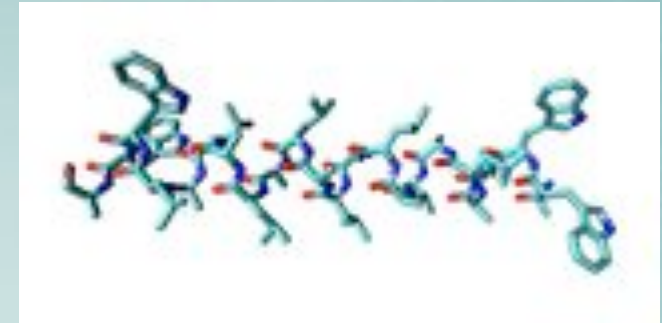
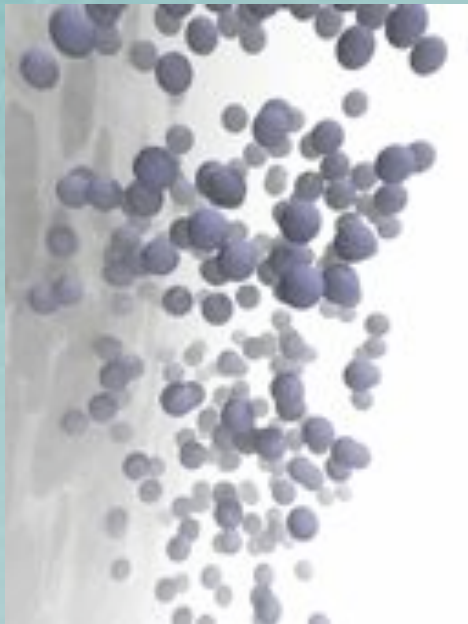


RELEASE OF CONTENT THROUGH MECHANO- SENSITIVE GATES IN PRESSURISED LIPOSOMES

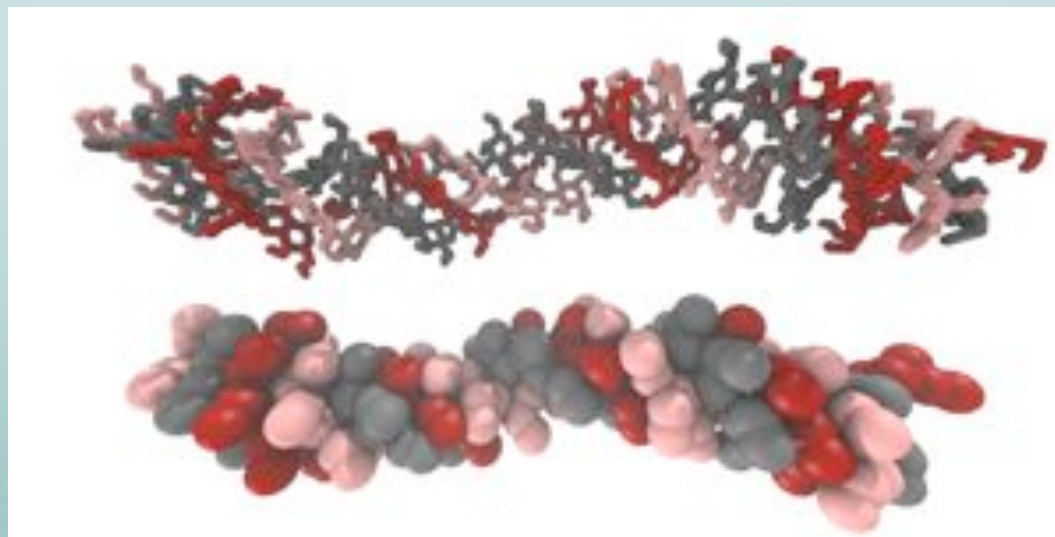
Martti Louhivuori
University of Groningen

www.cgmartini.nl

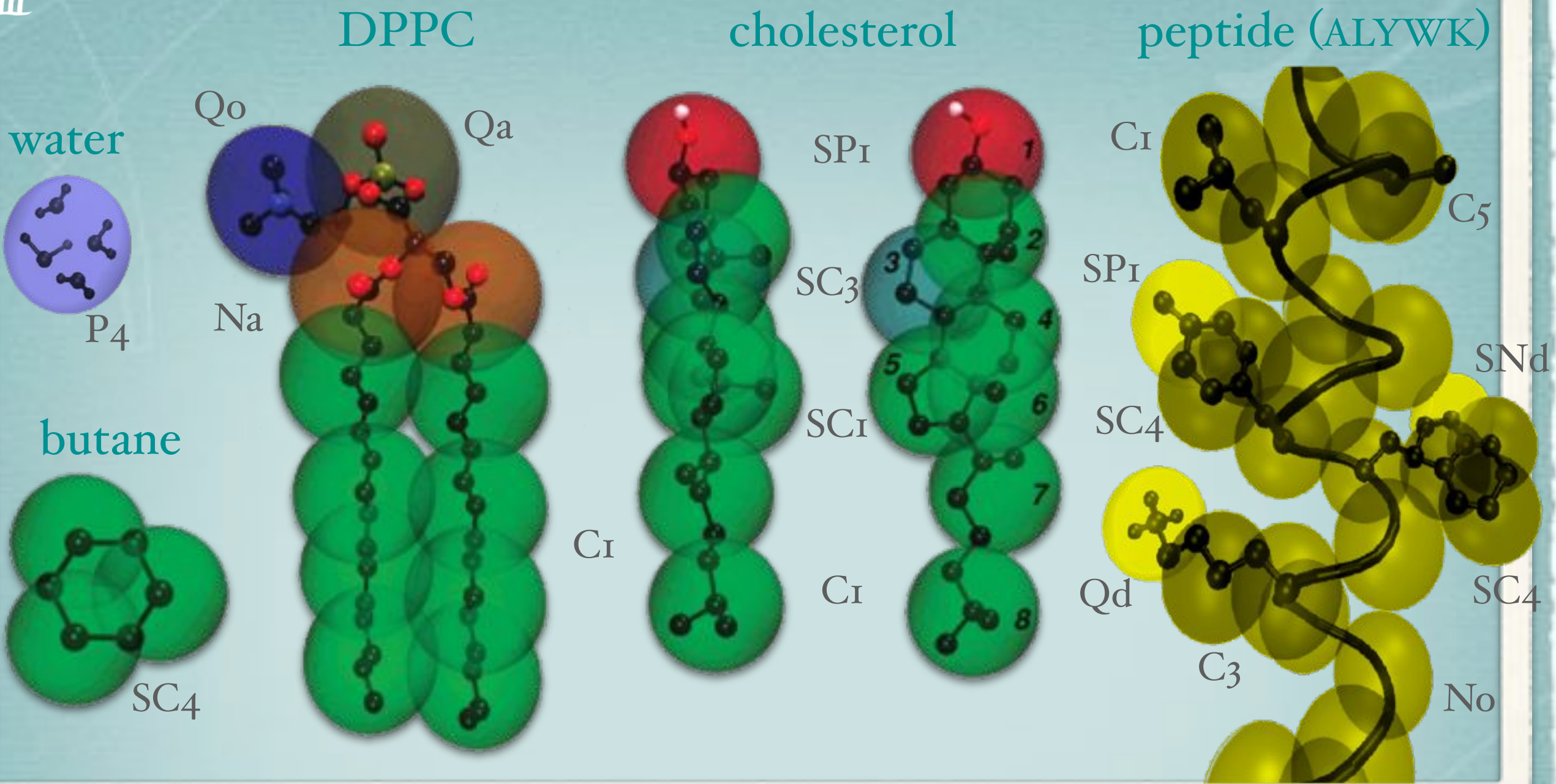


MARTINI

coarse-grained model



III

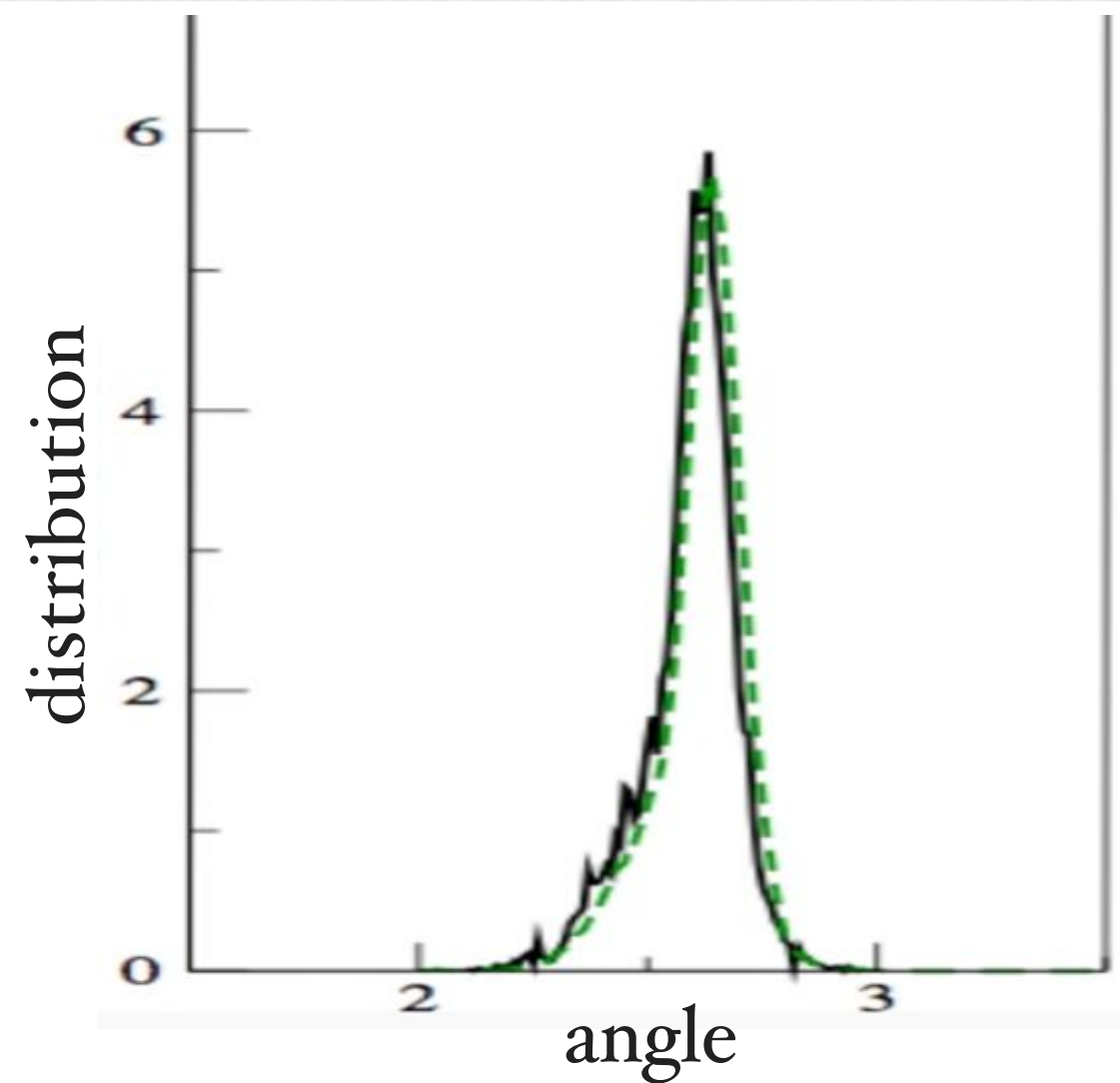
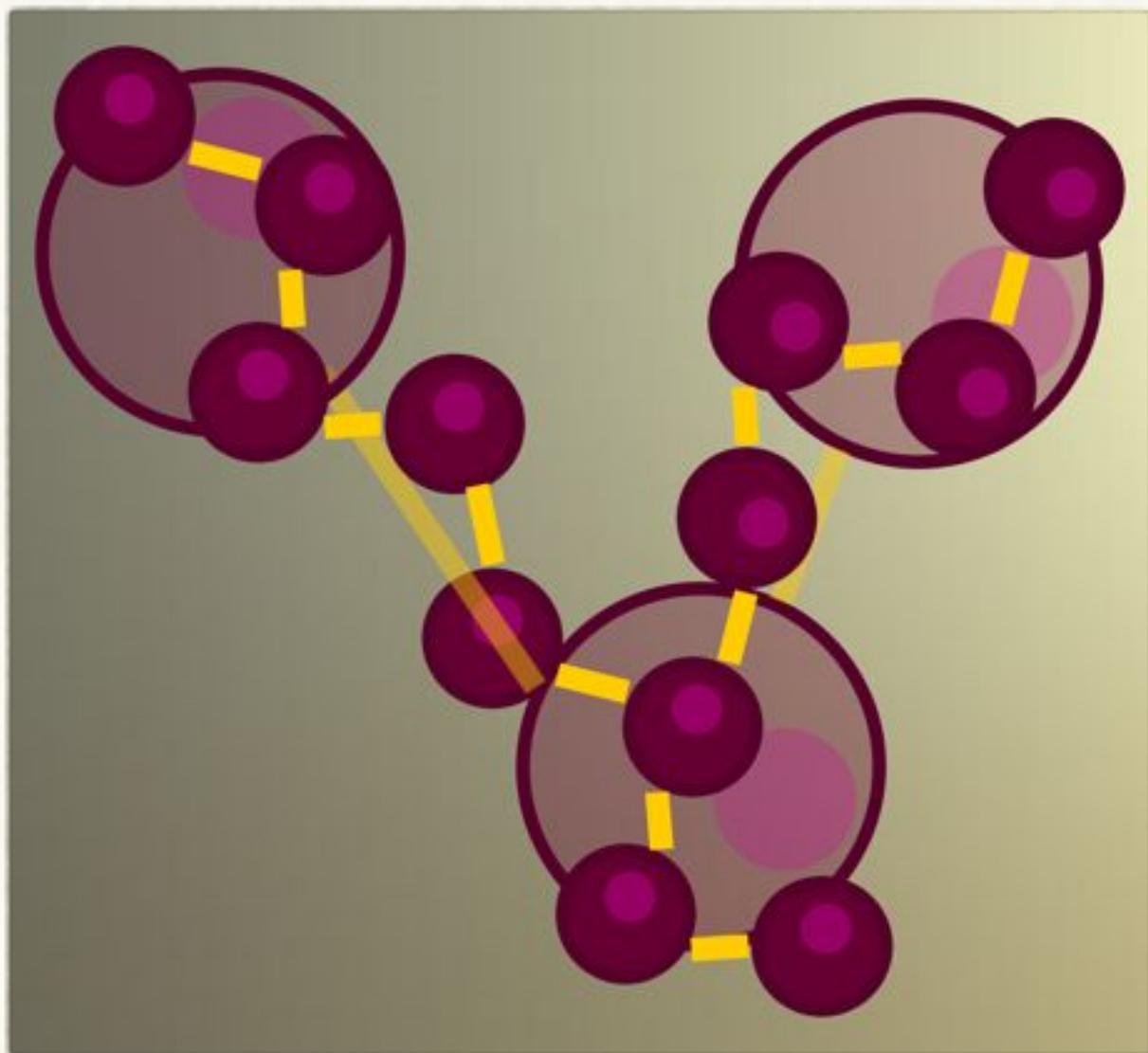


MARTINI CG model

interaction sites

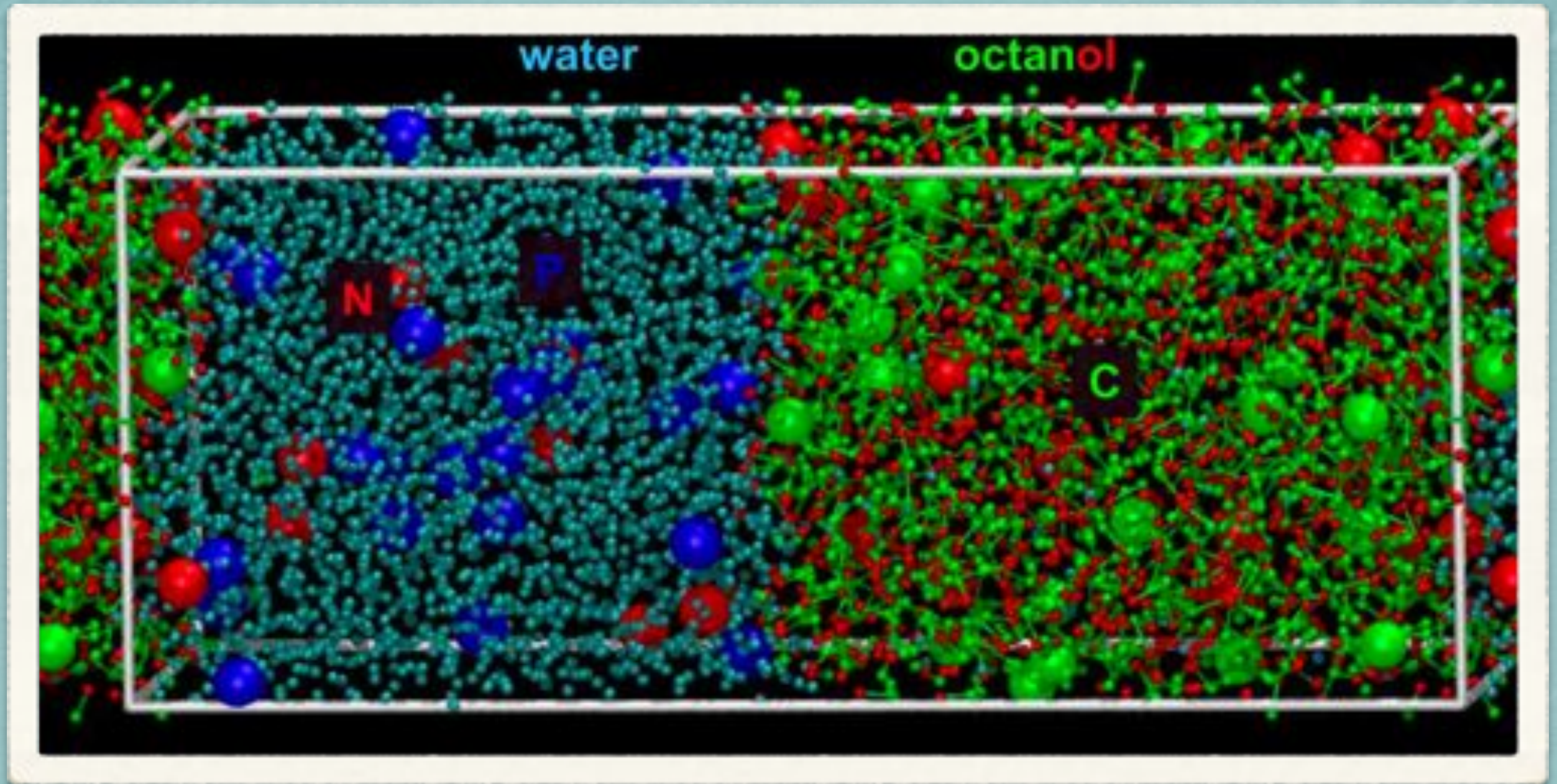
parametrisation of MARTINI

- * experimental (thermodynamic) data
 - non-bonded interactions
- * atomistic MD simulations
 - bonded interactions



