CMMP11, Manchester
December 2011

Protein amyloid self assembly:
nucleation, growth, and breakage

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Protein amyloids

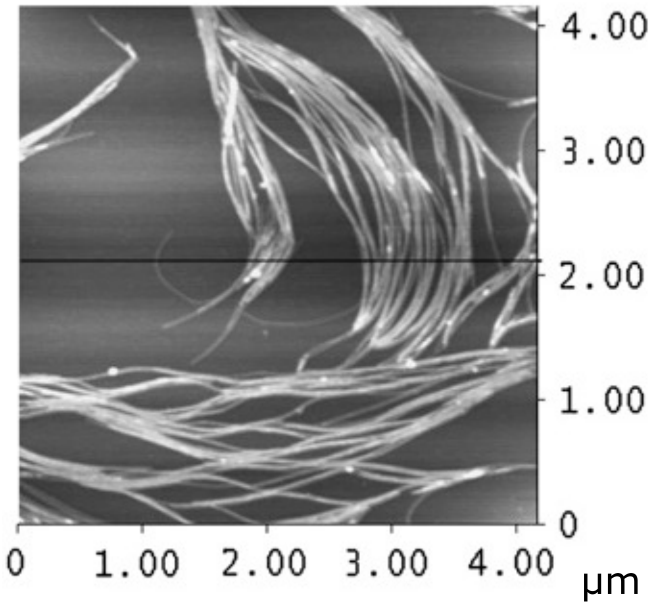
Amyloid fibrils are linear aggregates of proteins

Many proteins form amyloids

Many amyloid related diseases, e.g., Alzheimer’s, Parkinson, Type II diabetes

Amyloid fibrils form easily *in vitro*

IAPP

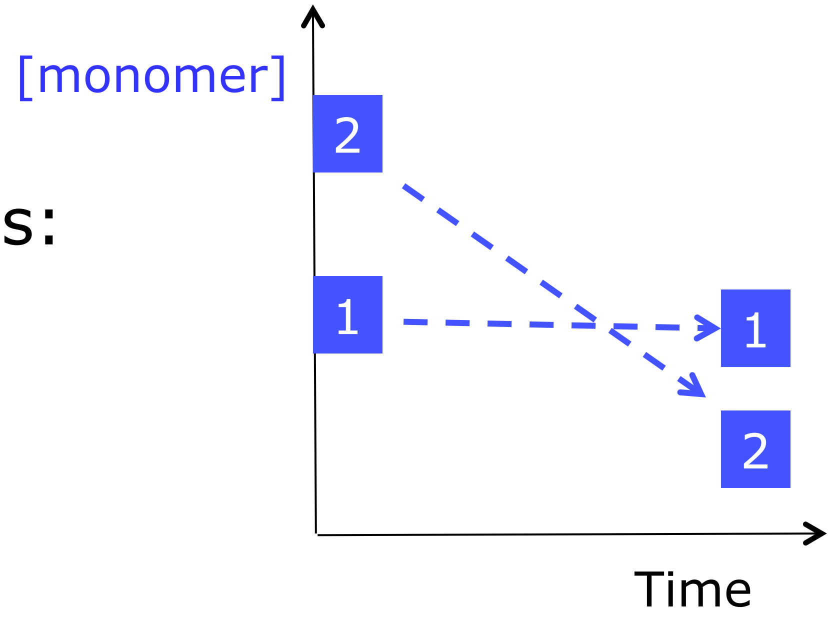


Lopes et al. (2007) *Biophys. J*

Plan

- Nucleation of amyloid fibrils
- Dynamics of fibril elongation
- Thermal breakage

