Molecular Dynamics Observation of Aβ16–22 Peptide Aggregation

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Feb. 24, 2005 @ Clark University

Why Study Peptide/Protein Aggregation?

- To understand mechanisms of more than 20 neurodegenerative **diseases**, such as Alzheimer's disease (AD), Parkinson's disease, Prion diseases, Mad cow disease...
  - –Protein/peptide aggregates are toxic to neurons.

- AD is the most common one among these diseases.
  - –AD directly affects 4 million Americans.

Aβ peptide aggregation is linked to AD

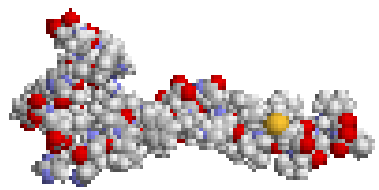
Aβ Peptides

- Aβ Peptides are short amino acid chains chopped from Amyloid β Precursor Protein (APP) in normal metabolism!

- Aβ 40 [42] peptides: ~140Å = 0.014 microns

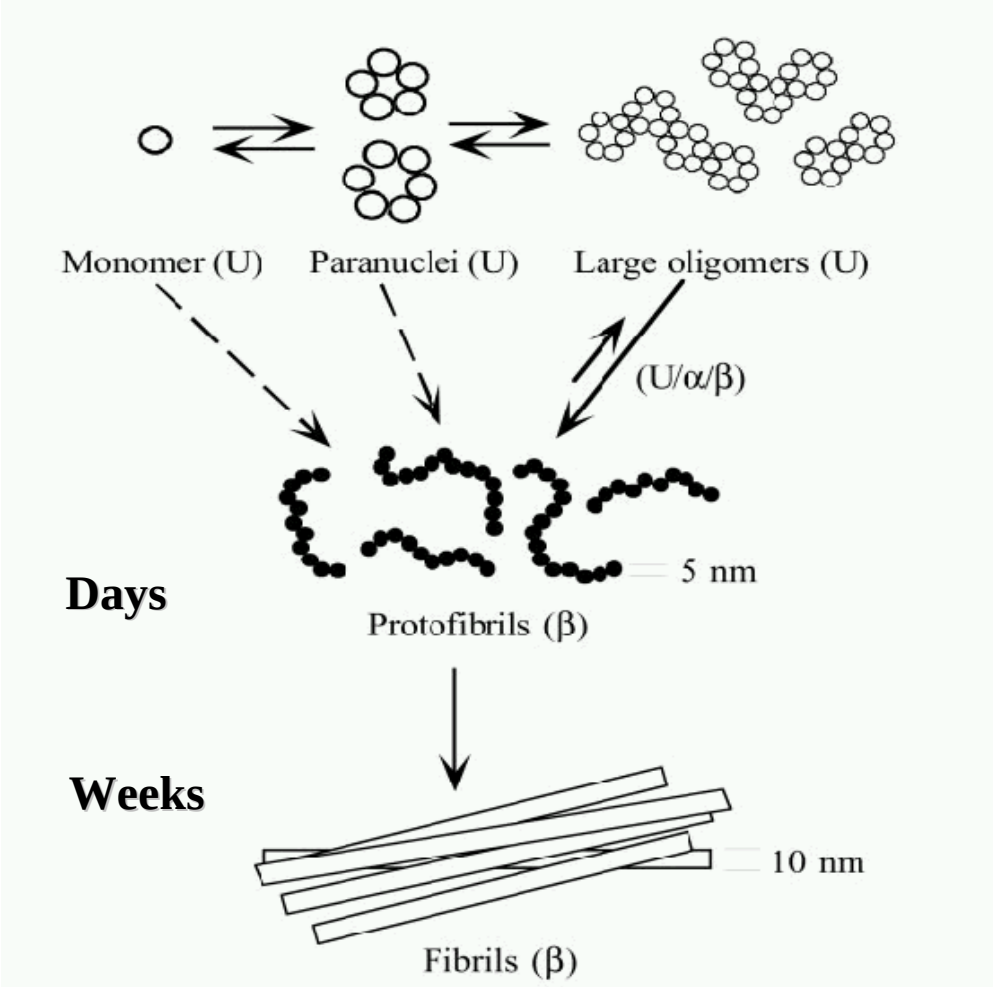
D$^-$AE$^-$FR$^+$HD$^-$SGYE$^-$VHHQK$^+$**LVFFAE**$^-$D$^-$VGSNK$^+$G**AII**G**LMV**GG**VV** [IA]

- 20 kinds of amino acids:
  - No side chain: G
  - Charged : D$^-$ E$^-$ R$^+$ K$^+$
  - Hydrophobic: **FLAM VIP**
  - Hydrophilic (Polar): STYHCNQW



Everybody has Aβ Peptides !

Beginning of AD & Shift in Research Focus



Oligomers are More Toxic!

- **Structure?**
- **Formation?**

Bitan et.al. PNAS 100:330-5, 2003

Difficulties for Experiments and Simulations

- Experiments:
  - Oligomers: Tiny (5~10nm) & Not Stable
    Not homogenous, No regular structures

- Simulations:
  - Traditional Molecular Dynamics simulation
    (all atoms, interactions taken into account)
    Simulate time-scale: ~ nanoseconds

