Minimal coarse-grained models for biological assembly

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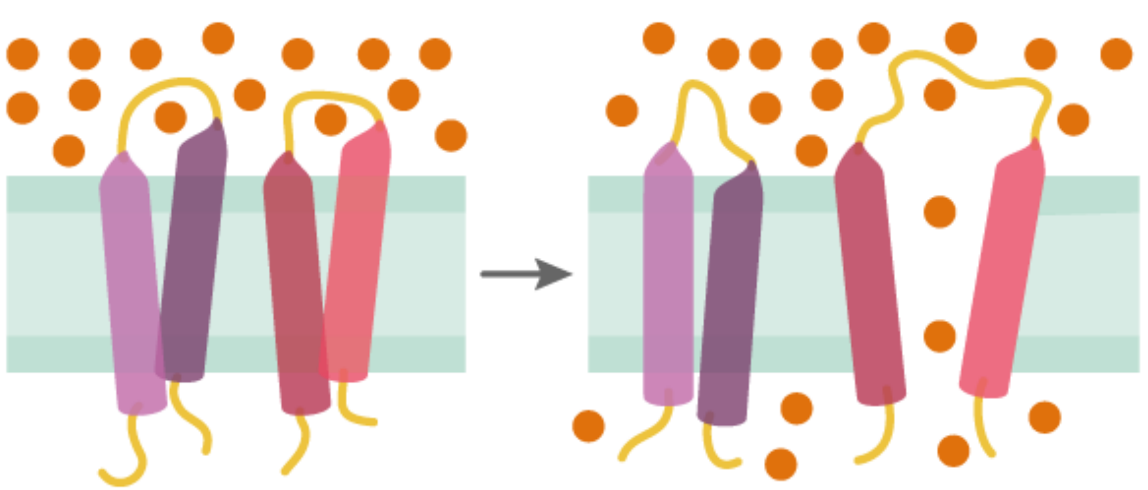
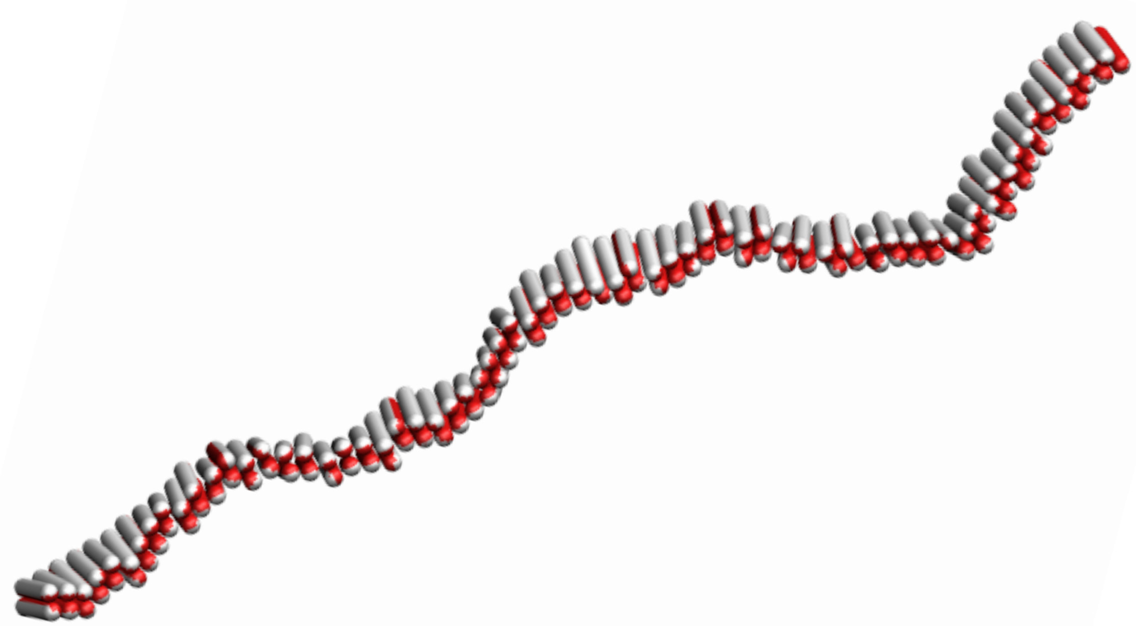
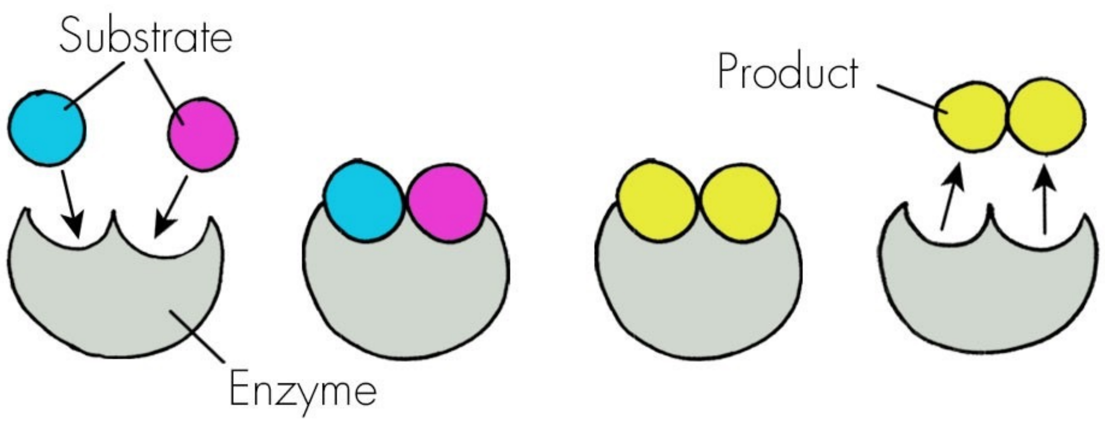




Proteins
Workhorses and building material of life

Single players

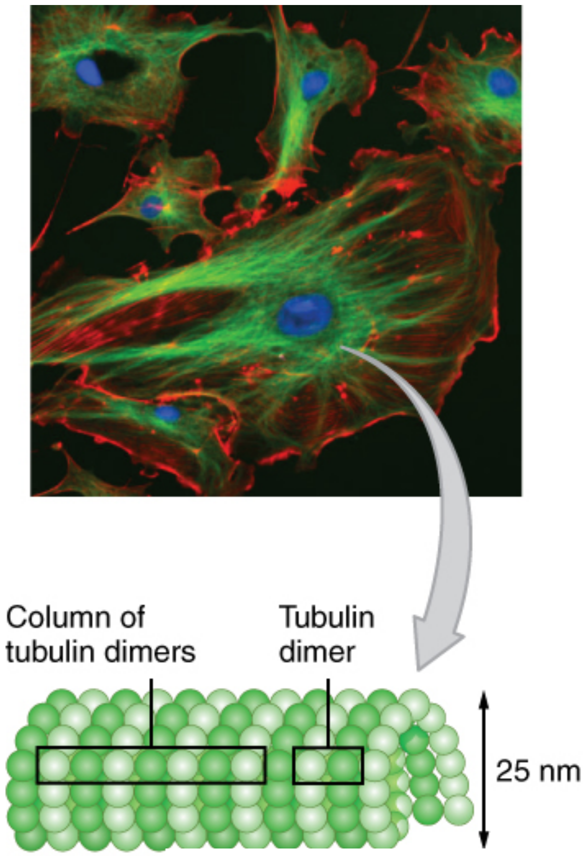


Team players

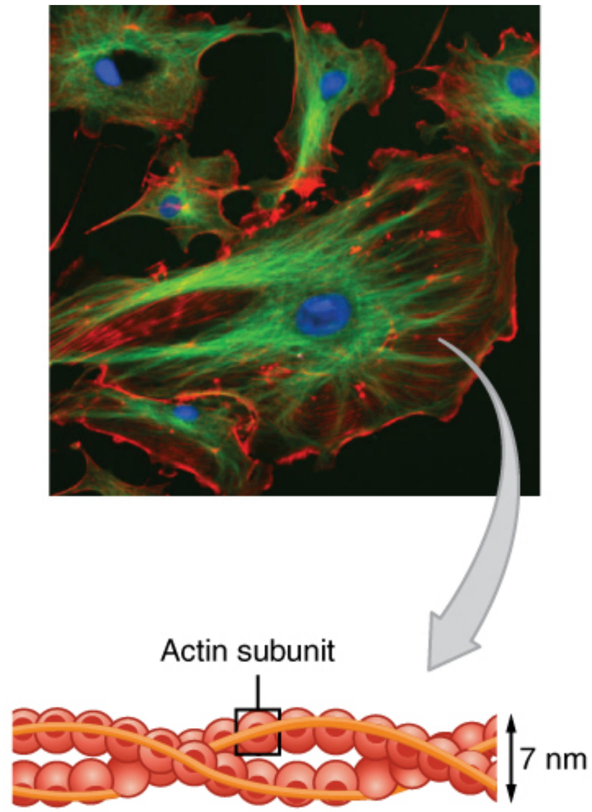
Proteins as team players

Good

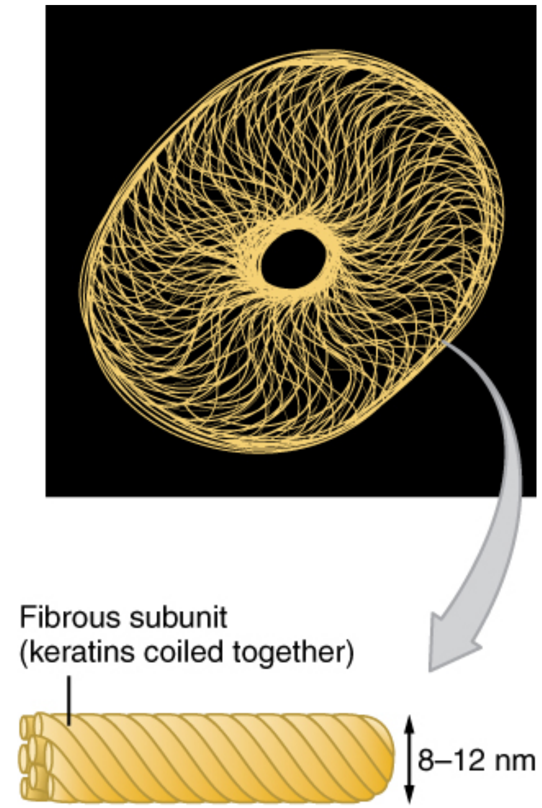
Microtubule



Actin

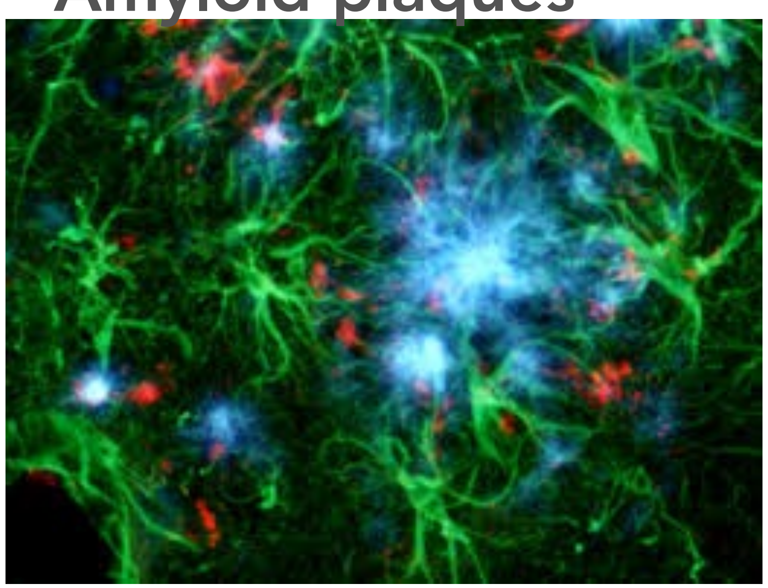


Intermediate filaments

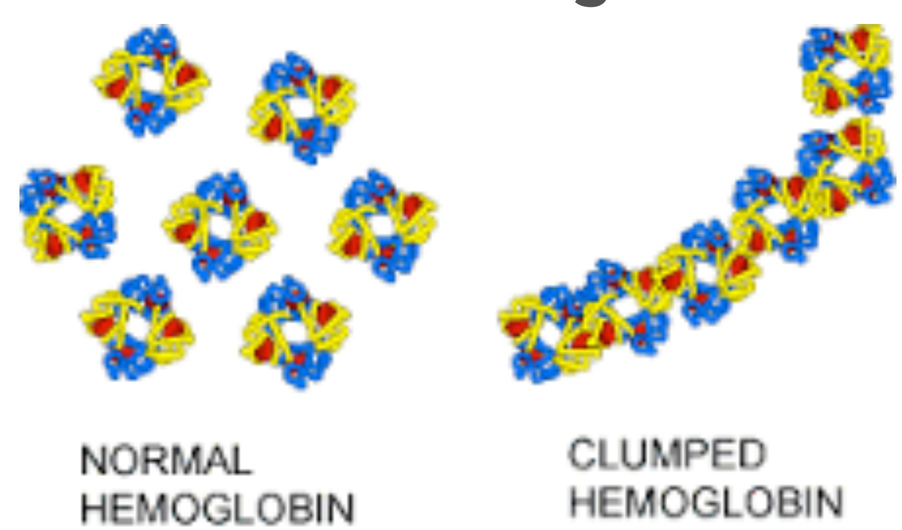


Gone bad

Amyloid plaques

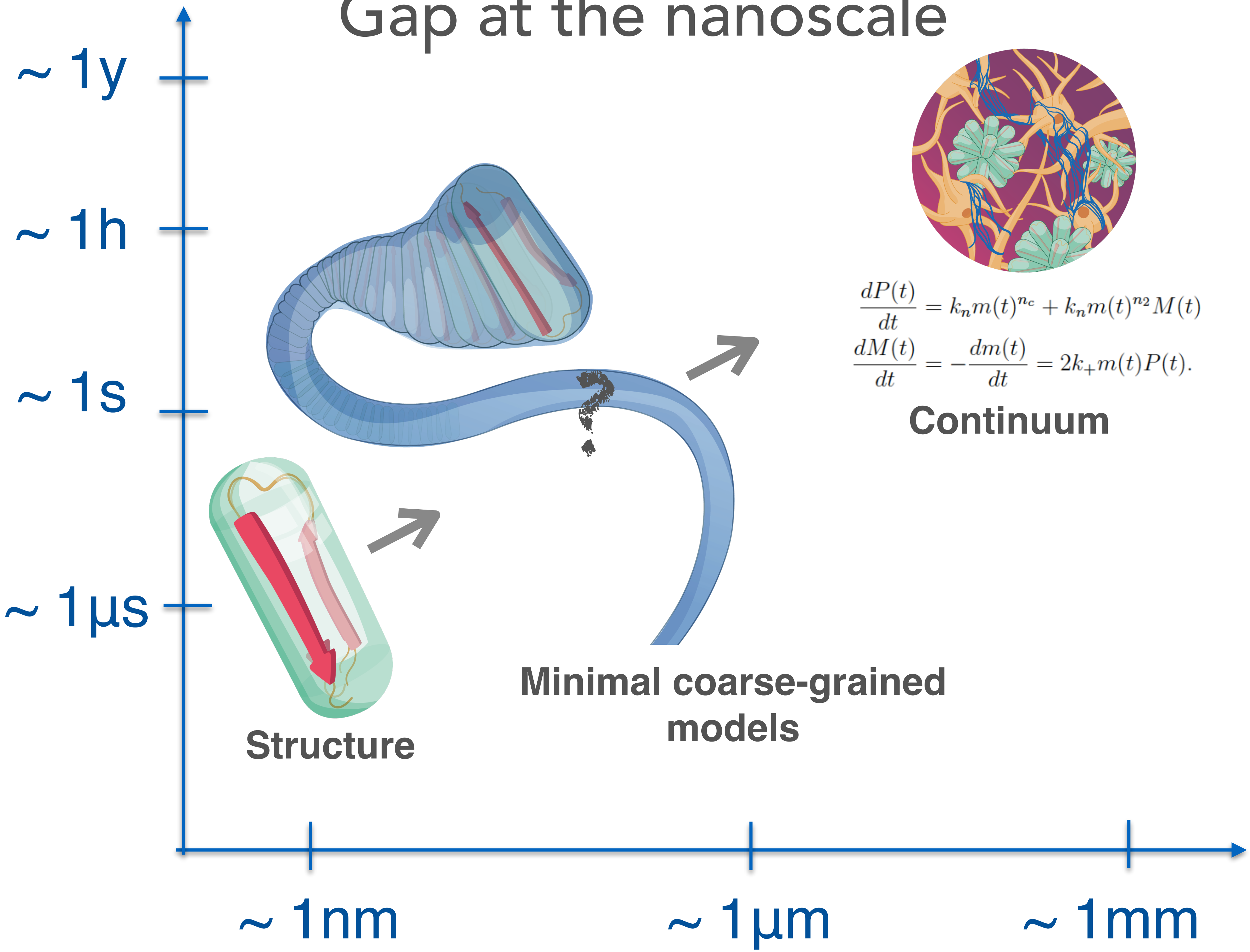


Sickle cell haemoglobin



Protein assembly & disassembly : multiscale problem

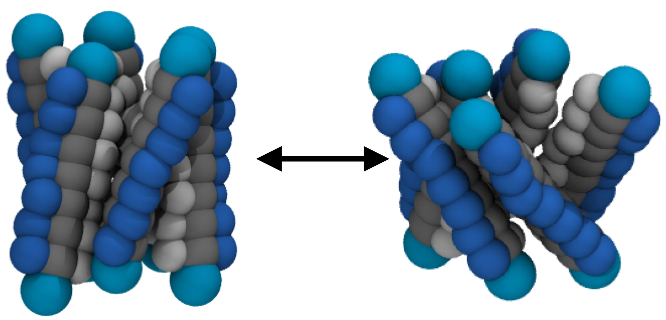
Gap at the nanoscale



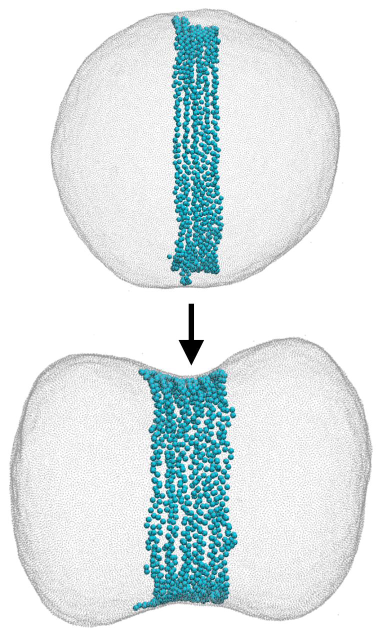
Our Research: modelling protein assembly

FUNCTIONAL

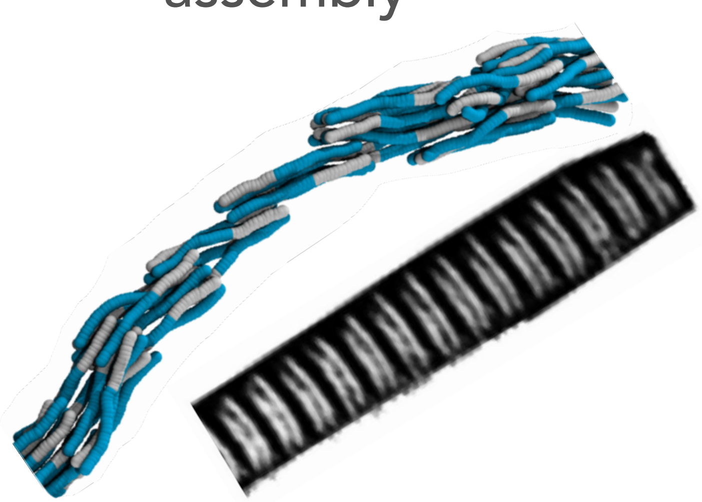
Mechanosensitive channel gating



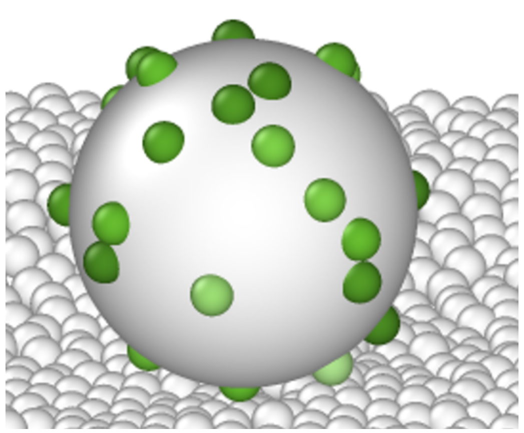
Protein filaments remodelling membranes



Extracellular matrix assembly

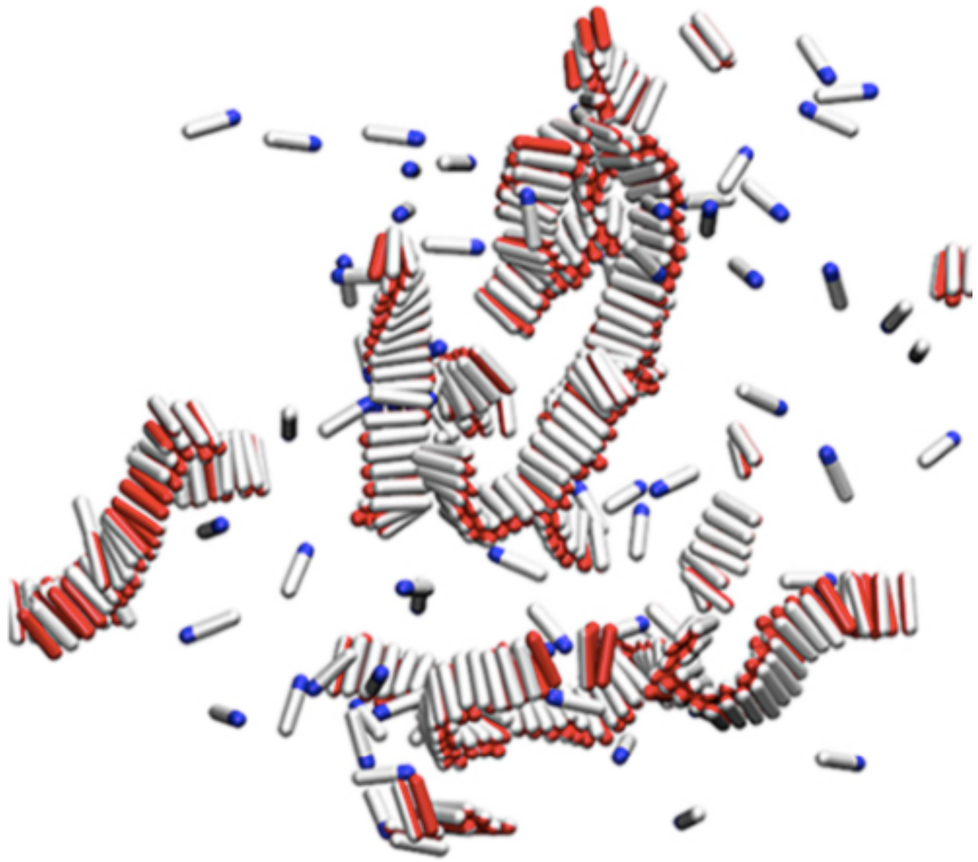


Cellular Uptake



PATHOLOGICAL

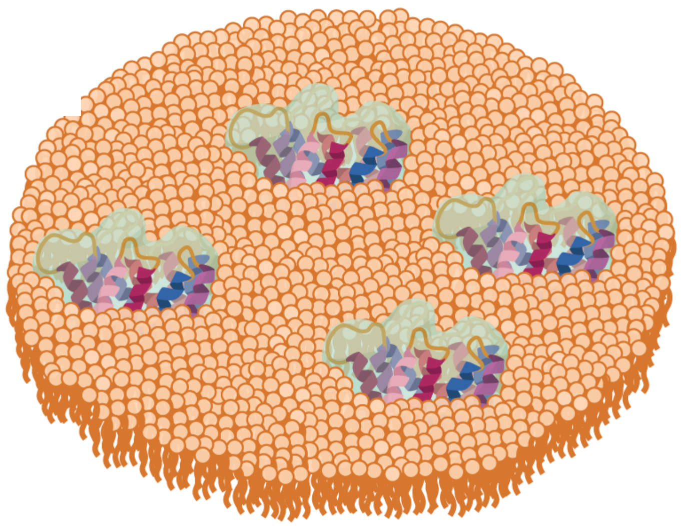
Amyloid aggregation



TODAY

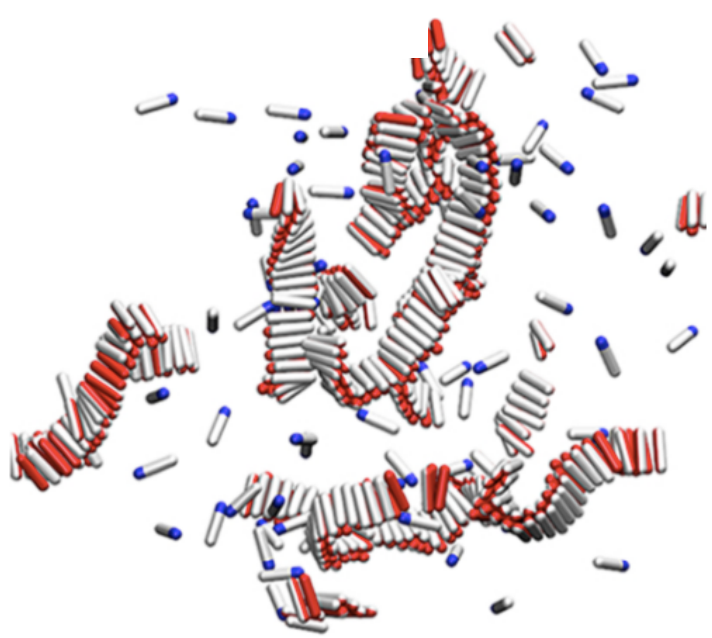
I: Functional Protein Aggregation

Bacterial mechanosensitive channels

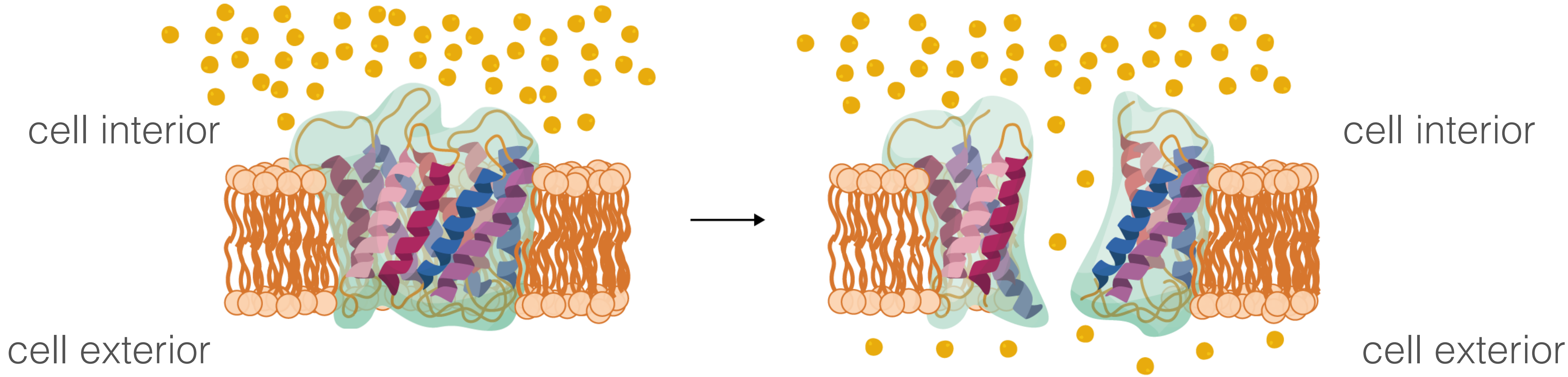


II: Pathological Protein Aggregation

Amyloid aggregation



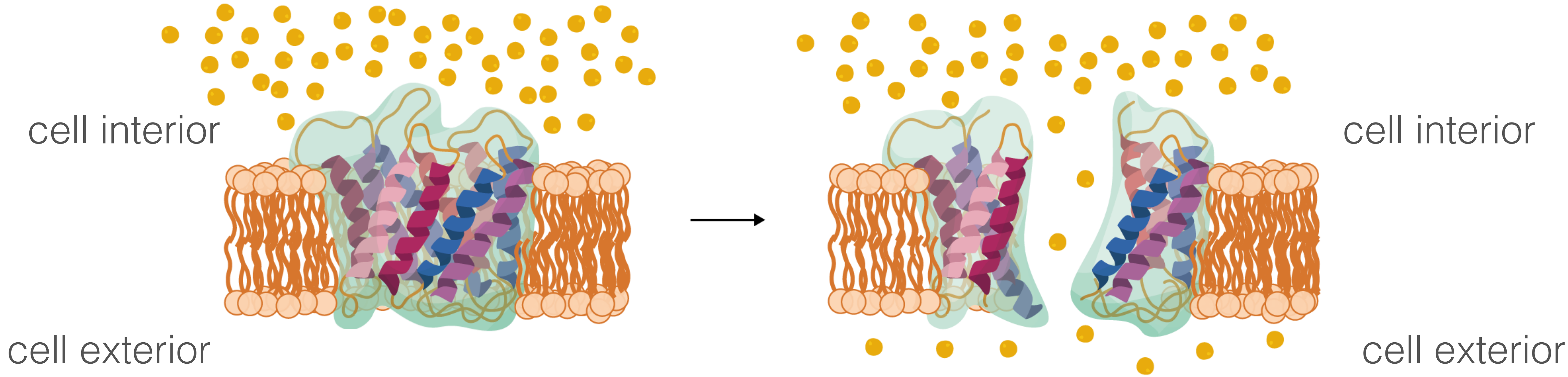
Simplest form of mechanosensing?
Bacterial mechanosensitive channels



Non-specific!

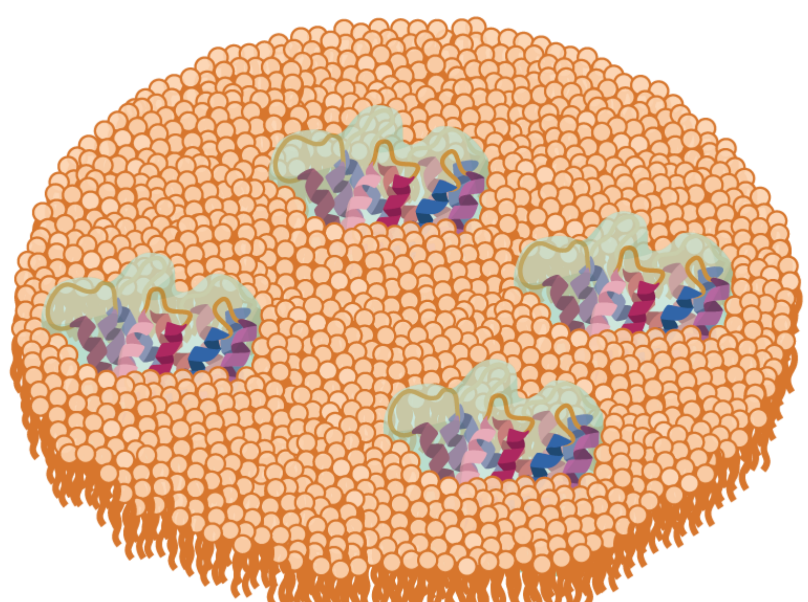
ms scale!

