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1845-18

Conference on Structure and Dynamics in Soft Matter and Biomolecules: From Single Molecules to Ensembles

4 - 8 June 2007

Simulations of Peptide Aggregation

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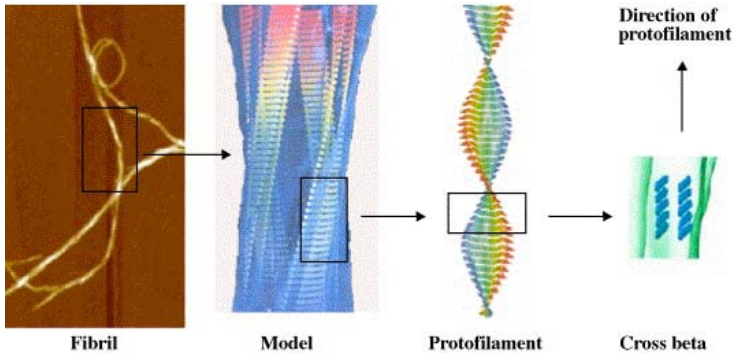
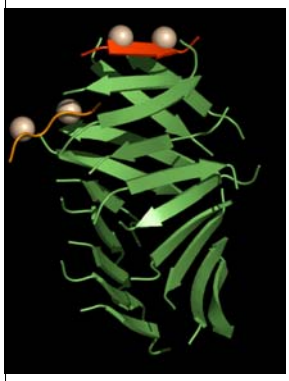
Simulations of Peptide Aggregation

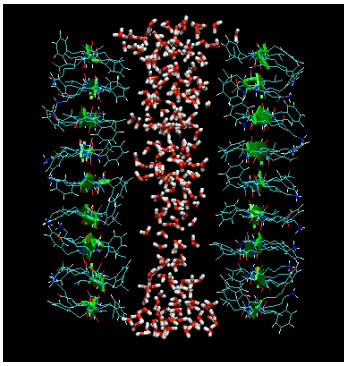


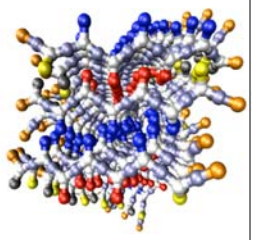
JOAN-EMMA SHEA, DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA, SANTA BARBARA

OUTLINE

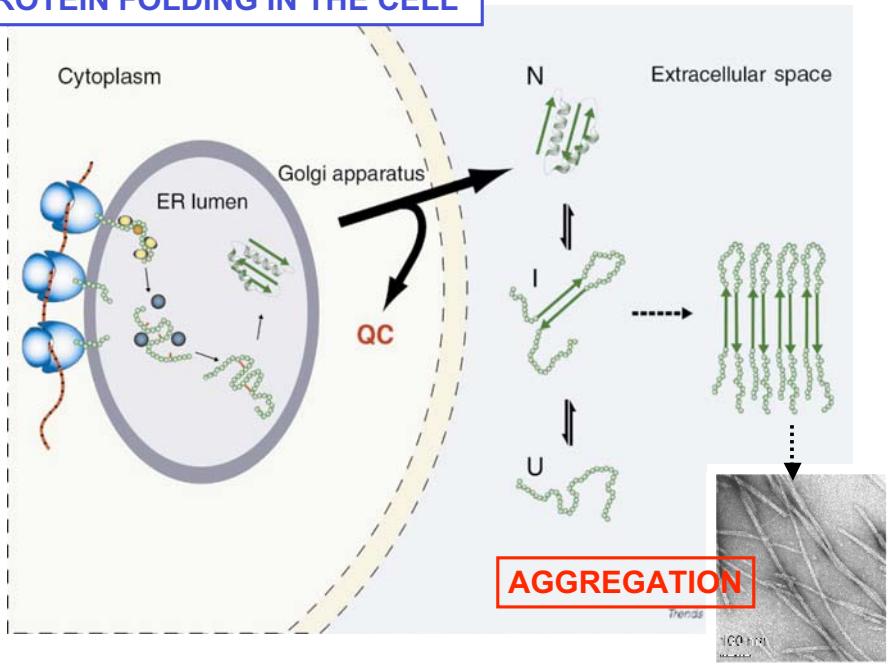
1. Aggregation Inhibition
2. Water and Assembly
3. Coarse-Grained models