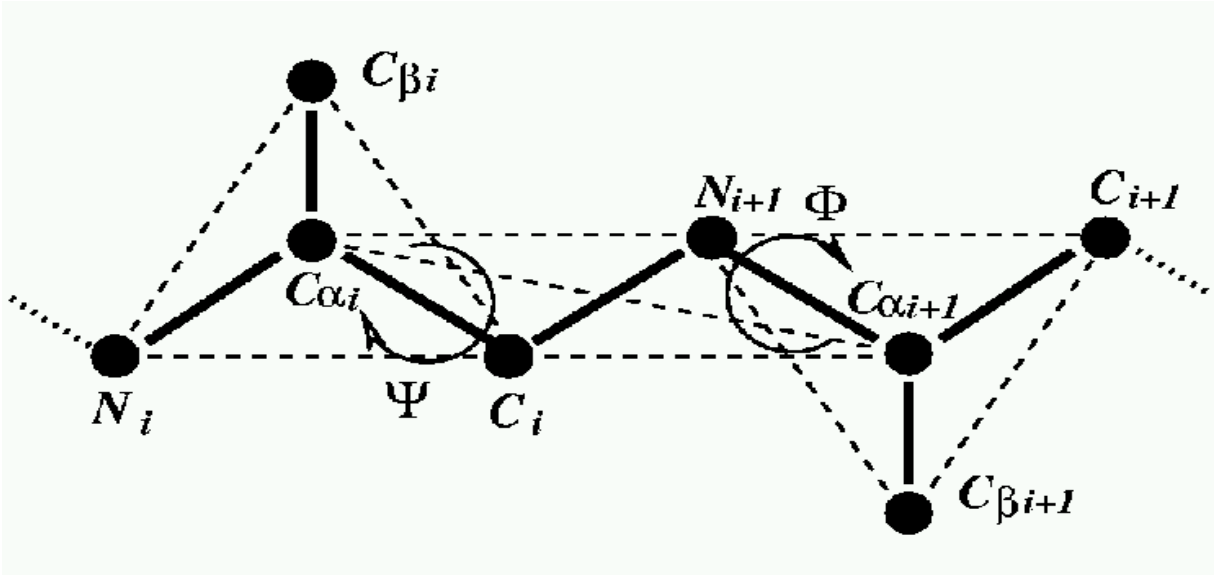
Need to Speed Up Simulations !

What do We do?

- Keep only essential part to speed up simulations:
  - Proteins are coarse-grained: 4-bead protein model
  - Interactions are simplified with potential wells

- Check whether simulations are able to show the fibril formation.
  - Search for interaction parameters with which the model peptides can aggregate into fibrils.
  - Check whether the fibrillar structures from simulations match the experimental results.

Coarse-grained 4-bead Protein Model



3 backbone beads

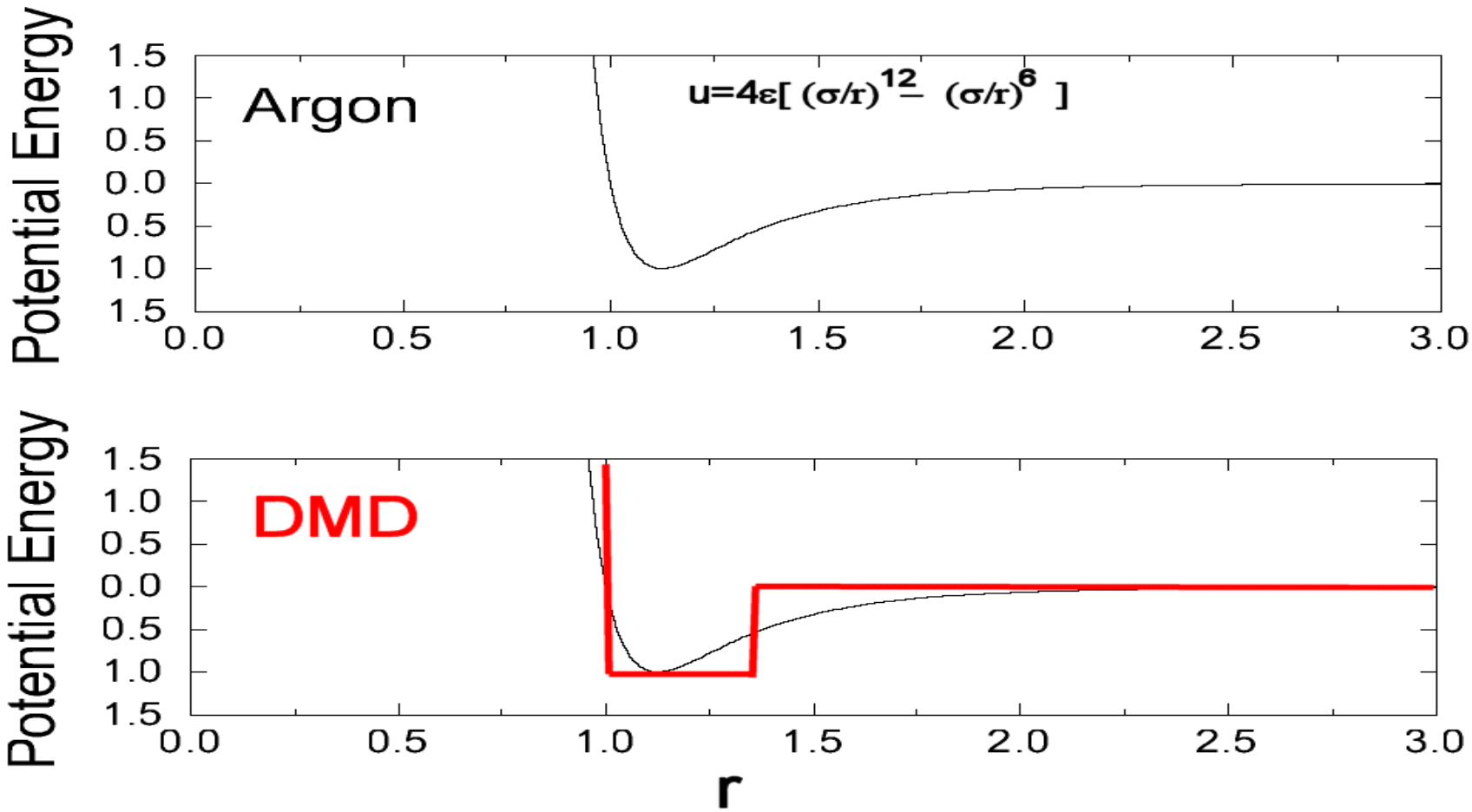
- To model the correct backbone geometry.

1 side chain bead except G

- To model the side chain.

Ding et. al. Proteins 53:220-8,2003

Interactions are Simplified with Potential Wells!