parametrisation

bonded interactions

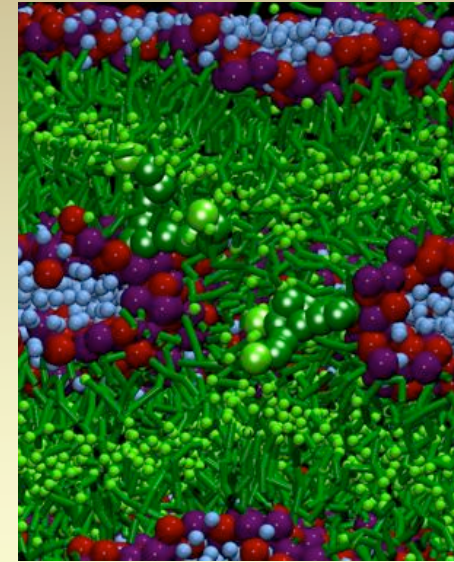
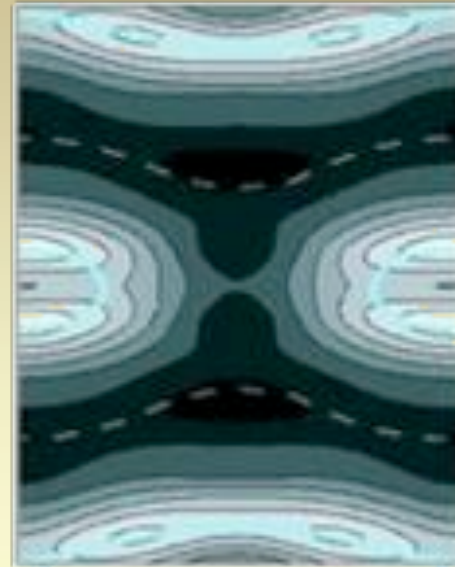
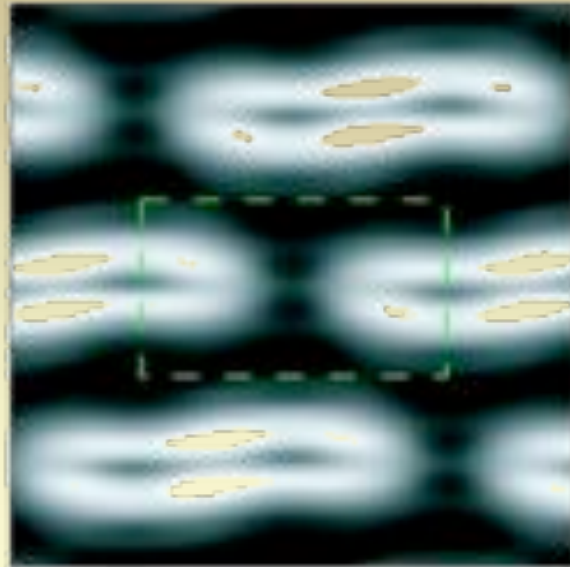


parametrisation

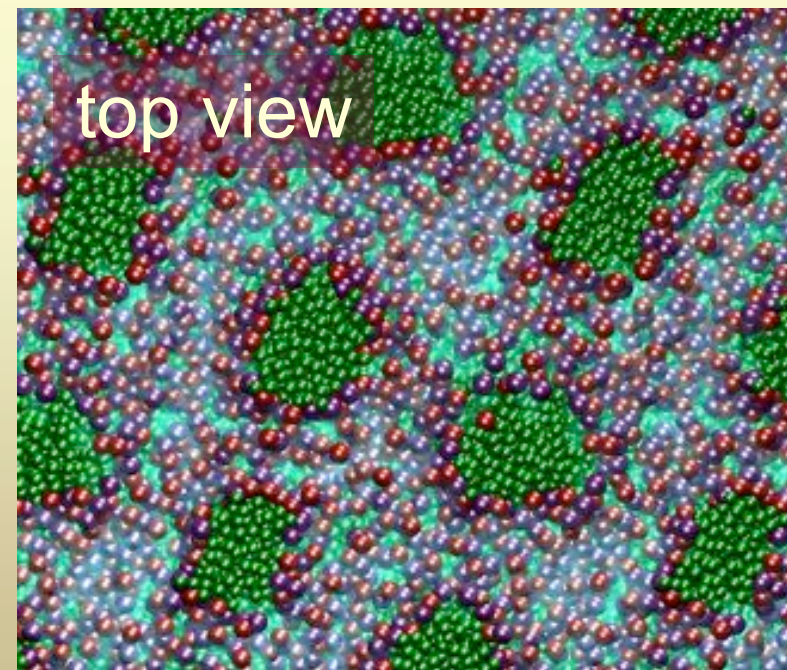
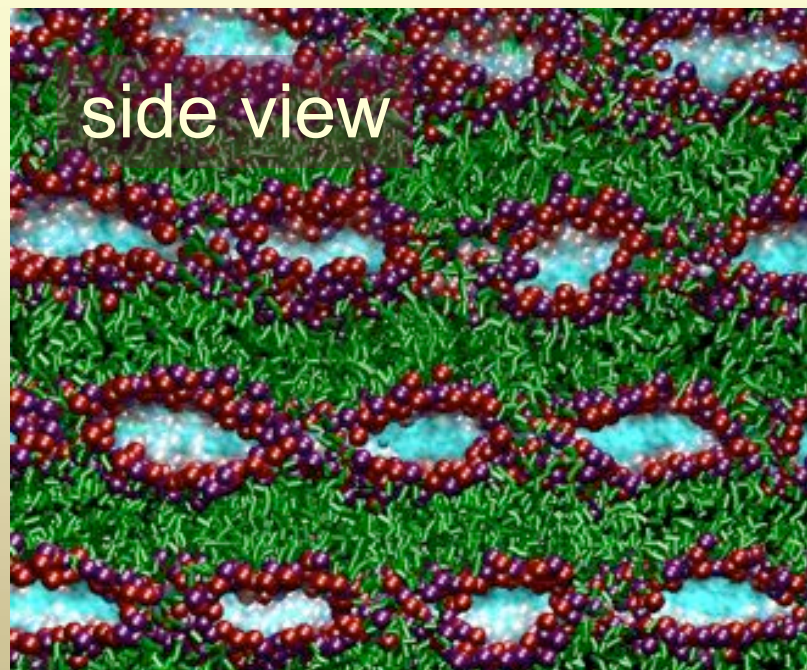
non-bonded interactions

THE VALIDATION

comparing to experimental measurements

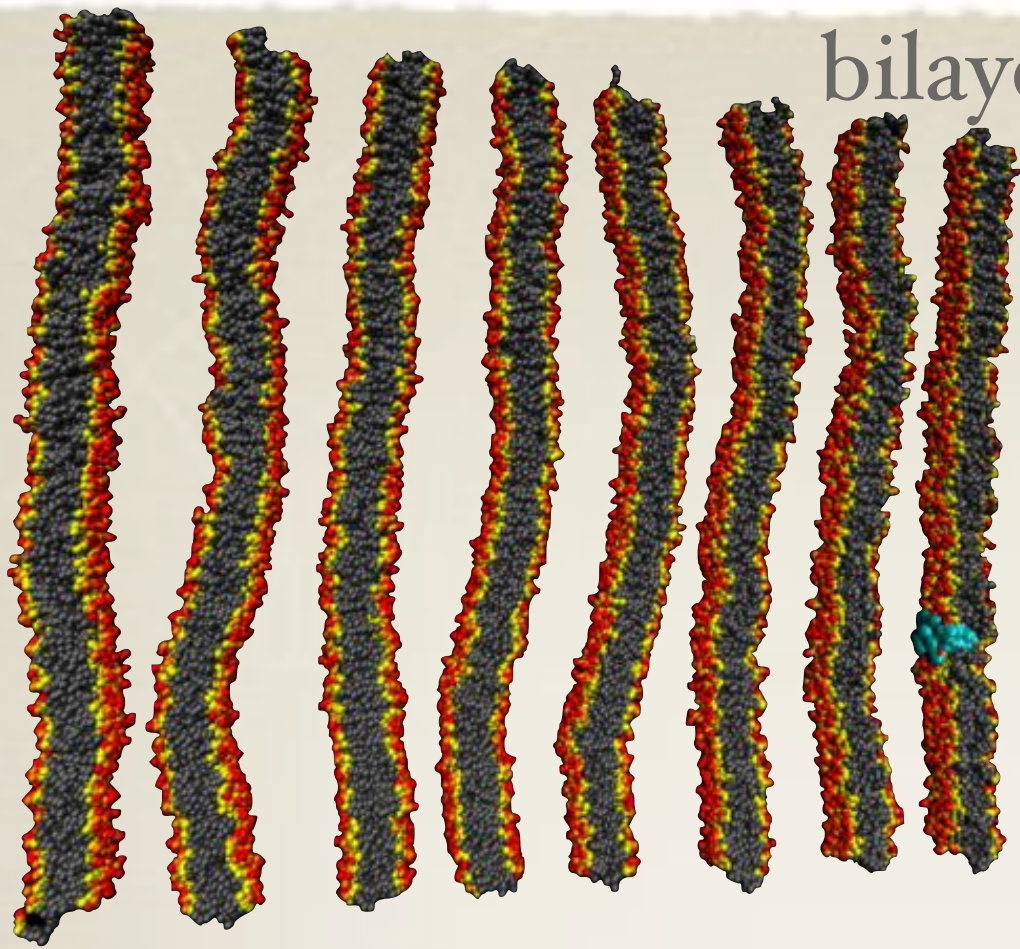


Rhombohedral phase (experimentally observed for DOPC/DOPE 3:1 and 2:1 *Lyan & Huang, 2002*)

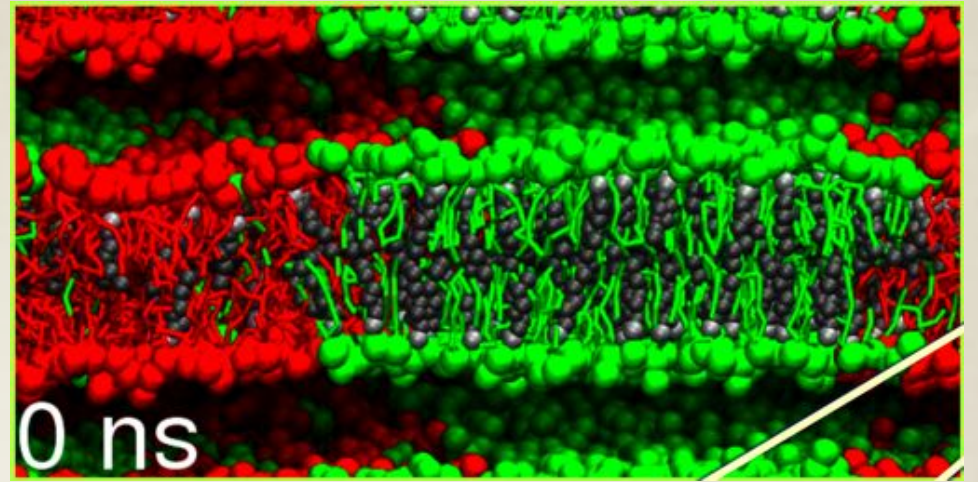


Reproduced in CG simulation (*Marrink & Mark, Biophys. J., 2004*)

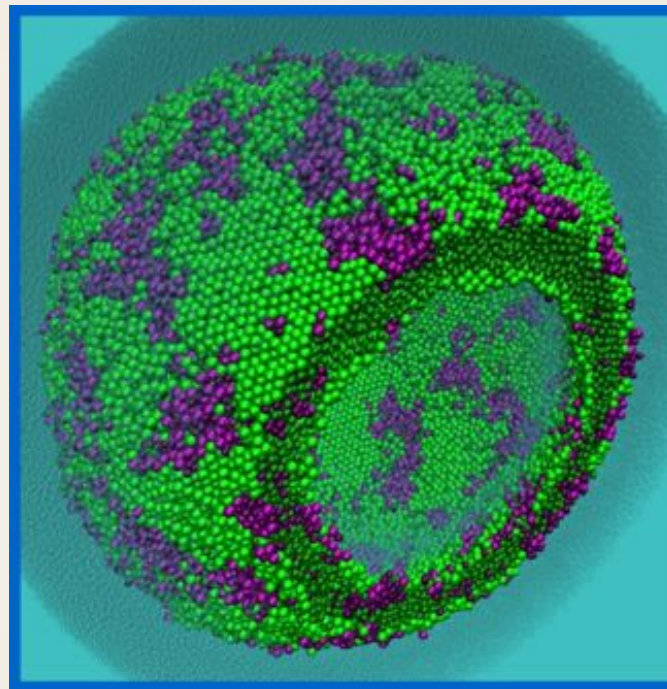
bilayers



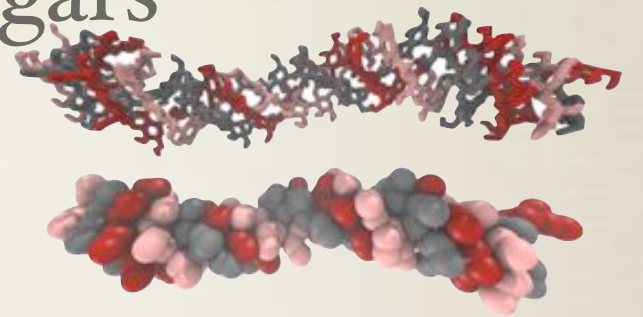
rafts



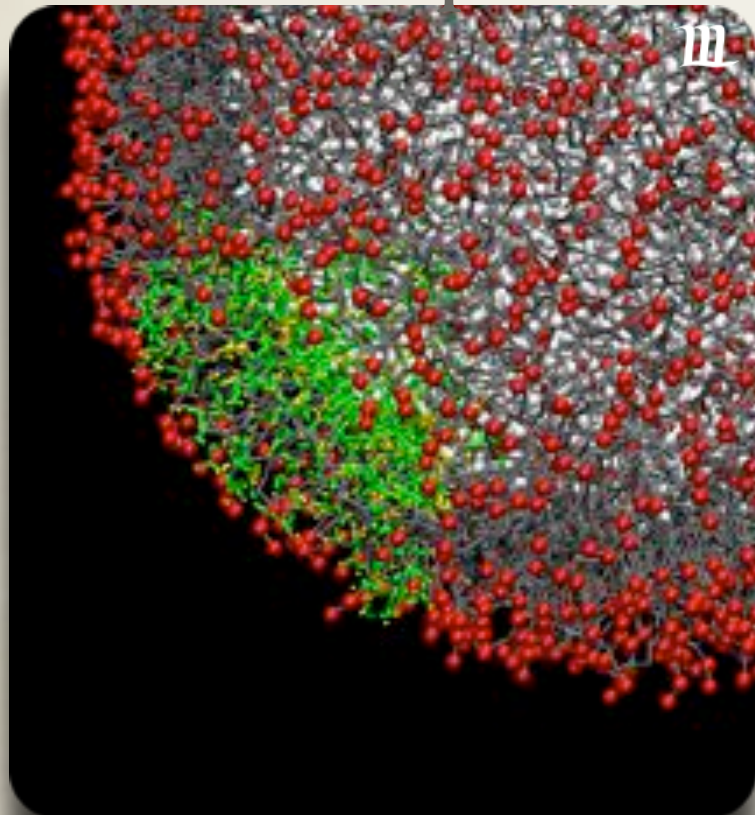
vesicles



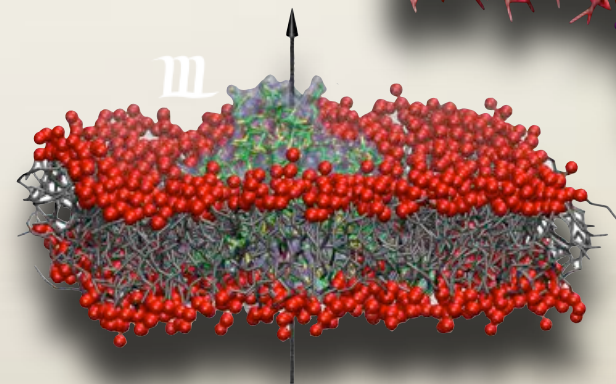
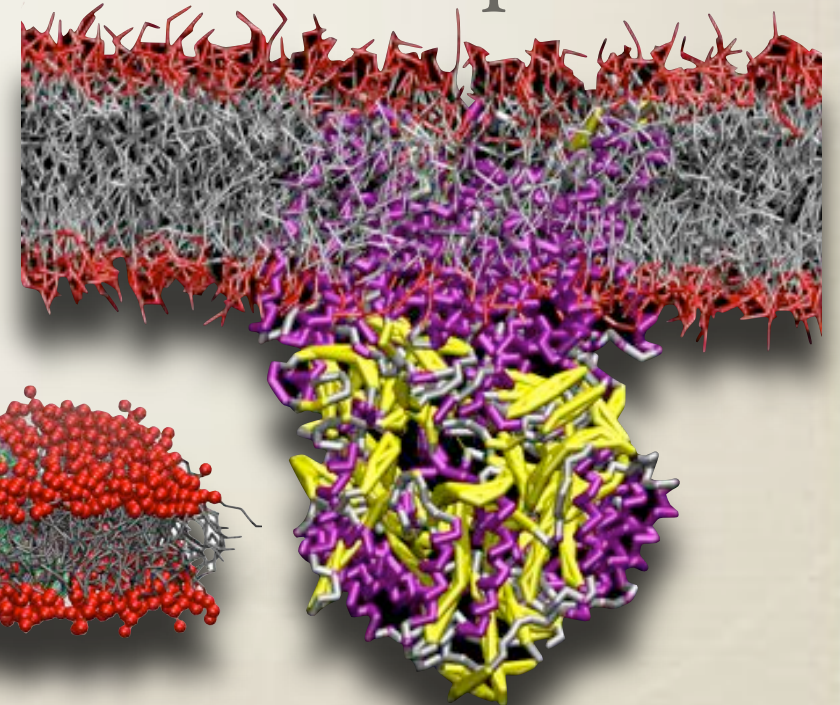
sugars



