In Silico Study of Amyloid β-protein (Aβ) Decapeptide Aβ(21-30)

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Aβ(21-30) Relevant to Alzheimer's Disease

Basic Background

• Experiments suggest Aβ(21-30) decapeptide may be the ***nucleating site*** for folding of full Aβ peptide.

• Aβ peptide is the ***building block*** of the fibrils observed in advanced-AD patients.

What is the Question?

• To determine the ***fold*** of Aβ(21-30) with atomic detail.

How does it help?

• The fold of Aβ(21-30) may provide plausible scenarios for the initial stages of fibril formation of full Aβ.

• Identification of amino acids important for folding.

What did we Find?

• Aβ(21-30) adopts a loop-like conformation with center in S26, stabilized by hydrophobic interactions between V24 and K28.

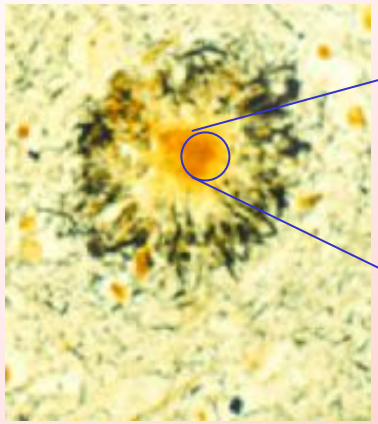
• There is a value for the strength of the electrostatic interaction that optimizes the stability of the loop.