Simplest form of mechanosensing?
Bacterial mechanosensitive channels



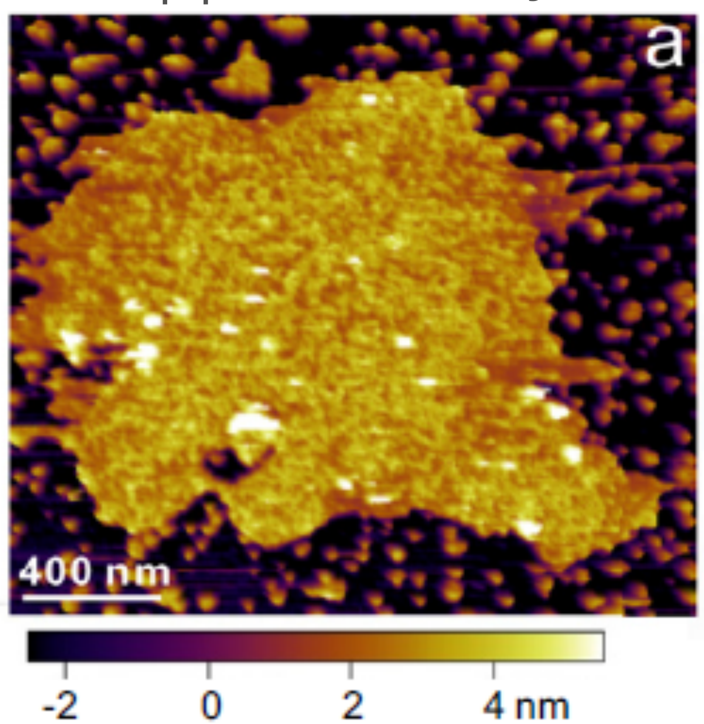
Non-specific!
ms scale!

Channels share the cell membrane:
Cooperative sensing?



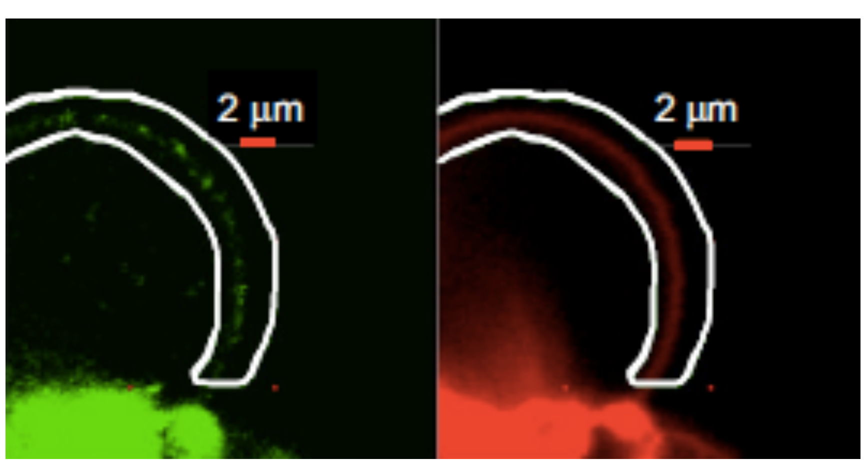
Assembly of mechanosensitive channels

AFM of channel clustering in supported bilayer.

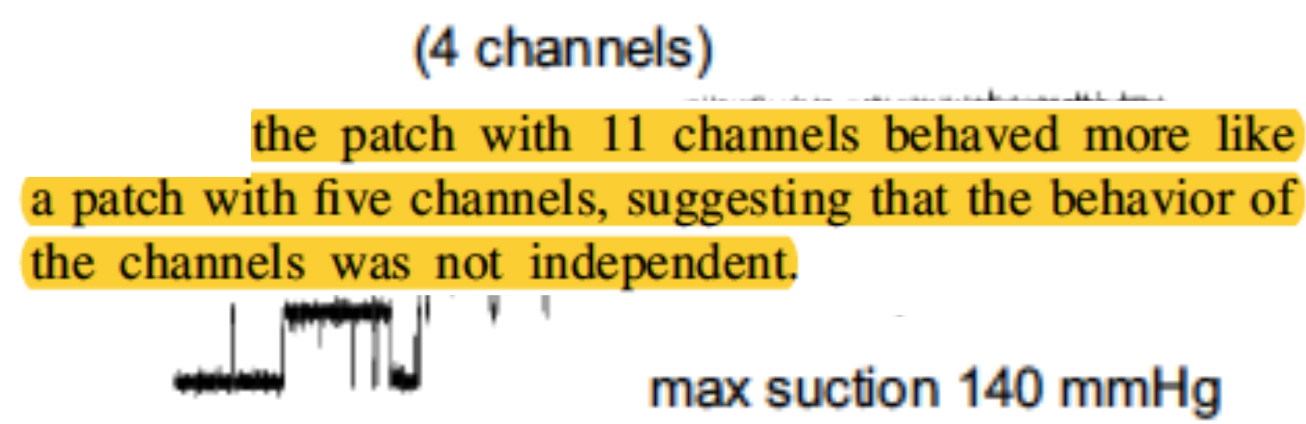


SR image of multi-channel clustering in live bacterium.

Channel clustering in liposome.

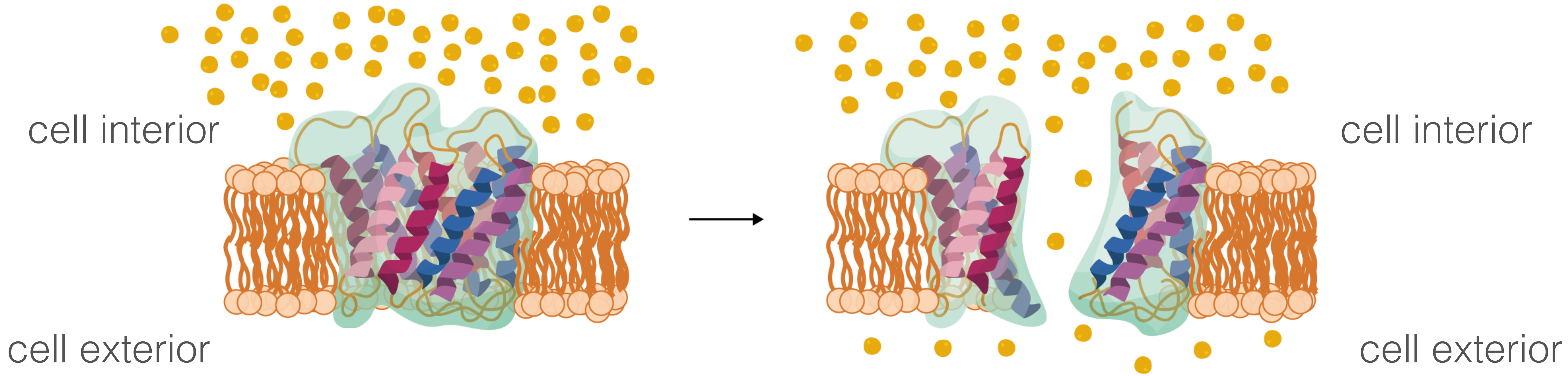


Channel clustering in liposome.



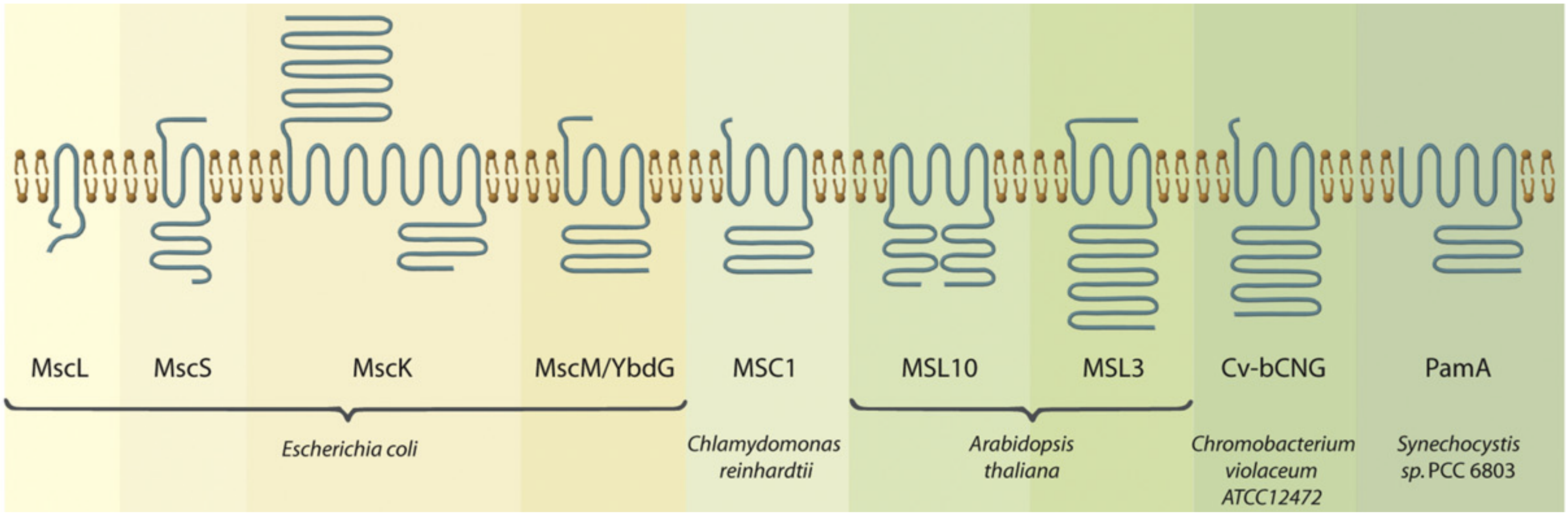
S. Grage, …, B. Martinac, *Biophys J,* 100 (2011).

Simplest form of mechanosensing?
Bacterial mechanosensitive channels



Non-specific!
ms scale!

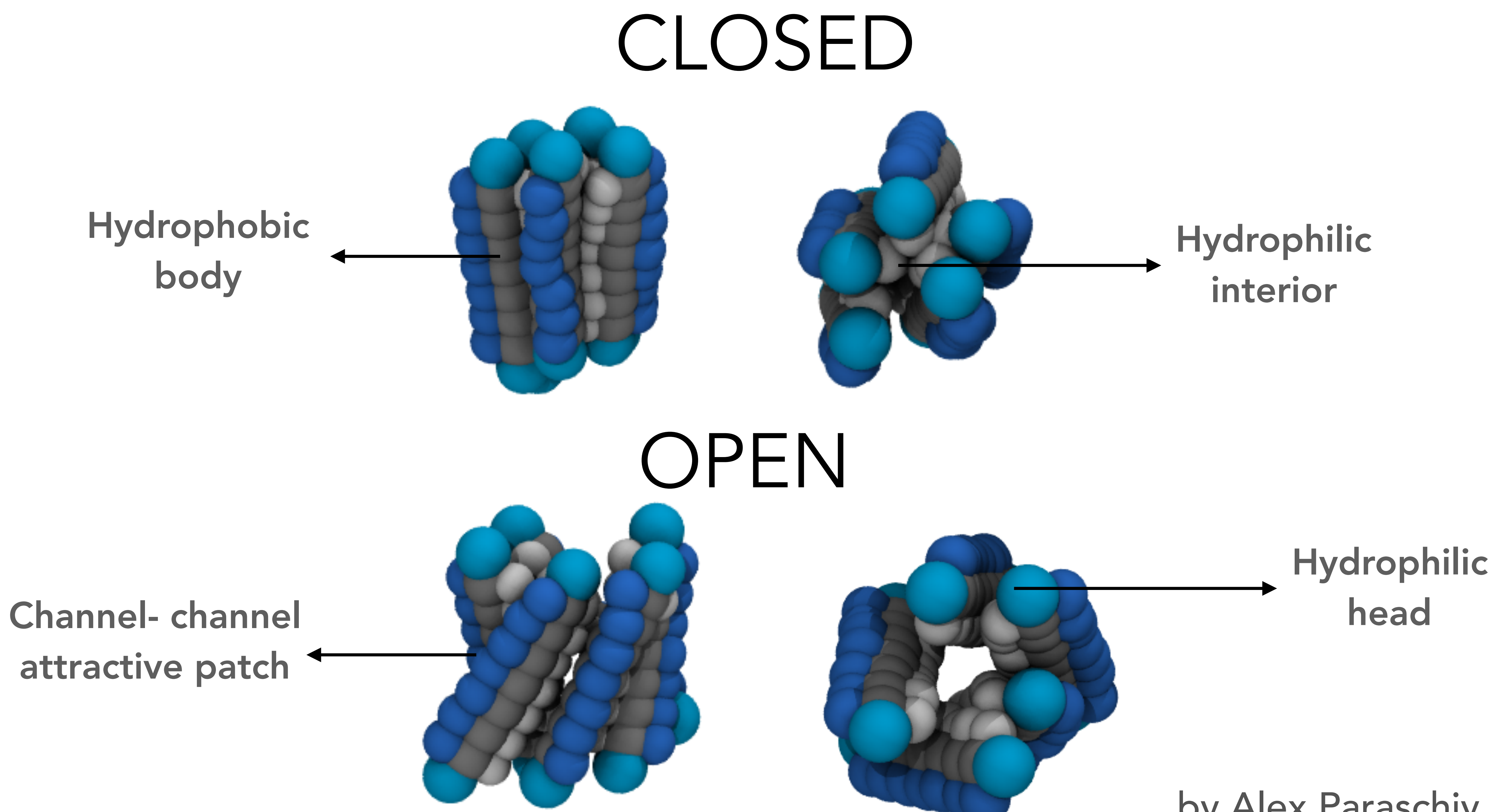
Structure (MscL)



E Haswell, R Phillips, DC Rees, *Structure* 19 (2011).

Minimal model of a mechanosensitive channel

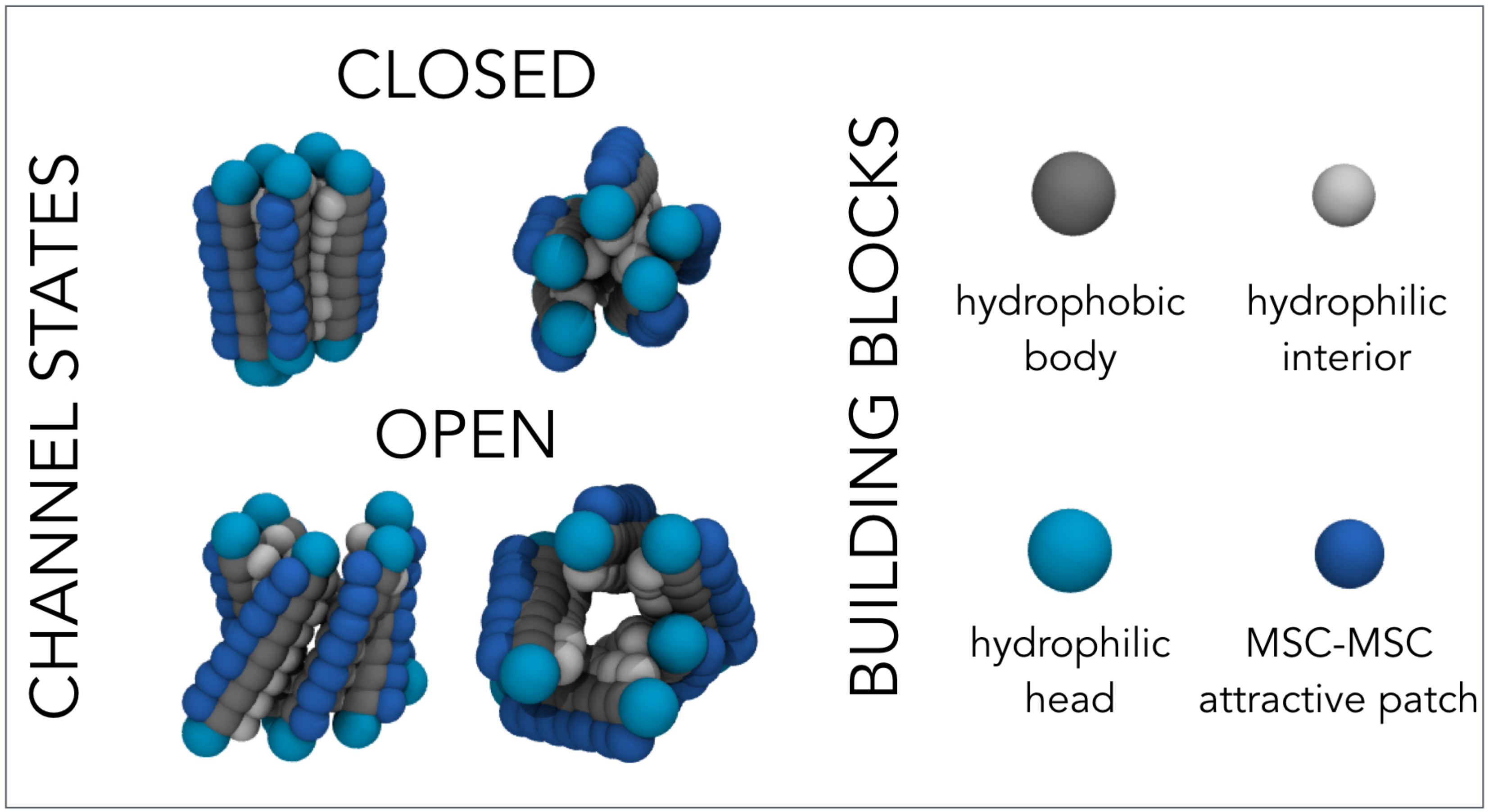
Aim: to understand collective behaviour of mechanosensitive channels



by Alex Paraschiv

Minimal model of a mechanosensitive channel

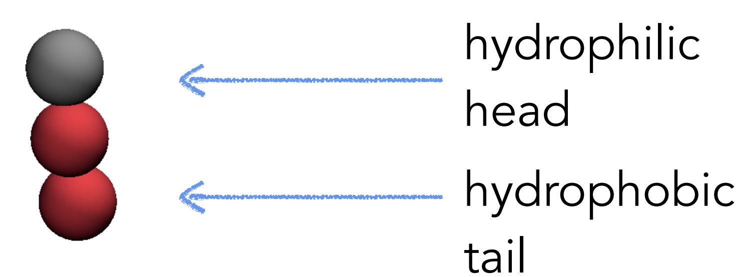
Details of the model



$$V_{rep}(r;b) = \begin{cases} 4\varepsilon\left[\left(\frac{b}{r}\right)^{12} - \left(\frac{b}{r}\right)^{6} + \frac{1}{4}\right], & r \le r_c \\ 0 & r > r_c \end{cases}$$

$$V_{attr}(r;b) = \begin{cases} -\varepsilon, & r < r_c \\ -\varepsilon cos^2 \frac{\pi(r - r_c)}{2w_c}, & r_c \le r \le r_c + w_c \\ 0, & r > r_c + w_c \end{cases}$$

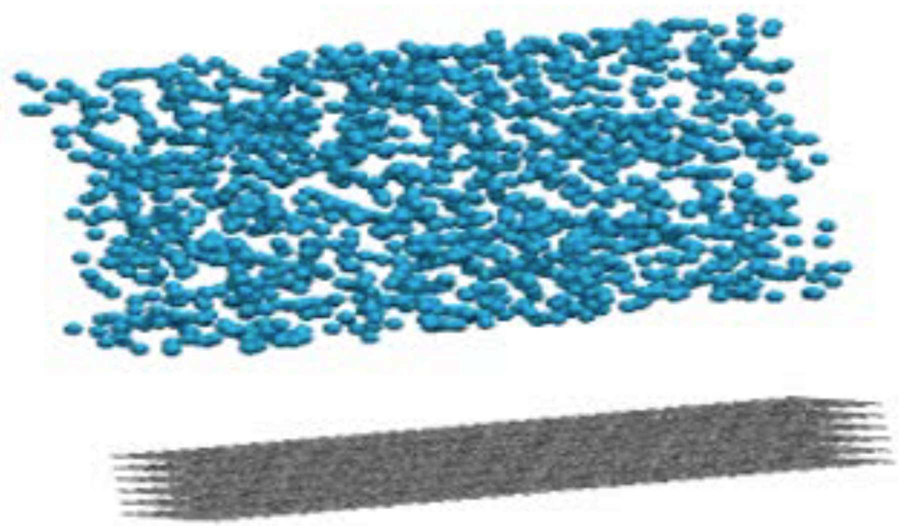
Lipids:



Cooke, Deserno, PRE 2005, 011506.

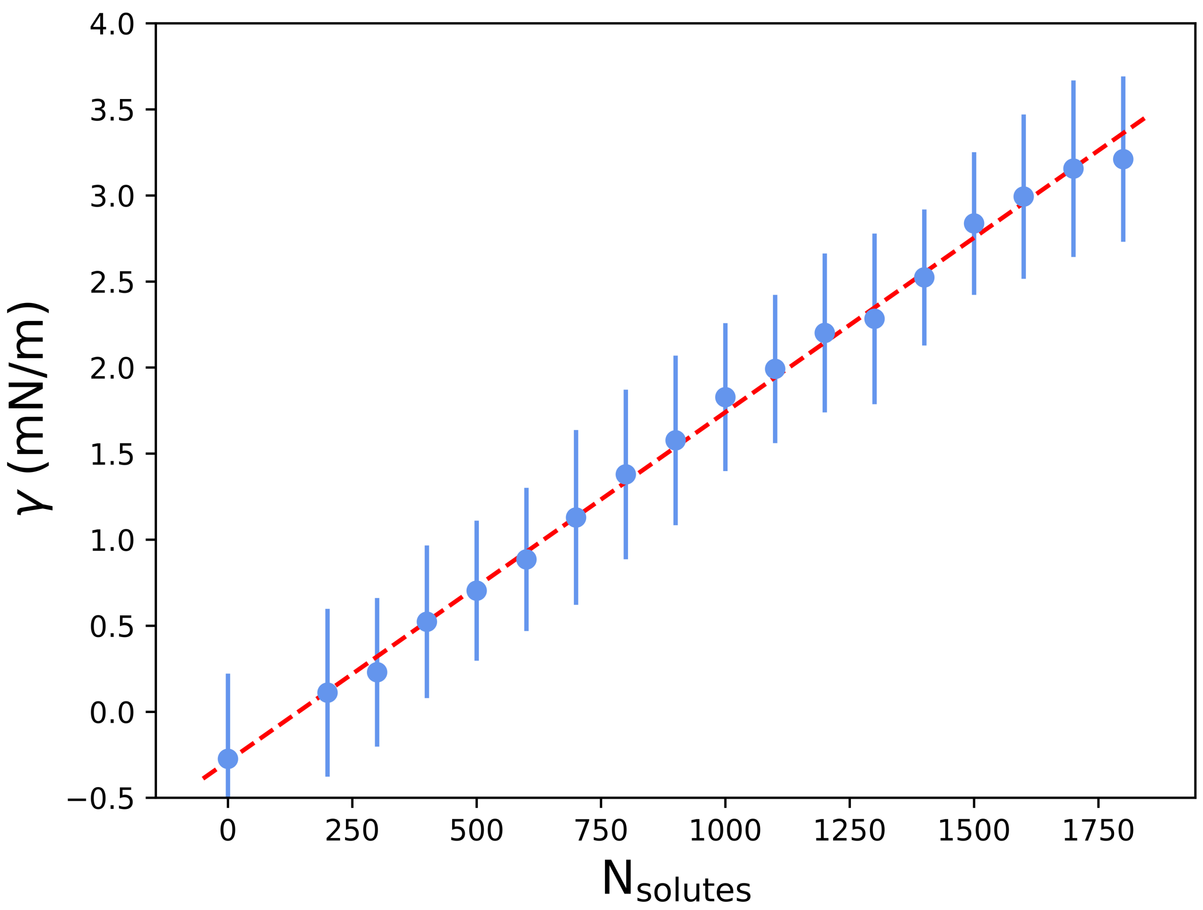
Minimal model of a mechanosensitive channel

Shock is applied by hard "solute" particles



Surface tension:

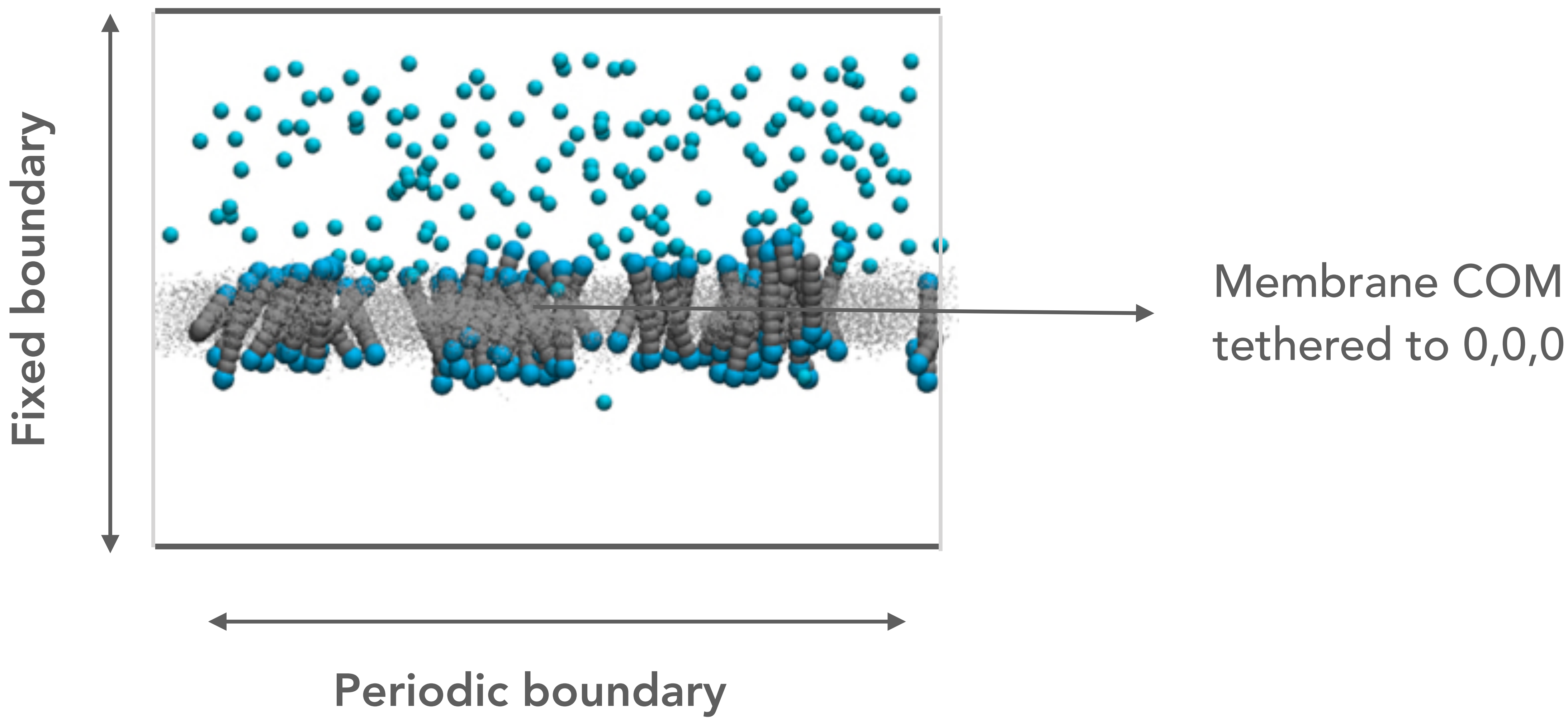
$$\gamma = \int [p_{zz} - \frac{1}{2}(p_{xx} + p_{yy})] \mathrm{d}z$$



Kirkwood, Buff, J Chem Phys, 17 1949

Minimal model of a mechanosensitive channel

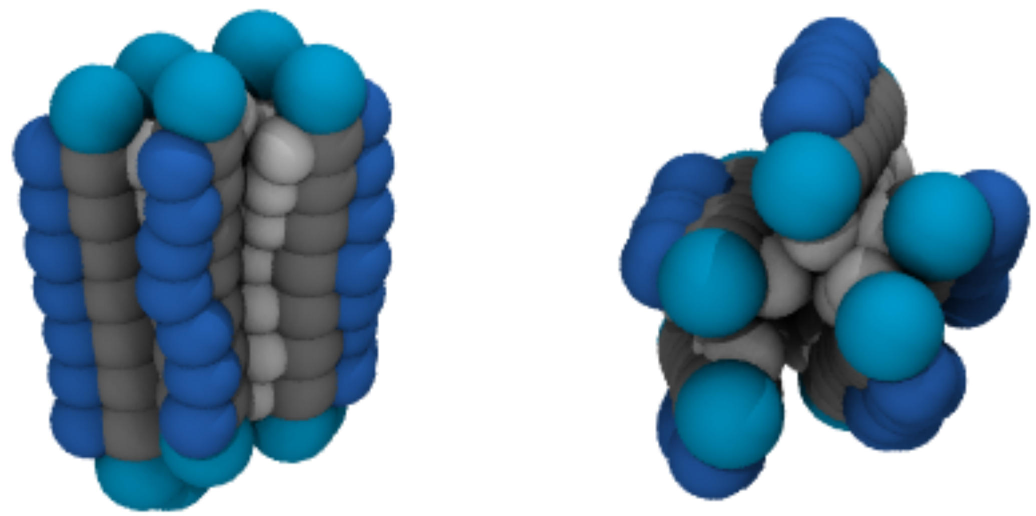
Shock is applied by hard "solute" particles



