

Enhanced Sampling Simulations of protein aggregation

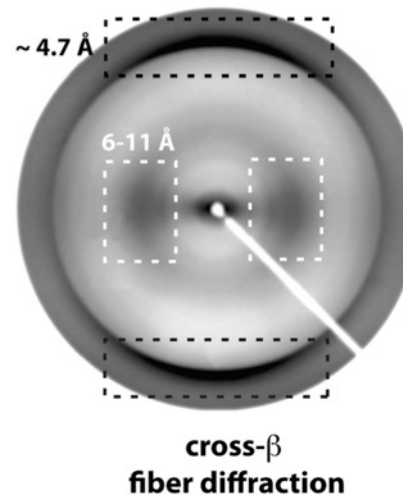
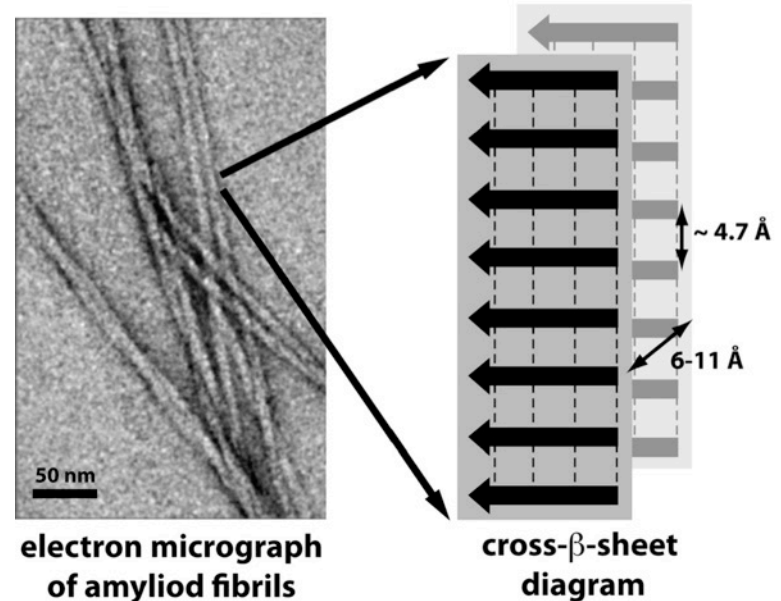
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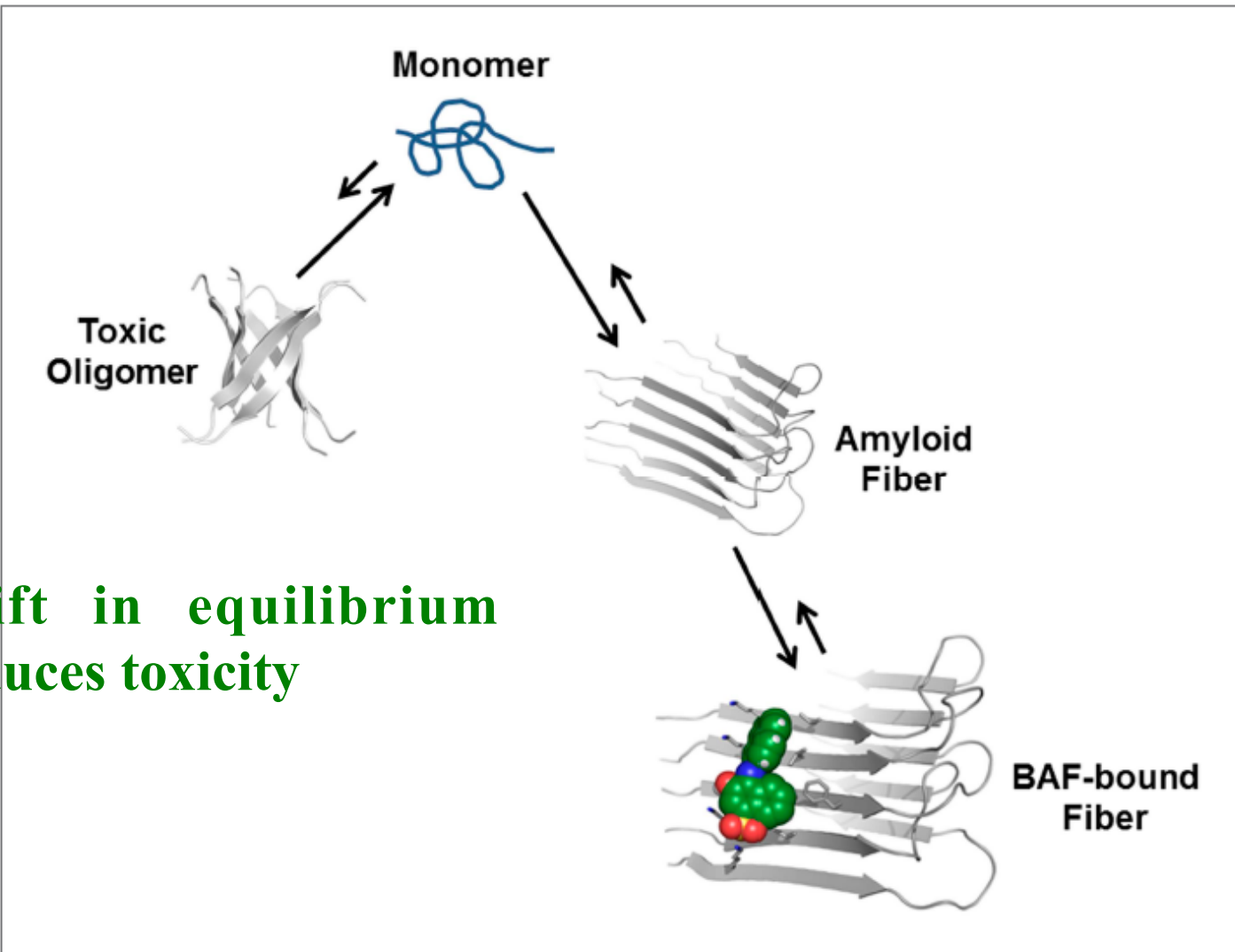
Misfolding and aggregation

- **Misfolding** and **aggregates** are associated with diseases:
 - Alzheimer's
 - Parkinson
 - Cystic Fibrosis
- marker for these disease are **amyloid fibril** deposits
 - 4.7 Å between β -strands perpendicular to fibril axis
 - 6-10 Å between neighboring β -sheets
- but **toxic** species: **solvable oligomers** rather than fibrils?



Greenwald J., Structure, 18 (2010) 1244

FIBER STABILITY AND TOXICITY



**Shift in equilibrium
reduces toxicity**

Jiang et al Elife. 2013. 2:e00857

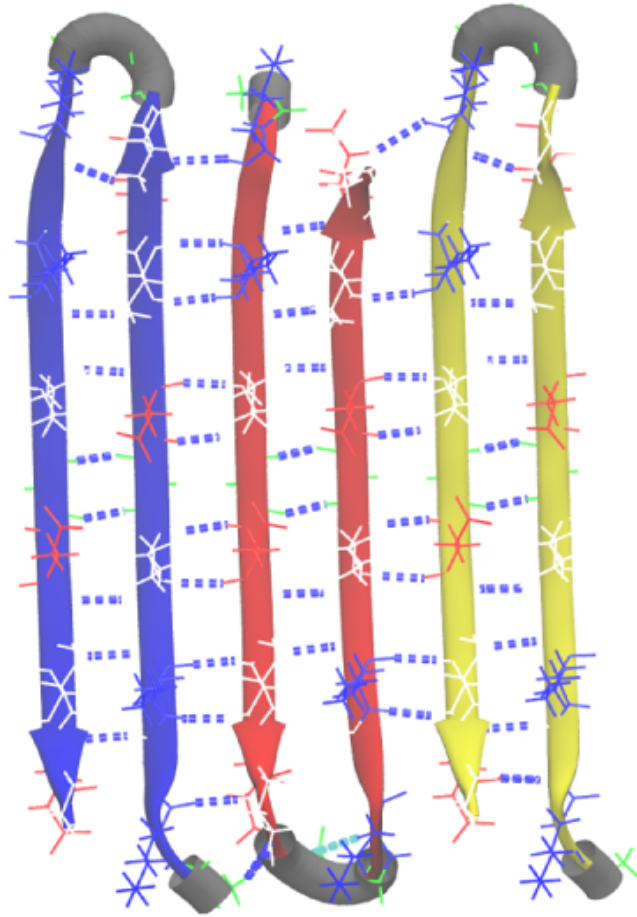
Cylindrin β -barrel amyloid oligomers

- six identical 11-residue peptides that form out-of-register antiparallel β -strands in the shape of a barrel, instead of the in-register β -strands typically observed in amyloid fibrils
- Model for solvable toxic oligomers
- What determines stability of the oligomers?
- On or off pathway to formation of unsolvable fibrils?
- Mechanism of toxicity?