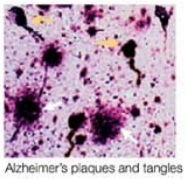


PROTEIN FOLDING IN THE CELL



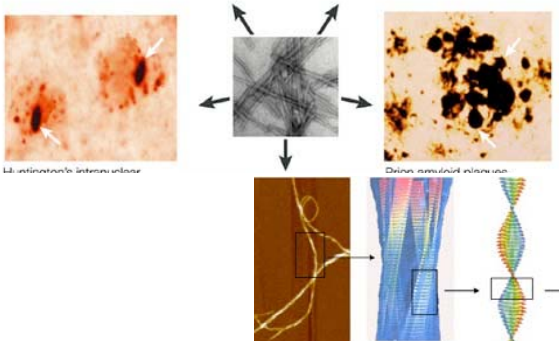
PROTEIN AGGREGATION AND DISEASE

Alzheimer



Parkinson

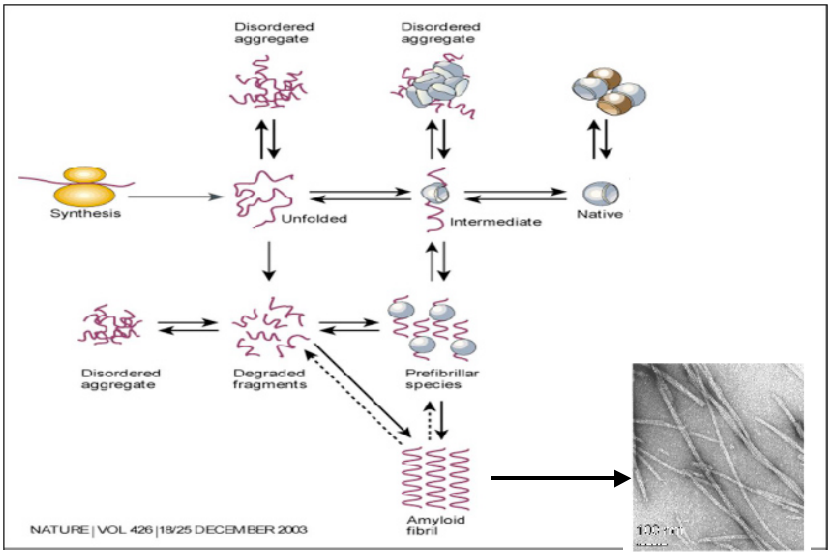
Huntington



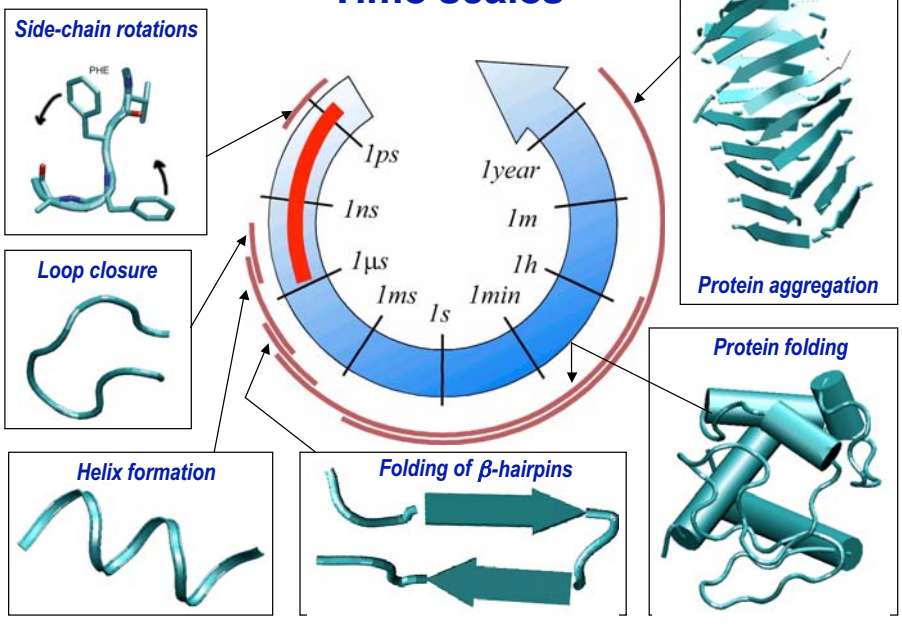
Prion
("Mad Cow")

Proteins not associated with a specific disease can also aggregate to form amyloid fibrils