Discrete Molecular Dynamics (DMD) Algorithm can be applied

Typical Interactions in Protein

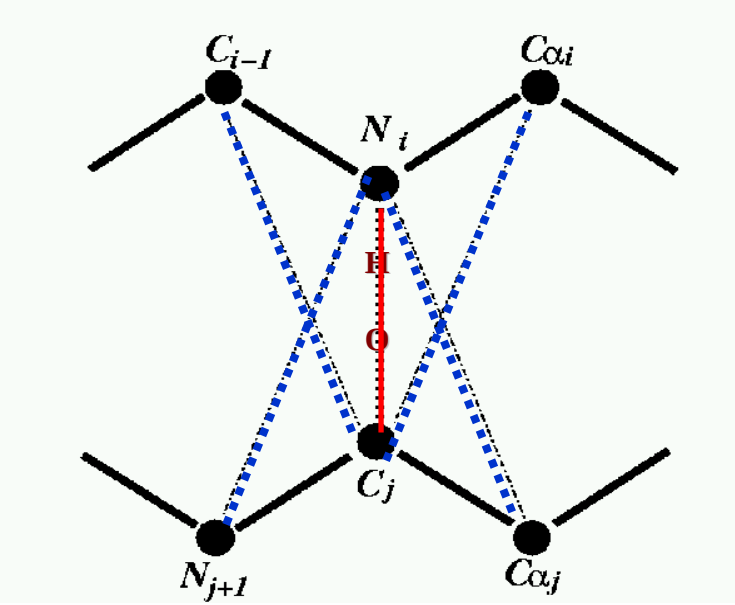
Hydrogen-bond (ε_{HB}): ~ 3-5 kcal/mol

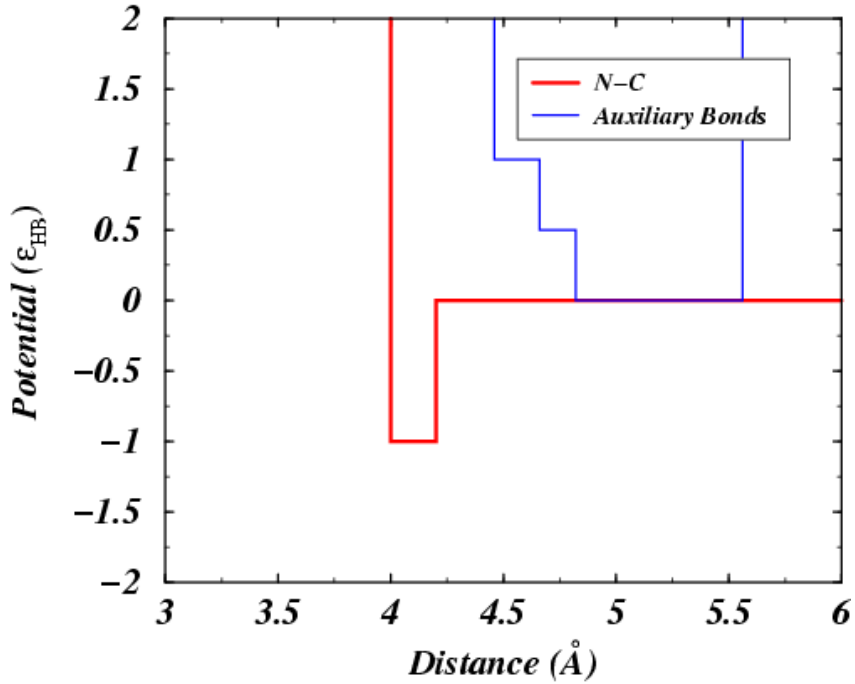
Hydrophobic (ε_{HP}): group property

Salt-bridge (ε_{SB}): ~ 4-7 kcal/mol

Room temperature ~ 0.6 kcal/mol

Modeling Orientation-Dependent Hydrogen Bond



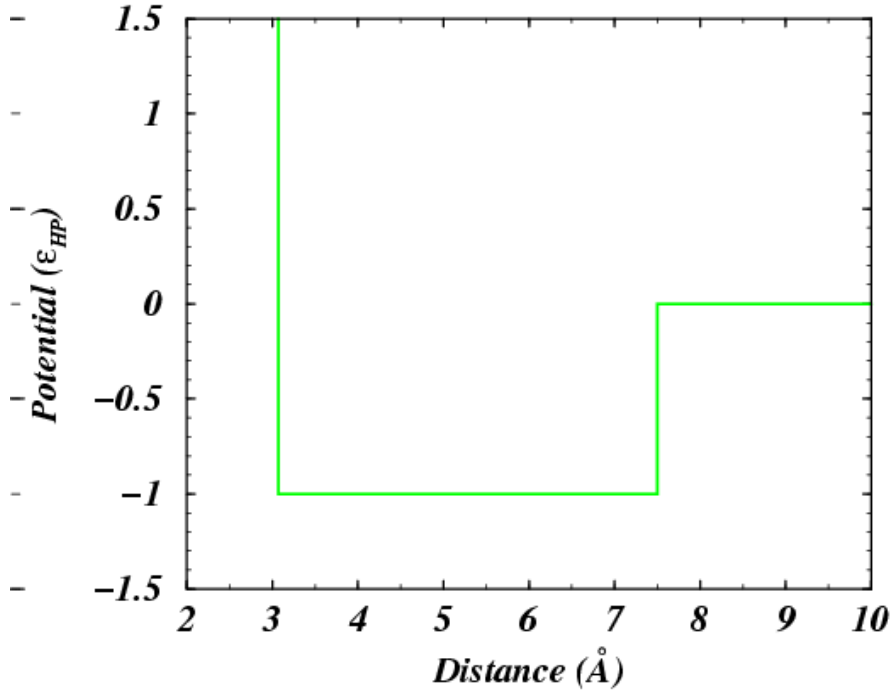


Whenever HB forms between N and C’,

4 auxiliary bonds are formed simultaneously to maintain its orientation.