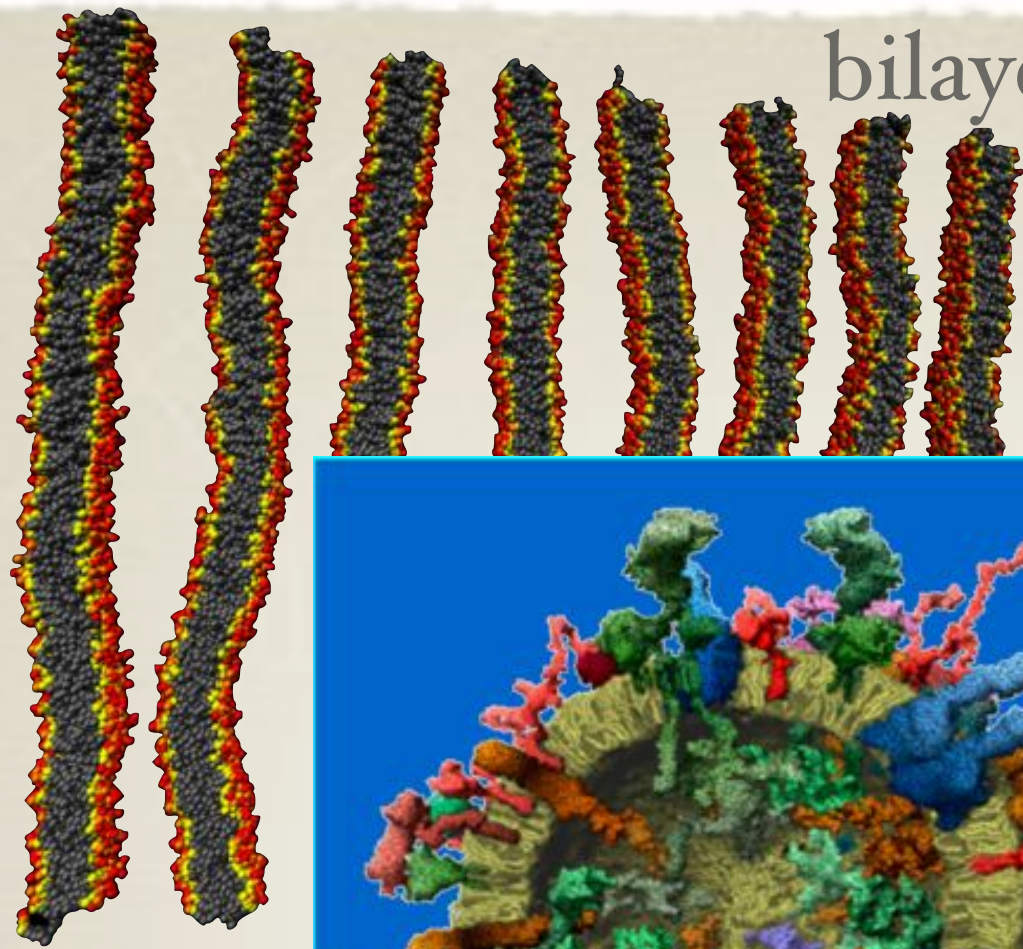
vesicles w/ proteins



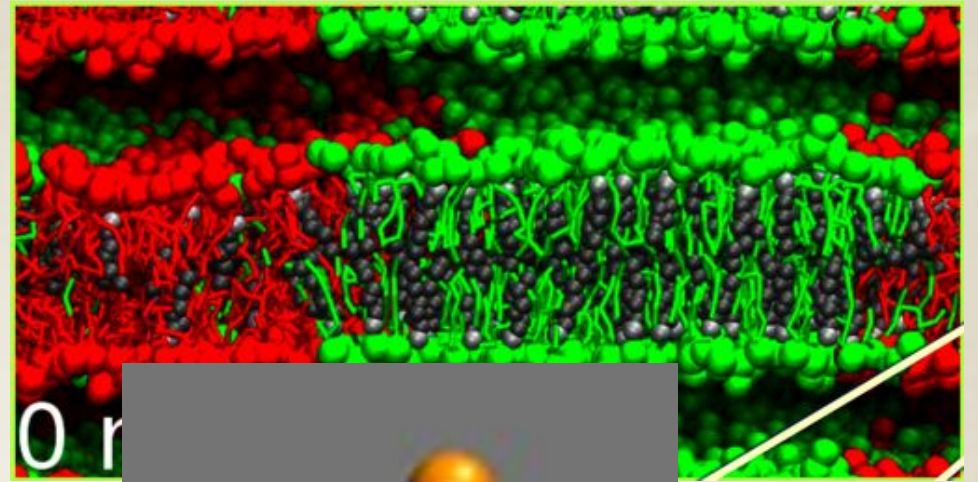
membrane proteins



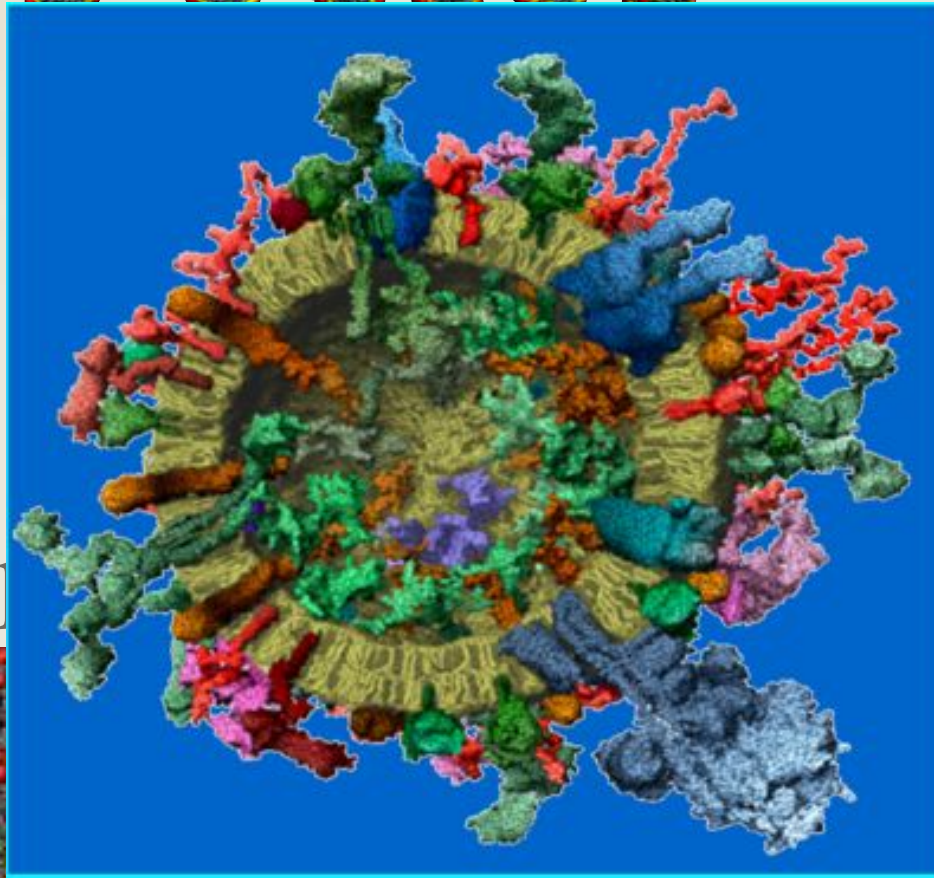
bilayers



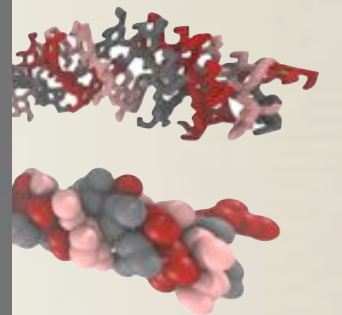
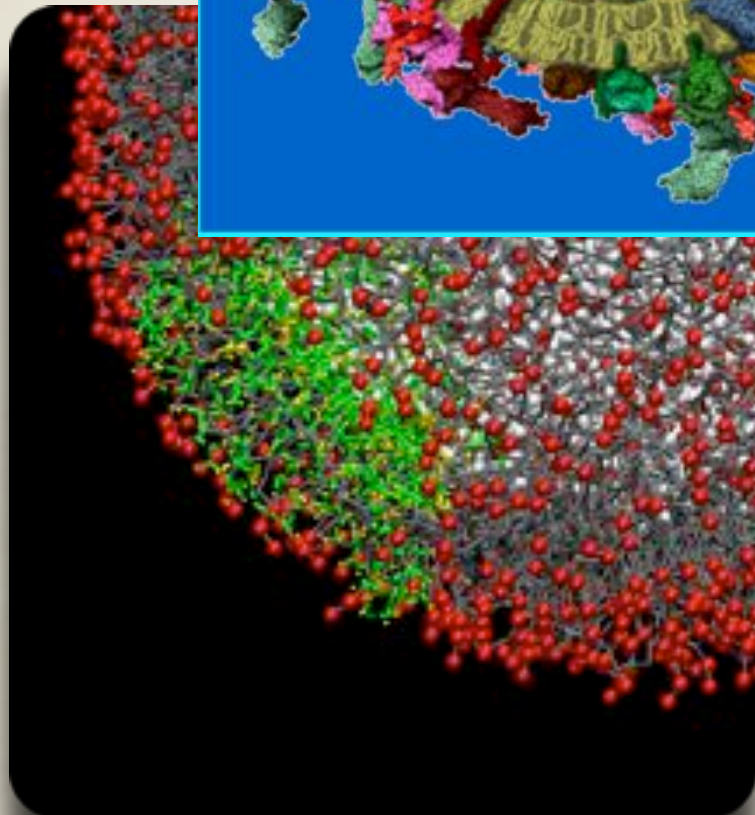
rafts



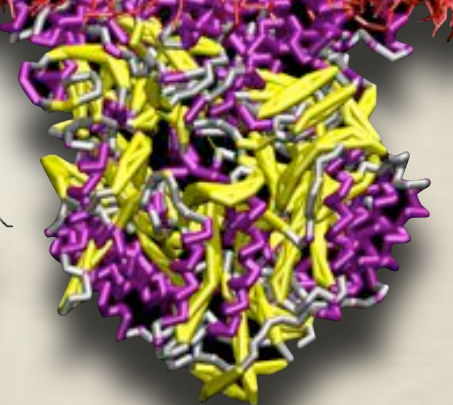
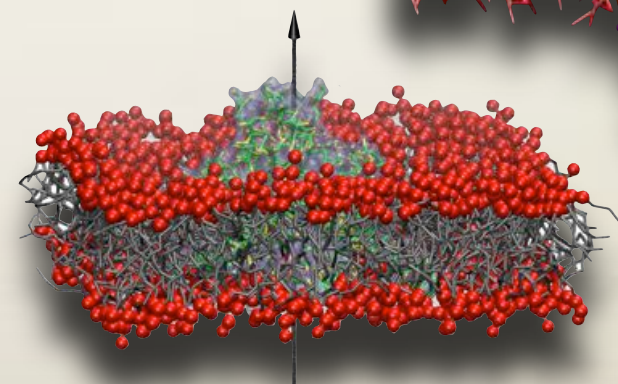
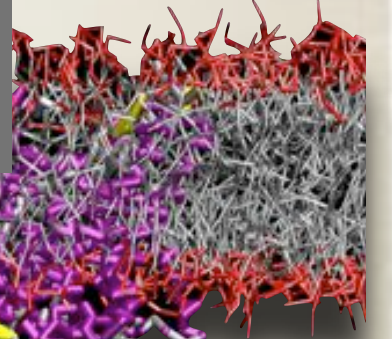
vesicles



vesicles



proteins



m

SPEED

short-range interactions
large time-step
few degrees of freedom

GENERAL

consistent modeling
biomolecular systems
easily extended

EASE of USE

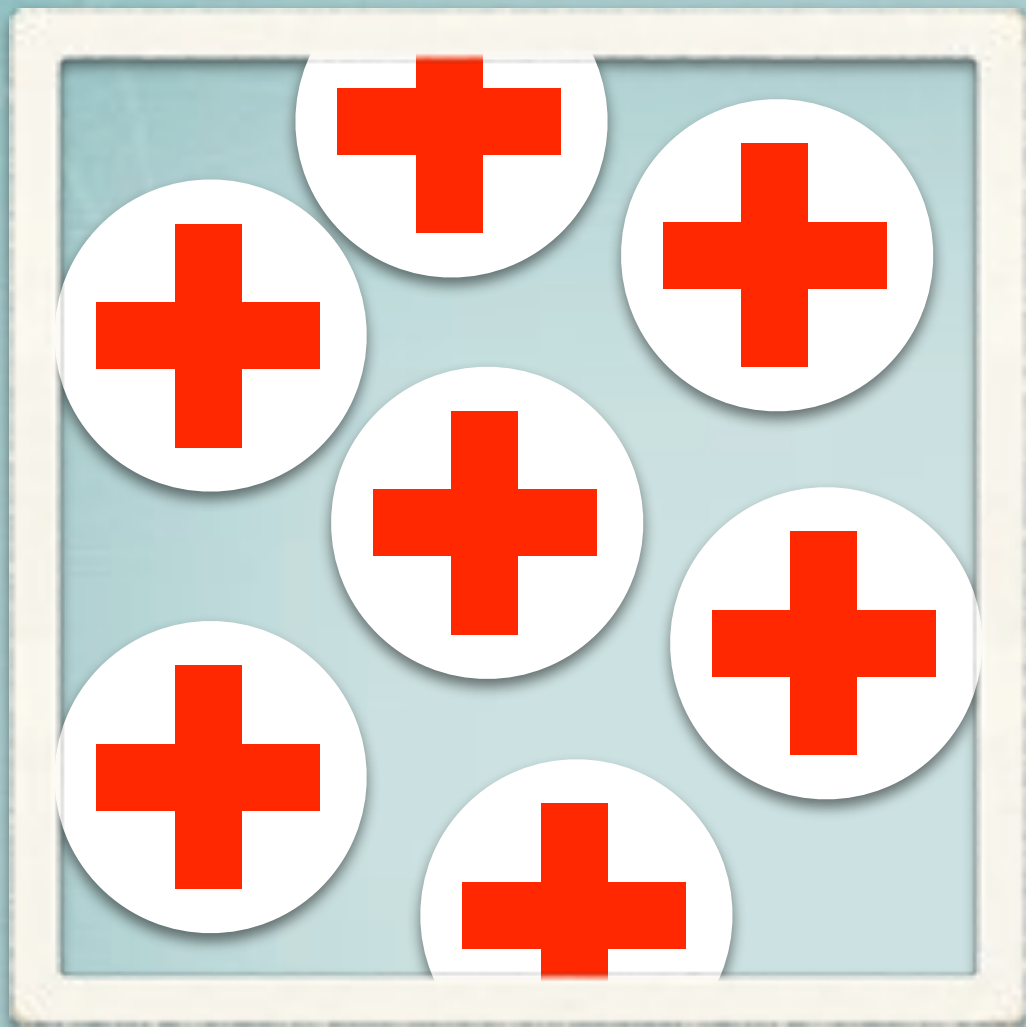
building-block approach
limited # of particles
physical units

ACCURACY

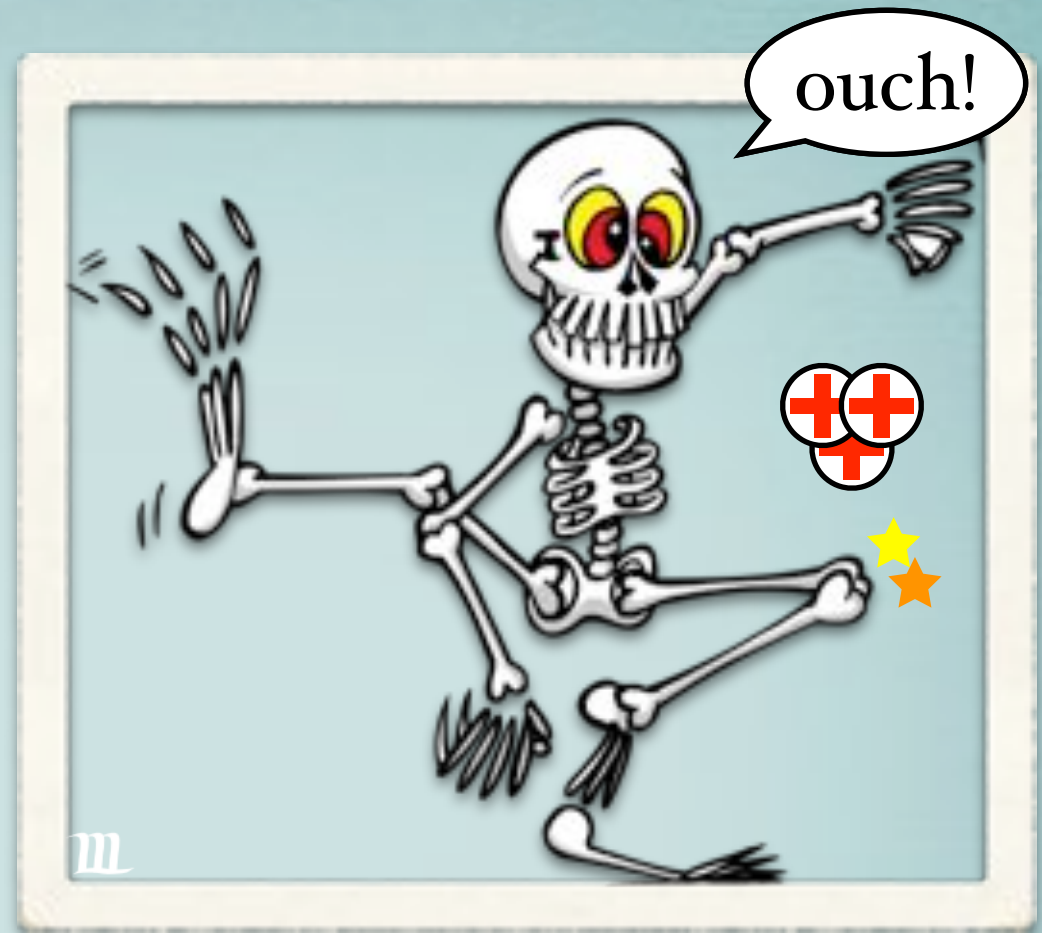
parametrisation based on
thermodynamic data
multi-level optimisation

MARTINI CG model

interaction sites



drugs

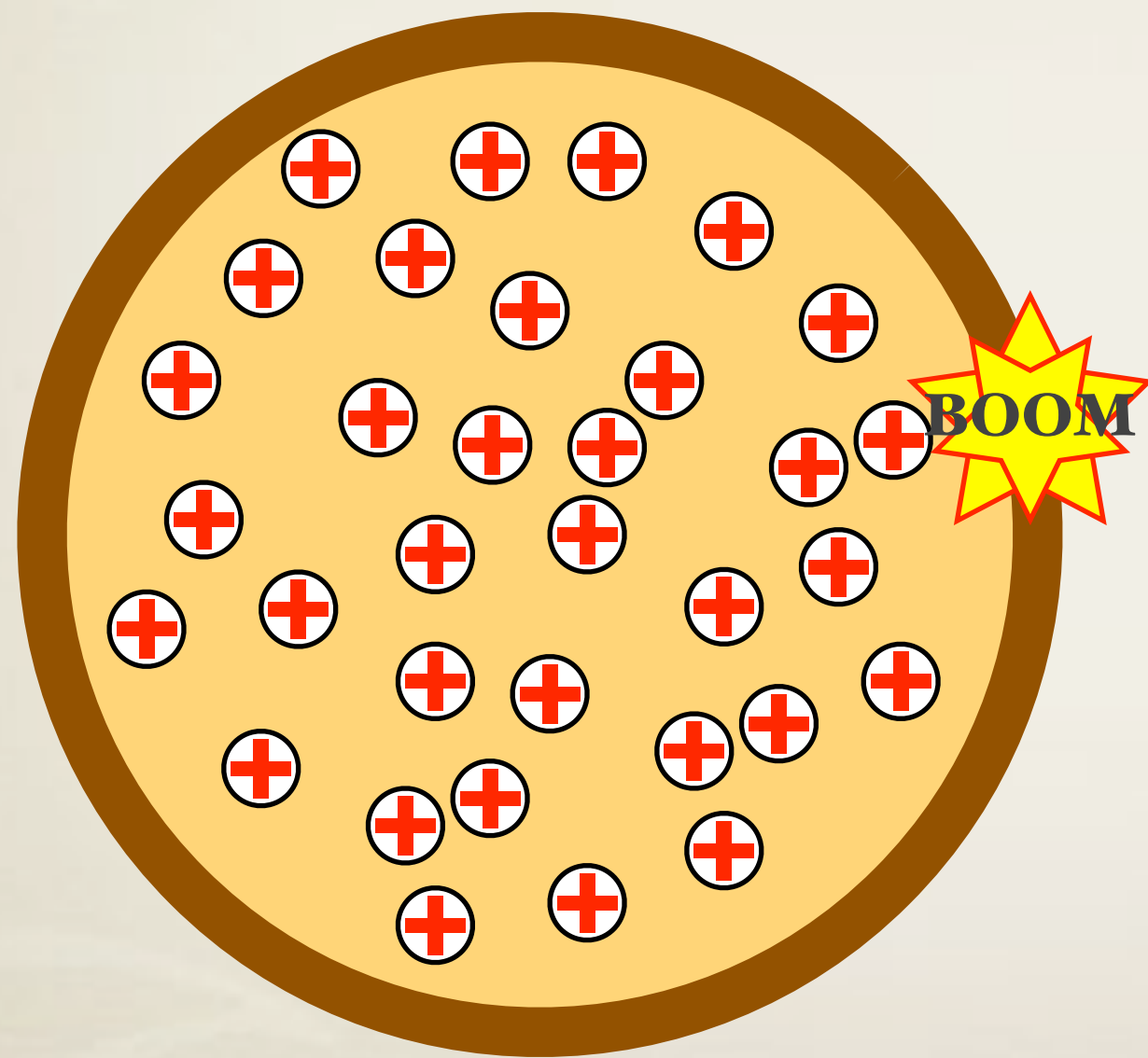


patient

targeted drug release.
how?

