Statistical physics approaches to Alzheimer's disease

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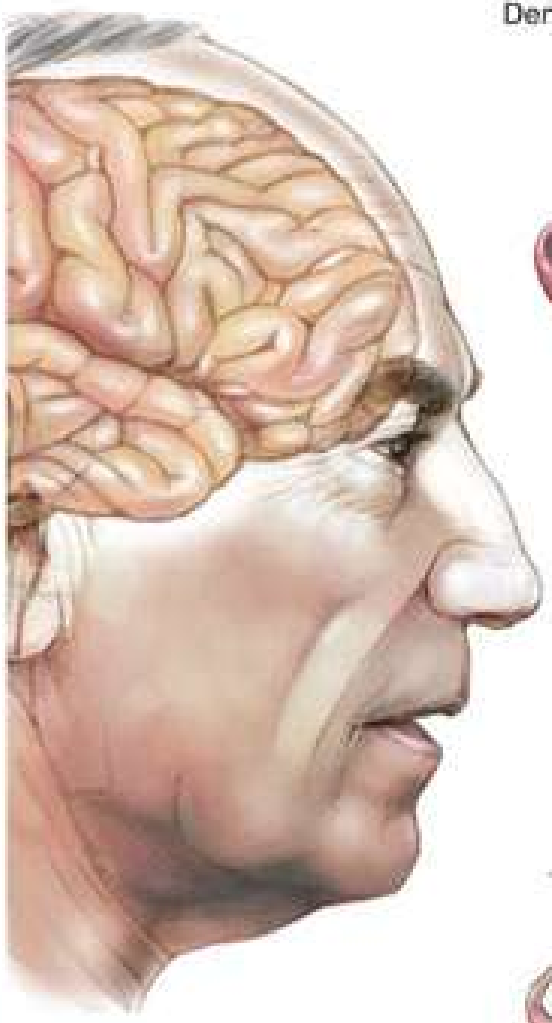
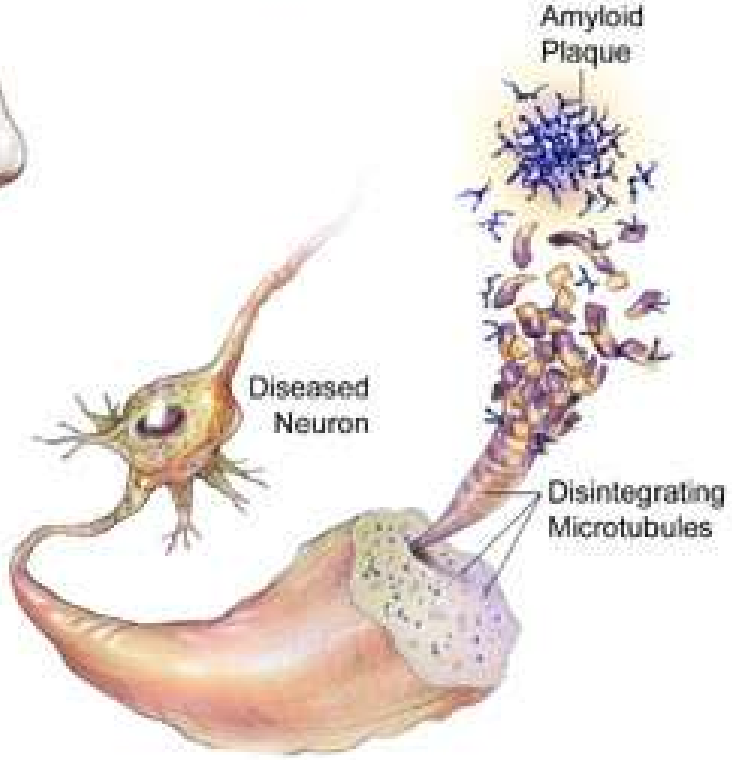
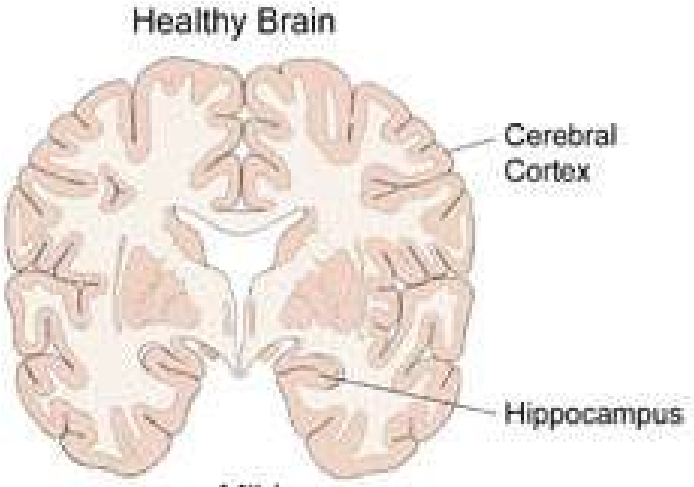
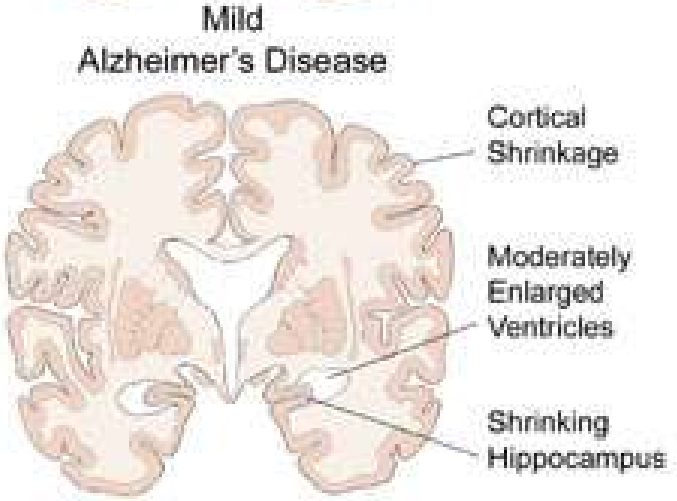
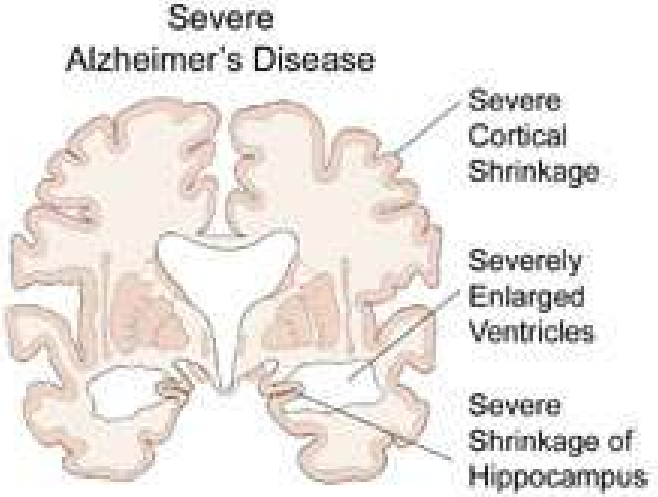
What is Alzheimer's disease?





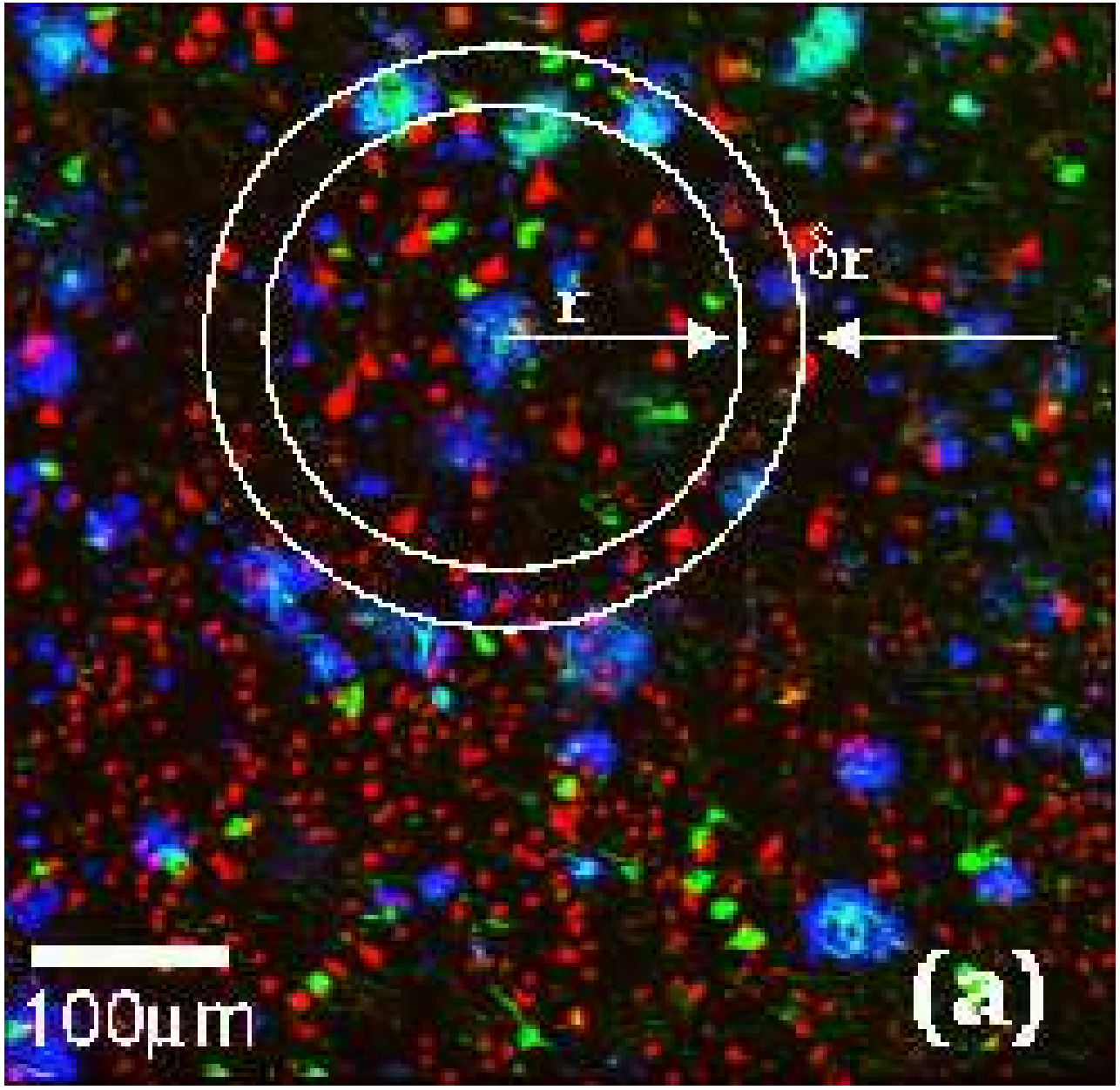






Q: Are plaques associated with neuronal loss in AD?

A: The fibrillar form of amyloid deposit is locally neurotoxic.



red: neuronal bodies
blue: amyloid deposits
green: fibrillar forms

Urbanc, Cruz, Le, Sanders, Hsiao-Ashe, Duff, Stanley, Irizarry, & Hyman, *Neurotoxic effects of thioflavin S positive amyloid deposits in Alzheimer's disease, PNAS (2002).*

Q: How to detect local changes in neuron density due to SPs?

A: Cross-correlation density map method

SUPERPOSE ALL NEURONAL FIELDS

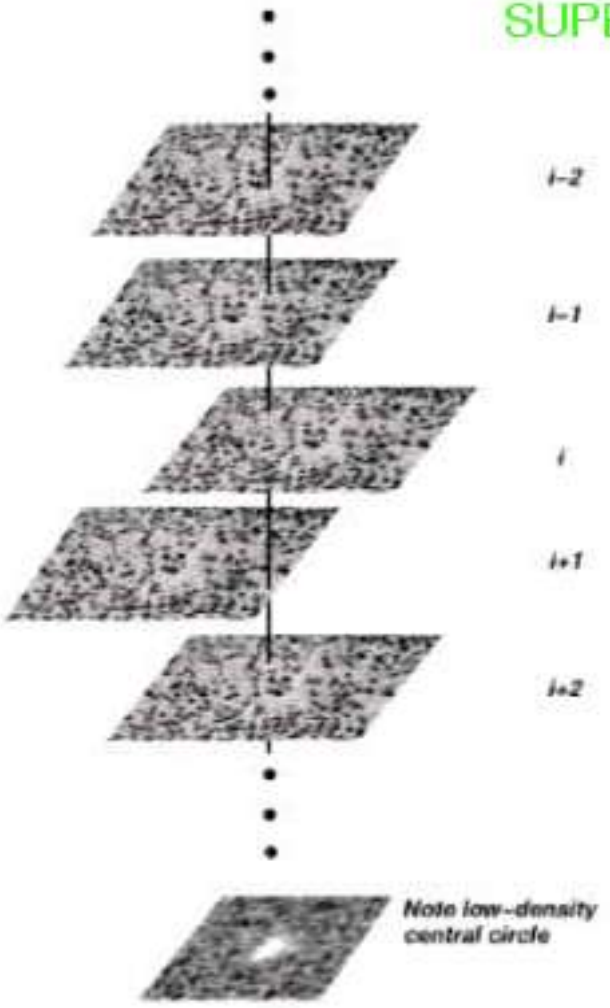
centered at SP # i-2

centered at SP # i-1

centered at SP # i

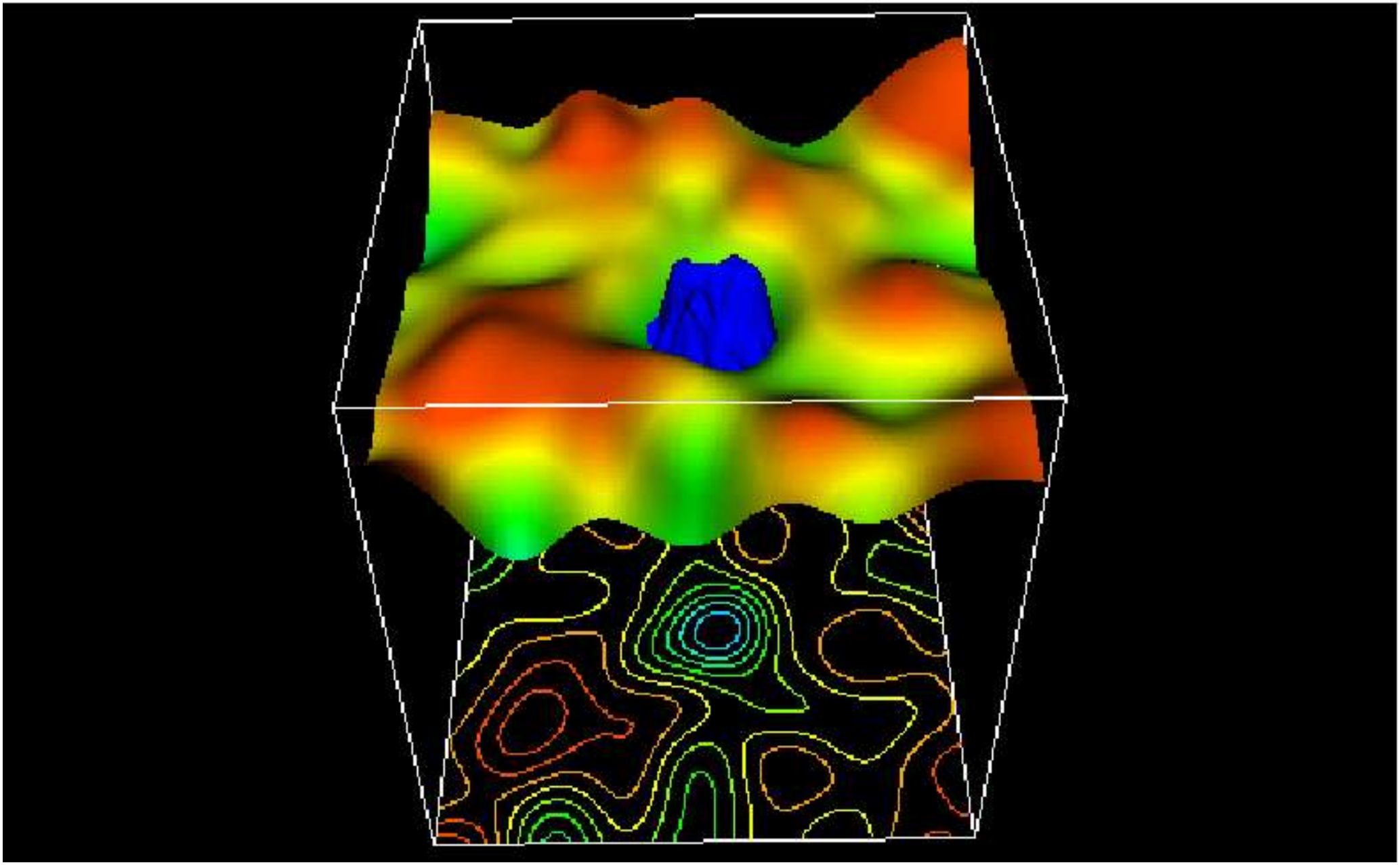
centered at SP # i+1

centered at SP # i+2



RESULT:

Local neuronal density around an average fibrillar amyloid deposit

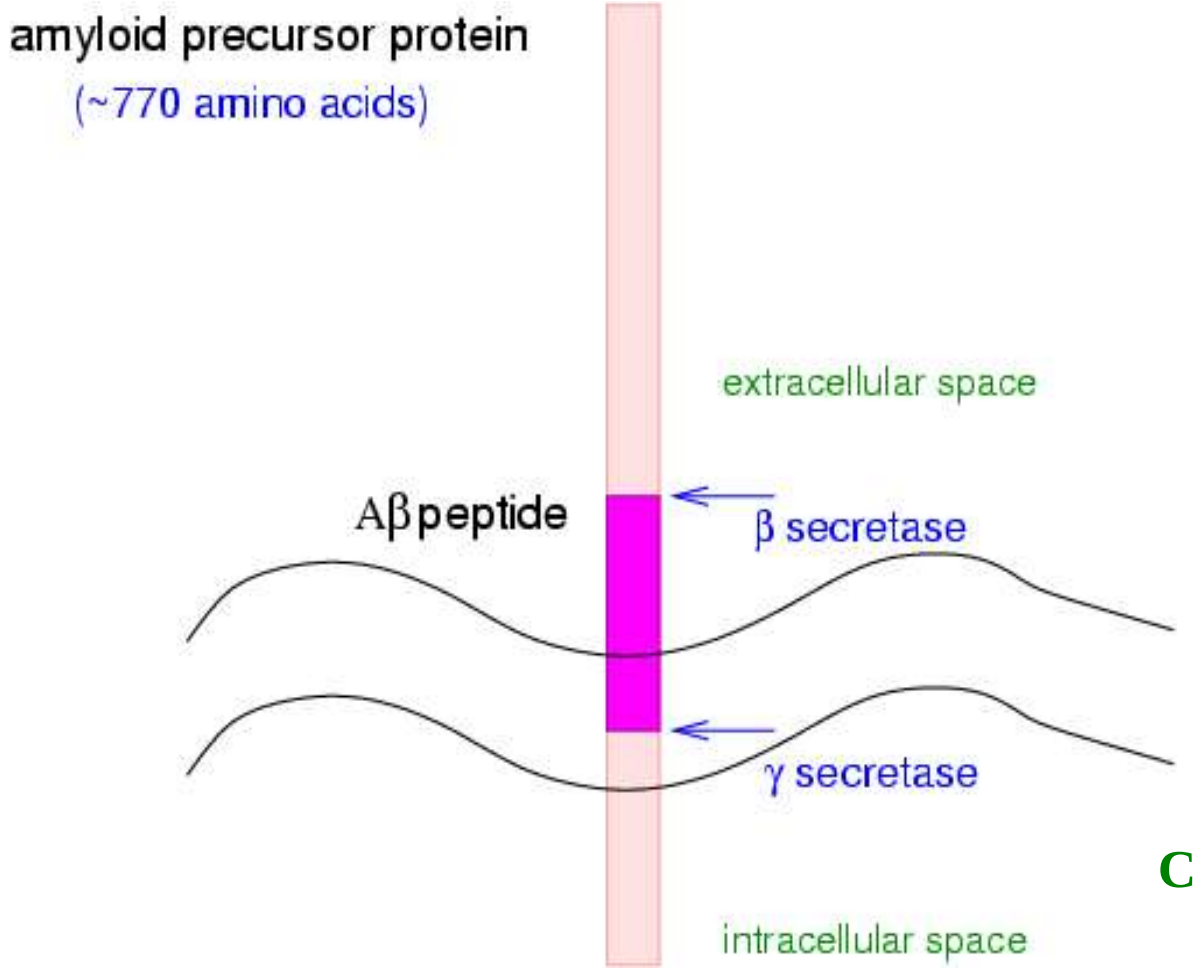


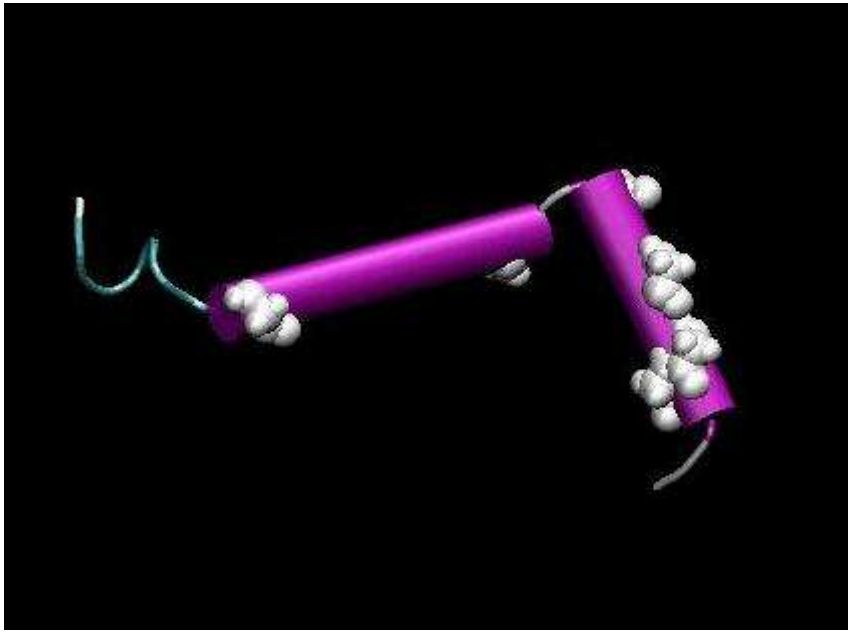
Q: What are plaques made of? How do they form?

A: Amyoid β-protein (Aβ). Nobody knows for sure.

Aβ(1-42) amino acid sequence:

DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA





Aβ in media that mimic apolar microenvironments

Crescenzi et al., Eur. J. Biochem. (2002)

Working hypothesis

Bitan, Kirkitadze, Lomakin, Vollers, Benedek, and Teplow, PNAS (2003).

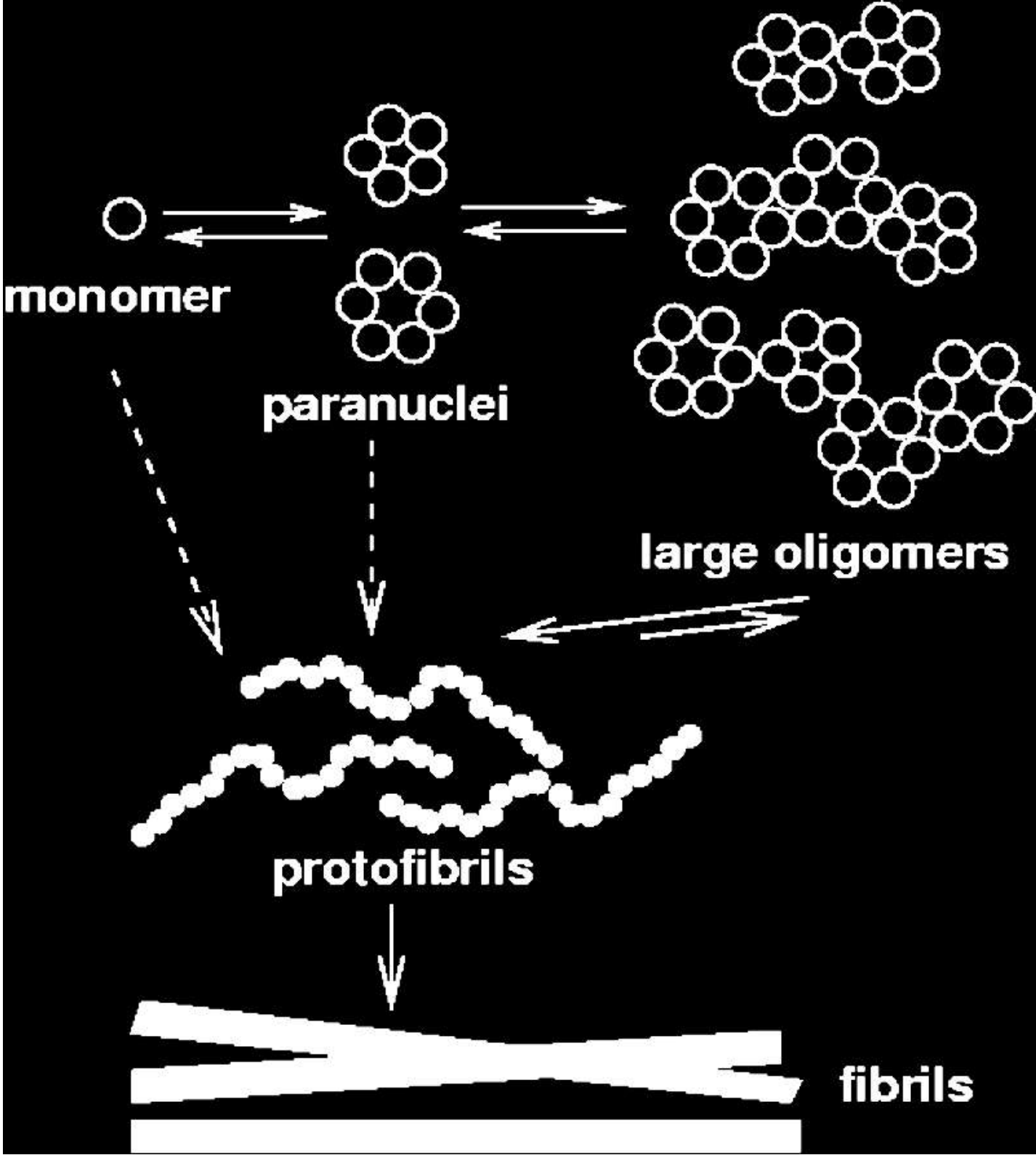
OLIGOMERS ARE THE MOST TOXIC!

Unstructured:

- **monomers**
- **pentamers/hexamers (paranuclei)**
- **large oligomers**

β-strand rich:

- **protofibrils**
- **fibrils**

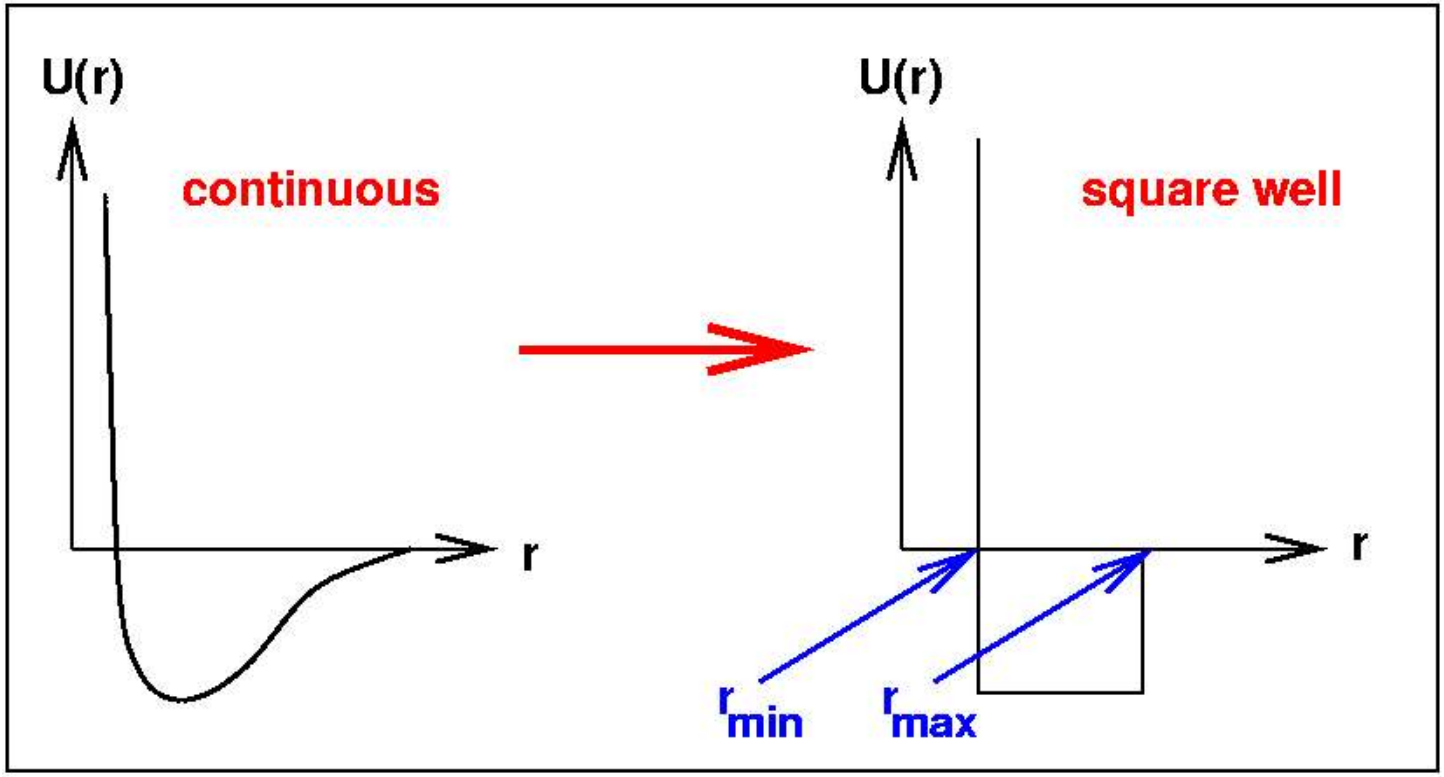


Q1: What are key principles giving rise to oligomer formation differences of Aβ40 versus Aβ42?

Q2: What is the 3D structure of Aβ40 versus Aβ42 oligomers?

