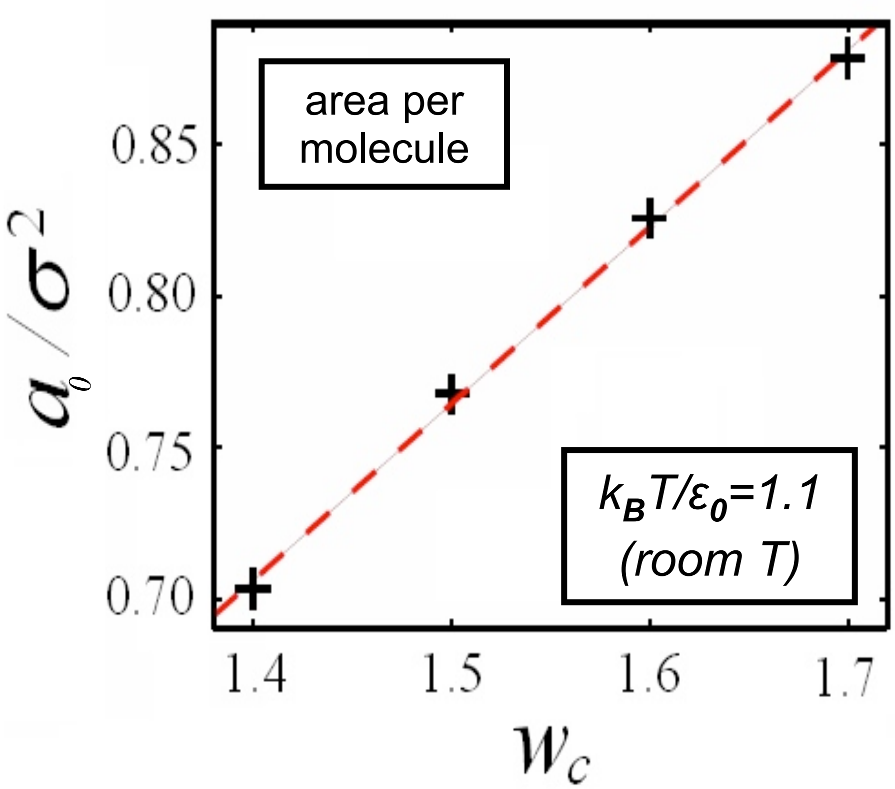

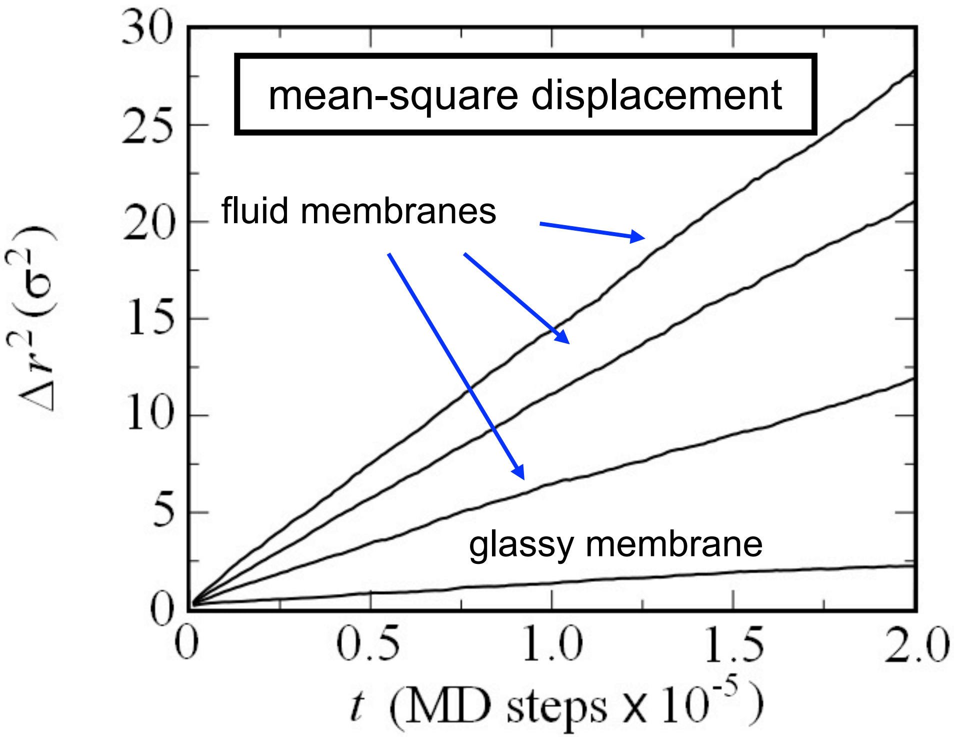

Properties of a physical membrane

- membrane thickness
- two-dimensional density
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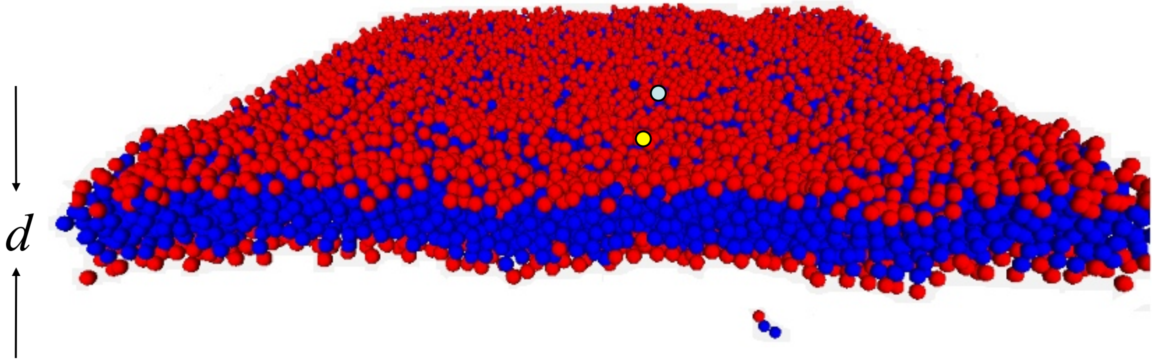
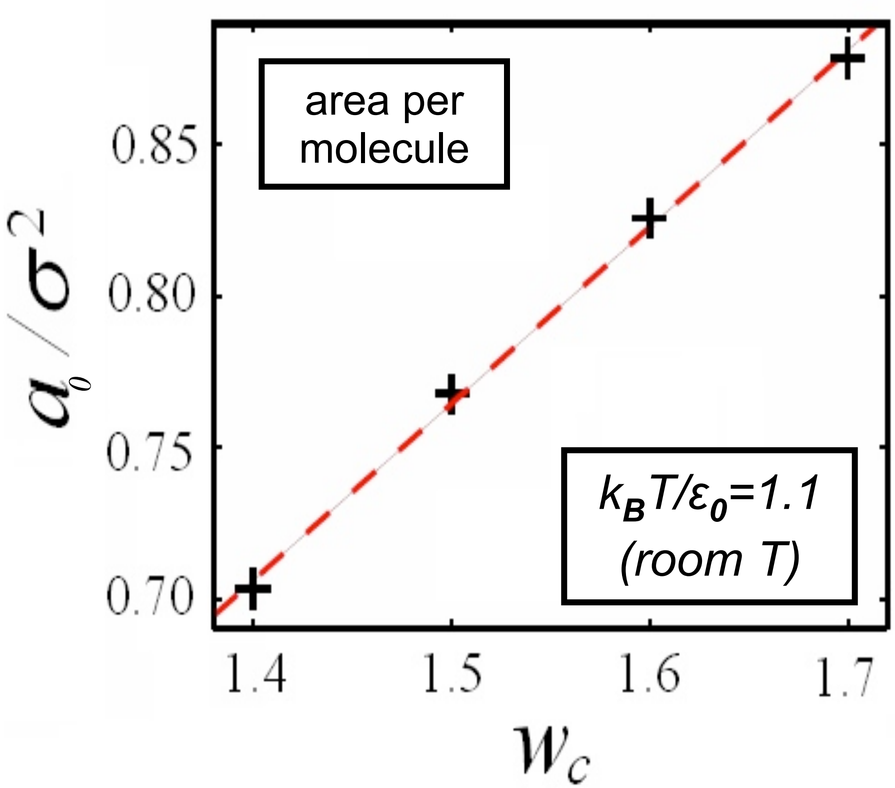
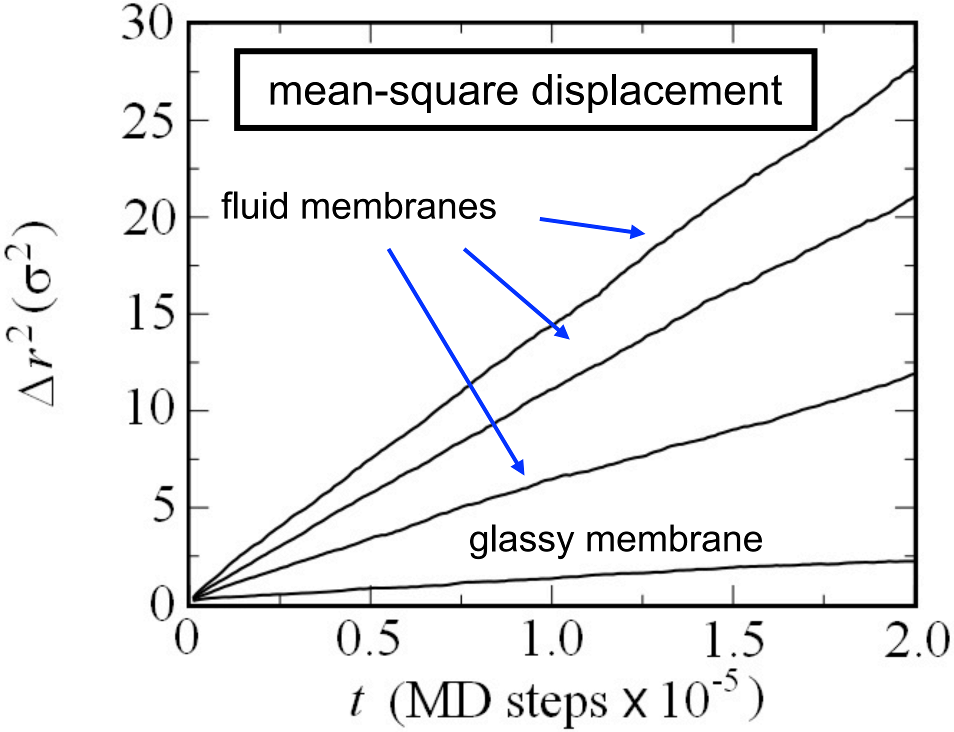
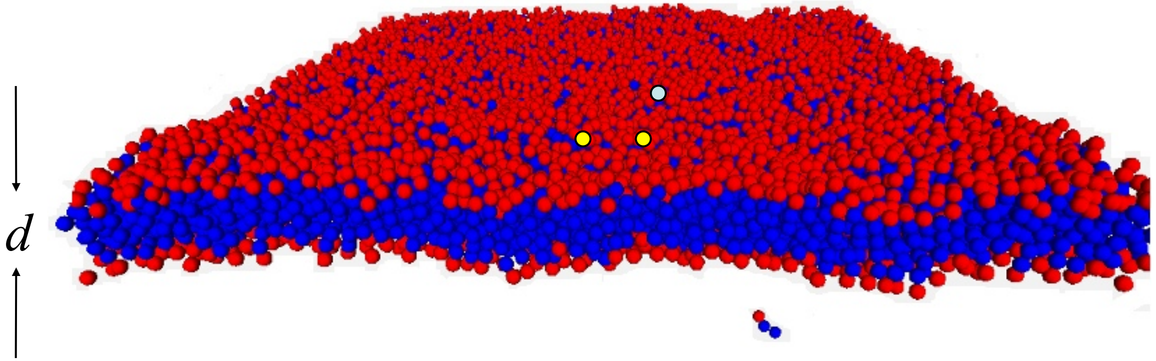