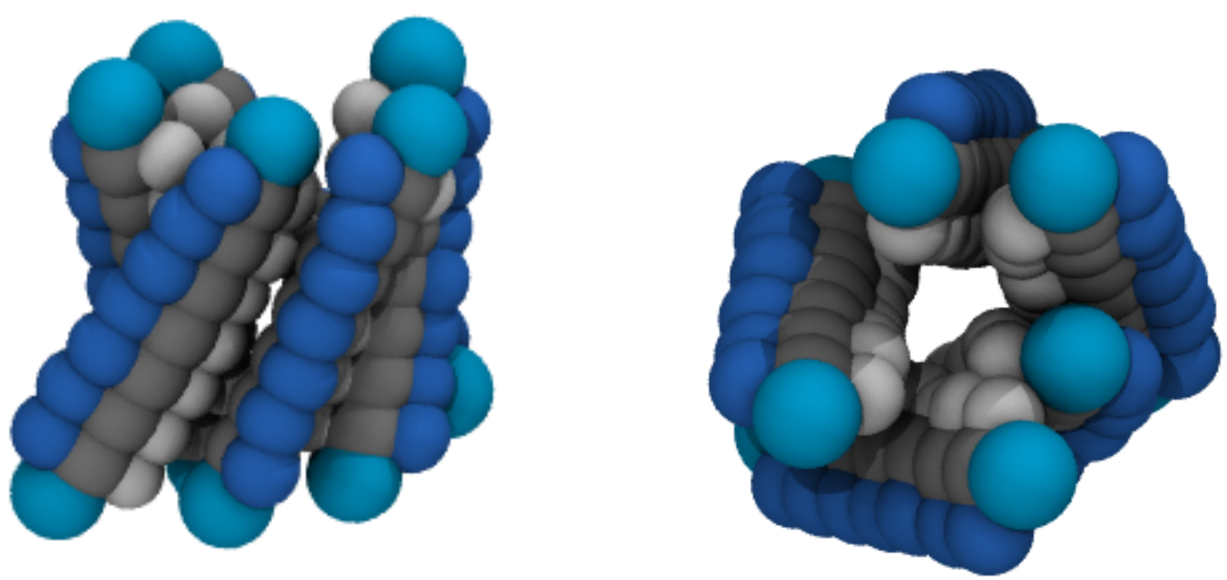
Minimal model of a mechanosensitive channel

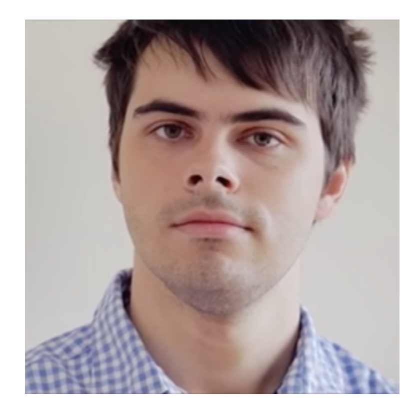
Aim: to understand collective behaviour of mechanosensitive channels

CLOSED



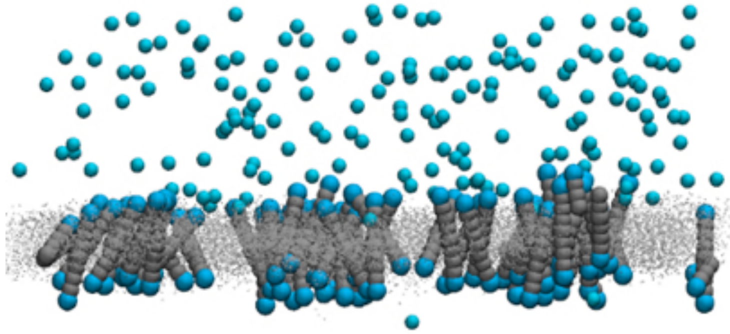
OPEN



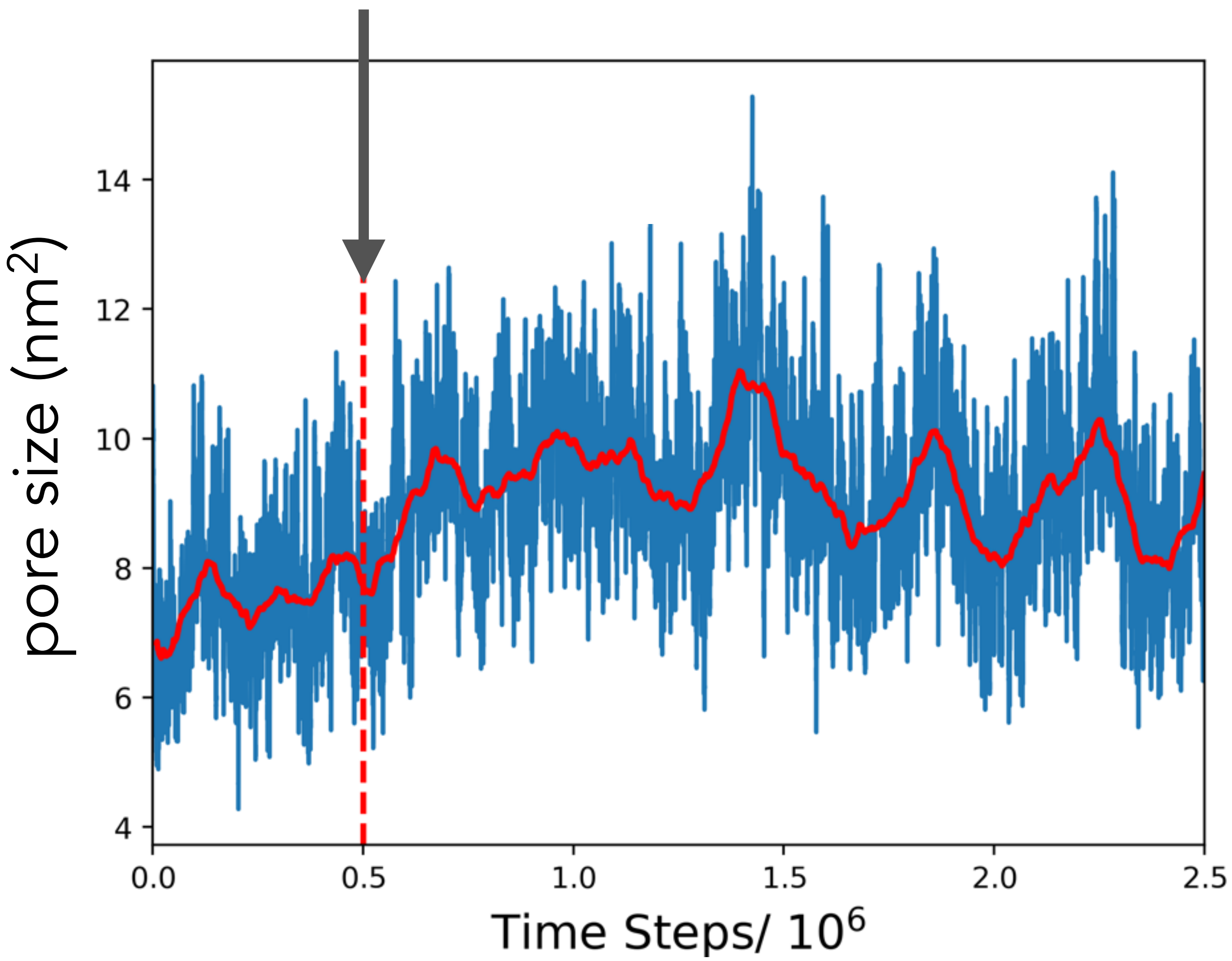


by Alex Paraschiv

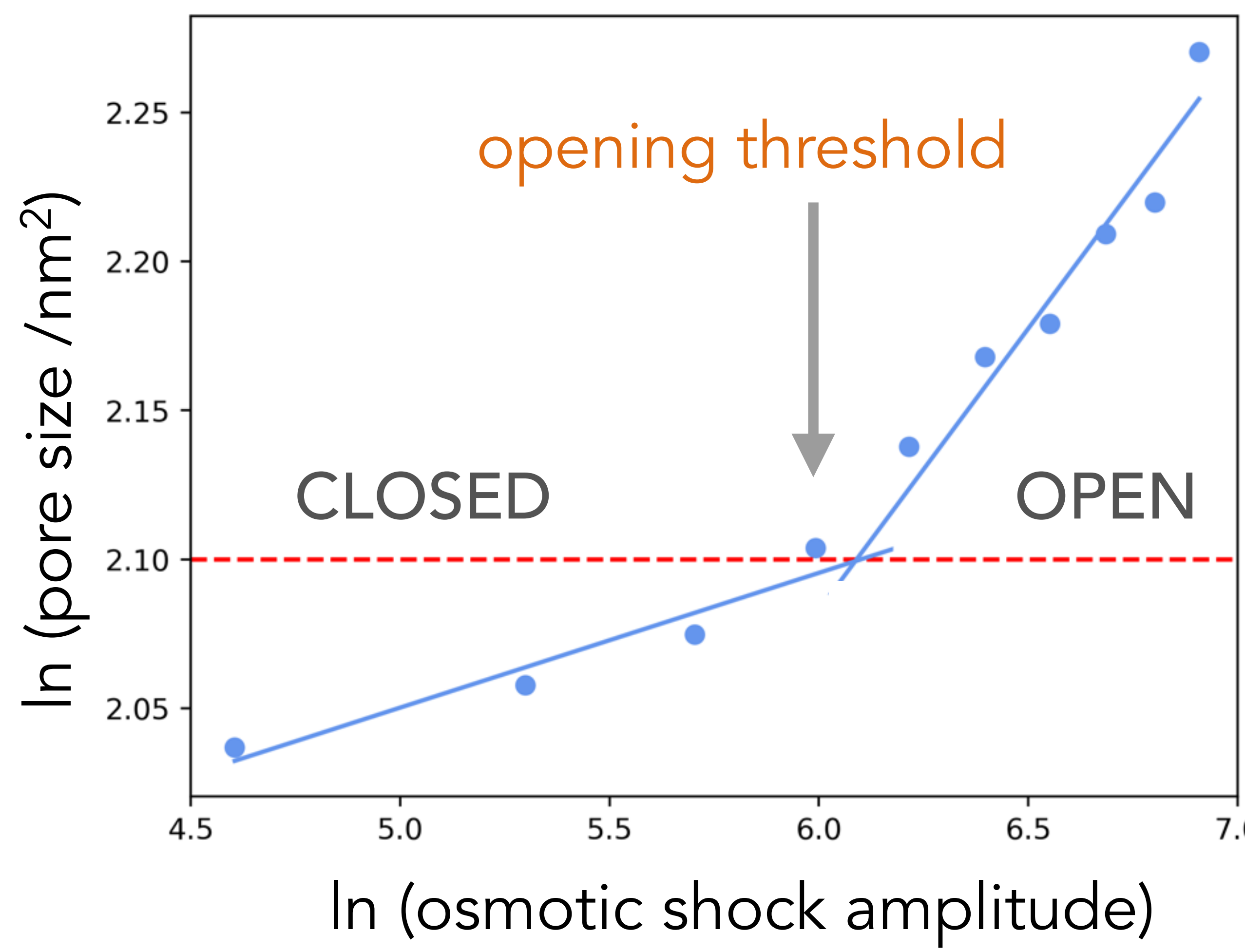
Single Channel Response

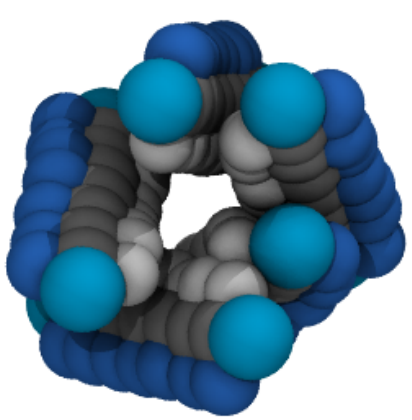


osmotic shock applied



MEASURING PORE SIZE

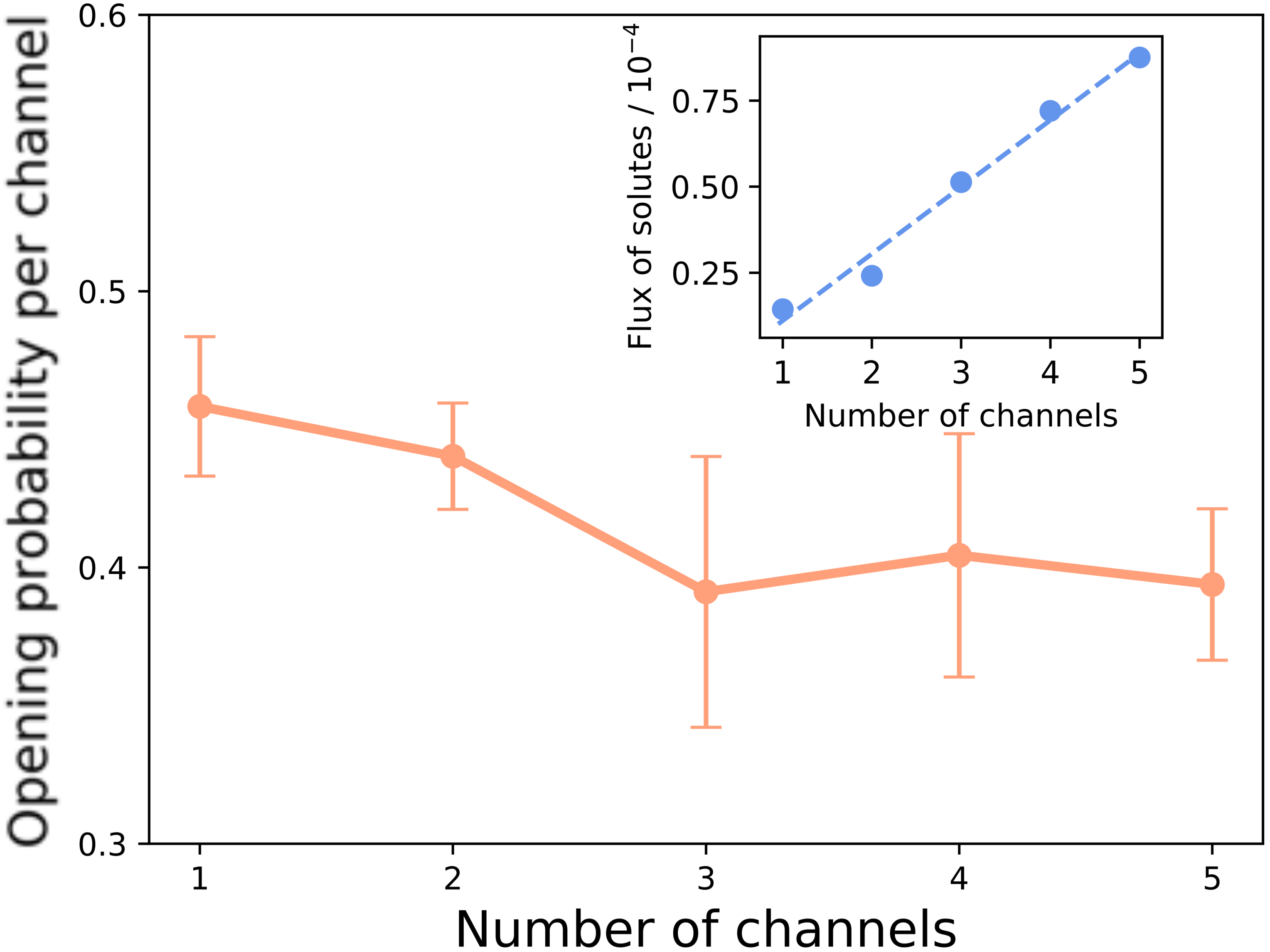




$$\text{channel state} = \begin{cases} \text{open}, & \text{pore size} \geq \text{threshold size} \\ \text{closed}, & \text{otherwise} \end{cases}$$