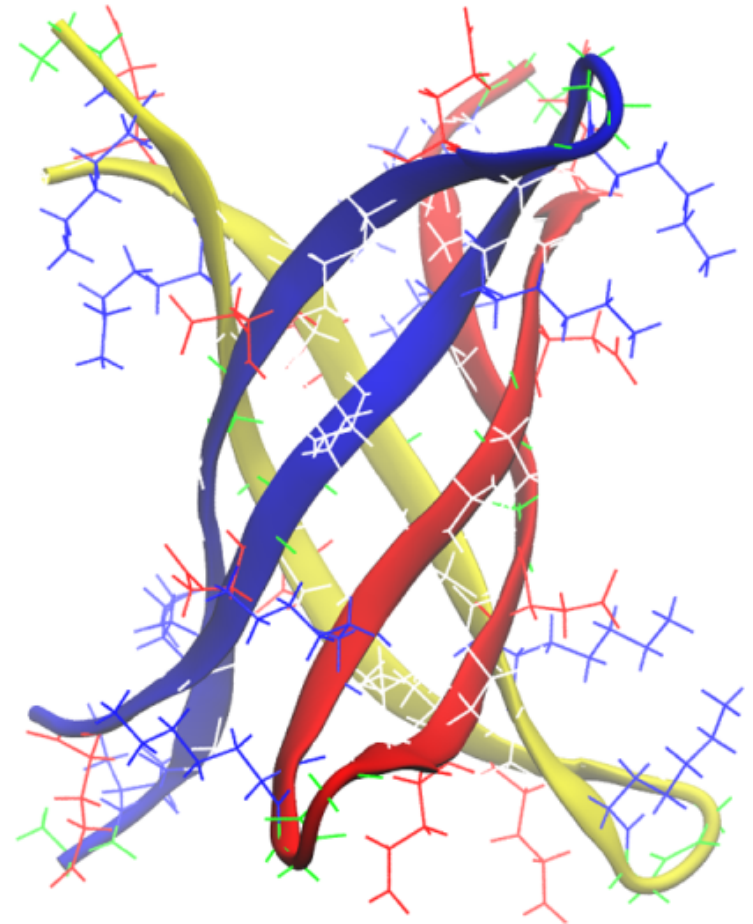


Cylindrin as Model System

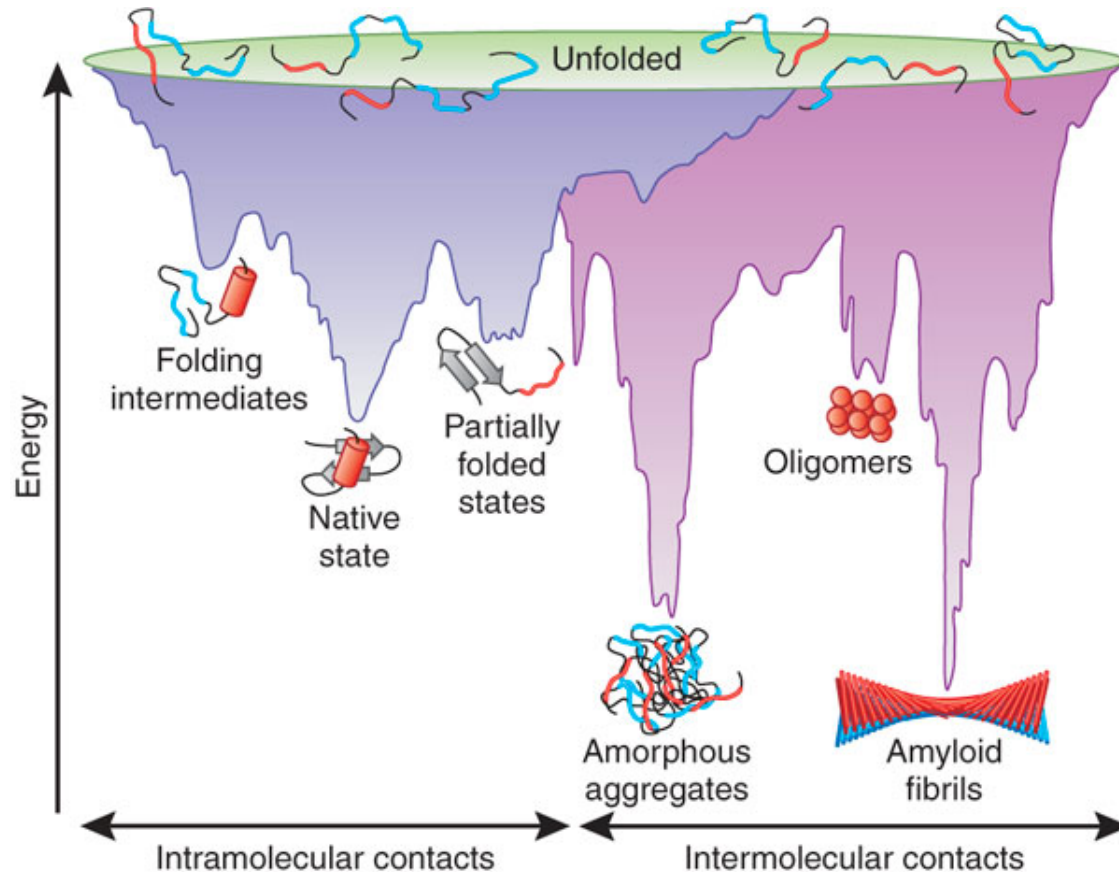
(a) fibril



(b) barrel



Folding and Aggregation Landscape?



U. Hartl & M. Hayer-Hartl,
Nat. Struc. Biol. 16 (2009) 574

- Rough energy landscape
- Folding takes $> ms - s$; aggregation takes even longer: $\approx h - d$
- Computational effort increases **exponentially** with system size (including **solvent!**)

Requirements on Sampling Methods

- Find local minima
- Escape out of local minima and continue search

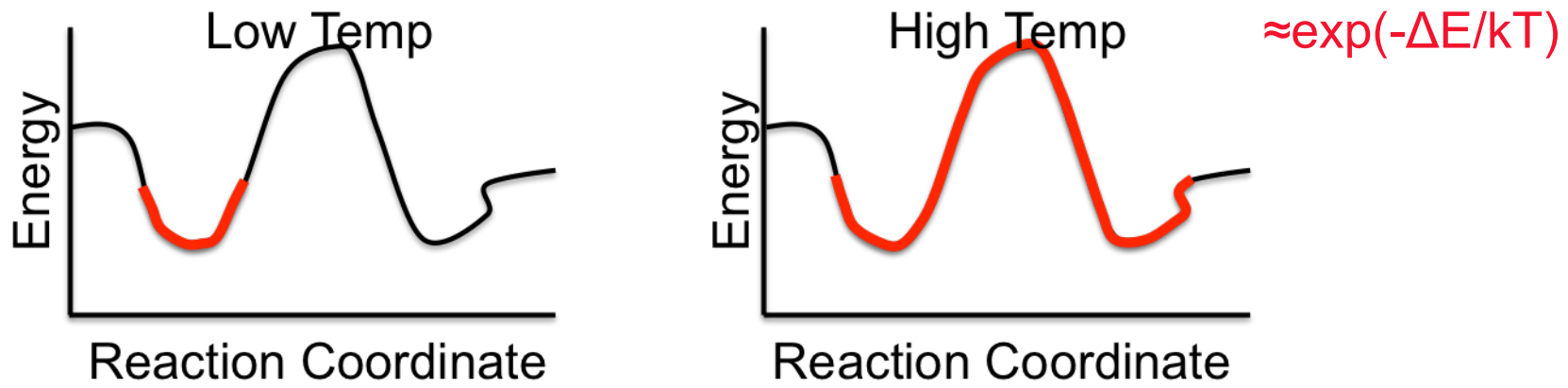
Can be achieved by:

- Improved/adaptive steps
- Improved/adaptive weights

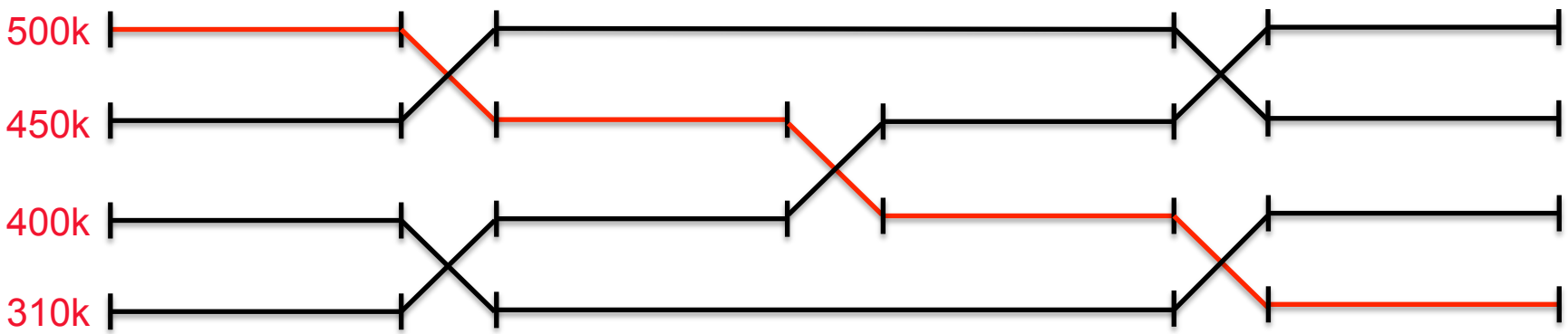


Replica Exchange Sampling (Parallel Tempering)

- The probability of crossing barriers increases with temperature



- Walk in temperature, replica exchange with $\min(1, \exp(\Delta\beta\Delta E))$, $\beta = 1/k_B T$



Replica Exchange with Tunneling

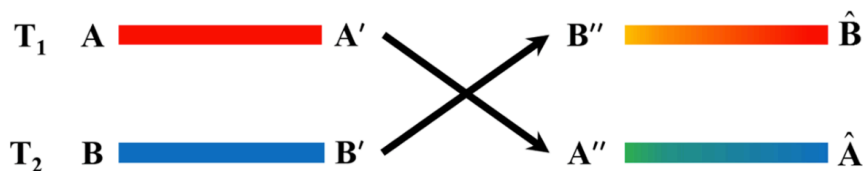
F. Yasar, N.A. Bernhardt & U.H.E. Hansmann, J. Chem. Phys., 143 (2015) 224102.

- **Common situation**: exchange move leads to energetically unfavorable state in Multi-Markov-chain → **low acceptance rate**
- But if accepted, the system quickly evolves to a state with energies similar to the state before the exchange move.
- Examples: **proteins in explicit solvent**, resolution exchange
 - Number of replicas increases rapidly with system size, otherwise low acceptance rates
 - Simulation time increases, too, as more time required for round trips
- How to “**tunnel**” through the unfavorable “transition state”?



Replica Exchange with Tunneling

F. Yasar, N.A. Bernhardt & U.H.E. Hansmann, J. Chem. Phys., 143 (2015) 224102



- **Microcanonical** molecular dynamics from A to A' (B to B')
- **Conditional** exchange of configurations, with **kinetic energies rescaled** such that total energies $E(B'') = E(A')$ and $E(A'') = E(B')$

$$v''_A = v'_A \sqrt{\frac{E_2 - E_{pot}(q'_A)}{E_{kin}(v'_A)}}$$

$$v''_B = v'_B \sqrt{\frac{E_1 - E_{pot}(q'_B)}{E_{kin}(v'_B)}}$$

- **Microcanonical** molecular dynamics from A'' to A-hat (B'' to B-hat)
- The configurations A-hat and B-hat are accepted with probability

$$\exp(-\beta_1(E_{pot}(\hat{q}_A) - E_{pot}(q_B) - \beta_2(E_{pot}(\hat{q}_B) - E_{pot}(q_A))))$$

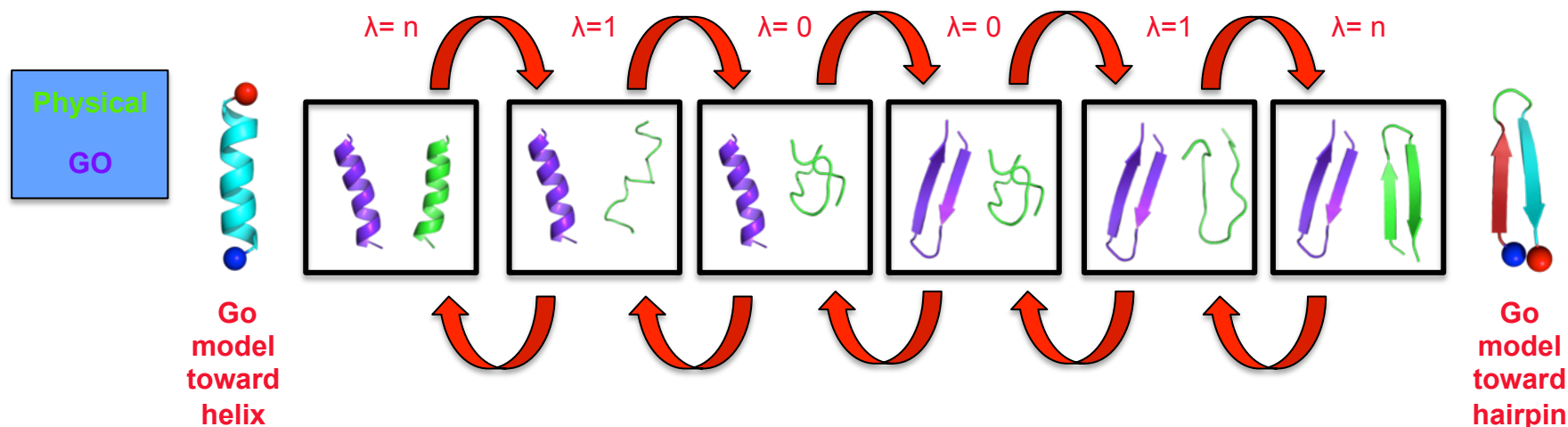
- If **rejected**, the simulation continues with **configurations A and B**



Systems With Competing Attractors

N.A. Bernhardt, W. Xi, W. Wang and U.H.E. Hansmann, JCTC 12 (2016) 5656.

- Problem: **conversion** between structures
- “**feeding**” of physical model by Go-model(s) $E = E_{phys} + \lambda E_{Go}$

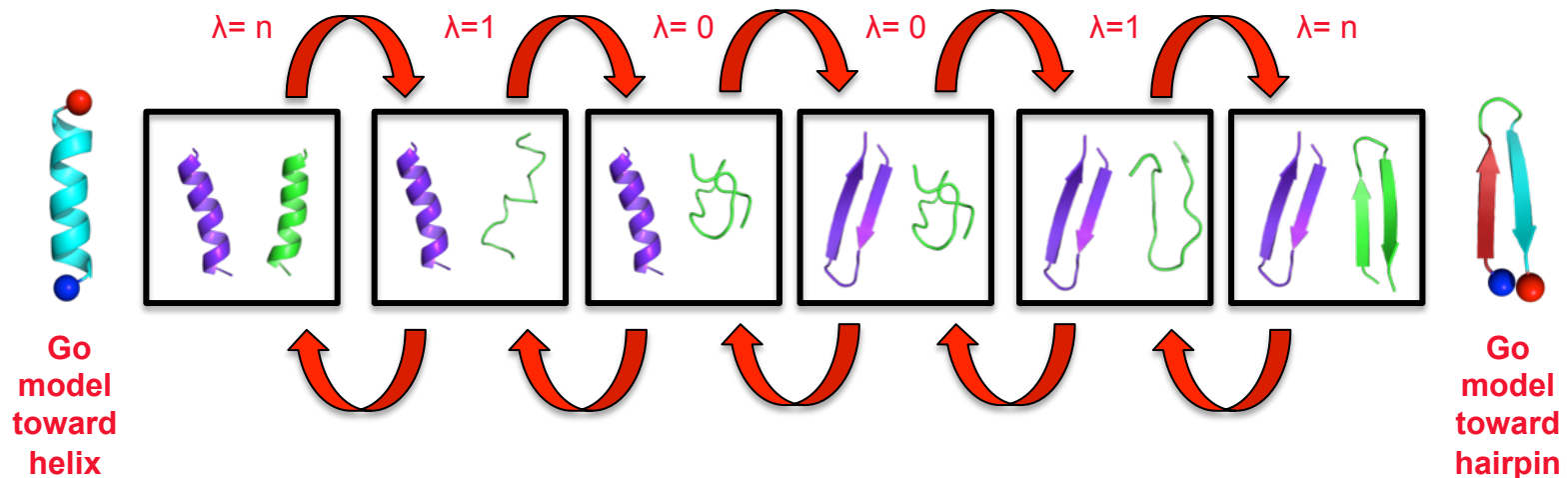


- Replicas walk between Helix and Sheet folds.
- Measurements only at $\lambda=0$ (no bias)
- Low Acceptance rate → **use RET!**