METHOD: discrete molecular dynamics (DMD)

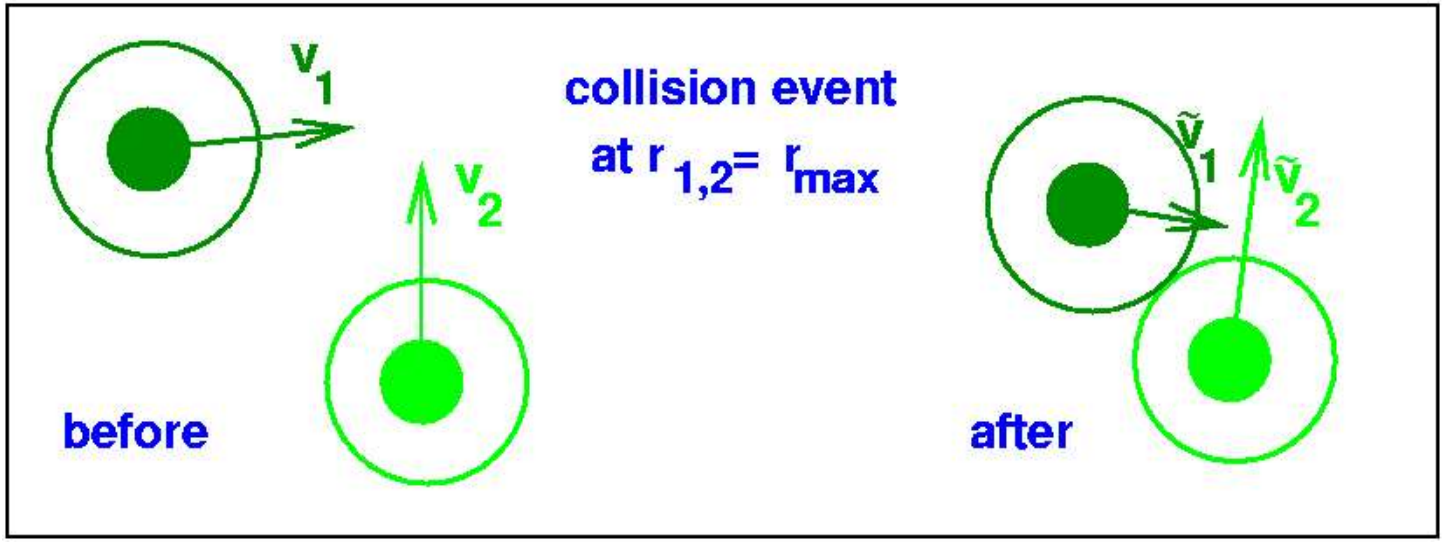
Interparticle potential



Keep track of collision events

Collisions conserve:

- **energy**
- **momentum**
- **angular momentum**

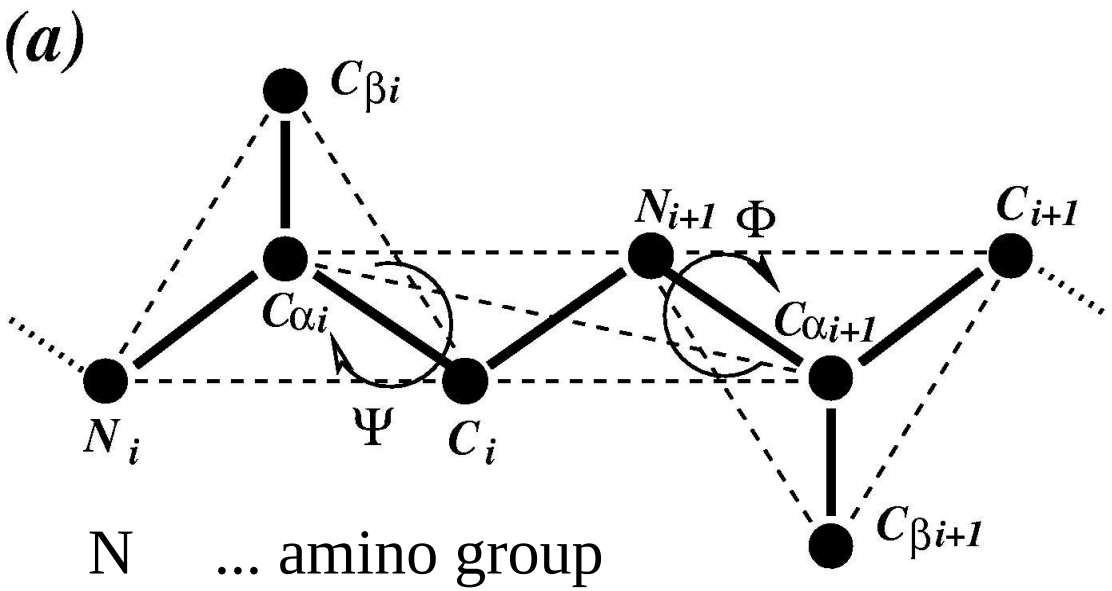


Zhou, Hall & Karplus, PRL, 1996; Zhou & Karplus, PNAS, 1997; Dokholyan, Buldyrev, Stanley & Shakhnovich, Fold. Des., 1998.

Four-bead peptide model

Ding, Borreguero, Buldyrev, Stanley & Dokholyan, Proteins, 2003.

beads, bonds, & constraints



N ... amino group

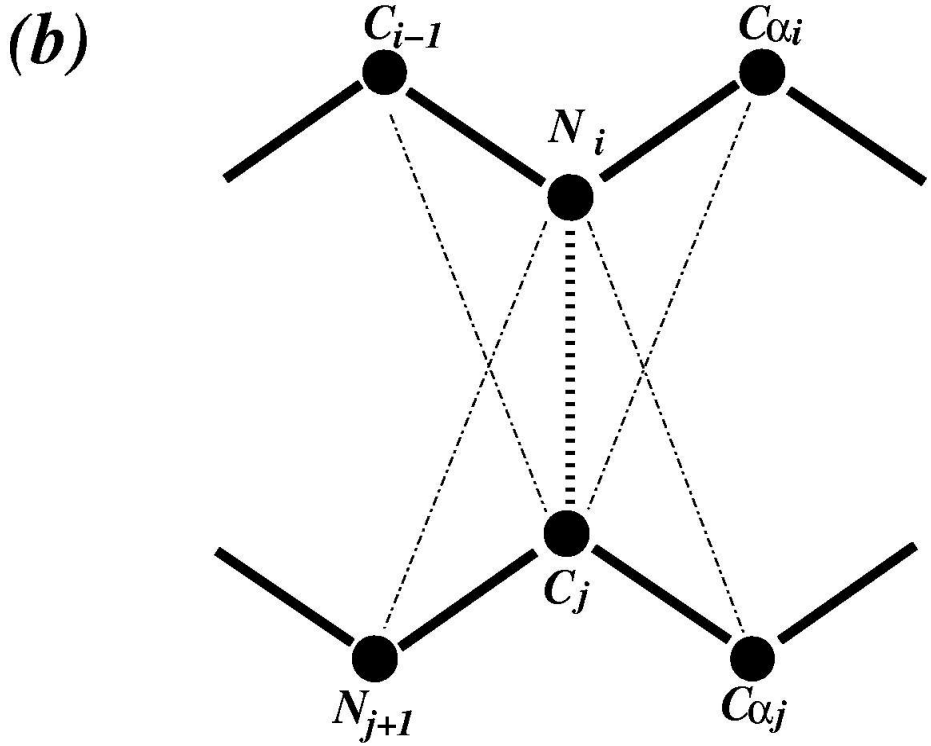
C_α ... α carbon group

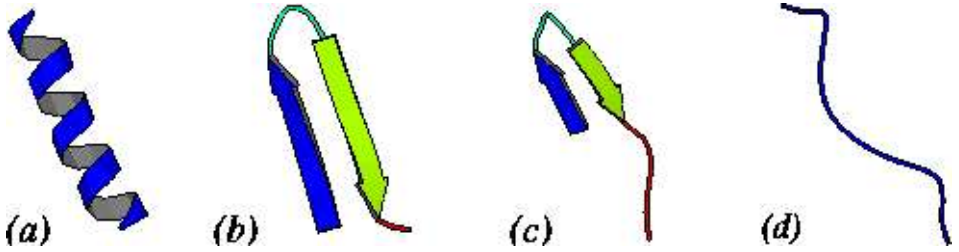
C' ... carboxyl group

C_β ... side chain group

α-helix to β-hairpin transition in polyalanine

hydrogen bond implementation

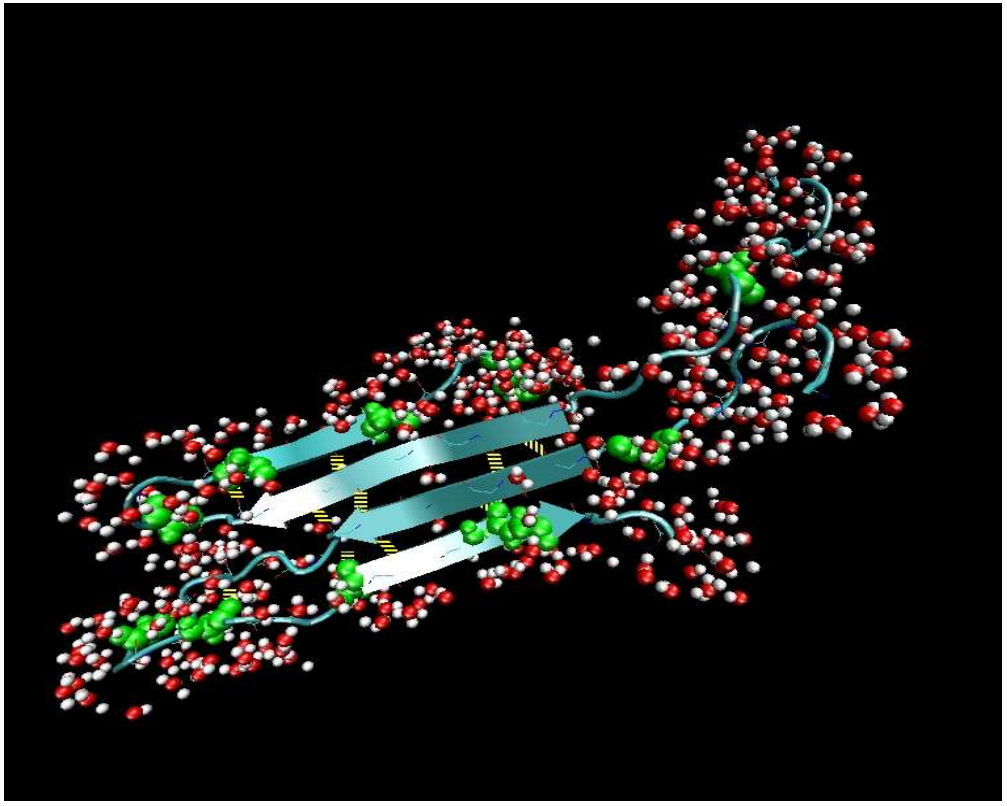




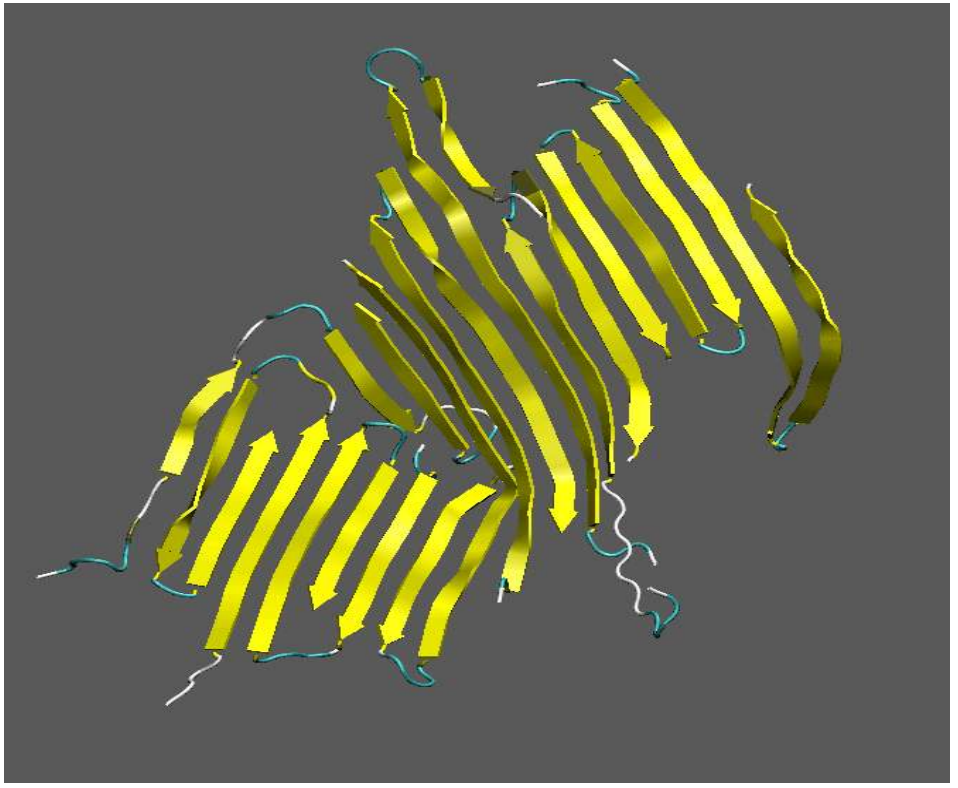
low temperature ---> high temperature

Four-bead model with hydrogen bonds predicts planar β-sheet dimers and single-layer β-sheet oligomer structure.

Planar β-sheet dimer in water



Single-layer β-sheet oligomer

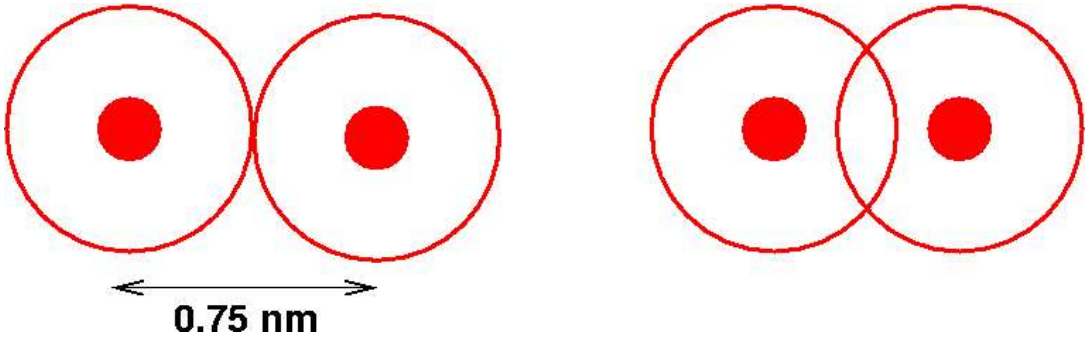


Urbanc, Cruz, Ding, Sammond, Khare, Buldyrev, Stanley & Dokholyan, Biophys. J., 2004.