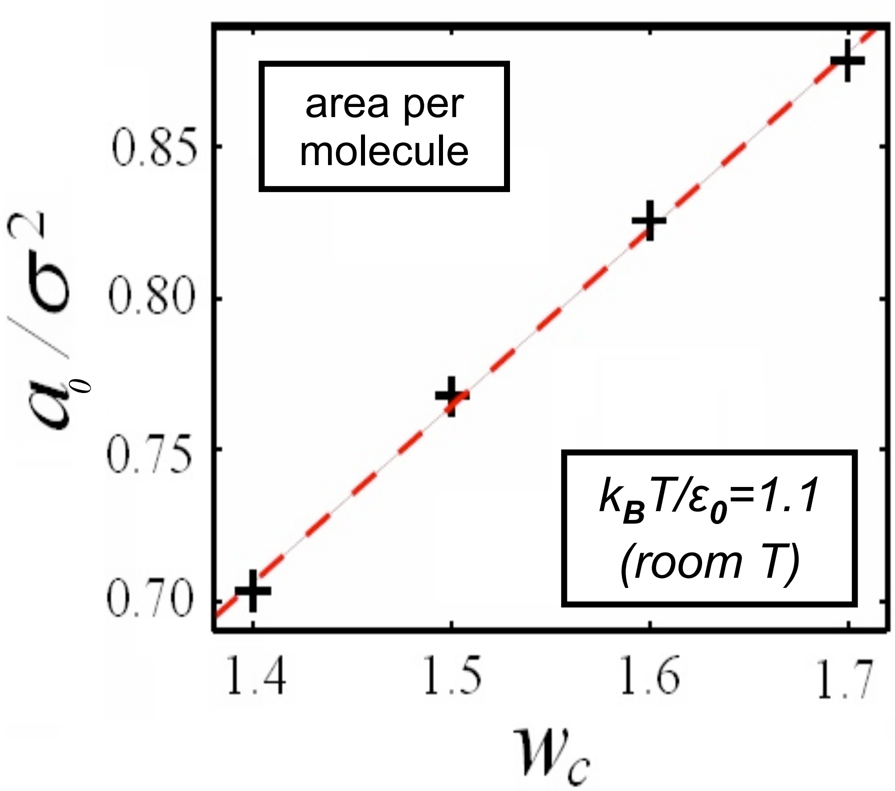




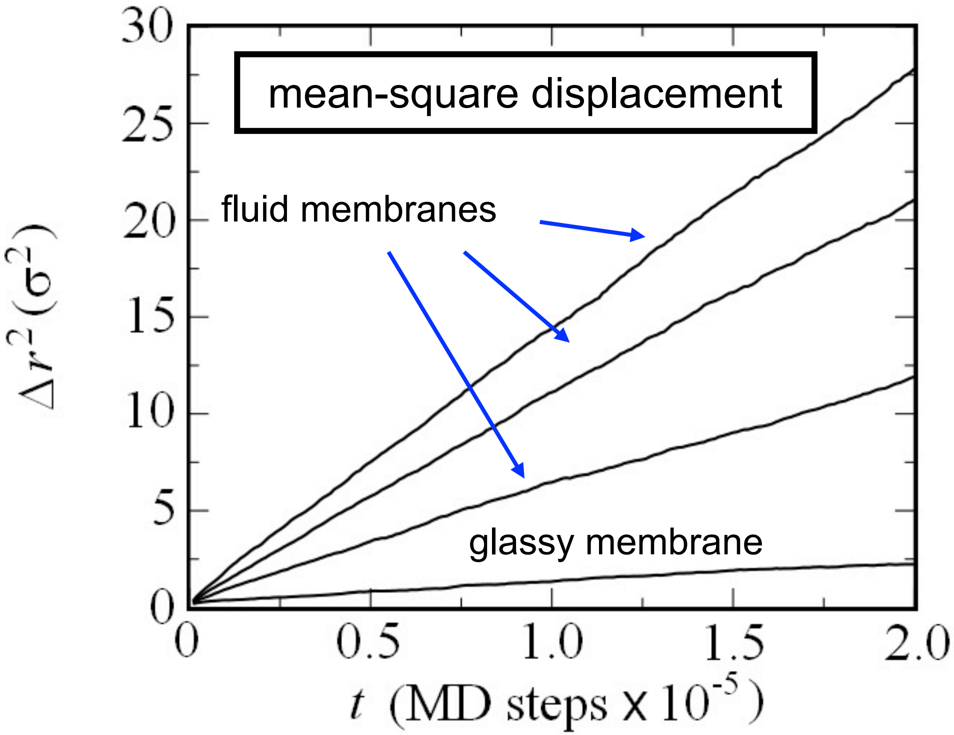
Properties of a physical membrane

- membrane thickness
- two-dimensional density
- molecular diffusion
- lateral compressibility



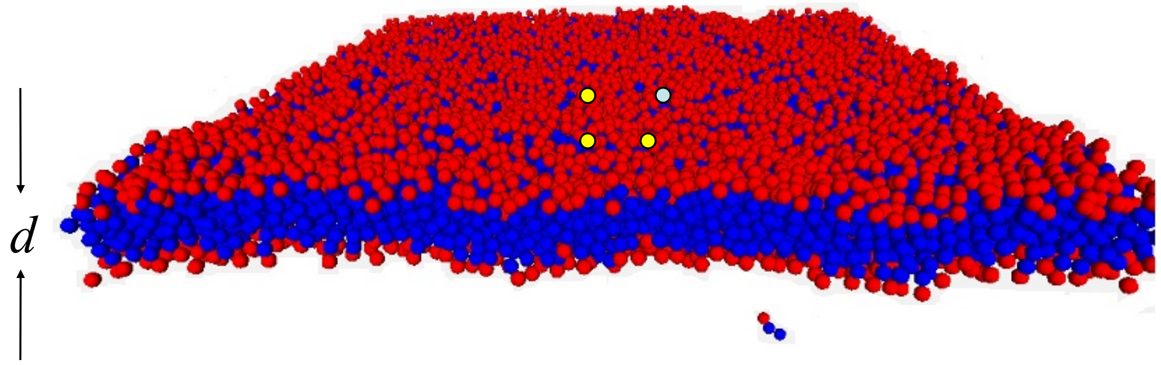

area per molecule

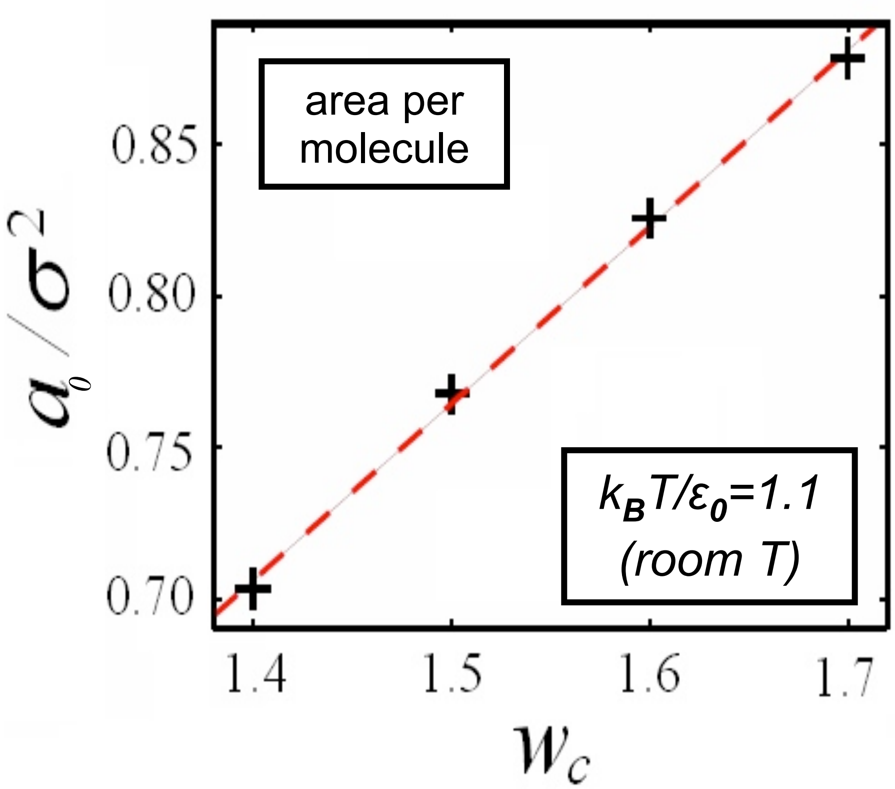
k_BT/ε_0=1.1
(room T)

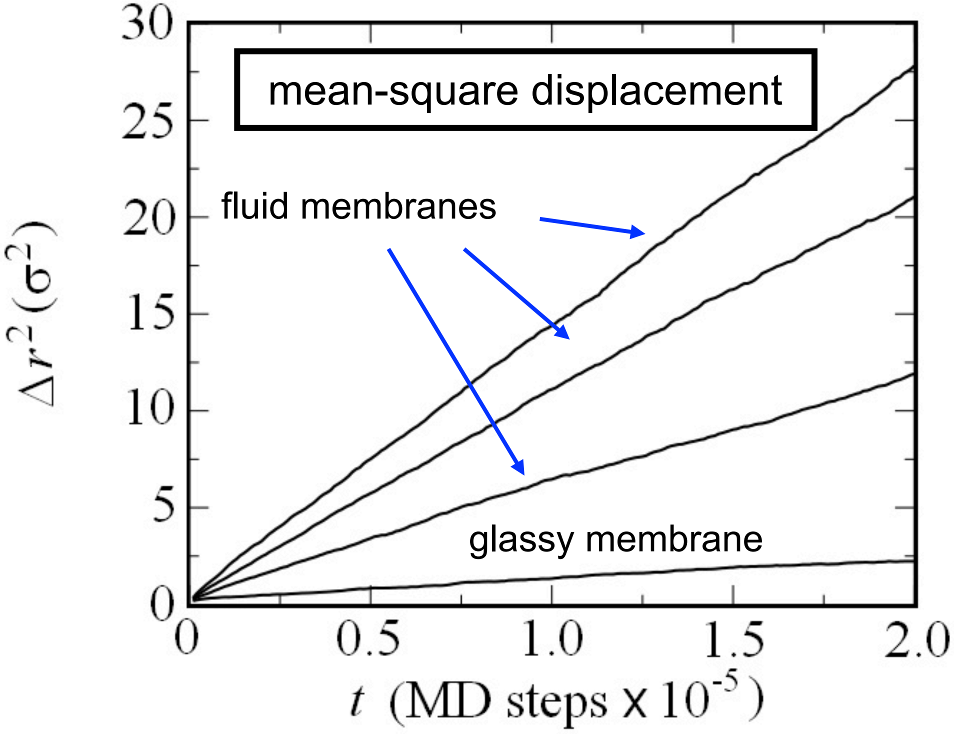

mean-square displacement

Properties of a physical membrane

- membrane thickness
- two-dimensional density
- molecular diffusion
- lateral compressibility