First Test: helix and sheet forming peptides

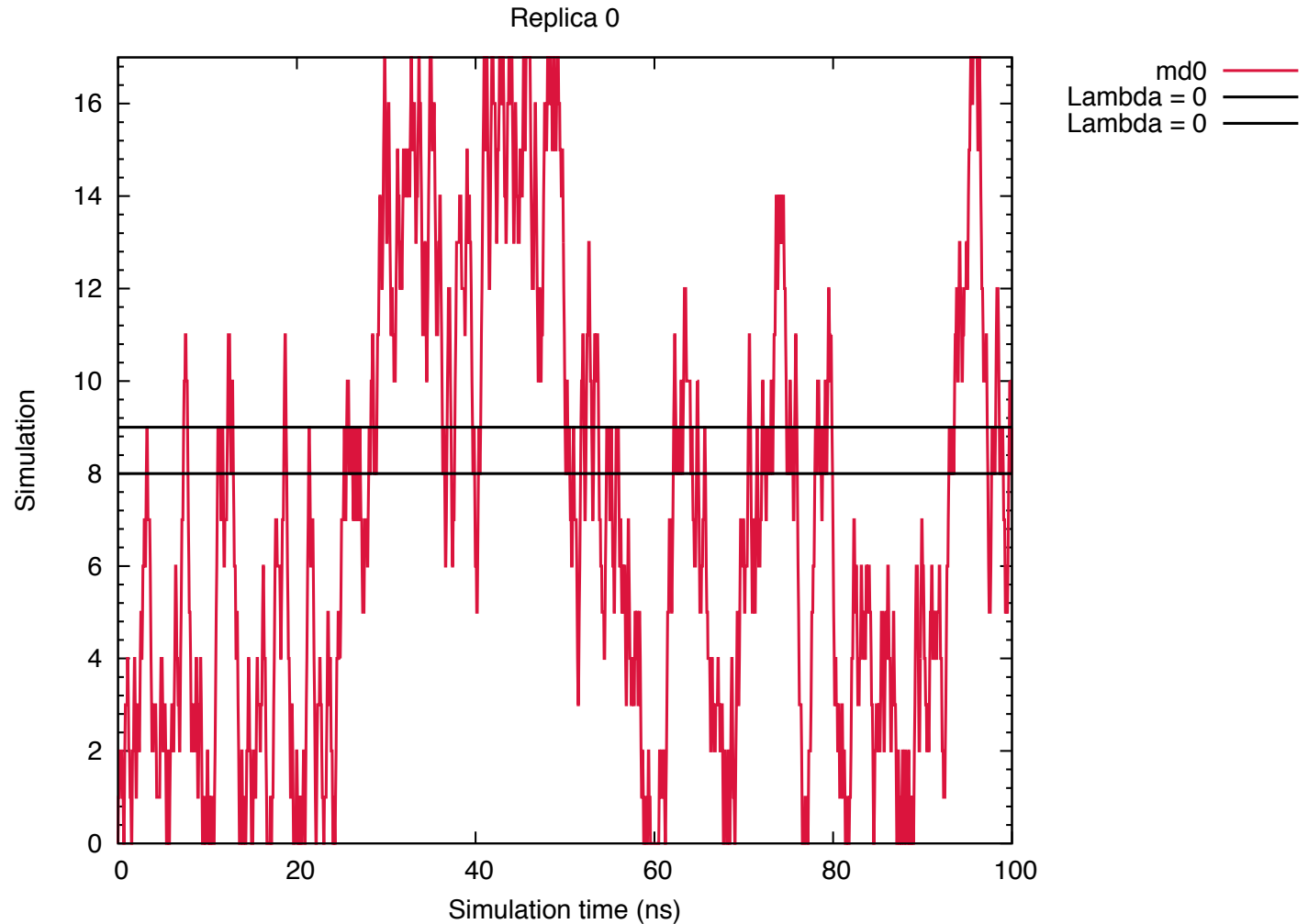
N.A. Bernhardt, W. Xi, W. Wang and U.H.E. Hansmann, JCTC 12 (2016) 5656.

- **AFP:** 11 residue long polypeptide sequence ELLEKLLLEKEK has 51% helicity at physiological temperature
- **BFP:** 16 residue long C-terminus of the B domain of protein G, known to form β -hairpins with a frequency of 42%



Walk in lambda-space

N.A. Bernhardt, W. Xi, W. Wang and U.H.E. Hansmann, JCTC 12 (2016) 5656.



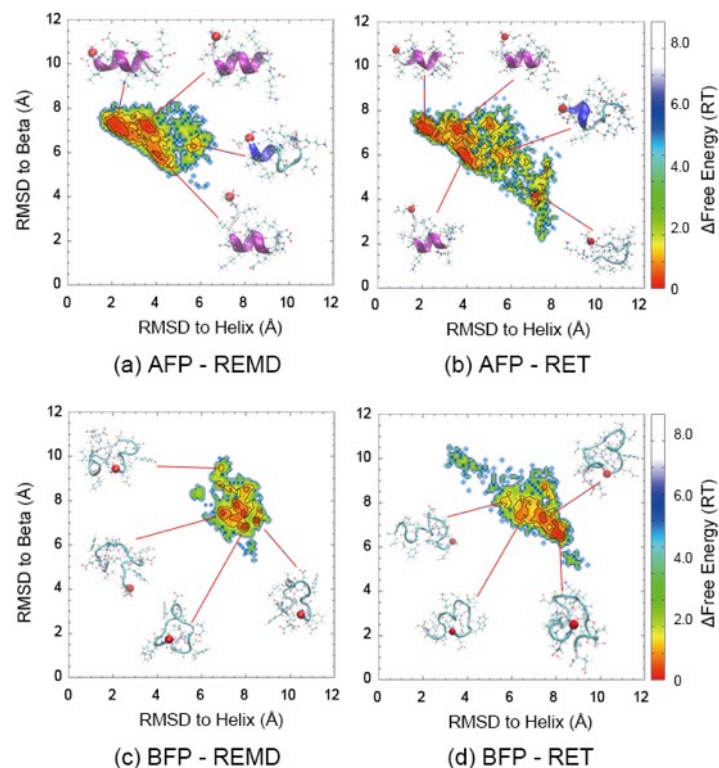
Go Model feeding does not lead to Bias

N.A. Bernhardt, W. Xi, W. Wang and U.H.E. Hansmann, JCTC 12 (2016) 5656.