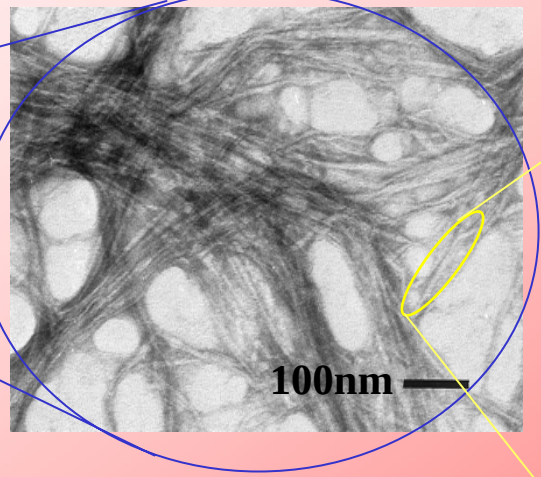
Aβ(21-30) and Alzheimer's Plaque

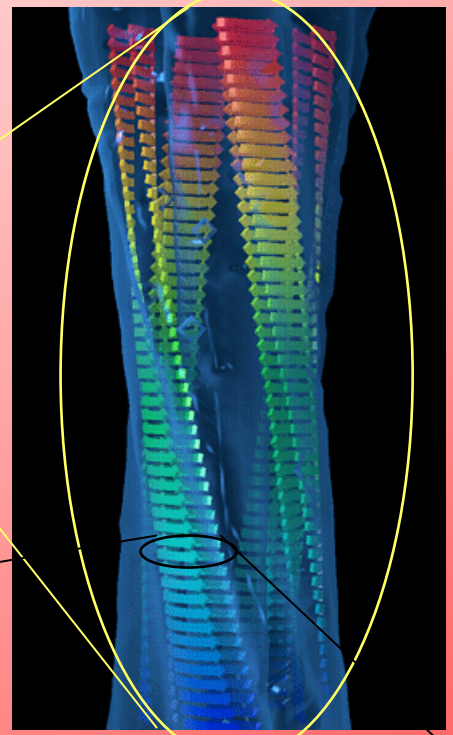
Plaque

Fibril Entanglement

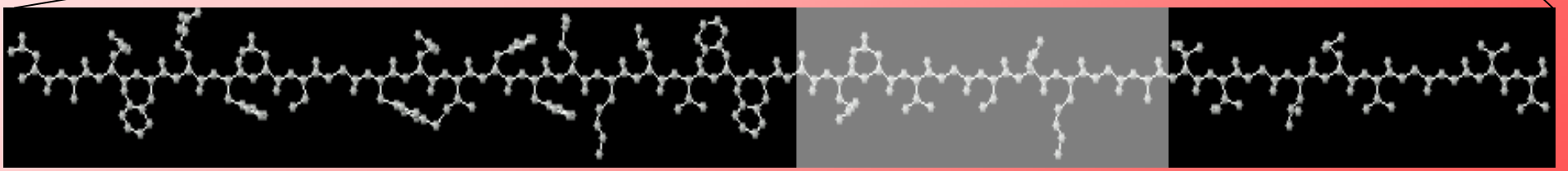
Fibril





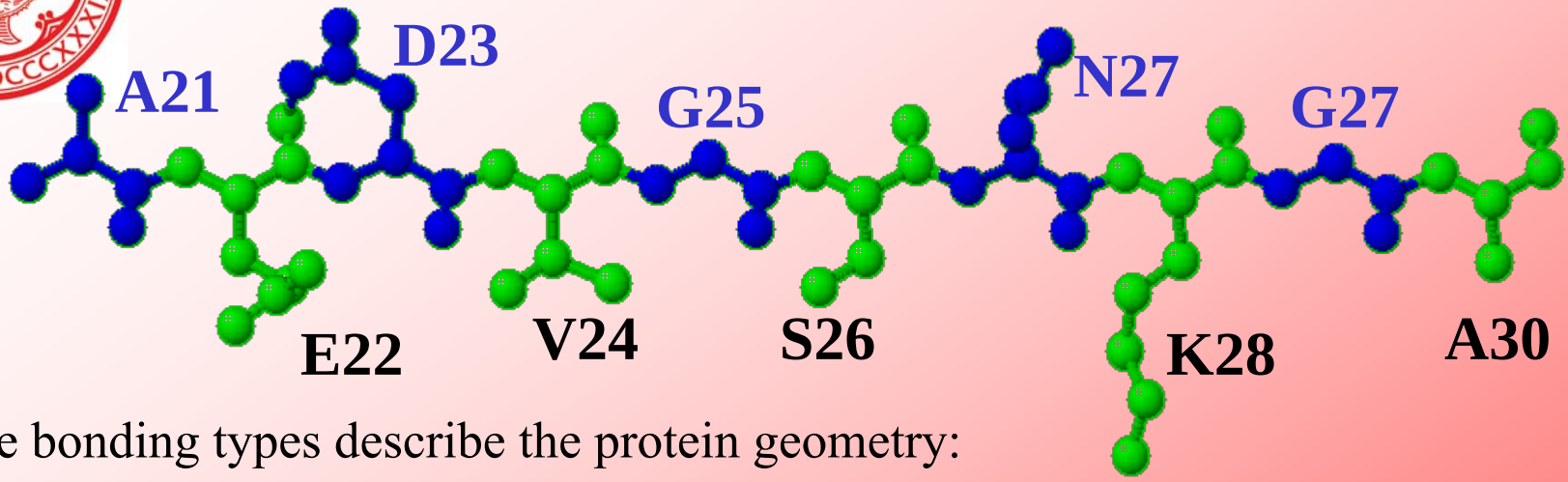


Aβ

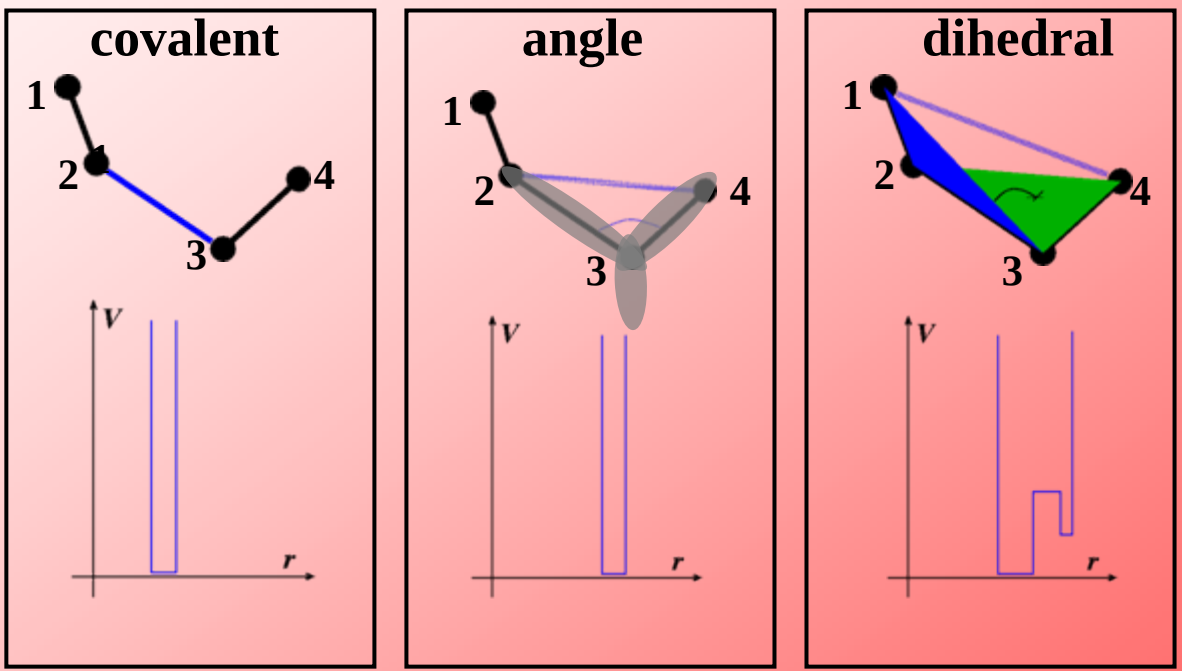