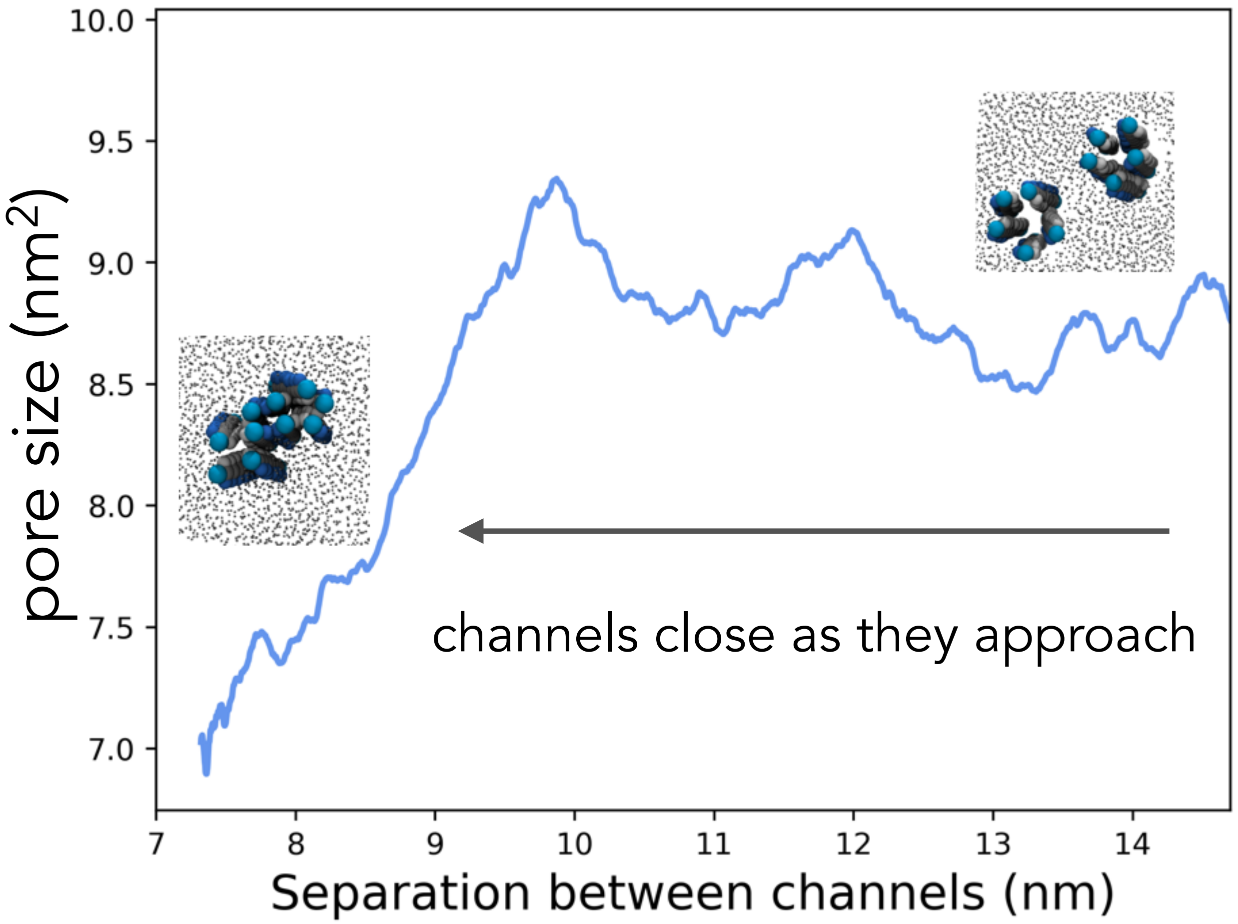
Multiple Channels Response

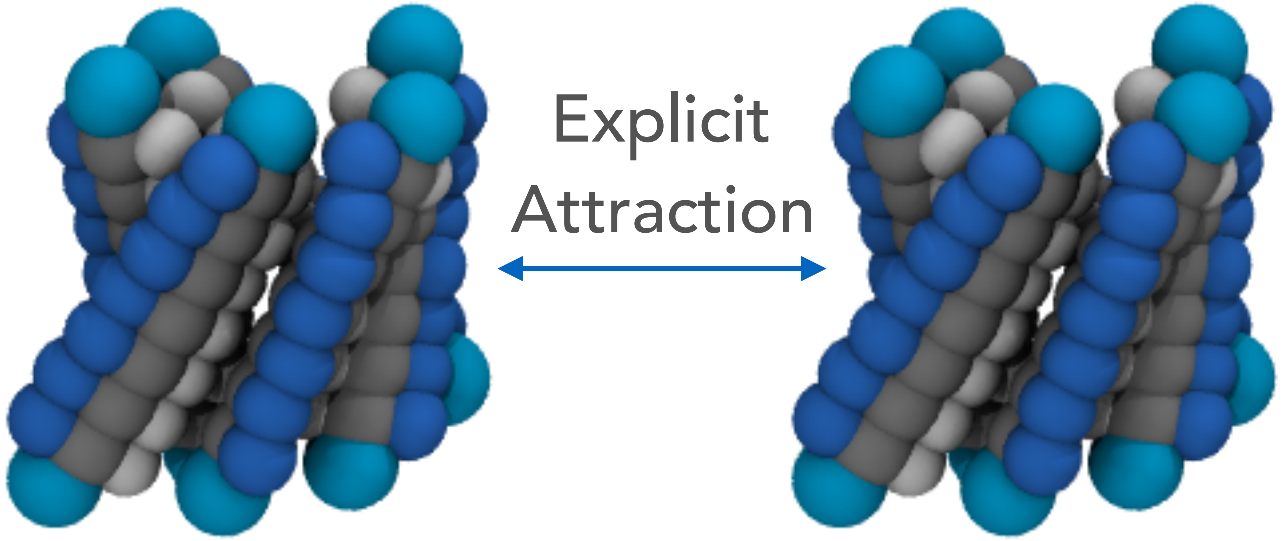
NON-AGGREGATING CHANNELS



Multiple Channels Response

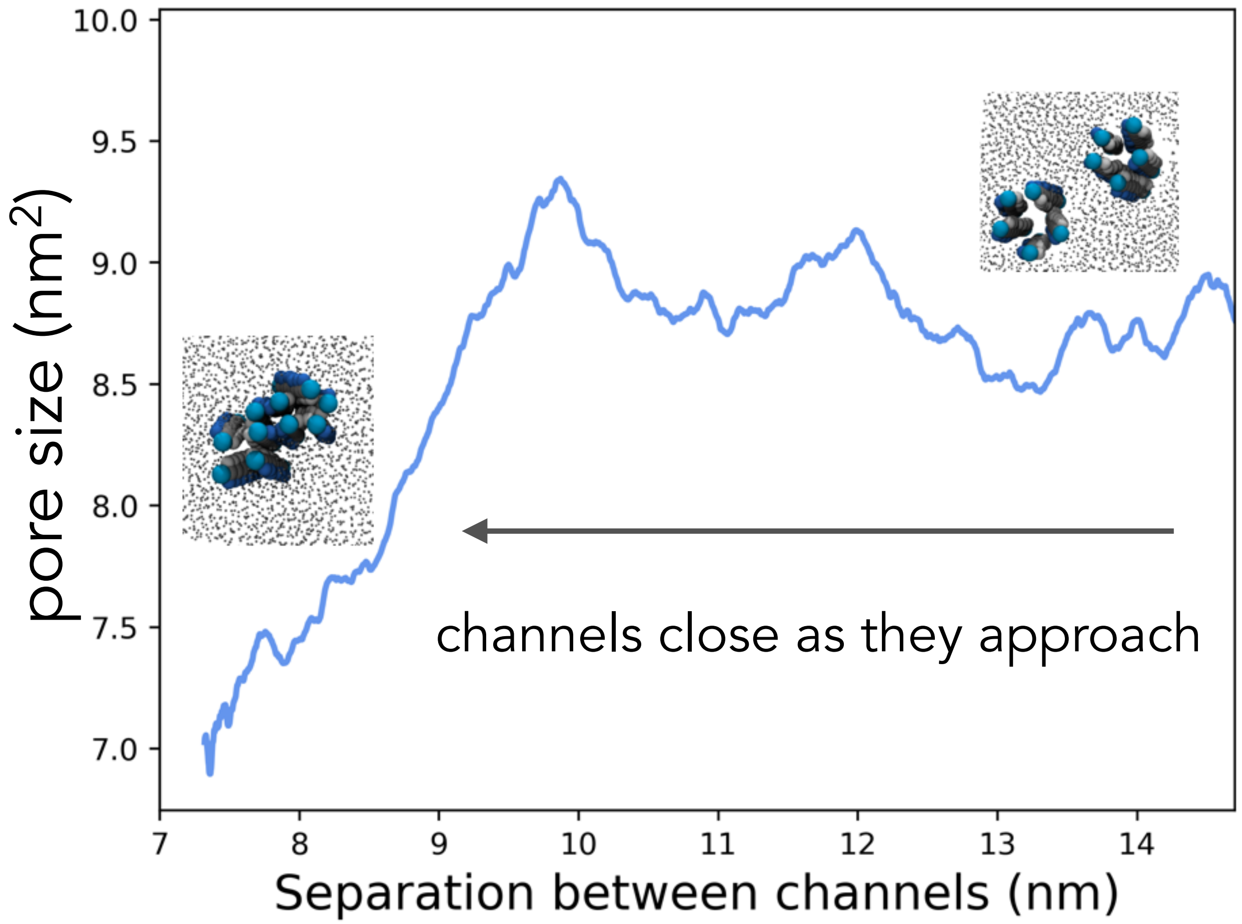
AGGREGATING CHANNELS

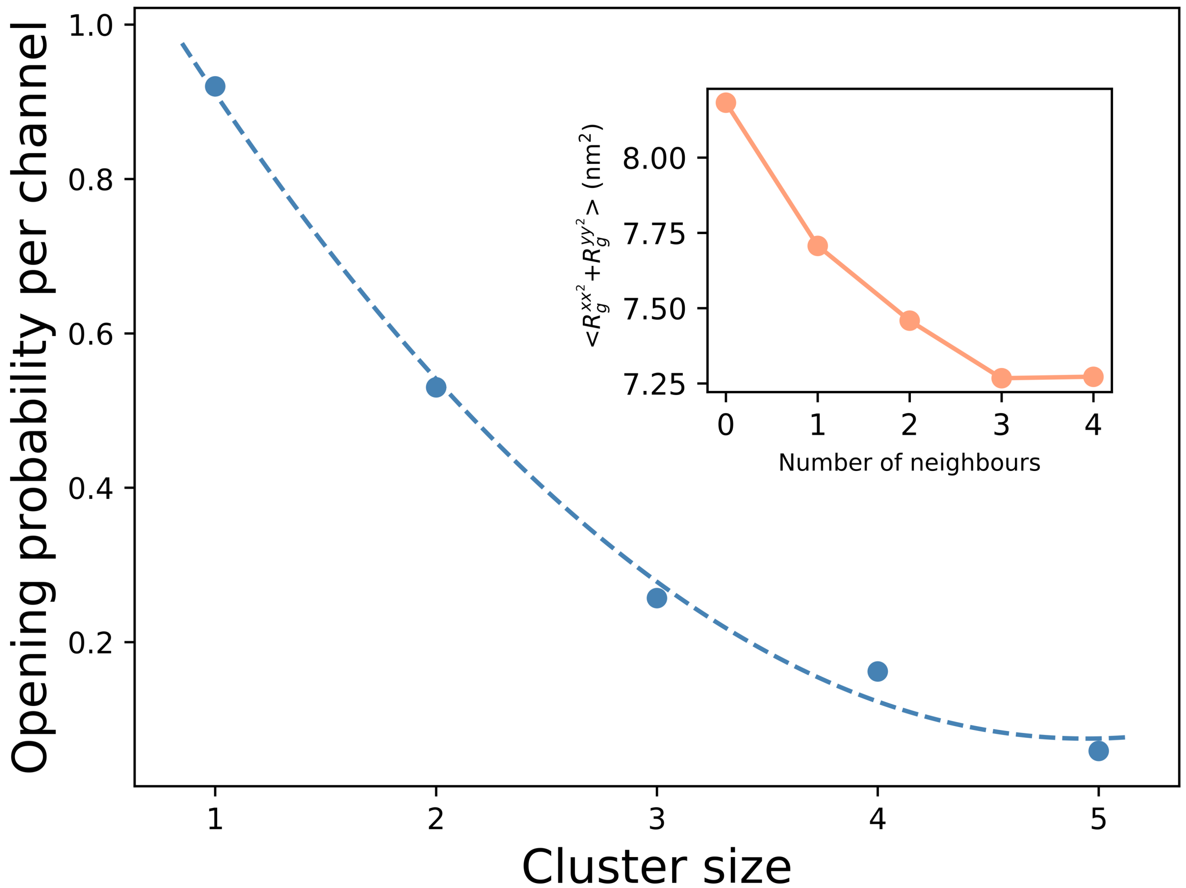




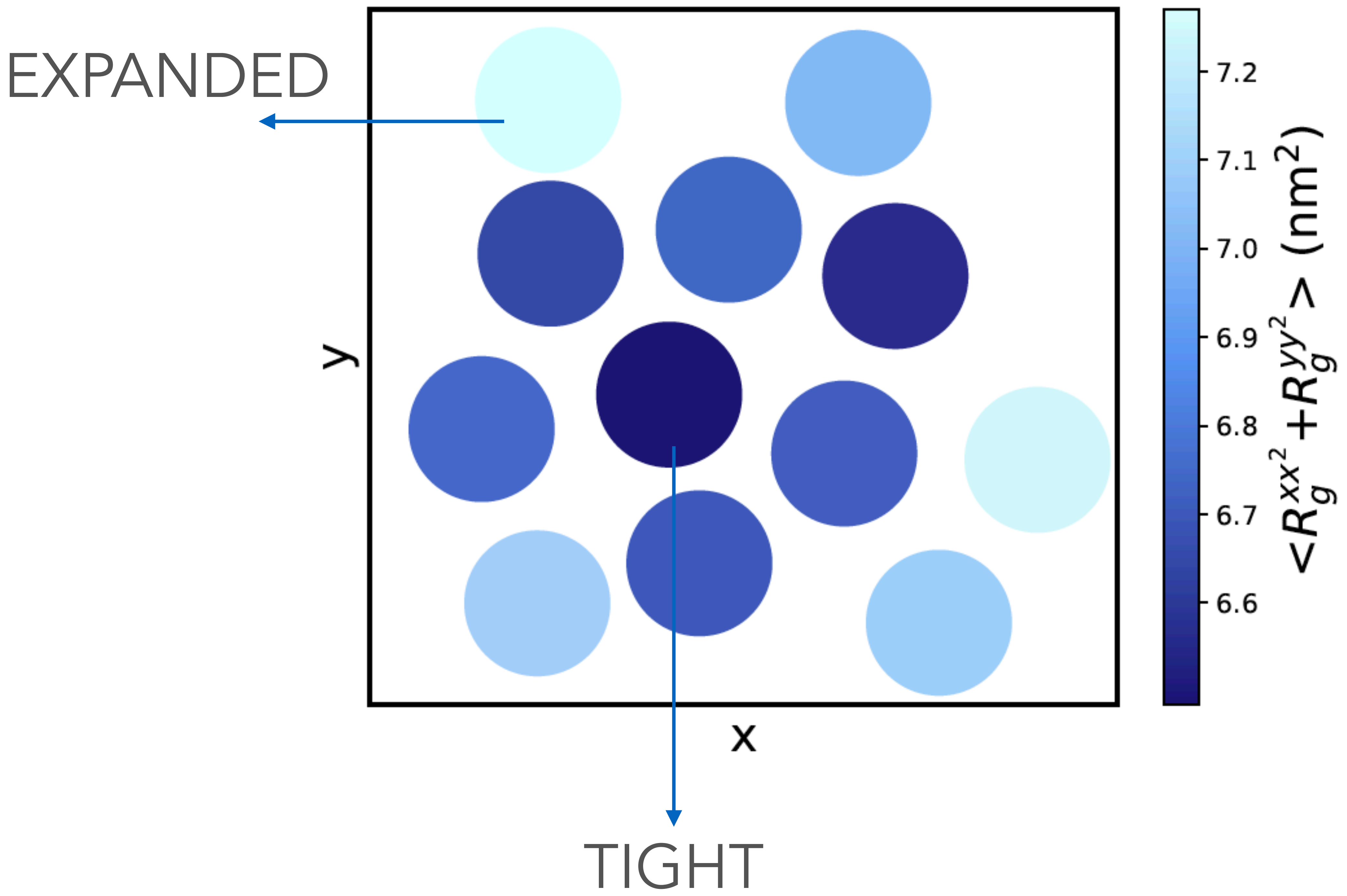
Multiple Channels Response

AGGREGATING CHANNELS

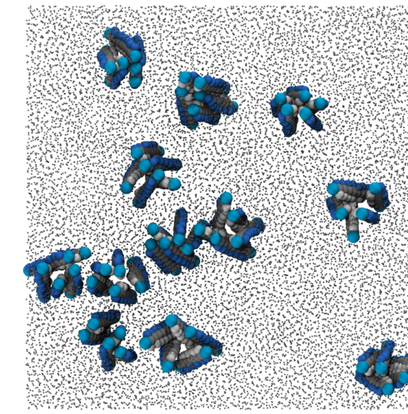




Channel heterogeneity within one cluster

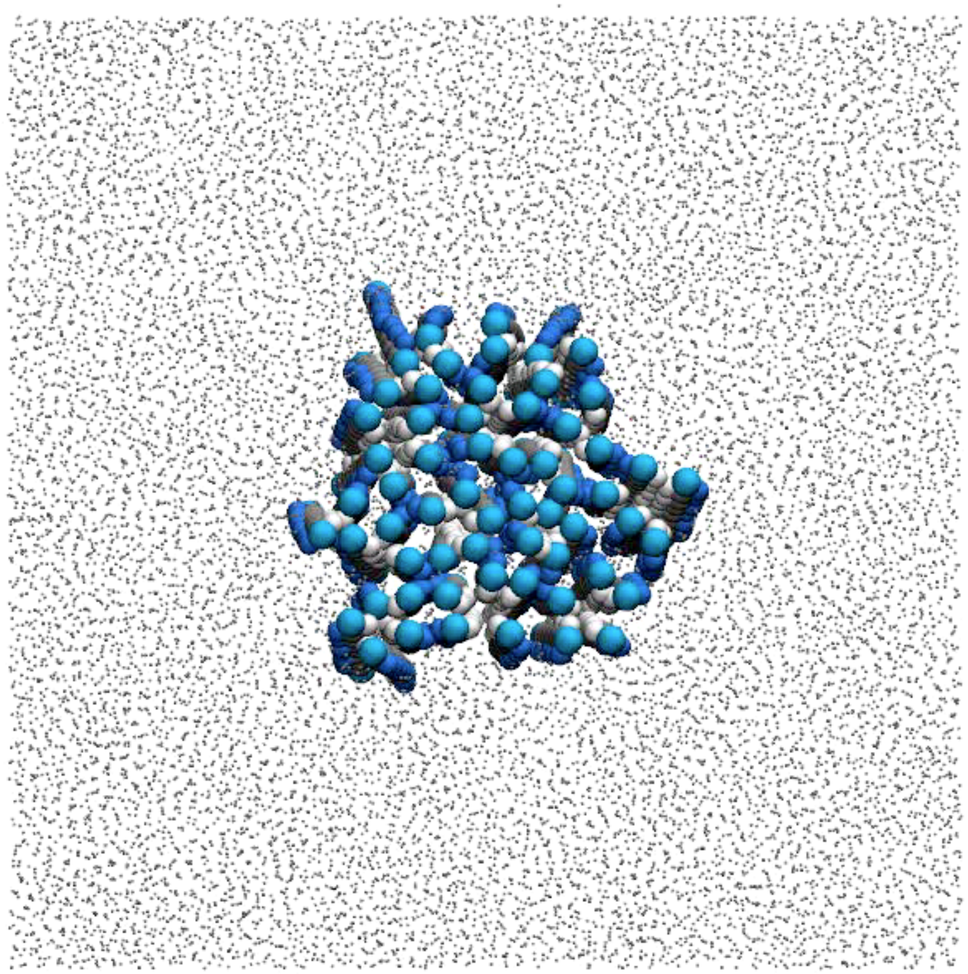


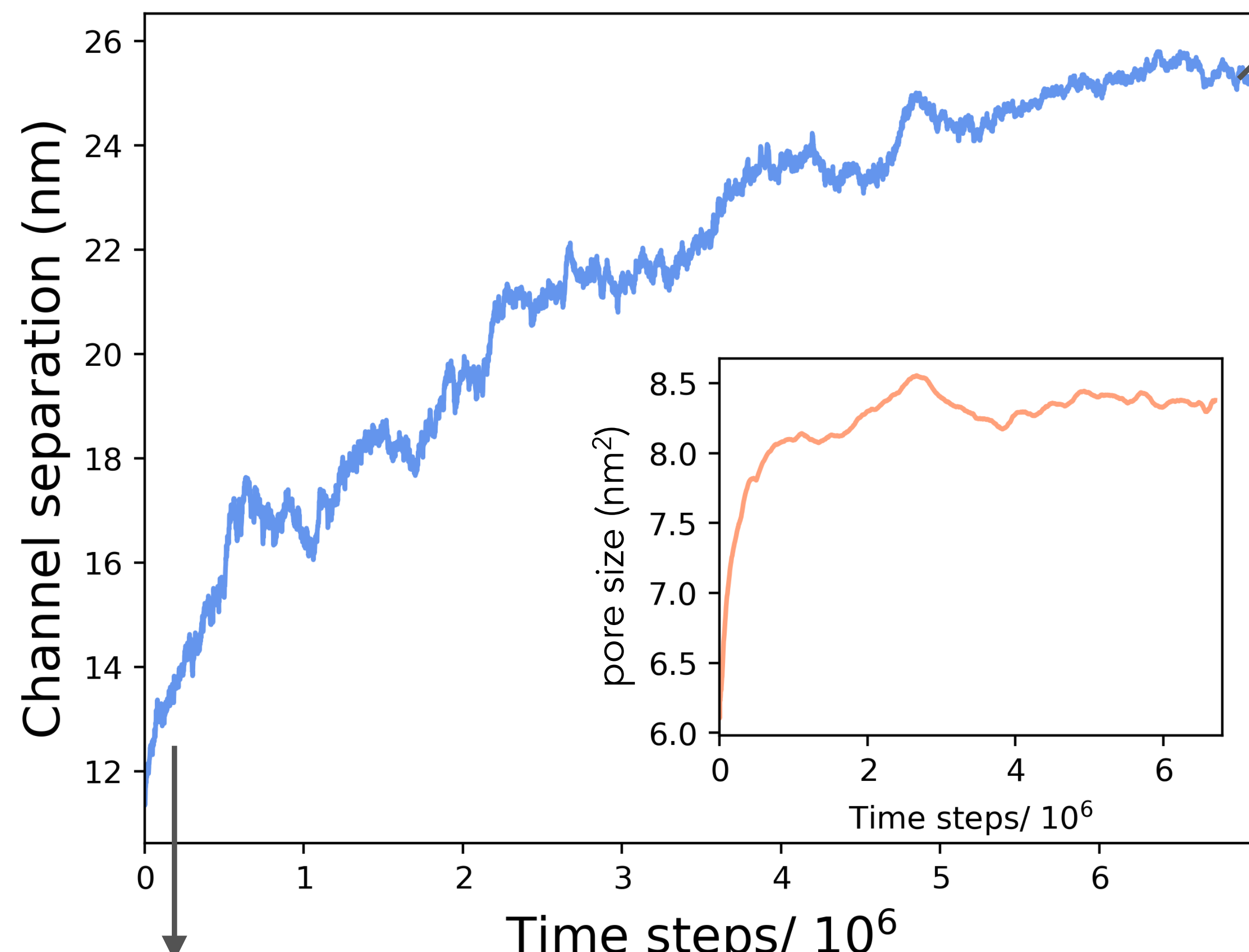
Dynamic channel aggregation

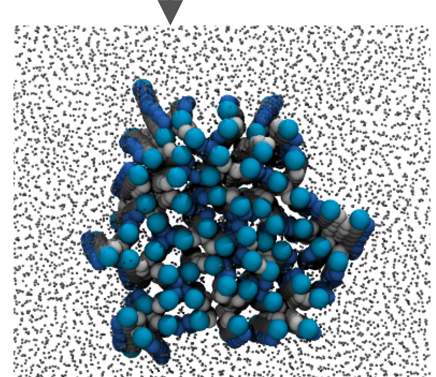


Clusters dynamically respond to osmotic shock

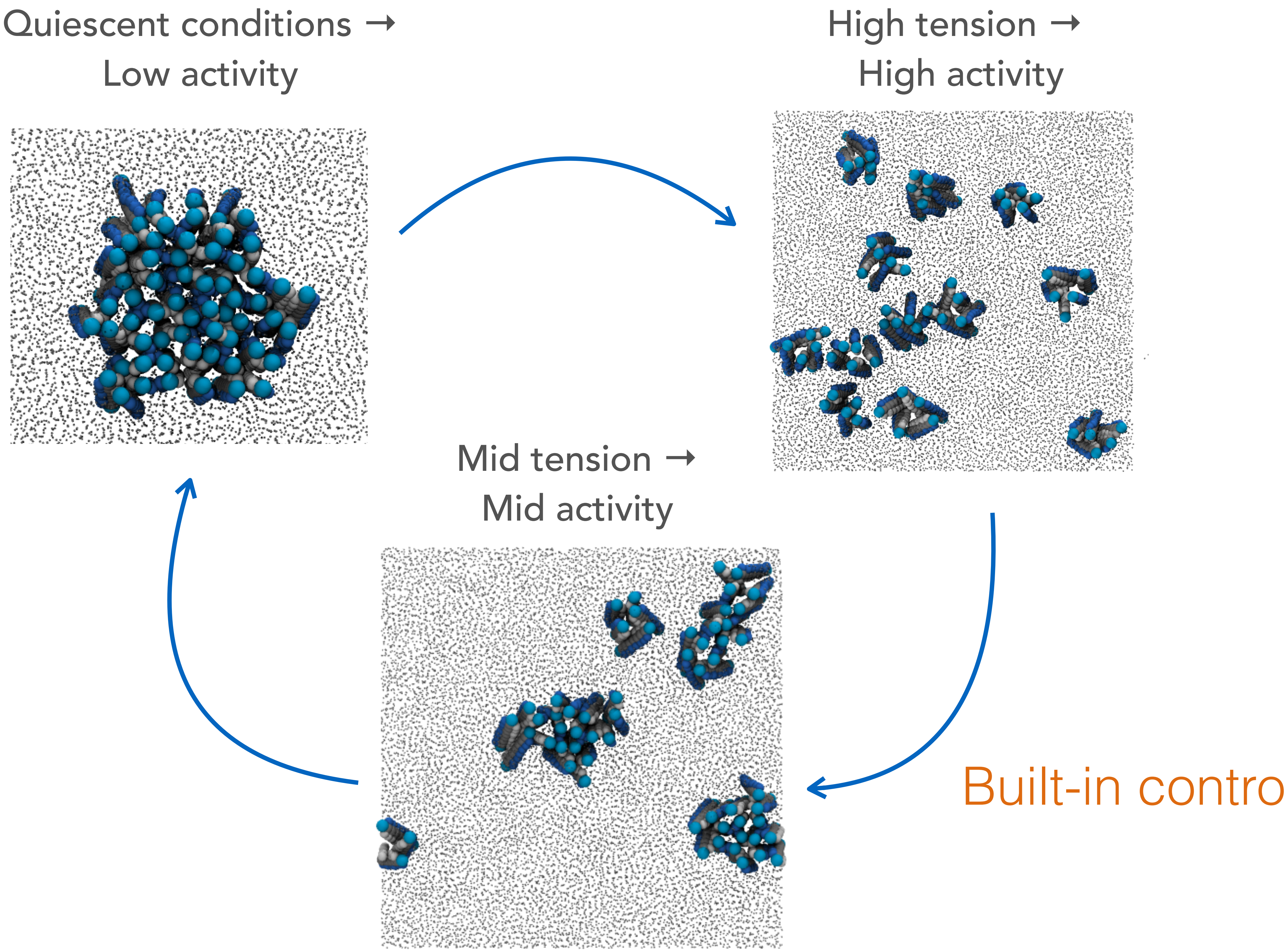
Osmotic shock applied!



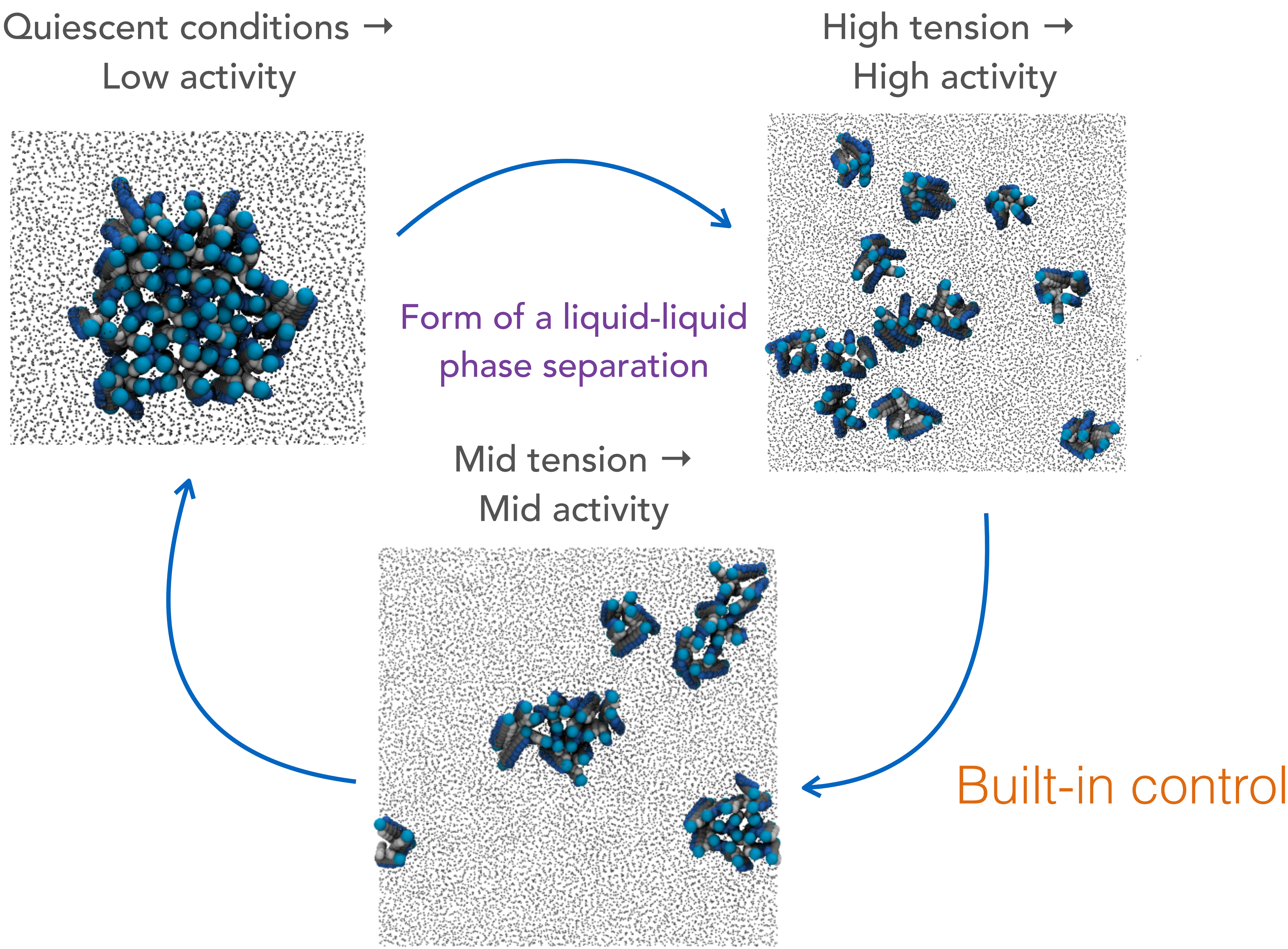




Dynamic channel aggregation

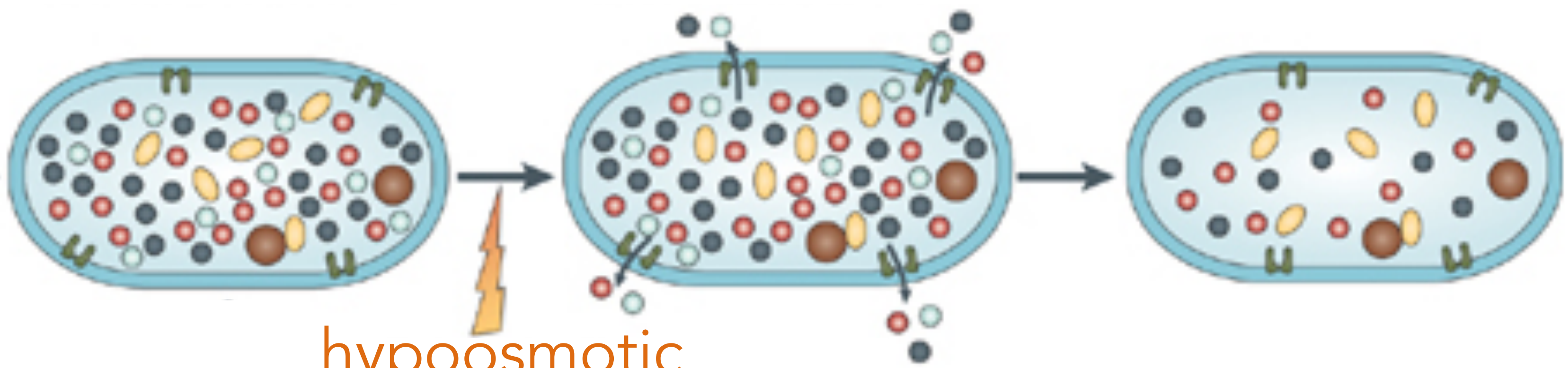


Dynamic channel aggregation



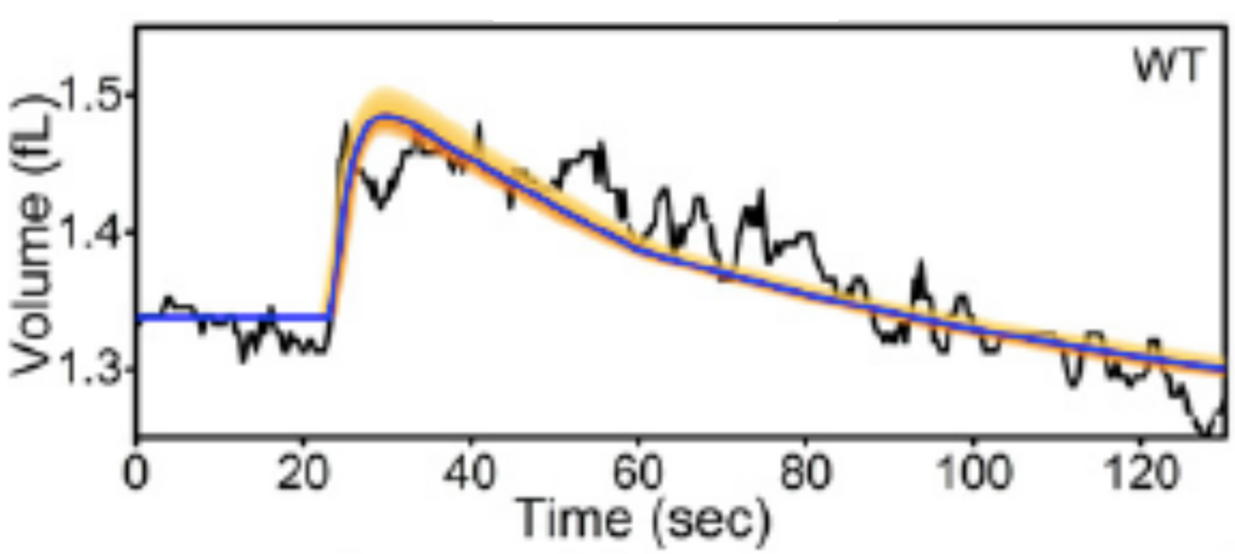
Functional role of channel aggregation

Bacterial cell under osmotic shock:



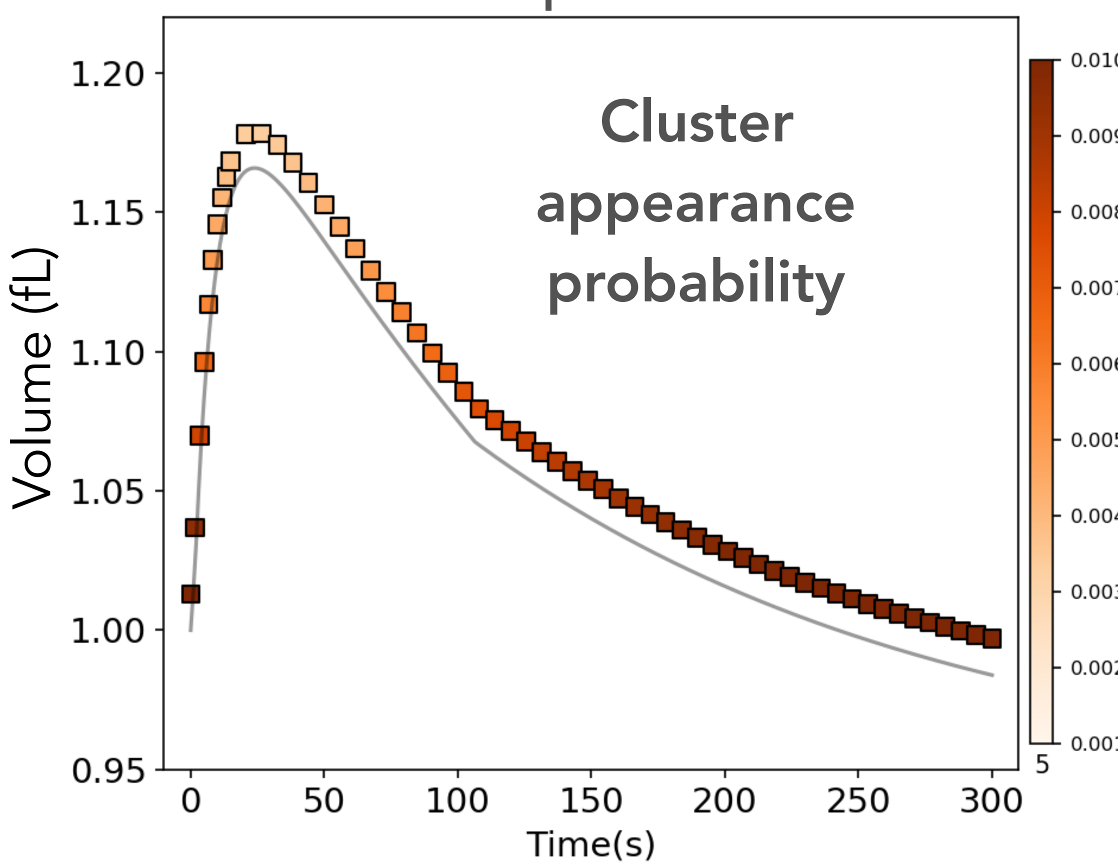
COMPARISON WITH EXPERIMENTS: Tracing cell volume

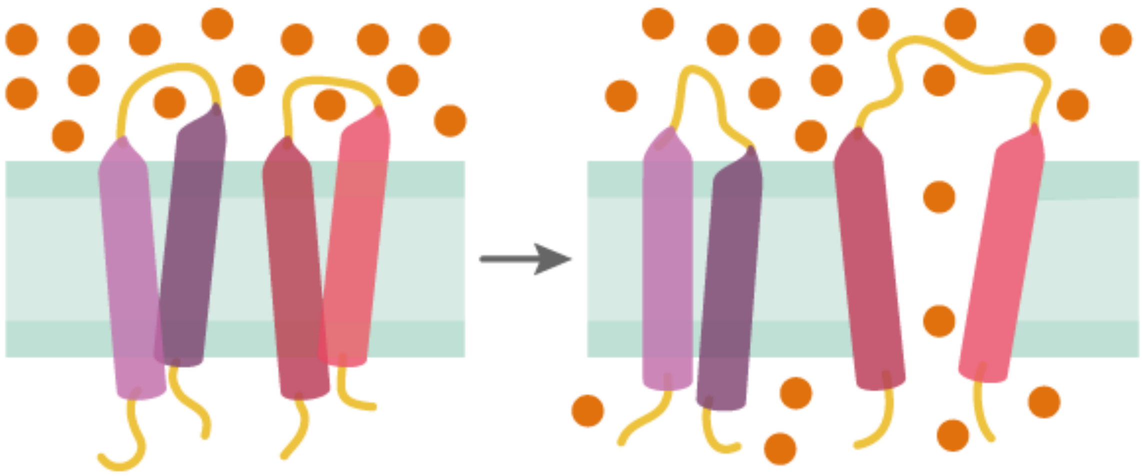
Experiments



with T. Pilizota, Edinburgh

Simulation predictions





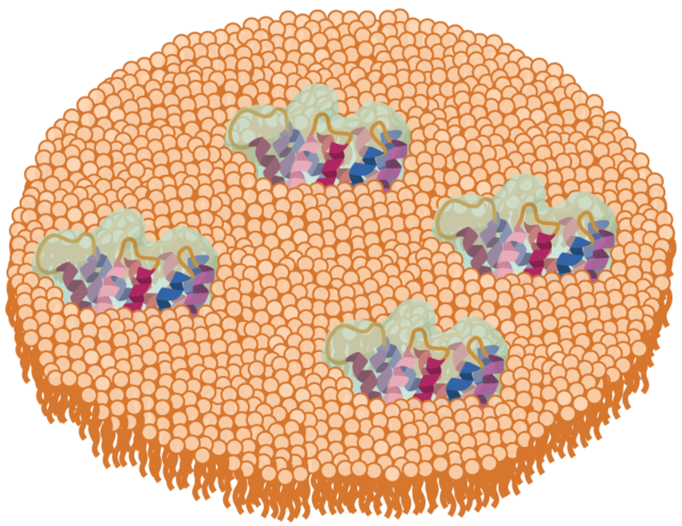
Cooperative activity of mechanosensitive channels

- Channel clustering decreases activity
- Clustering ↔ Activity are coupled, and shock-dependent
- Effective adjustment mechanism
- Possibly a control mechanism to sequester unnecessary channels and prevent over-gating

TODAY

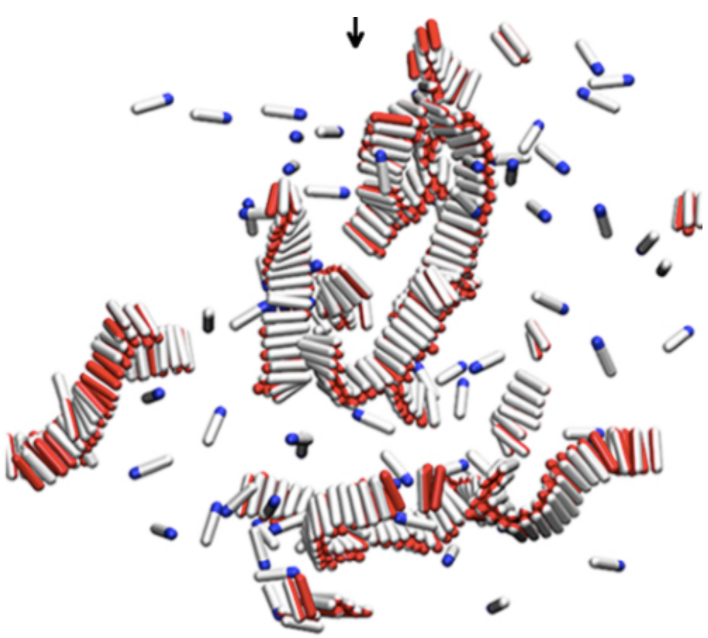
I: Functional Protein Aggregation

Bacterial mechanosensitive channels



II: Pathological Protein Aggregation

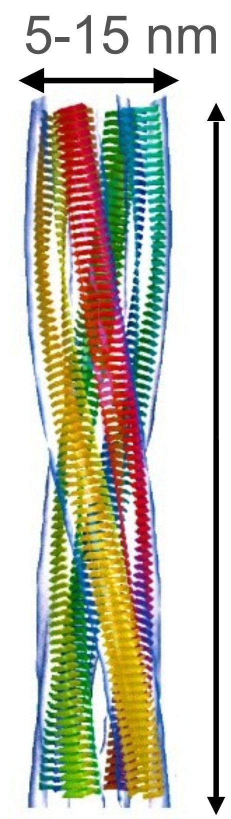
Amyloid aggregation



Amyloid aggregation

"Healthy" proteins

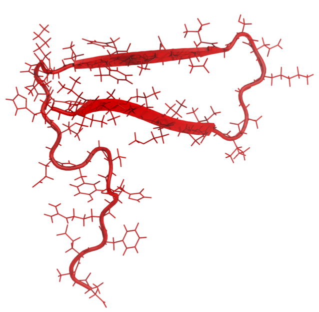
Amyloid fibril



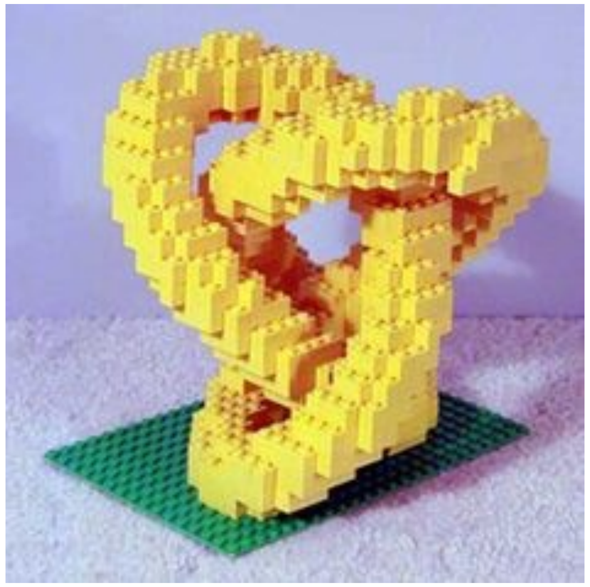
cross-β-sheet

~μm

Fibrils are built out of **β-sheet**



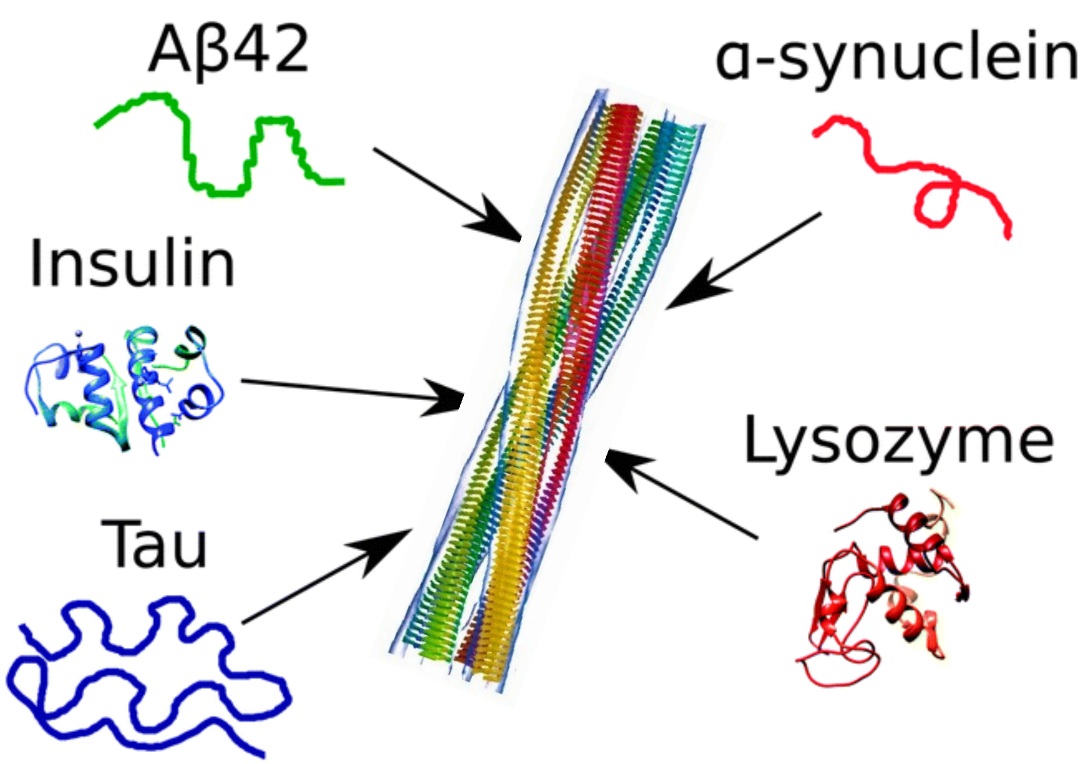
Self-assembly



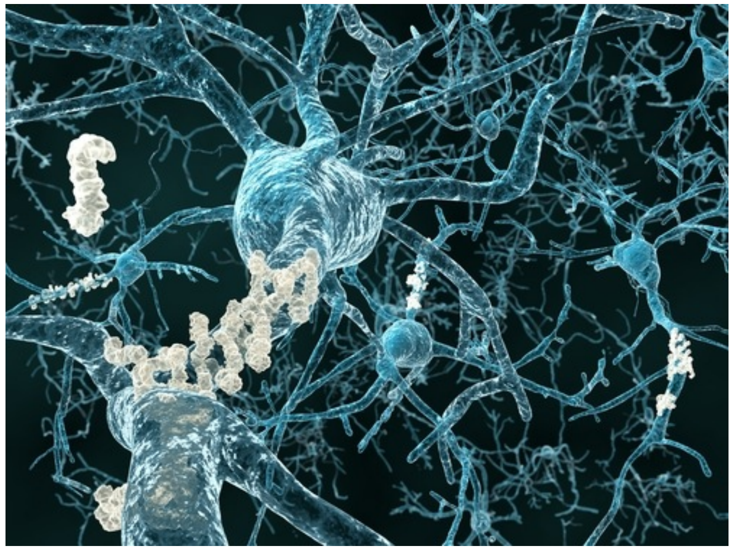
Randomly dispersed

Aggregated (self-assembled)