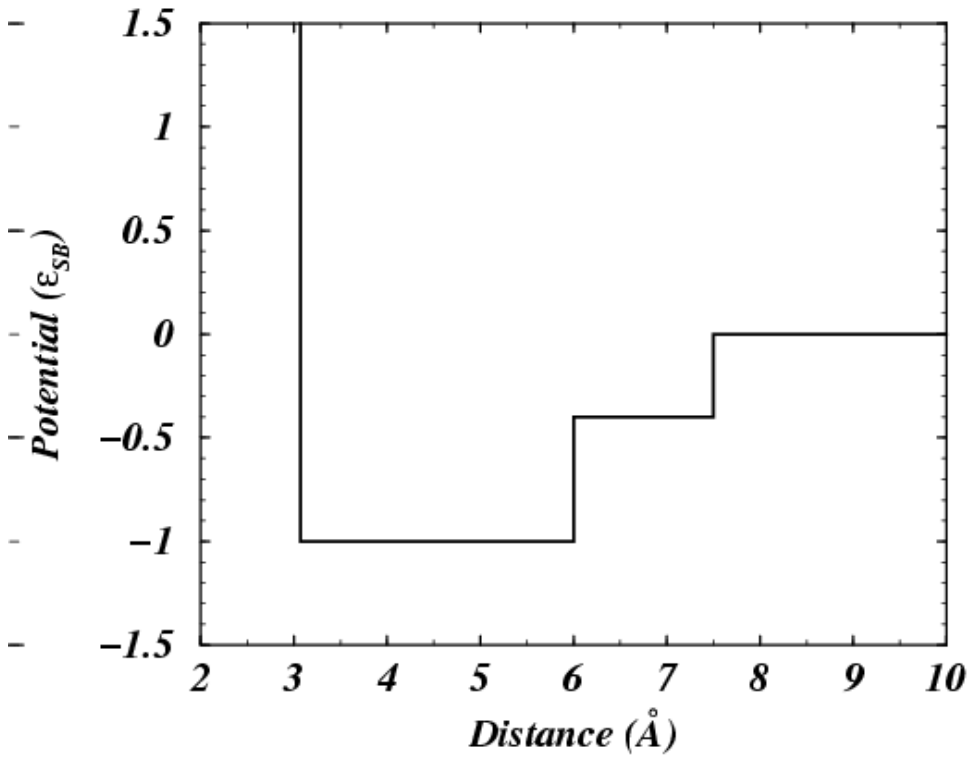
Ding et. al. Proteins 53:220-8,2003

Modeling Hydrophobic Interactions



Hydrophobic interactions are modeled between side chain beads of hydrophobic amino acids.

Modeling Salt-bridge Interactions



Salt-bridge interactions are modeled between side chain beads of charged amino acids.

DMD Simulations of Aggregation of $A\beta_{16\text{-}22}$ peptides

Why Choose Aβ16-22 Peptides ?

$K^{+}LVFFAE^{-}$

$D^{-}AE^{-}FR^{+}HD^{-}SGYE^{-}VHHQ\ K^{+}LVFFAE^{-}\ D^{-}VGSNK^{+}GAIIGLMVGGVV$ [IA]

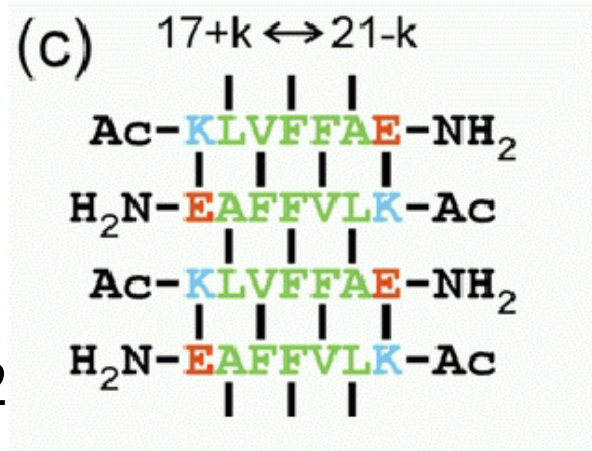
1. Contains Central Hydrophobic Cluster (CHC) L17-A21, which is essential for fibril formation of Aβ in reality.
2. Among the shortest fibril forming fragments of full-length Aβ reported to date
3. Experimental Fibrillar Structure

   (***Balbach et.al. Biochem, 39:13748-13759, 2000***)

   Anti-parallel in-register well-ordered

   (Petkova et.al. JMB 335:247-60, 2004)
4. Traditional MD simulation of 3 Aβ16-22

   (Klimov et al Structure 11: 295-307, 2003)