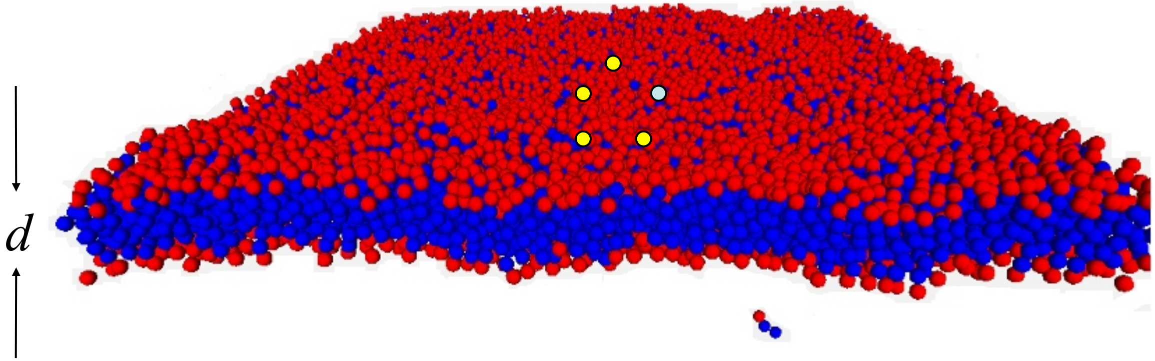


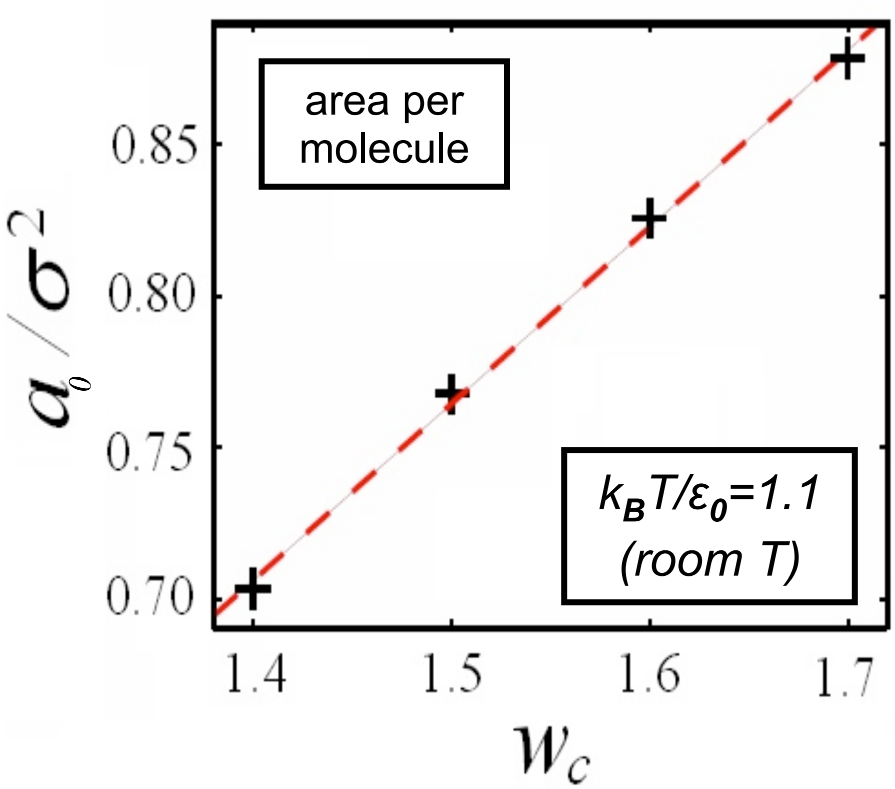


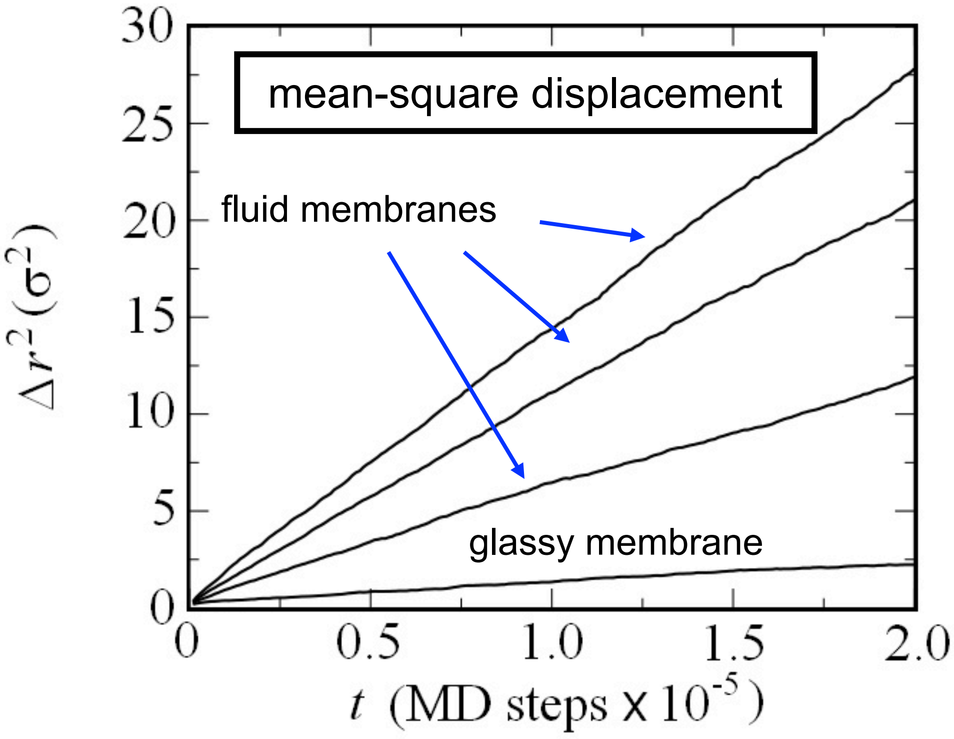


Properties of a physical membrane

- membrane thickness
- two-dimensional density
- molecular diffusion
- lateral compressibility







Properties of a physical membrane

- membrane thickness
- two-dimensional density
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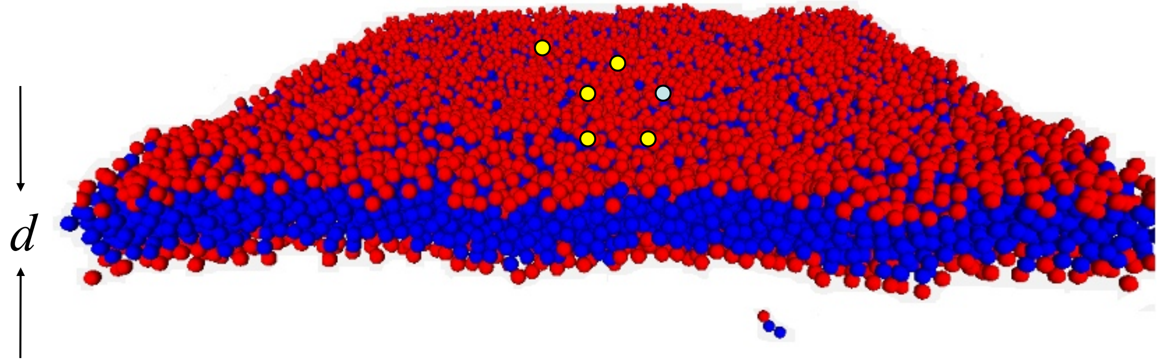
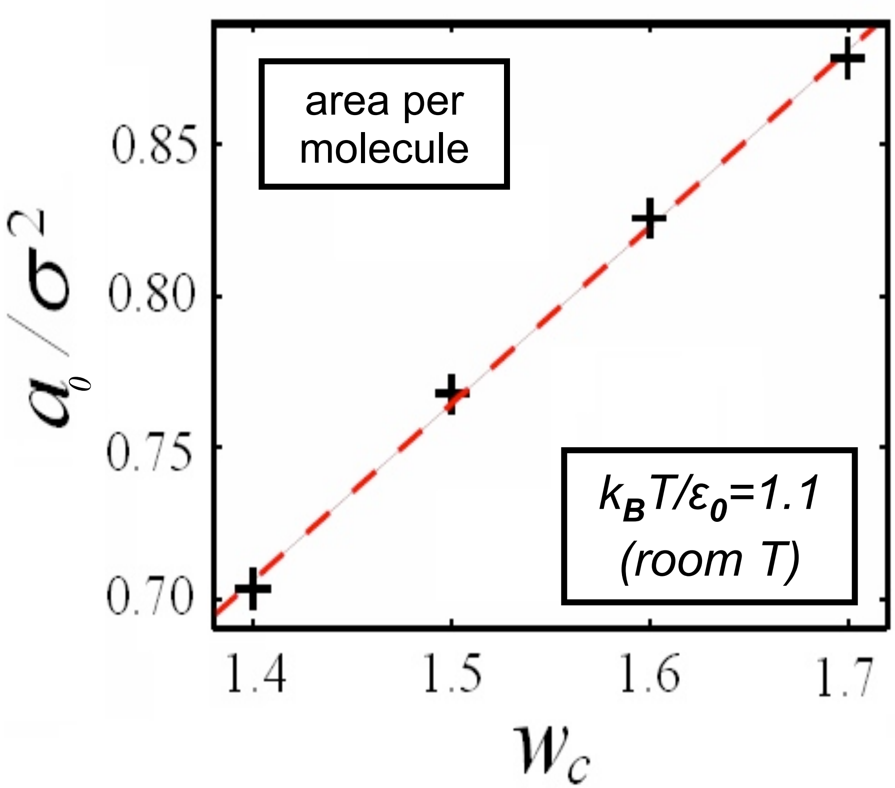
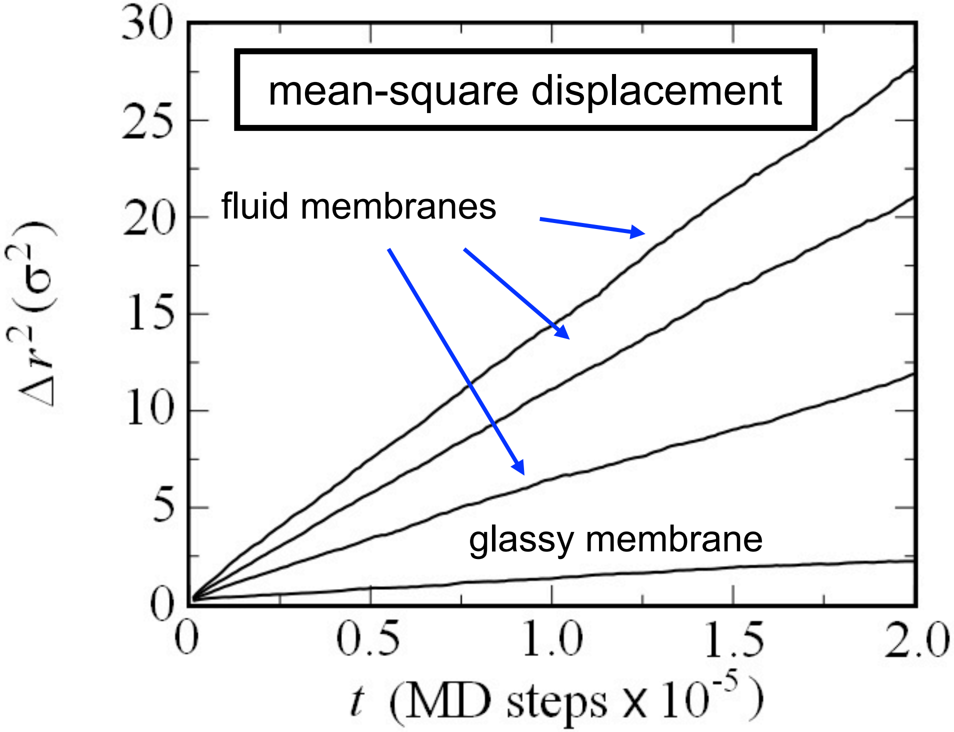
- lateral compressibility