Amyloid aggregation & diseases

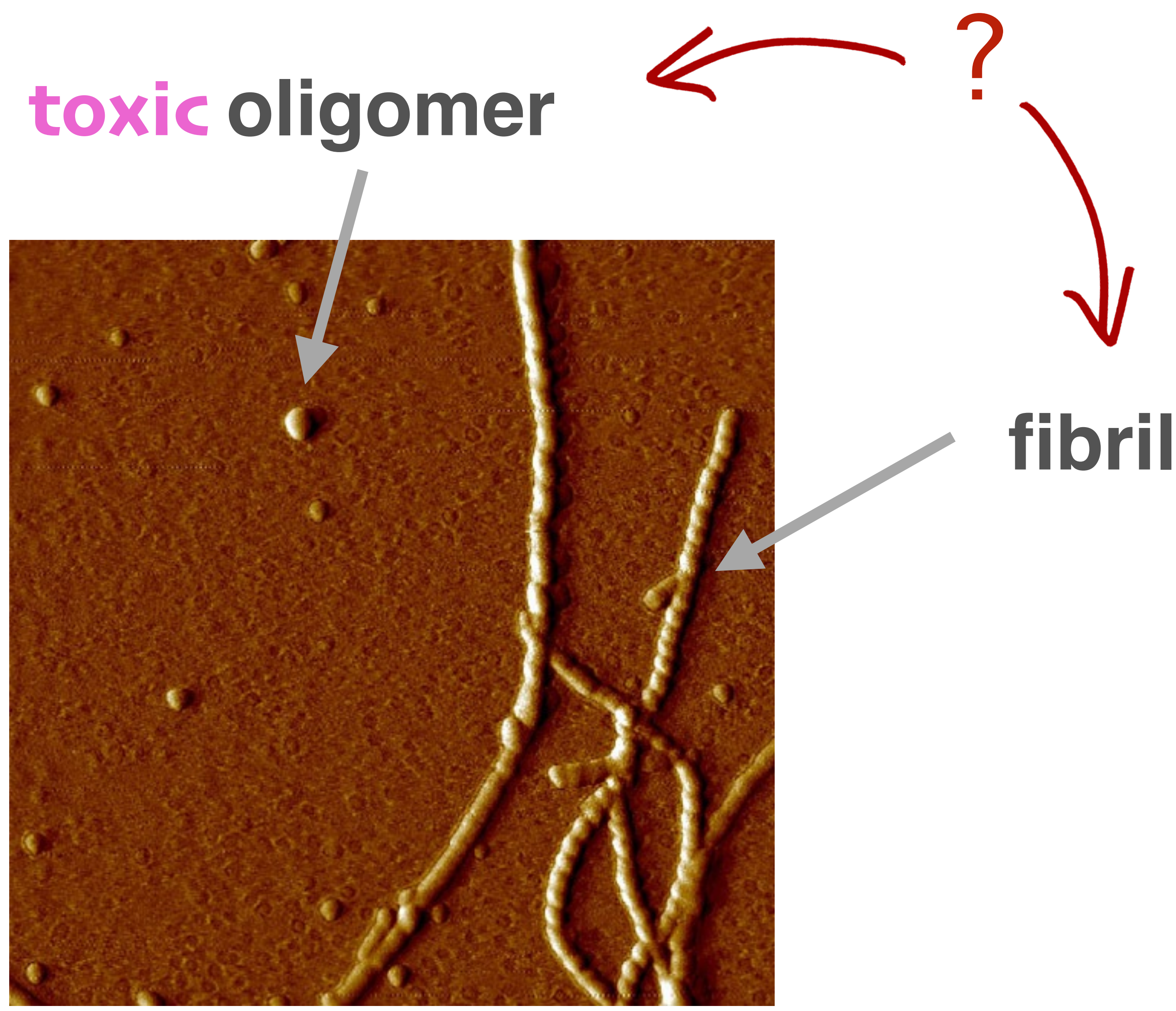


Amyloid plaque



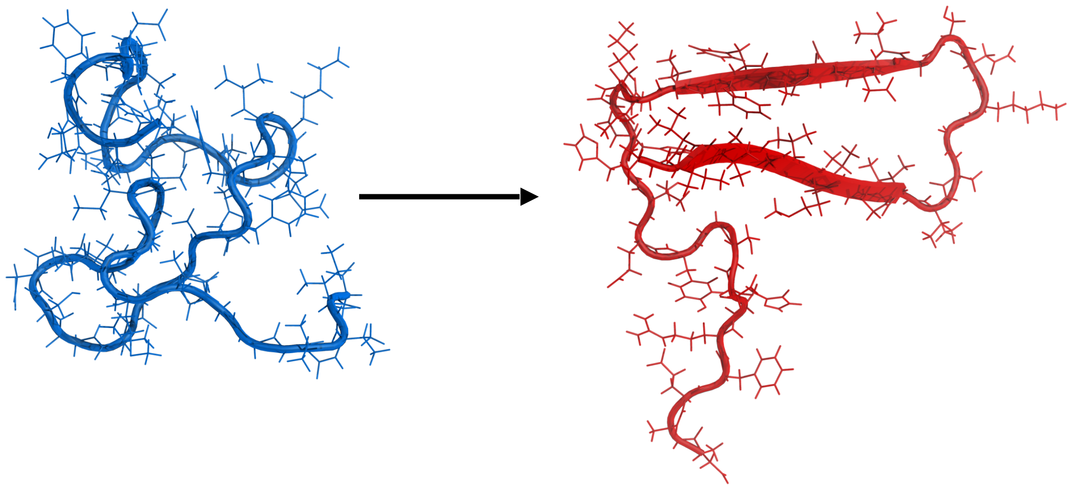
Amyloid proteins and clinically relevant diseases	
Protein	**Clinical syndrome**
Amyloid-β peptides (40 and 42)	Alzheimer's disease
Islet amyloid polypeptide (IAPP)	Type II diabetes
α-Synuclein	Parkinson's disease
Prion protein	Creutzfeldt-Jakob disease
Tau	Fronto-temporal dementias
Huntingtin (polyQ)	Huntington disease
Lysozyme	Systemic amyloidoses

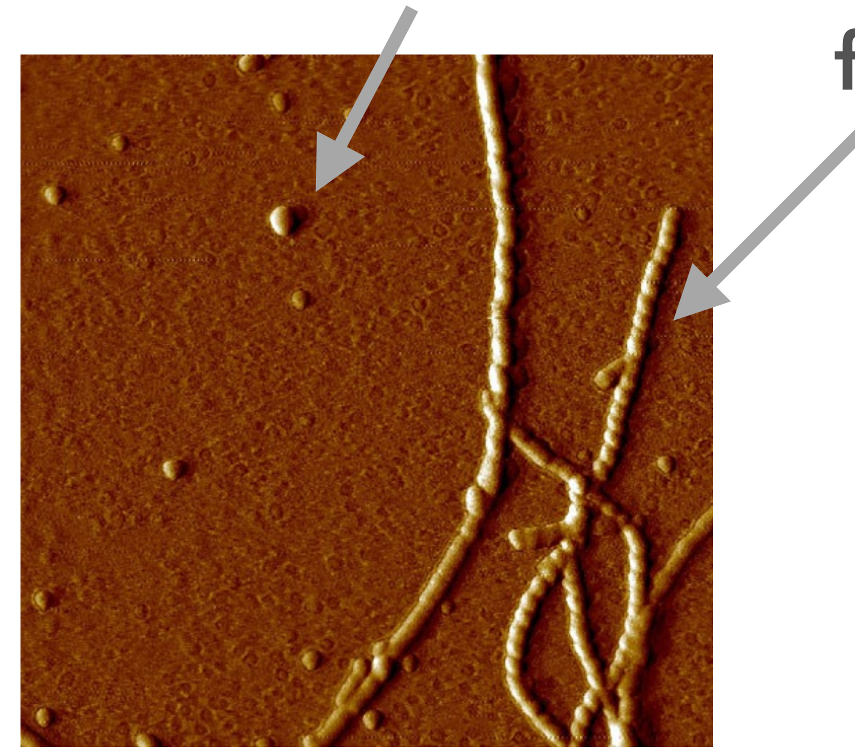
Amyloid nucleation and toxic oligomers



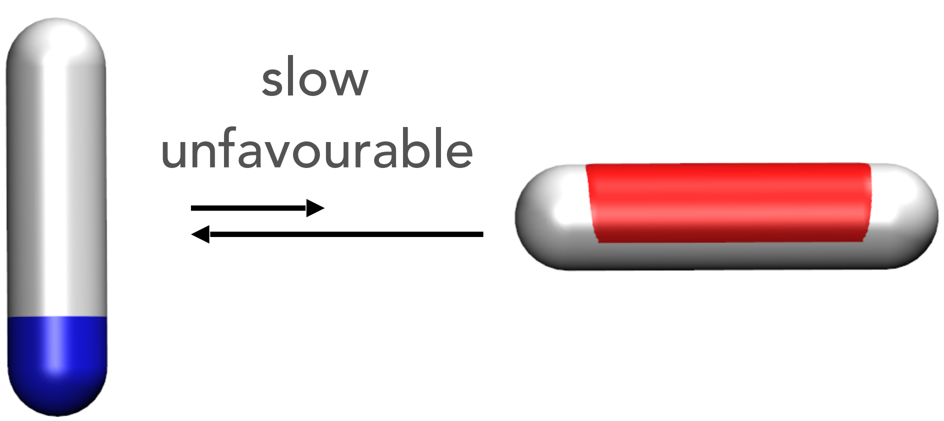
J. Lee et al., *Nat. Chem. Biol.* 2011

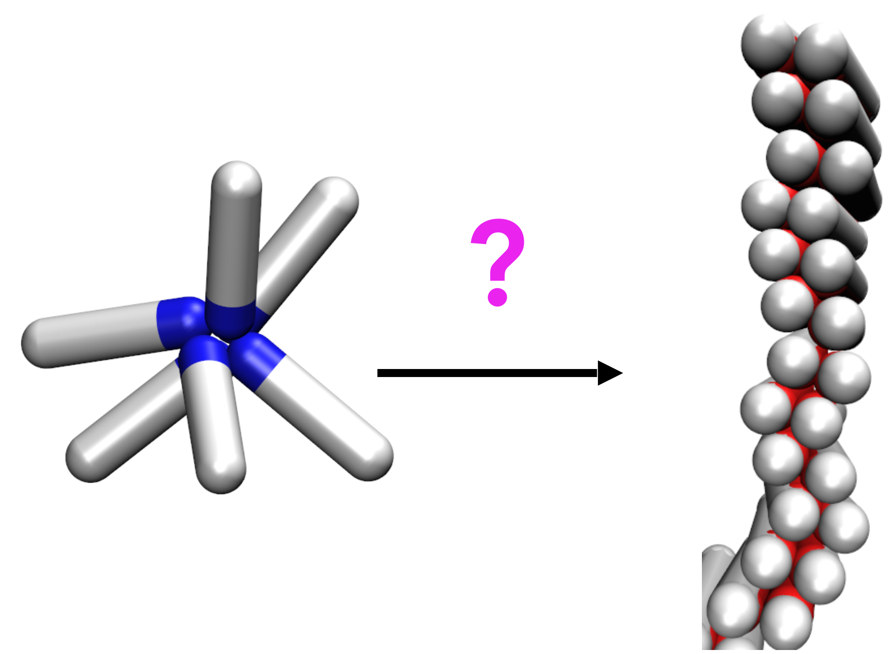
Amyloid aggregation: Minimal model





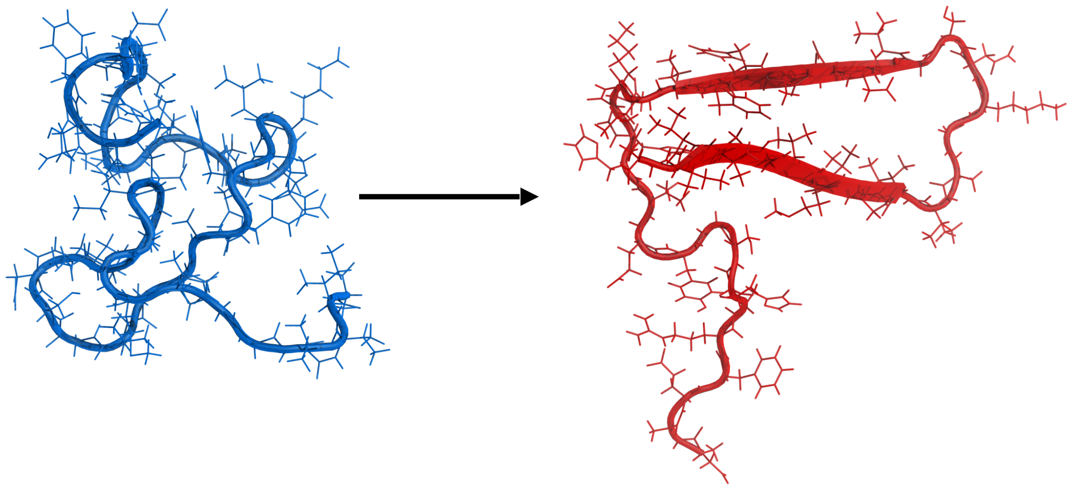
J. Lee et al., *Nat. Chem. Biol.* 2011



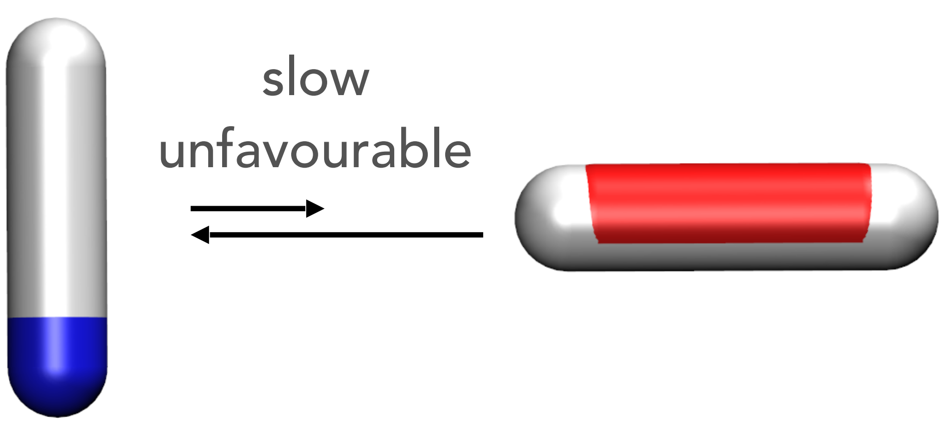


A. Šarić, Y. C. Chebaro , T. P. J. Knowles and D. Frenkel, *PNAS*, 111, 17869 (2014).

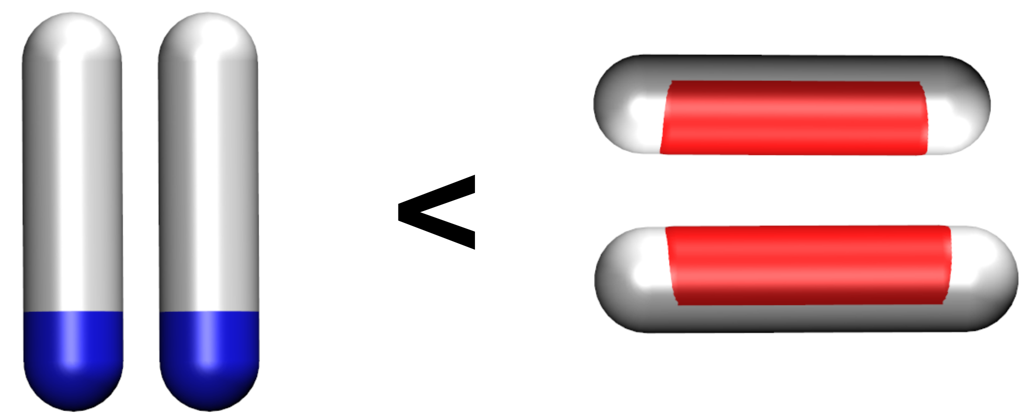
Amyloid aggregation: Minimal model



"healthy" fibril-forming



healthy state fibril-forming state

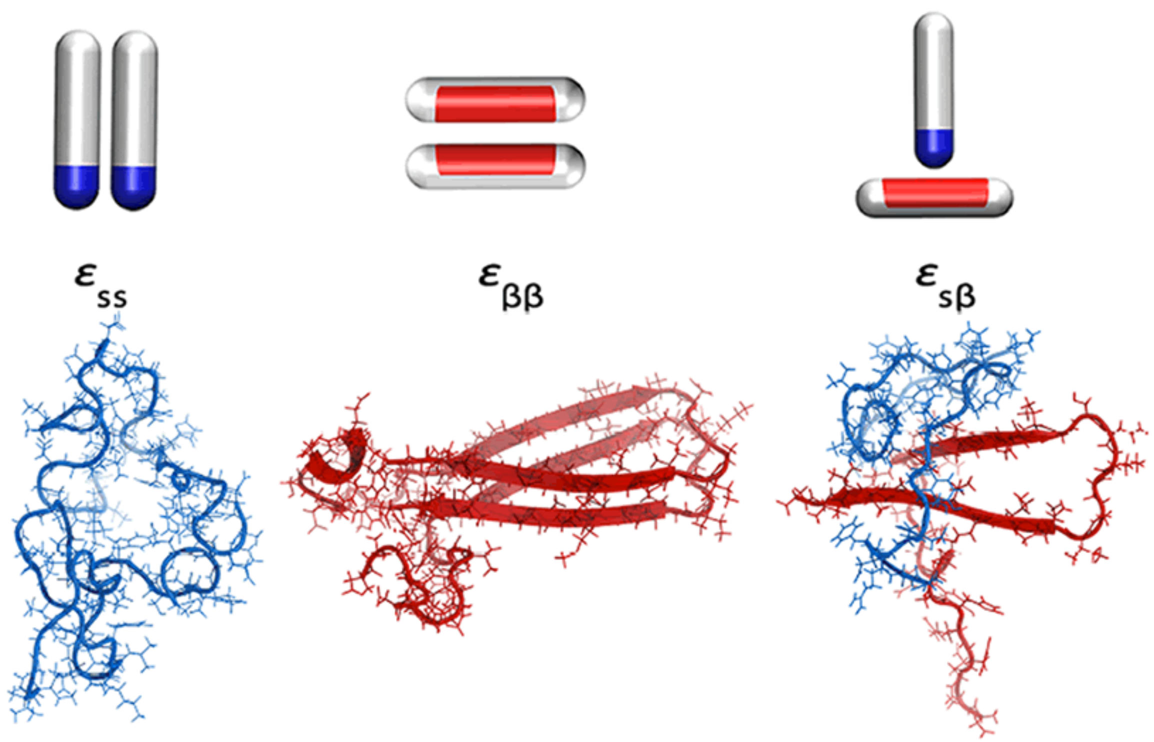


<u>interactions</u>
charged
hydrophobic

<u>interactions</u>
charged
hydrophobic
H-bonding

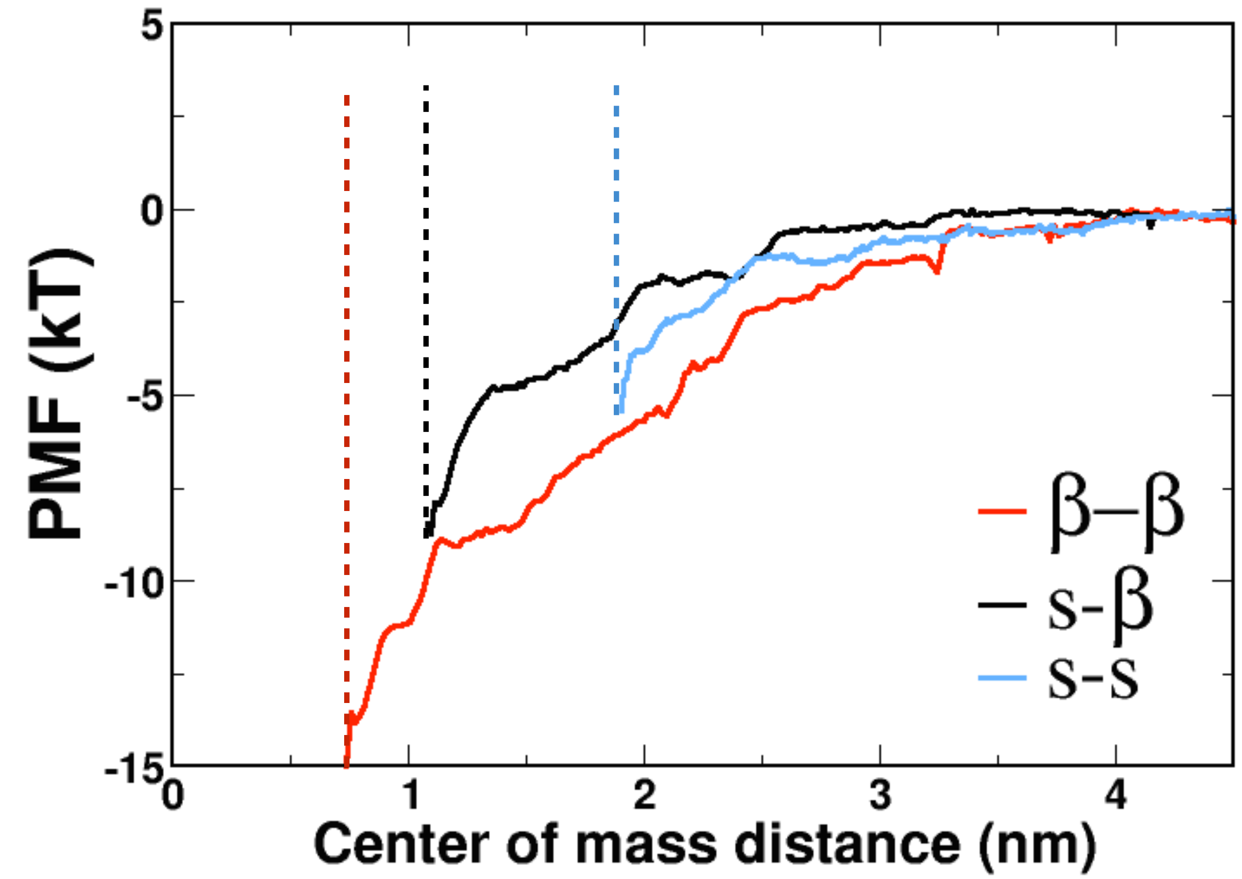
A. Šarić, Y. C. Chebaro , T. P. J. Knowles and D. Frenkel, *PNAS*, 111, 17869 (2014).

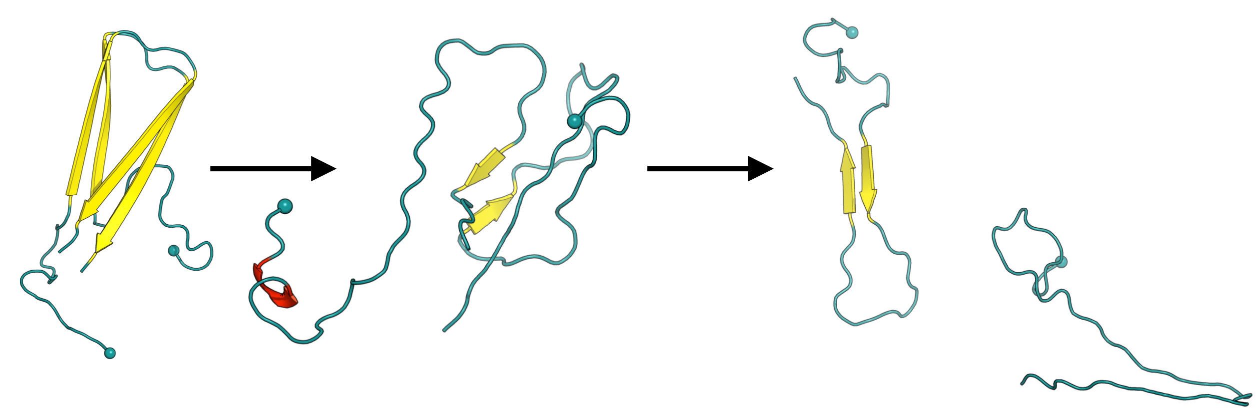
How do we obtain parameters?



$\varepsilon_{ss} < \varepsilon_{s\beta} < \varepsilon_{\beta\beta}$

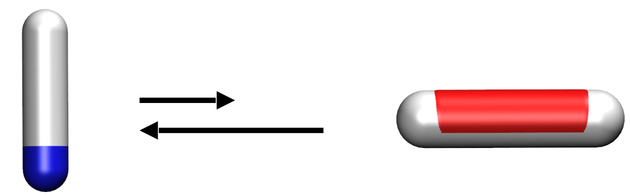
Atomistic explicit water simulations to obtain PMF:





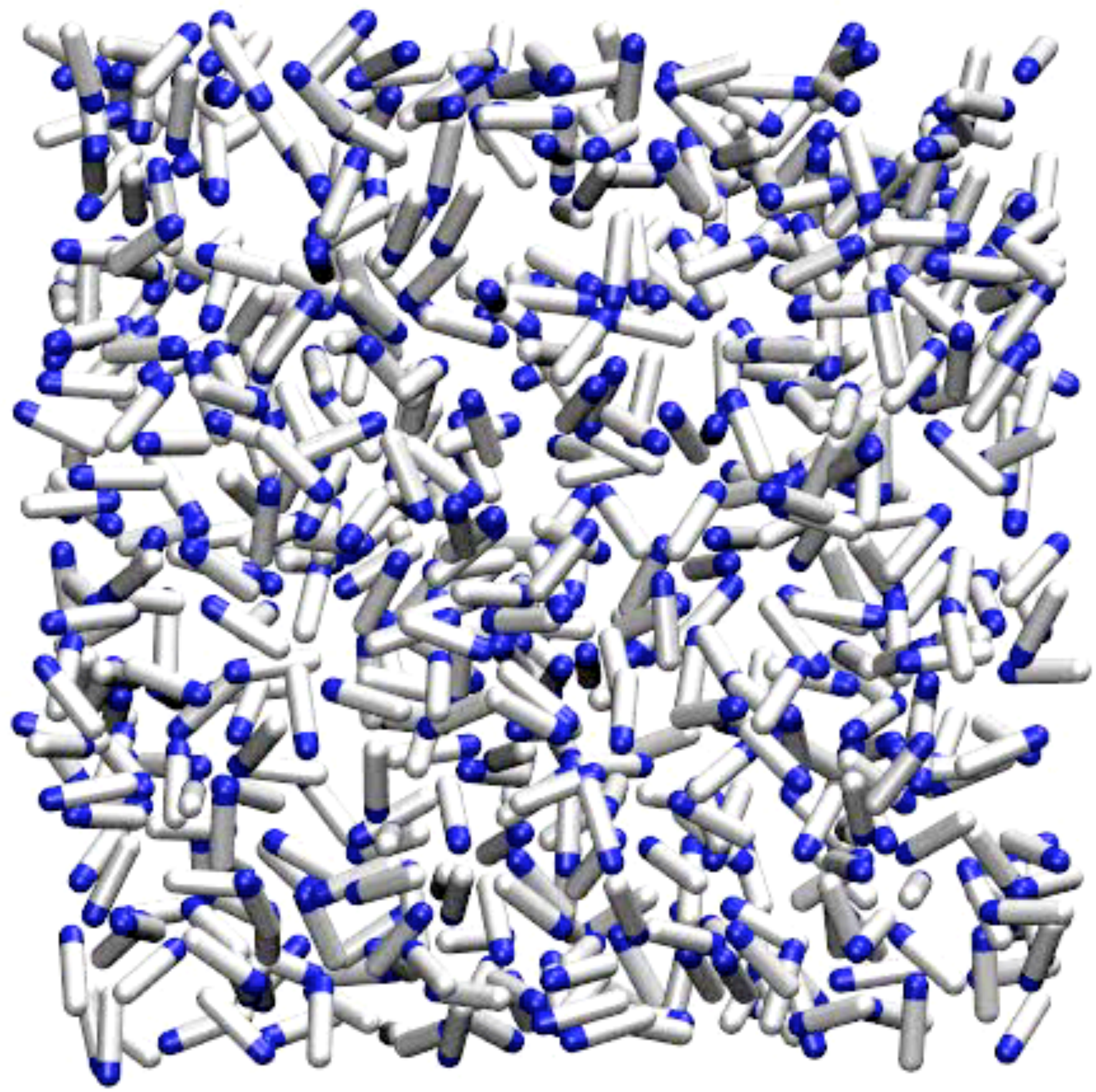
A. Šarić et al, *PNAS*, 111, 17869 (2014).