1 ---------- 21 ---------- 30 ---------- 40

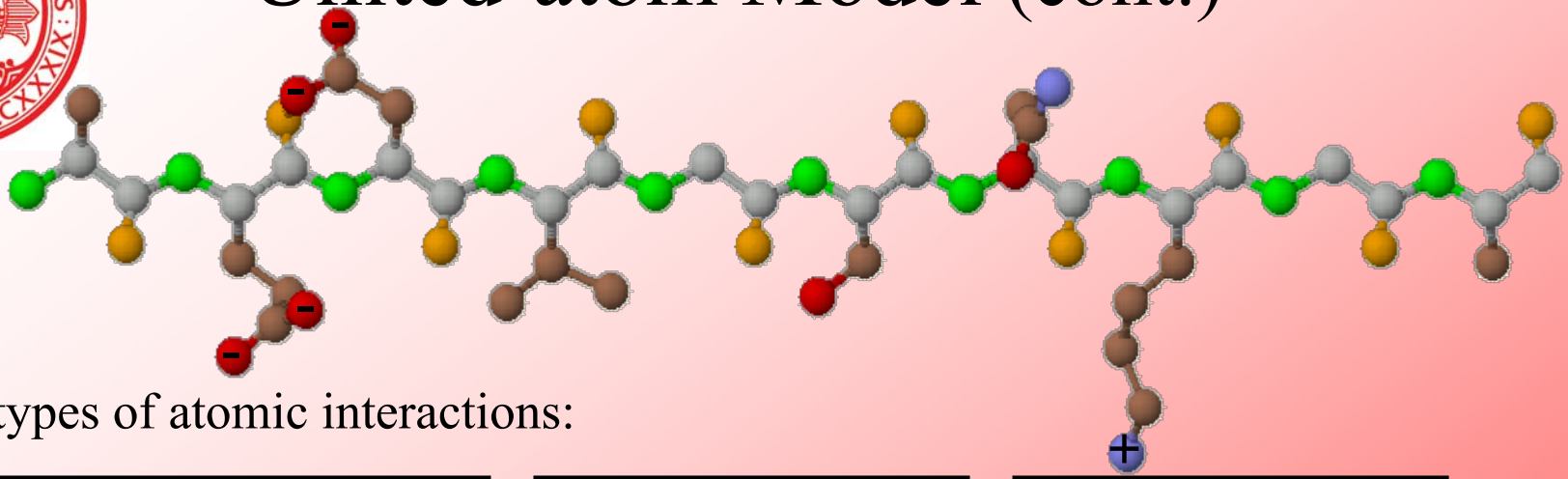
United-atom Model



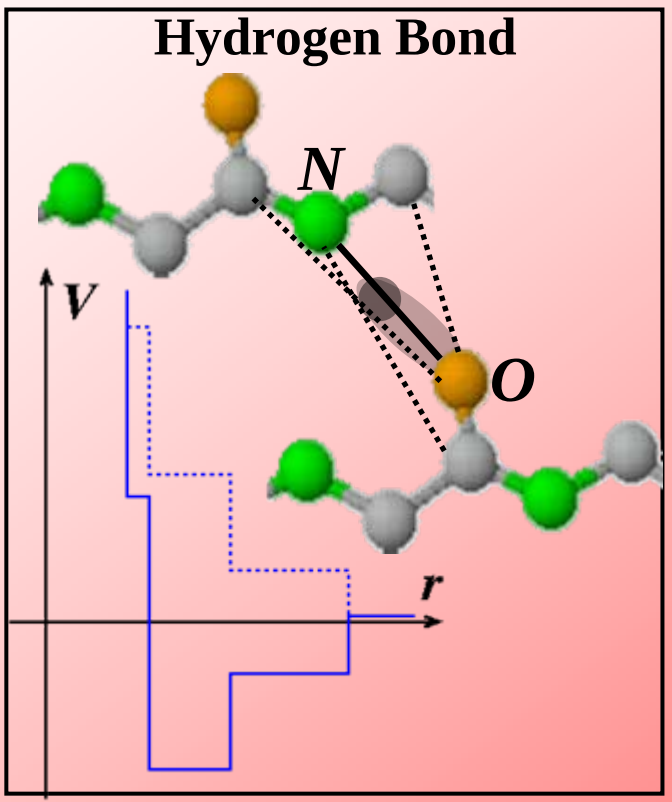
Three bonding types describe the protein geometry:

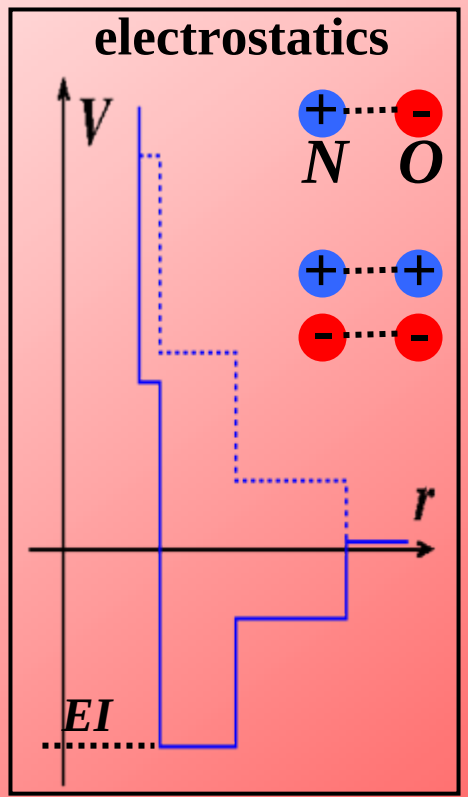


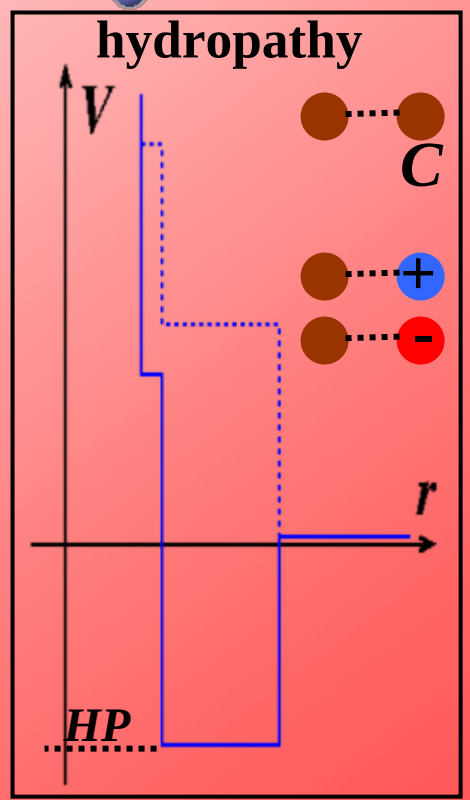
United-atom Model (cont.)