Interactions Parameters in Protein Model

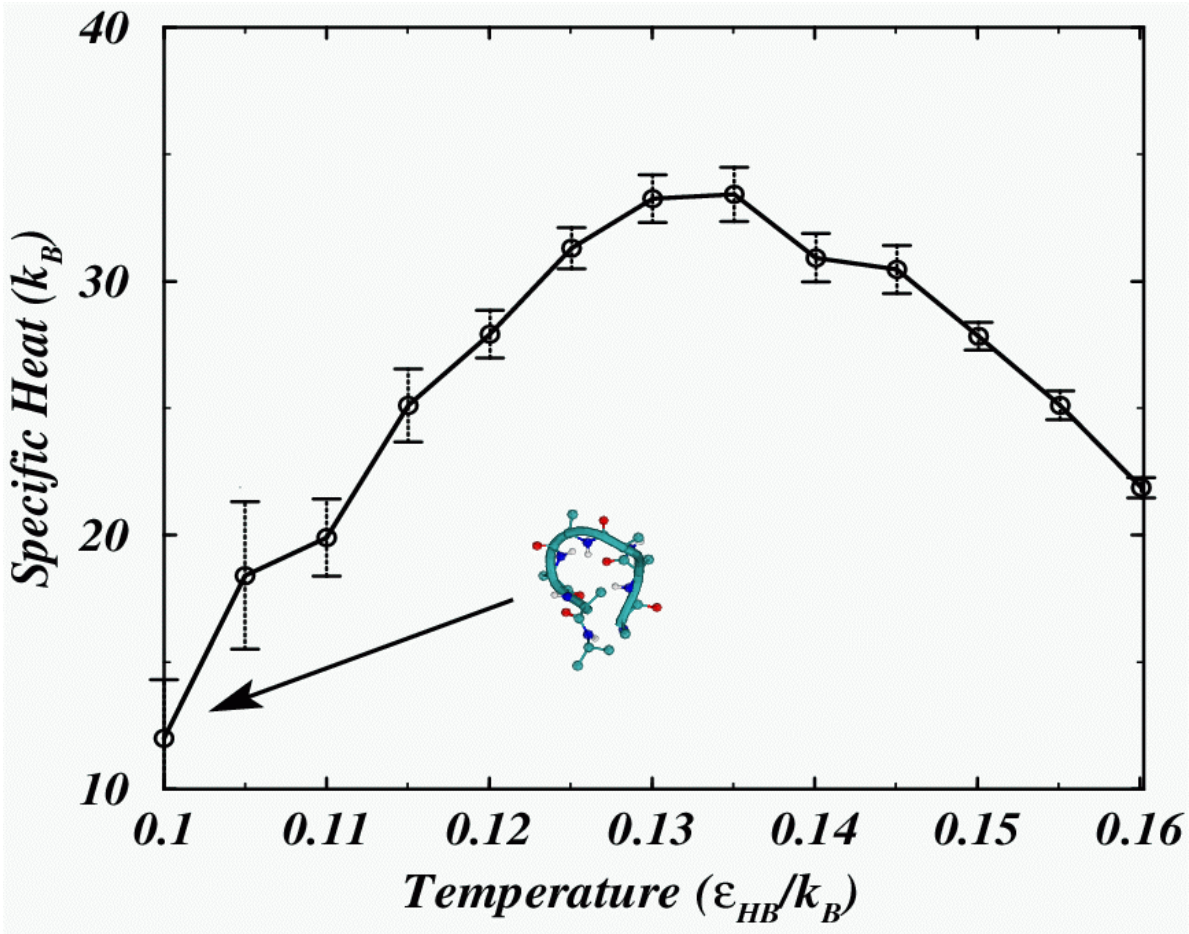
	Strength	Cutoff-Range (Å)
Hydrogen-bond (ε_{HB}):	1	Directional
Hydrophobic (ε_{HP}):	0.15	7.5
Salt-Bridge (ε_{SB}) :	1	7.5

If ε_{HB} =1 corresponds to 5 kcal/mol,

T_{room} =0.6 kcal/mol would be 0.12 in simulation

Aβ16-22 Peptide Monomer

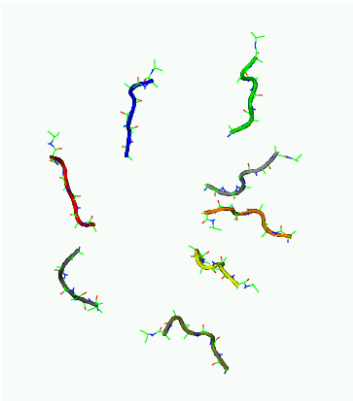
$K^{+}LVFFAE^{-}$



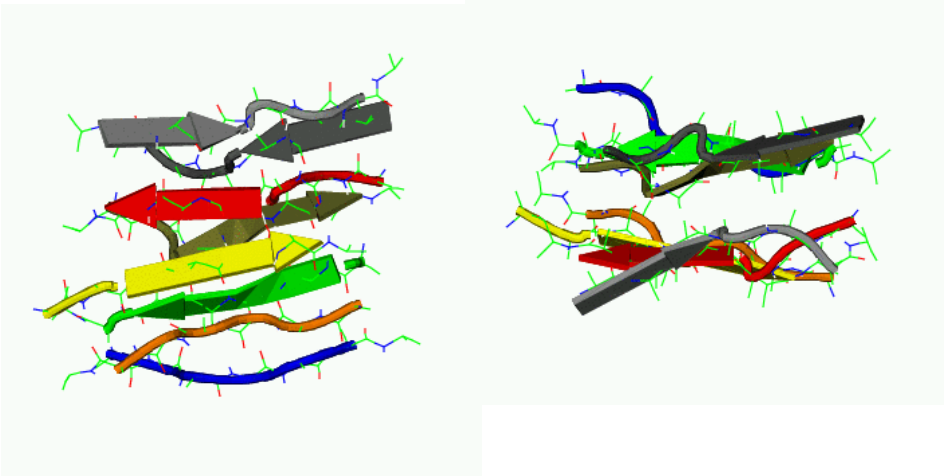
Simulation Result of 8 Aβ16-22 peptides @ T=0.145

$K^+LVFFAE^-$

Initial configuration



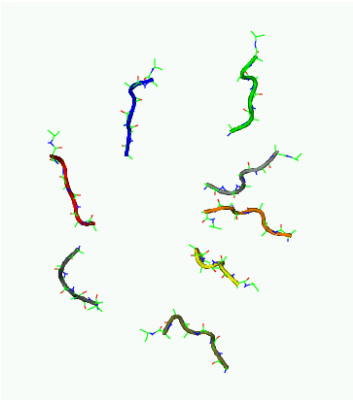
10 M time units



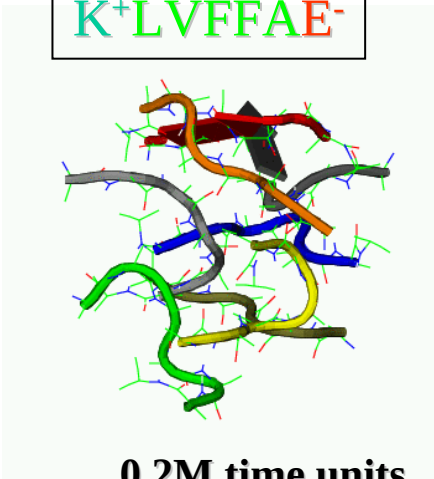
Backbone HB interactions → (Anti-)Parallel β-strands in β-sheets
Salt-bridge interactions → Preferring Anti-parallel well-ordered
Hydrophobic interactions → Packing sheets together