Properties of a physical membrane

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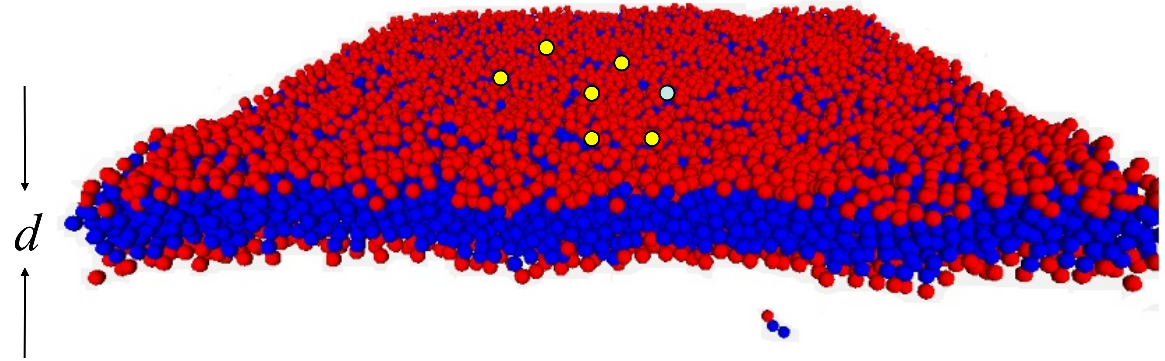

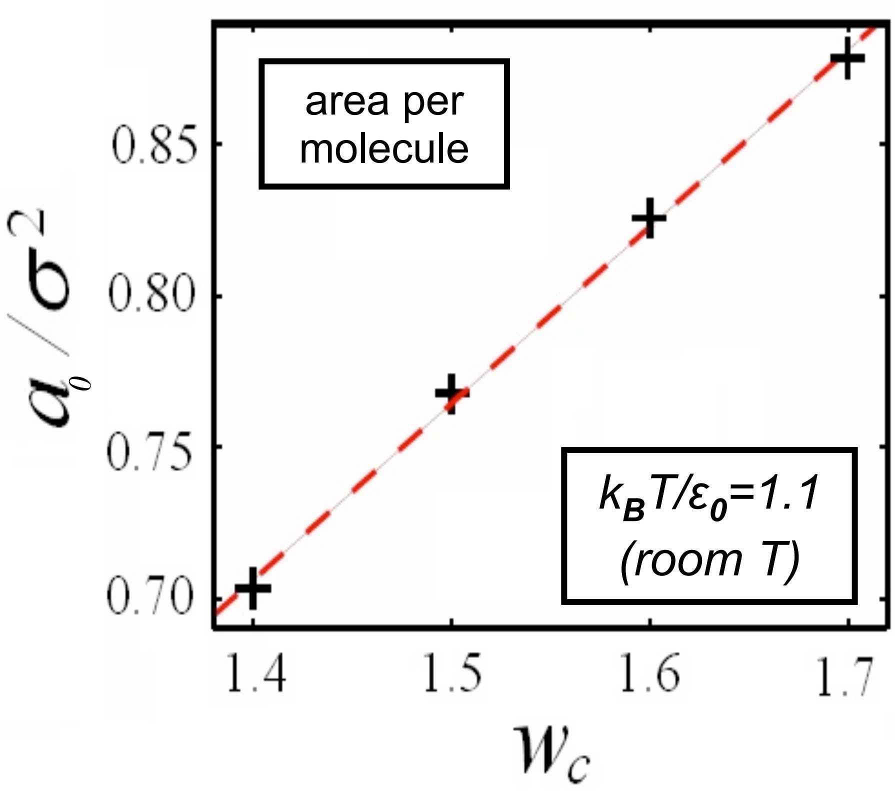

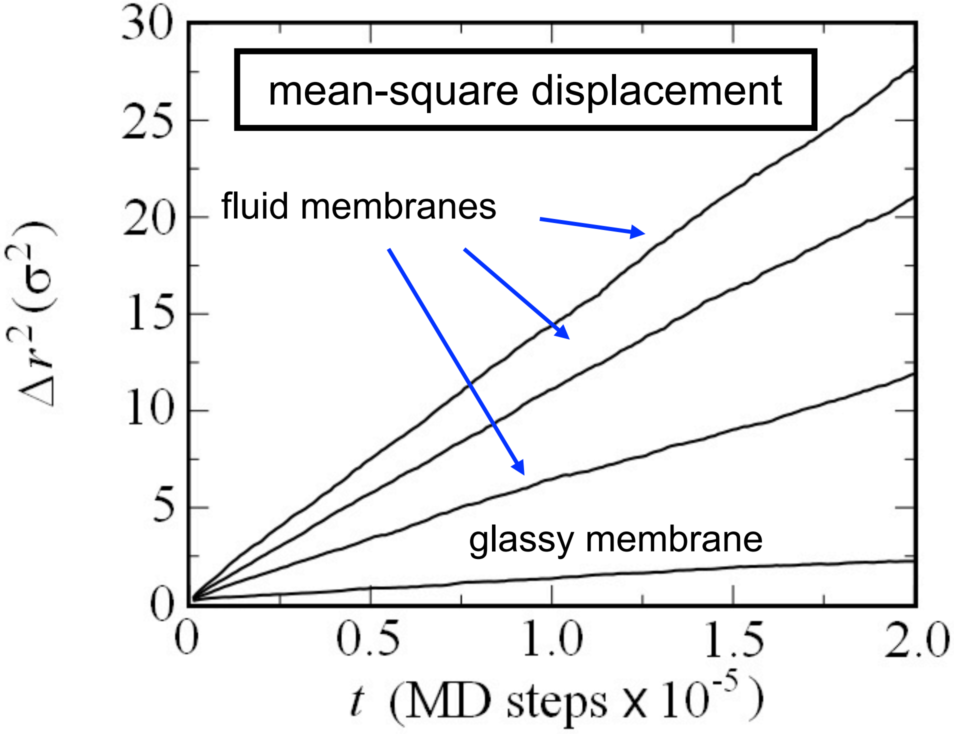

Properties of a physical membrane

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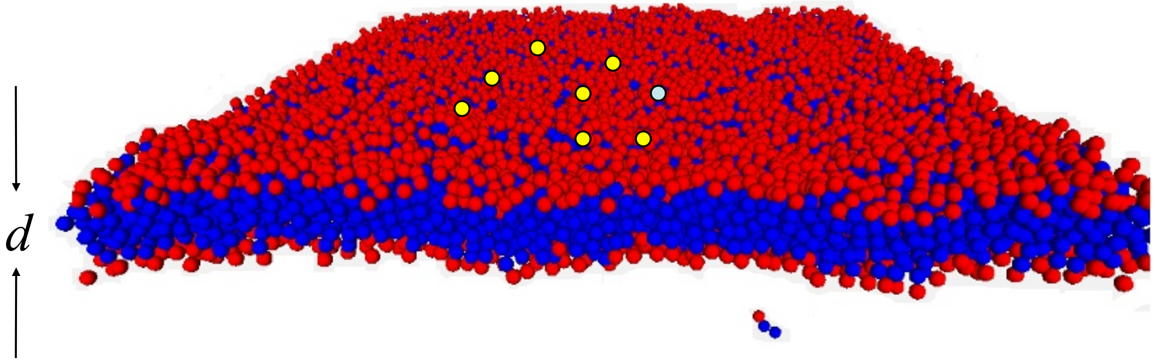