Three types of atomic interactions:





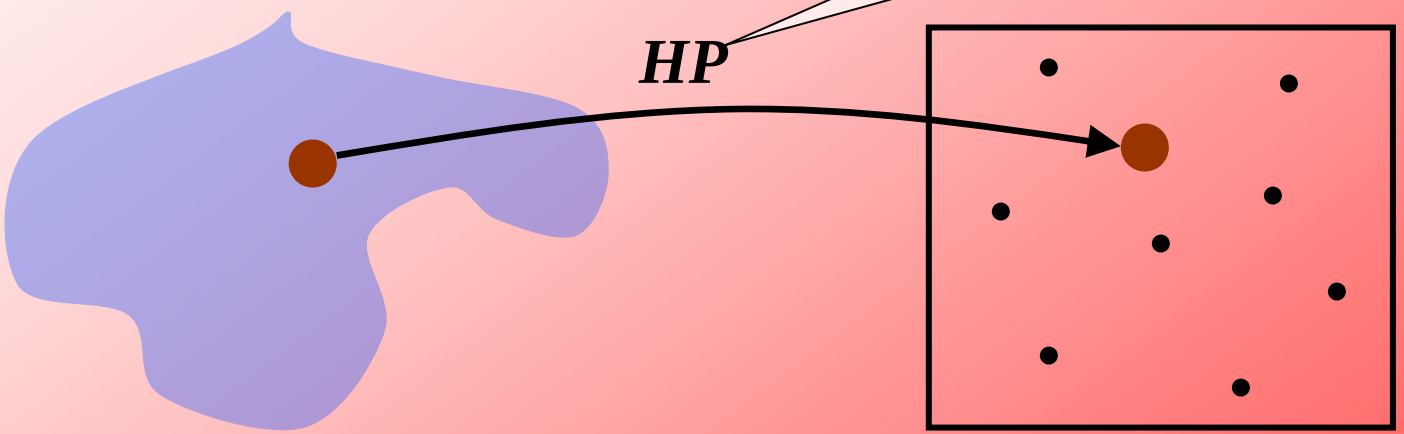


Hydropathy Interactions

When two atoms ***i*** and ***j*** make a contact, they interact with a hydropathy strength.

$$HP_{ij}=HP_i+HP_j \ ,$$

HP : free energy of transfer



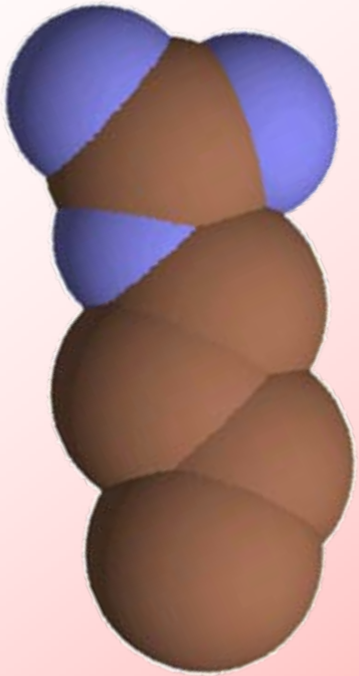
$$HP_i=\Delta SAS_i \cdot \sigma_i$$

σ : atomic solvation parameter

Atomic Solvation Parameters

$$HP_i = \Delta SAS_i \cdot \sigma_i$$

Arginine (R)

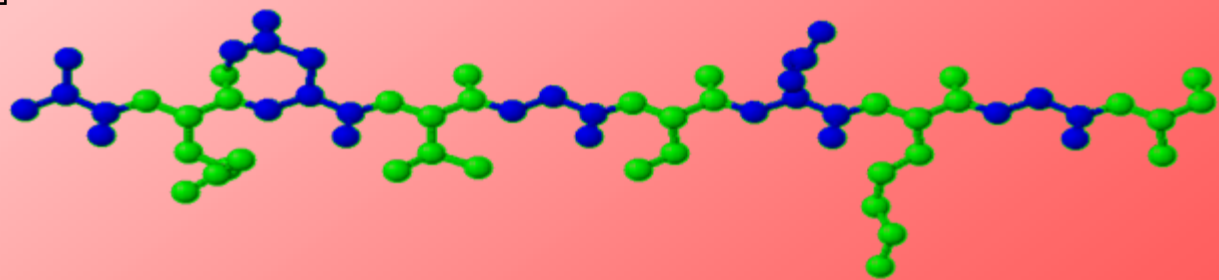


Lysine (K)

$$\Delta F_R = \sigma_C \cdot (\Sigma_{Ci}\, SAS_{Ci}) + \sigma_N \cdot (\Sigma_{Ni}\, SAS_{Ni})$$

$$\Delta F_K = \sigma_C \cdot (\Sigma_{Ci}\, SAS_{Ci}) + \sigma_N \cdot SAS_{Ni}$$

Solve for σ_C and σ_N



Simulation Set-up

Simulate Aβ(21-30) in a cubic box with periodic boundary conditions for 50ns.

Simulation Parameters

- $k_B T = 0.592$ Kcal/mol (room temperature).
- We perform simulations for different electrostatic interaction strengths**:**

$$0.00 < EI < 1.5 \text{ Kcal/mol (typical in the surface of proteins)}$$

$$1.50 < EI < 2.5 \text{ Kcal/mol (typical in the interior of proteins)}$$

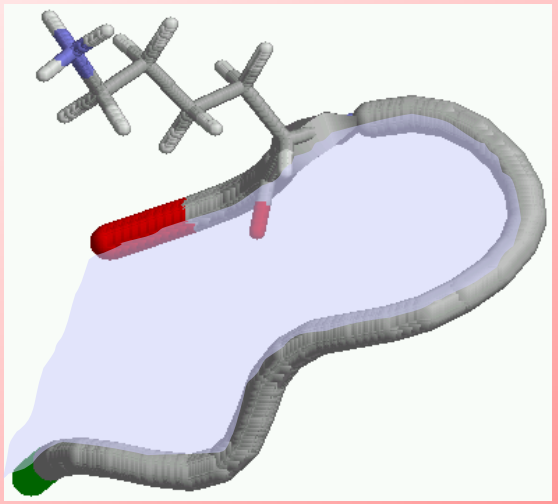
- Hydrogen-Bond strength = 3.5 Kcal/mol (typical in the surface of proteins)
- HP values in the range $-9.3 < HP < 1.3$ Kcal/mol (negative stands for repulsive)