Amino acid-specific interactions: Hydrophilic vs. Hydrophobic

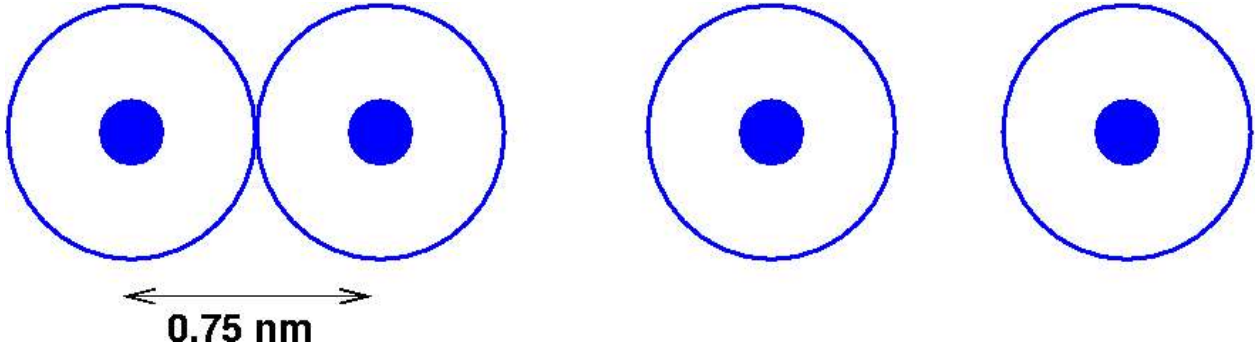
Phenomenological hydropathy scale: Kyte & Doolittle, JMB, 1982.

hydrophobic residues: (from the most to the least hydrophobic)
Ile, Val, Leu, Phe, Cys, Met, Ala
hydrophobic effect --> minimize the ``solvent''exposed surface --> attraction



two hydrophobic side chains:
attractive square well

hydrophilic residues: (from the most to the least hydrophilic)
Arg+, Lys+, Asp-, Glu-, Asn, Gln, His
hydrophilic effect --> maximize the ``solvent''exposed surface-->repulsion



two hydrophilic side chains:
repulsive square well

8 trajectories of each Aβ40 and Aβ42 with 32 peptides in a cubic box of 25 nm

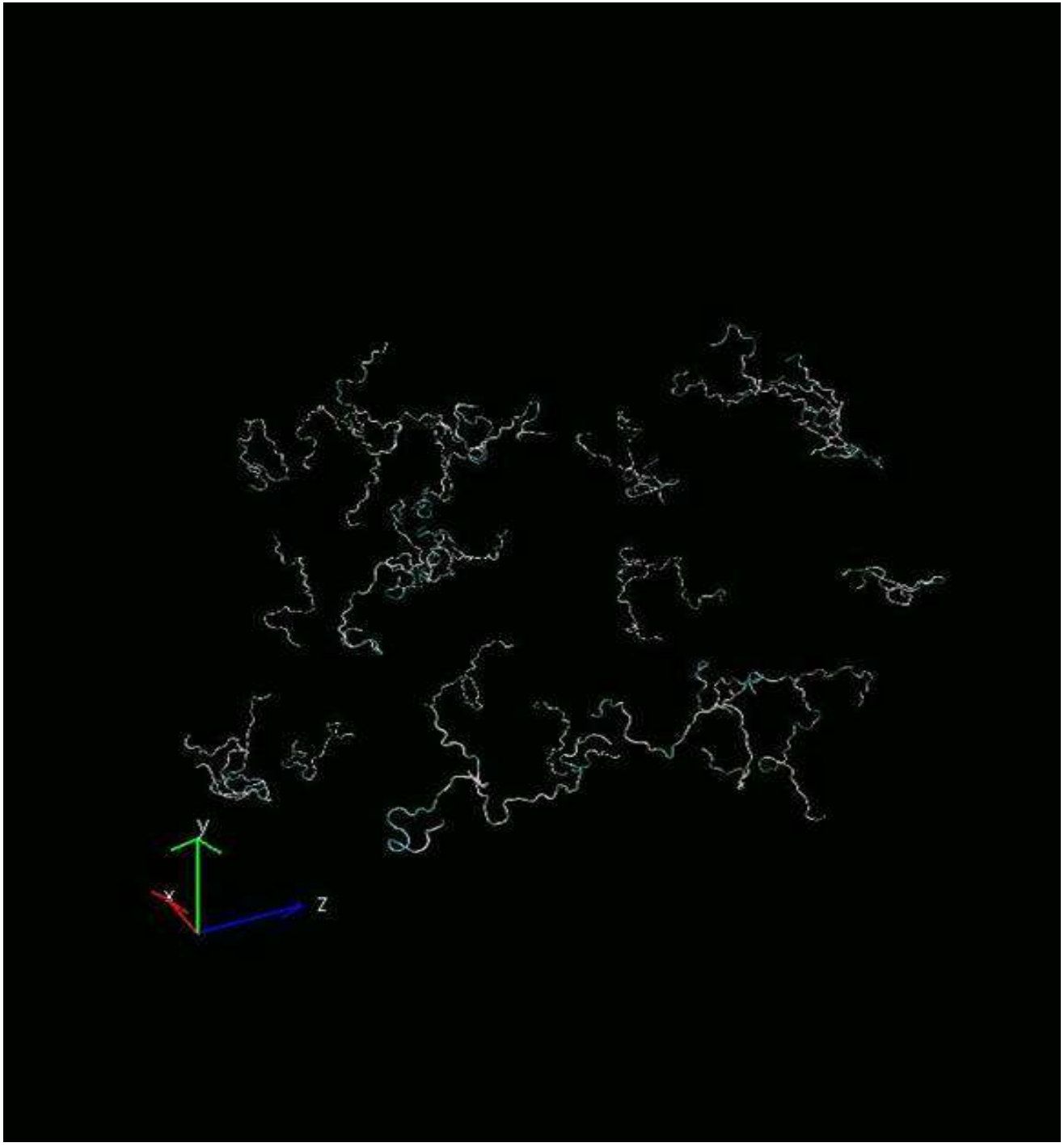
Parameters:

$E_{HB} = 1$

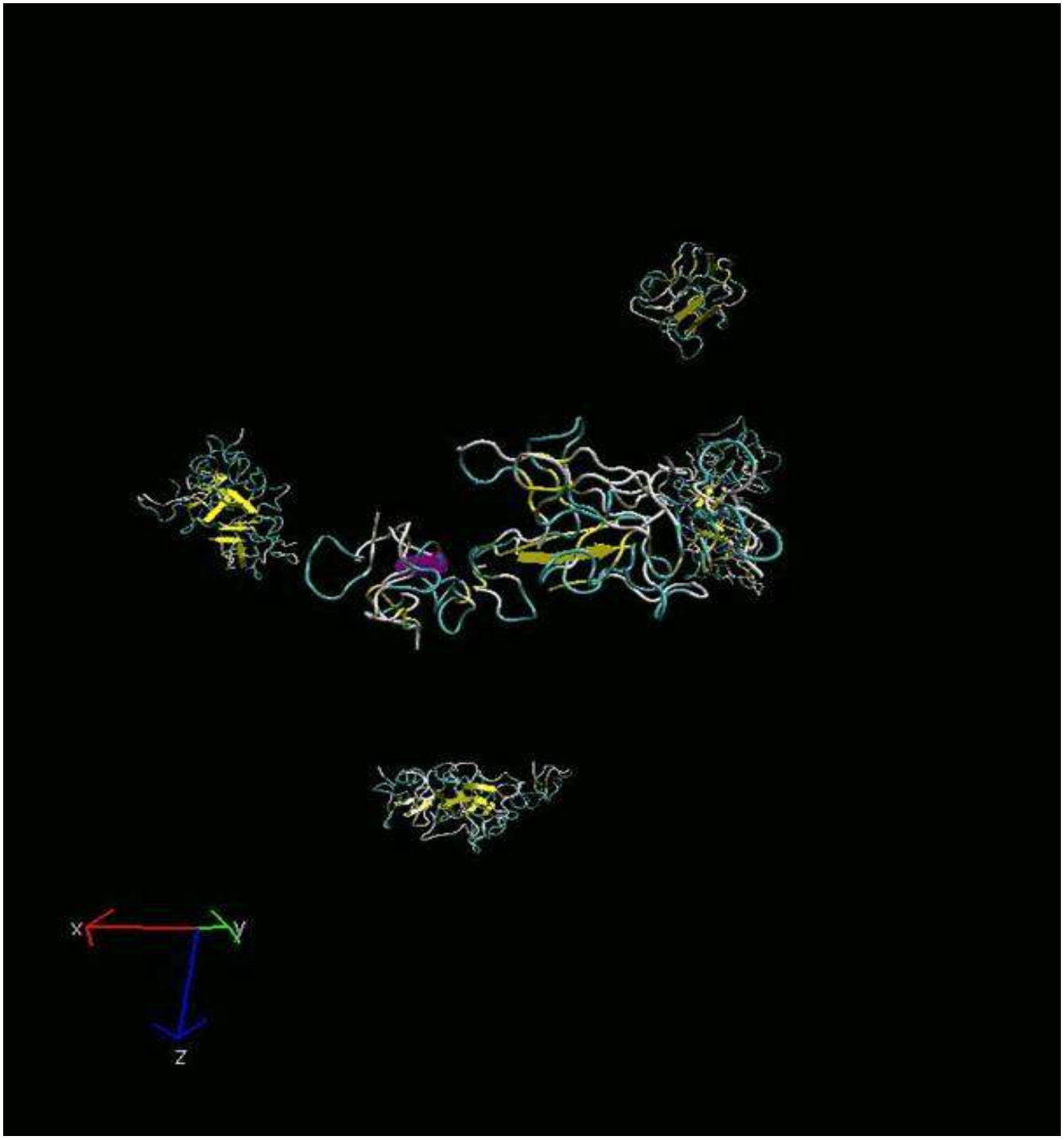
$E_{HP} = 0.3$ (Ile--Ile)

$T = 0.15\ [E_{HB}/k]$

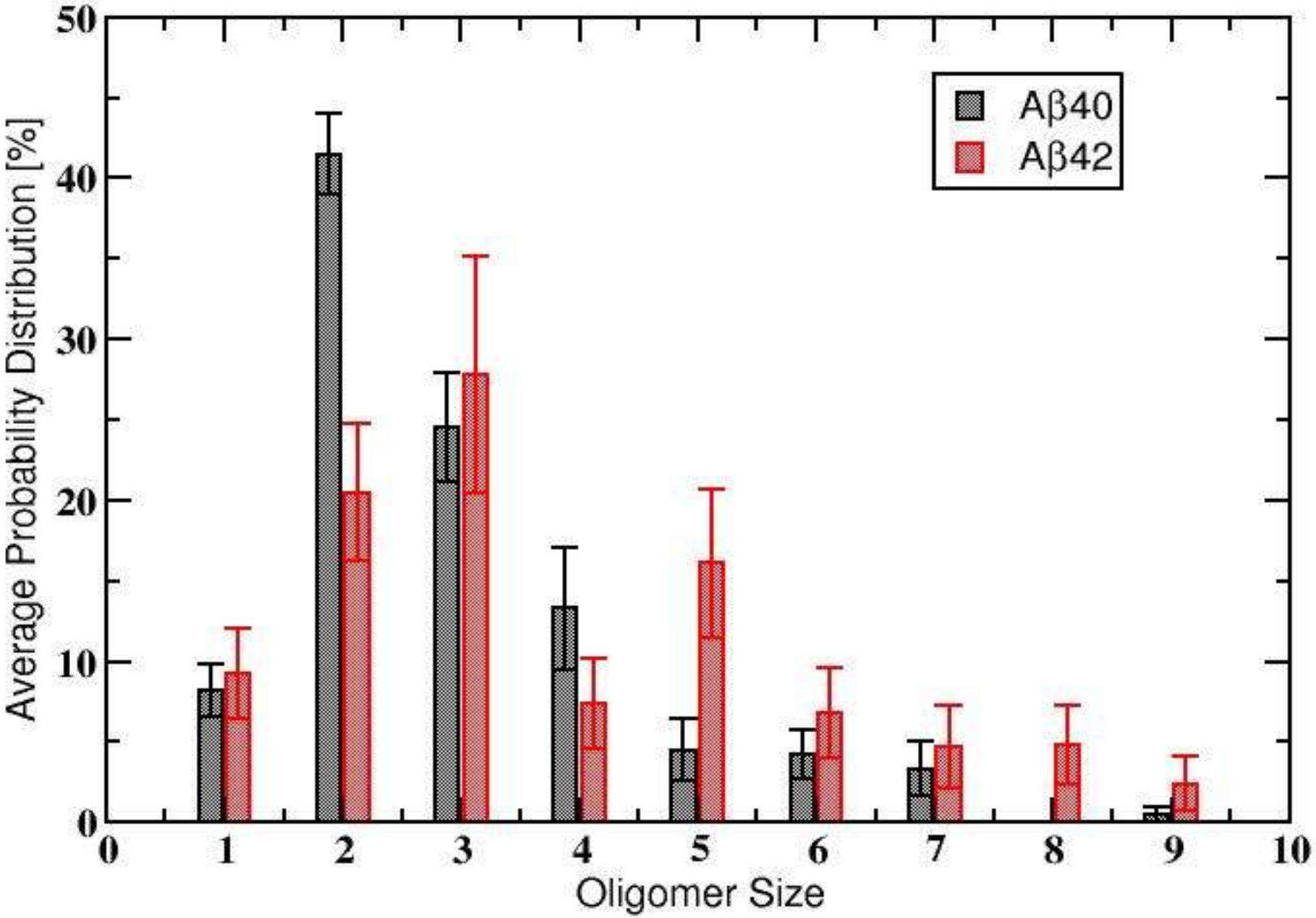
Initially peptides are in unfolded, zero-energy conformations.



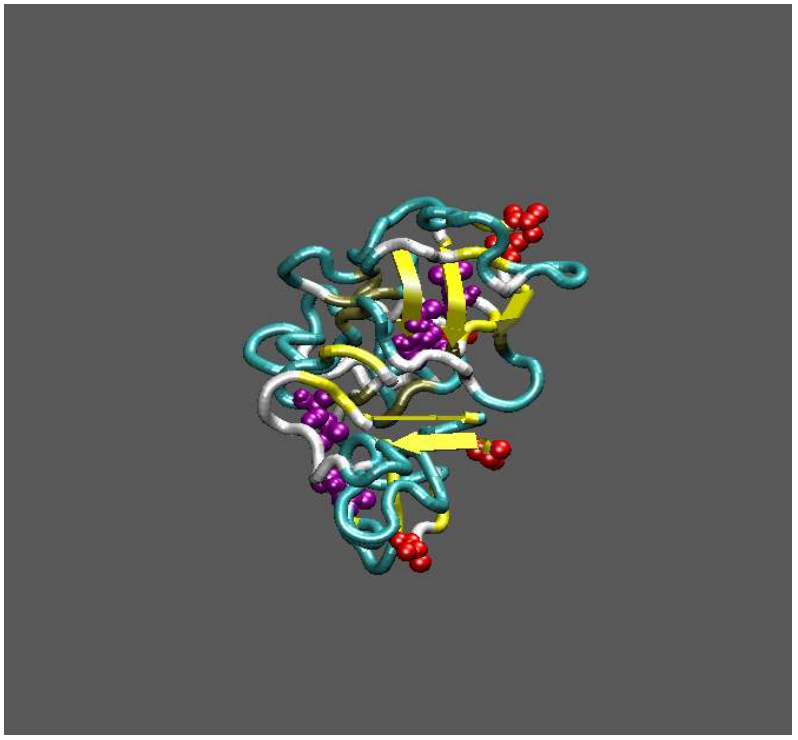
After 6 M simulation steps, monomers and oligomers are in a quasi-steady state.

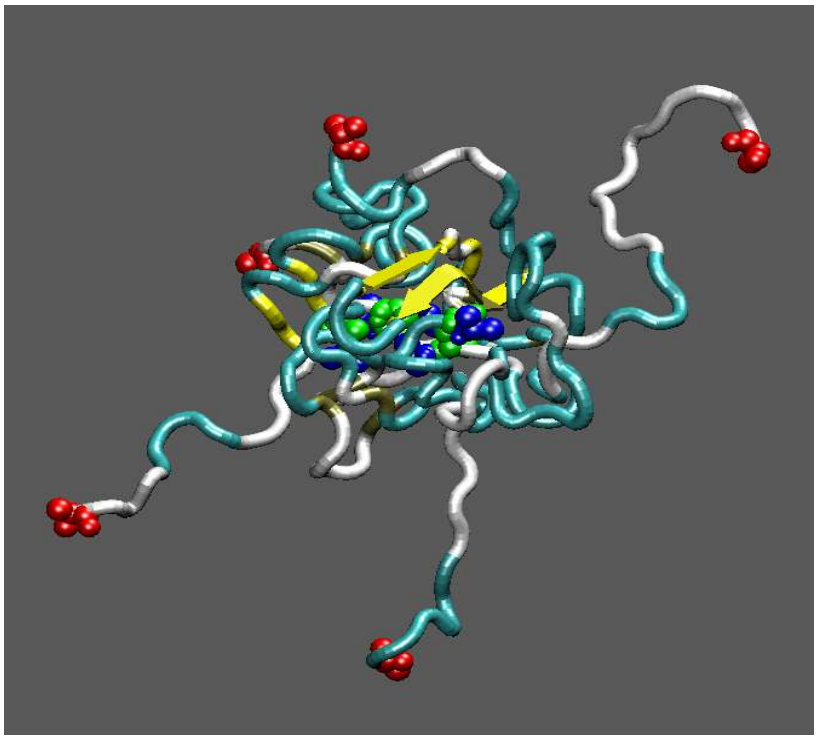


Aβ42 forms significantly more pentamers than Aβ40



3D structure of Aβ40 and Aβ42 pentamers





Aβ40 **Aβ42**

red spheres	... Asp1	**yellow** ribbon	... β-strand
purple spheres	... Val40	**turquoise** tube	... turn
green spheres	... Ile 41	**silver** tube	... no s.s.
blue spheres	... Ala42		

VMD Software Package (Humphrey et al, JMG, 1996).