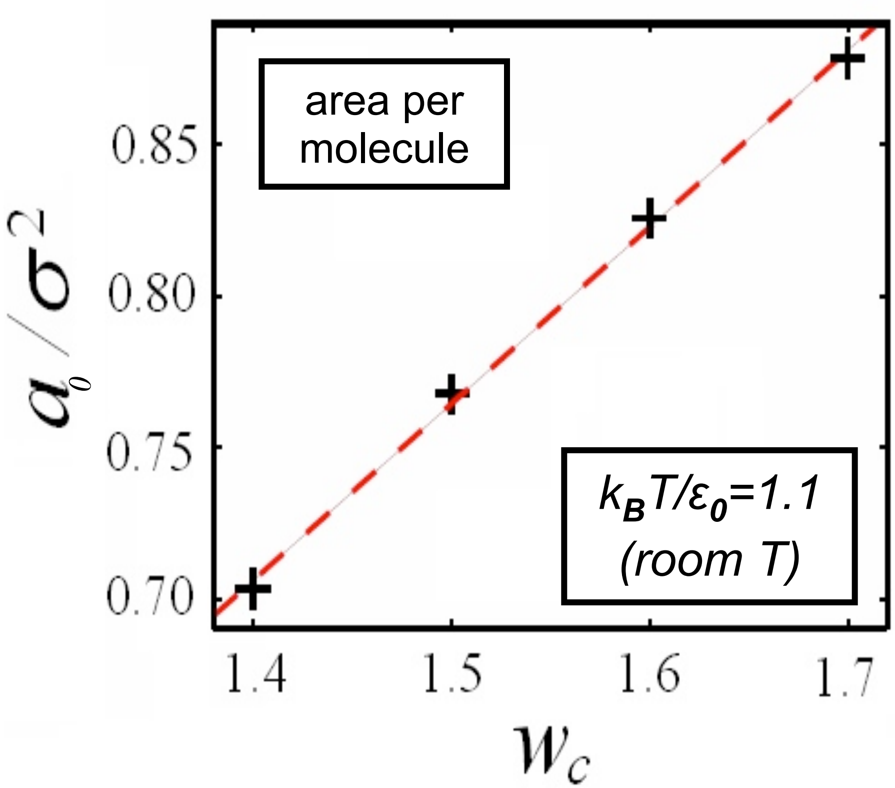

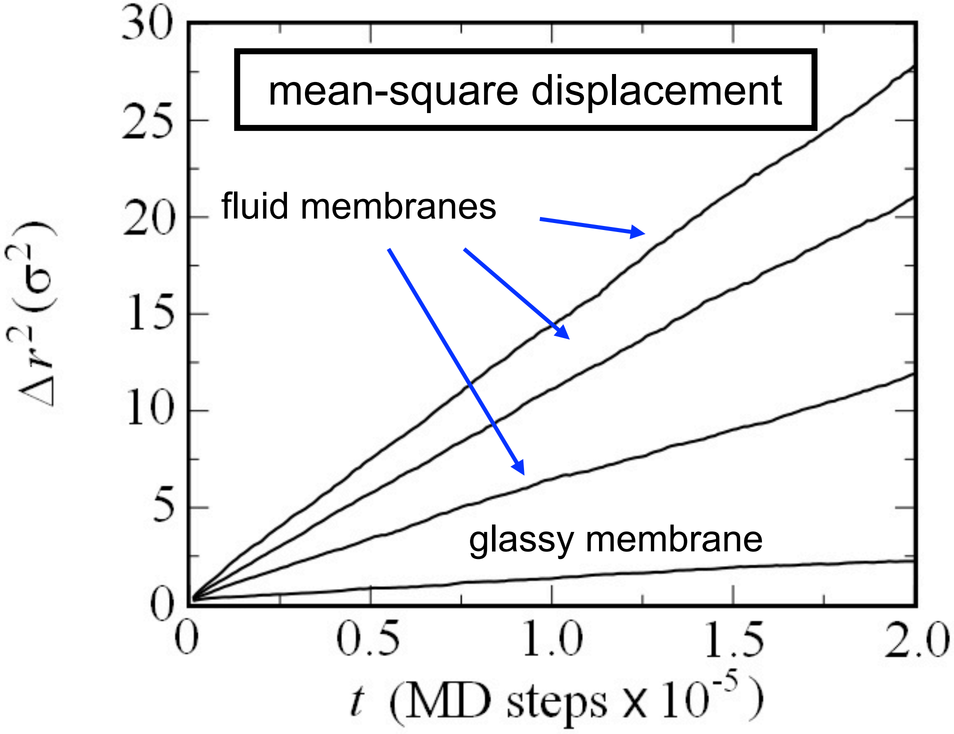

Properties of a physical membrane

- membrane thickness
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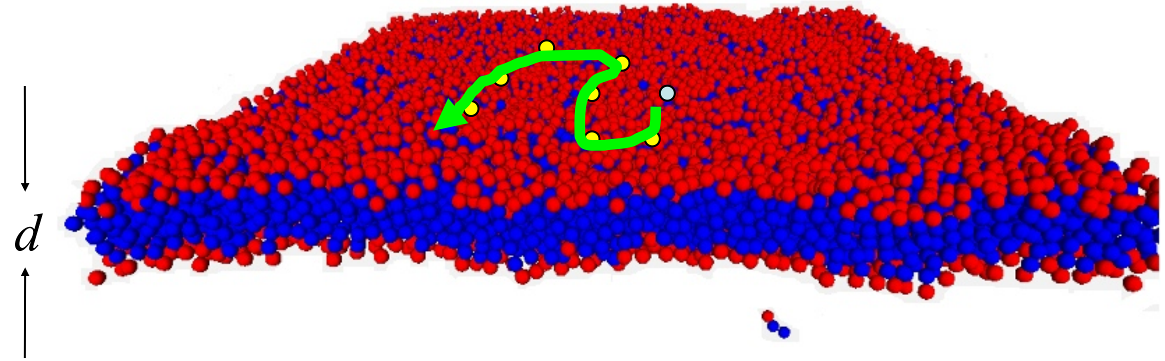
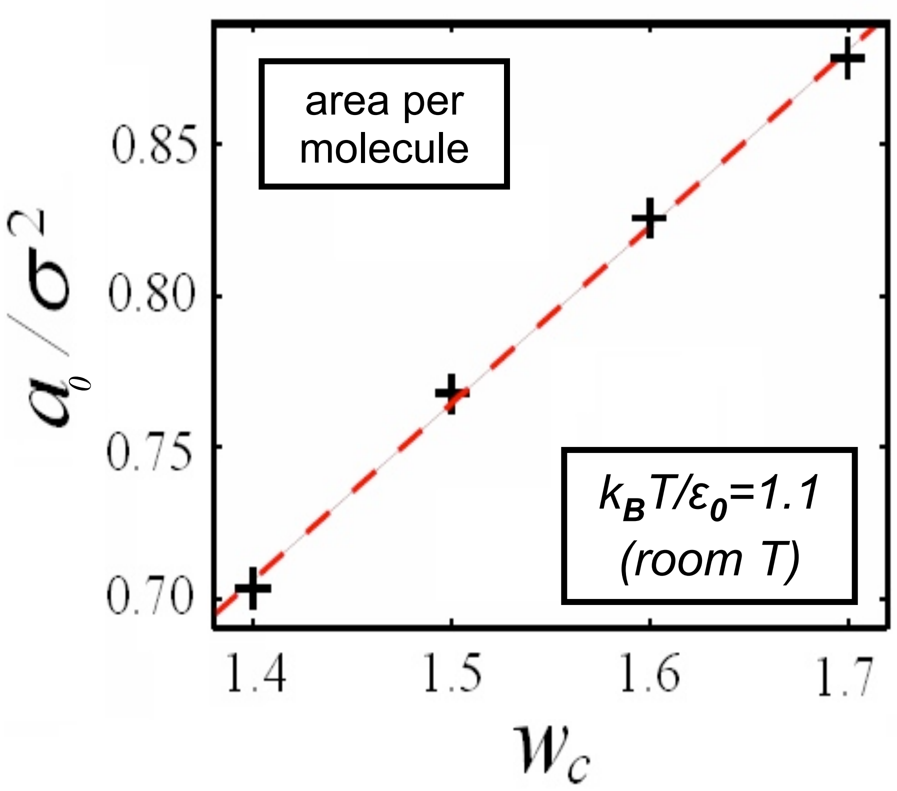
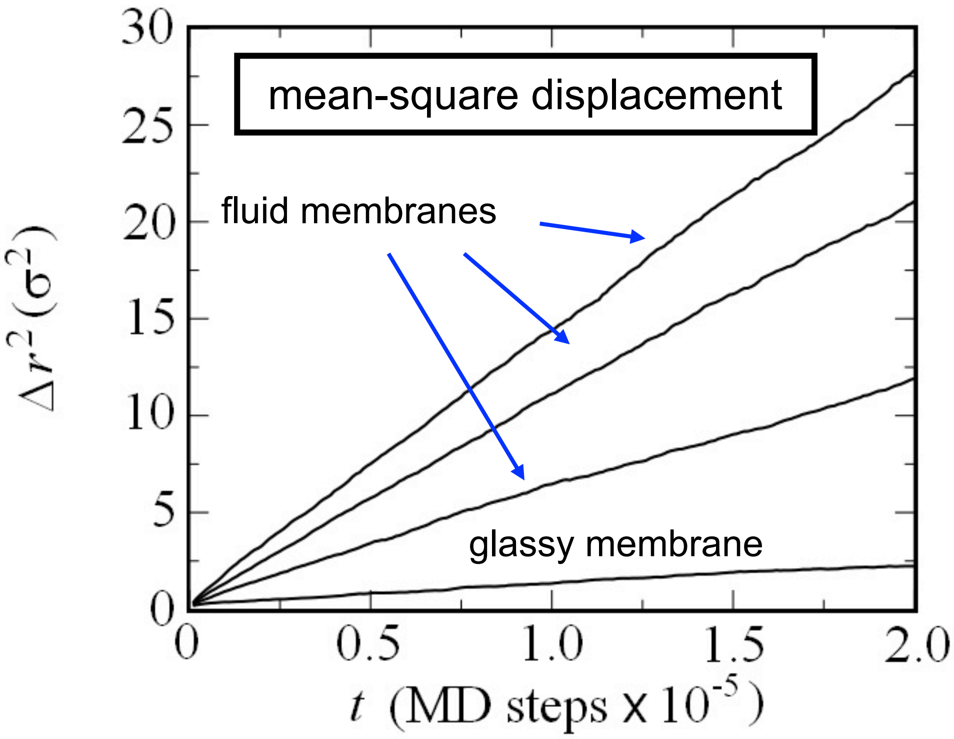
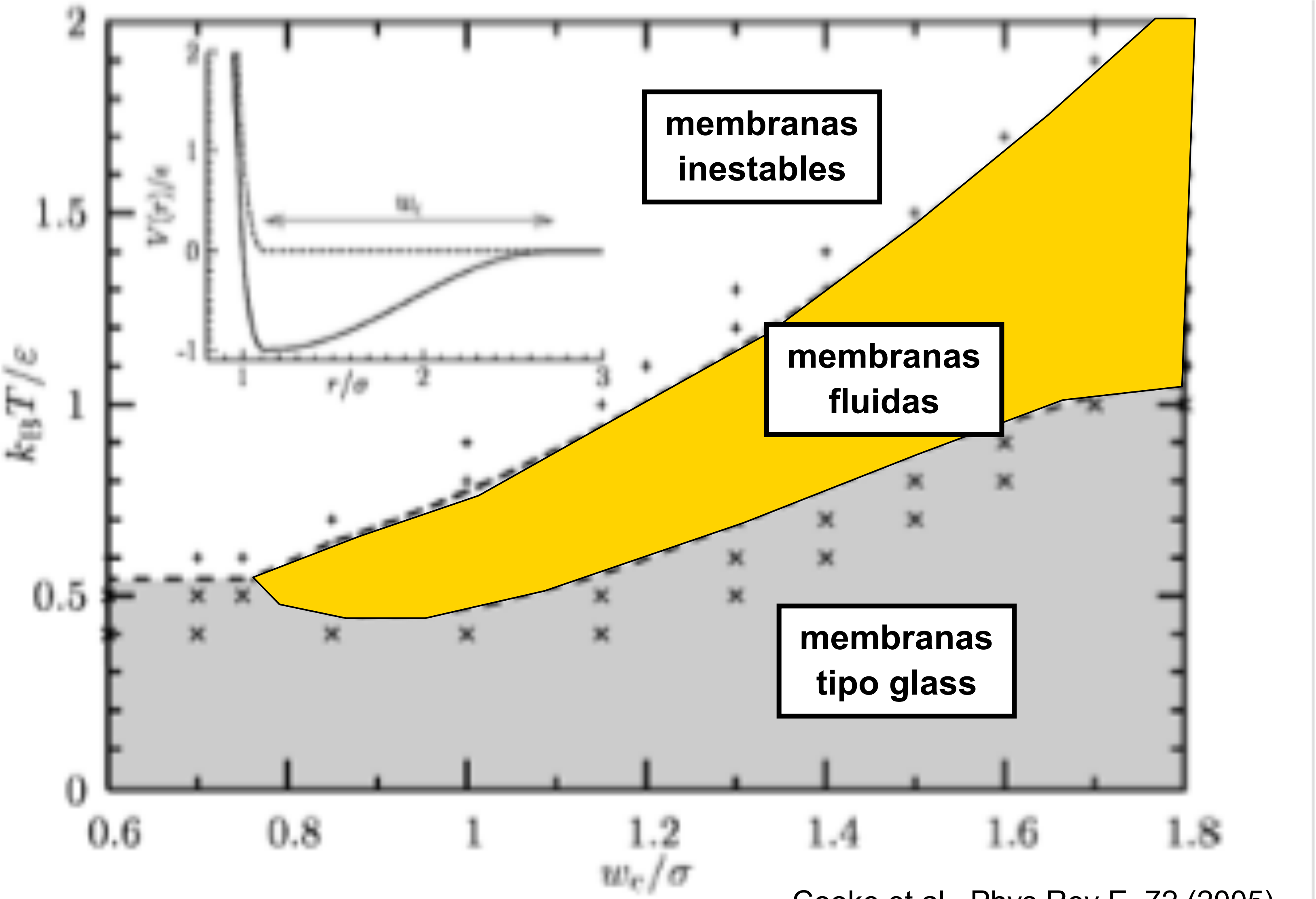