Protein and Peptide Aggregation



Time scales

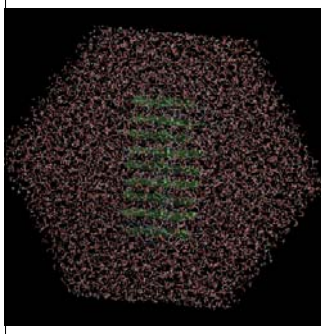


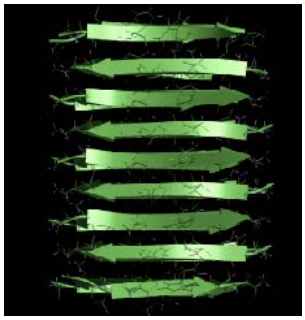
TYPES OF SIMULATIONS

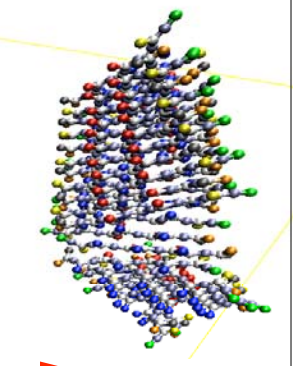
All-atom: (MD)
With EXPLICIT
Solvent

All-atom:
IMPLICITsolvent

Off-lattice minimalist:
Langevin dynamics

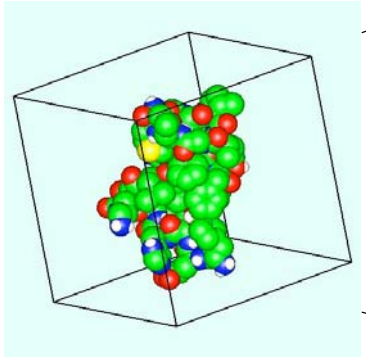


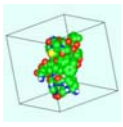


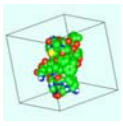


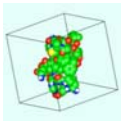
COARSE GRAINING

Simulation protocol: Replica Exchange MD









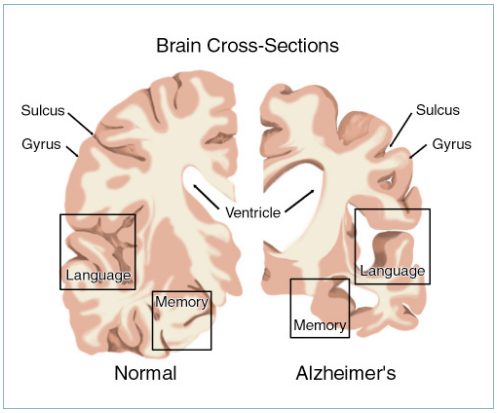
T_1

T_2

T_N

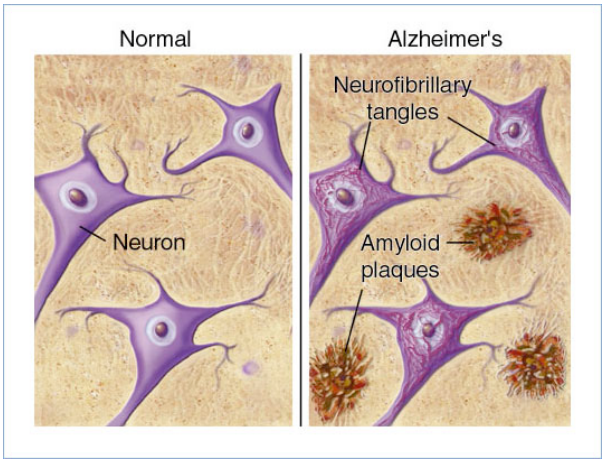
$$\min\left\{1, e^{(\beta_j-\beta_i)(E_n-E_m)}\right\}$$

PEPTIDE INHIBITORS OF ALZHEIMER Aβ AGGREGATION

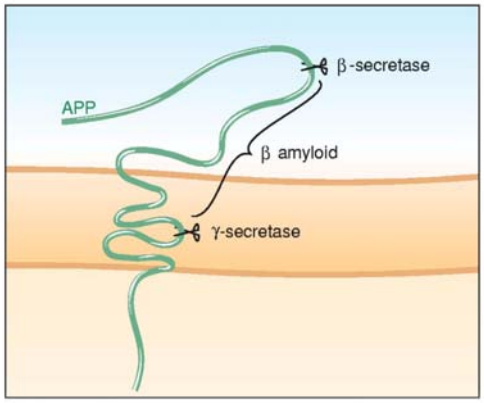


Alzheimer's disease (AD) is a neurodegenerative disease of the central nervous system.

ALZHEIMER DISEASE IS CHARACTERIZED BY THE PRESENCE OF NEUROFIBRILLAR TANGLES AND AMYLOID PLAQUES IN THE BRAIN



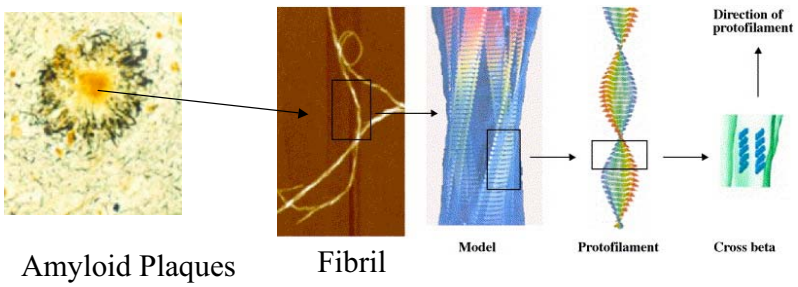
AMYLOID PLAQUES CONSIST OF AMYLOID BETA (Aβ) PEPTIDES GENERATED FROM THE PROTEOLYTIC CLEAVAGE OF THE APP TRANSMEMBRANE PROTEIN



Aβ40: DAEFRHDSGYEVHHQ^{16}KLVFFA^{22}EDVGSNKGAIIGLMVGGVV

Aβ42: DAEFRHDSGYEVHHQ^{16}KLVFFA^{22}EDVGSNKGAIIGLMVGGVVIA

In healthy individuals, the Aβ peptides are broken down and eliminated. In AD, these peptides self-assemble into amyloid fibrils



Amyloid Plaques Fibril

Aβ42: DAEFRHDSGYEVHHQK^{17}LVFFA^{22}EDVGSNKGAIIGLMVGGVVIA

Central Hydrophobic Core

Bend region that nucleates the folding of Aβ

J.-E Shea and co-workers: JACS (2005) 127: 2075-2084; Prot. Sci. (2006) 15: 420-428; Prot. Sci. (2006) 15: 1239-1247; JMB (2006), 362: 567-579; JMB (2007) 366: 275-285

Both small soluble oligomers and fibrils appear to be toxic to cells.