- RET simulations were compared to REMD simulations

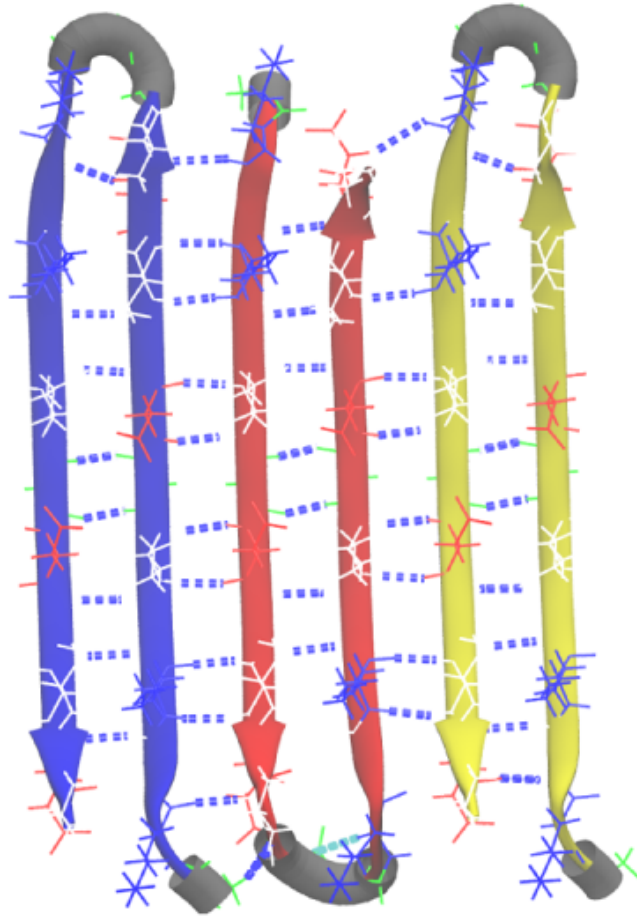
AFP		
	% Helix	% Hairpin
RET	42	0
REMD	53	0
Experiment	51	0