A Paradox



In vitro observations:
2 experiments

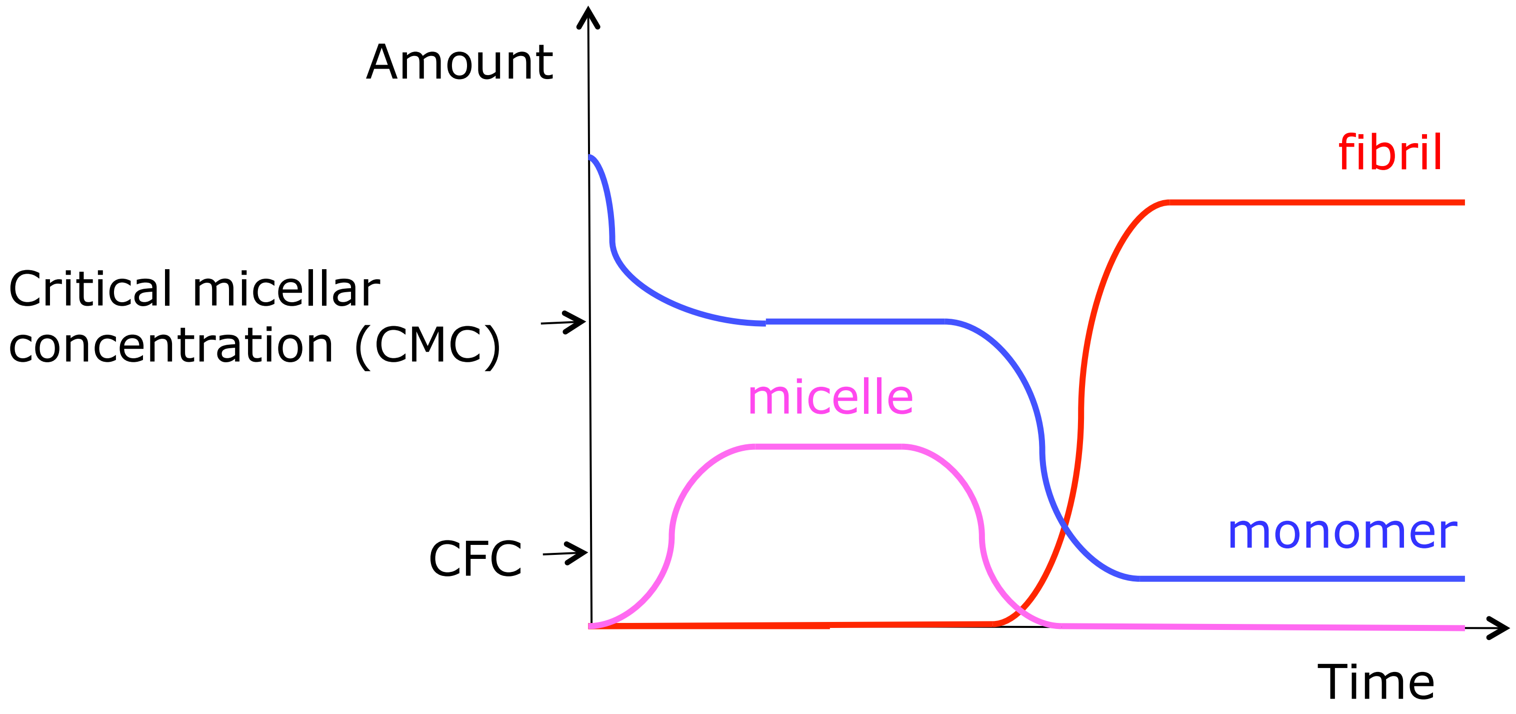
Expt 1: Medium [monomer] -> medium [monomer]
Expt 2: High [monomer] -> low [monomer]

→ Nucleation pathway: monomer -> micelle -> nucleus (fibril)

Lomakin, Teplow, Kirschner and Benedek (1997) *PNAS* **94**, 7942

A second critical conc.

Observable pathway: monomer -> micelle -> nucleus (fibril)



Lomakin, Teplow, Kirschner and Benedek (1997) *PNAS* **94**, 7942
Lee (2009) *PRE* **80**, 031922