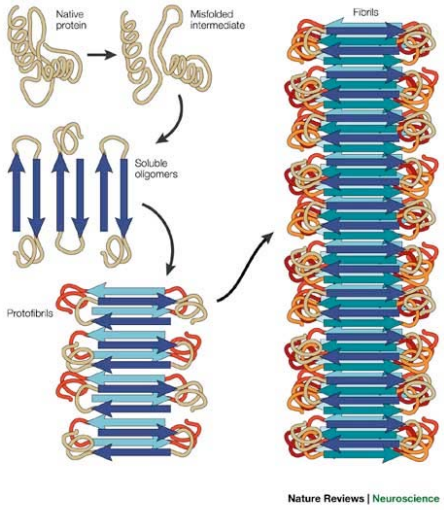
Misfolded Protein

Fibril

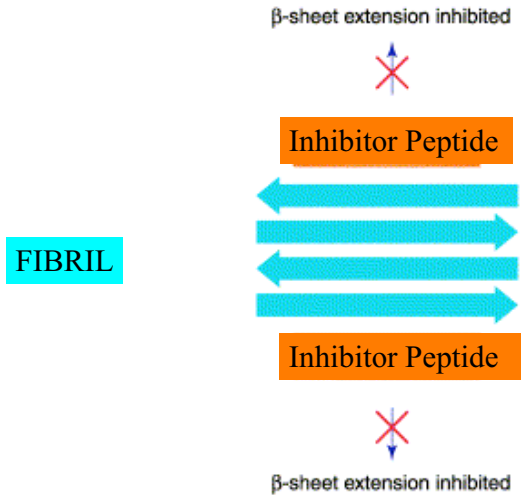
Native Protein

Soluble Oligomer

Protofibrils



Inhibition Strategies



J M Mason, N Kokkoni, K Stott and A J Doig
Curr Op Struct Bio, 2003, 13:526-532

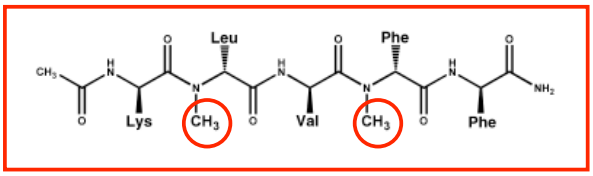
N-METHYLATED PEPTIDE INHIBITORS

Aβ42: DAEFRHDSGYEVHHQK[17]LVFFA[22]EDVGSNKGAIIGLMVGGVVIA

Central Hydrophobic Core

Aβ16-22: K[17]LVFFA[22]E Aggregates!

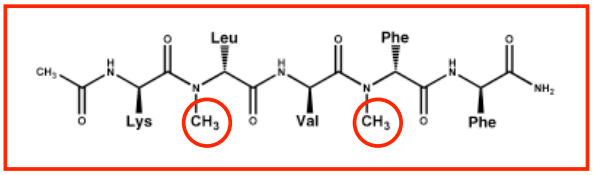
The Inhibitor: **Aβ16-20m: [16]K(me)LV(me)FF**

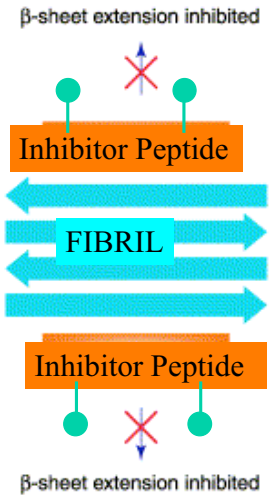


Acts on **Aβ16-22 and Aβ40/42**

Inhibition Strategies

The Inhibitor: **Aβ16-20m: [16]K(me)LV(me)FF**



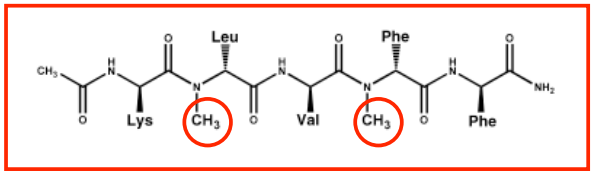


J M Mason, N Kokkoni, K Stott and A J Doig
Curr Op Struct Bio, 2003, 13:526-532

N-METHYLATED PEPTIDE INHIBITORS

N-methylated Aβ(16-20)m peptides can:

1) **prevent the aggregation of Aβ40/42 and Aβ16-22 peptides**
2) **disassemble existing fibrils and possibly small oligomers.**



^{16}K(me)LV(me)FF

Aβ40: DAEFRHDSGYEVHHQ^{16}KLVFFA^{22}EDVGSNKGAIIGLMVGGVV

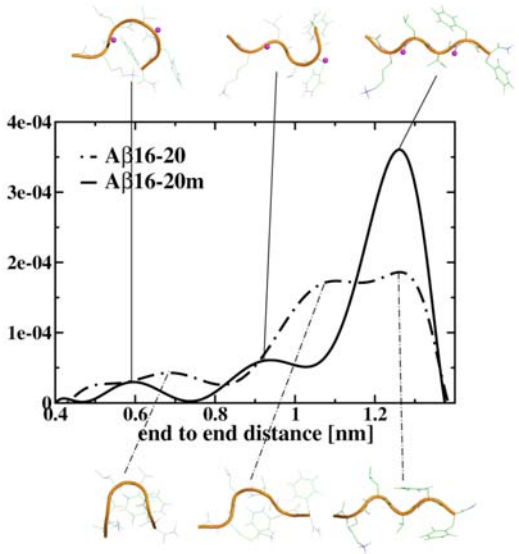
Fibrils of Aβ(1-40) peptides

After Incubation with Aβ(16-20)m peptides

Meredith and co-workers, J. Pep. Res. (2002) **60**, 37-55

Conformational Space of of N-methylated Aβ(16-20)m Inhibitor Peptide is Restricted

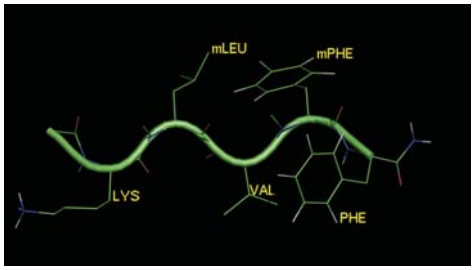
Replica Exchange Molecular Dynamics, 30 replicas, 20 ns per replica



N-methylated Aβ(16-20)m peptide

Aβ(16-20) peptide

Structure of N-methylated Aβ(16-20)m Inhibitor Peptide

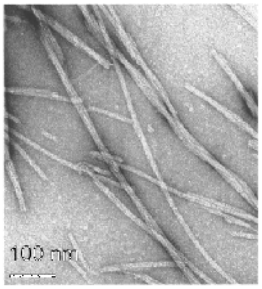


Aβ(16-20)m more rigid than Aβ(16-22), with β-strand content:
This pre-organization may allow Aβ(16-20)m to successfully compete with free Aβ(16-22) for binding to fibril.