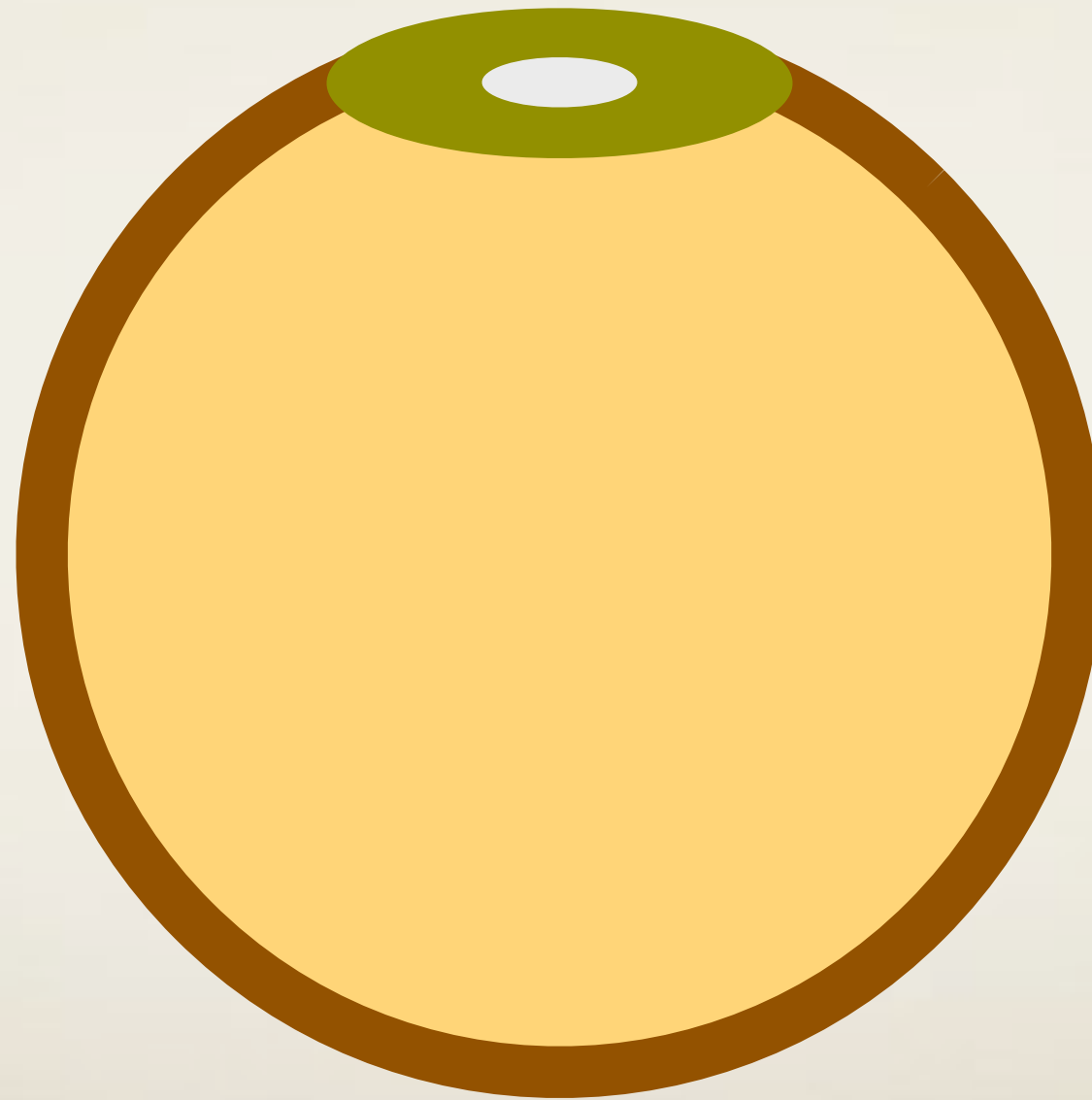
drug delivery vehicle

“nanobot”



drug delivery vehicle

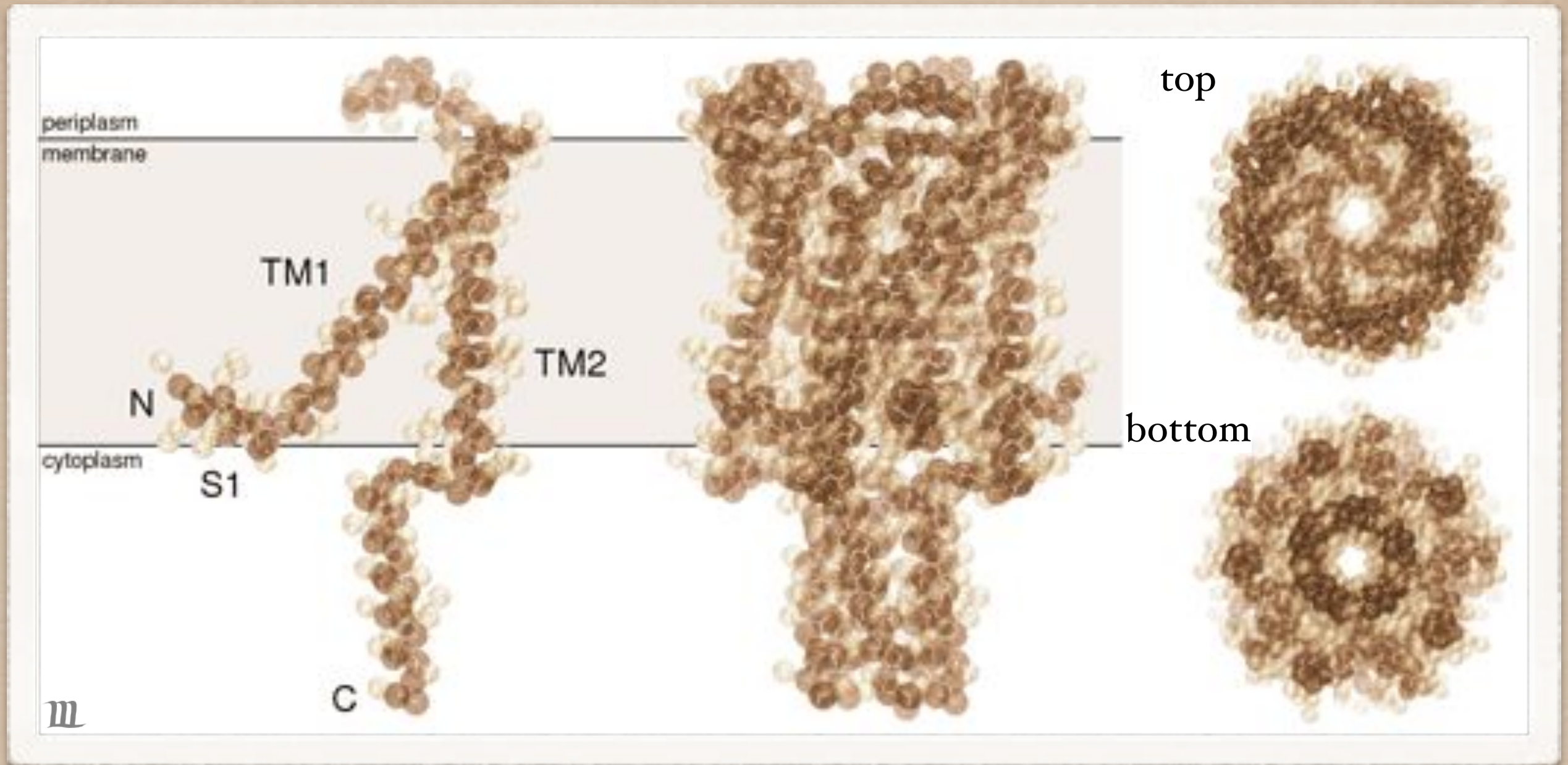
“nanobot”



mechano-sensitive channels

- * “safety valves” of cell
- * sense tension in the membrane
- * MscL, MscK, MscS, MscM
- * $< 10 \text{ mN/m}$



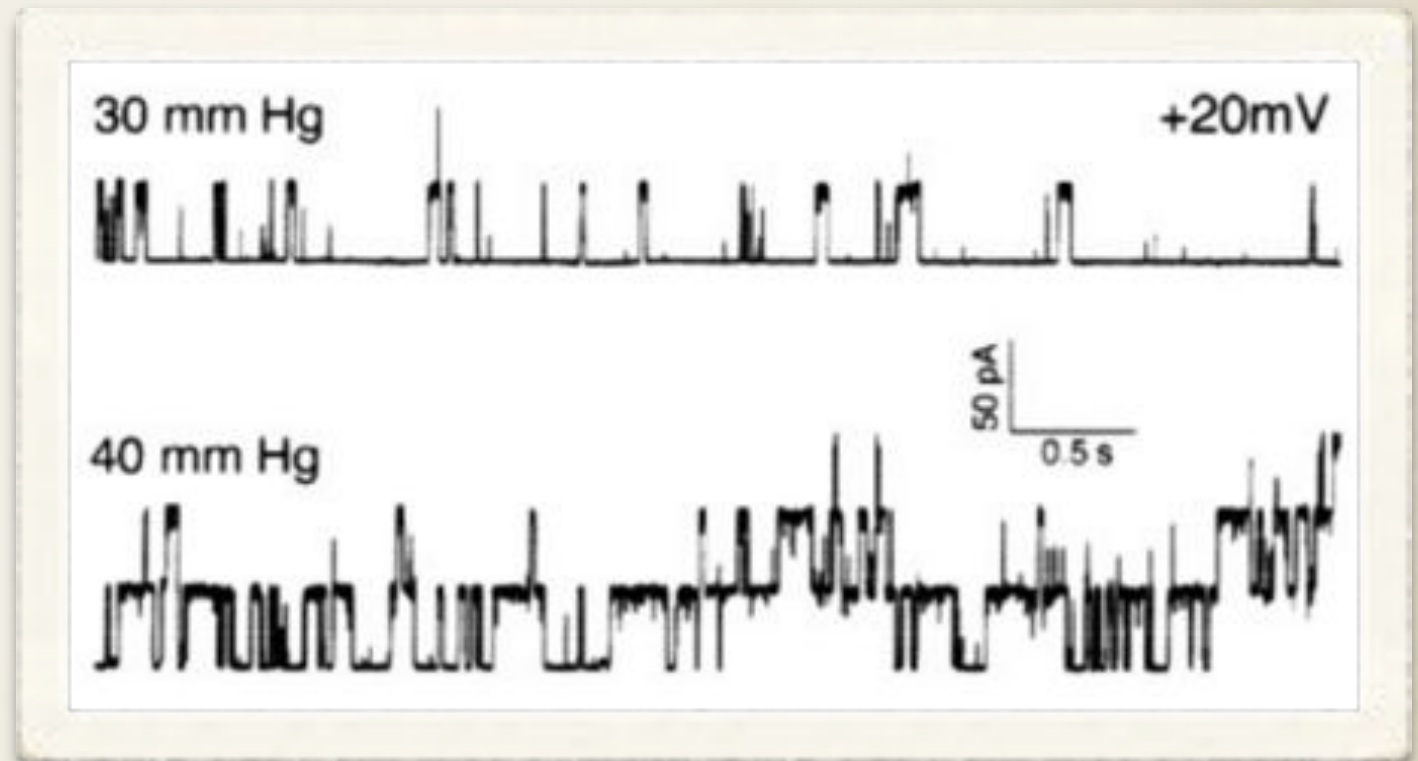


MscL

controllable activation & non-selective conductance

MscL activity

- * flickering conductivity
- * multiple levels
→ subconductive states
- * activation < 1 ms
- * de-activation 1–100 ms

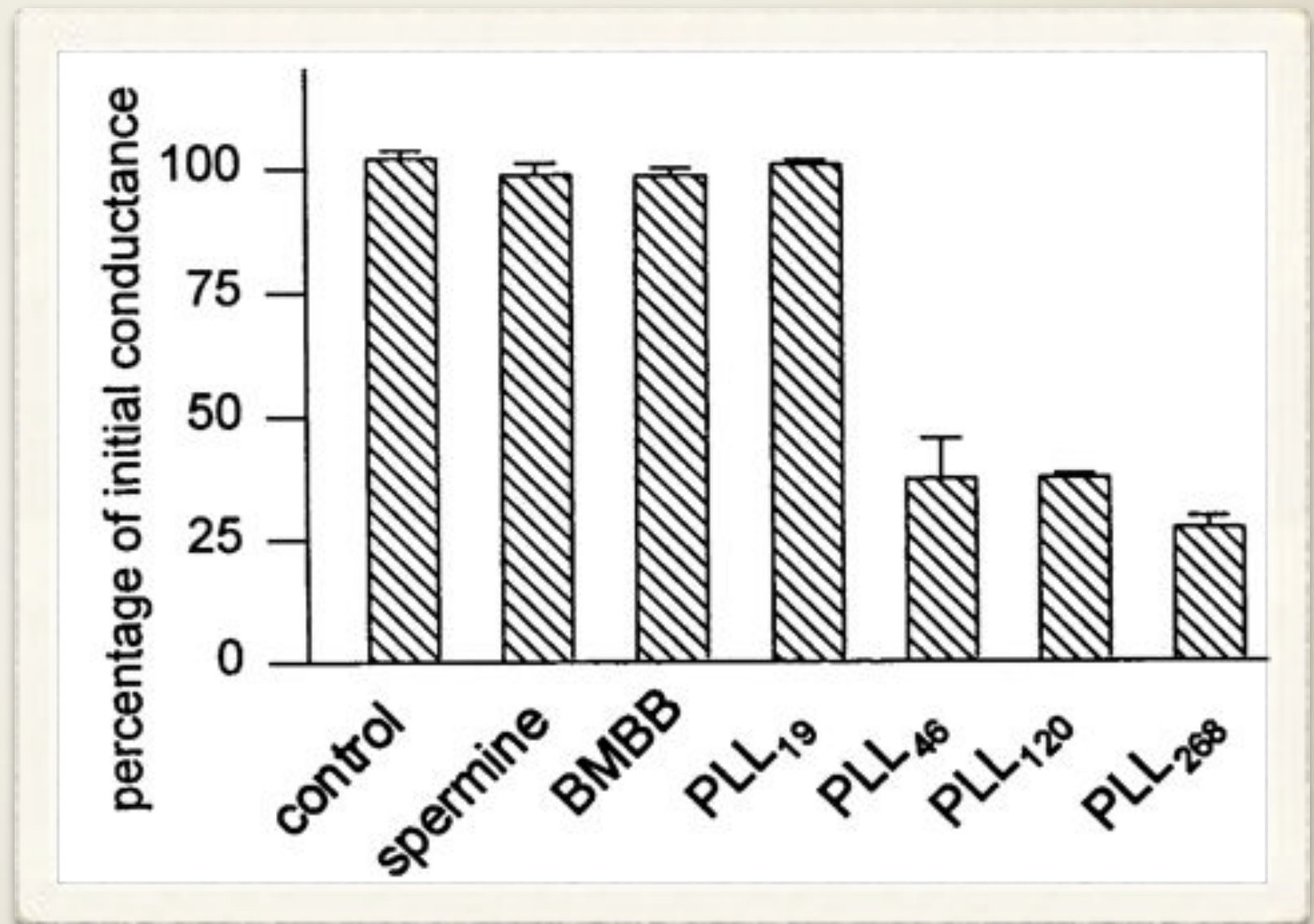


Sukharev *et al.* (1997)