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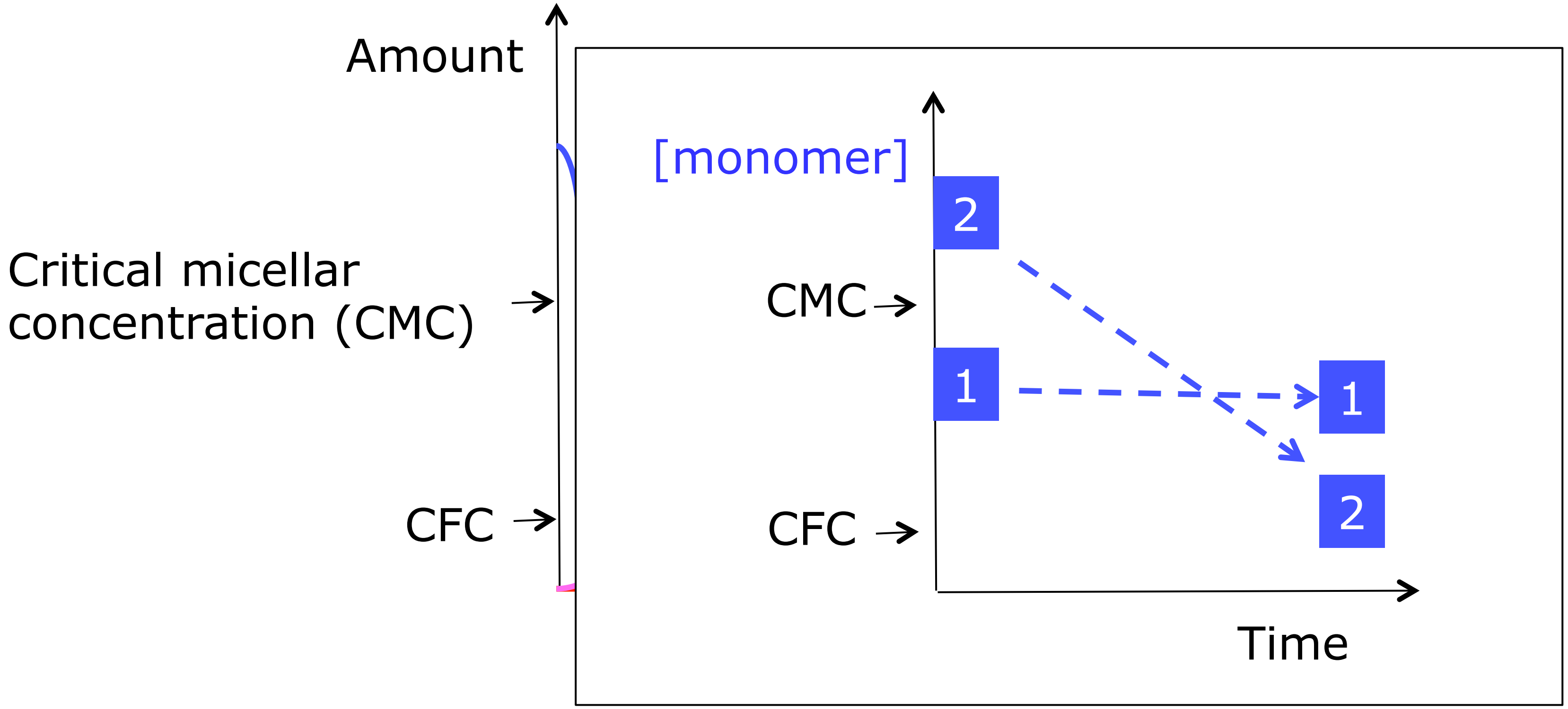
