PROJECT 4:

Ab Initio Molecular Dynamics of Aβ Folding and Assembly

Strong collaboration with Lazo, Teplow (Project 1), Lomakin, Benedek (Project 2), Bowers, Shea (Project 3) and Bitan (Project 5)

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Experience:

- **molecular dynamics (MD) simulations of water**
  96 papers, 6 in *Nature*
- **discrete MD with coarse-grained models of proteins**
  13 papers
- **statistical physics approach to AD research**
  15 papers, 10 in *PNAS*

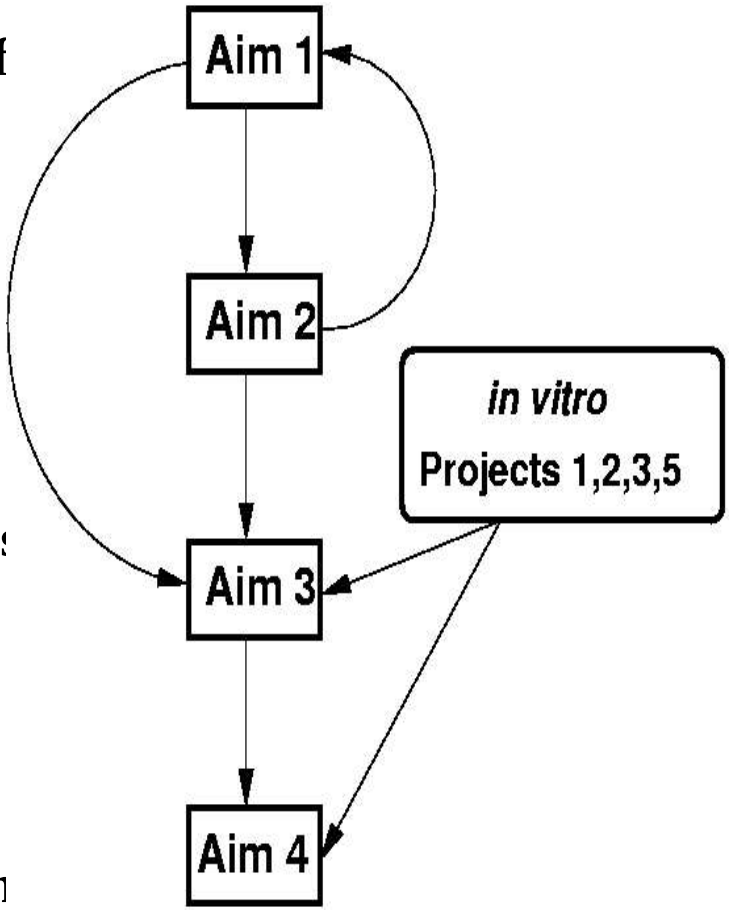
OUTLINE OF SPECIFIC AIMS:

<u>Aim 1:</u> Develop the first-generation coarse-grained Aβ models to be used in the DMD studies of Aβ folding and assembly;

<u>Aim 2:</u> Employ the all-atom MD in explicit solvent for stability analysis and to validate the DMD approach;

<u>Aim 3:</u> Develop the second-generation DMD models based on *in silico*<--->*in vitro* synergistic feedback among the projects;

<u>Aim 4:</u> Generalize the DMD approach and apply it to a study of mixtures of full-length Aβ with oligomerization inhibitors to achieve rapid *in silico* screening.