BFP		
	% Helix	% Hairpin
RET	0	48
REMD	0	38
Experiment	0	42

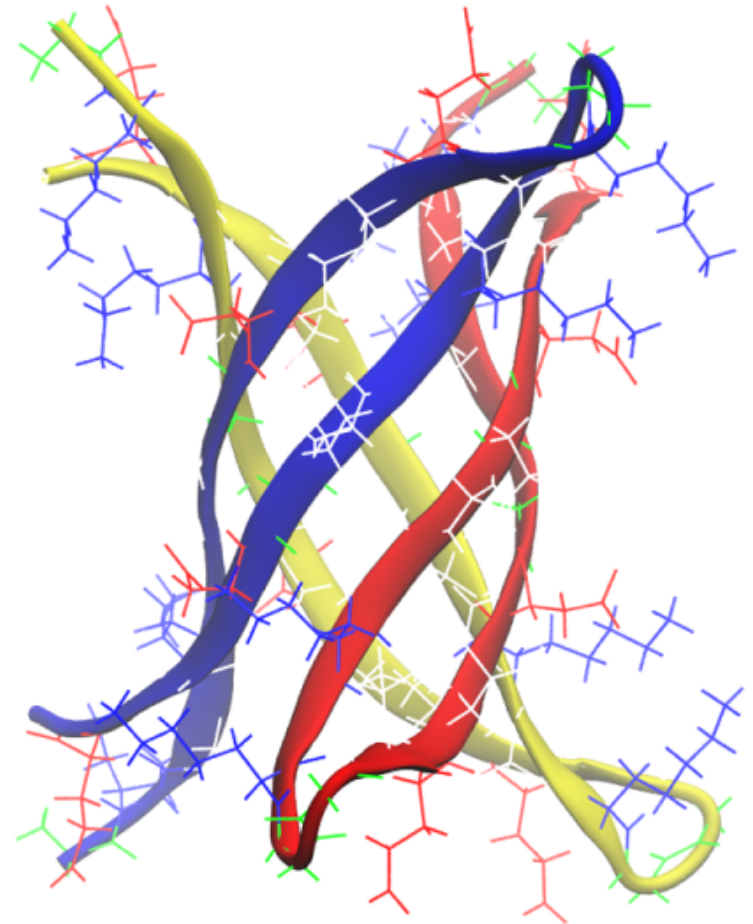


Cylindrin as Model System

(a) fibril

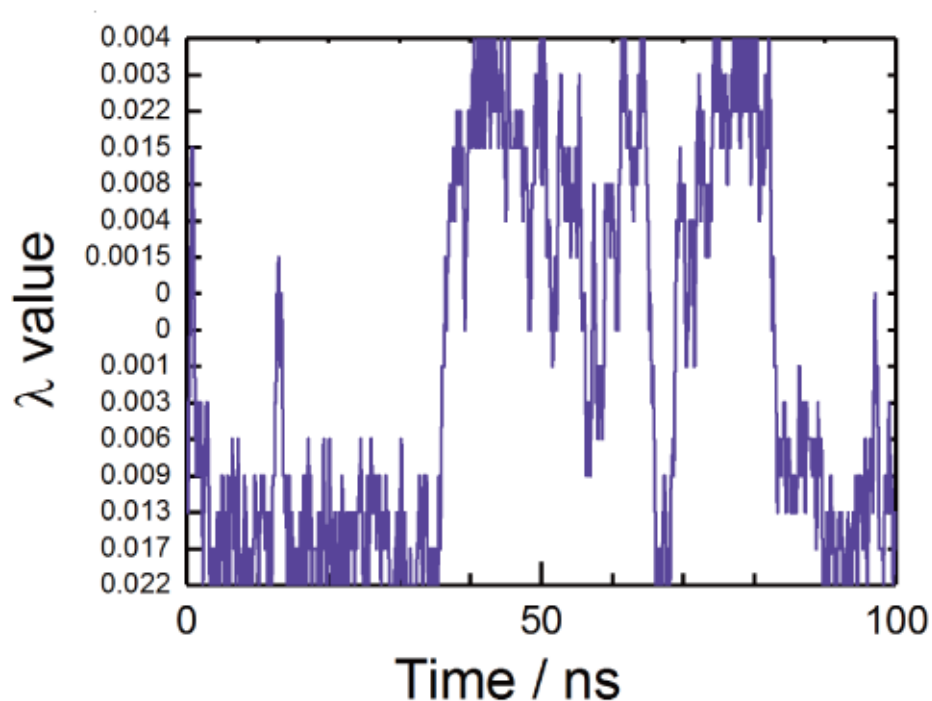


(b) barrel

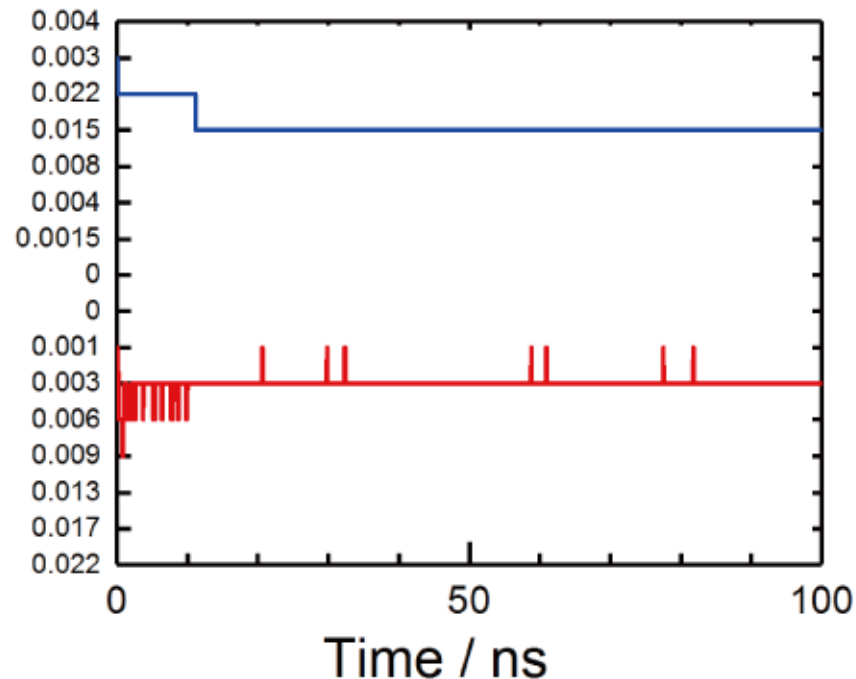


Walk in λ -Space

H. Zhang, W. Xi, U.H.E. Hansmann and Y. Wei, JCTC, 13 (2017) 3936



RET

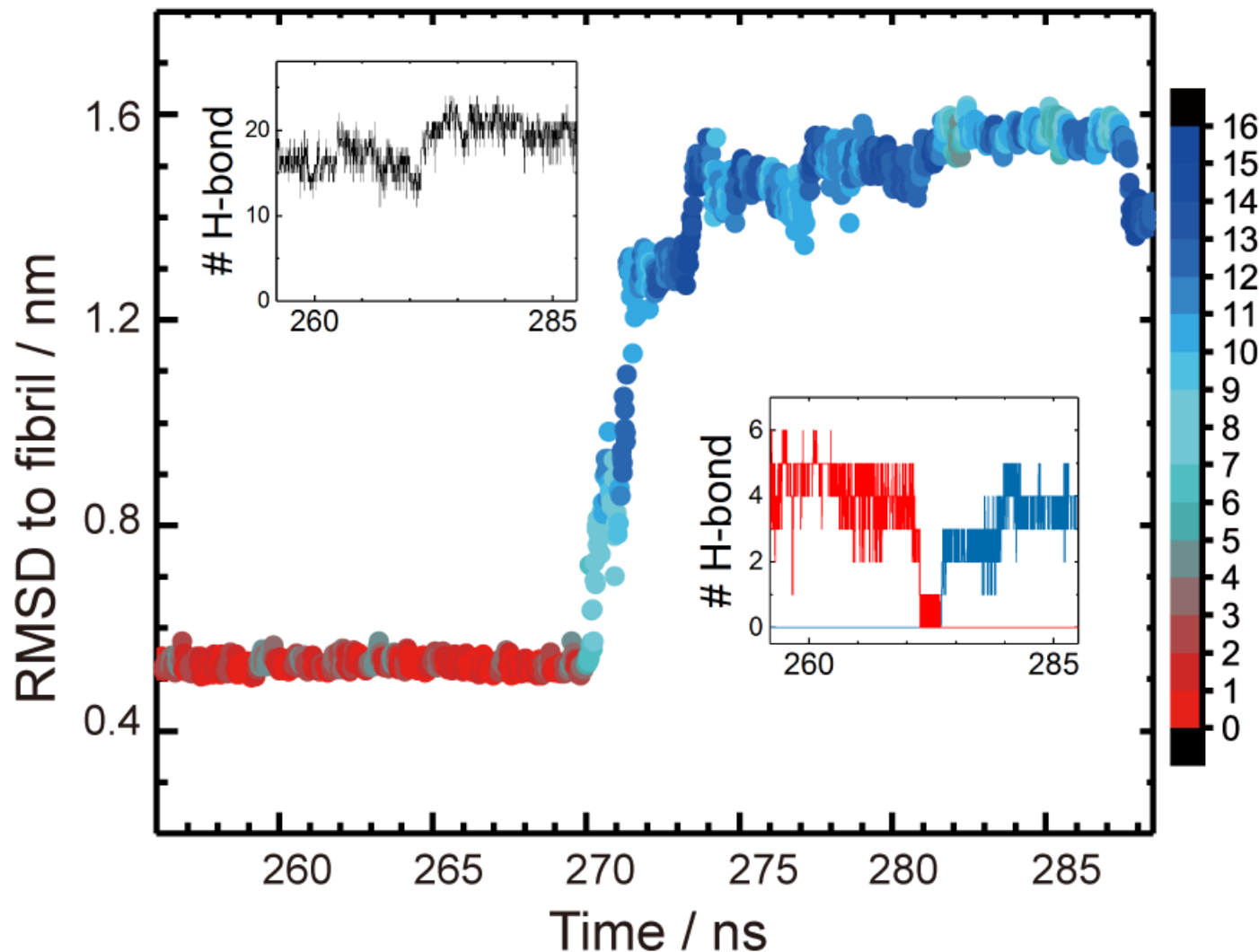


Regular H-REX



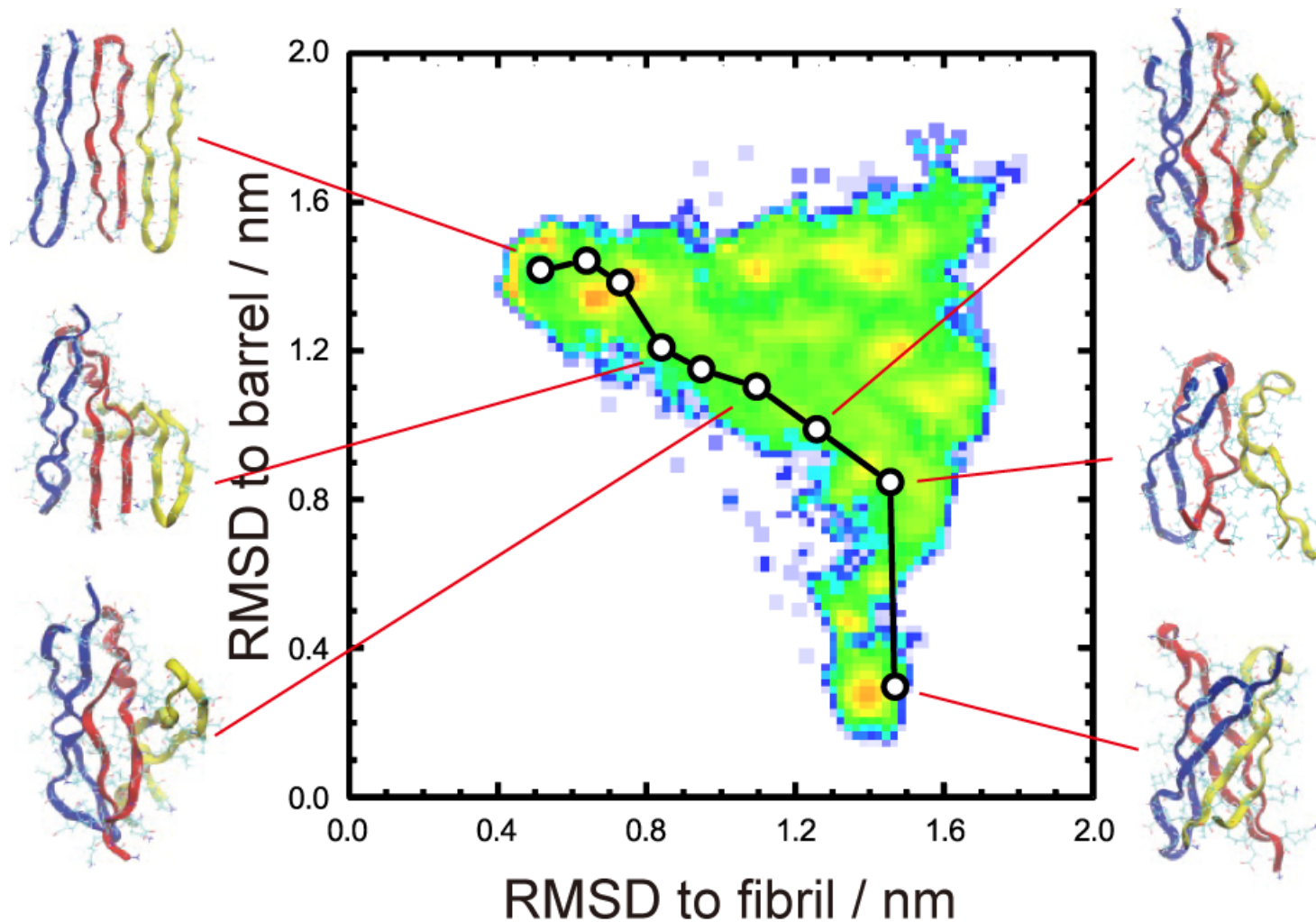
Walk in λ -Space

H. Zhang, W. Xi, U.H.E. Hansmann and Y. Wei, JCTC, 13 (2017) 3936



Free Energy Landscape

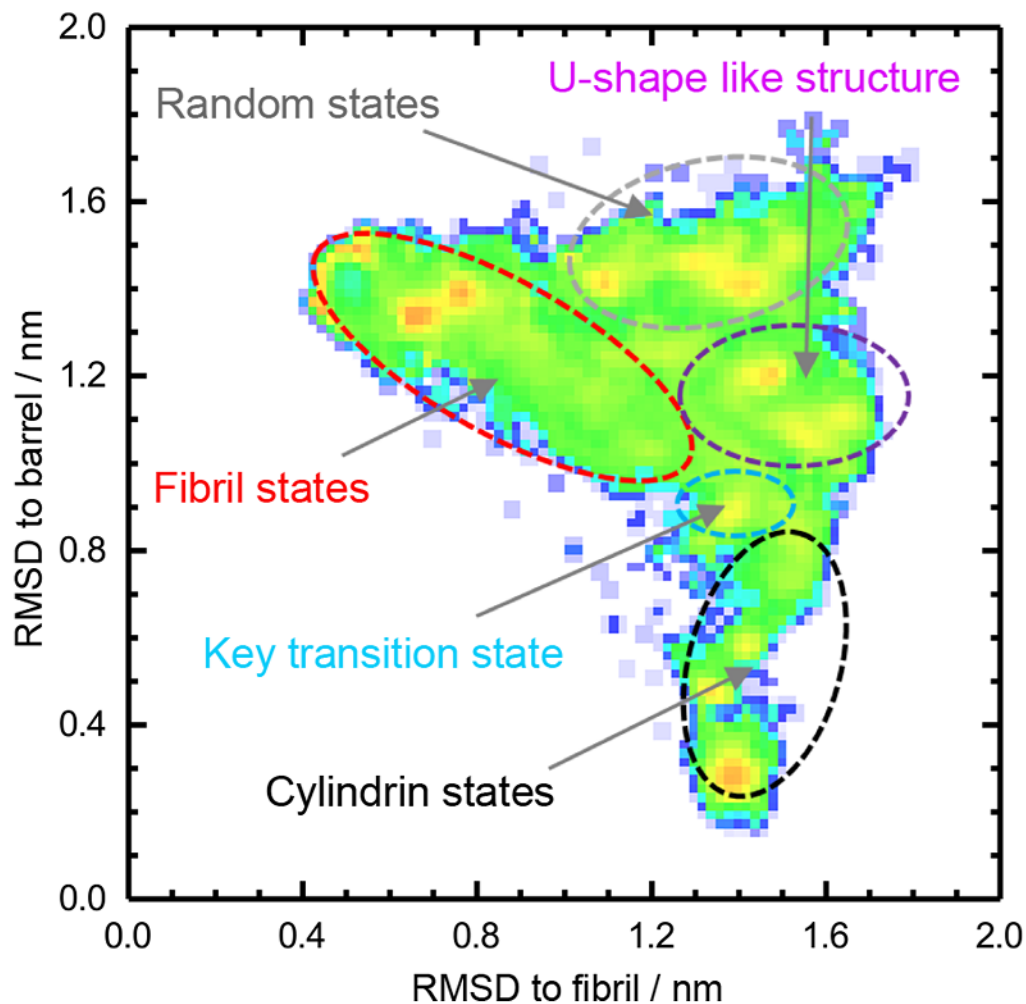
H. Zhang, W. Xi, U.H.E. Hansmann and Y. Wei, JCTC, 13 (2017) 3936