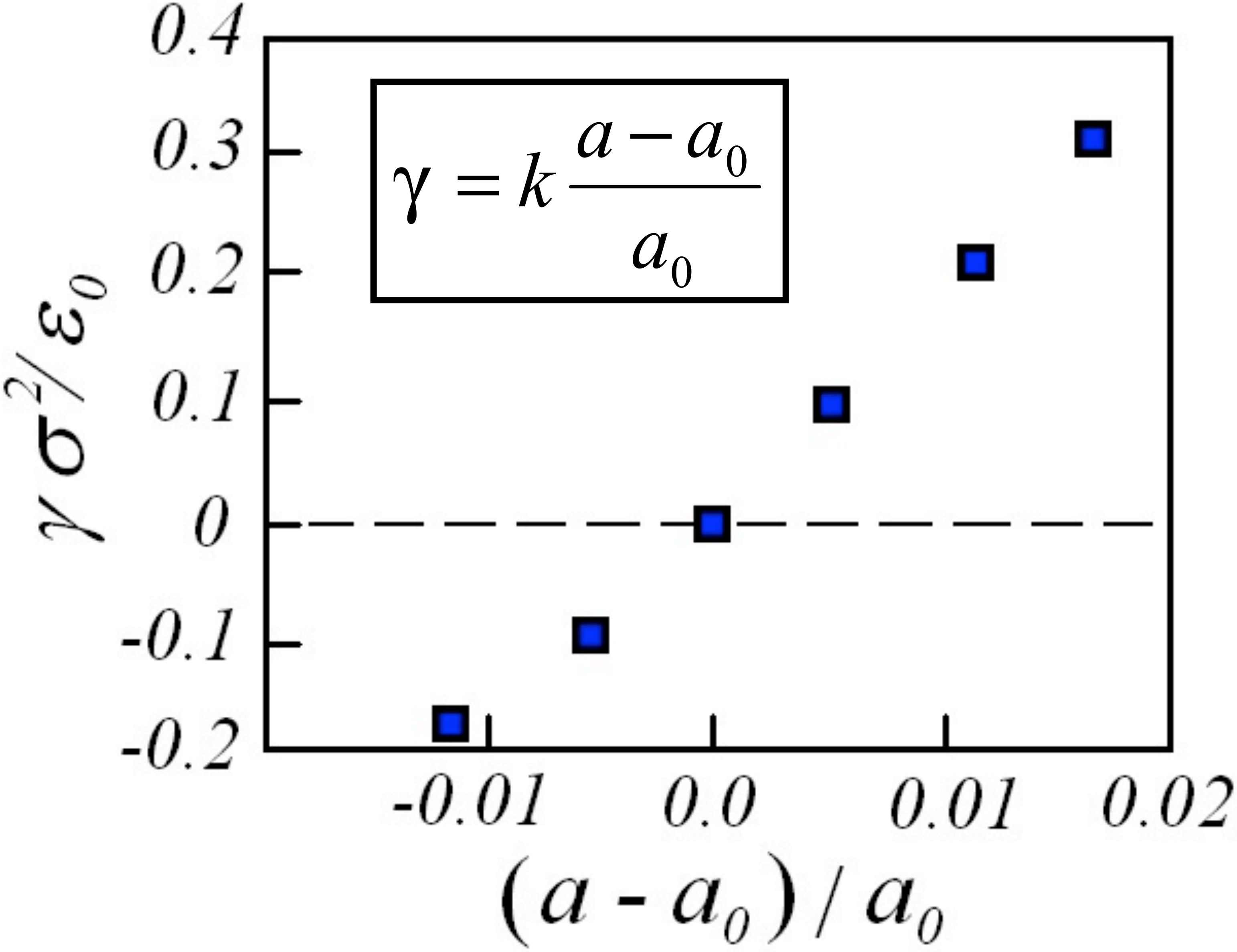


Influencia del parámetro de alcance w_c



Cooke et al., Phys Rev E, 72 (2005)

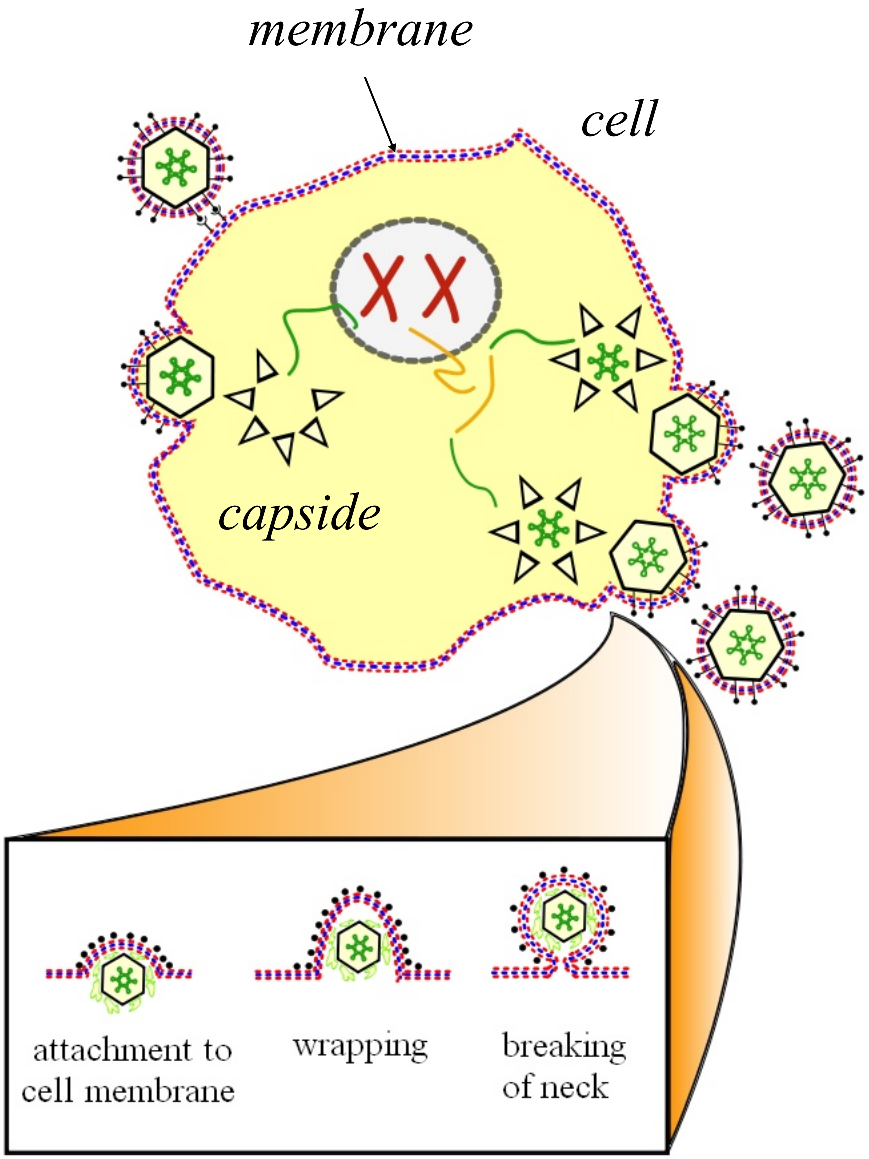
lateral compressibility, *k*


$$\gamma = k\,\frac{a - a_0}{a_0}$$

Application: wrapping and budding of viruses

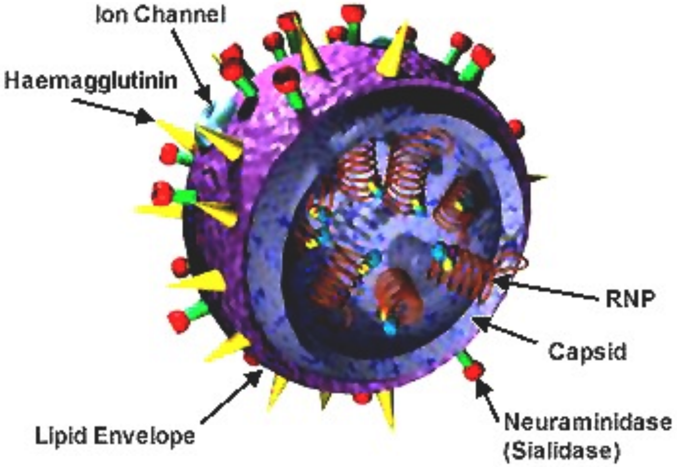
After using the cell machinary to replicate, some viruses leave the cell by acquiring a membrane coating

We aim at understanding the physics of the problem using a very simplified model



enveloped
virus

d= 10 nm



$2R$

40 – 600 nm

$$\frac{2R}{d} = 4 - 60.$$

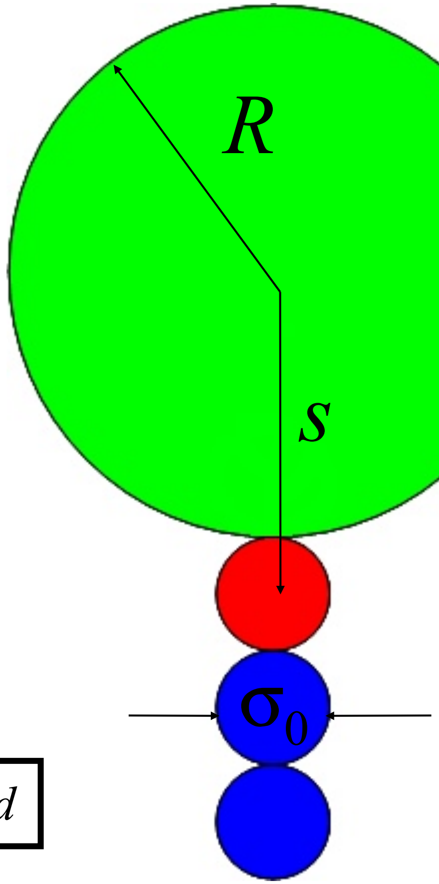
Since $d = 6\sigma_0$, we have:

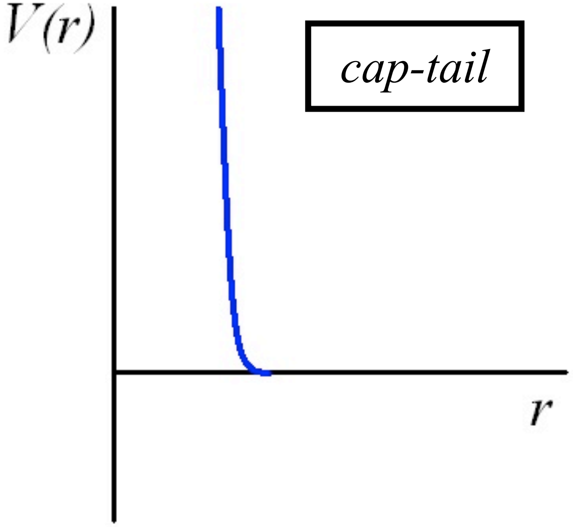
$$R = 12 - 180\sigma_0$$

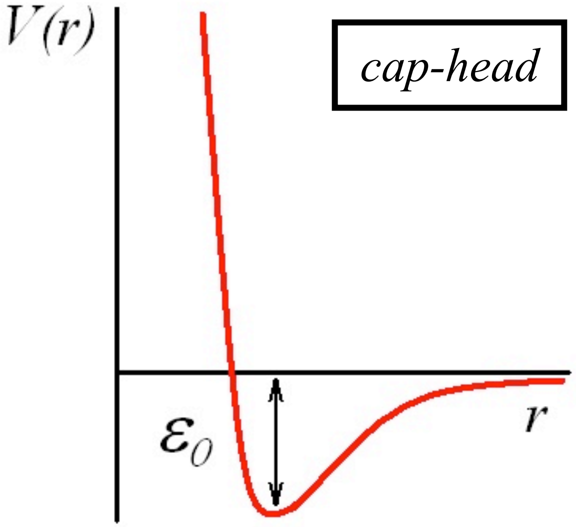
Membrane-particle interaction:

$$V_{cap-tail}(r) = 4\varepsilon_0 \begin{cases} \left[\left(\dfrac{\sigma_0}{r-s}\right)^{12} - \left(\dfrac{\sigma_0}{r-s}\right)^{6} + \dfrac{1}{4}\right], & r < r_c, \\ 0, & r > r_c. \end{cases}$$

$$V_{cap-head}(r) = 4\varepsilon_s \left[\left(\dfrac{\sigma_0}{r-s}\right)^{12} - \left(\dfrac{\sigma_0}{r-s}\right)^{6}\right]$$