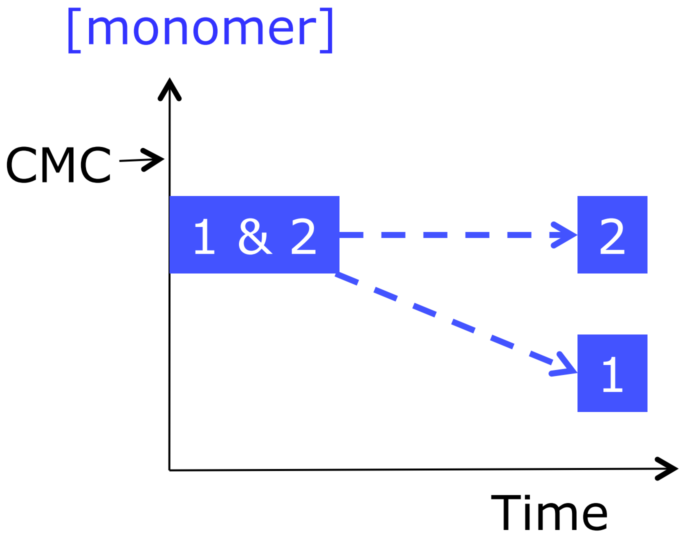
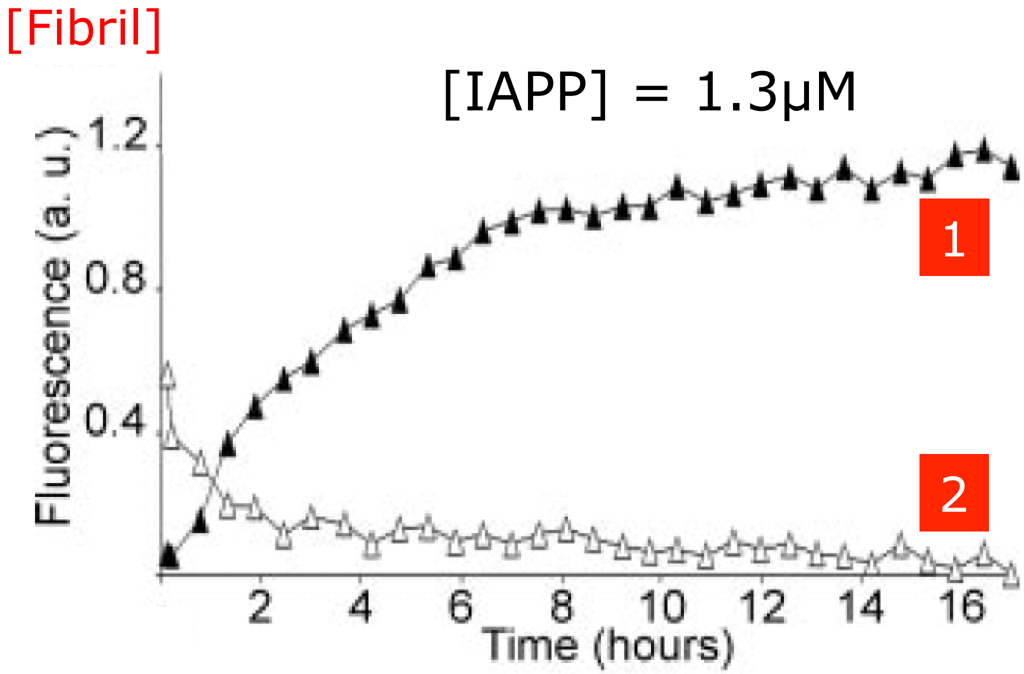