Preliminary Experimental Observations

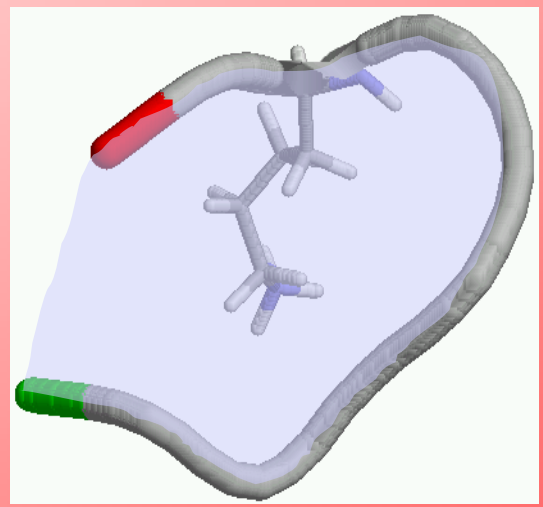
Lazo et at. have proposed two model structures from their Nuclear Magnetic Resonance experiments of Aβ(21-30) in solution:

- In both model structures, Aβ(21-30) adopts a loop-like conformation.
- In both model structures, V24 and K28 are close.
- Model structures differ in the orientation of K28 with respect to the loop plane

K28 above loop

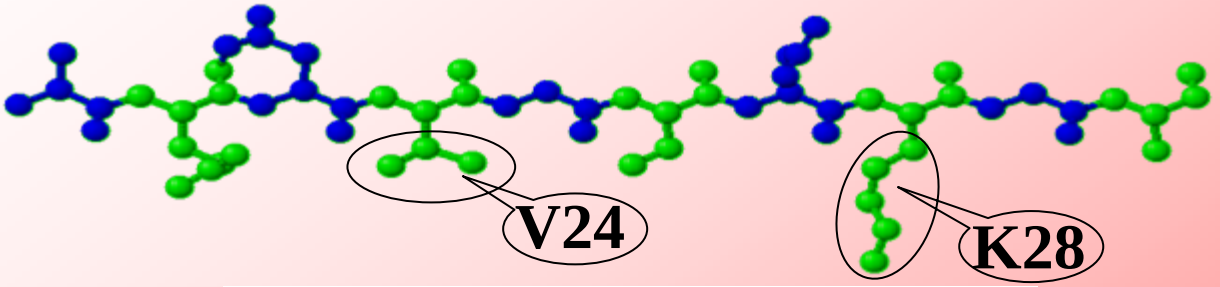


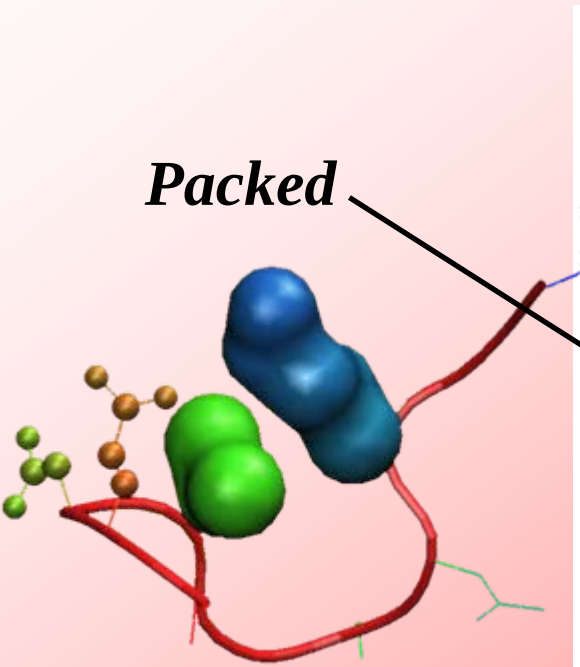
K28 below loop



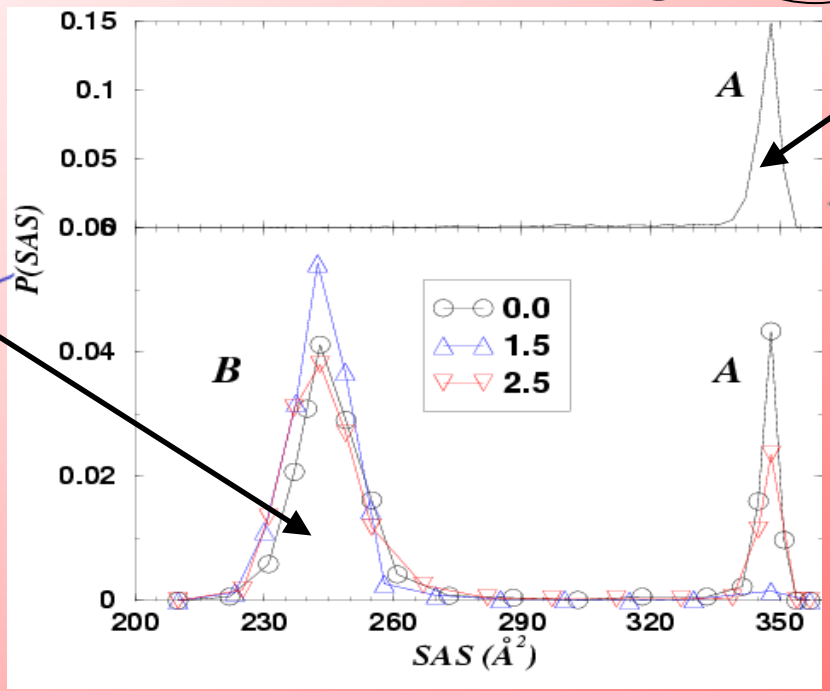
Lazo et at., *submitted to J. Mol. Biol.*