Simulation Result of 8 Aβ16-22 peptides @ T=0.13

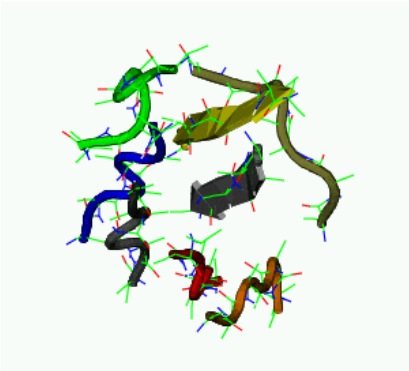
$K^+LVFFAE^-$



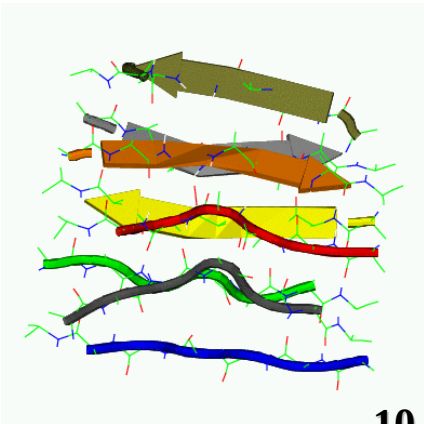
Initial configuration

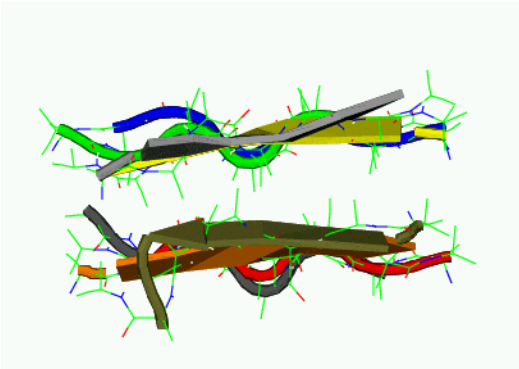


0.2M time units



2M time units

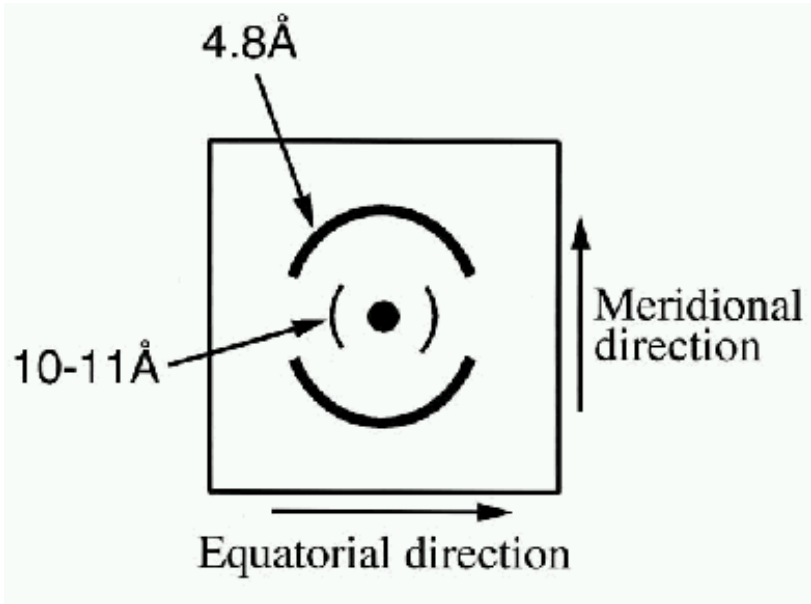




10 M time units

Hydrophobic Interactions help to bring Monomers together

Experiments: X-ray Fiber Diffraction

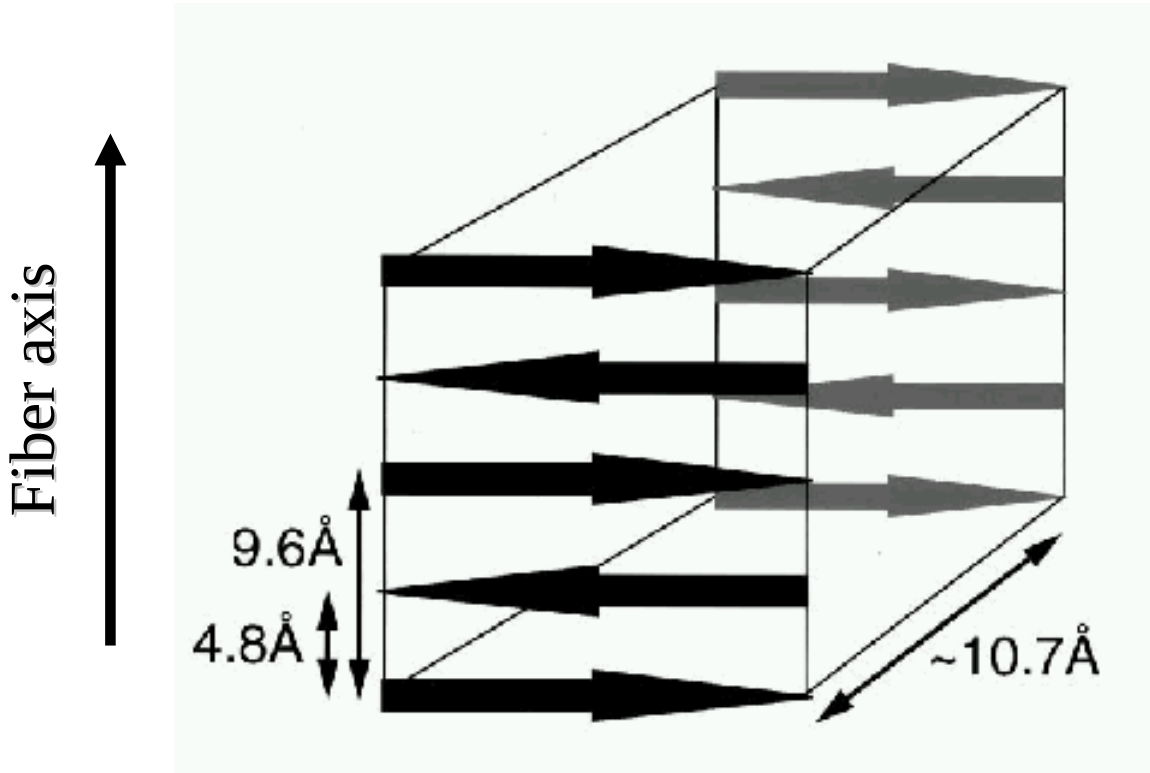