STRIDE program for s.s. calculation (Heinig and Frishman, 2004).

ANSWERS:

Q1: What are key principles giving rise to different pathways of Aβ40 versus Aβ42 oligomer formation?

- **hydrophobic/hydrophilic effective interactions are key driving ints in Aβ oligomer formation that underly differences between Aβ40 and Aβ42;**

Q2: What is the 3D structure of Aβ40 versus Aβ42 oligomers?

- **oligomers have globular structure with C-termini within the core and N-termini at the surface;**

- **N-termini of Aβ40 oligomers are more spatially restricted than in Aβ42 and form a β-strand structure at Ala2-Phe4 ---> hydrophobic core of Aβ42 oligomers is more exposed ---> Aβ42 more prone to aggregate further.**

Urbanc, Cruz, Yun, Buldyrev, Bitan, Teplow & Stanley, PNAS, 2004.

NEW DEVELOPMENTS

- **Study the effects of interaction between charged amino acids on Aβ folding and oligomerization:**

  Yun, Urbanc, Cruz, Bitan, Teplow & Stanley, *Role of electrostatic interactions in Aβ oligomer formation: A discrete molecular dynamics study*, manuscript in preparation.

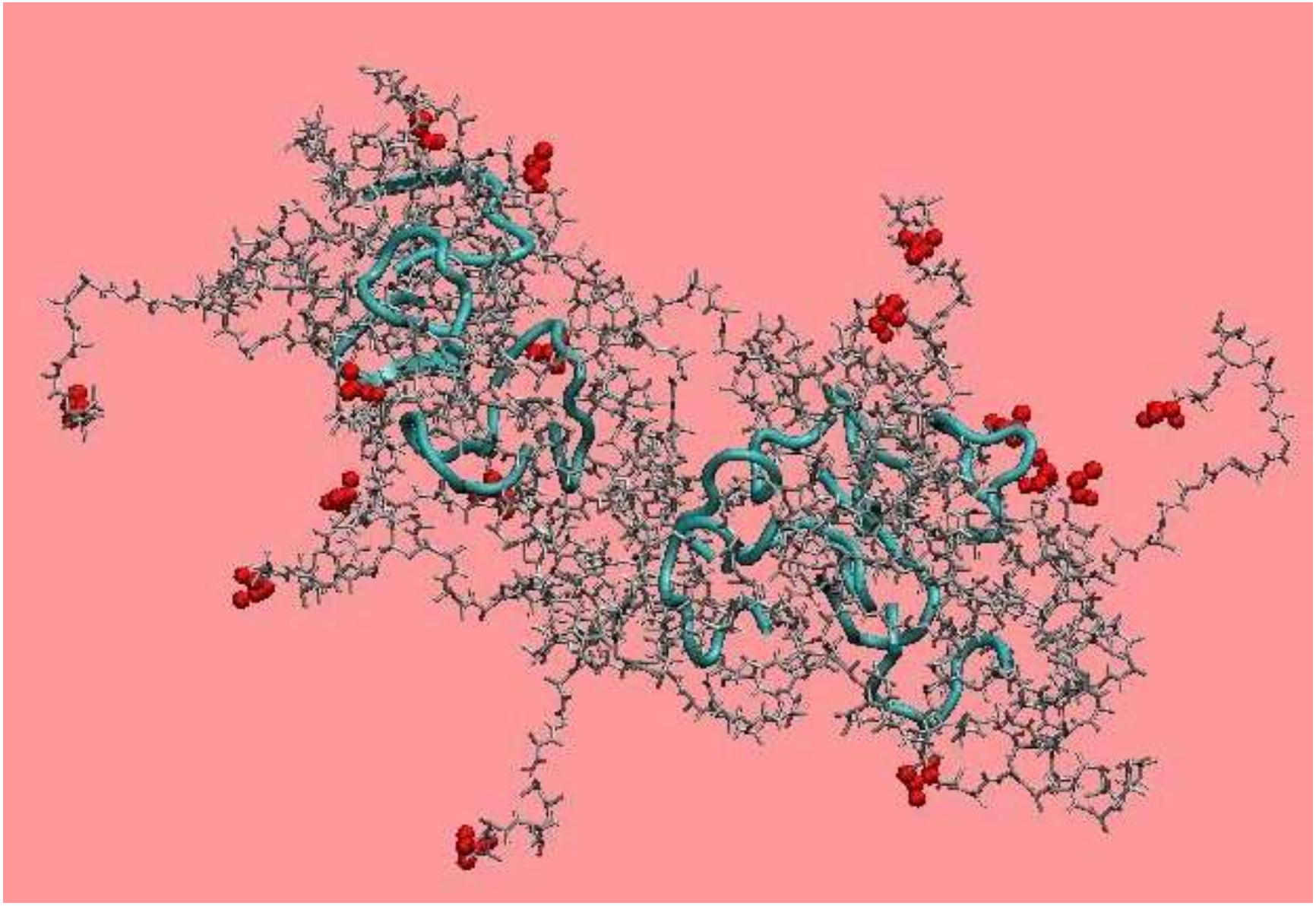
- **Apply a united-atom model to studies details of side chain-side chain interactions:**

  Borreguero, Urbanc, Lazo, Buldyrev, Teplow & Stanley, *Folding events in the 21-30 region of amyloid β-protein (Aβ) studied in silico*, PNAS (2005).

- **Apply an all-atom model with explicit solvent to study solvent effects:**

  Cruz, Urbanc, Borreguero, Lazo, Teplow & Stanley, *Solvent and mutation effects on the nucleation of amyloid β-protein folding*, PNAS, in press.

We have generalized the DMD code to describe assembly of two different peptides (“proof of concept”).



Oligomer composed of 16 Aβ(1-42) and 16 Aβ(31-42) peptides

Biological relevance of our approach: the four bead model

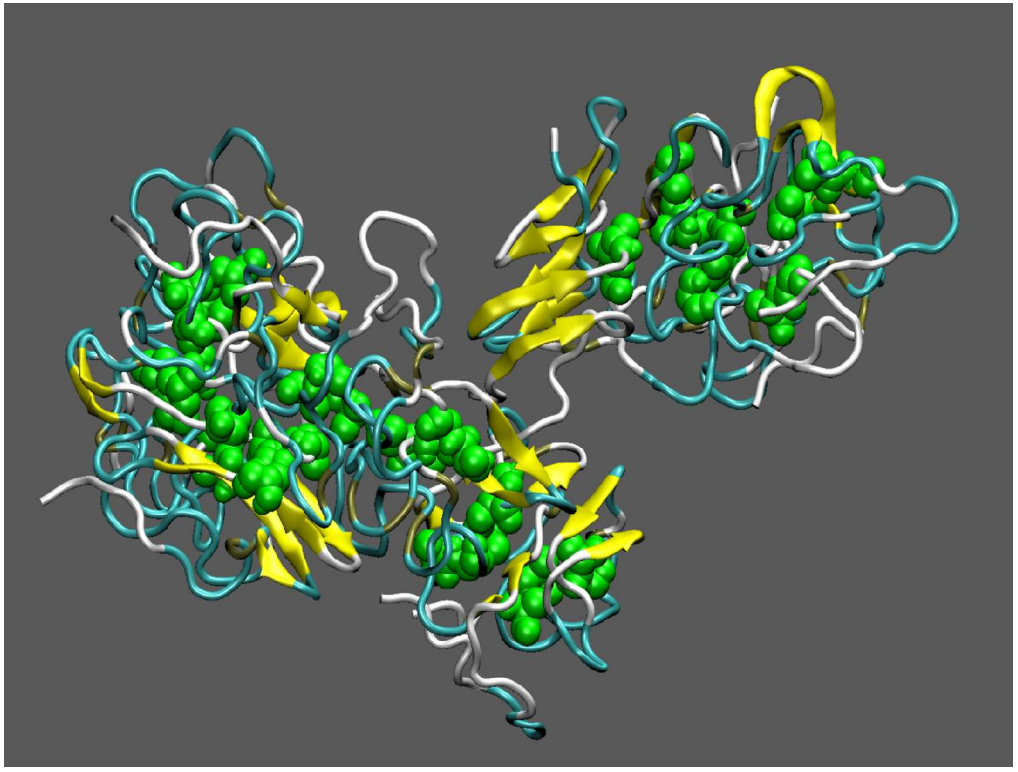
Aβ(1-40) and Aβ(1-42) oligomer formation

-four-bead protein model with amino acid-specific interactions due to hydropathy

-in agreement with *in vitro* findings of Bitan

-yields new structural predictions amenable to *in vitro* testing

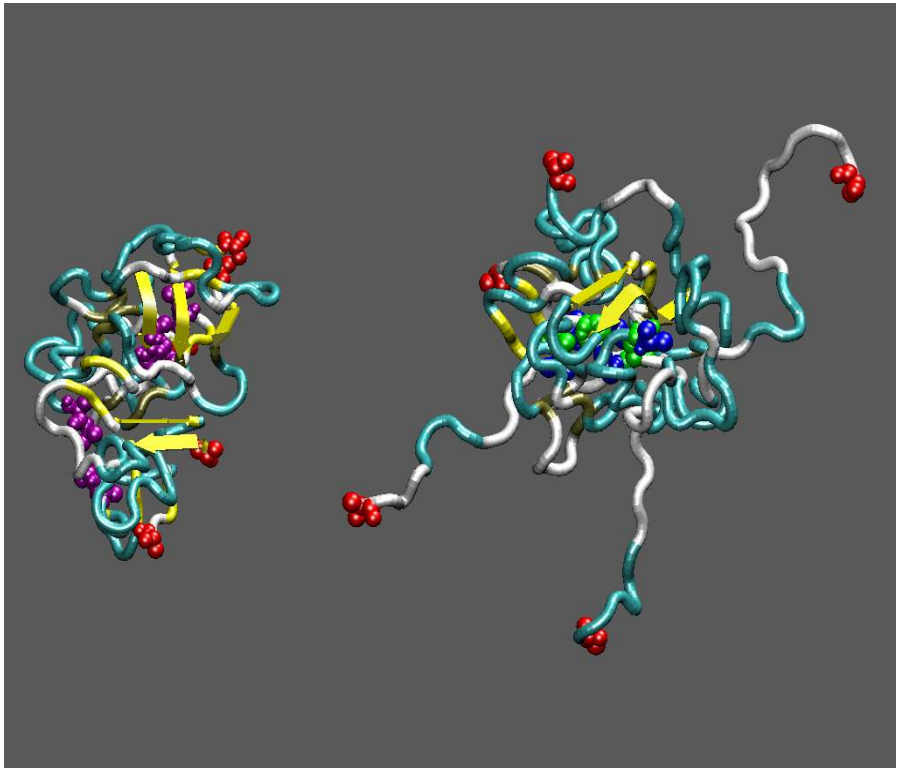
Aggregate of 16 Aβ(1-42)



Ile31, Ile32, Ile41 (green)

β-strand (yellow ribbon)

Aβ(1-40) and Aβ(1-42) pentamers



Asp1 (red), Val40 (purple), Ile41 (green),

Ala42 (blue)

Urbanc, Cruz, Yun, Buldyrev, Bitan, Teplow & Stanley, PNAS (2004).

Biological relevance of our approach: a united-atom model

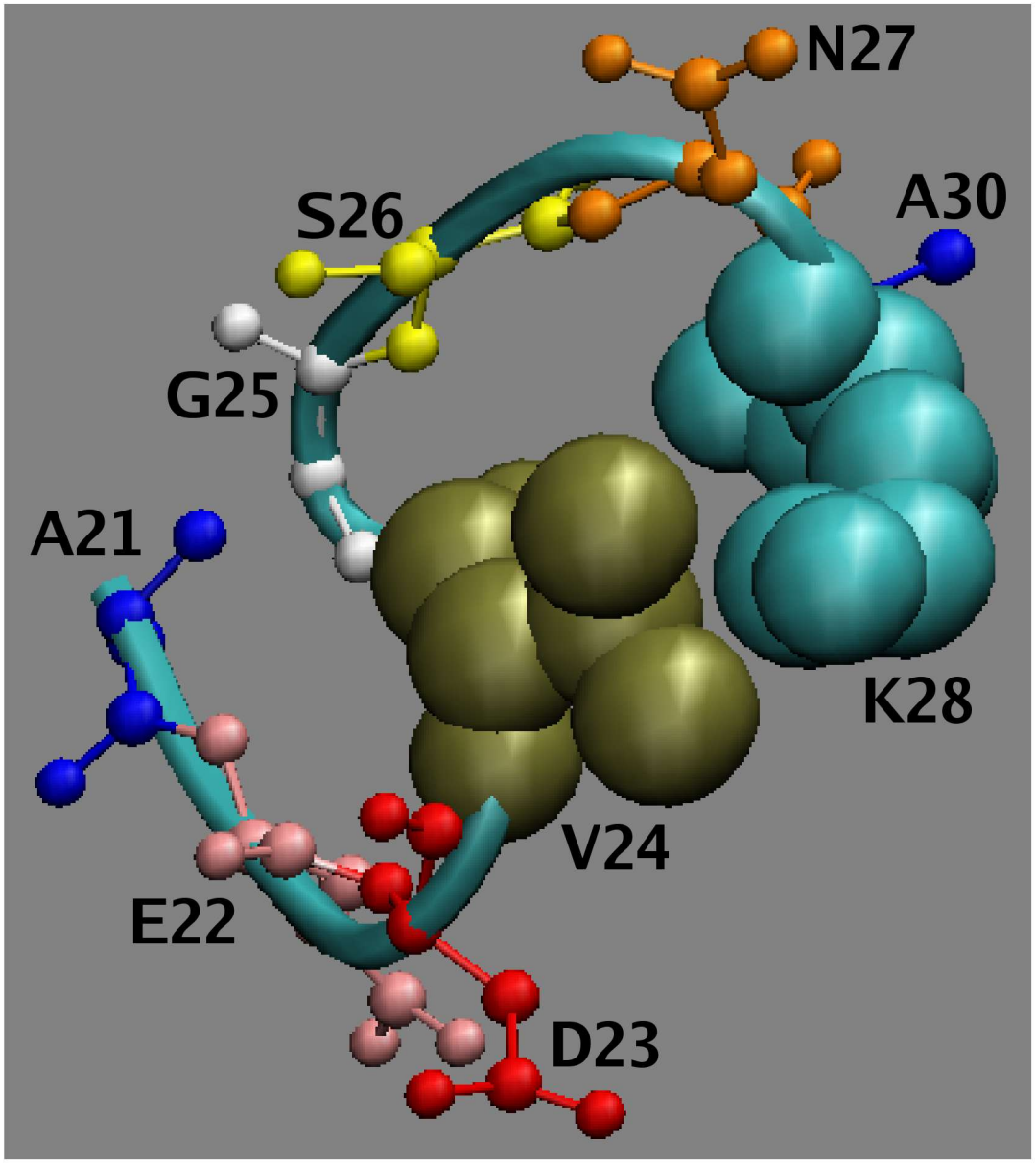
DMD Aβ(21-30) folding

-united-atom protein model with explicit heavy side-chain atoms

-shows Val24-Lys28 packing due to the hydrophobic effect

-salt bridge Glu22-Lys28 stabilizes the fold at an intermediate strength of electrostatic interactions