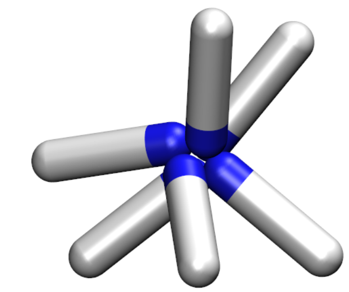
Amyloid nucleation and oligomers



“healthy" state

fibril-forming state



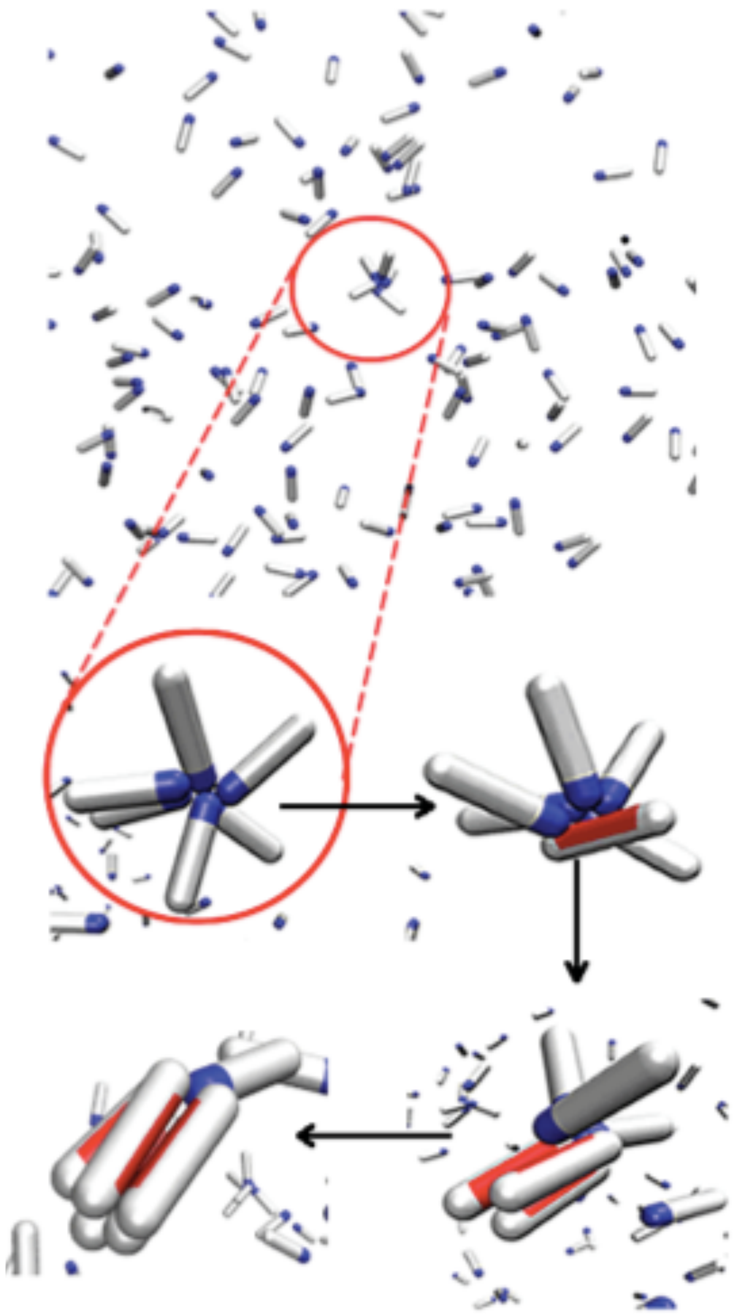


oligomer

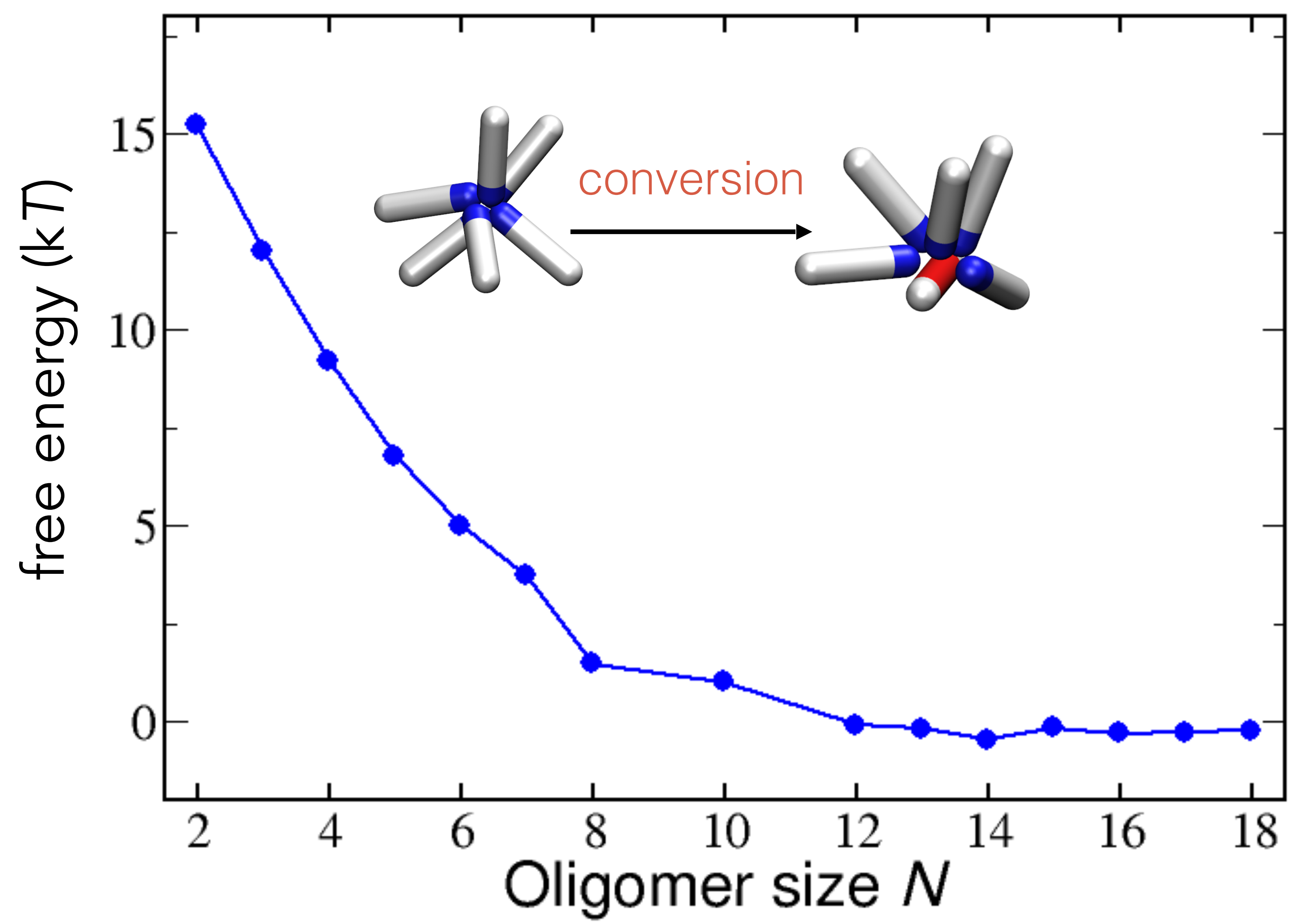
Oligomers are fibril-nucleation centres.

Primary amyloid nucleation and oligomers

Nucleation via oligomers

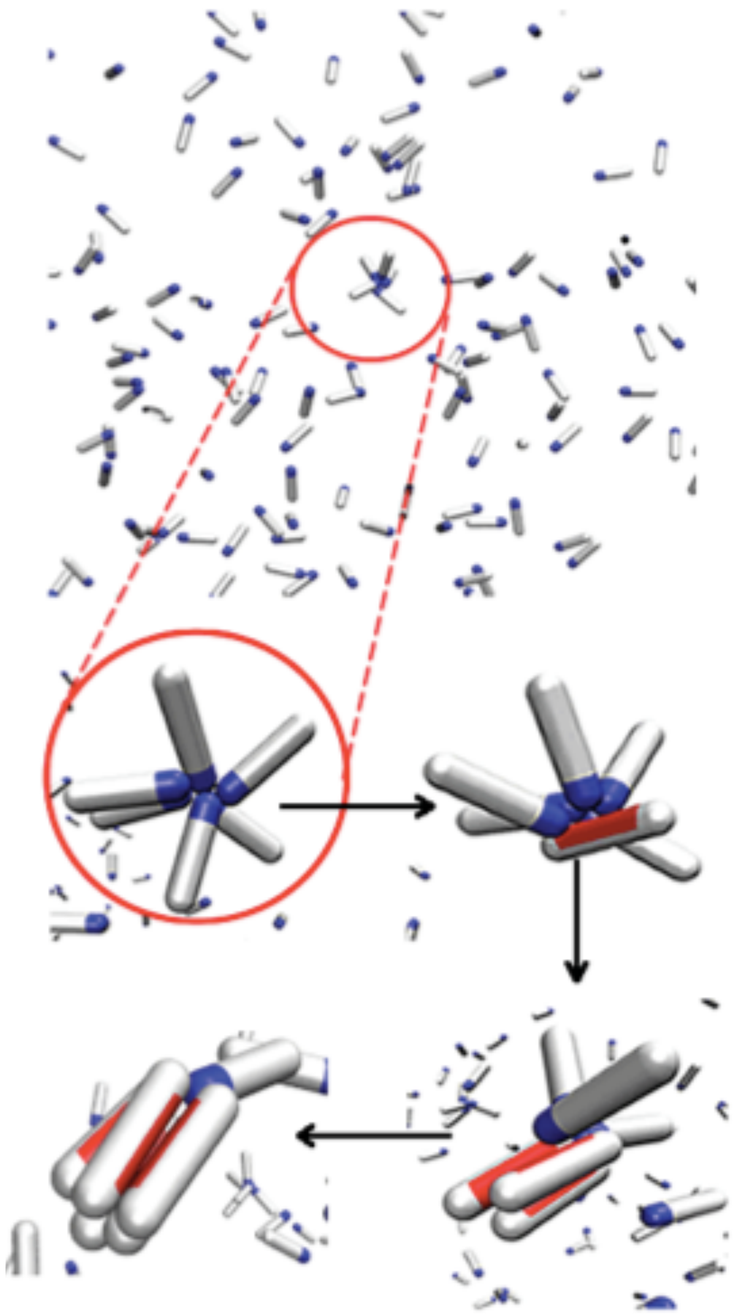


Nucleation is easier inside bigger oligomers: cooperativity

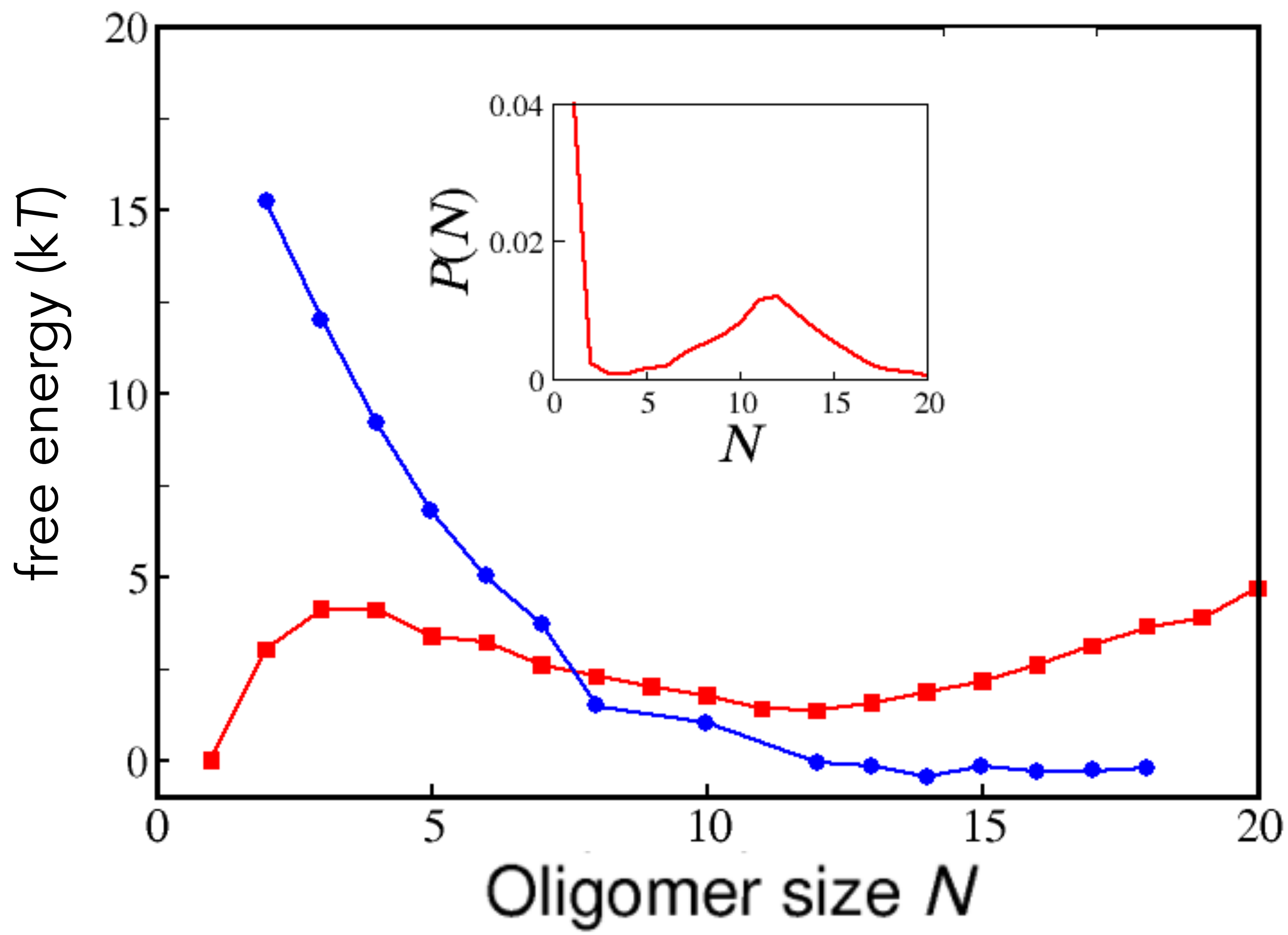


Primary amyloid nucleation and oligomers

nucleation via oligomers

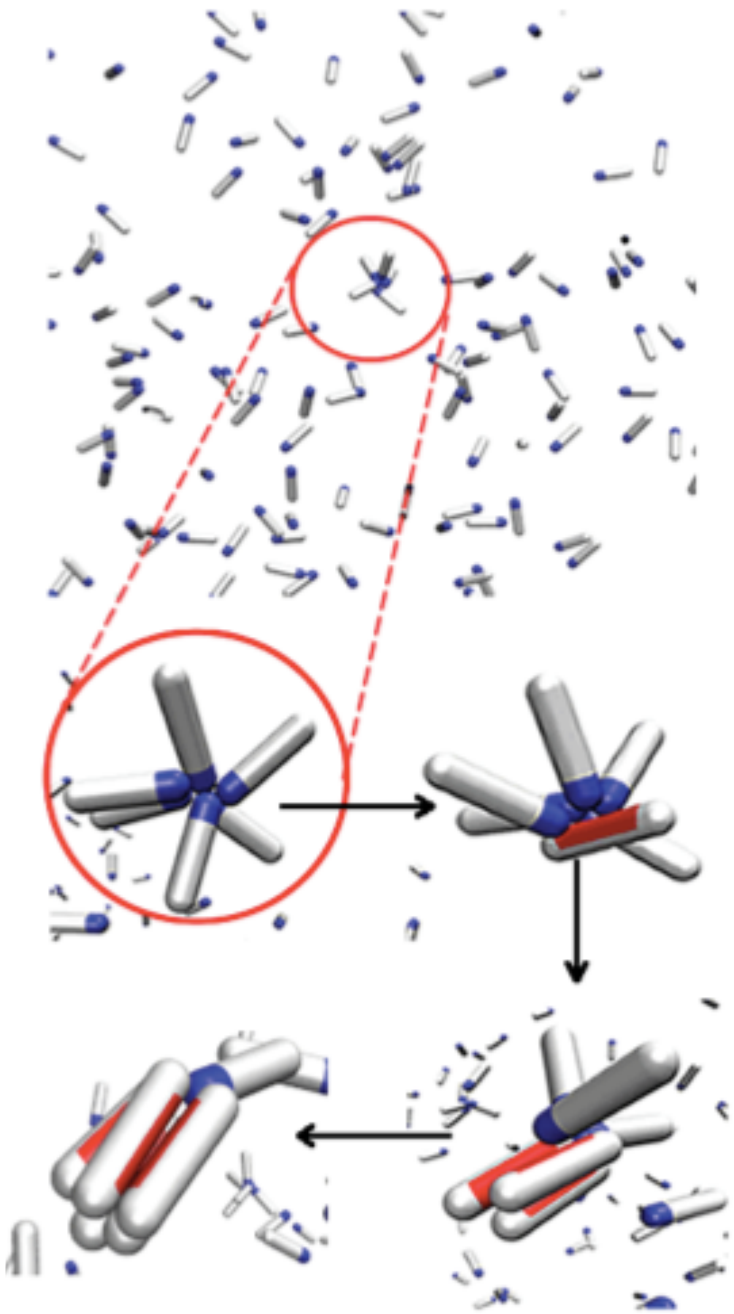


...but it is unfavourable to make big oligomers...

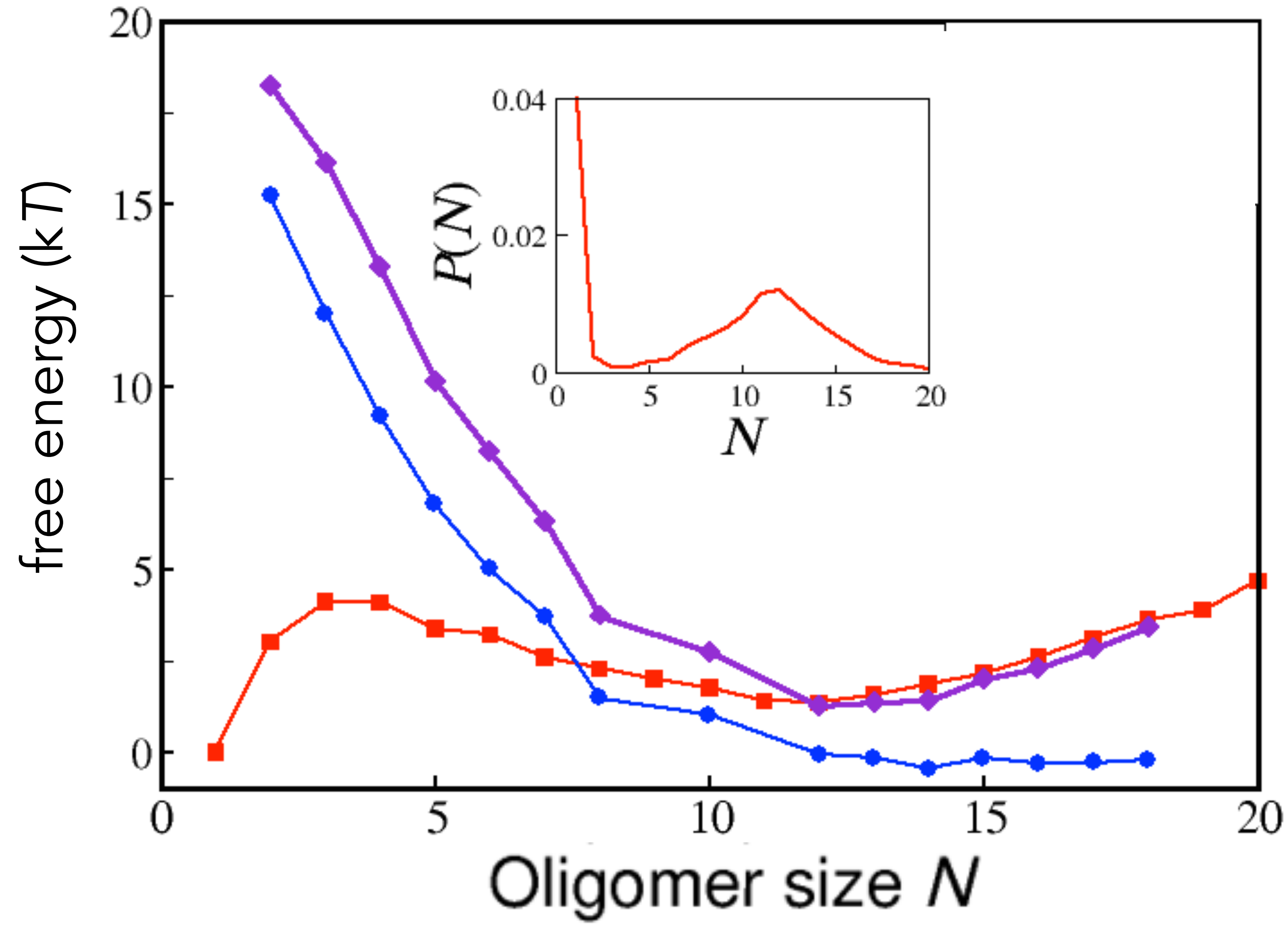


Primary amyloid nucleation and oligomers

nucleation via oligomers



...but it is unfavourable to make big oligomers at low concentrations...

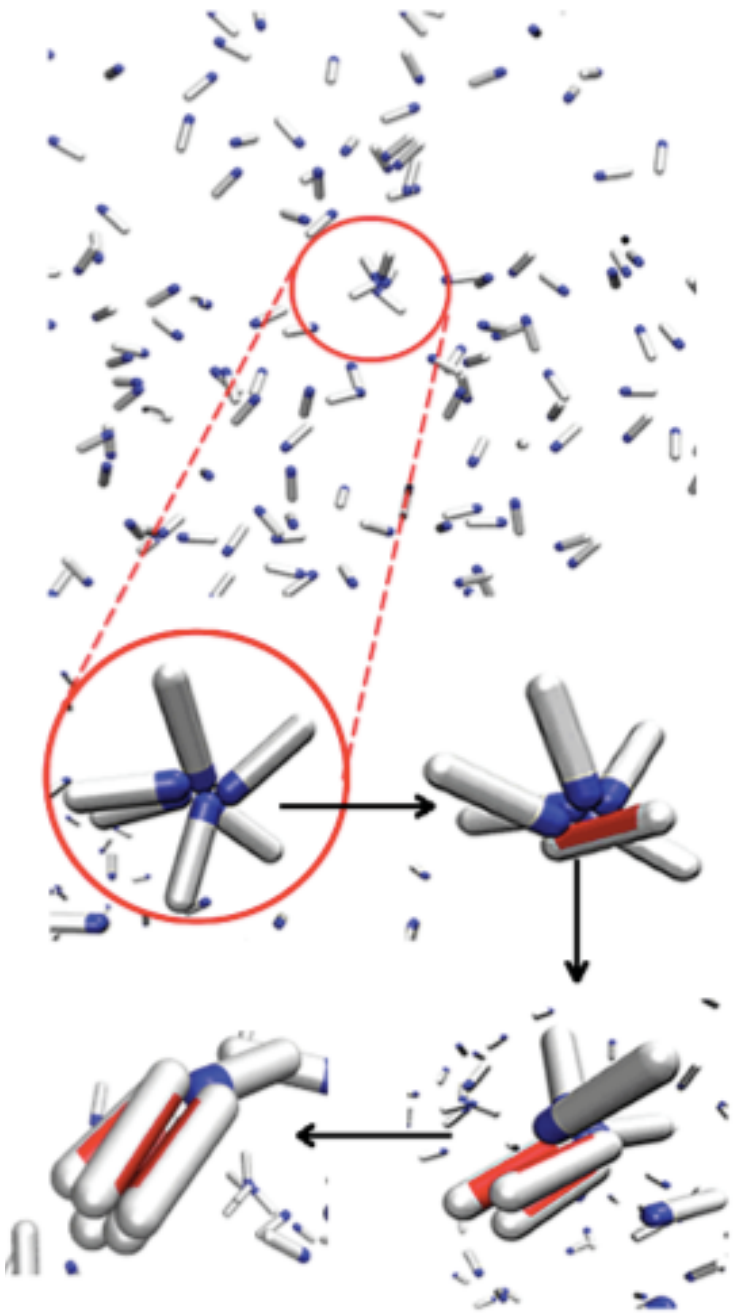


$$\Delta F^*(N) = \Delta F_o(N) + \Delta F_c(N)$$

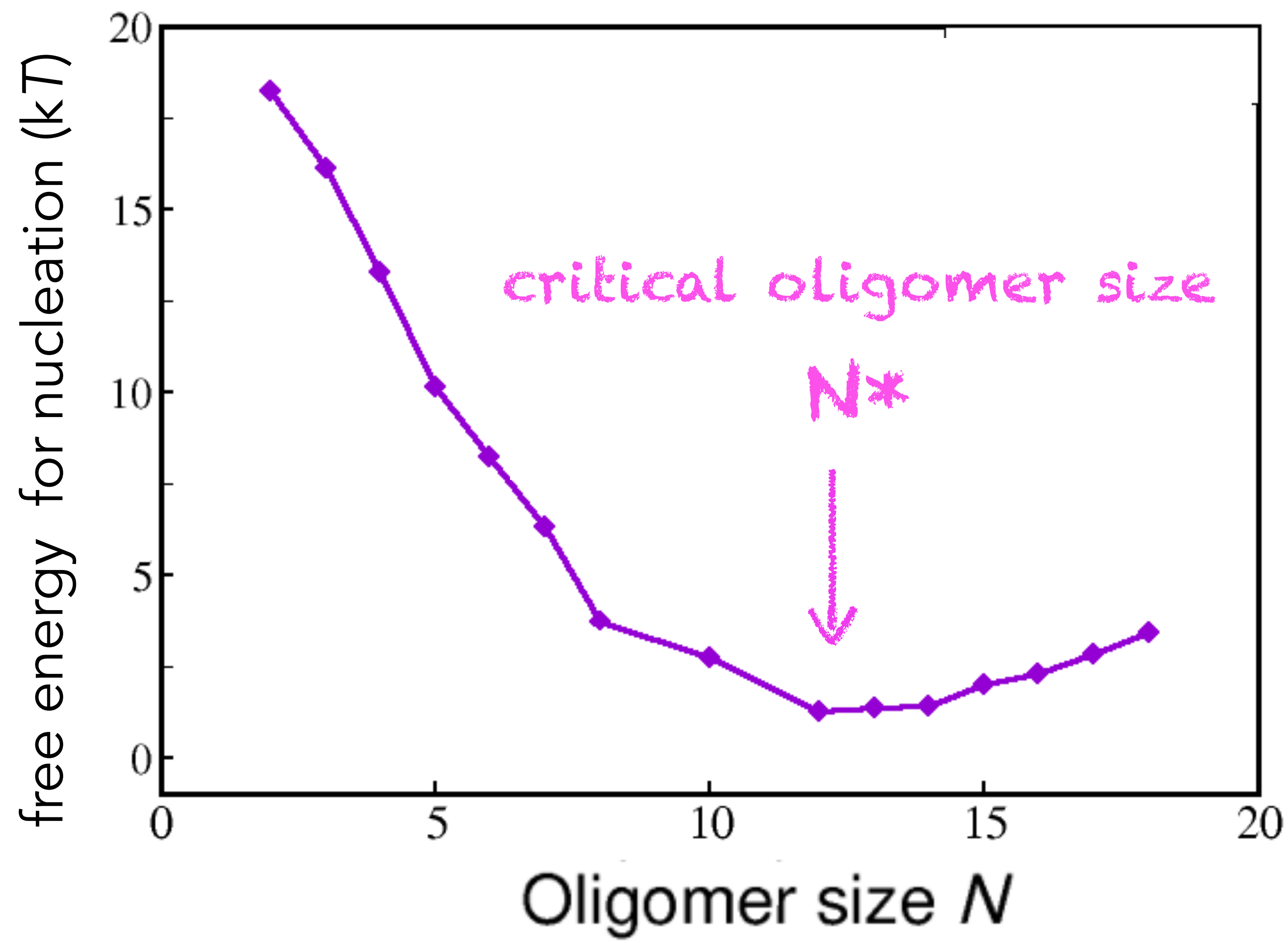
fibril formation oligomerisation conversion