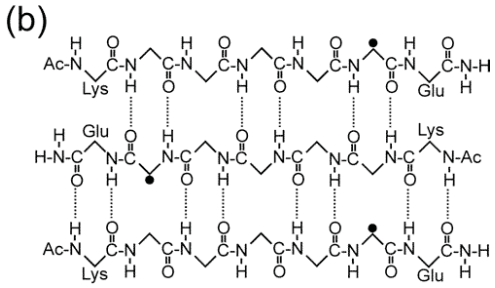
Interaction of the Inhibitor with Aβ(16-22)

Aβ42: DAEFRHDSGYEVHHQK[17]LVFFA[22]EDVGSNKGAIIGLMVGGVVIA

Central Hydrophobic Core



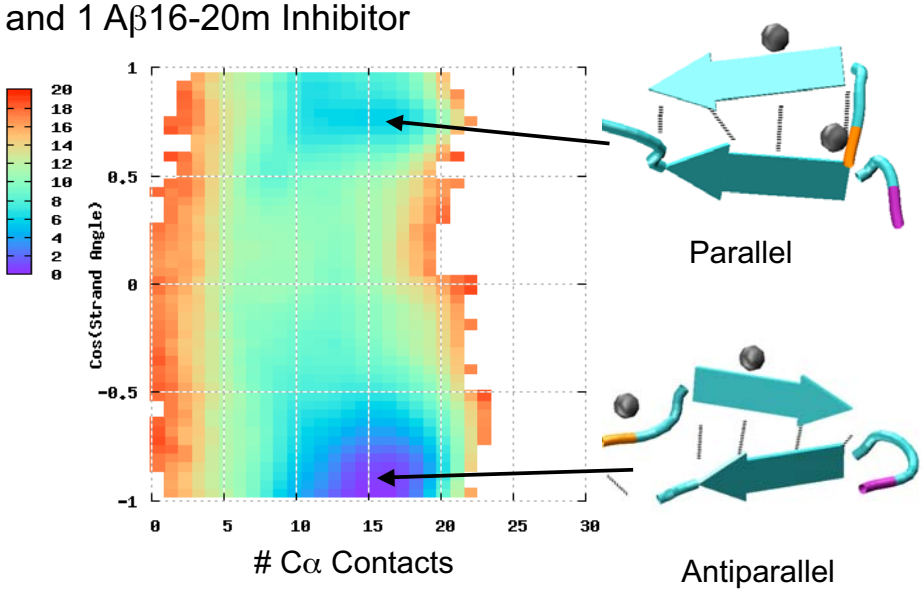
Fibrils of Aβ16-22: K[17]LVFFA[22]E



Antiparallel arrangements from solid state NMR

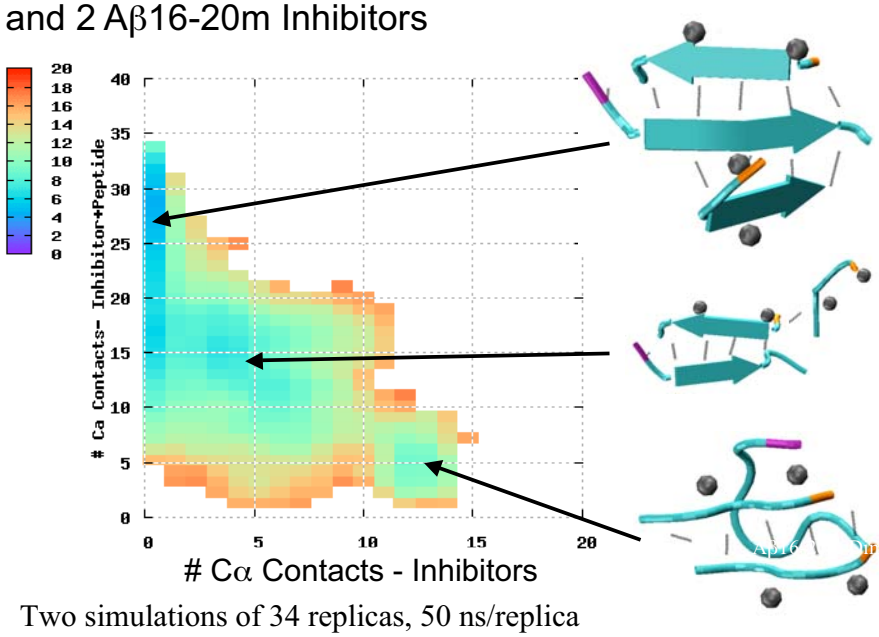
Tycko et al. Biochemistry, 39 (45), 13748 -13759, 2000

Replica exchange simulations of 1 Aβ16-22 Peptide and 1 Aβ16-20m Inhibitor



34 replicas, 50 ns/replica

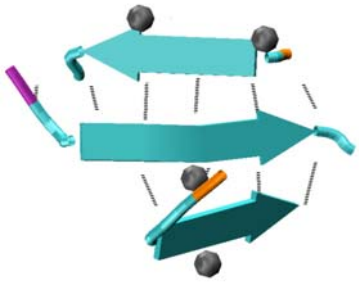
Replica exchange simulations of 1 Aβ16-22 Peptide and 2 Aβ16-20m Inhibitors



Two simulations of 34 replicas, 50 ns/replica

PREDOMINANT STRUCTURE:

TWO Aβ16-20m (Inhibitor) + ONE Aβ16-22



MONOMER POPULATION DEPLETED

Aβ(16-22) KLVFFAE PROTOFILAMENT

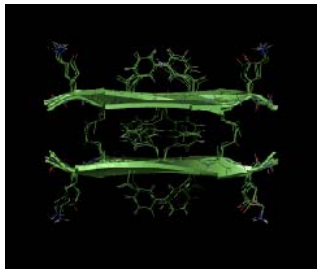
INITIAL STRUCTURE:

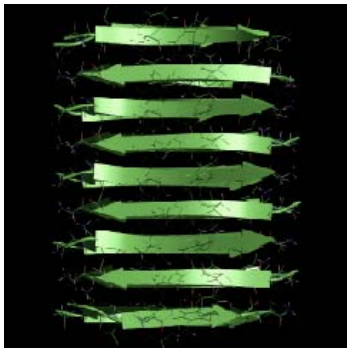
Two parallel bilayers

Peptides in layer antiparallel

lys^{16} and glu^{22} point to solvent

leu^{17}, phe^{19}, ala^{21} point inside core





Aβ(16-22) KLVFFAE PROTOFILAMENT

INITIAL STRUCTURE:

Two parallel bilayers
Peptides in layer antiparallel

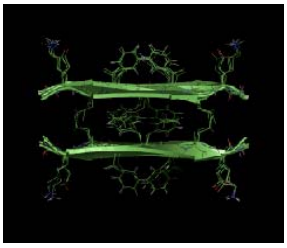
lys^{16} and glu^{22} point to solvent

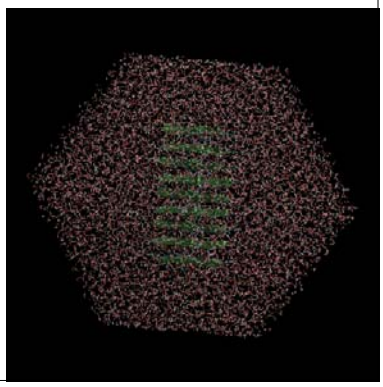
leu^{17}, phe^{19}, ala^{21} point inside core

GROMOS96 FORCE FIELD
EXPLICIT SPC WATER (23000 atoms)

REACTION FIELD/ PME

TWO 100 NS SIMULATIONS

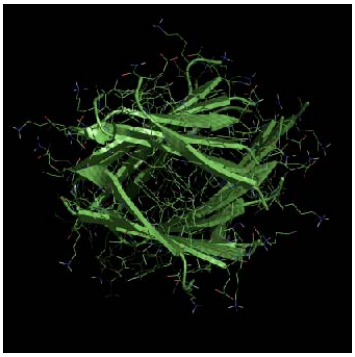


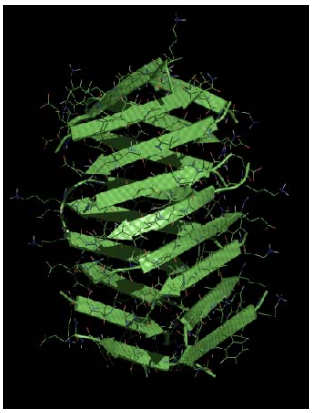


REPRESENTATIVE Aβ(16-22) PROTOFILAMENT

(100 NS SIMULATION)

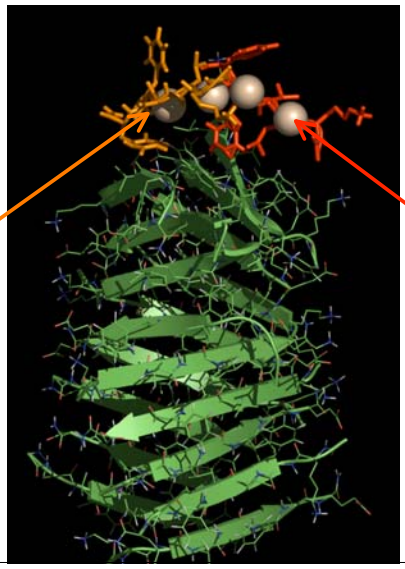
Distance between bilayers: 0.93 nm (Tycko: 0.99nm)
Distance between peptides: 0.44-0.52 nm (Tycko: 0.47 nm)





Interaction of Aβ(16-20)m Inhibitor Peptide with protofibril

INITIAL STRUCTURE



Aβ(16-20)m with N-methyl groups pointing toward fibril

Aβ(16-20)m with N-methyl groups pointing away fibril

Interaction of Aβ(16-20)m Inhibitor Peptide with protofibril

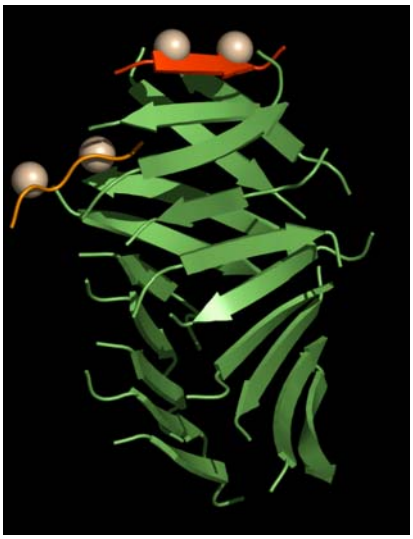
Aβ(16-20)m with N-methyl groups pointing toward fibril