Annu Rev Physiol 59: 633–657

non-selective channel

- * no ion selectivity
- * even small proteins pass through! 15–20 Å

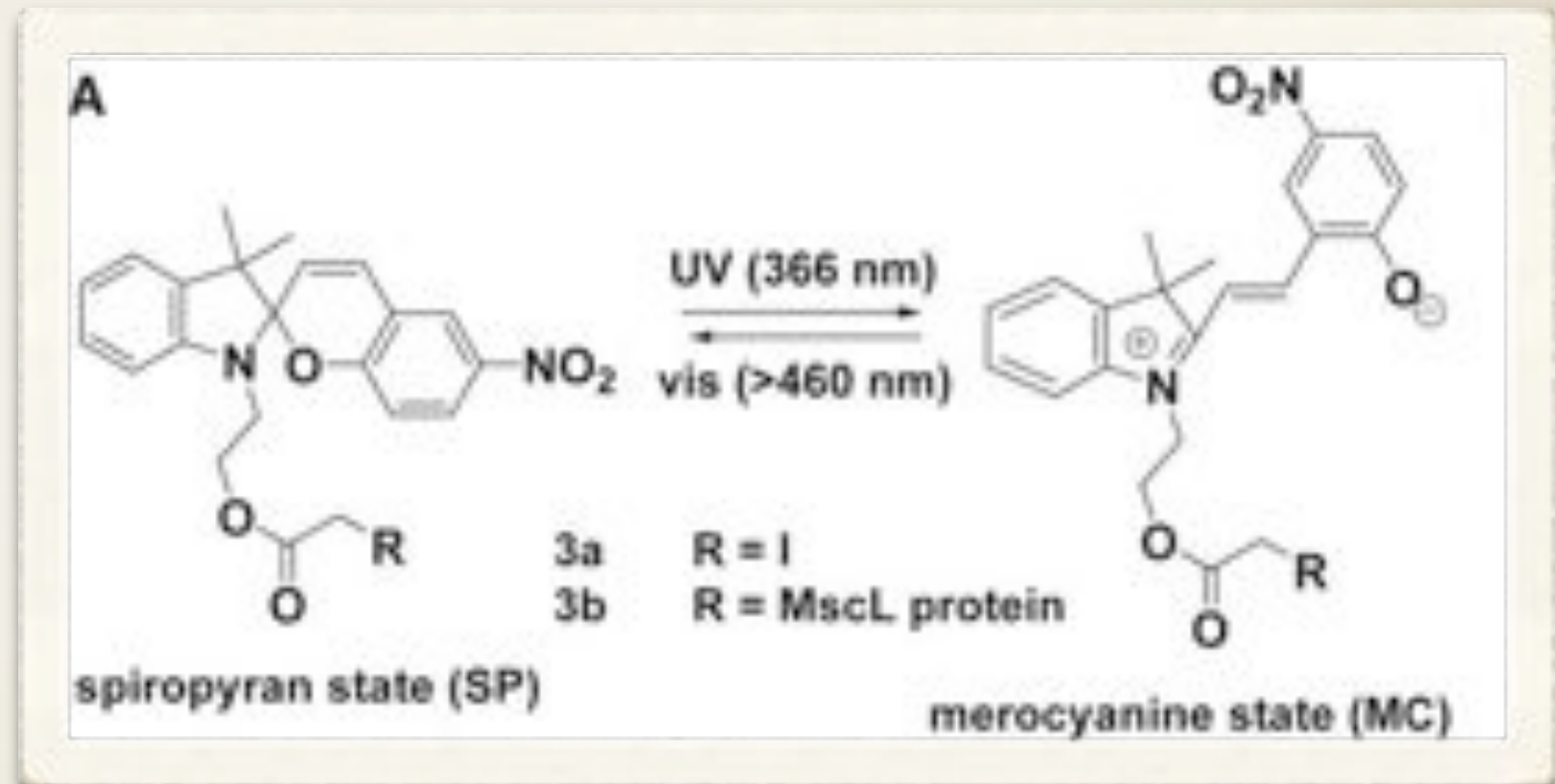


Cruickshank *et al.* (1997)

Biophys J 73: 1925–1931

photosensitvivity

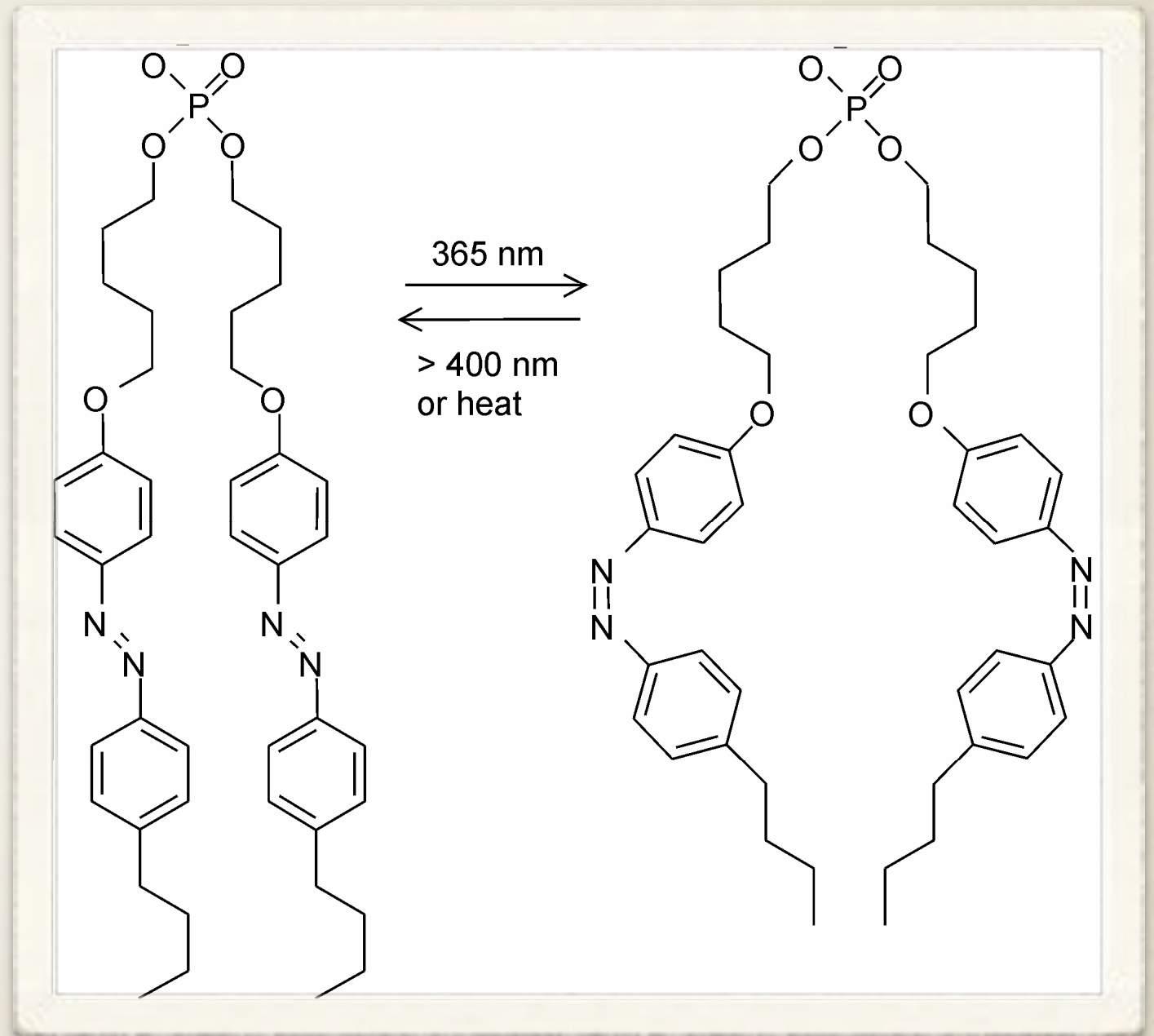
- * attached compound undergoes light induced charge separation
- * reversible
- * localised



Koçer *et al.* (2005)
Science 309: 755-758

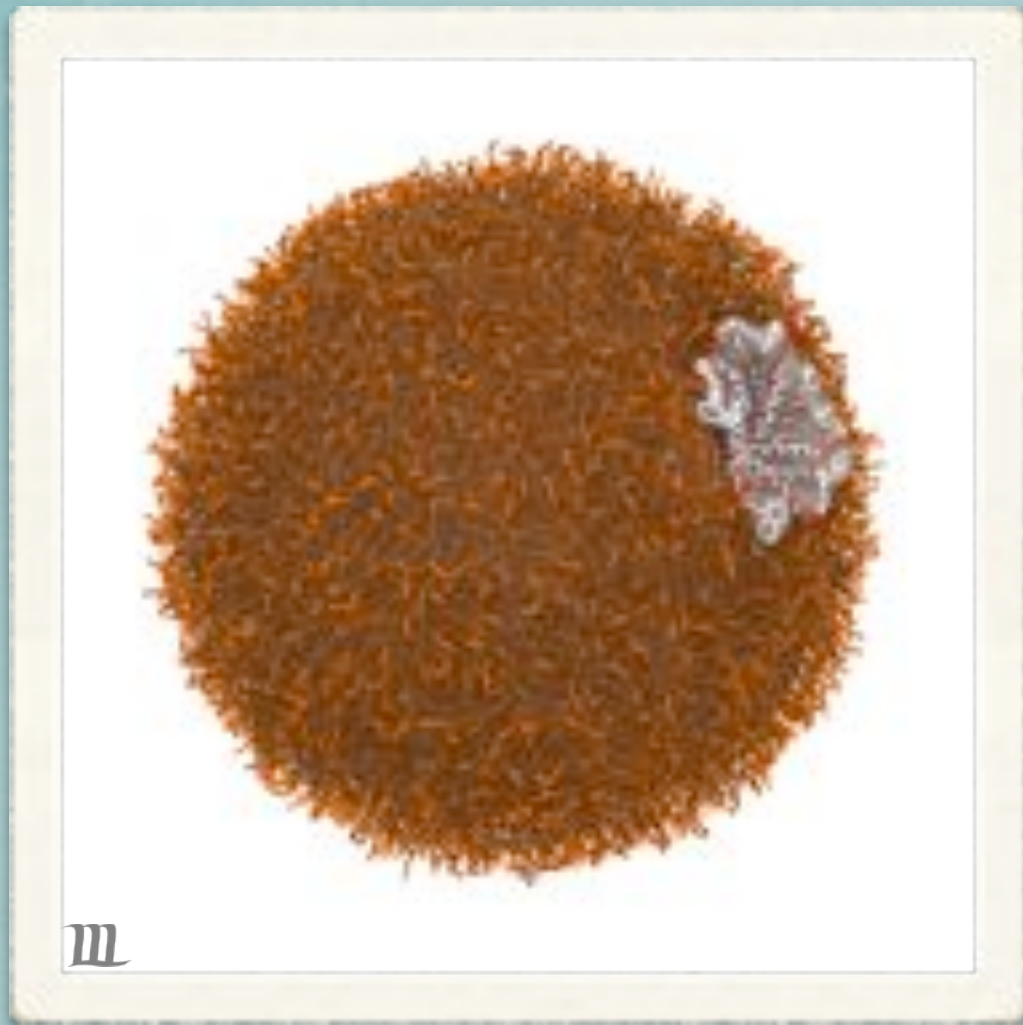
photosensitvivity

- * photosensitive lipids used to transfer signal to mechanical stress
- * reversible
- * localised

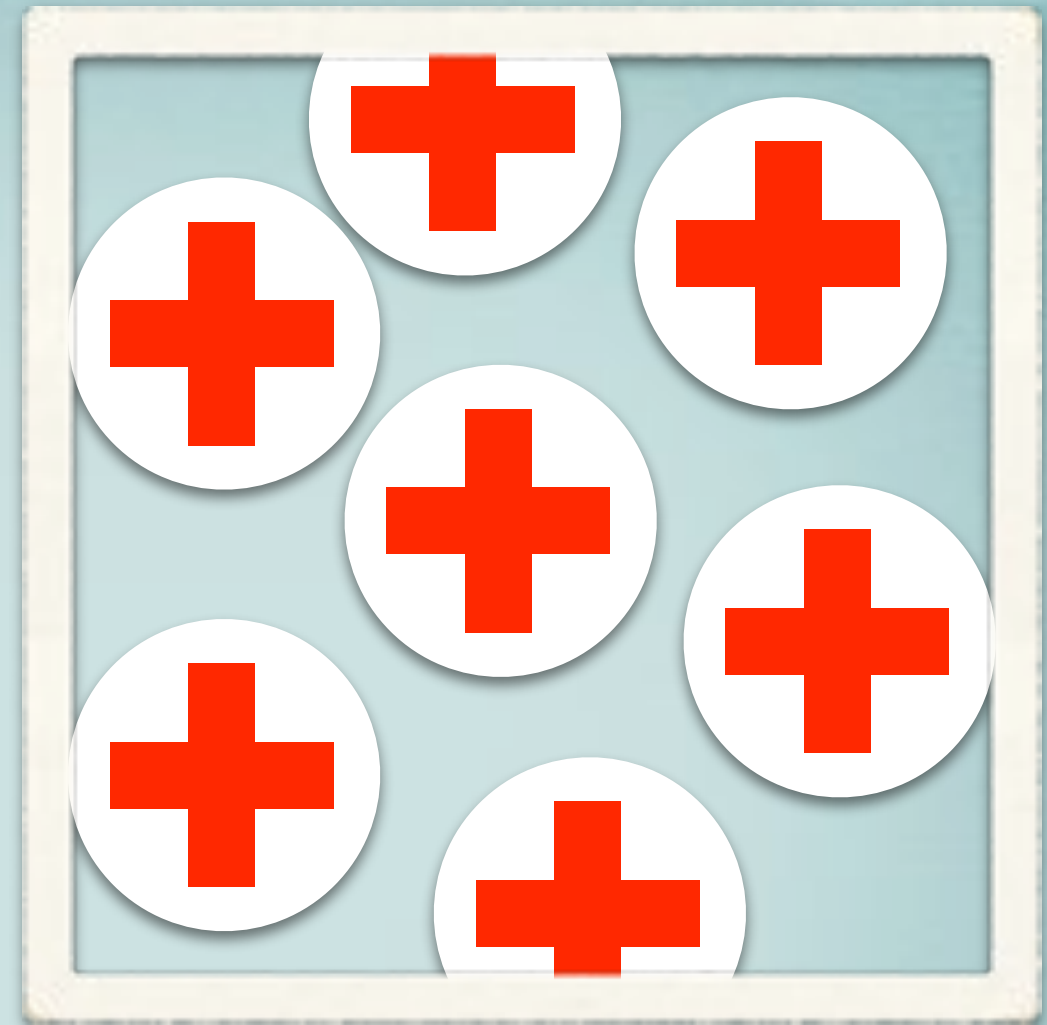


Folgering *et al.* (2004)

Langmuir 20: 6985–6987



nano-container
aka liposome



nano-particles
aka drugs

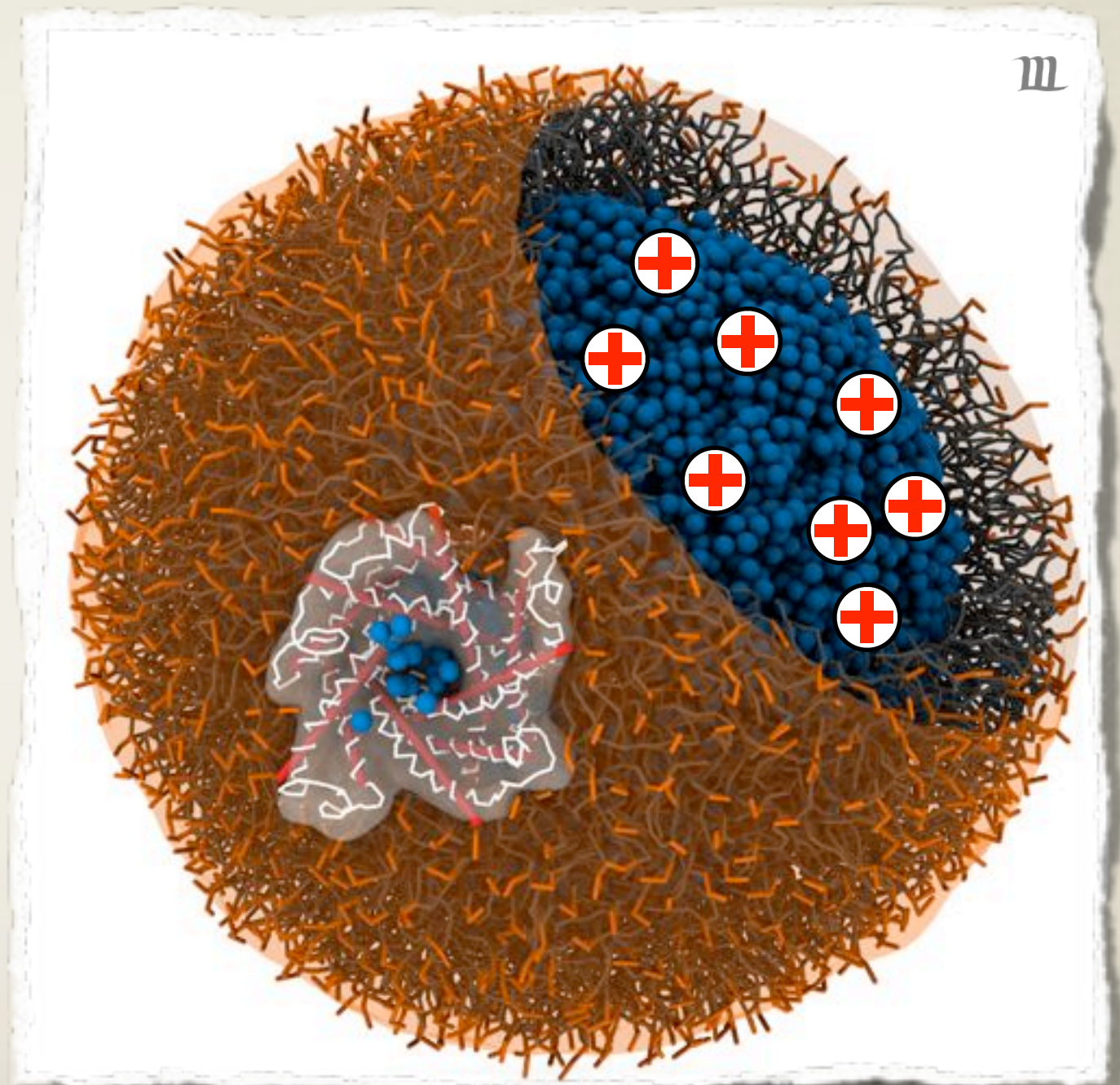
nano-transporter

LIPOSOMES

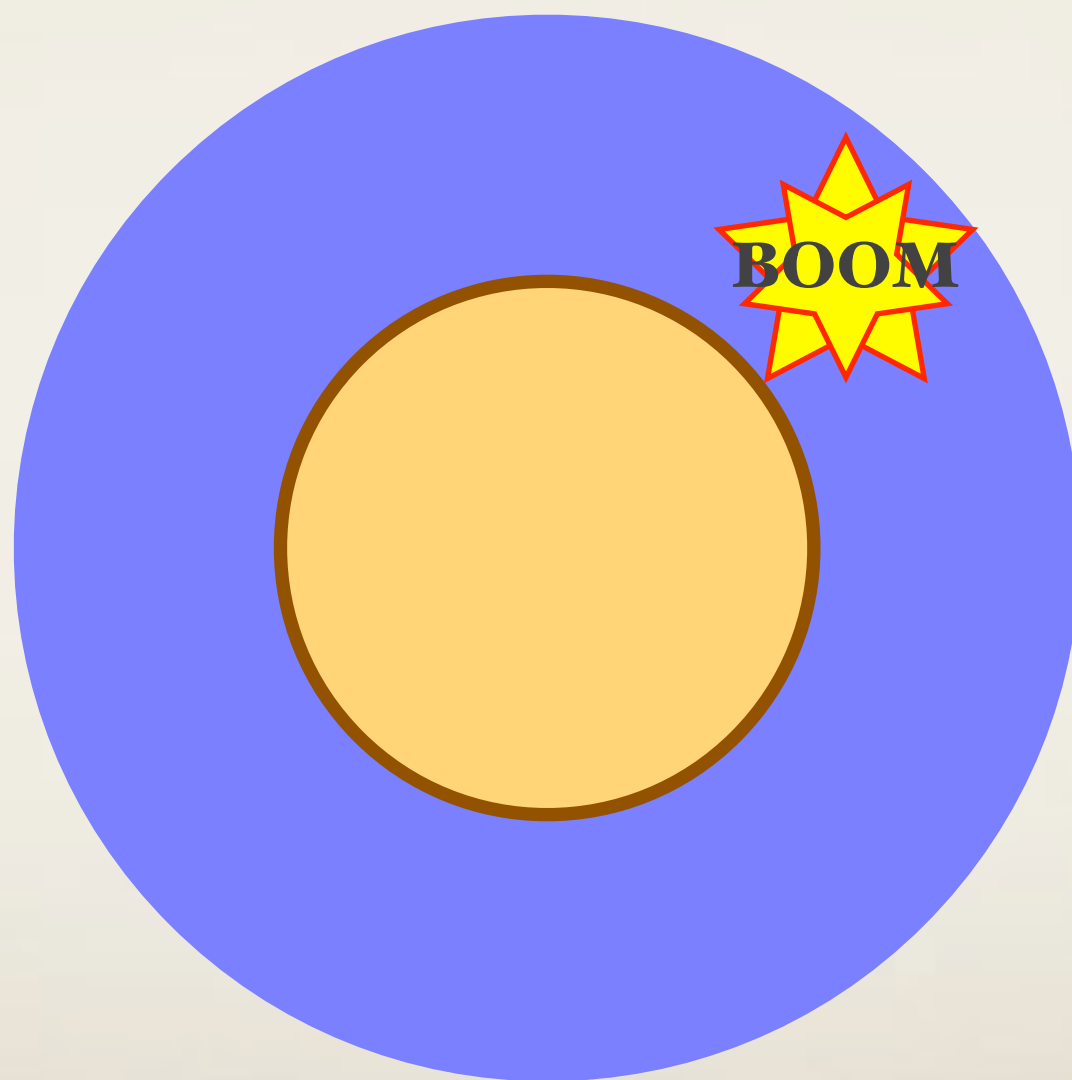
- * tiny lipid vesicles
 - * membrane fusion
 - * trans-membrane transport
 - * drug delivery
 - * curvature effects