-salt bridge Asp23-Lys28 destabilizes the fold at a large strength of electrostatic interactions



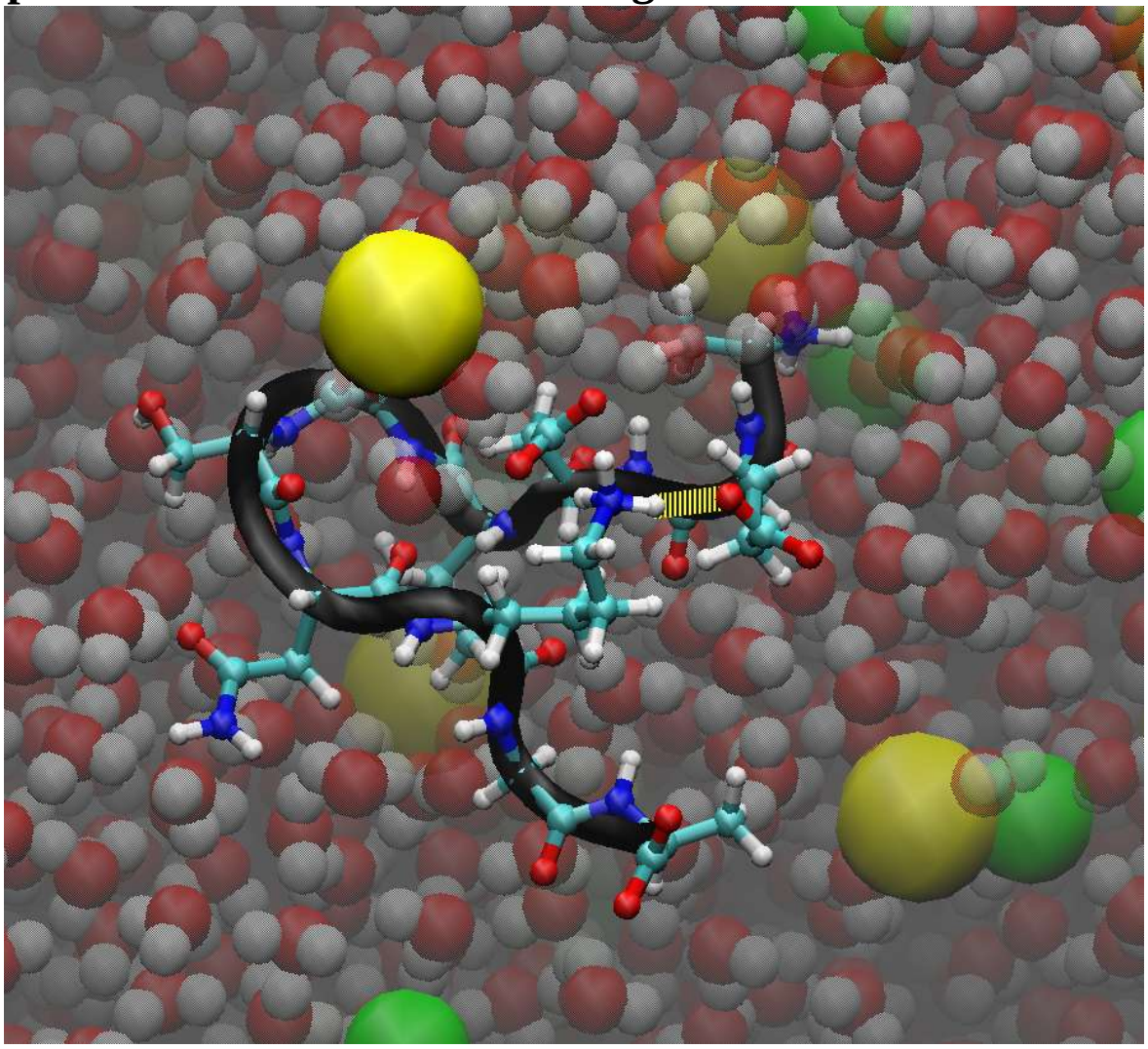
Borreguero, Urbanc, Lazo, Buldyrev, Teplow & Stanley, PNAS (2005).

Biological relevance of our approach: all-atom MD study

All-atom folding of Aβ(21-30) and its mutant (Glu22Gln)

-MD in explicit solvents: normal water, reduced-density water and water with salt ions

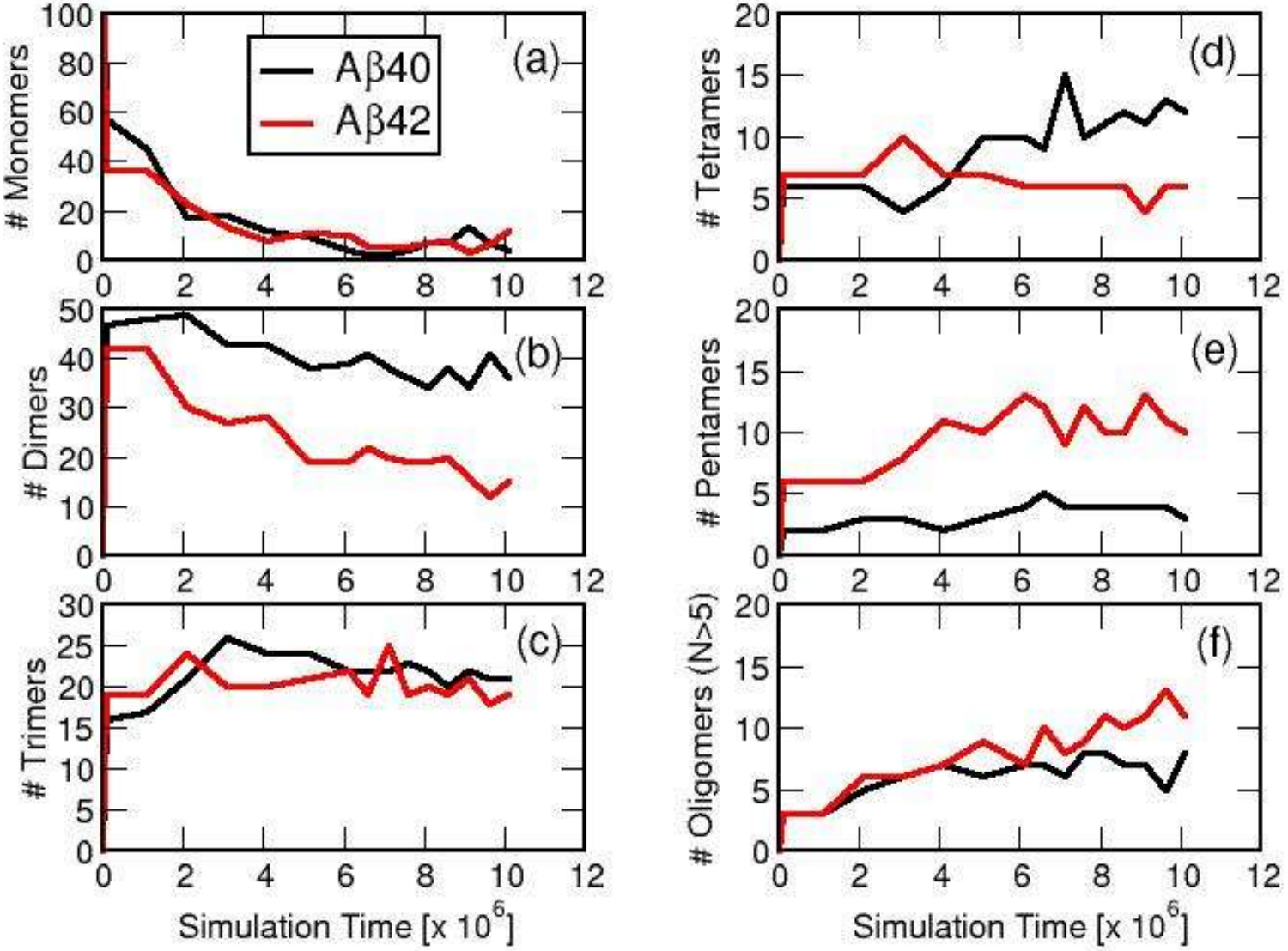
-in agreement with *in vitro* and previous DMD studies & folding is sensitive to solvent and mutation

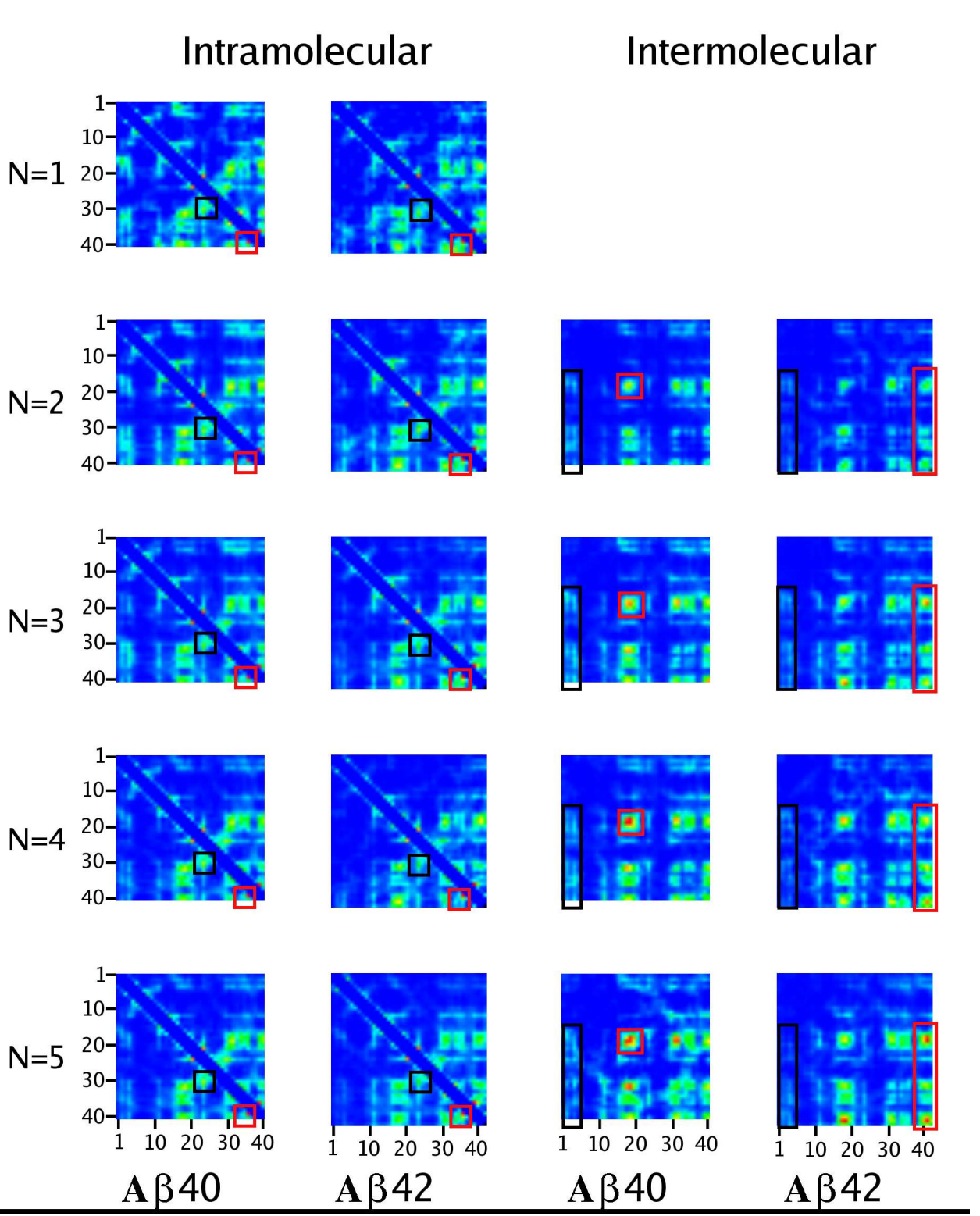


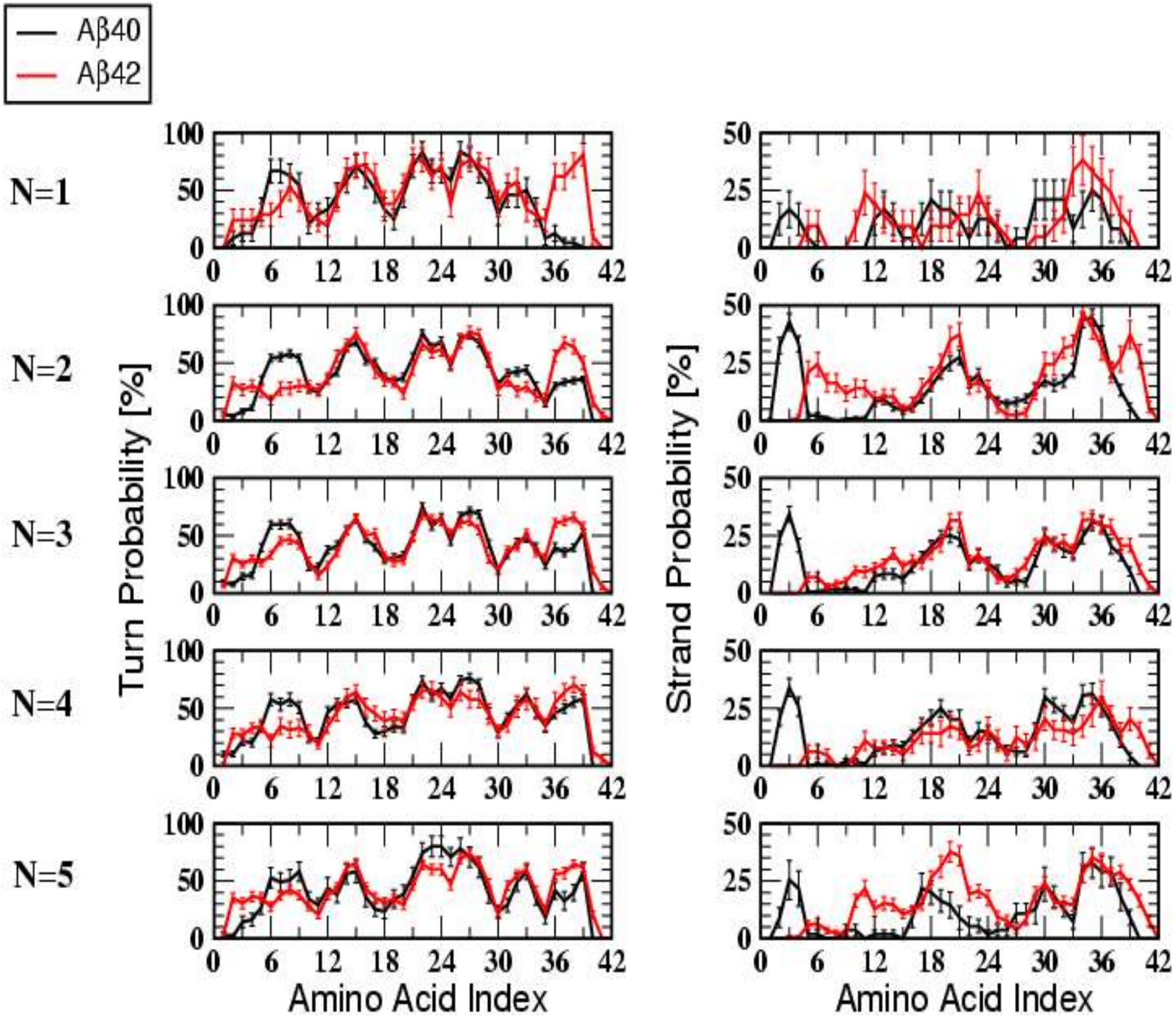
black tube ... backbone
red sphere ... O
white sphere ... H
green sphere ... Na+
yellow sphere ... Cl-
cyan sphere ... C
blue sphere ... N
yellow hashed line ...
Glu22-Lys28 salt bridge

Cruz, Urbanc, Borreguero, Lazo, Teplow & Stanley, PNAS, in press.