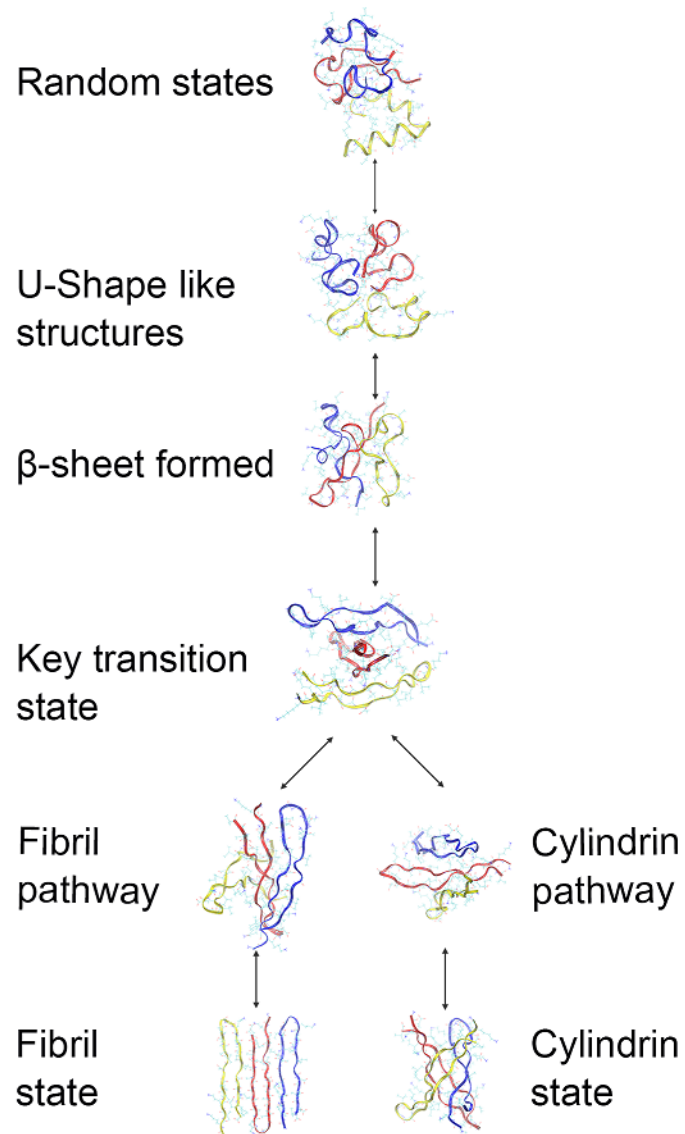
Conversion between fibril and barrel

H. Zhang, W. Xi, U.H.E. Hansmann and Y. Wei, JCTC, 13 (2017) 3936

(a)



(b)

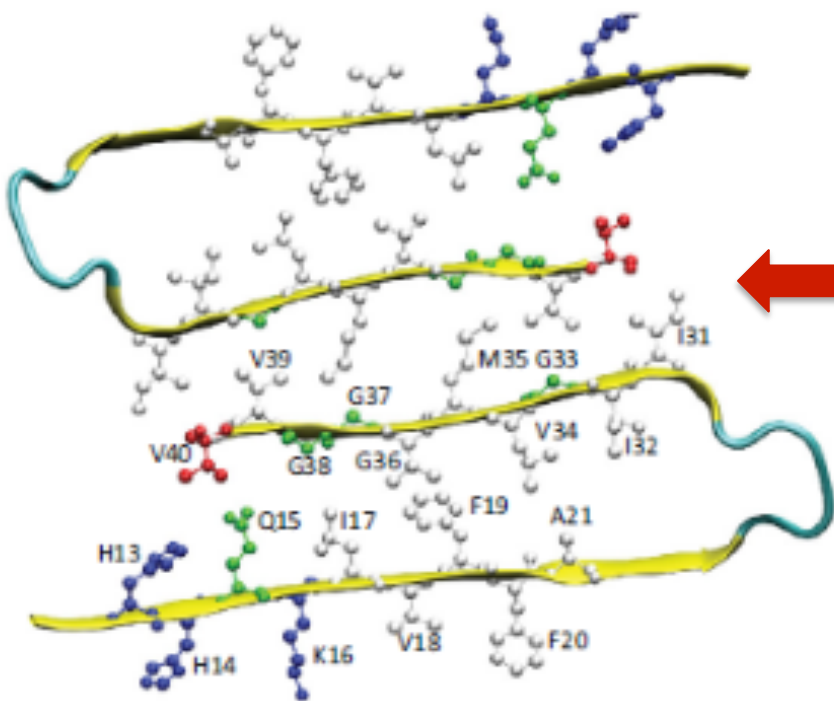


In vitro and patient-derived A β -fibrils

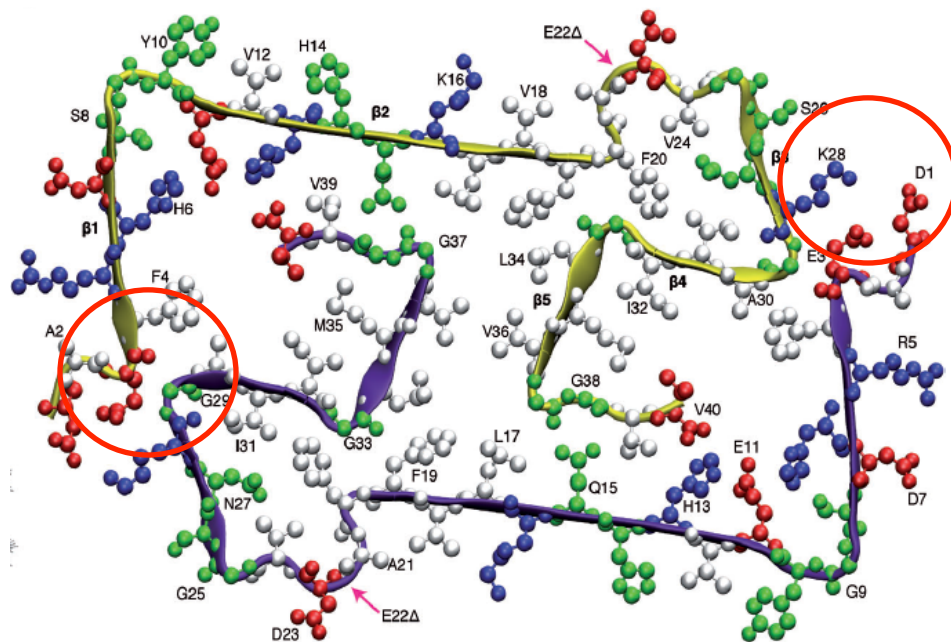
- *In vitro* generated A β -fibrils are polymorphic
- In patient-derived fibrils only **one** form found
J-X Lu et al., Cell **154** (2013) 1257
- This difference is **not** because of higher stability of patient-derived form!
E.J. Alred, E.G. Scheele, W.M. Berhanu & U.H., JCP, **141** (2014) 175101.
- Are some A β -fibril structures “infectious”?