Common diffraction pattern suggests Common Core Structure !

Sunde et al, JMB 273: 729-739, 1997

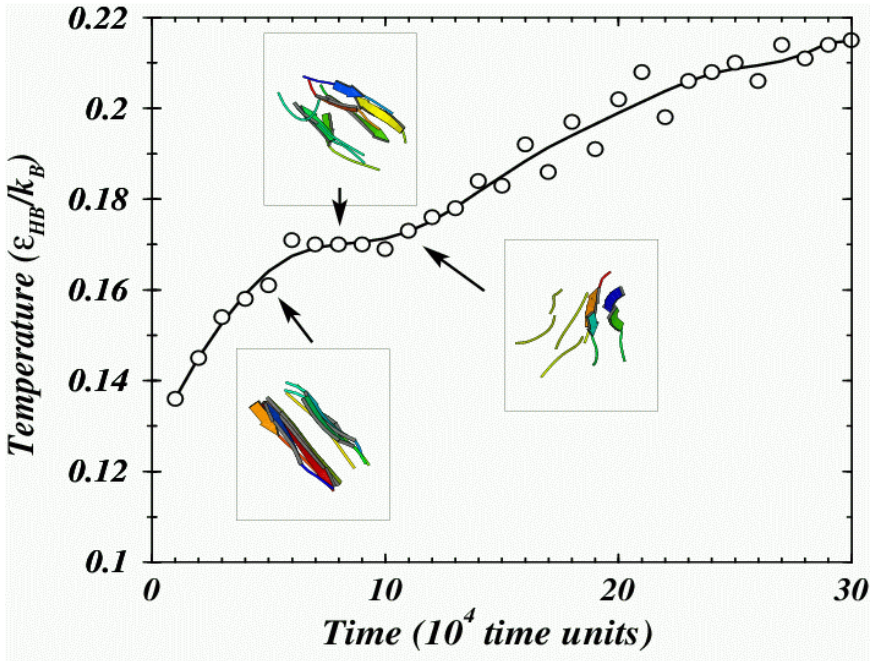
Serpell L.C. BBA 1502: 16-30, 2000

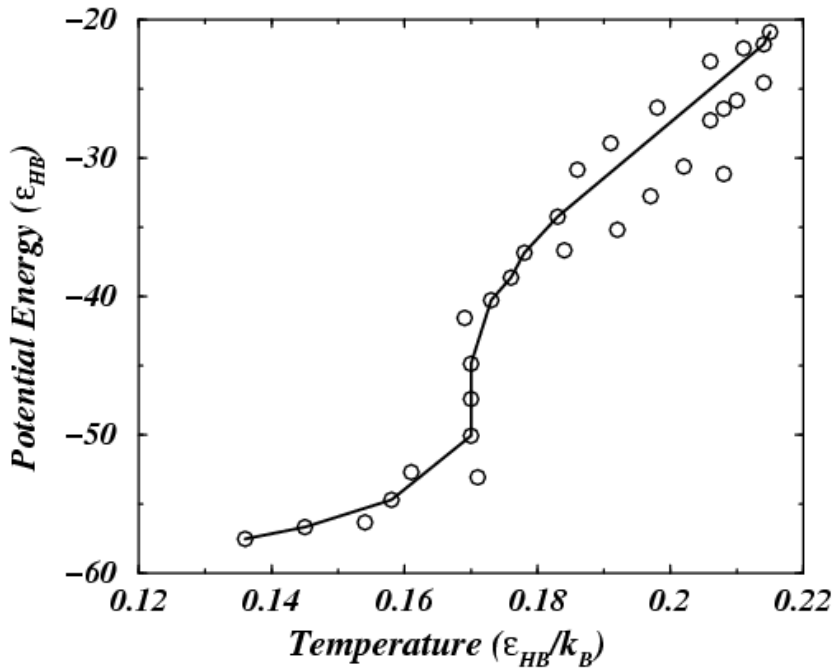
Cross-β Fibrillar Structure



Serpell L.C. BBA 1502: 16-30, 2000

Stability of Fibrillar Subunits from T=0.13



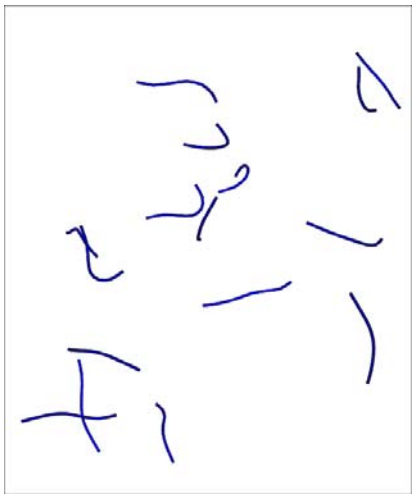


Fibrillar Subunits are stable up to T=0.17

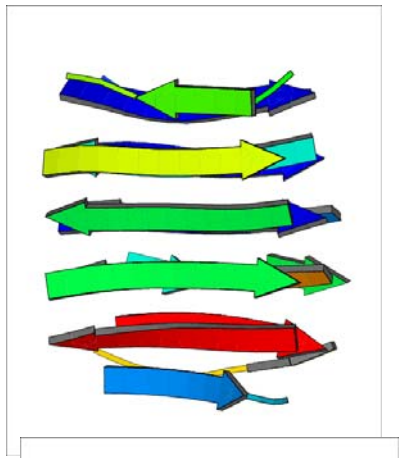
Simulation Result of 16 Aβ16-22 peptides @ T=0.155