Hydrophobicity Produces Loop

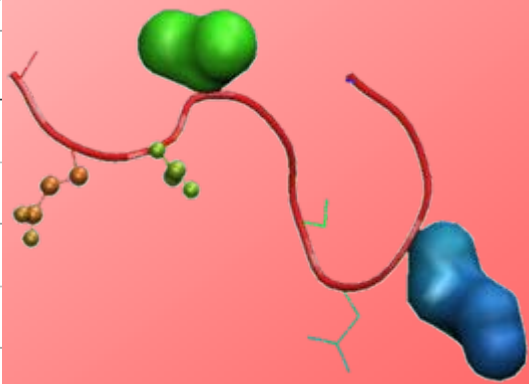




Packed

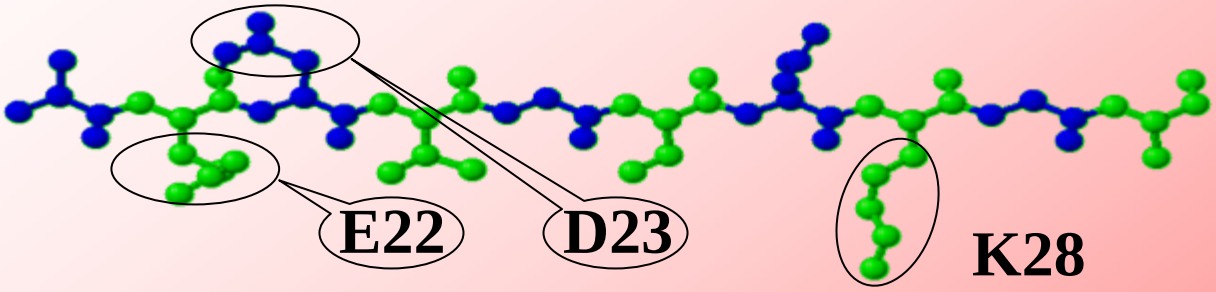


Unpacked



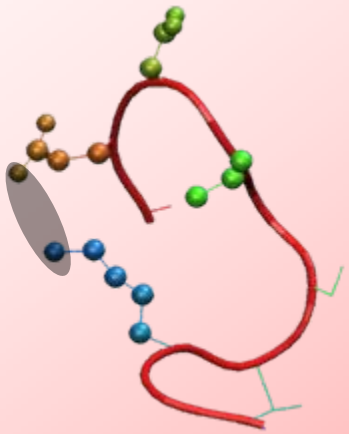
- Hydrophobic attraction responsible for packing of V24 and K28.
- Electrostatic interaction of 1.5Kcal/mol optimizes V24 and K28 packing.

Results: D23 Relevant under Strong EI

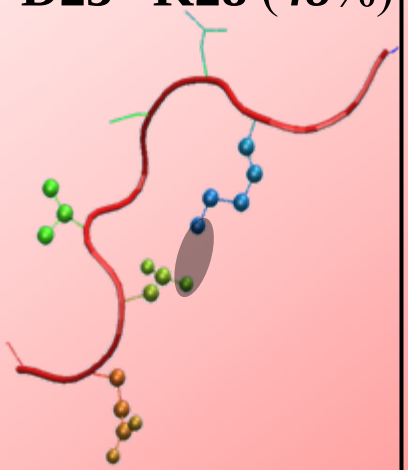


→ New unpacked conformations have strong electrostatic interactions!

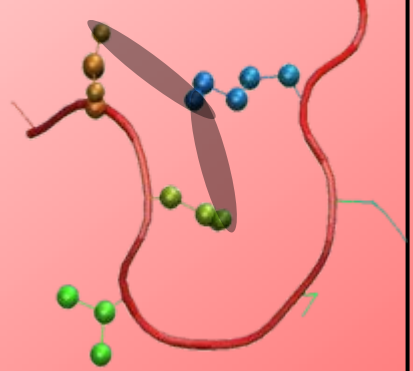
E22···K28 (*23*%)



D23···K28 (***48***%)