Free energy of nucleation via small oligomers

nucleation via oligomers



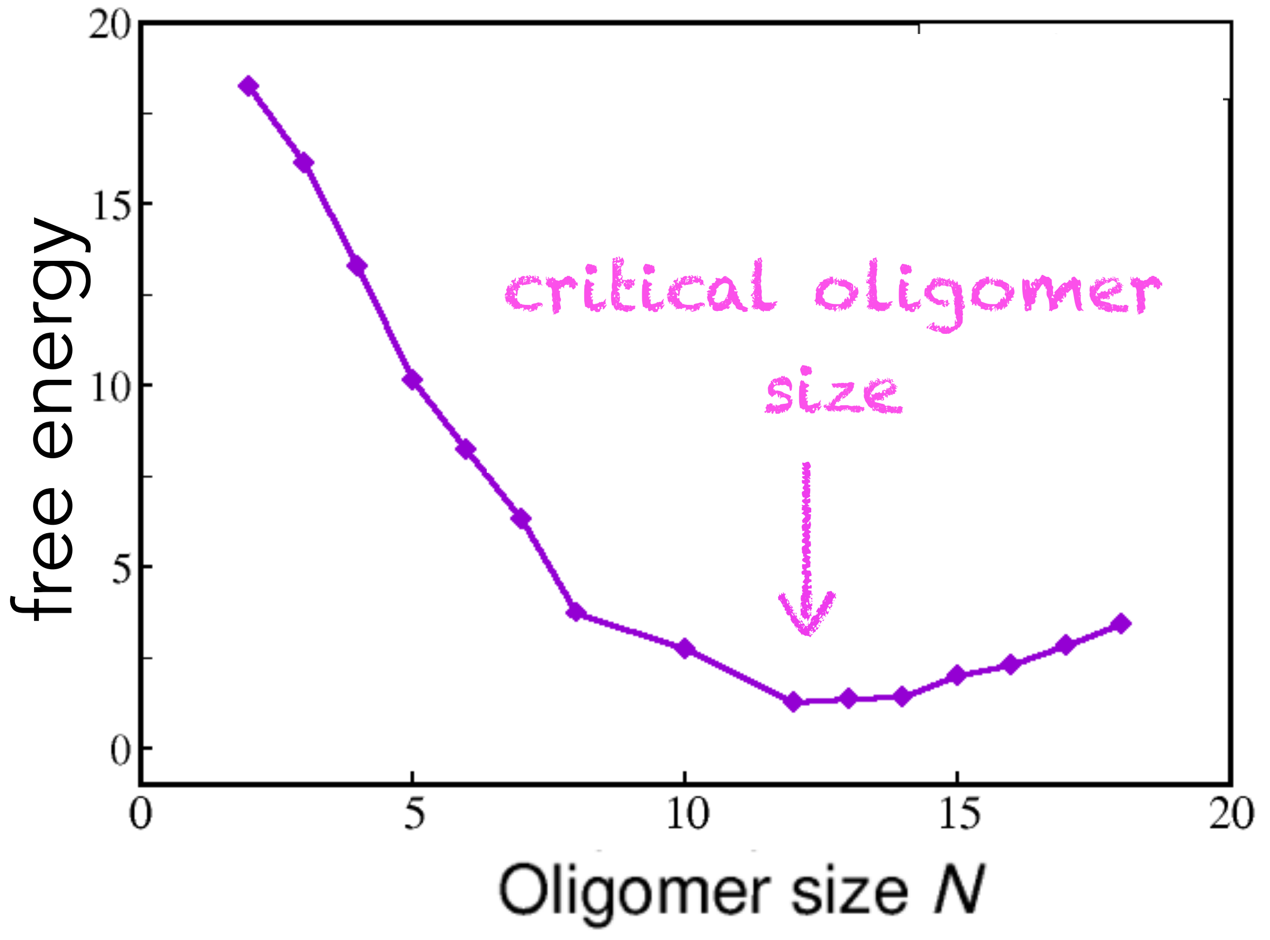
...the most probable nucleating oligomer:



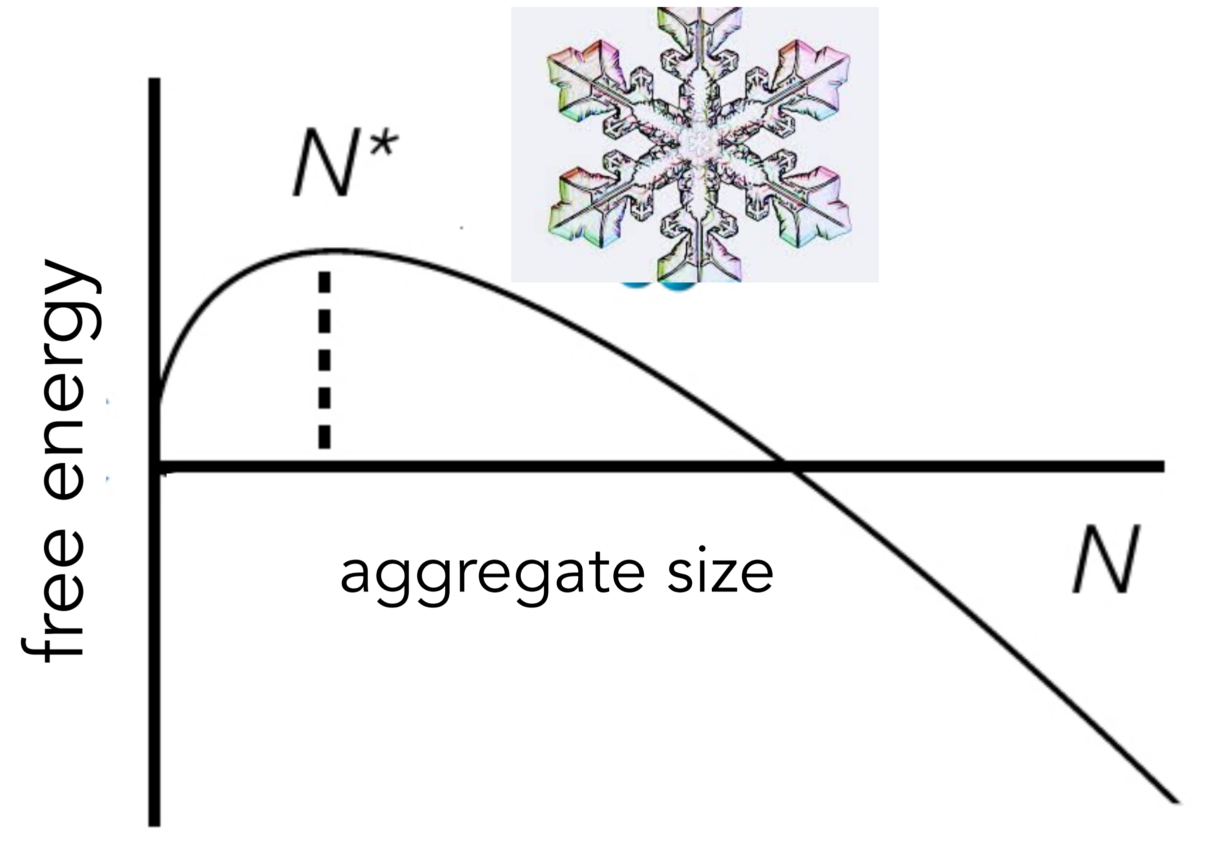
A. Šarić, Y. C. Chebaro , T. P. J. Knowles and D. Frenkel, *PNAS*, 111, 17869 (2014).

Very different from classical nucleation (ice, bubbles, ...)

Amyloid nucleation



Classical nucleation



A. Šarić et al, *J Chem Phys* (2016).

A. Šarić et al, *PNAS*, 111, 17869 (2014).

Amyloid nucleation

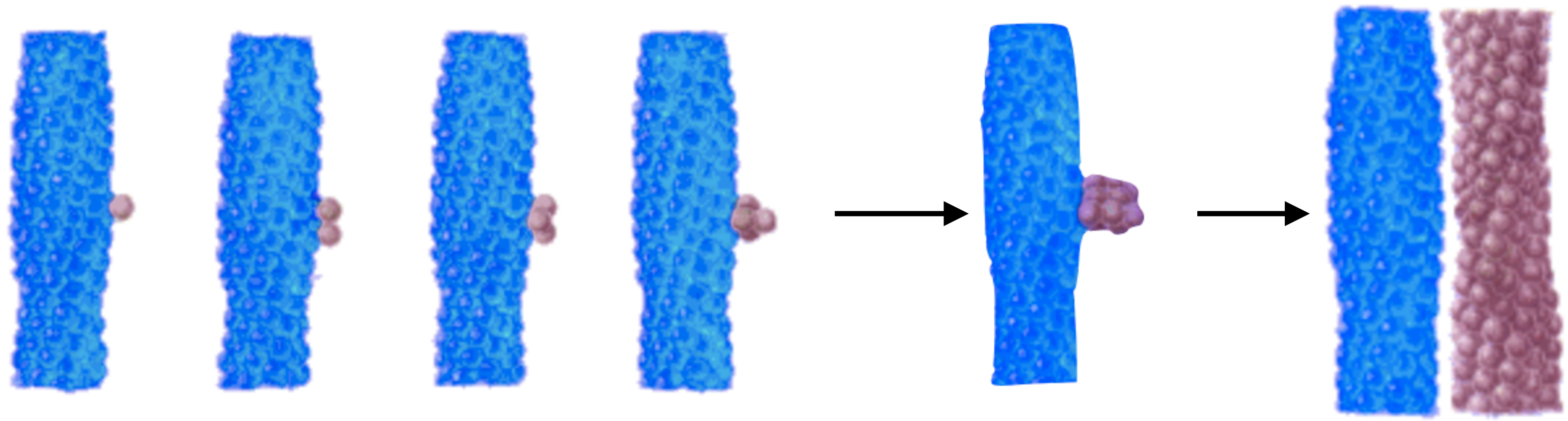
- At **physiological conditions**, amorphous oligomers serve as nucleation centres for amyloid fibrils, and are necessarily **on-pathway**

- **Distinct class of a nucleation mechanism:** involves a dynamic change of the nucleating building-block

Illustration: Ivan Barun, dr med

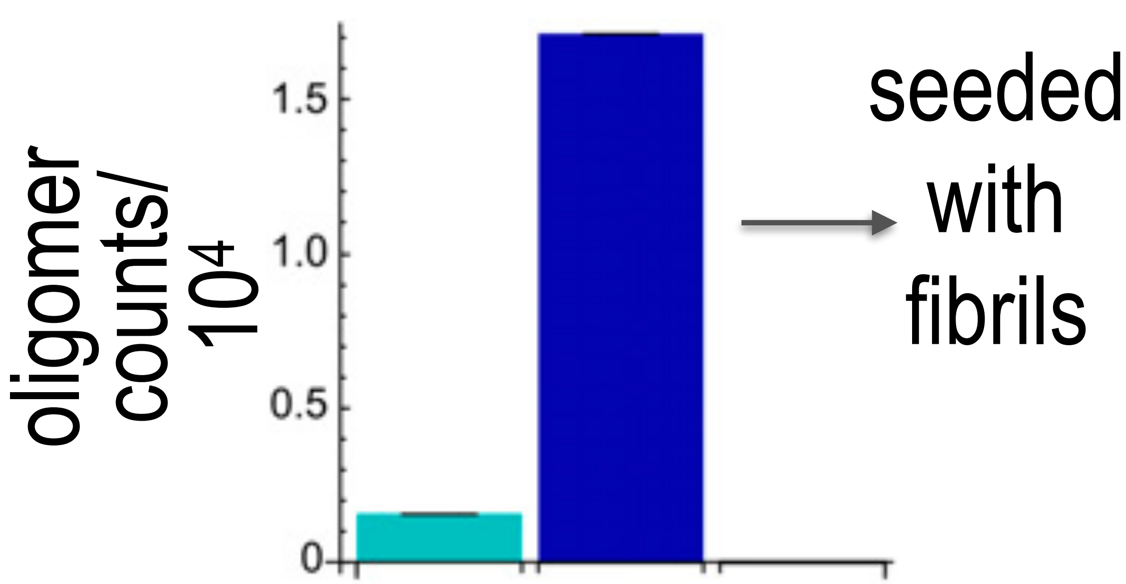
Positive feedback: Self-replication of protein fibrils

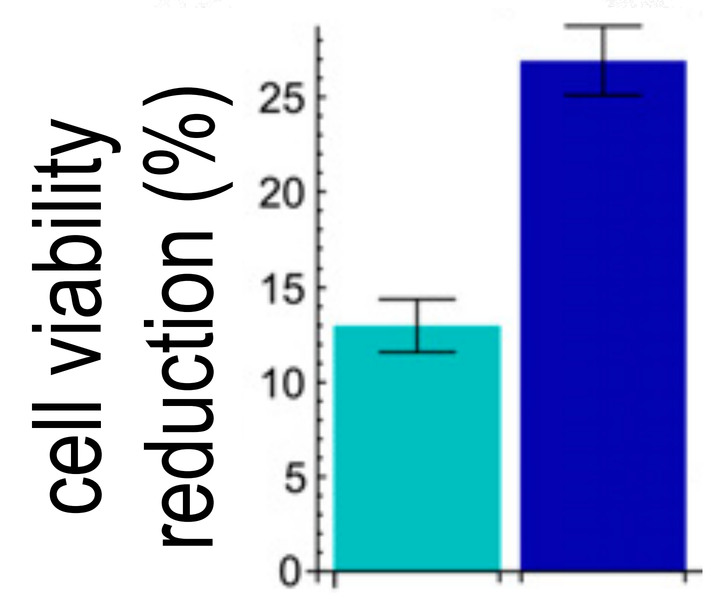
- Fibril surface **catalyses** formation of new growth centres



F. A. Ferrone, J. Hofrichter and W A. Eaton, *J. Mol. Biol.* (1985).

- Produces **oligomers** and **dominates** the aggregation
- **~8 orders** of magnitude faster than spontaneous nucleation (Alzheimers' Aβ)

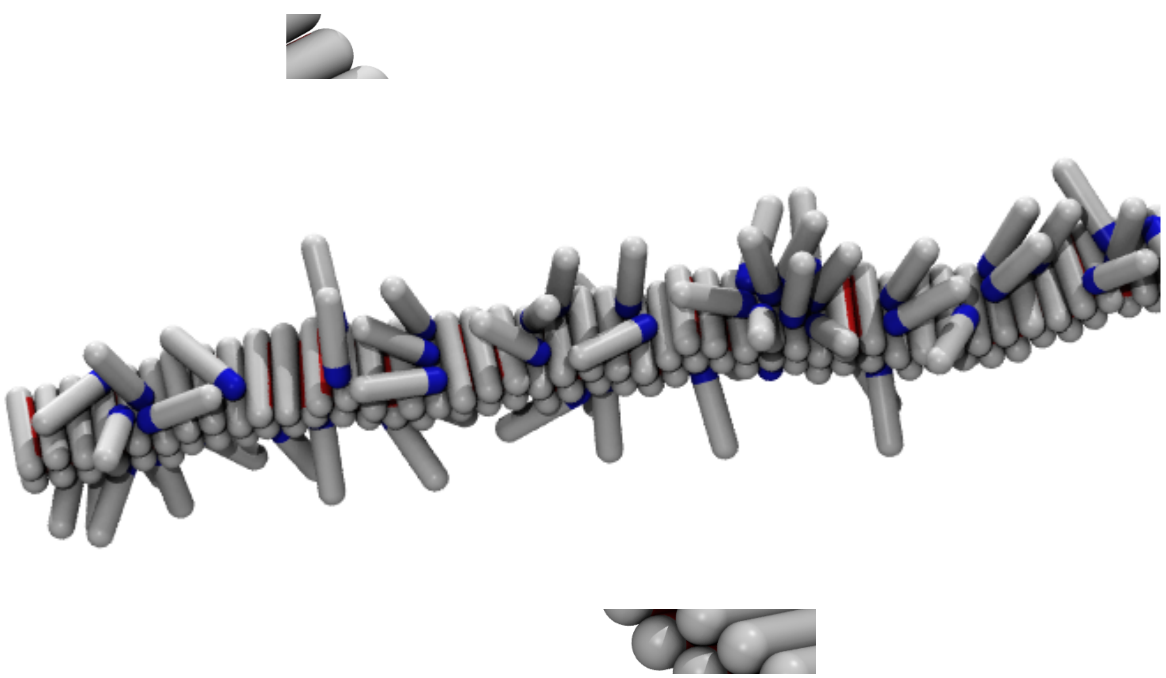




S. A. Cohen et al., PNAS (2013).

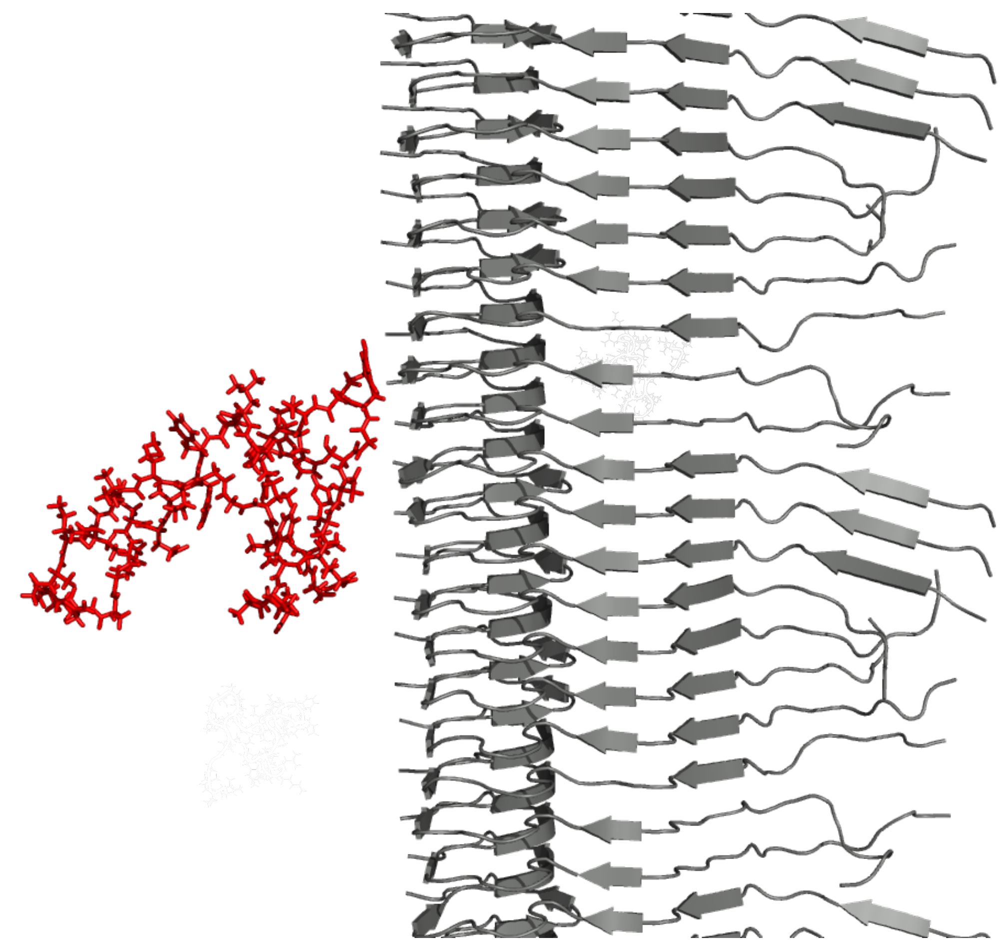
Self-replication of protein fibrils

- Extension of the model:



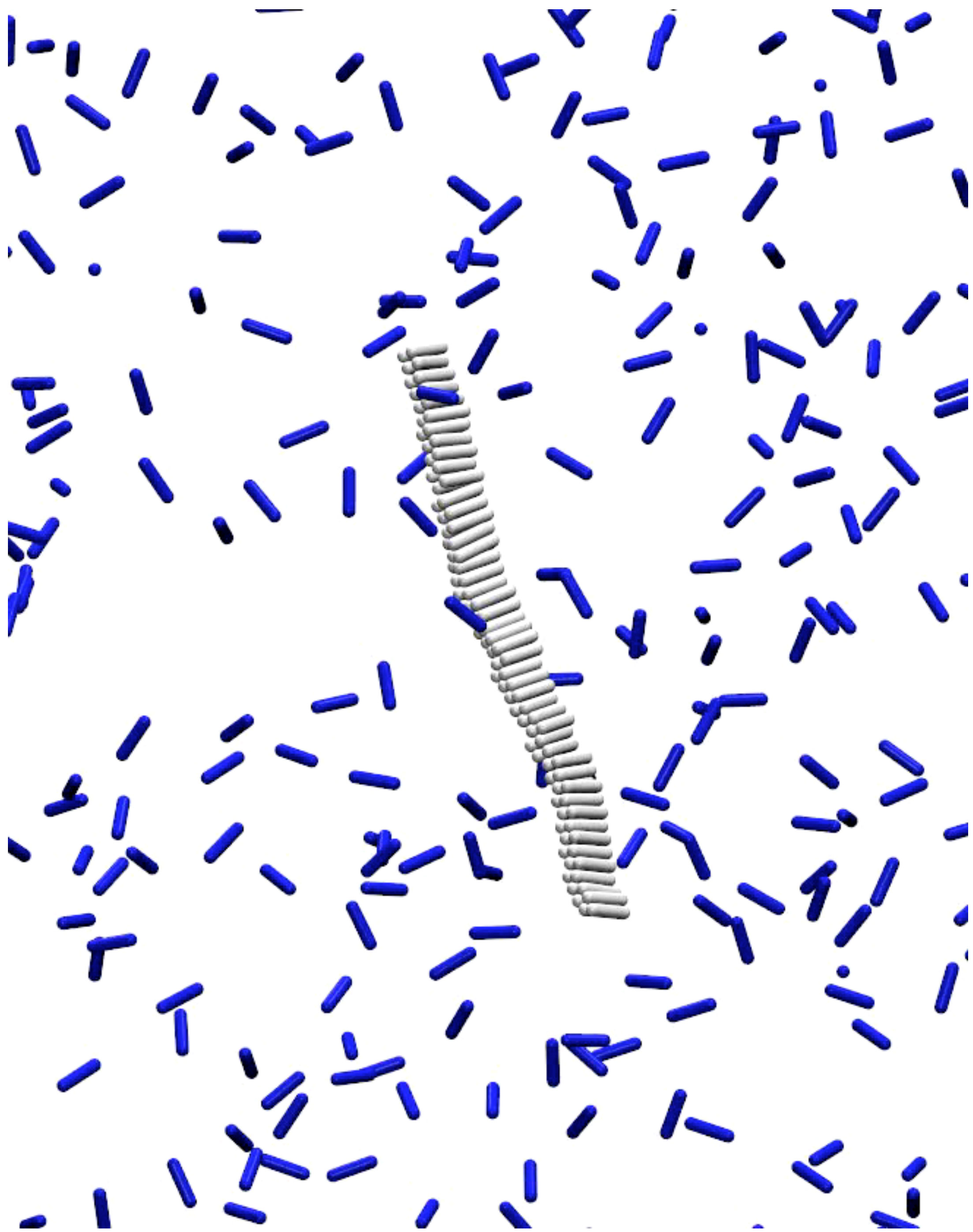
Proteins adsorb onto fibrils.

For Aβ measured Kd ≈ 50μM



recent MD simulations
by M. Bellaiche & R. Best, NIH.

Minimal model for fibril self-replication



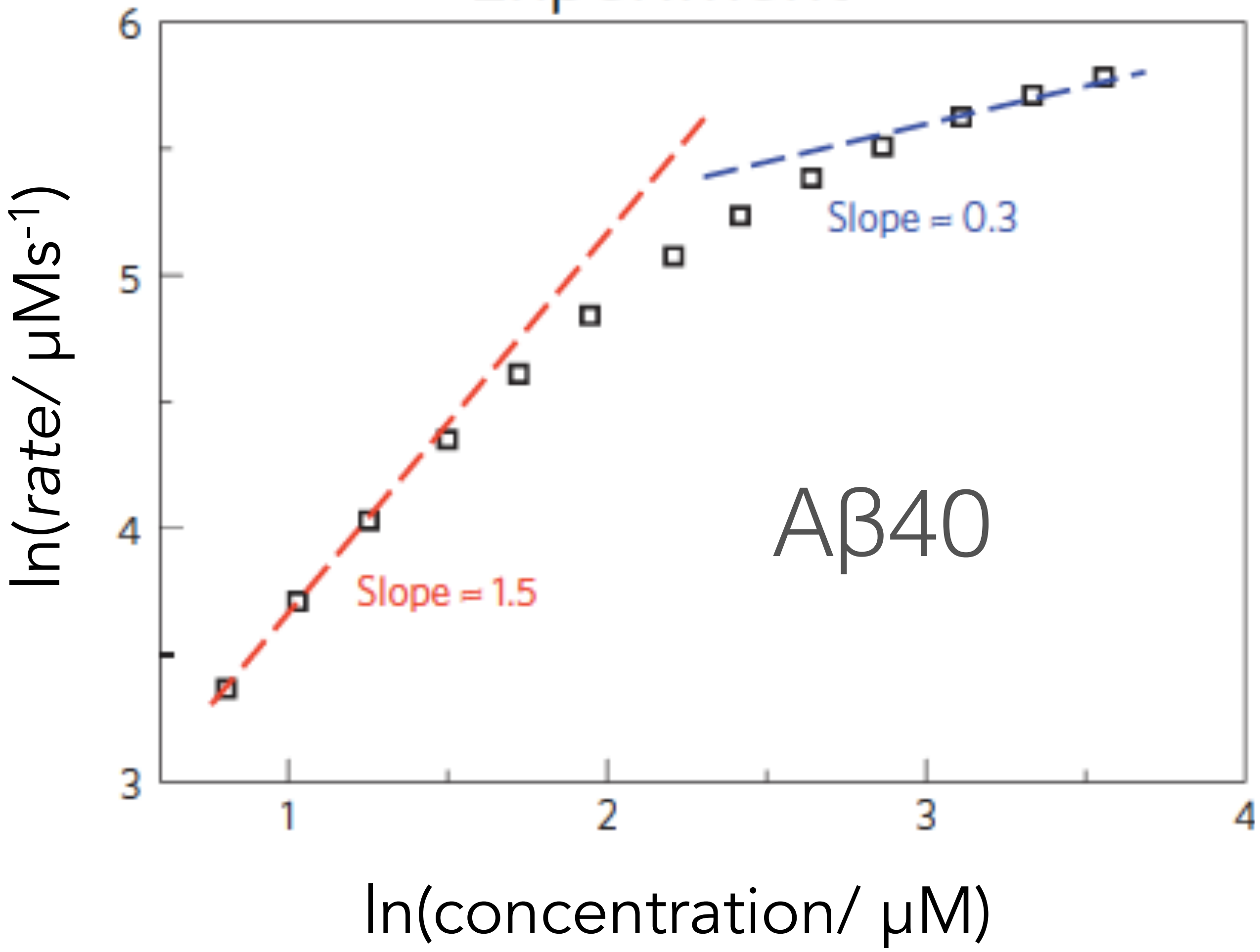
Fibril-catalysed nucleation.