Number of monomers and oligomers versus simulation time



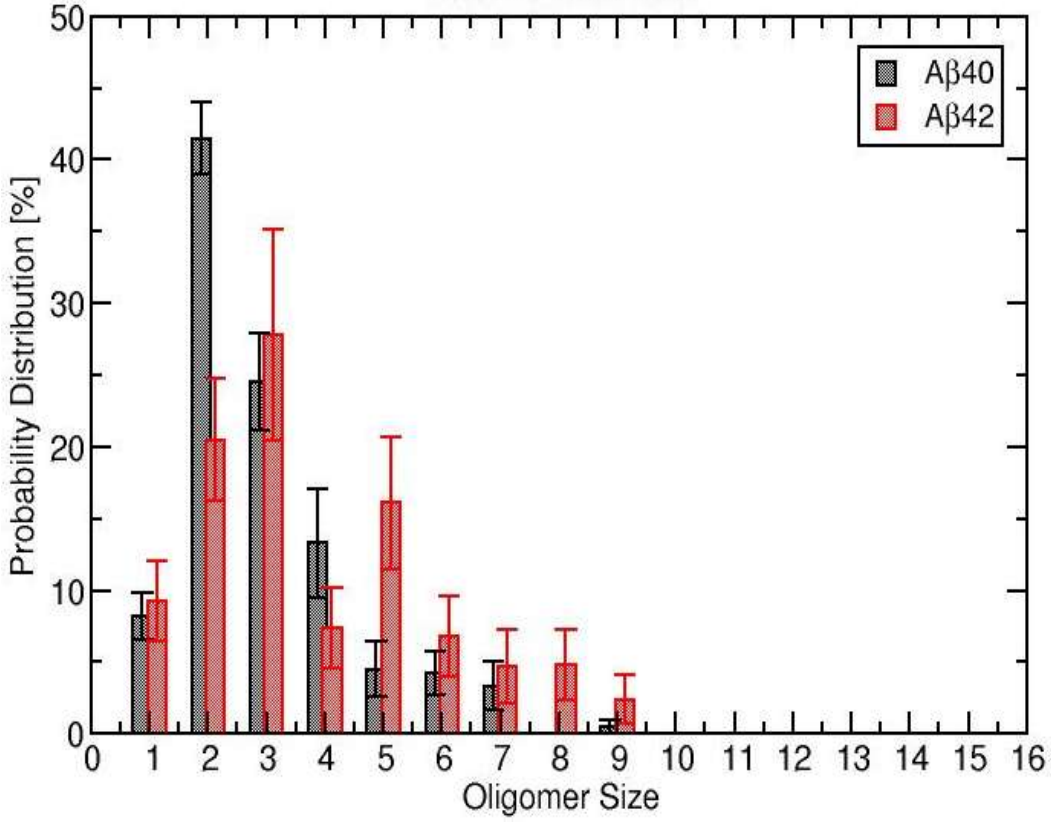

Intramolecular
Intermolecular
N=1
N=2
N=3
N=4
N=5
1
10
20
30
40
Aβ40
Aβ42
Aβ40
Aβ42


Aβ40
Aβ42
N=1
N=2
N=3
N=4
N=5
Turn Probability [%]
Strand Probability [%]
Amino Acid Index
Amino Acid Index

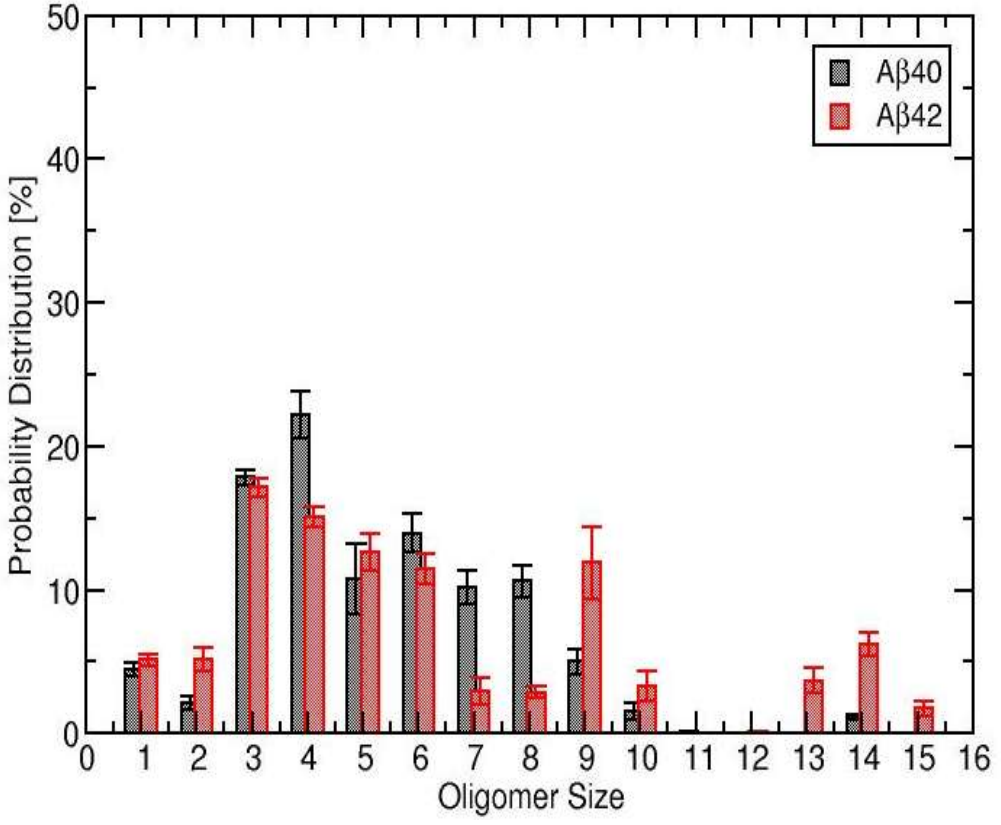
Effects of the interaction between two charged side chains on oligomer size distribution

Size distribution without electrostatic interaction

Urbanc et al. 2004 PNAS

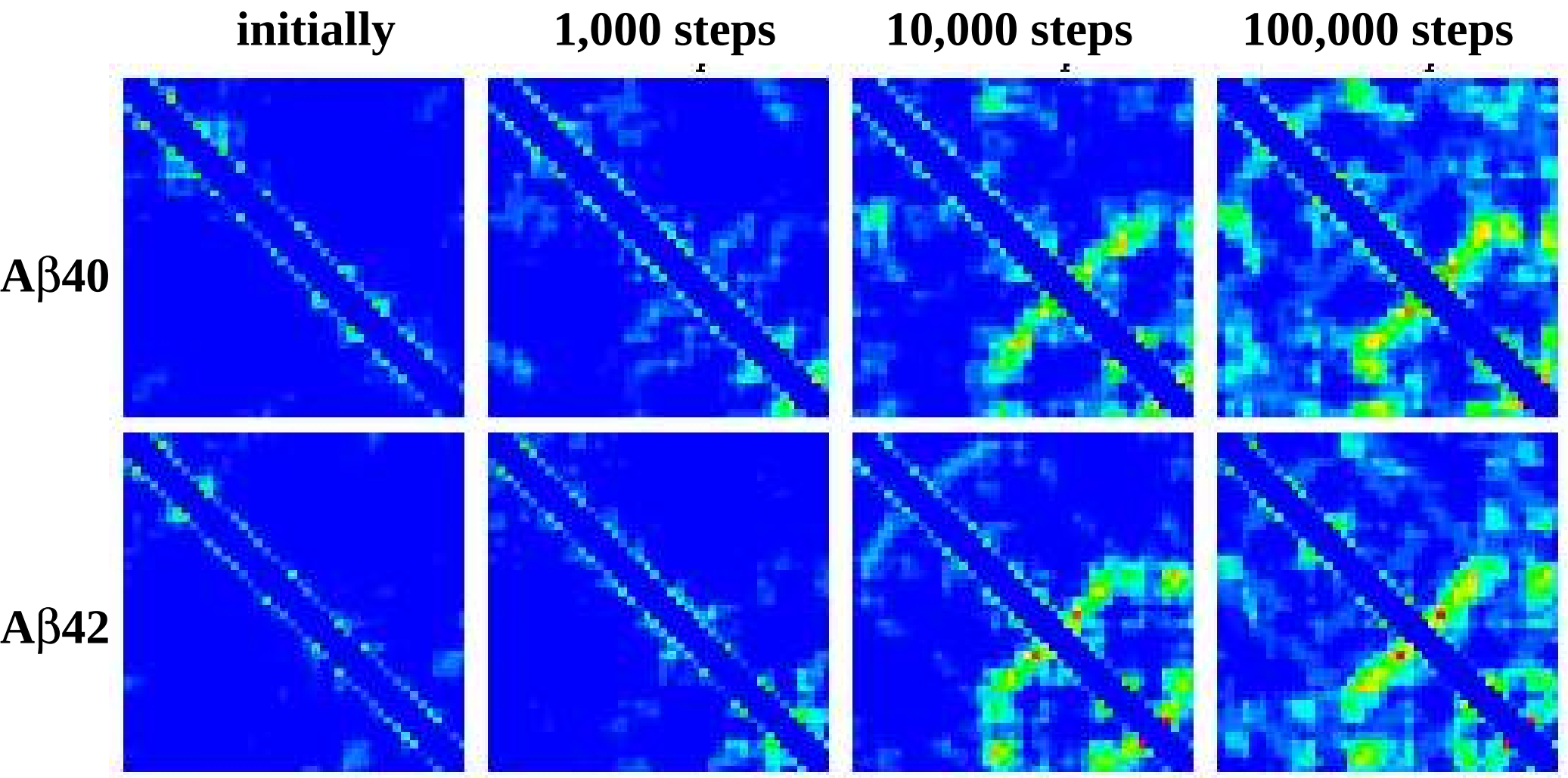


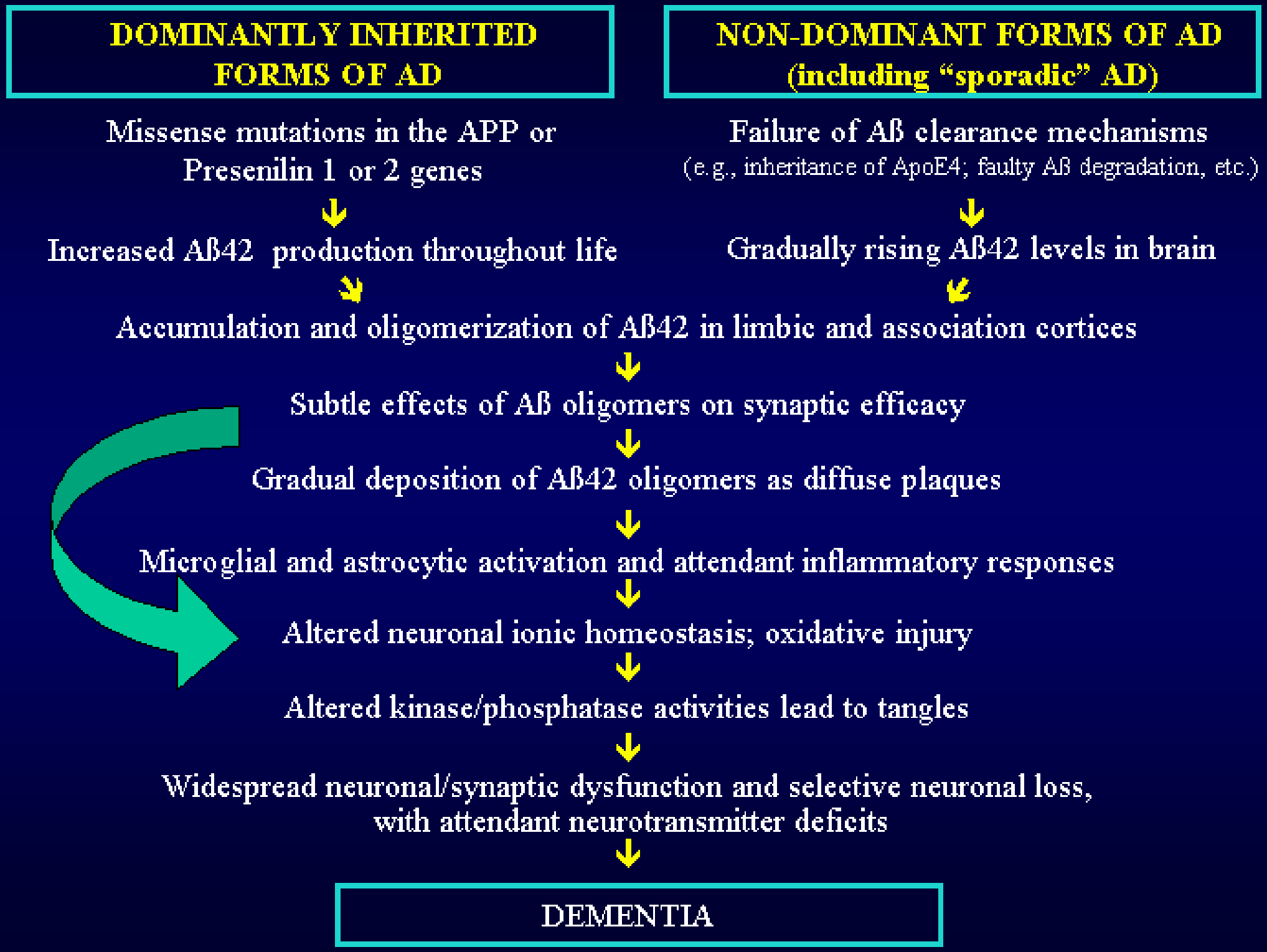
Size distribution with electrostatic interaction



Interactions between charged side chains speed up oligomerization, but do not affect the degree of the difference between Aβ40 and Aβ42.

Time evolution of monomer folding: Hydropathy and Charge




DOMINANTLY INHERITED FORMS OF AD
NON-DOMINANT FORMS OF AD (including "sporadic" AD)
Missense mutations in the APP or Presenilin 1 or 2 genes
Failure of Aß clearance mechanisms
(e.g., inheritance of ApoE4; faulty Aß degradation, etc.)
Increased Aß42 production throughout life
Gradually rising Aß42 levels in brain
Accumulation and oligomerization of Aß42 in limbic and association cortices
Subtle effects of Aß oligomers on synaptic efficacy
Gradual deposition of Aß42 oligomers as diffuse plaques
Microglial and astrocytic activation and attendant inflammatory responses
Altered neuronal ionic homeostasis; oxidative injury
Altered kinase/phosphatase activities lead to tangles
Widespread neuronal/synaptic dysfunction and selective neuronal loss, with attendant neurotransmitter deficits
DEMENTIA

WHAT DO *IN VITRO* STUDIES SHOW?