Lomakin, Teplow, Kirschner and Benedek (1997) *PNAS* **94**, 7942
Lee (2009) *PRE* **80**, 031922

Interfacial effect



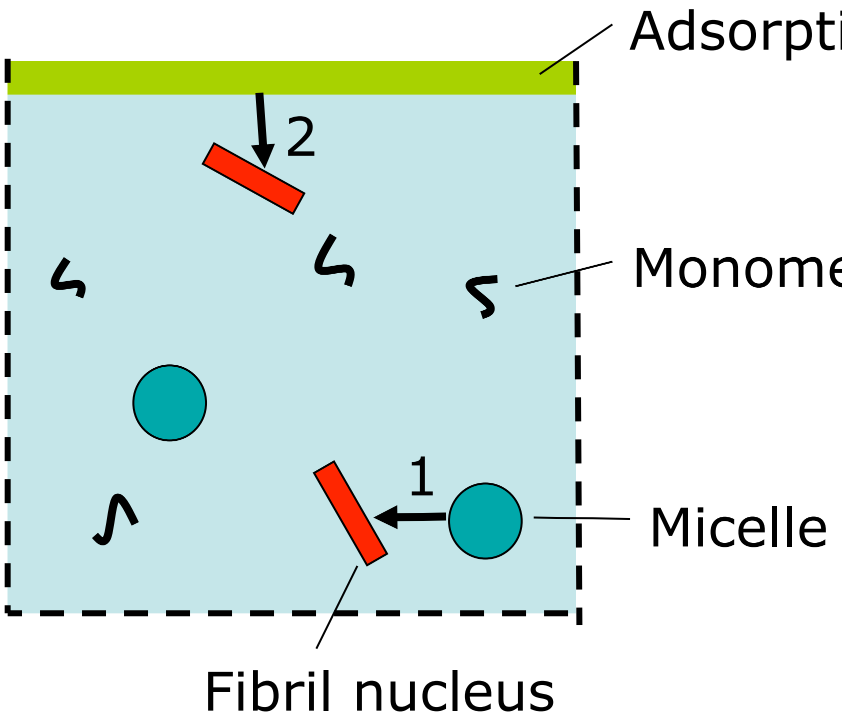
Fibrilization assay

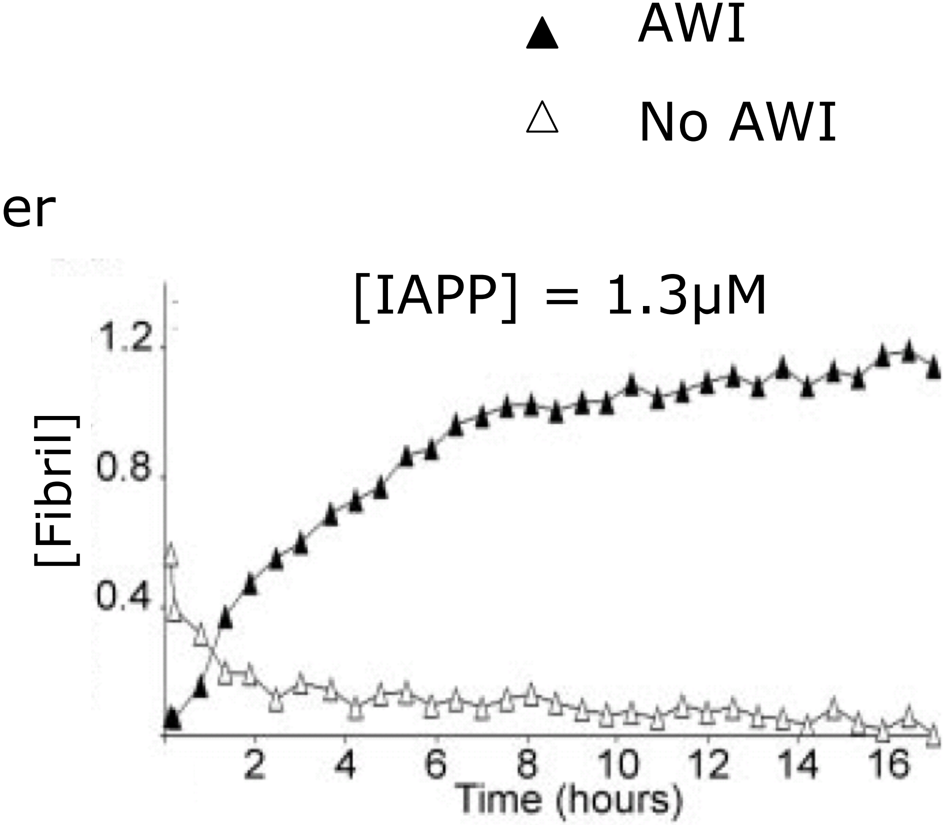


Expt 1: with Air-Water Interface (AWI), ▲
Expt 2: no AWI, △

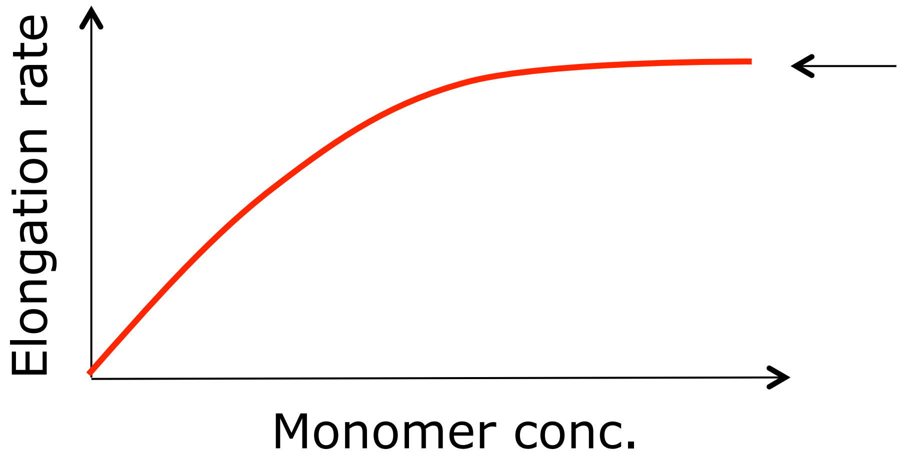
Jean, Lee, Lee, Shaw and Vaux (2010) *FASEB Journal* **24**, 309