Kinetics of Aβ40 self-replication

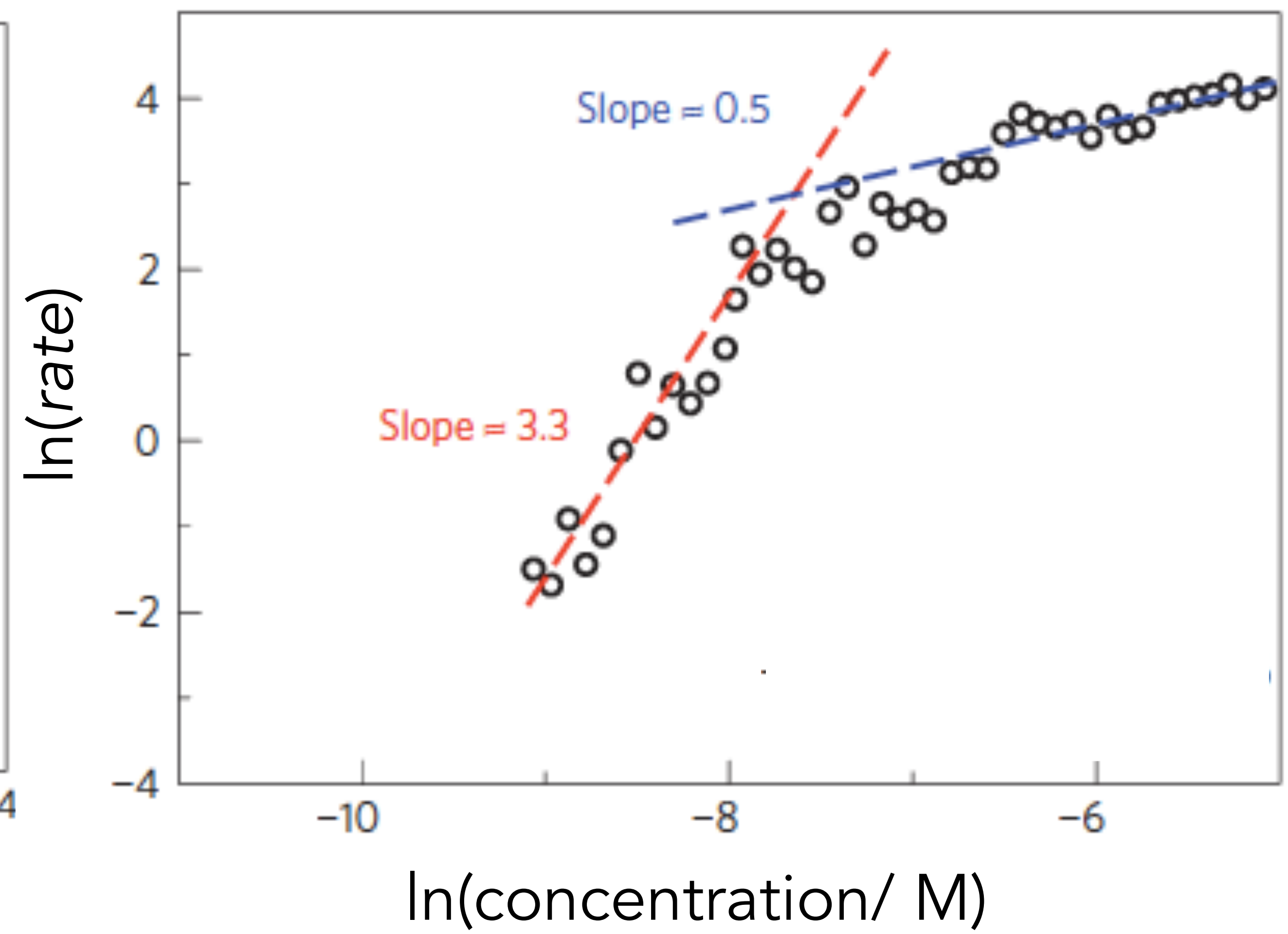
rate ~ concentration$^{\gamma}$

slope: reaction order

Experiment

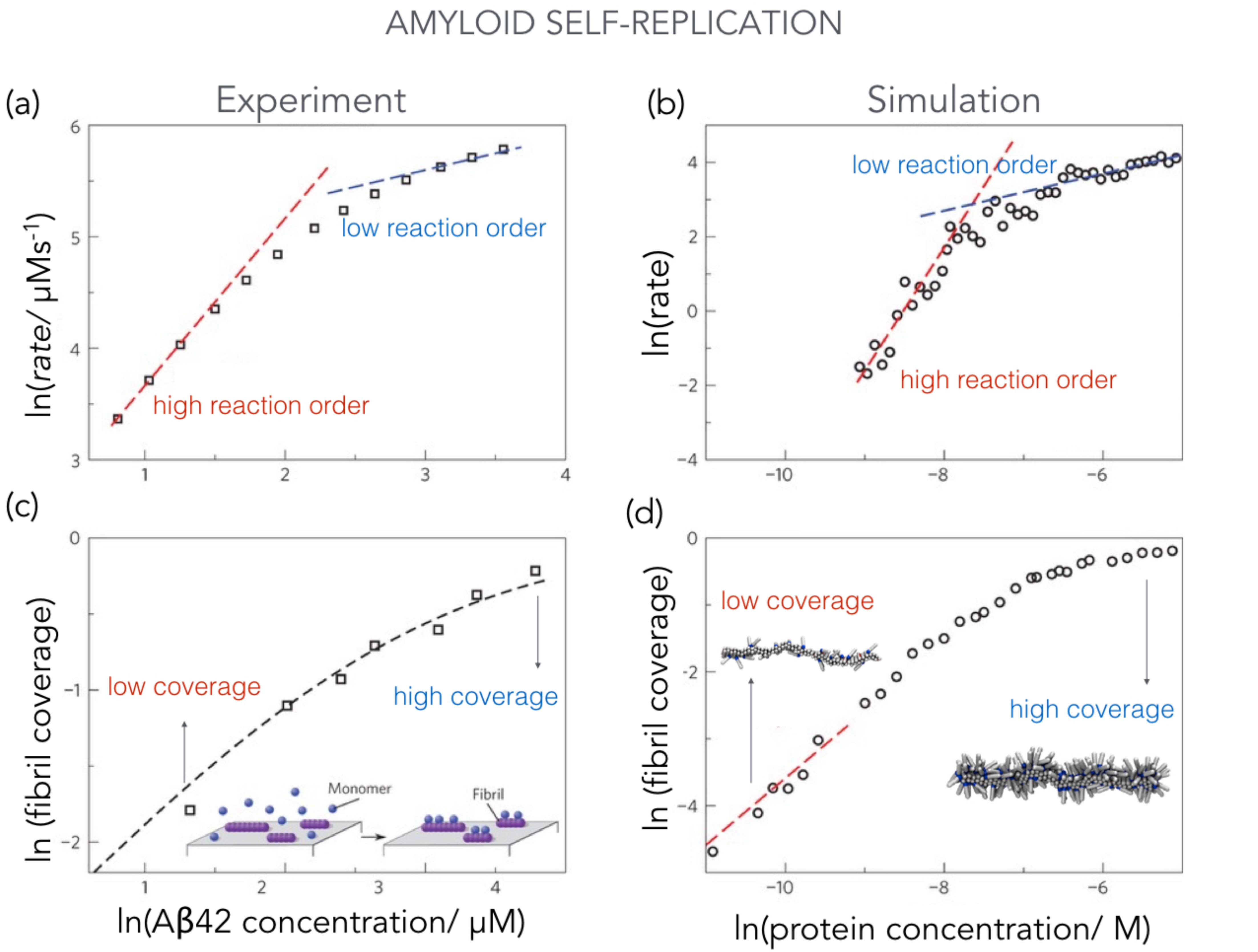


Simulation



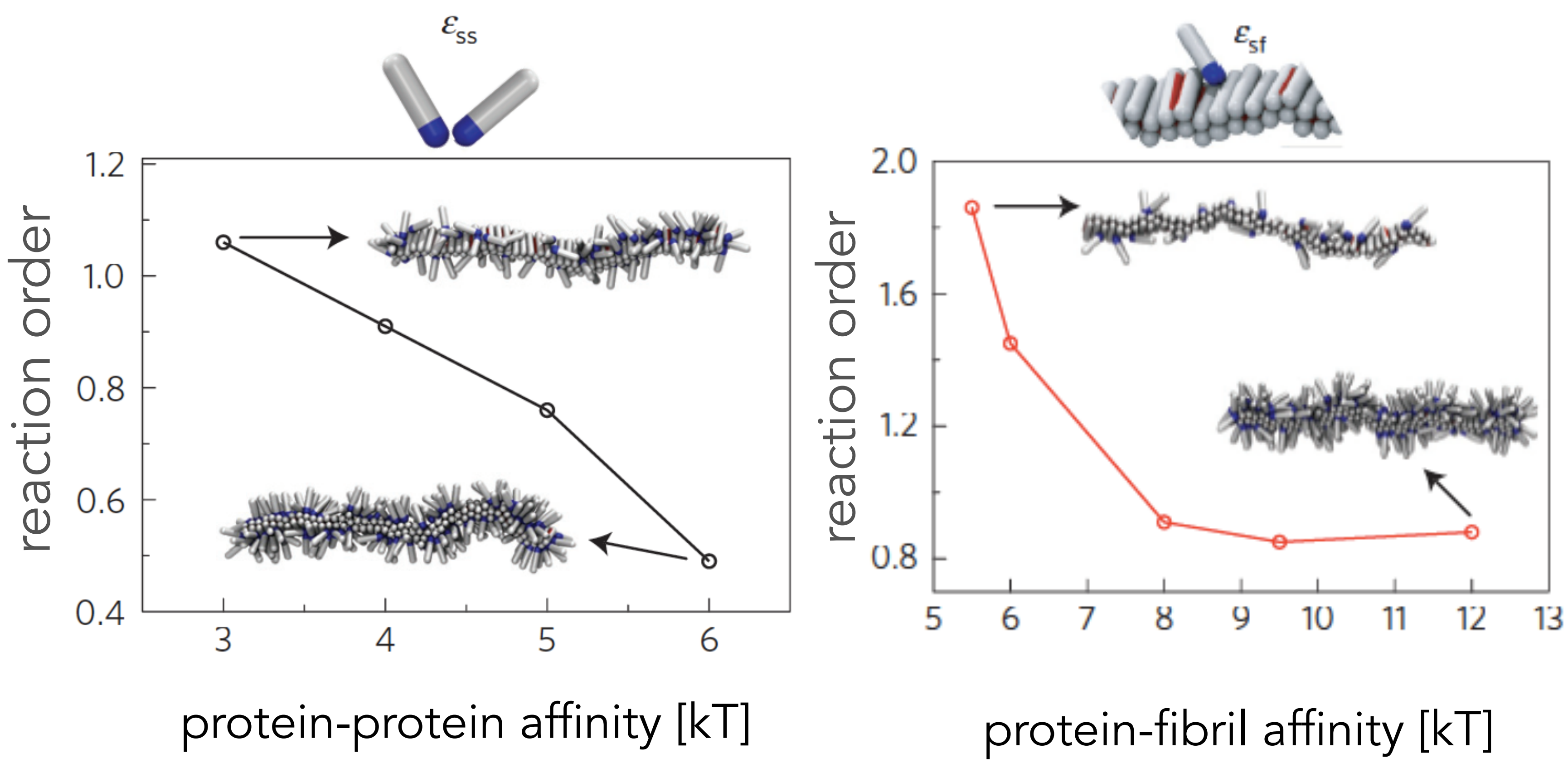
with Tuomas Knowles, Sara Linse

Self-replication: governed by surface coverage



A. Šarić et al, *Nature Physics* 12, 874 (2016).

Controlling self-replication
by modulating the surface coverage of fibrils

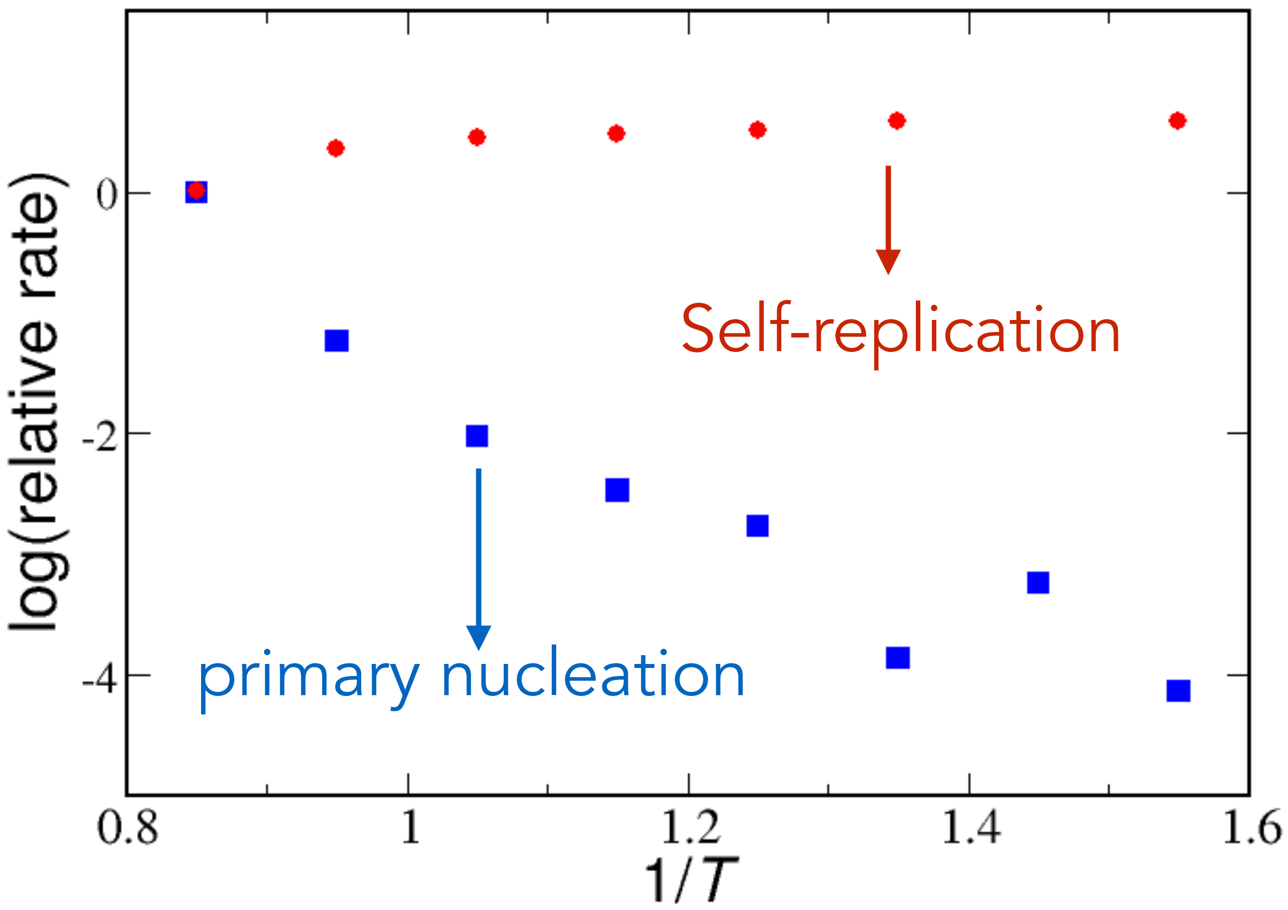


- Protein-fibril affinity as a target in bypassing fibril self-replication and propagation of cytotoxic species.

A. Šarić et al, *Nature Physics* 12, 874 (2016).

Comparison of spontaneous formation and self-replication
Thermodynamic signatures

Simulation

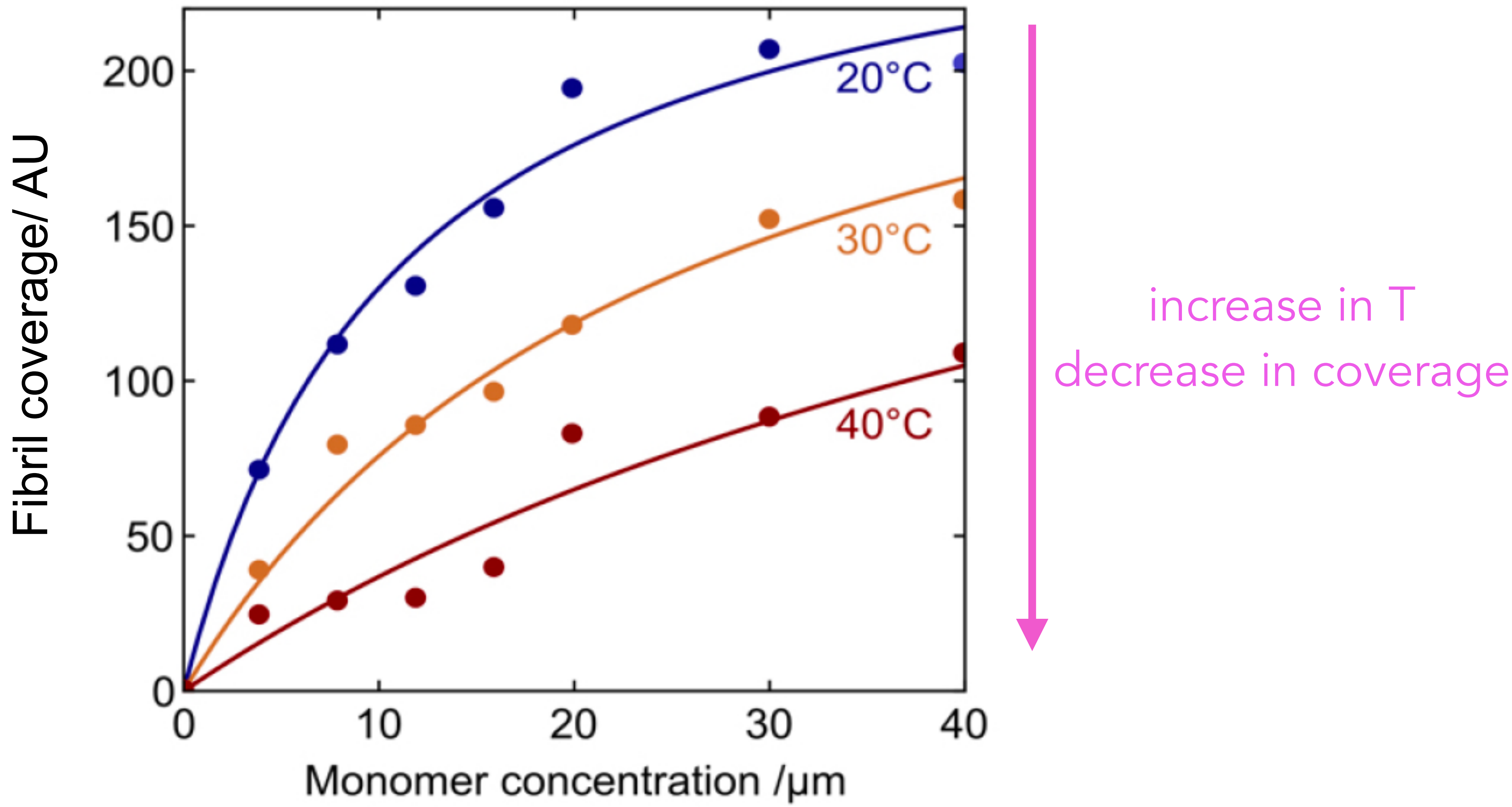


$$\frac{\partial \log k}{\partial(1/T)} = -\frac{\Delta H^{\ddagger}}{R}$$

S.I.A. Cohen et al., *Nature Chemistry*, 2018.

with Tuomas Knowles, Sara Linse

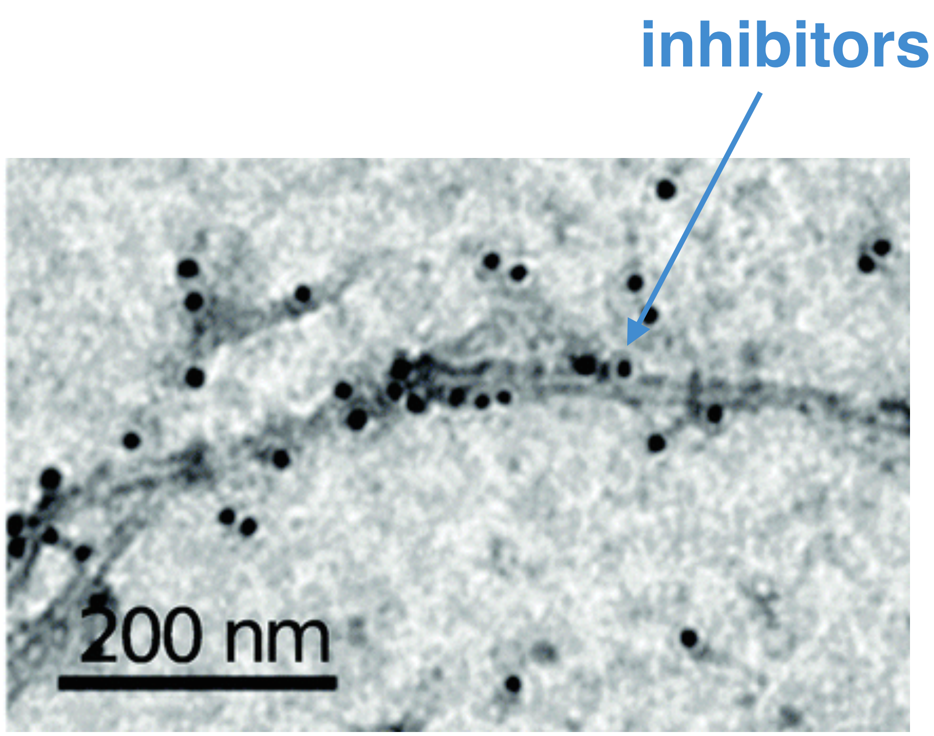
Comparison of spontaneous formation and self-replication
Why is self-replication slower at higher T?



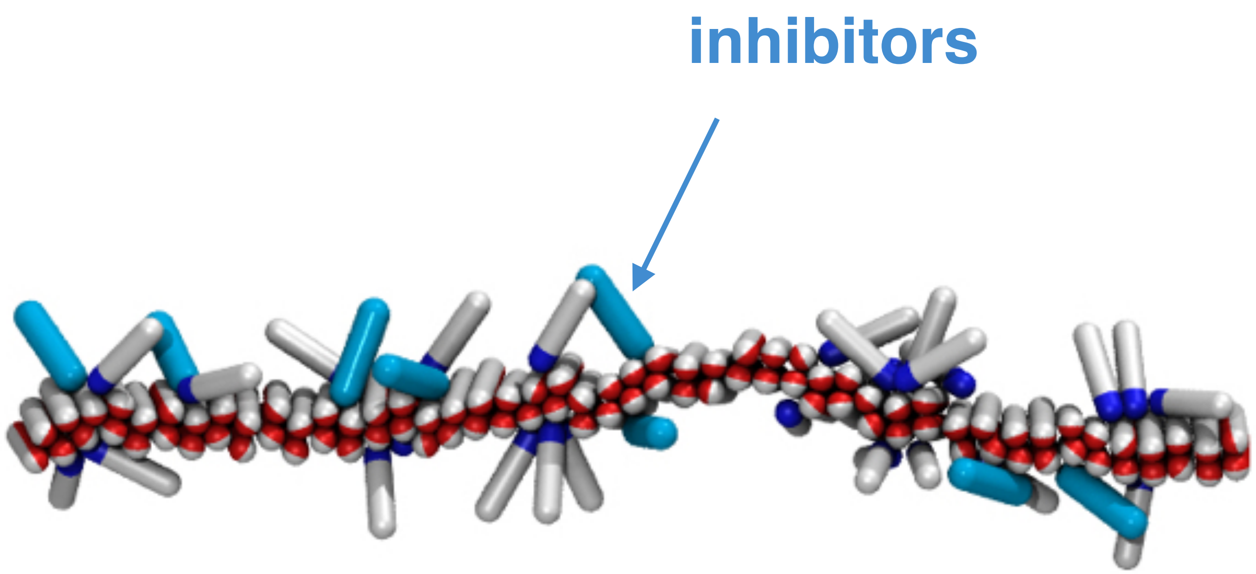
S.I.A. Cohen et al., *Nature Chem*, 2018.
T.C.T. Michaels et al., *Mol Phys* 2018.

by Tuomas Knowles, Sara Linse

Controlling Aβ self-replication
by inhibitors



Brichos chaperone inhibits self-replication

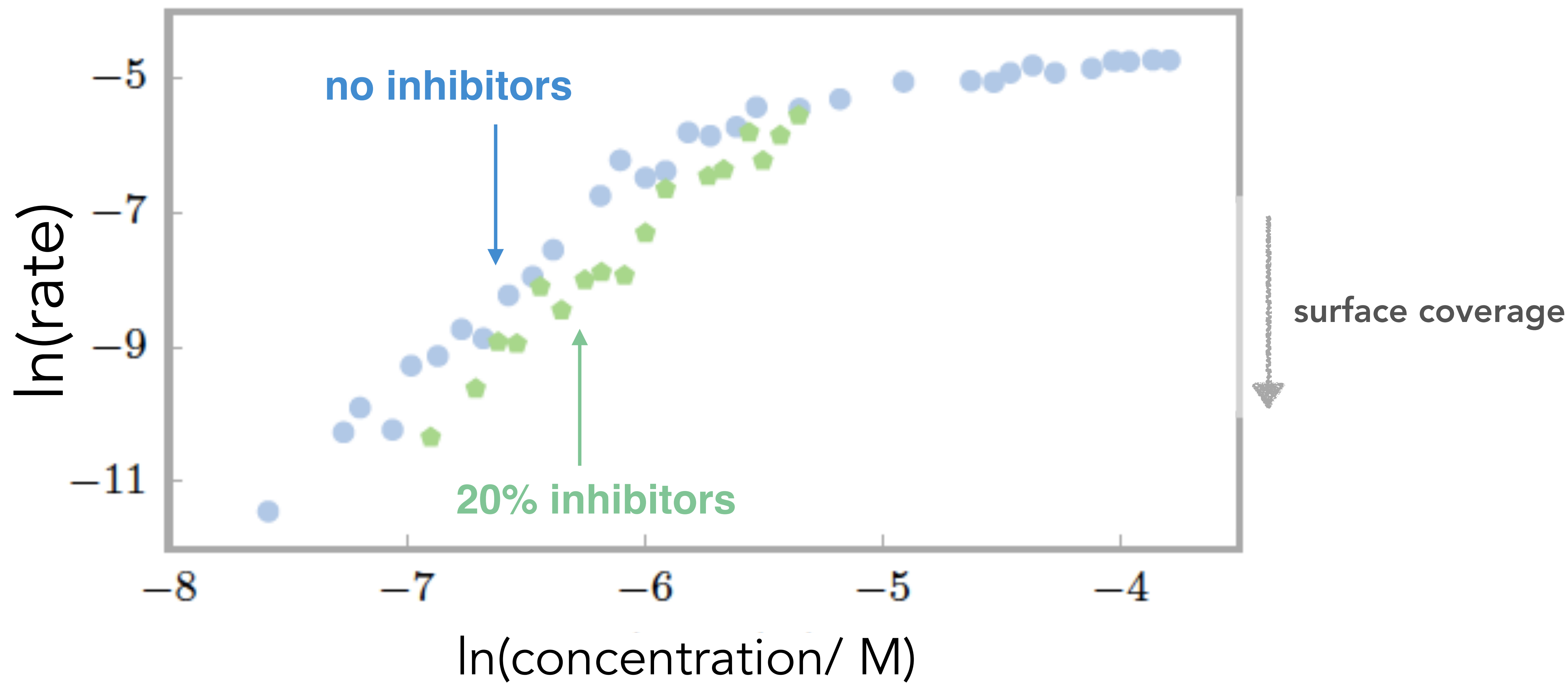


Binders to the fibril surface.

- What is the inhibition mechanism?
- Can we design inhibitors?

S. I. A. Cohen et al., *Nat. Struct. Mol. Biol*, 2015
P. Arosio et al., *Nat. Comm.*, 2016.

Inhibiting Aβ42 fibril self-replication



by Samo Curk

in preparation

Amyloid self-replication

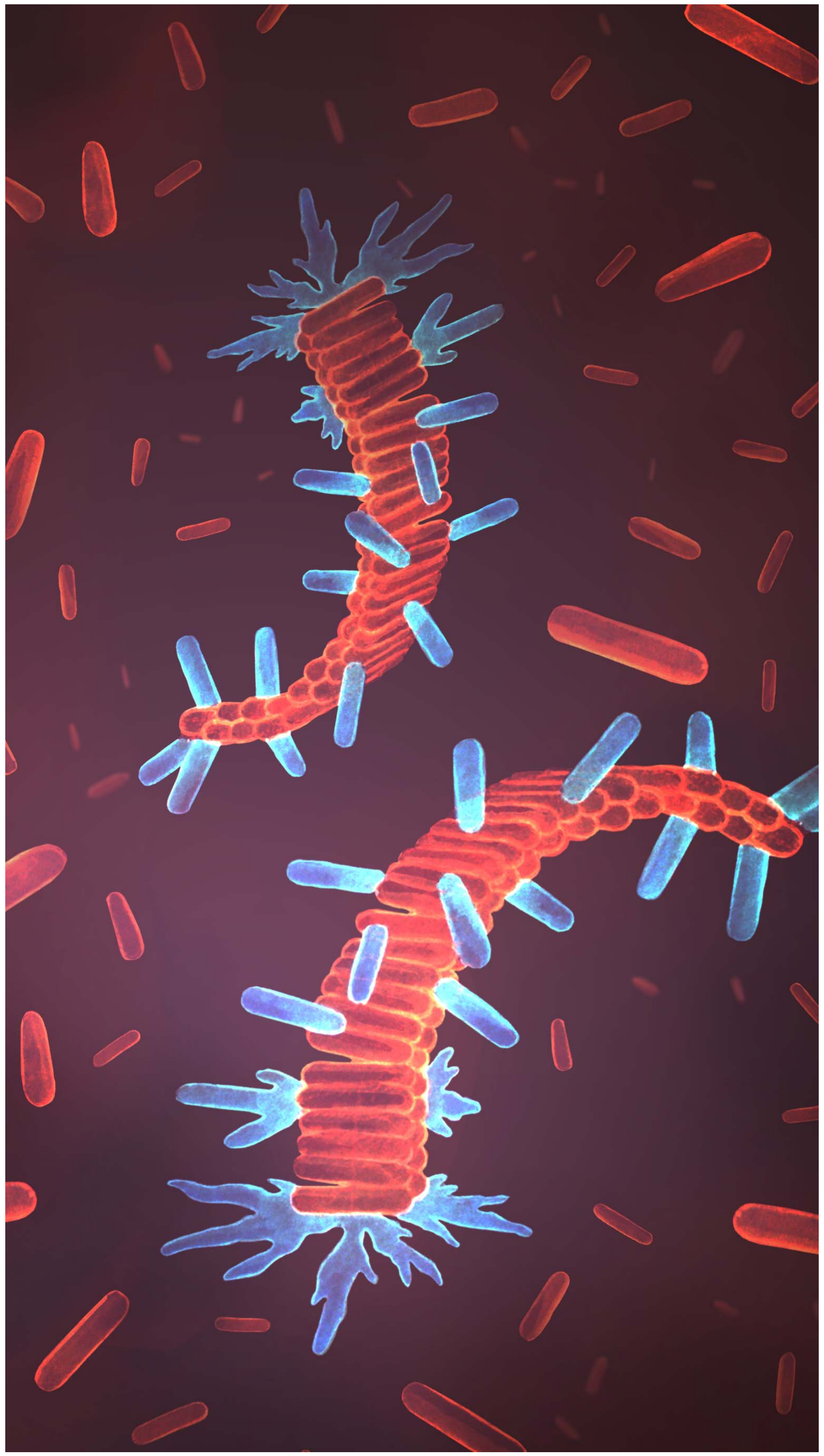
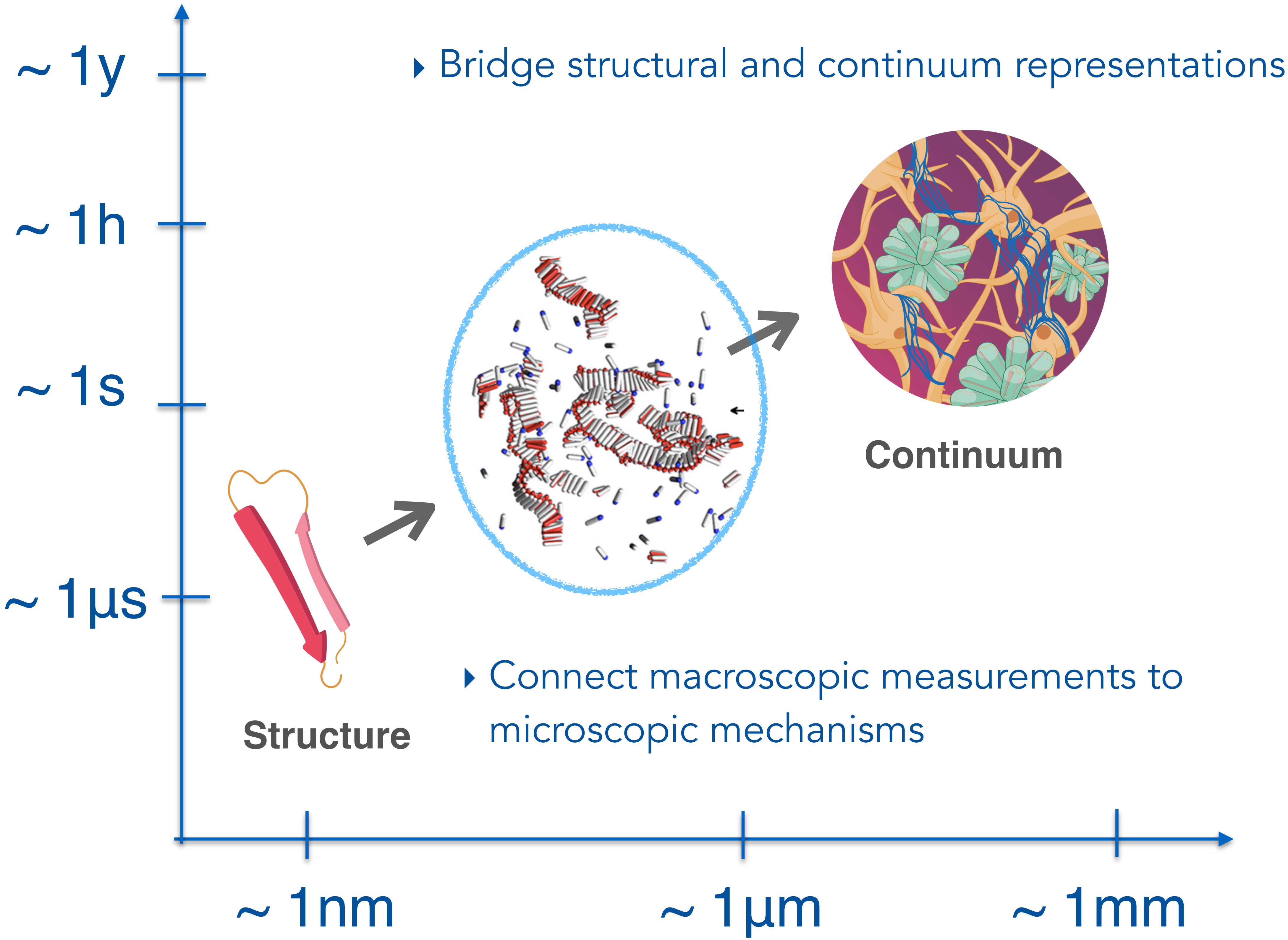


Illustration: Ivan Barun, dr med

- **Fibril self-replication** is governed by a single process of protein **adsorption** onto the fibril surface
- Self-replication be **controlled** by modulating protein-fibril affinity, or protecting the fibril surface
- Searching for **design rules** for efficient inhibition

Modelling biological assembly



- Bridge structural and continuum representations
- Connect macroscopic measurements to microscopic mechanisms

MANY THANKS

UCL IPLS
Institute for the Physics of Living Systems

UCL

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- Sara Linse, Lund
- Chris Dobson, Cambridge
- Buzz Baum, UCL
- Bart Hoogenboom, UCL
- Ewa Paluch, UCL

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