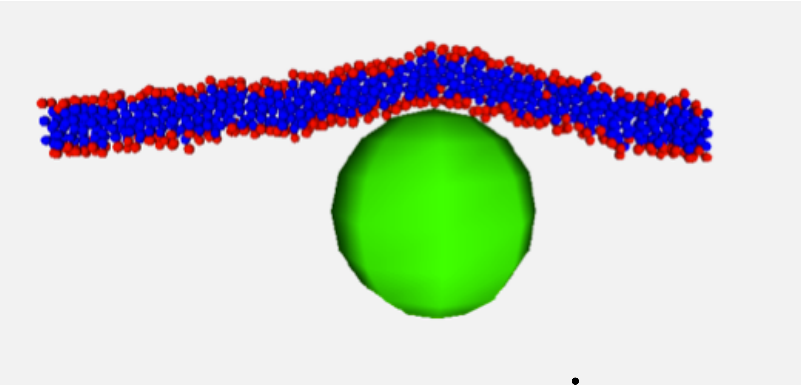




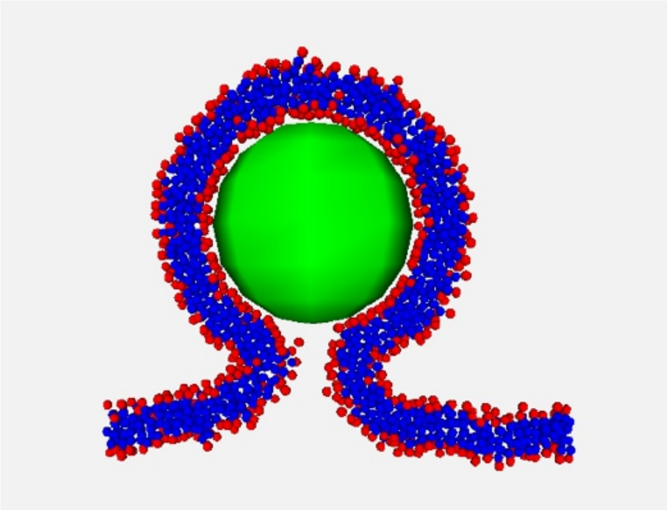


$$s = R + \frac{\sigma_0}{2}$$

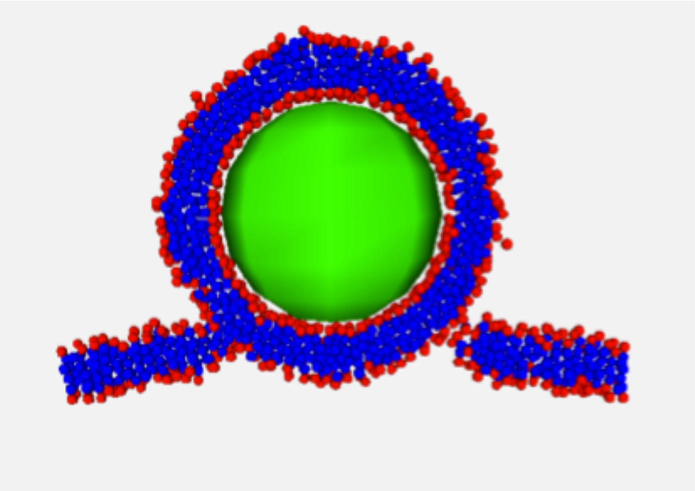
Typical behaviours



non-wrapping



wrapping &
budding

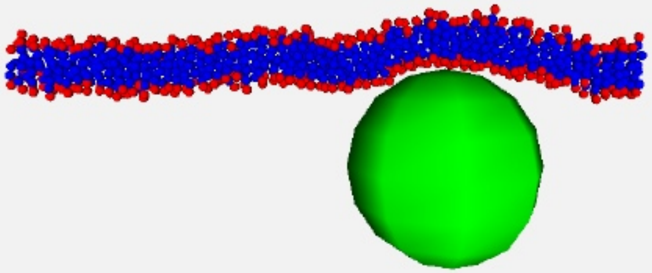


membrane
breaking

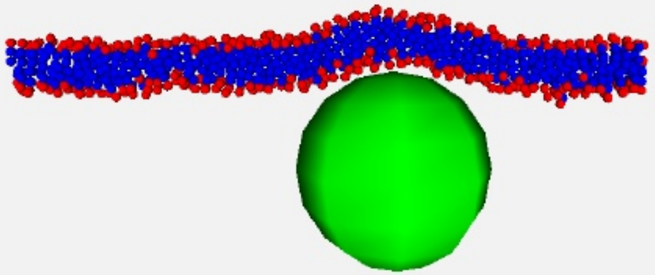
NON - WRAPPING

$\tau_0 = 9.85$ ps

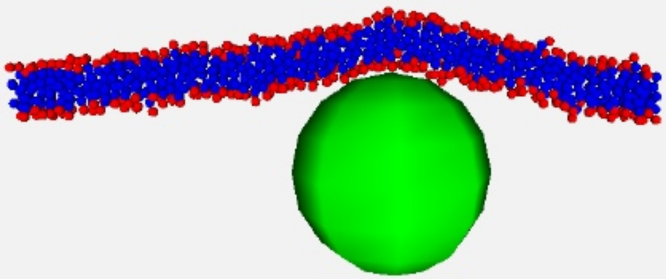
$R = 10\,\sigma_0$



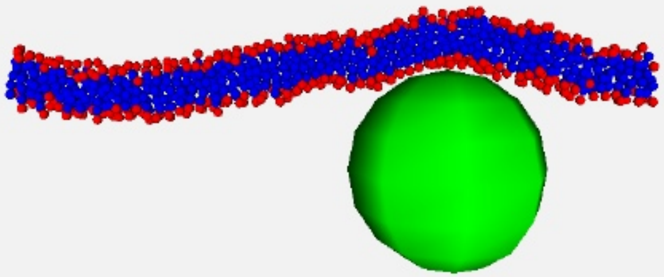
$\tau/\tau_0 = 10^3$



$\tau/\tau_0 = 5\text{x}10^3$

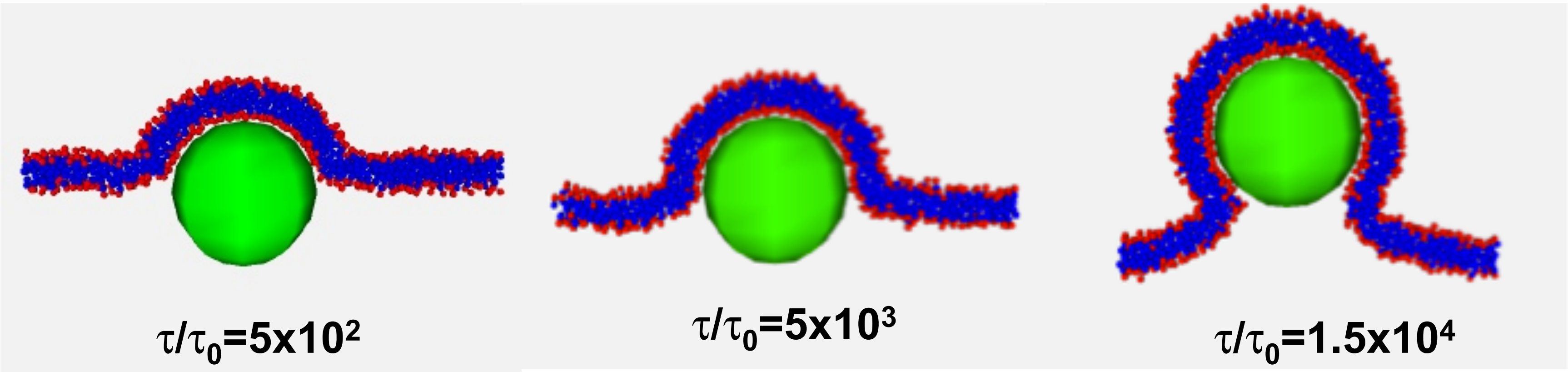


$\tau/\tau_0 = 10^4$



$\tau/\tau_0 = 3\text{x}10^4$

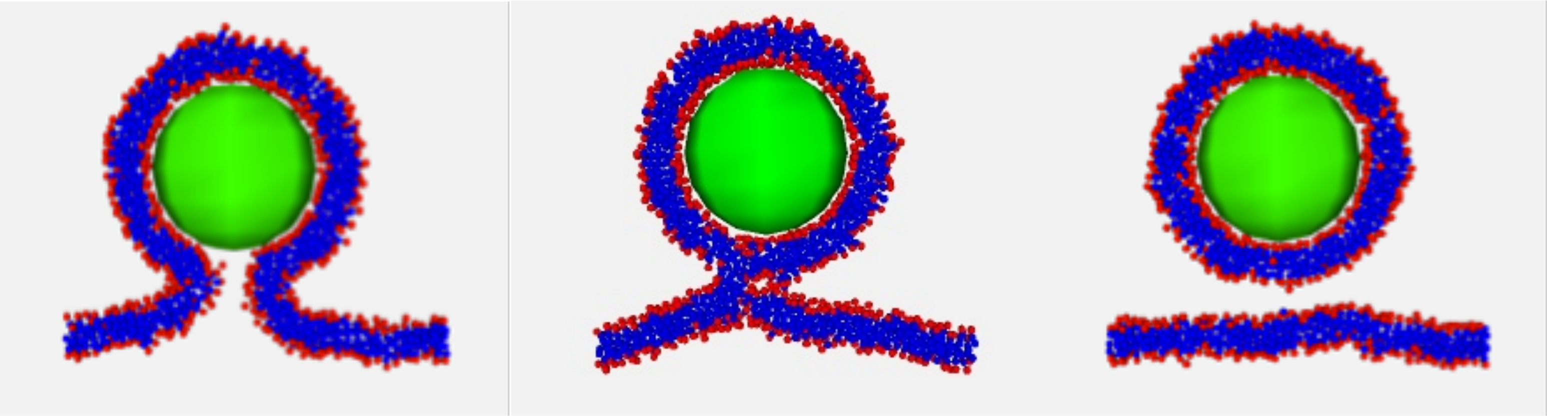
WRAPPING



$\tau/\tau_0=5x10^2$

$\tau/\tau_0=5x10^3$

$\tau/\tau_0=1.5x10^4$

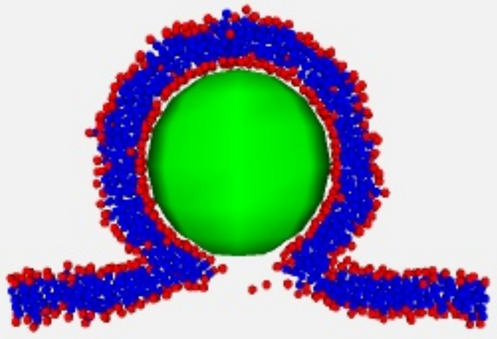


$\tau/\tau_0=1.55x10^4$