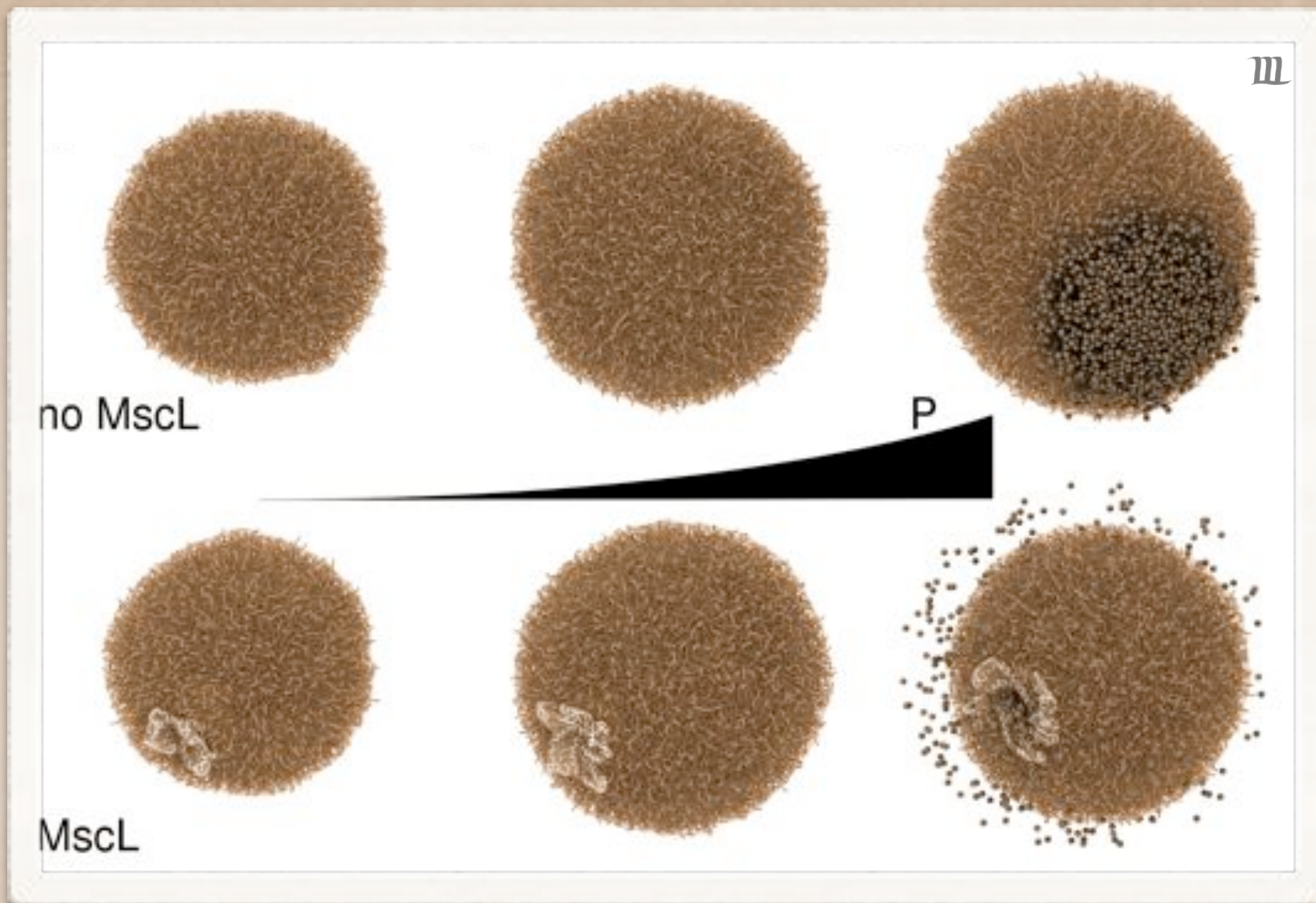
MSCL

- * mechano-sensitive
 - * pressure valves of cells
 - * touch & hear
- * non-selective, large membrane channel



game plan



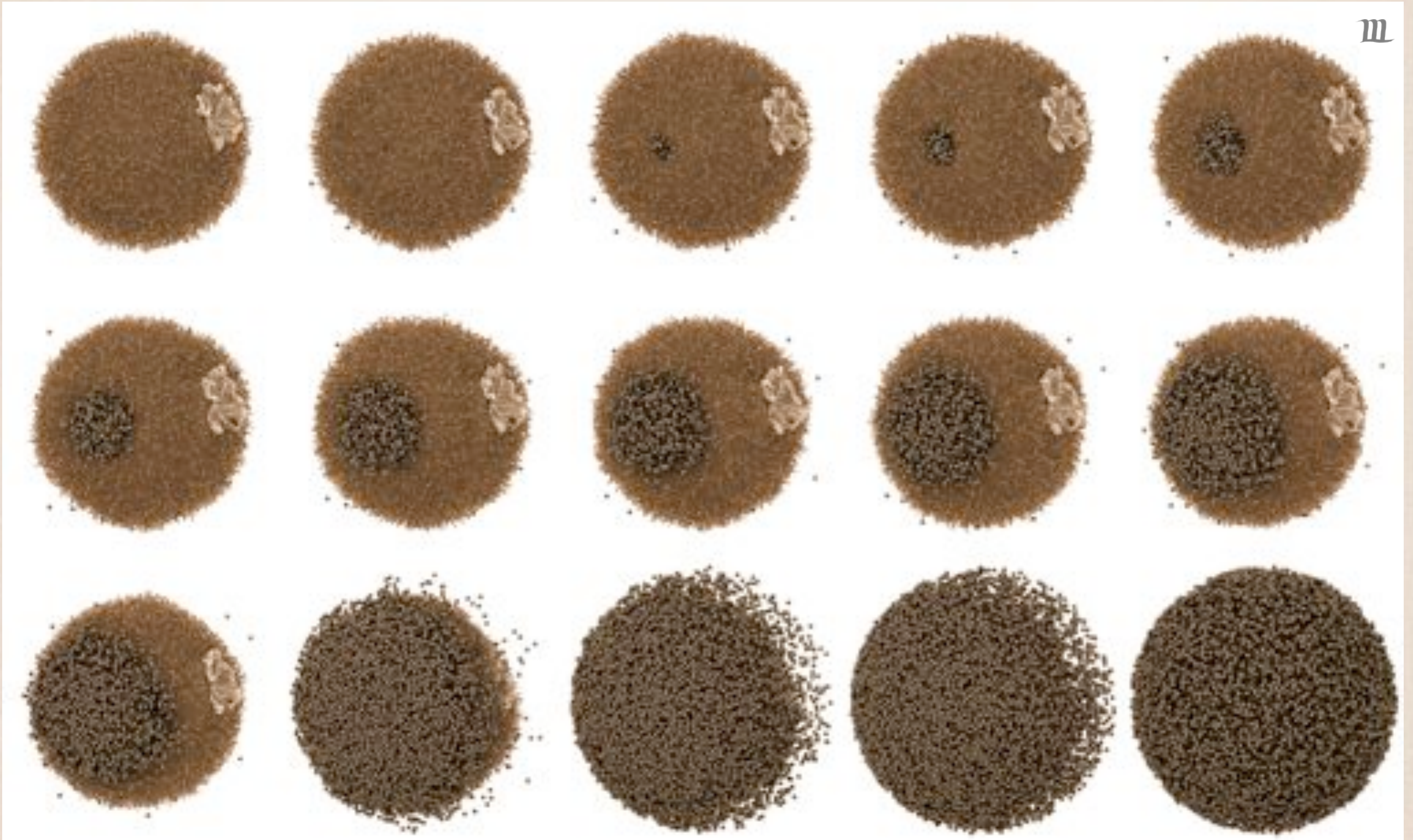


MscL saves the day

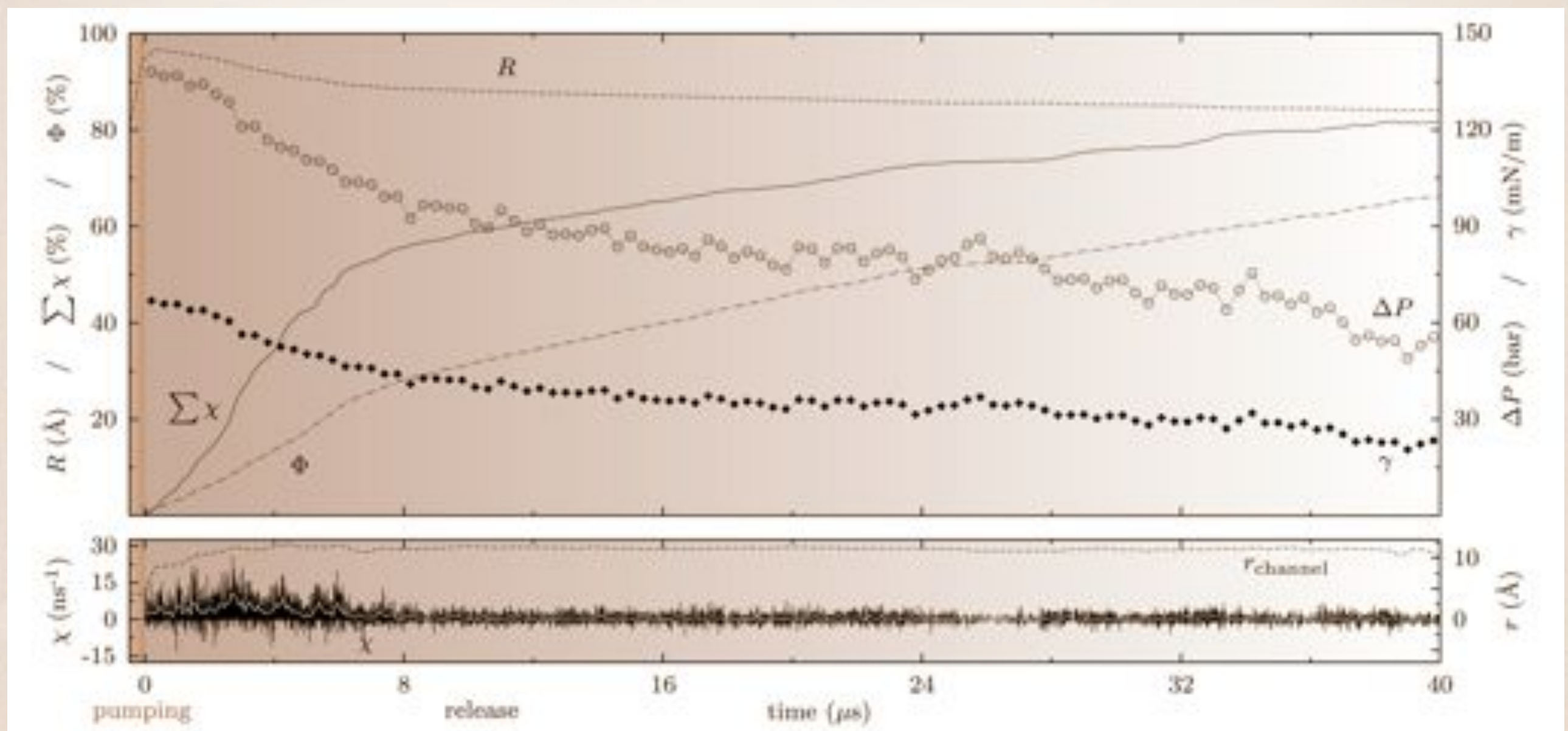
660 kN/m·s → lysis
140 kN/m·s → ok

oh-oh!

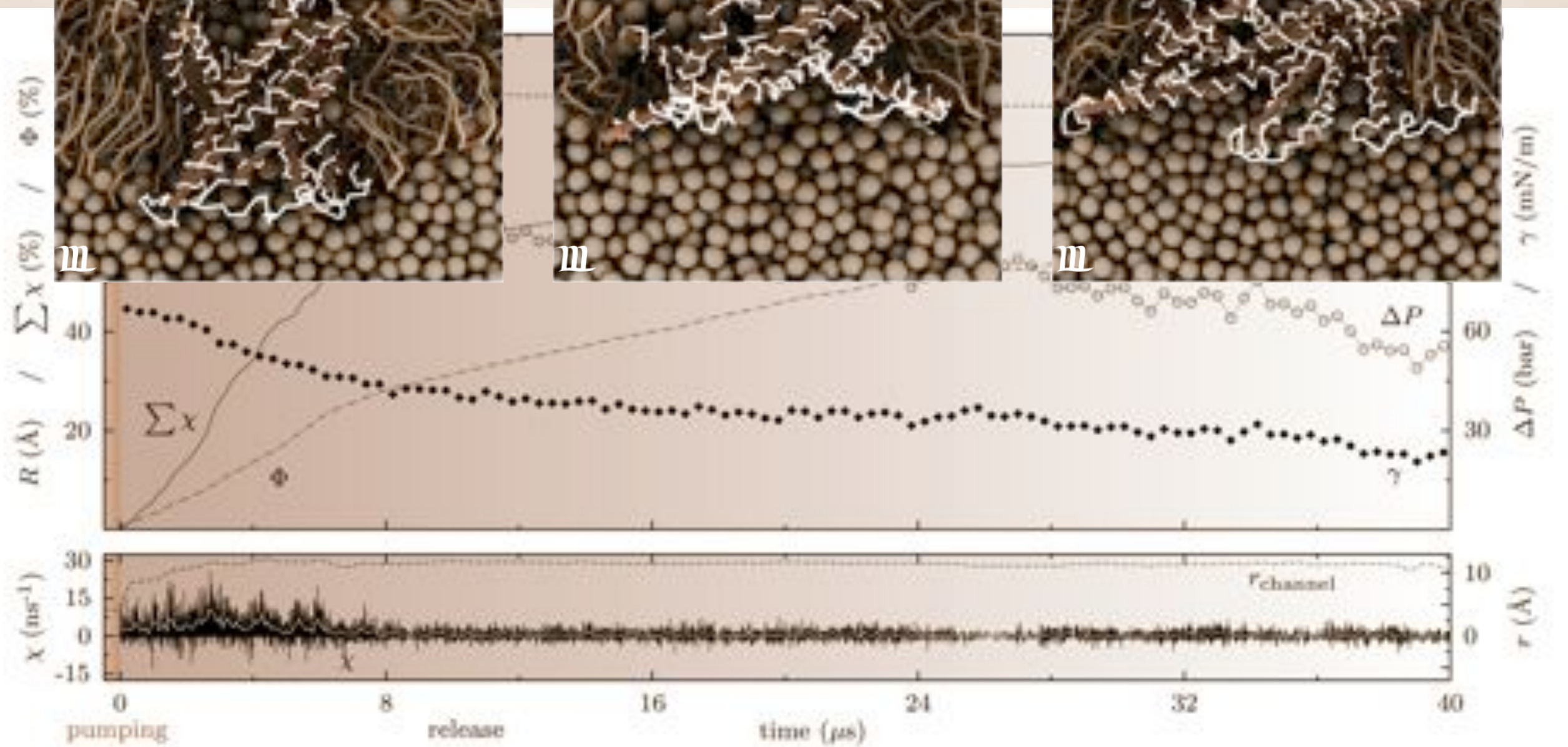
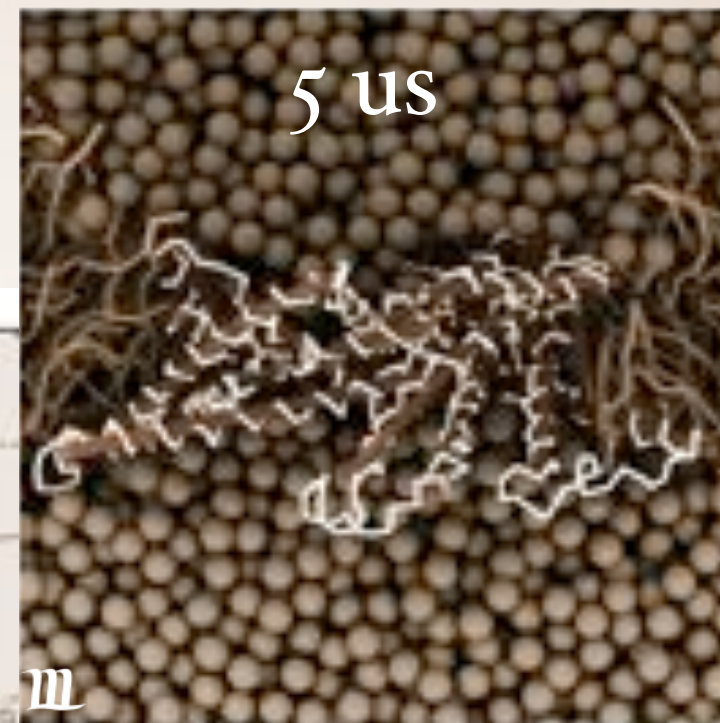
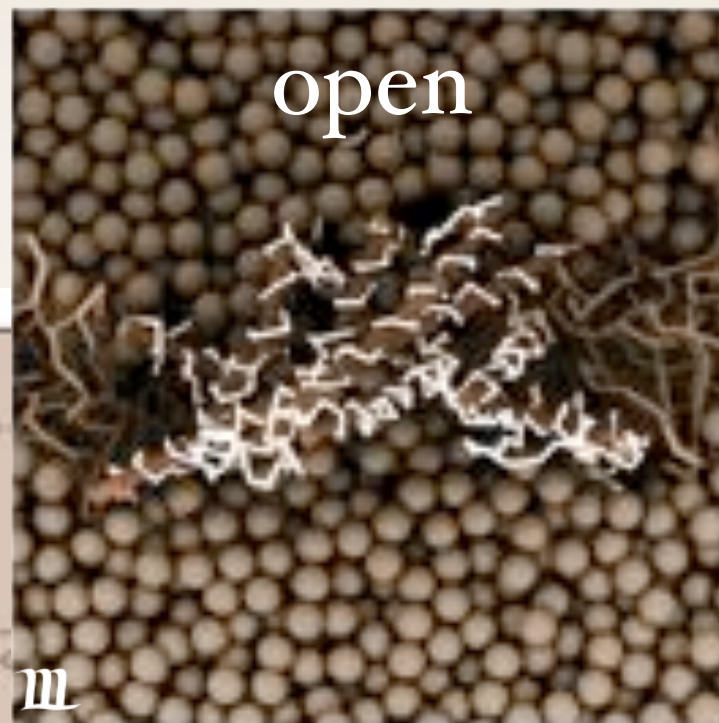
m