Biological relevance of the DMD approach: the four bead model

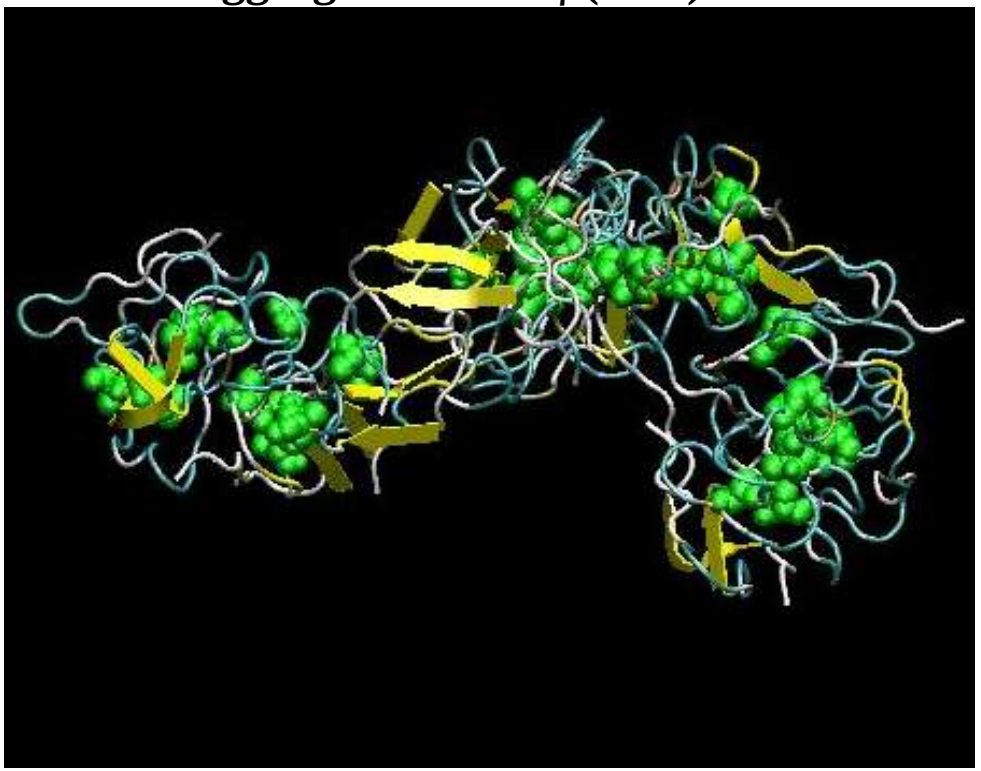
Aβ(1-40) and Aβ(1-42) oligomer formation

-four-bead protein model with amino acid-specific hydropathy

-in agreement with *in vitro* findings of Bitan

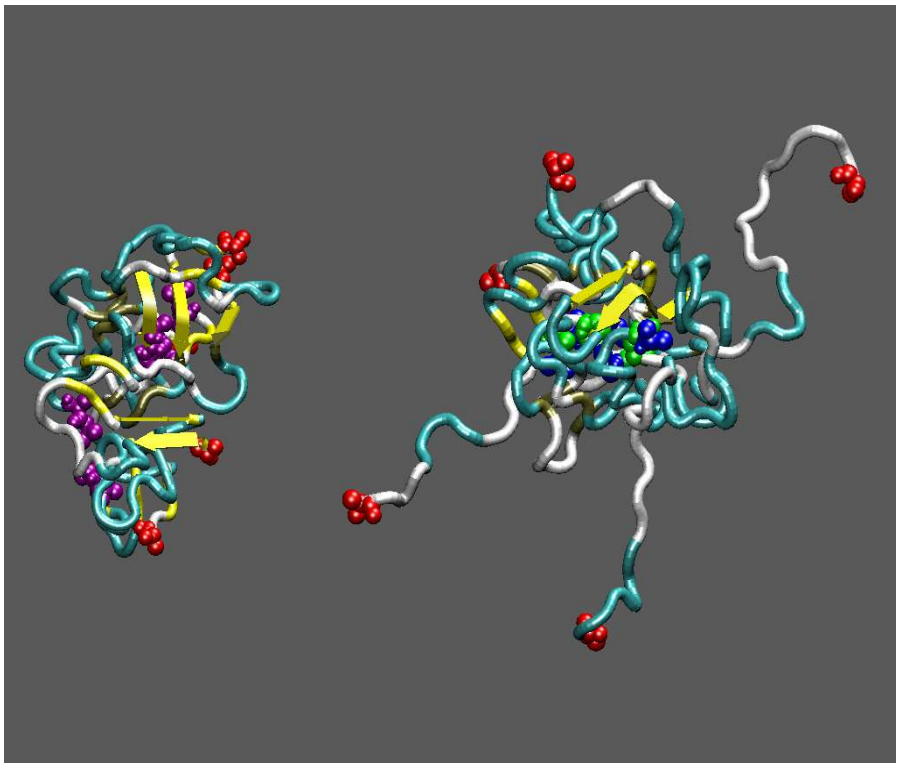
-yields new structural predictions amenable to *in vitro* testing

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, and Stanley, PNAS (2004).