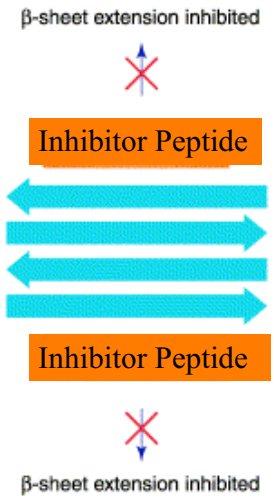
Intercalates between layers

Aβ(16-20)m with N-methyl groups pointing away fibril

Forms hydrogen bonds with fibril (antiparallel)

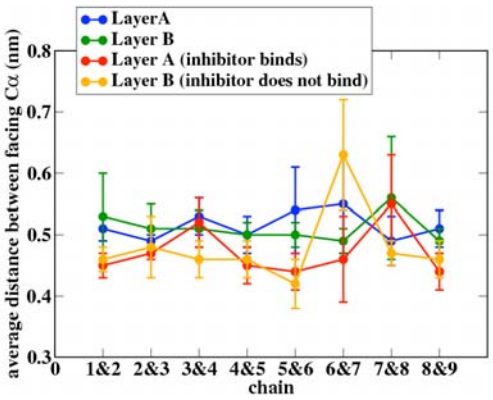
FIBRIL INHIBITION IN THE DIRECTION OF LONGITUDINAL GROWTH

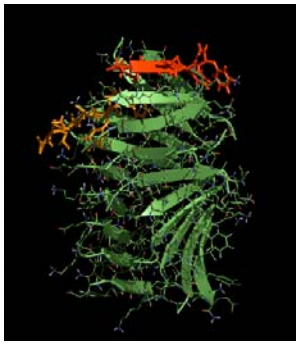




FIBRIL INHIBITION IN THE DIRECTION OF LATERAL GROWTH

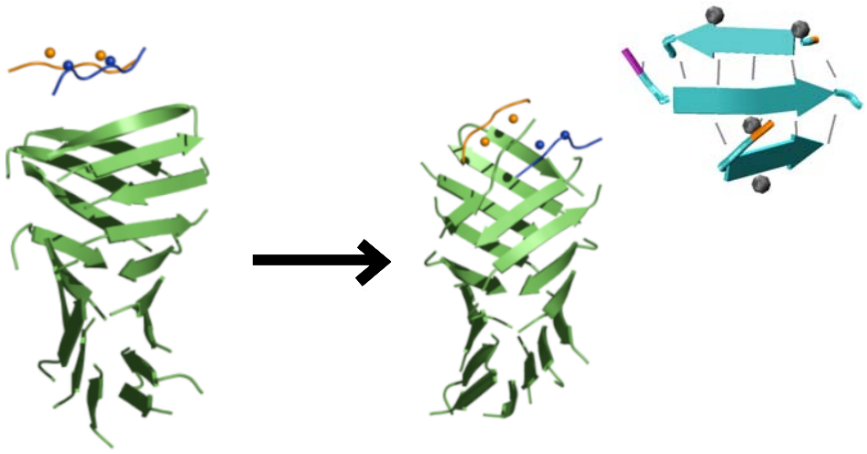
Inhibitor drifts from edge of fibril to side and inserts in fibril (between strands 6 and 7) with Lys pointing to solvent and hydrophobic residues inserted in fibril.



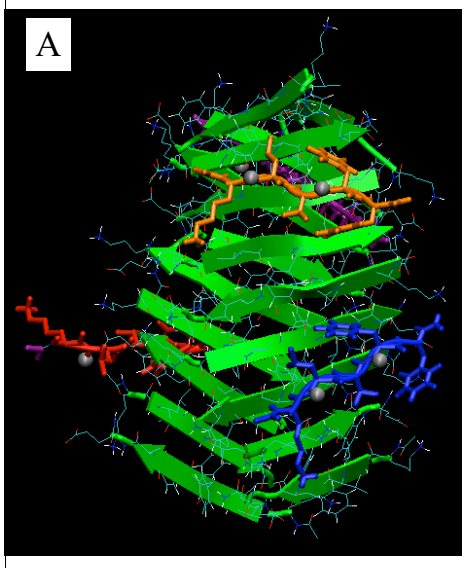


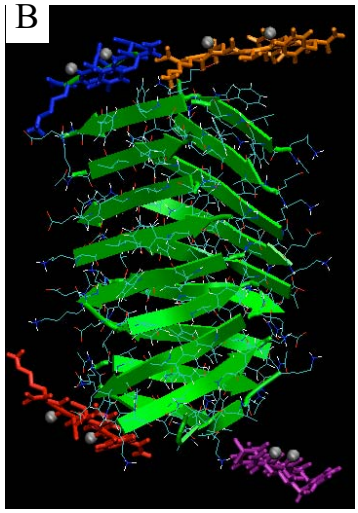
PROTOFILAMENT STRAND REMOVAL

Two Inhibitors attack one strand: one binds to the terminal strand, and the other intercalates between the terminal strand and the previous one.