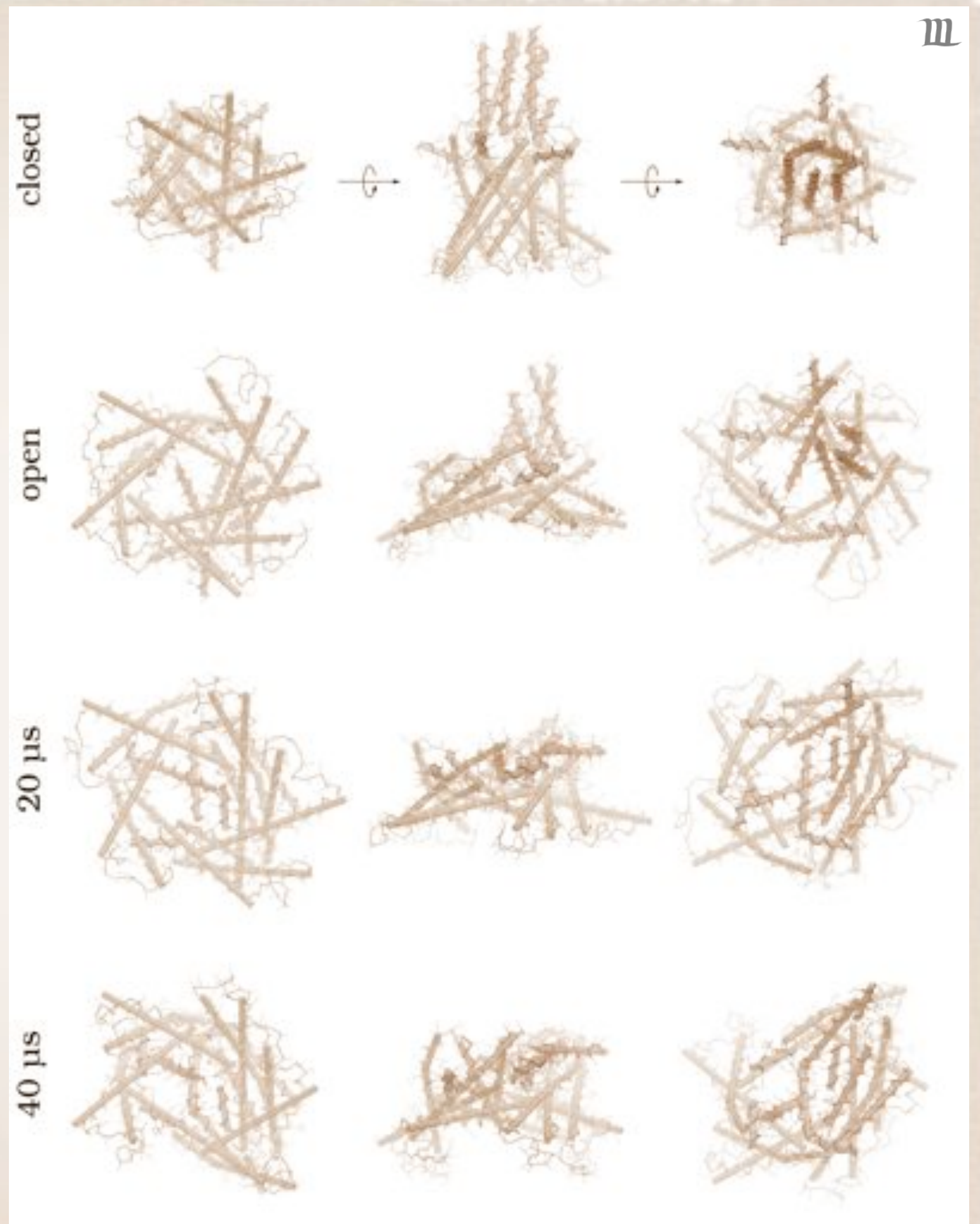
analysis



analysis



activation mechanism



post- activation

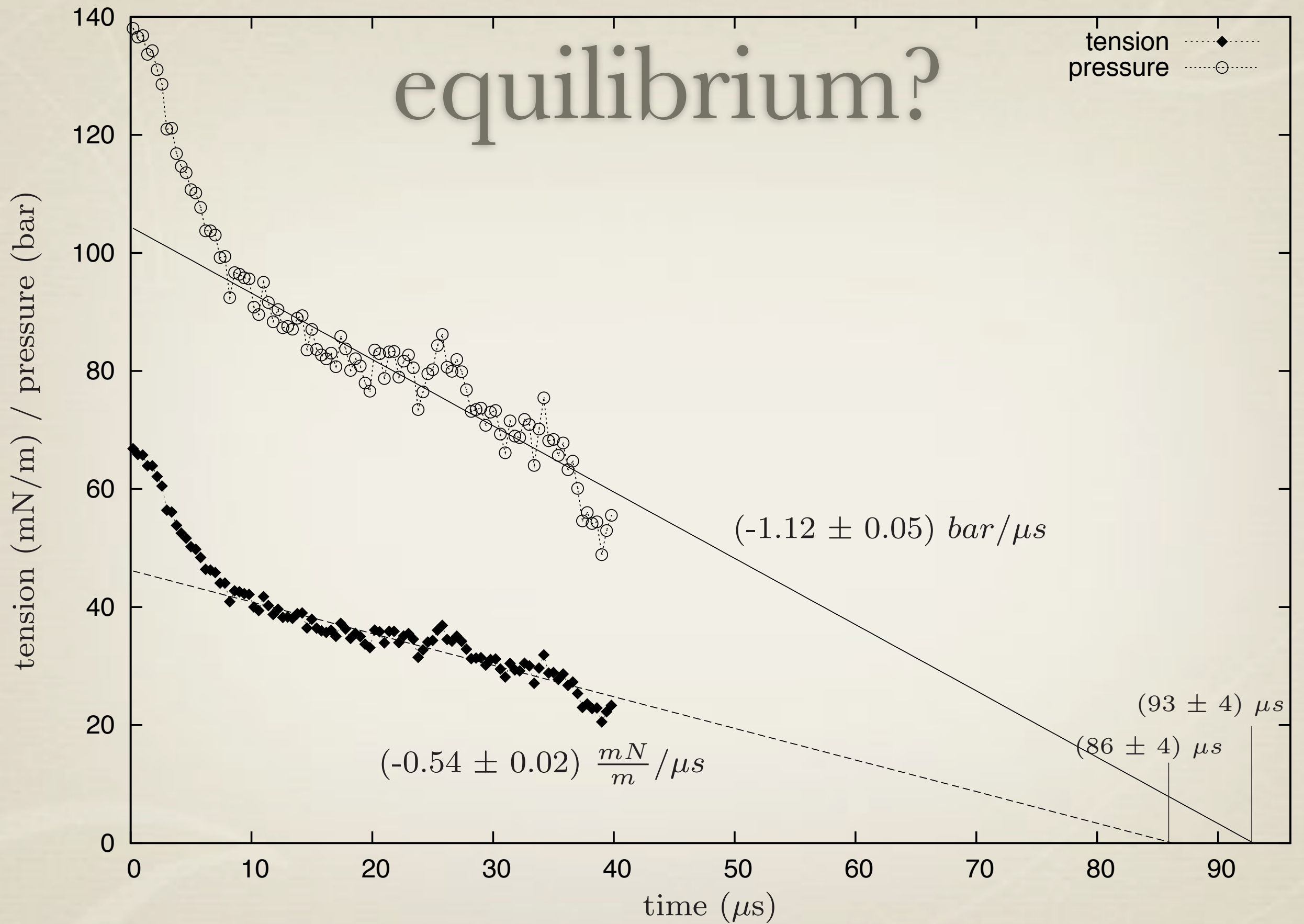
67 mN/m

∅ 24 nm

1.04 H₂O / ns

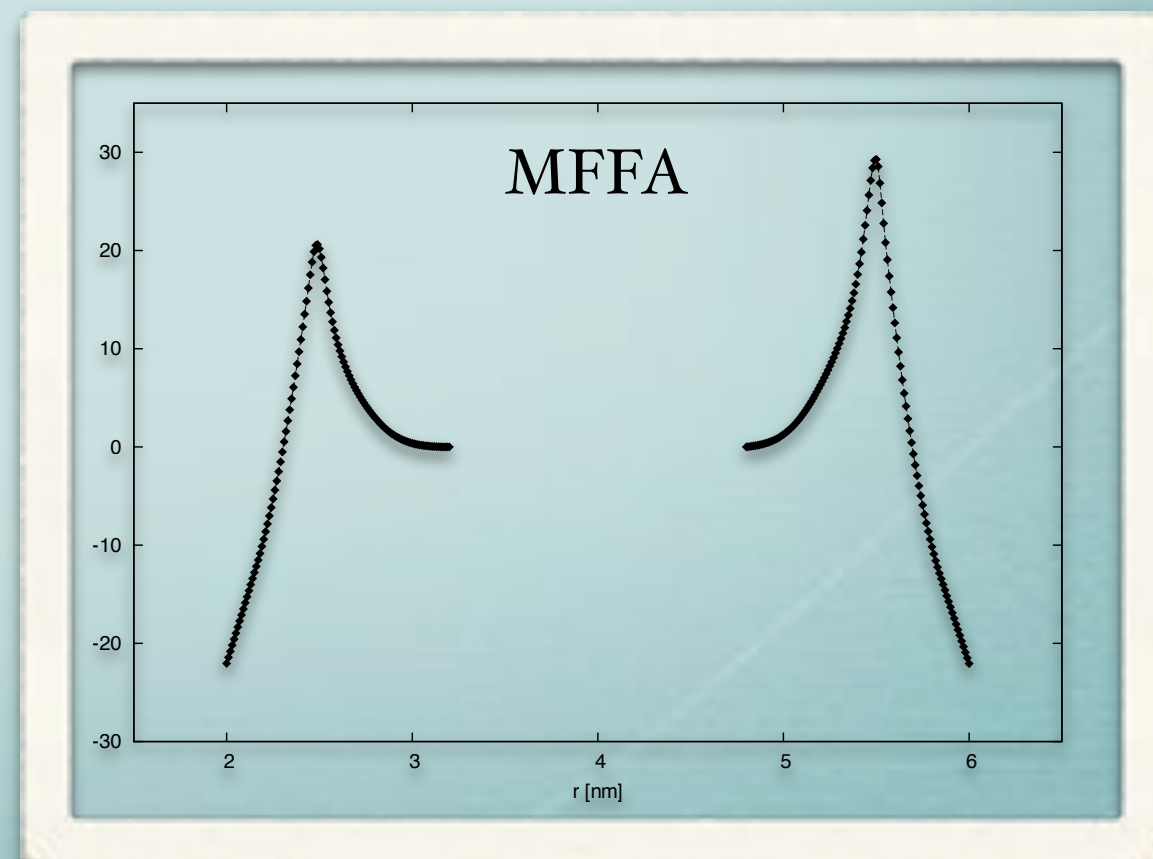
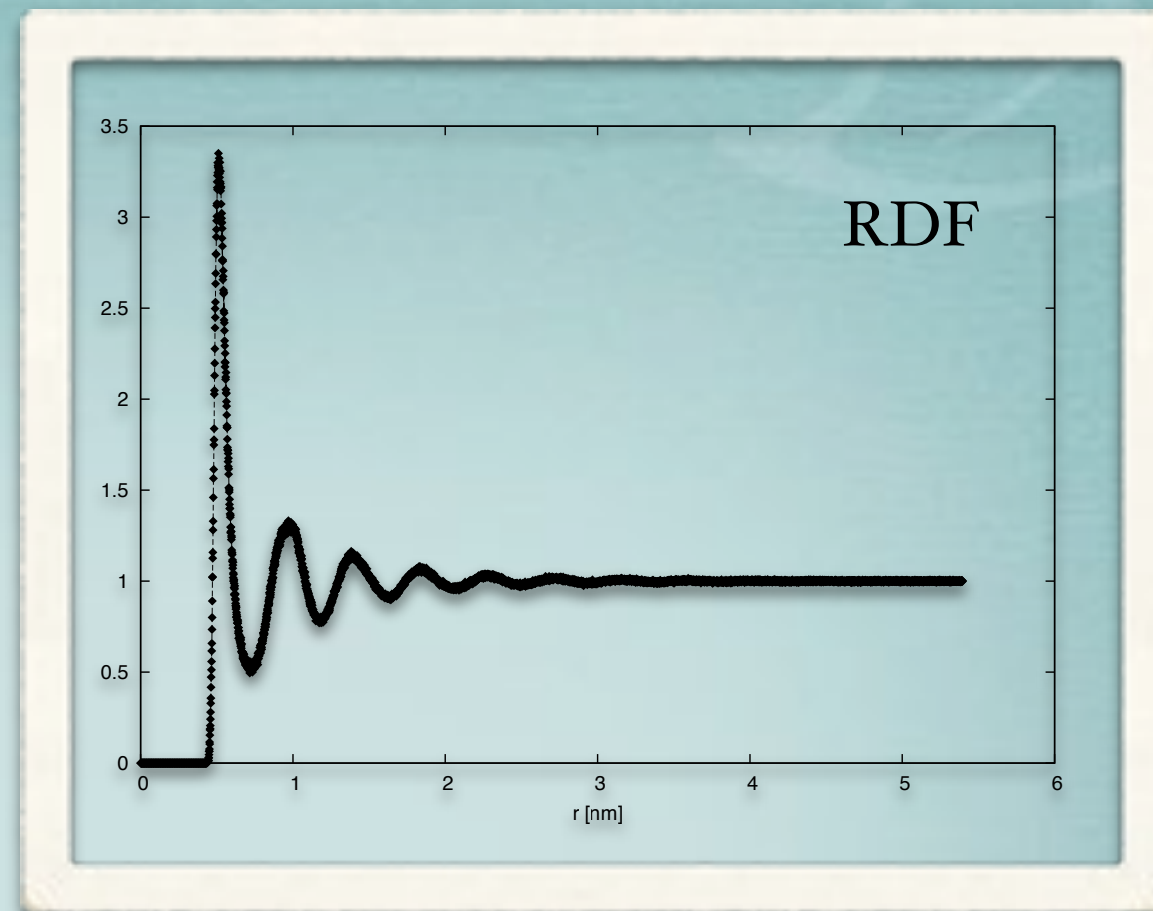


equilibrium?