Two fibrilization pathways





Fibril Elongation

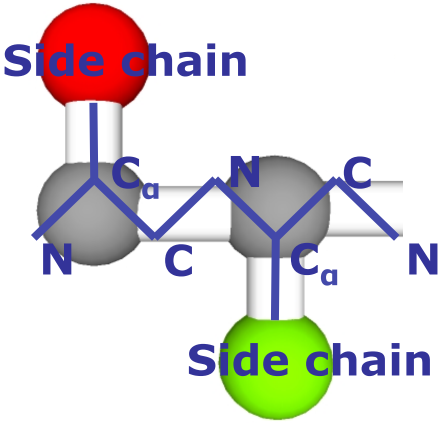


~ 1 monomer/sec
Aβ single fibril elongation rate
from TIRF experiment
[Ban et al. JMB (2004)]

Question:

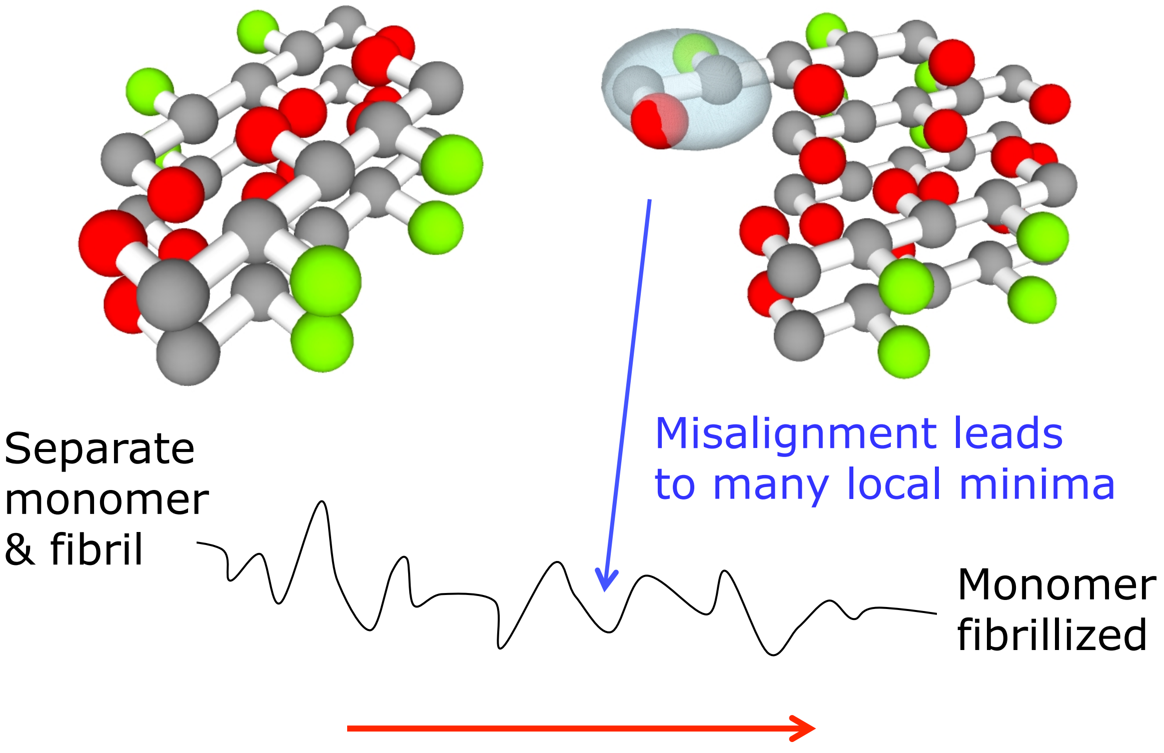
Can we explain the time scale observed?

