Molecular Dynamics Observation of $\text{A}\beta_{16-22}$ Peptide Aggregation

Shouyong Peng

Physics Department, Boston University

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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: \(~140\text{Å} = 0.014\text{ microns}\)

\[
\text{D-AE-FR^+HD-SGYE-VHHQK}^+\text{LVFFAE-D-VGSNK}^+\text{GAIIGLMVGGVV} [\text{IA}]
\]

- 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: \( \sim \) 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!

![Potential Energy Graph](image)

\[ u = 4\varepsilon\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^6 \]

Discrete Molecular Dynamics (DMD) Algorithm can be applied
Typical Interactions in Protein

Hydrogen-bond ($\mathcal{E}_{\text{HB}}$): $\sim 3-5$ kcal/mol

Hydrophobic ($\mathcal{E}_{\text{HP}}$): group property

Salt-bridge ($\mathcal{E}_{\text{SB}}$): $\sim 4-7$ kcal/mol

Room temperature $\sim 0.6$ kcal/mol
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*
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 $\text{A}\beta_{16-22}$ peptides
Why Choose Aβ16-22 Peptides?

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
# Interactions Parameters in Protein Model

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Strength</th>
<th>Cutoff-Range (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen-bond ($\varepsilon_{HB}$)</td>
<td>1</td>
<td>Directional</td>
</tr>
<tr>
<td>Hydrophobic</td>
<td>$0.15$</td>
<td>7.5</td>
</tr>
<tr>
<td>Salt-Bridge</td>
<td>1</td>
<td>7.5</td>
</tr>
</tbody>
</table>

If $\varepsilon_{HB} = 1$ corresponds to 5 kcal/mol, $T_{room} = 0.6$ kcal/mol would be 0.12 in simulation.
Aβ16-22 Peptide Monomer

K$^+$LVFFAE$^-$

![Graph showing specific heat versus temperature](image)
Simulation Result of 8 Aβ16-22 peptides @ T=0.145

Initial configuration

10 M time units

Backbone HB interactions $\Rightarrow$ (Anti-)Parallel $\beta$-strands in $\beta$-sheets
Salt-bridge interactions $\Rightarrow$ Preferring Anti-parallel well-ordered
Hydrophobic interactions $\Rightarrow$ Packing sheets together

K$^+$LVFFAE$^-$
Simulation Result of 8 Aβ16-22 peptides @ T=0.13

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

Initial configuration

4 M time units

K⁺LVFFAE⁻

3-layered
Computed Diffraction Pattern

(a) y

(b) 4.8 Å

6.4 Å
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.
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Thank you for your attention !