MFFA boundary potentials

mimic interactions with
bulk solvent

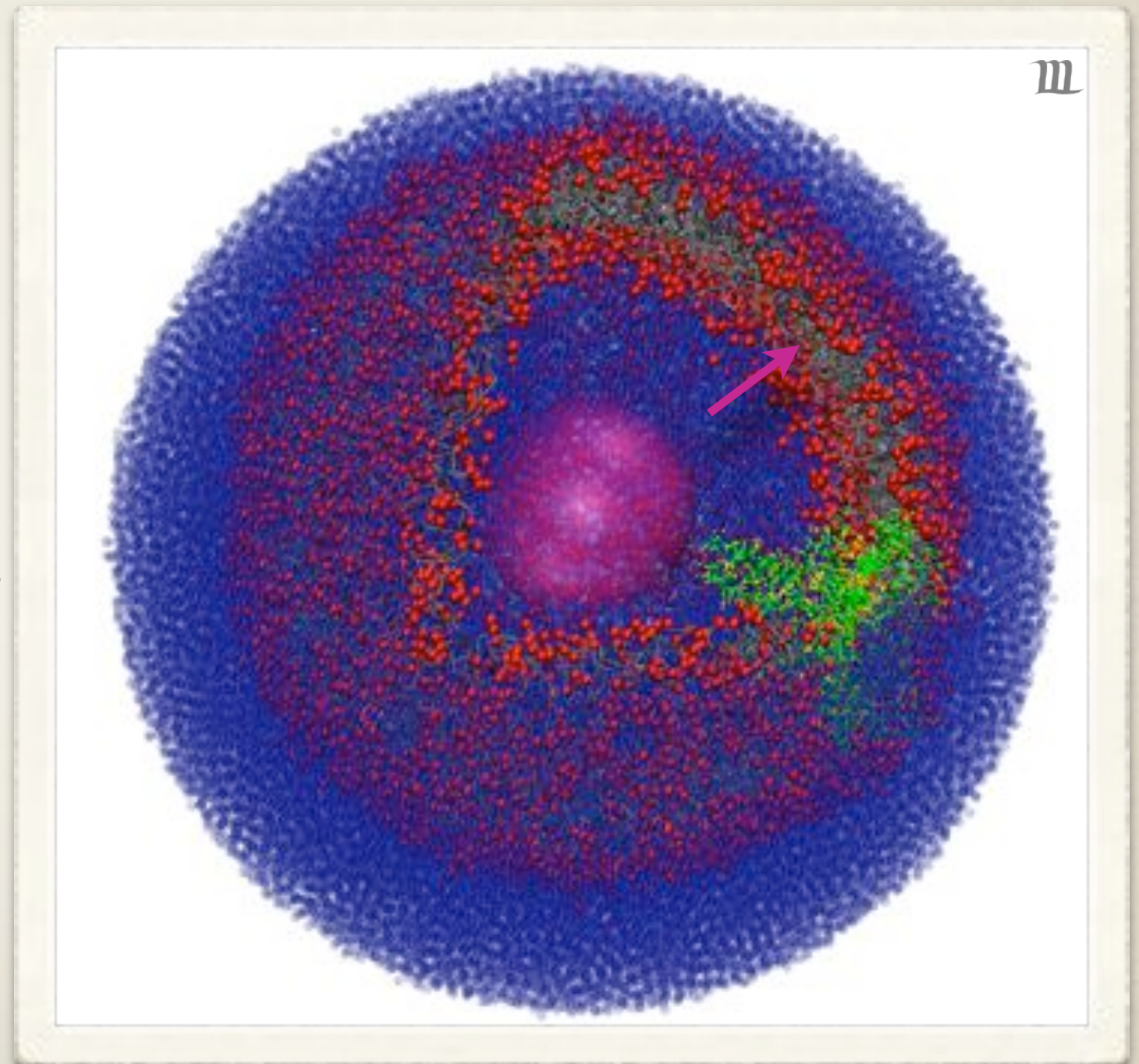


Risselada *et al.* (2008)

J Phys Chem B 112: 7438-7447

pumping water into liposomes

- * additional mean-field potential inside the liposome
- * start with $r = 0.01$ nm
- * increase slowly for 20ns until $r = 3.9$ nm
- * fill the cavity with water, relax and repeat as needed



water-repellant lipid tails

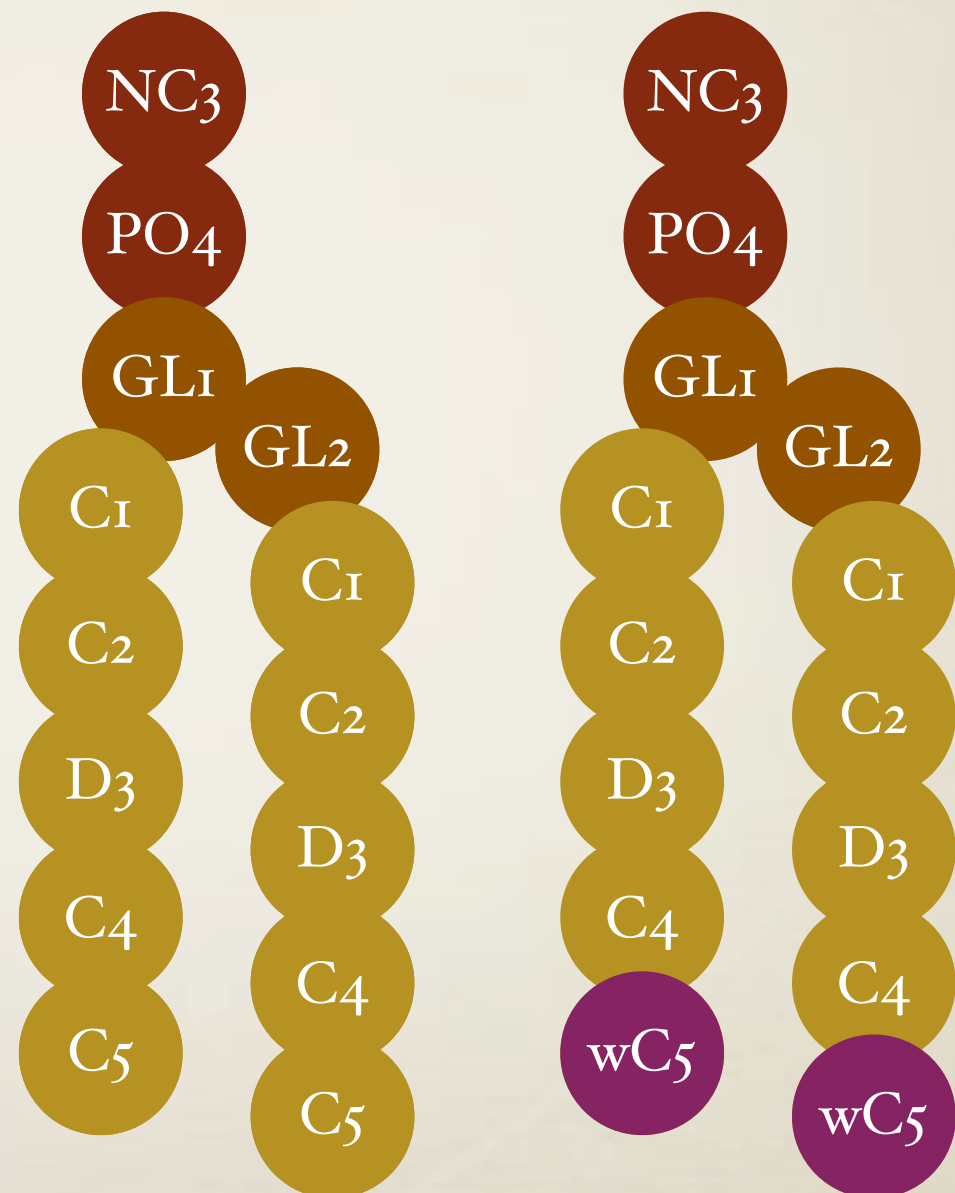
* modified Lennard-Jones potential against water

	C5	wC5
epsilon	2.0	2.0
sigma	0.47	0.7

$$V(r) = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right]$$

DOPC

wDOPC

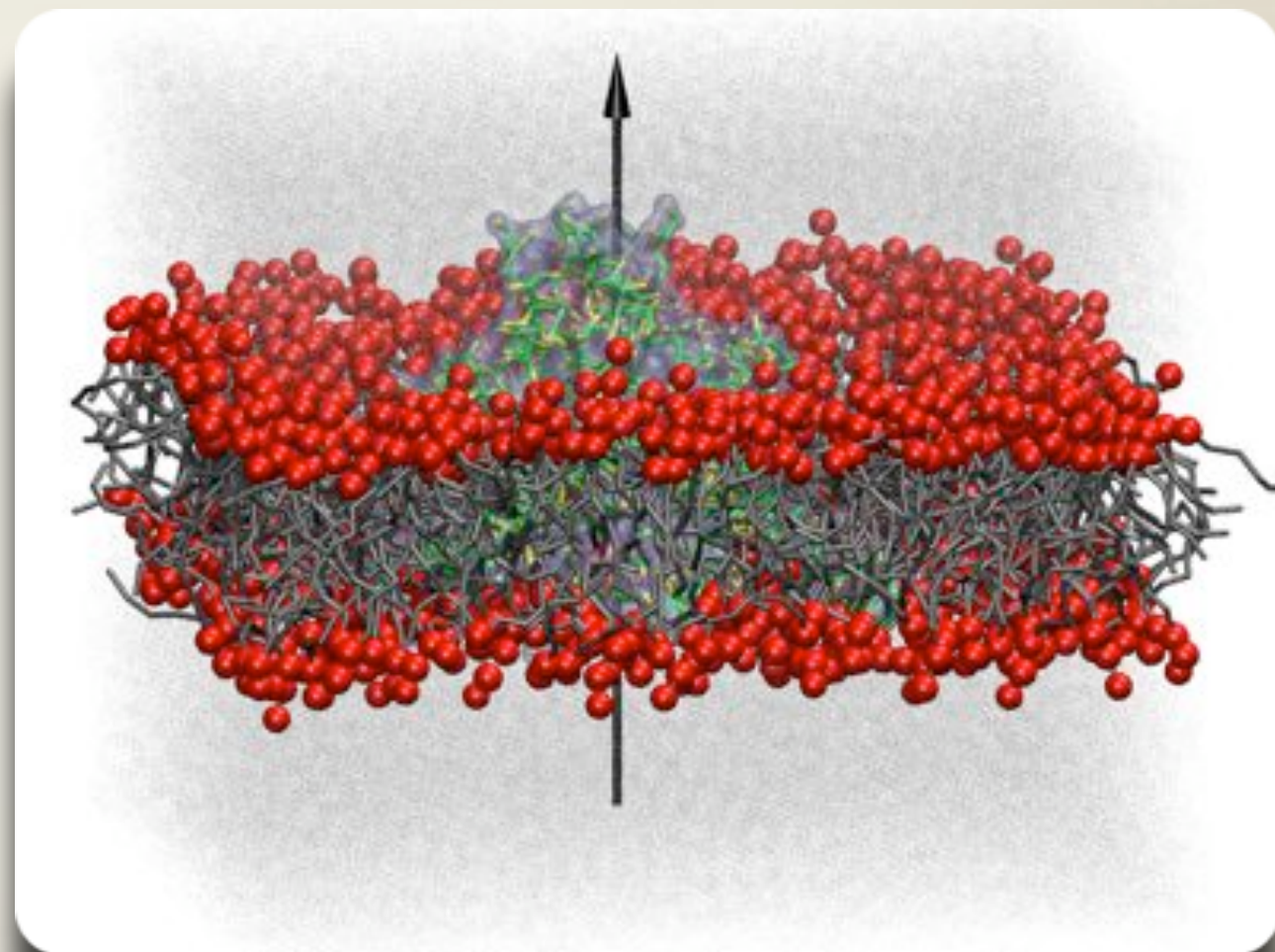


3D pressure fields

Ollila et al. (2009)

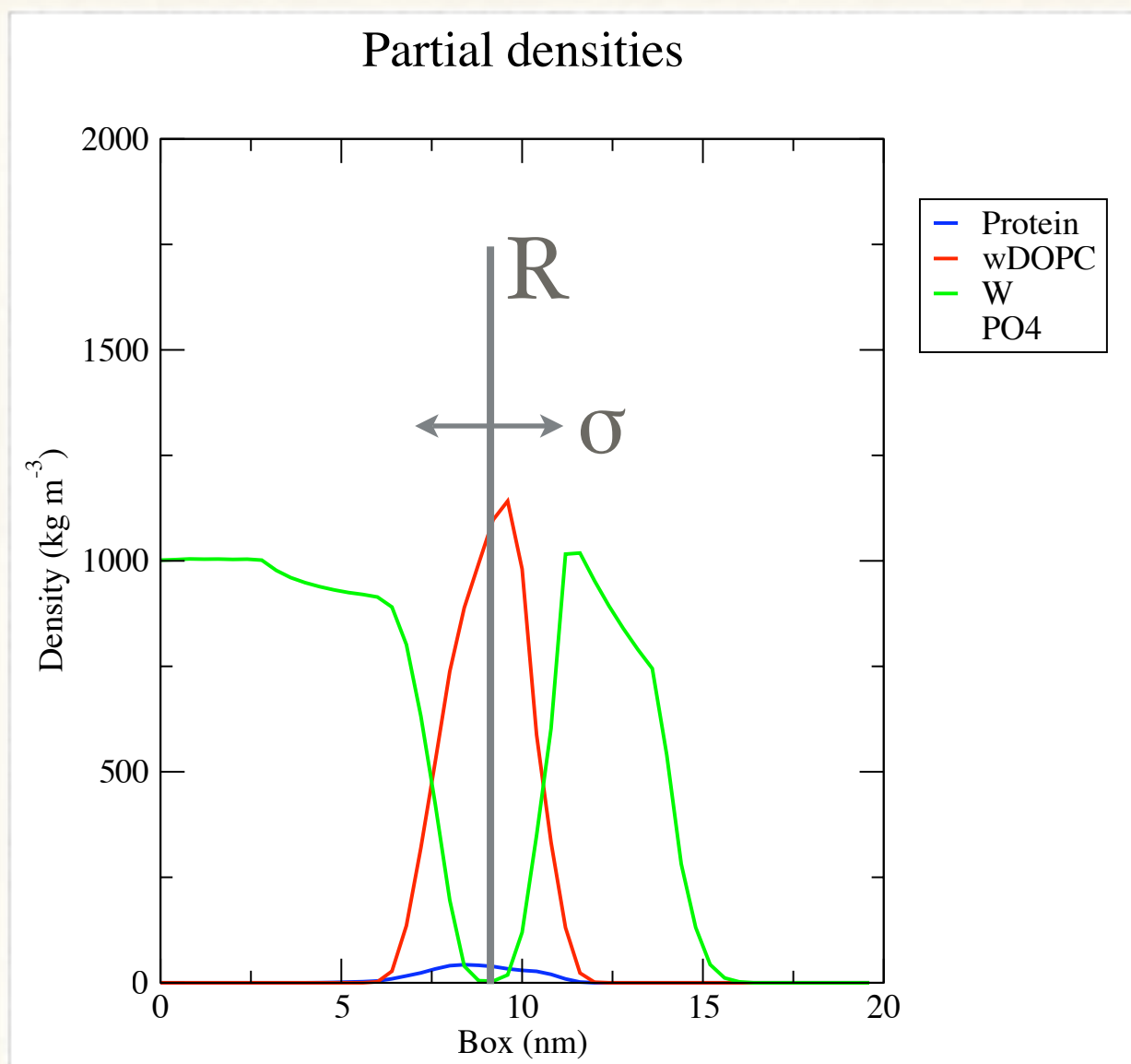
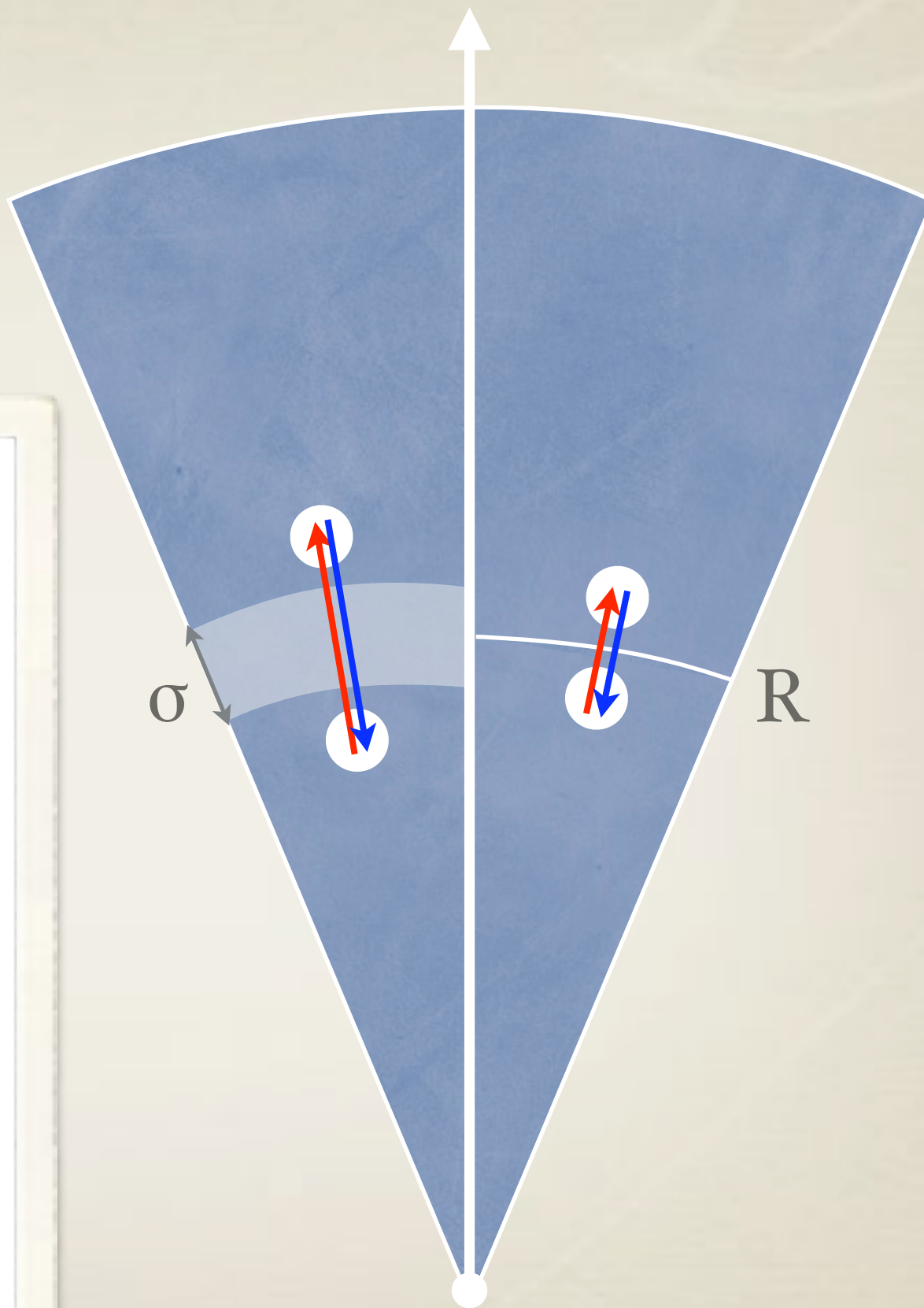
Phys Rev Lett, 102: 078101

- * divide system into a 3D grid
- * use local virial for each volume element
- * calculate averages



$$P_{local}(r) = \frac{1}{V} \left[\sum_i \delta(r - r_i) m_i v_i \otimes v_i + \frac{1}{2} \sum_{i \neq j} F_{ij} \int_{C_{ij}} \delta(r - l) dl \right]$$

flow rate



summary

- * large-scale biological systems accessible to CG simulations
- * water flux
 - OUT: (6.0 ± 1.3) ions/ns
 - IN: (1.7 ± 0.3) ions/ns
 - MODEL: $0.2-40$ ions/ns
 - Steinbacher et al. (2007)
CurrTopicsMembranes 58:1-24
- * release of an osmotic shock via MscL activation achieved
- * pore radius (11.6 ± 0.8) Å
 - (exp. $15-20$ Å)
- * MscL activation is indeed a last-ditch effort to prevent lysis
- * blocking of the channel by the cytoplasmic helices a first step in closure?
- * iris-like, non-symmetric opening

future

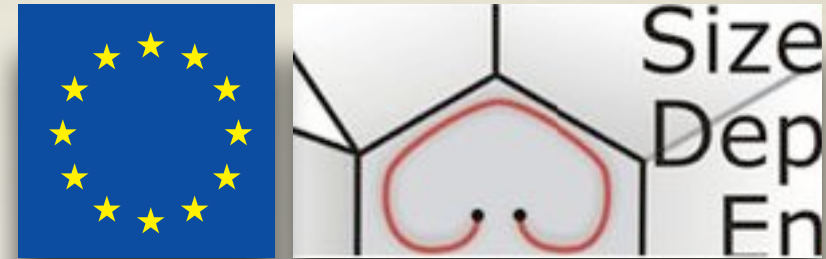
- * dye molecules to directly compare our release of nano-particles to experimental data
- * nano-pores formed by other molecules, e.g. anti-microbial peptides
- * activation of the channel using lyso-lipids





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Erik Lindahl