Biological relevance of the DMD approach: a united-atom model

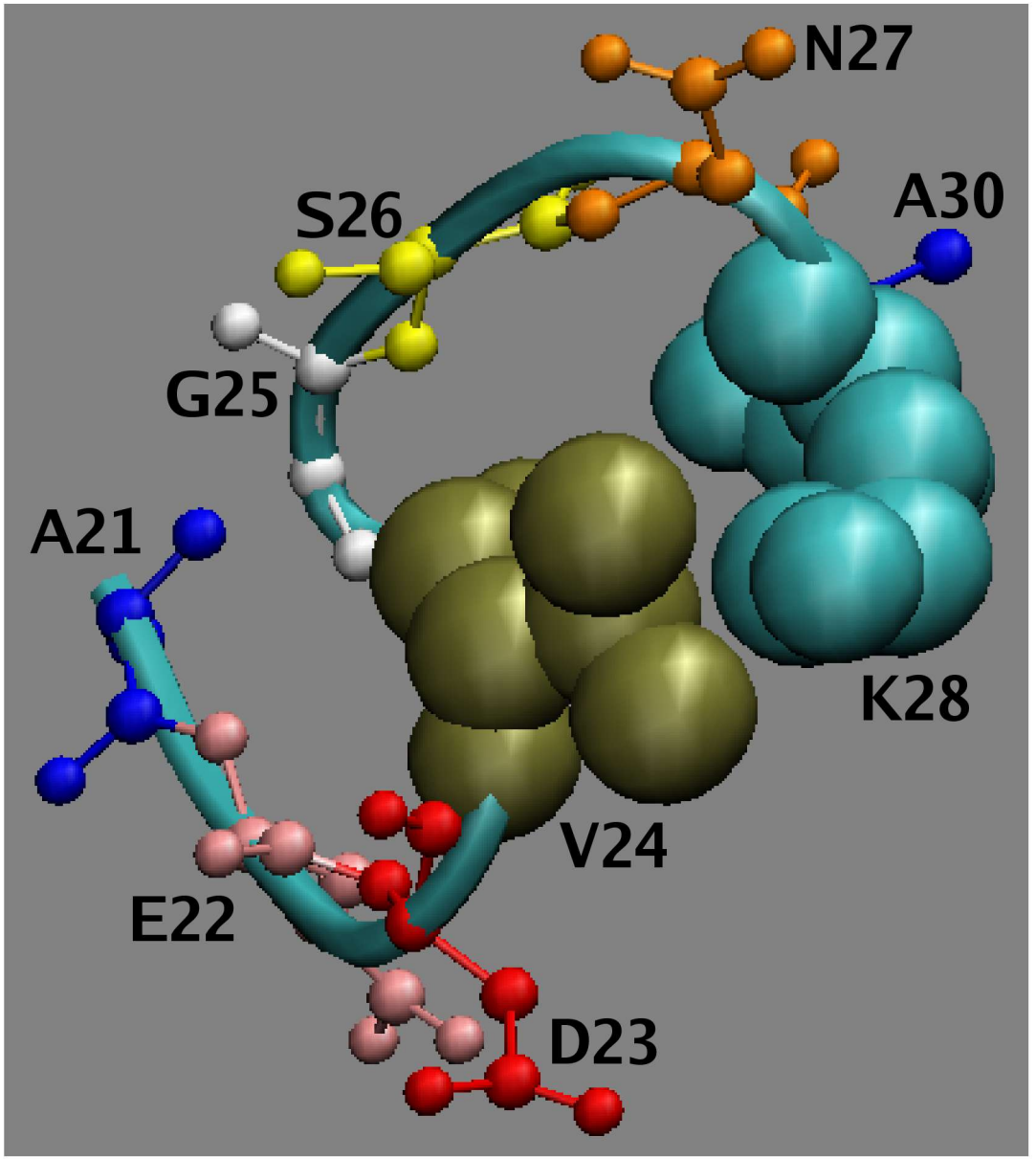
DMD Aβ(21-30) folding

-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



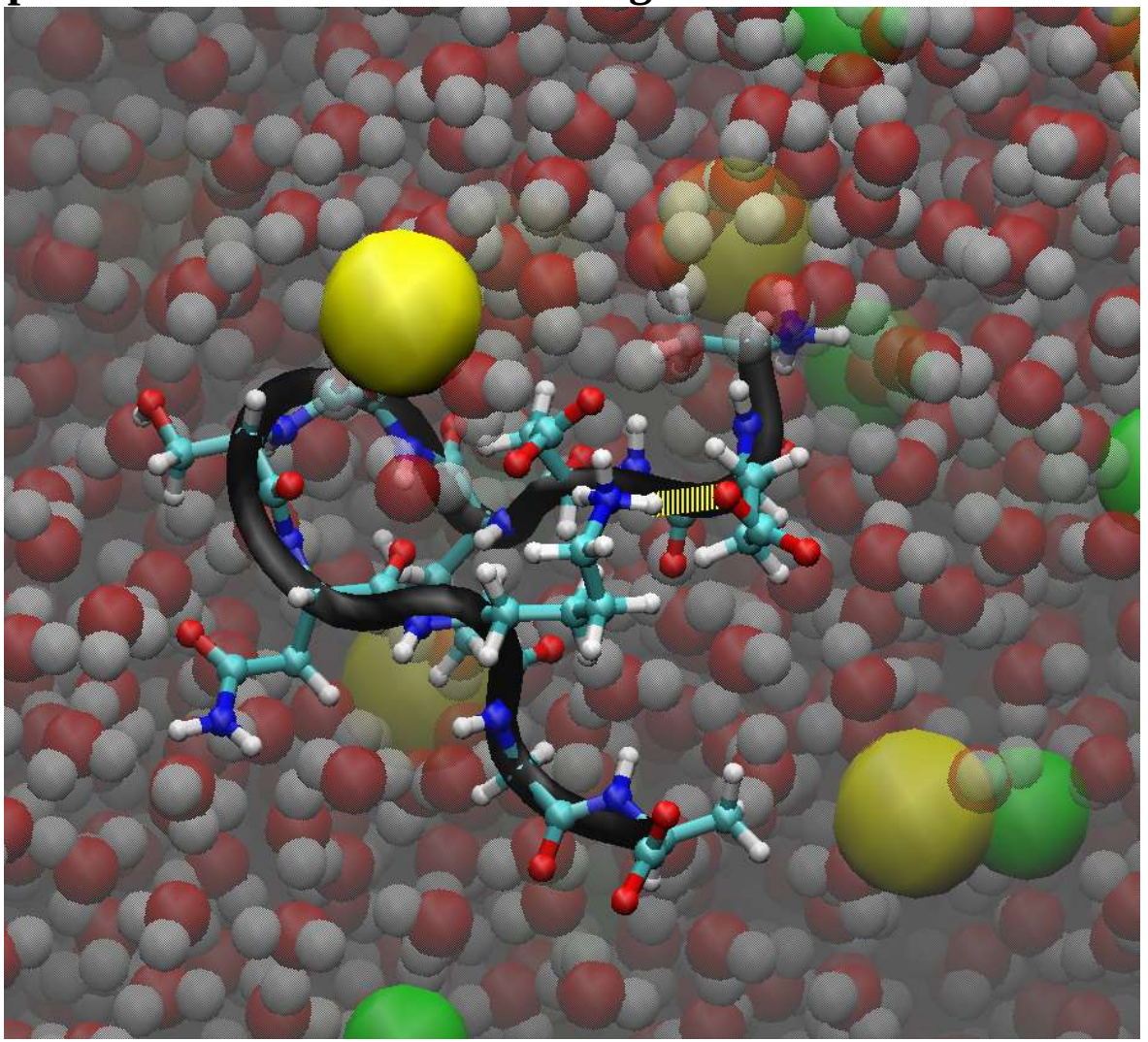
Borreguero, Urbanc, Lazo, Buldyrev, Teplow, and Stanley, PNAS (2005).

Biological relevance of the DMD 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 & 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, and Stanley, PNAS, in press.

NEW PRELIMINARY WORK:

<u>Aim 1:</u> The role of electrostatic interactions between charged amino acids on assembly of Aβ(16-22) and full-length Aβ(1-40) and Aβ(1-42):