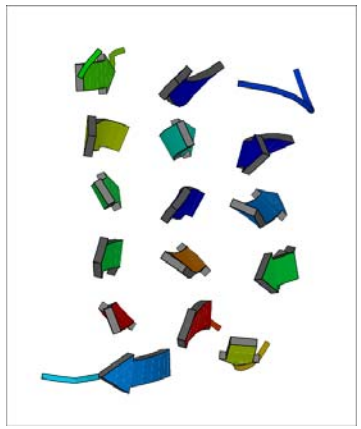
$K^+LVFFAE^-$

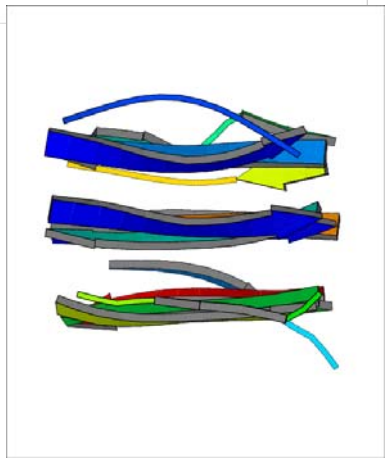
Initial configuration



4 M time units

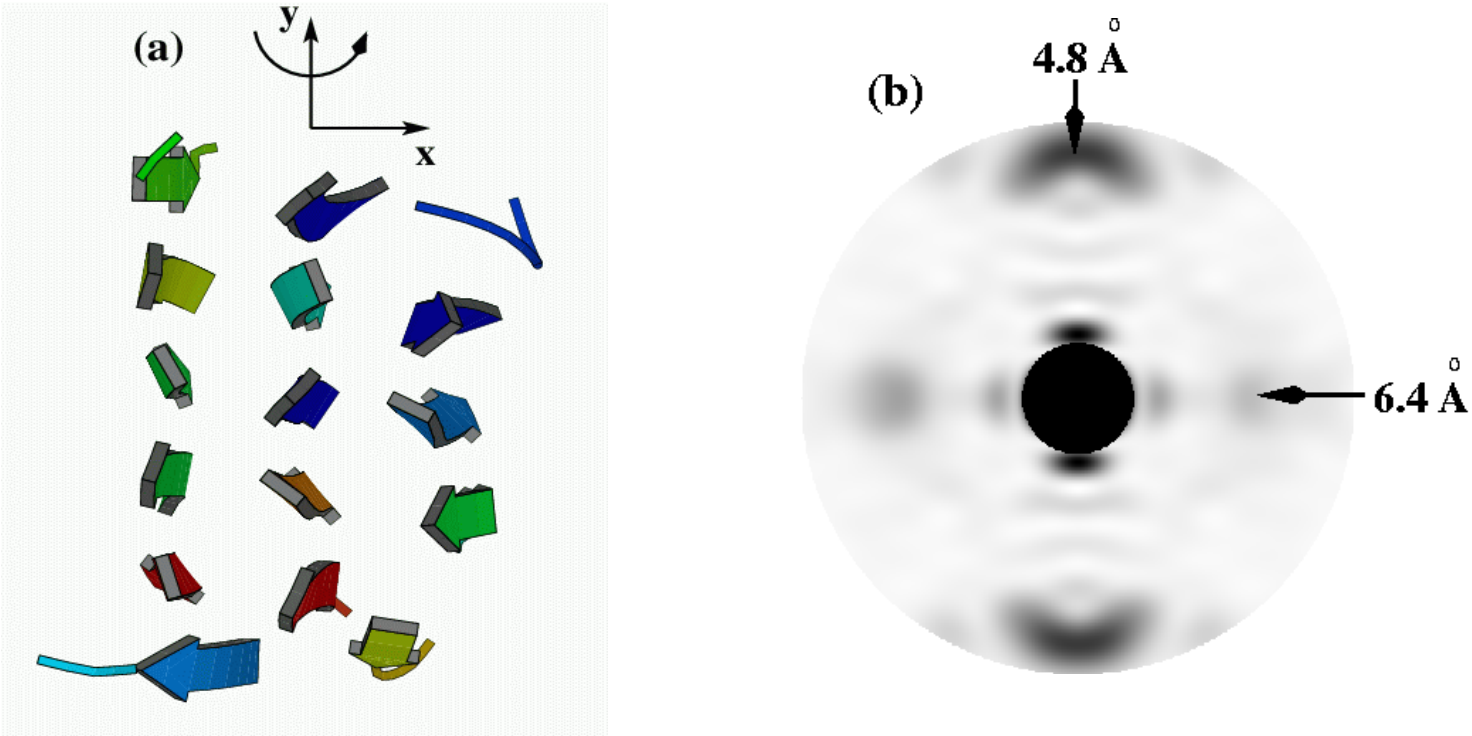






3-layered

Computed Diffraction Pattern



Conclusion

- DMD simulations (with coarse-grained protein model and simplified interaction potentials) show the process of aggregation from monomers to fibrils.

- The fibrillar structure agrees (qualitatively) with experimental results.

- Further study of intermediate states would be able to shed light on structure and assembly mechanisms of oligomers.

Acknowledgements

Advisor: H. Eugene Stanley

Collaborators

Brigita Urbanc
Luis Cruz
Sijung Yun

Nikolay Dokholyan (UNC)
Feng Ding (UNC)

Sergey V. Buldyrev (Yeshiva U., NY)

David T. Teplow (UCLA)

Thank you for your attention !