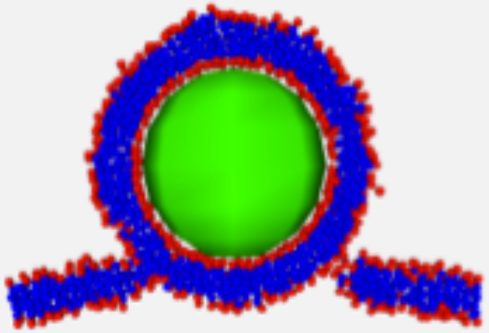
$\tau/\tau_0=1.6x10^4$

$\tau/\tau_0=1.65x10^4$

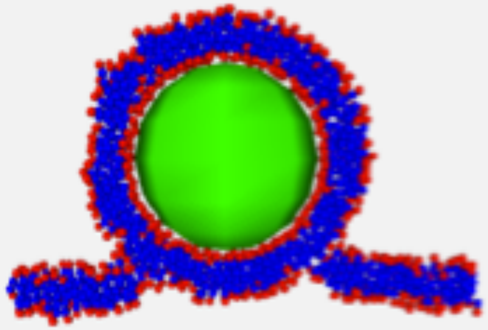
MEMBRANE BREAKING



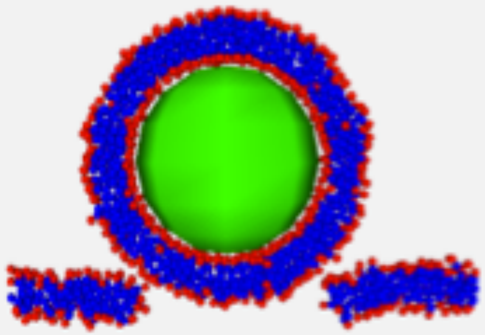
$\tau/\tau_0=5.5x10^3$



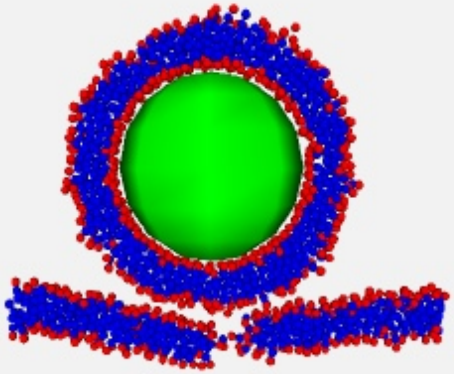
$\tau/\tau_0=6x10^3$



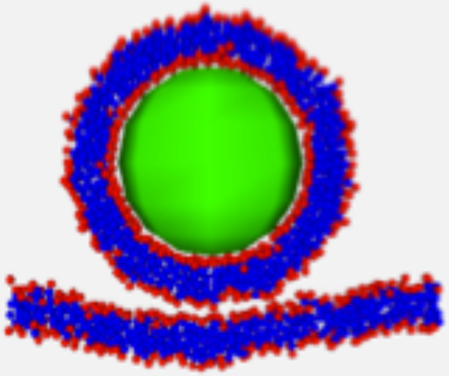
$\tau/\tau_0=7x10^3$



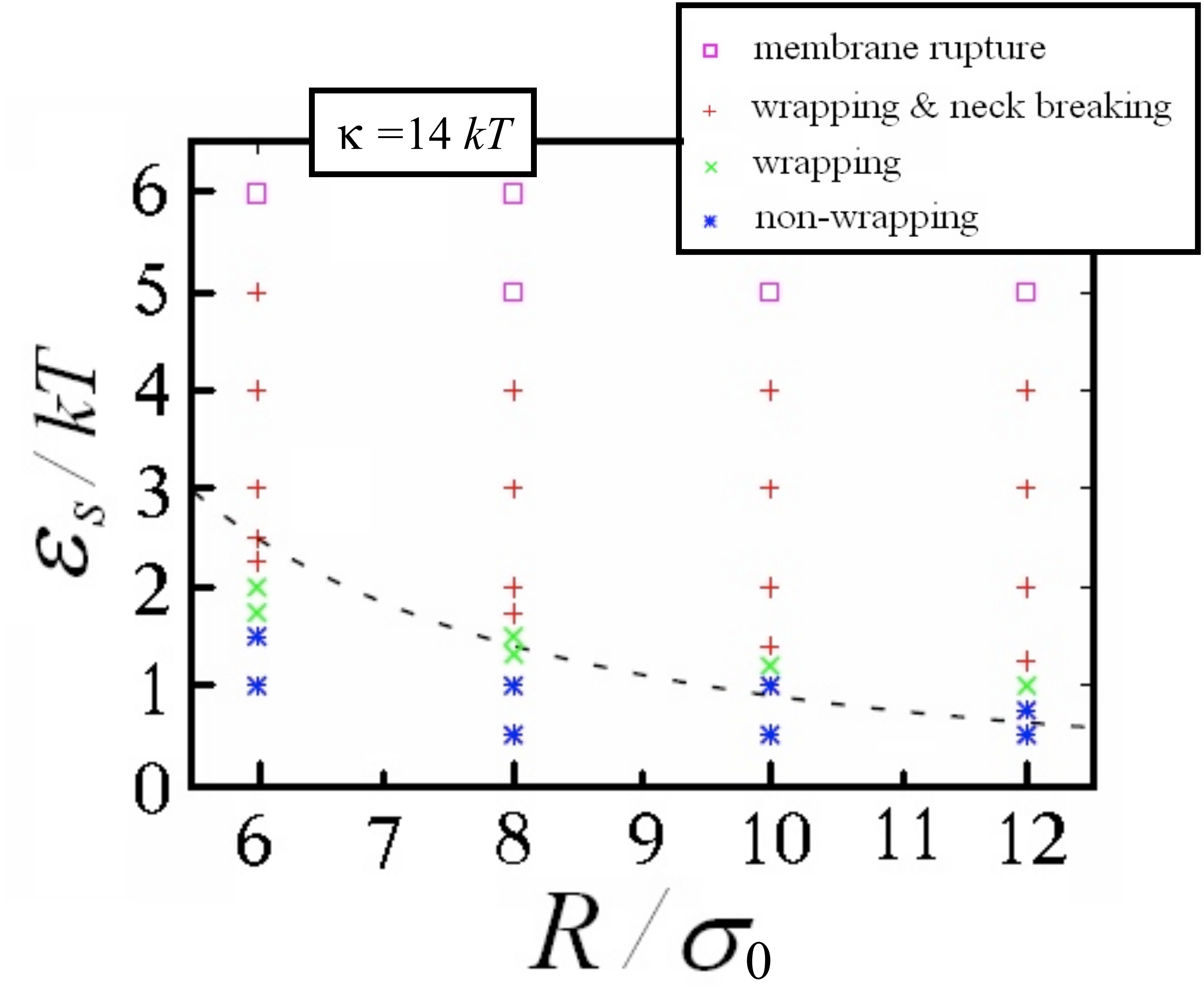
$\tau/\tau_0=7.5x10^3$

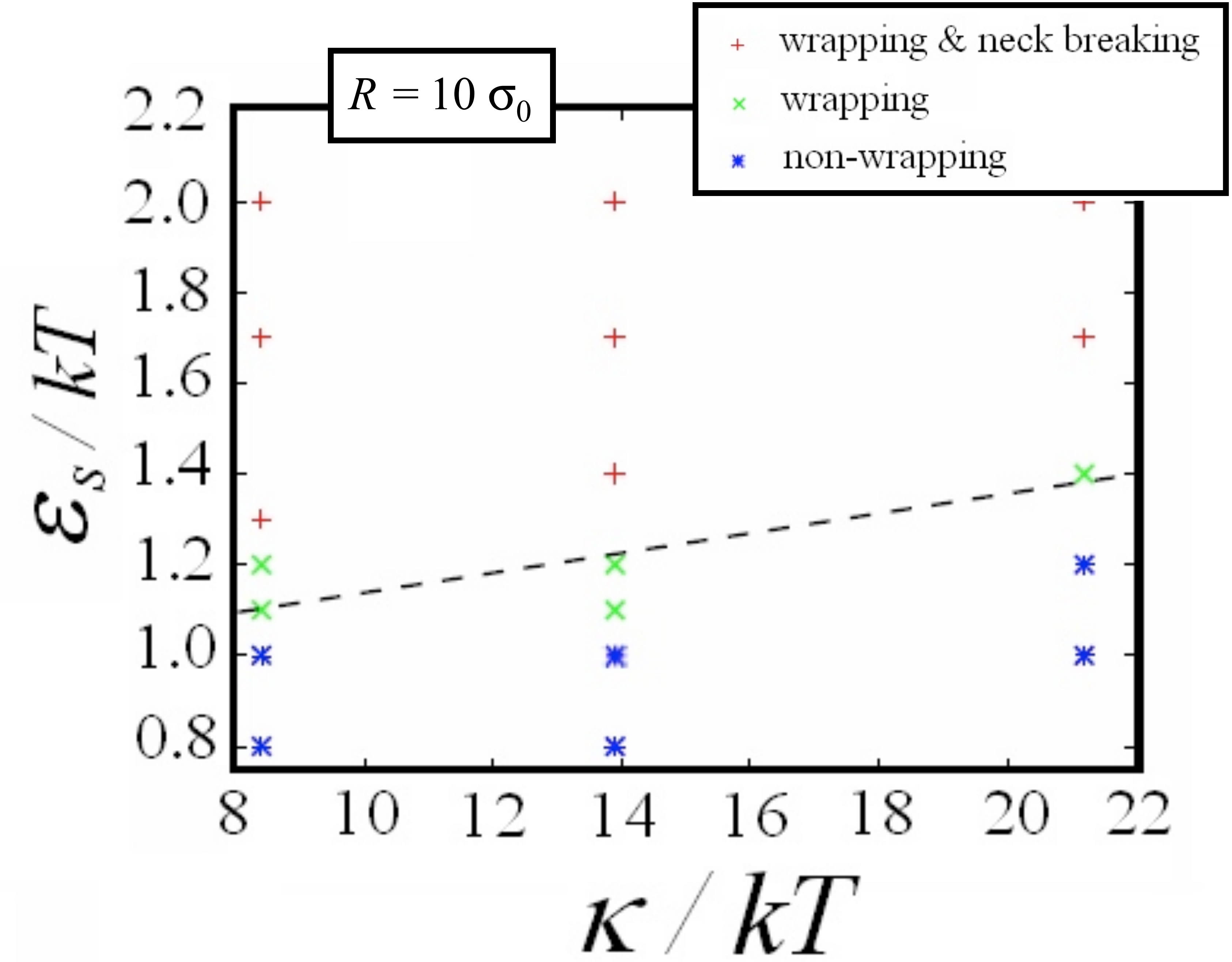


$\tau/\tau_0=9.5x10^3$



$\tau/\tau_0=10^4$


κ =14 kT
□ membrane rupture
+ wrapping & neck breaking
× wrapping
✱ non-wrapping
ε_S / kT
0
1
2
3
4
5
6
R / σ_0
6
7
8
9
10
11
12


$R = 10\ \sigma_0$
+ wrapping & neck breaking
× wrapping
* non-wrapping
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
ε_s / kT
8
10
12
14
16
18
20
22
κ / kT