Comparison of the two polymorphic forms of $A\beta$ wild-type and $A\beta_{1-40}$ E22 Δ



$A\beta_{1-40}$ WT



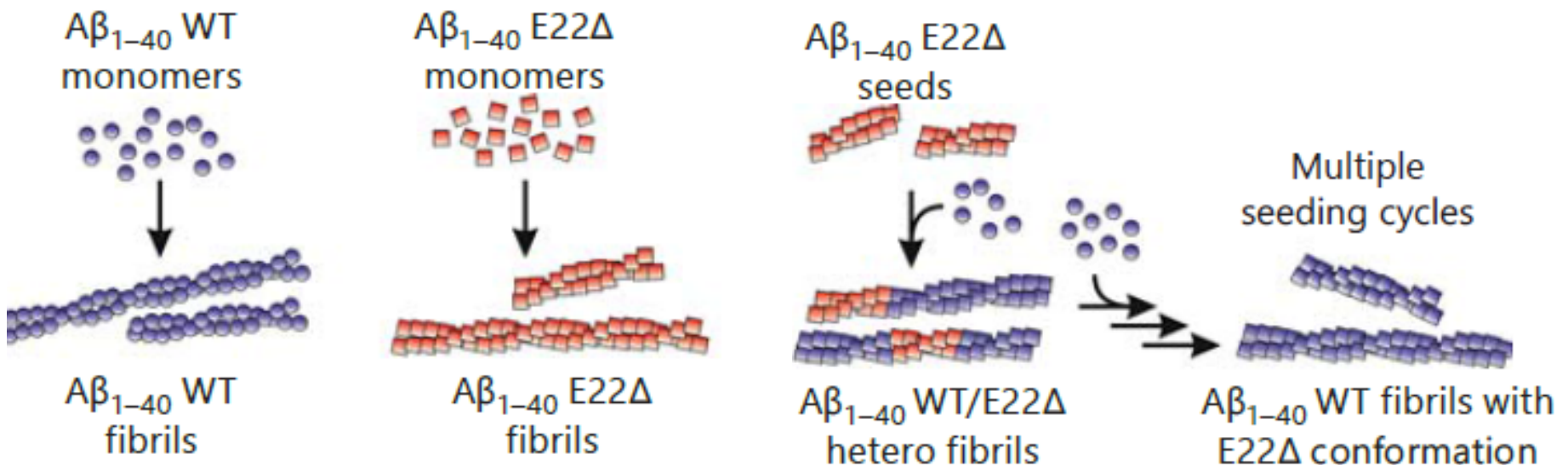
$A\beta_{1-40}$ E22 Δ

Angew. Chem. Int. Ed. **2015**, *54*, 331–335
J Am Chem Soc 2011, *133*:16013–16022



Cross-seeding and infectious strains

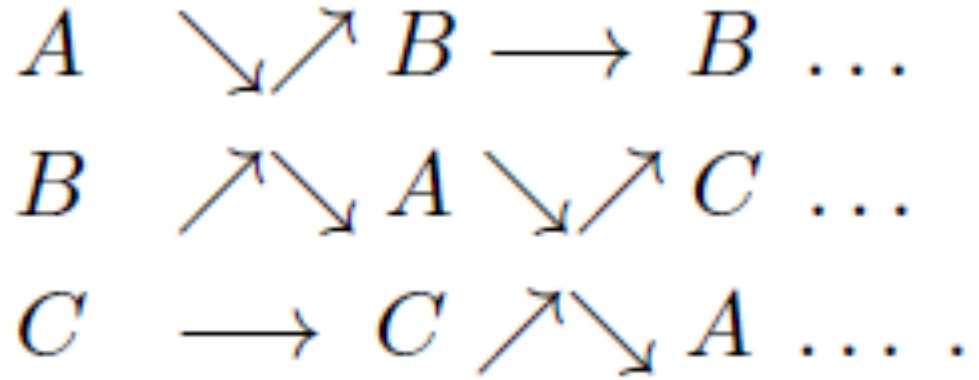
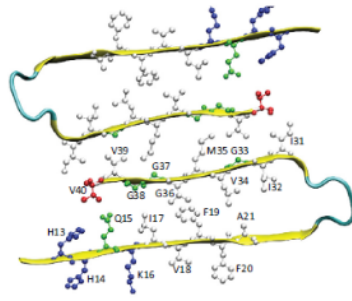
- $A\beta_{1-40}$ WT fibrils can be seeded with $A\beta_{1-40}$ E22 Δ nuclei
- But not $A\beta_{1-40}$ E22 Δ fibrils with $A\beta_{1-40}$ WT nuclei
- Polymorphism of $A\beta$ wild type
- $A\beta$ wild type can form “infectious” strains



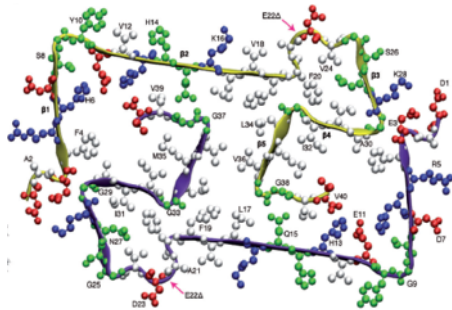
Neurodegener Dis 2014;14:151–159 ;Angew. Chem. Int. Ed. 2015, 54, 331 –335

Hybrid model simulation are used to study inter-conversion of two forms

Go - model

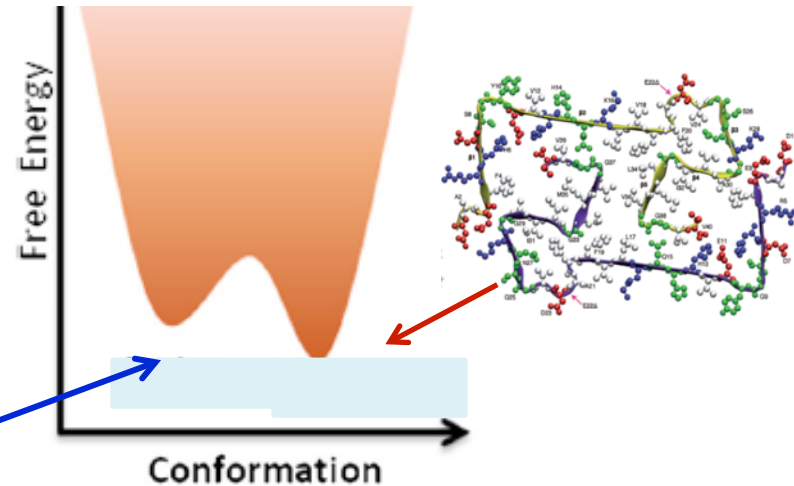
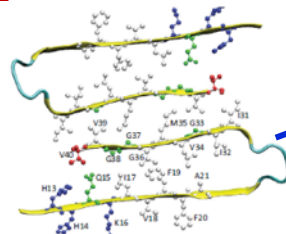


physical force field



Go - model

Free energy landscape as function ????



Co-worker:

-
- **Workalemahu Berhanu (OU)**
- **Wei Wang (OU)**
- **Wenhui Xi (OU)**

- **Erik Alred (OU)**
- **Nathan Bernhard (OU)**
- **Wenhua Wang (OU)**

- **Michael Nguyen (OU)**
- **Maggie Martin (OU)**
- **Elliott Vanderford (OU)**

- **Fatih Yasar (Hacettepe U)**
- **Yanjie Wei (SIAT)**