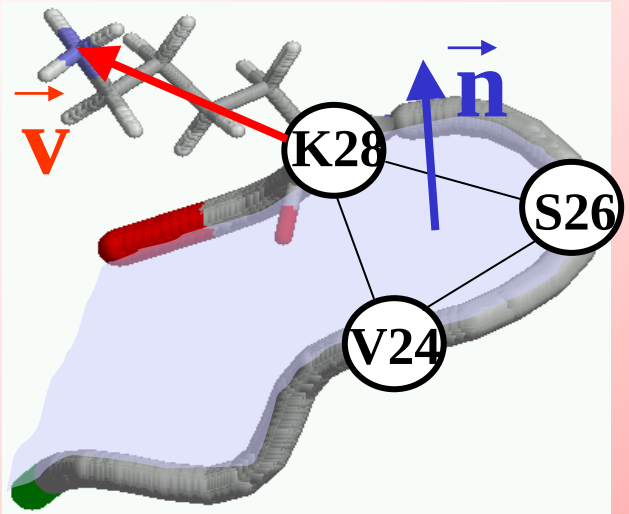


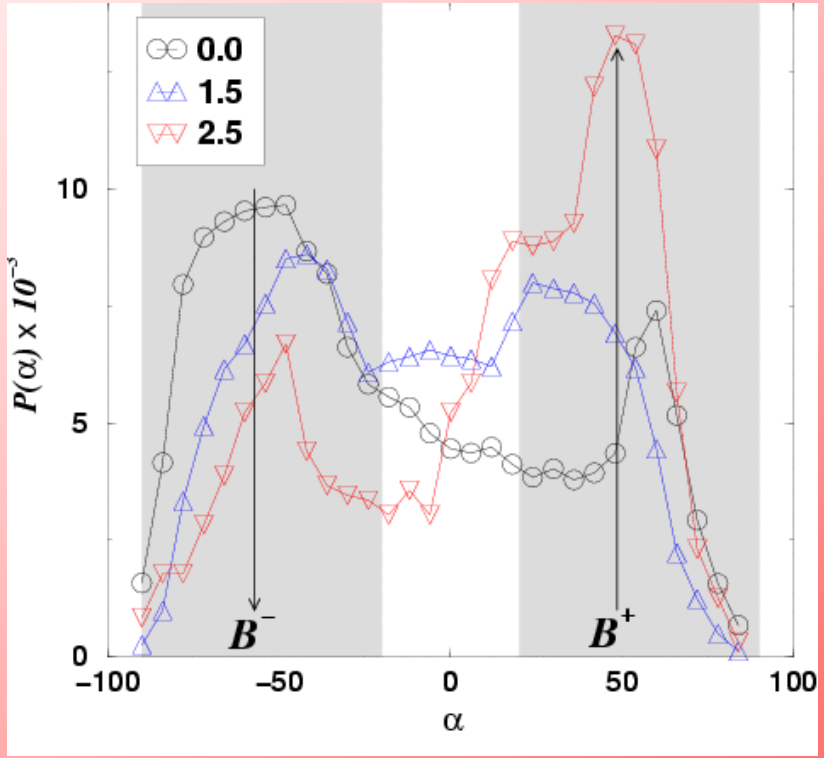
E22···K28
D23···K28 (*29*%)



• We hypothesize that Aβ(21-30) may **undergo partial unpacking** of V24···K28 contacts and form D23···K28 electrostatic interactions upon fibril formation.

Results: K28 orientation

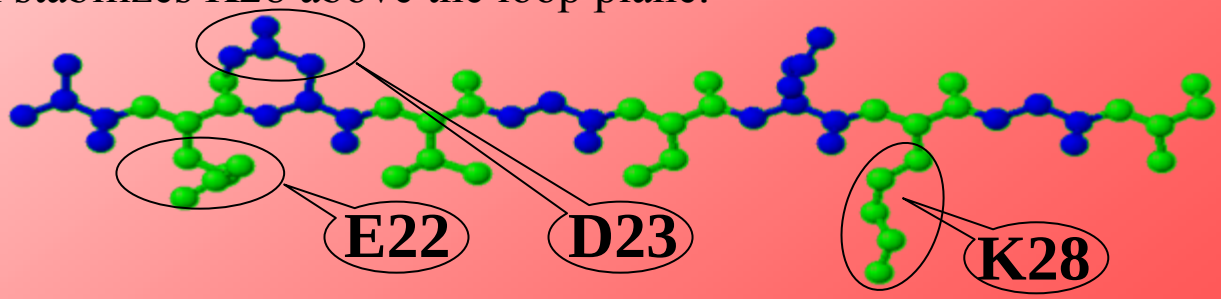




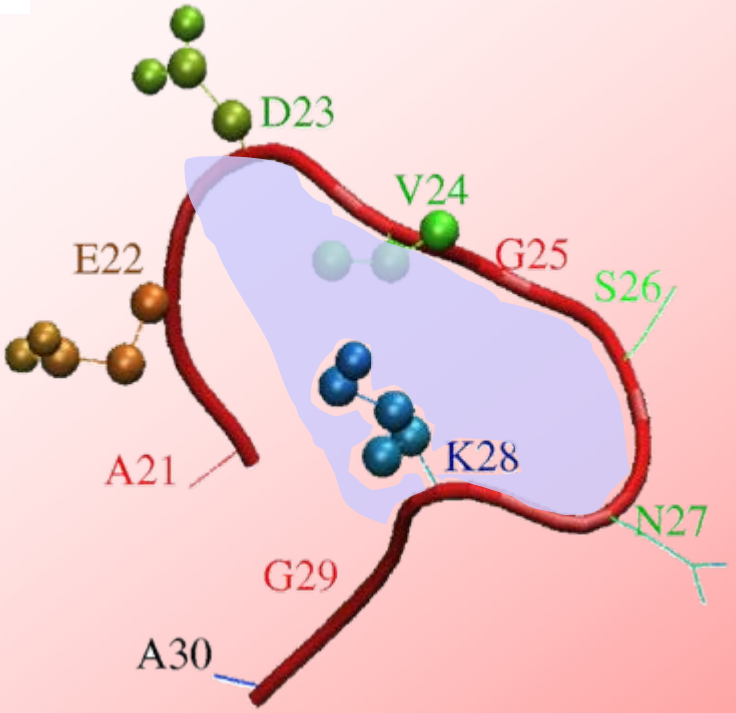
•Electrostatic interaction stabilizes K28 above the loop plane.