- **Aβ40: monomers to tetramers, Aβ42: paranuclei (pentamers/hexamers) and larger oligomers, multiples of paranuclei (10-12, 15-18):**

  Bitan, Kirkitadze, Lomakin, Vollers, Benedek & Teplow, PNAS (2003);

- **hydrophobic nature of C-terminal Ile41 and Ala42 plays a key role in Aβ42 paranuclei formation:**

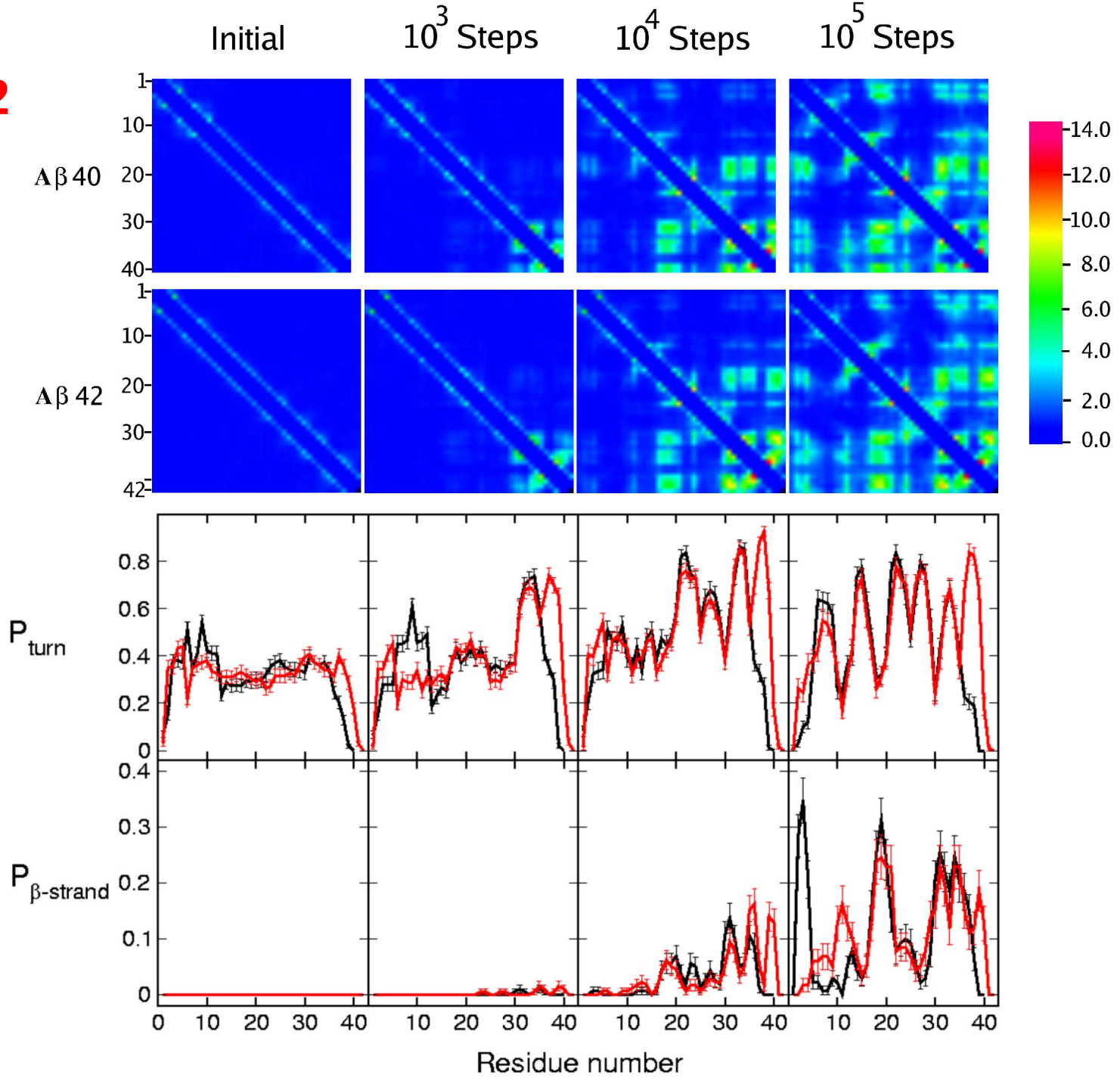
  Bitan, Vollers & Teplow, JBC (2003);

- **oxidation of Met35 disruptsAβ42 paranuclei formation:**

  Bitan, Tarus, Vollers, Lashuel, Condron, Straub & Teplow, JACS (2003).

Aβ40 versus Aβ42 monomer folding

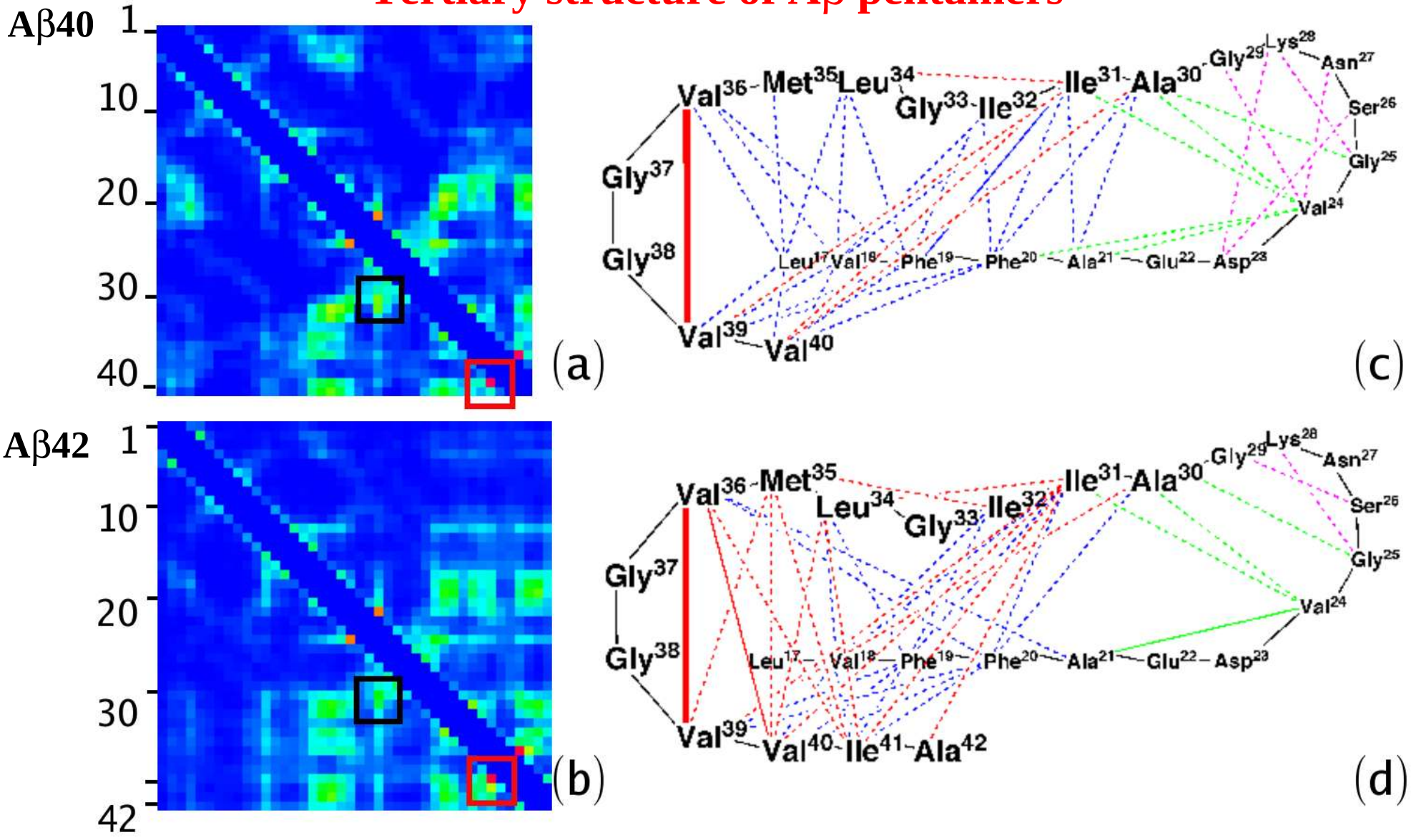
- **contacts form first at the C-termini**
- **turn at Gly37-Gly38 forms in Aβ42 only**
- **β-strand at Ala2-Phe4 forms in Aβ40 only**



Bitan, Tarus, Vollers, Lashuel, Condron, Straub & Teplow, JACS (2003).

Oxidation of Met35 blocks Aβ42 paranuclei (pentamer/hexamer) formation

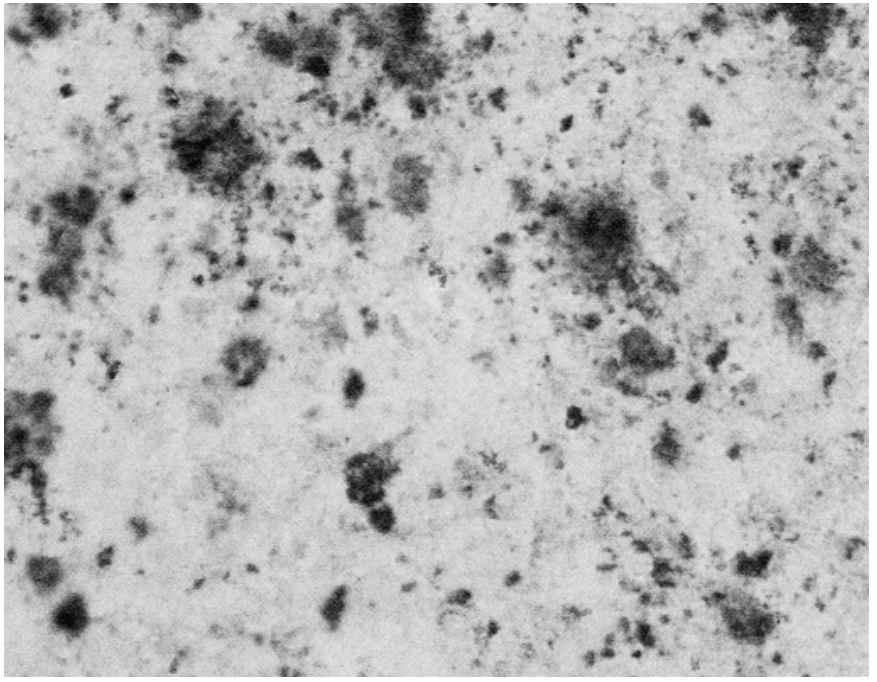
Tertiary structure of Aβ pentamers



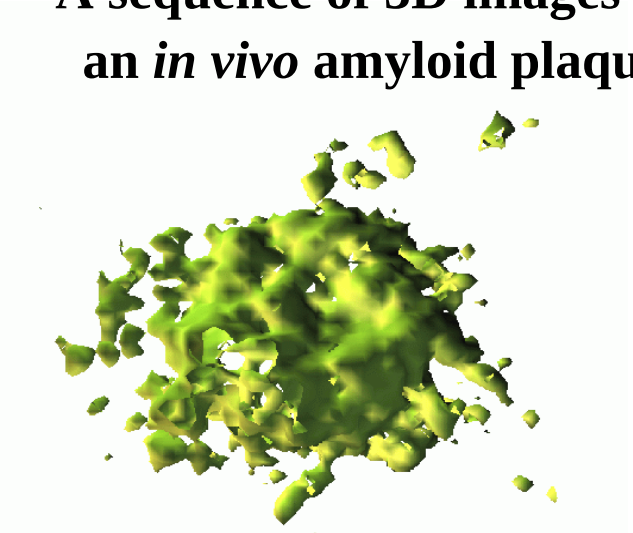
Leu34,Met35,Val36 strongly connected to Val40,Ile41,Ala42 in Aβ42, not in Aβ40

Puzzle of amyloid plaques

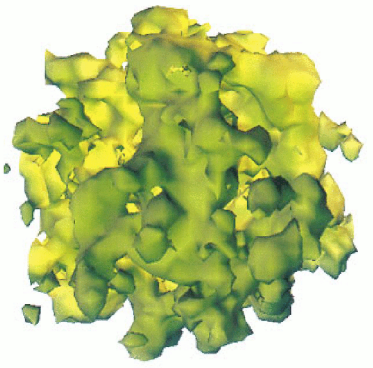
Optical microscope image of a human Nissl stained section



A sequence of 3D images of an *in vivo* amyloid plaque

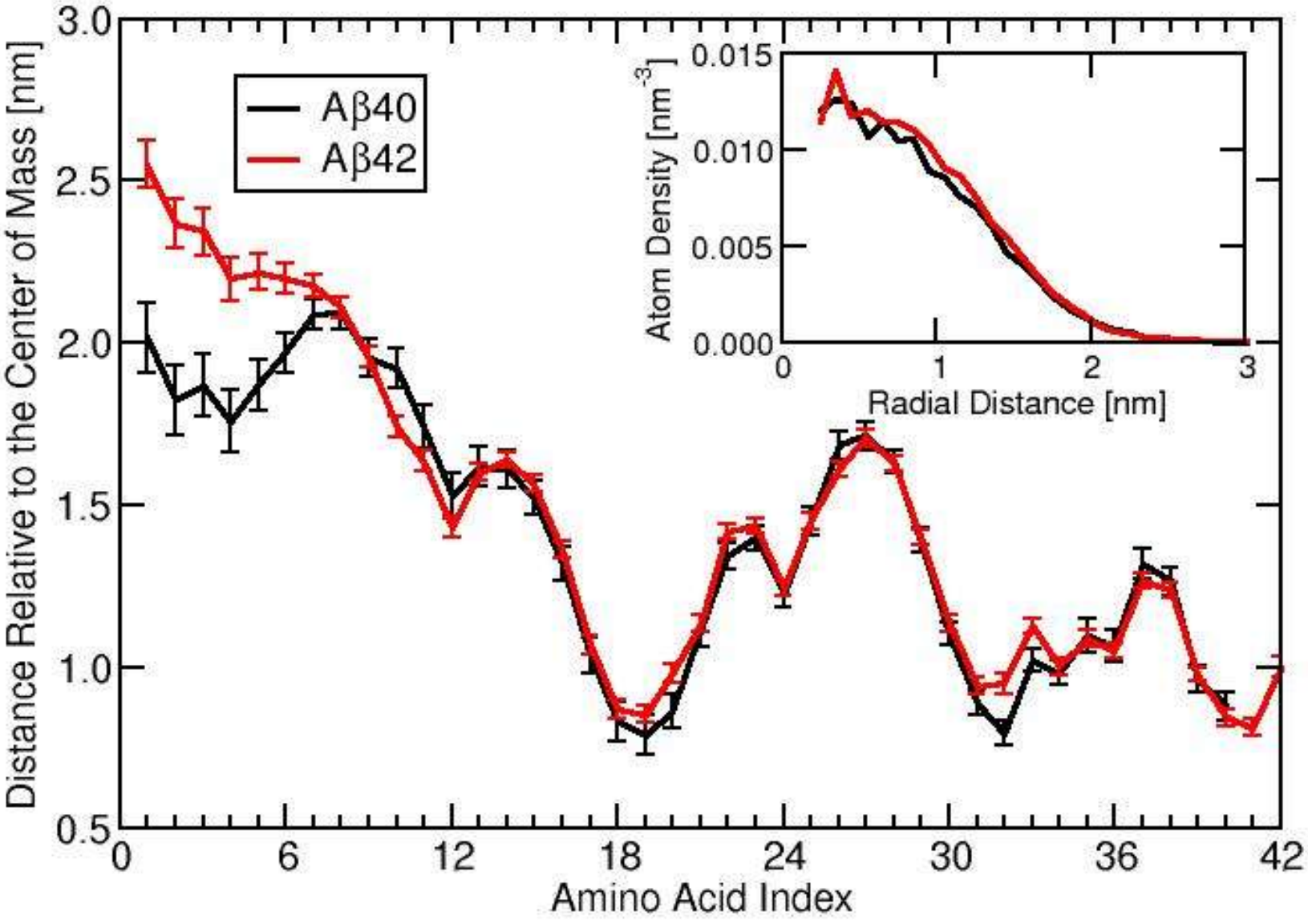


3D model of amyloid plaque growth



Cruz, Urbanc, Buldyrev, Christie, Gomez-Isla, Havlin, McNamara, Stanley, and Hyman, *Aggregation and disaggregation of senile plaques in Alzheimer disease*, PNAS (1997).

Geometrical characteristics of Aβ40 versus Aβ42 pentamers



Geometrical characteristics of Aβ40 versus Aβ42 pentamers