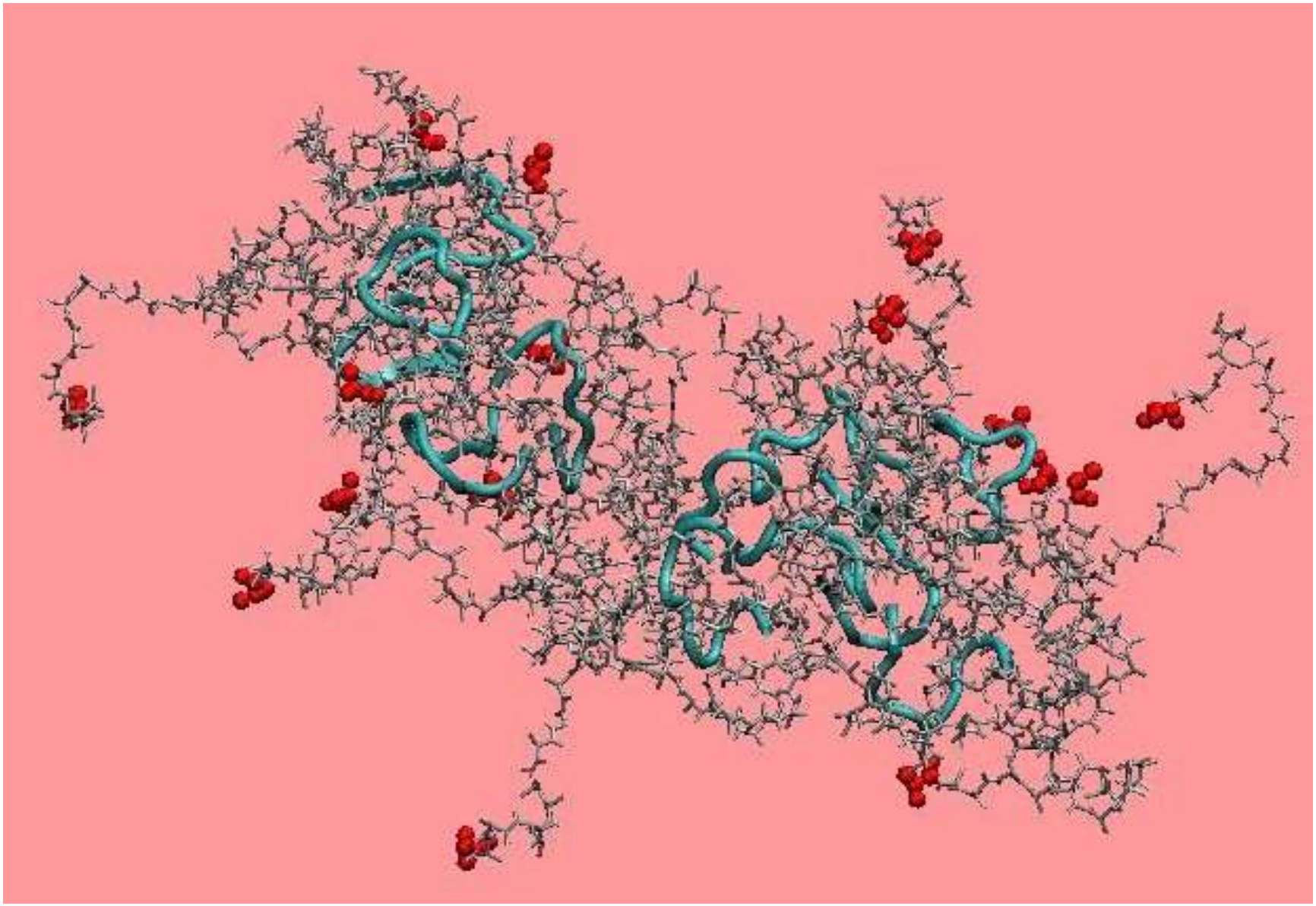
- **Peng, Urbanc, Buldyrev, Cruz, Yun, Teplow, and Stanley: ``Discrete molecular dynamics study of Aβ(16-22) folding and aggregation,'' submitted.**
- **Yun, Urbanc, Cruz, Bitan, Teplow, and Stanley: ``Role of electrostatic interactions in Aβ oligomer formation: A discrete molecular dynamics study,'' in preparation.**
- **Urbanc, Borreguero, Cruz, and Stanley: ``Amyloid β-protein aggregation: *Ab initio* discrete molecular dynamics approaches,'' submitted to *Methods in Enzymology*.**

<u>Aim 2:</u> All-atom MD simulations of Aβ(21-30) in normal water, reduced-density water, and water with salt ions:

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

<u>Aim 3:</u> The second-generation four-bead model is under development: different-size side-chain beads and more precise hydropathic interactions are implemented and are being tested.

<u>Aim 4:</u> The DMD code has been generalized to account for assembly studies of two different peptides.



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

FUTURE PLANS

Aim 1: -Study the role of electrostatic interactions on Aβ folding & assembly, in particular the effects of charged termini;
-Study the effect of amino acid substitutions on Aβ folding & oligomer formation.

Aim 2: -Test stability of Aβ conformers in different solvents & at different external conditions (temperature, pressure, ...).

Aim 3: -Refine the four-bead and united-atom model by implementing more specific interactions, consistent with *in vitro* findings of the Teplow, Bowers, Shea, and Bitan groups.

Aim 4: -Apply the DMD approach to study mixtures of full-length Aβ and peptide inhibitors, such as C-terminal fragments.