E22···K28

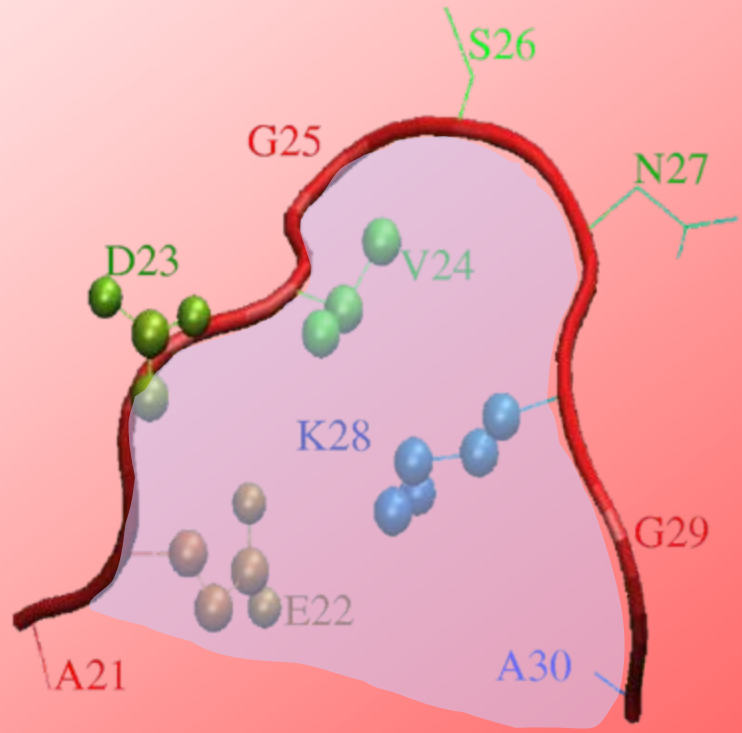
D23···K28



Two Representative Conformations

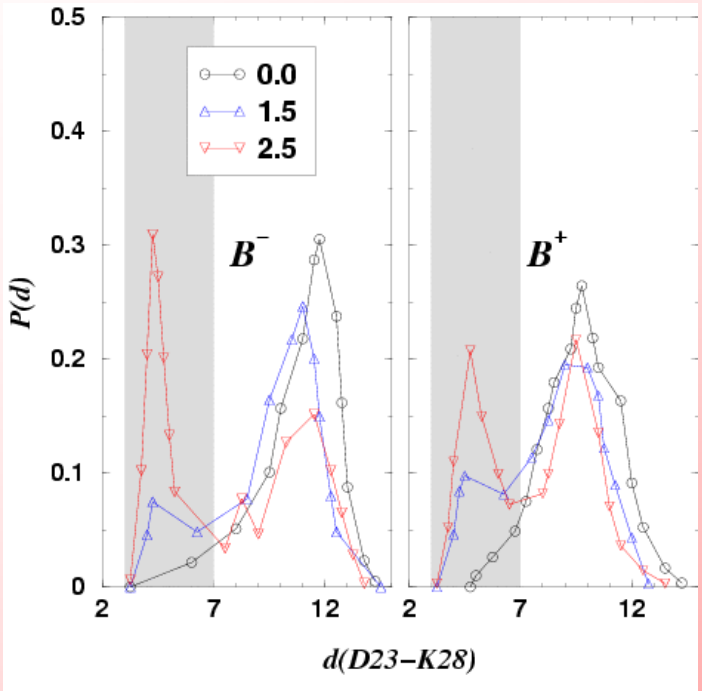


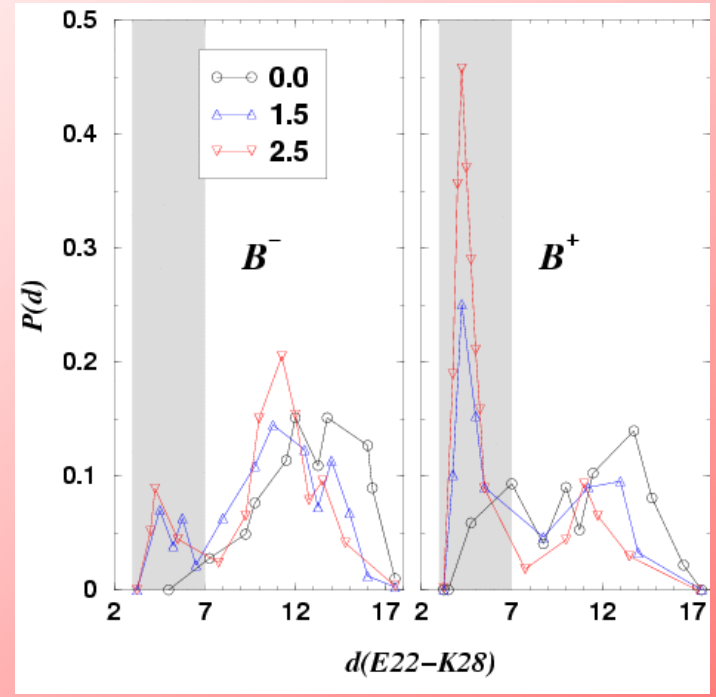
K28 below loop plane



K28 above loop plane
E22-K28 interaction shown

E22 Stabilizes the Loop





	B-	B+
0.0	1	1
1.5	7	9
2.5	11	13

	B-	B+
0.0	1	5
1.5	6	16
2.5	5	21

- E22 tends to suppress loop conformations with K28 pointing below the loop (Lazo et al. observe that E22 is more close than D23 to K28 when K28 above the loop plane).
- D23 does not show any preference with K28 orientation.

Conclusions

- Aβ(21-30) adopts a loop-like conformation centered at S26, stabilized by hydrophobic interactions between V24 and K28.
- There is a particular electrostatic interaction strength that optimize the stability of the loop conformations.
- Electrostatic interactions strengths typical of the interior of proteins destabilize the loop conformations and form strong electrostatic interactions, preferentially D23···K28.
- We hypothesize that Aβ(21-30) undergoes partial unfolding of V24-K28 and formation of electrostatic interaction D23-K28 upon fibril formation,

Collaborators

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