Coarse-grained molecular dynamics simulations



Diffusion in rugged energy landscape [Zwanzig, PNAS ('88)]

$$D_{eff} = D\exp\left[-\left(\frac{\Delta E}{k_B T}\right)^2\right]$$



Separate monomer & fibril

Misalignment leads to many local minima

Monomer fibrillized

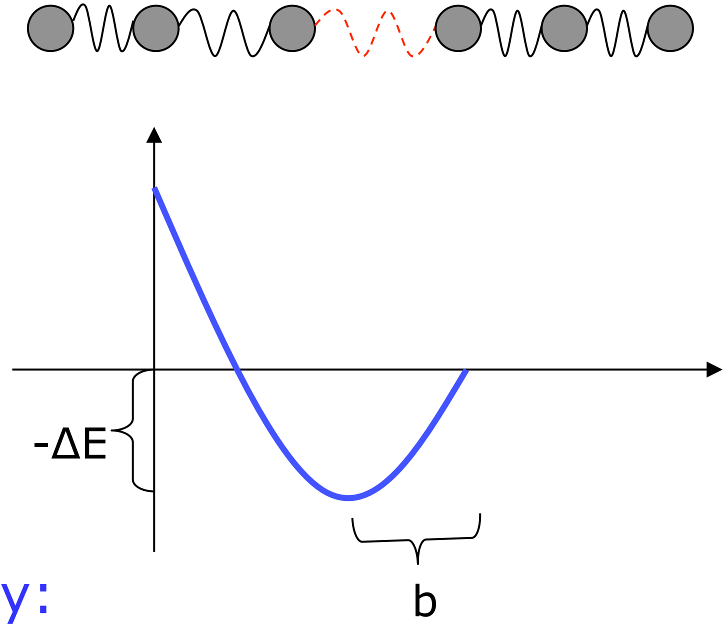
correct hydrogen bonds

Lee, Loken, Jean and Vaux (2009) Physical Review E 80, 041906

Thermal Breakage

M beads connected by springs in 1D

$$\underbrace{\zeta}_{\text{Friction coefficient}} \frac{dx}{dt} = f(x) + \sqrt{2\zeta k_B T}\, g(t)$$

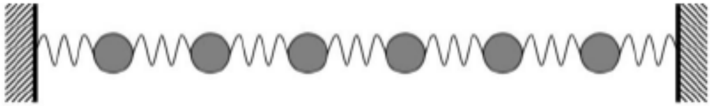


Multidimensional Kramers escape theory:

Breakage rate: $$R = \frac{8\Delta E^{3/2} M}{b^2 \zeta \sqrt{\pi k_B T}} \exp\left[-\Delta E / k_B T\right]$$

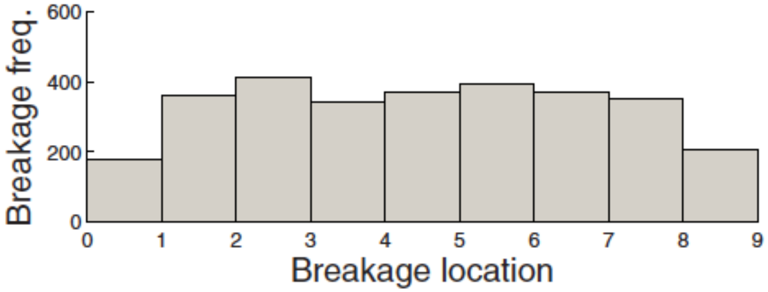
Lee (2009) Phys. Rev. E 80, 031134

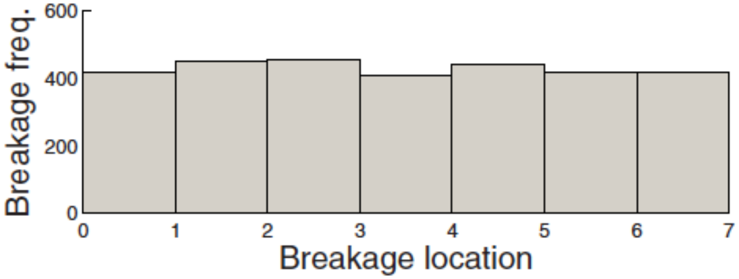
Breakage Profile



(a)

(b)





Lee (2009) Phys. Rev. E 80, 031134

Summary

- Protein amyloids are physiologically and technologically important
- Heterogeneous nucleation
  - Interface dominated at low concentration
- Slow dynamics of fibril elongation
  - Diffusion in a rugged energy landscape due to misalignment
- Thermal breakage
  - Multidimensional Kramers problem
  - Uniform breakage propensity for free fibrils
  - Tethered points break half as often

Thanks

Oxford's Dunn School of Pathology (experiments)
Catherine Davison
Chongsoo Lee
Michael Shaw

Oxford's Particle Physics Sub-Department
(grid computation infrastructure)
James Loken
Rhys Newman
Jeff Tseng

Thank you!

References

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