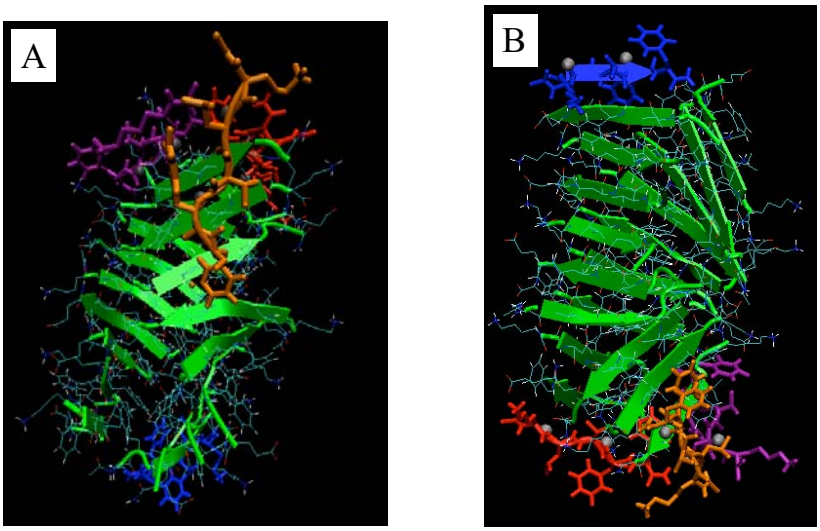


Fibril + 4 Aβ16-20m Inhibitors: Initial Configurations



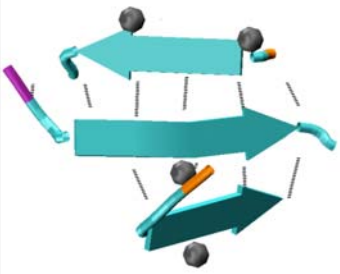


Fibril + 4 Aβ16-20m Inhibitors: After 50 ns

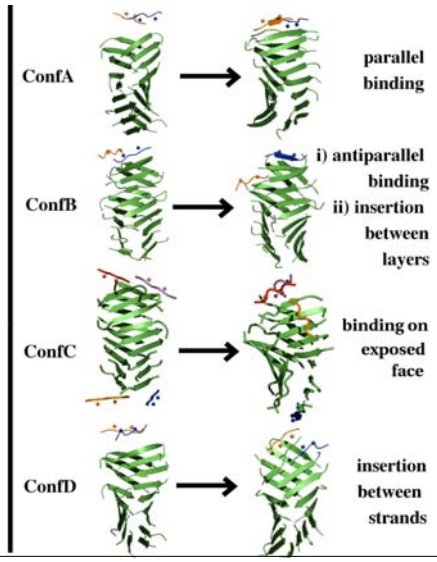


Summary

Binding to Monomer



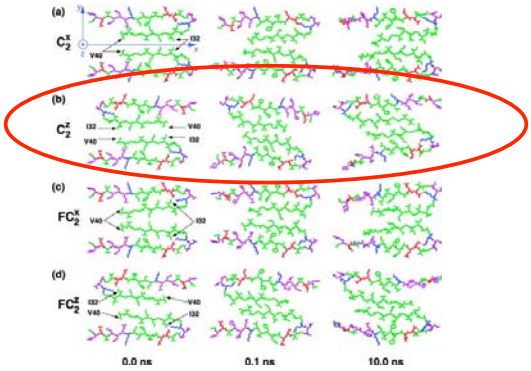
Binding to Fibril



Aβ9–40 fibrils

R. Tycko and co-workers: 2002 PNAS 99,16742 and 2006 Biochem 45, 498

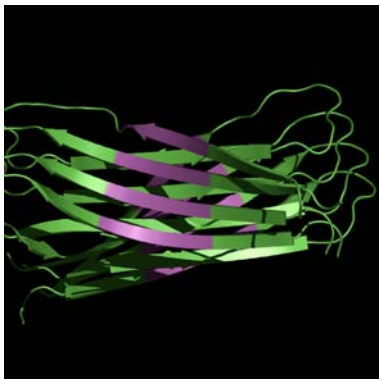
G. Hummer and co-workers: 2005 J Mol Biol 353, 804 and 2007 Biophys J 92, 3032



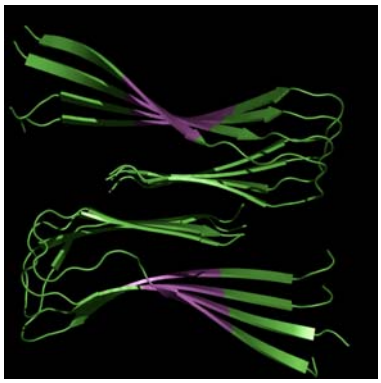
Our model: C_{2z} from G. Hummer 2005 and 2007

Interactions of the inhibitor with the longer Aβ(9-40) peptide.

Aβ(9-40) side view



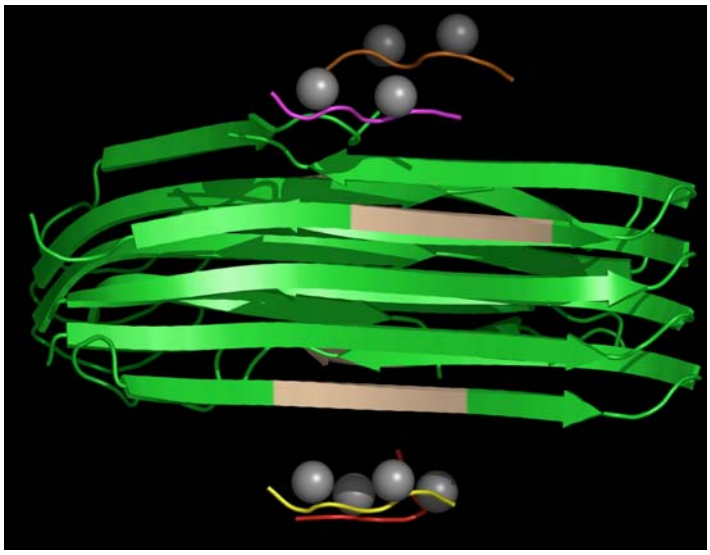
Aβ(9-40) top view



Gerhard Hummer

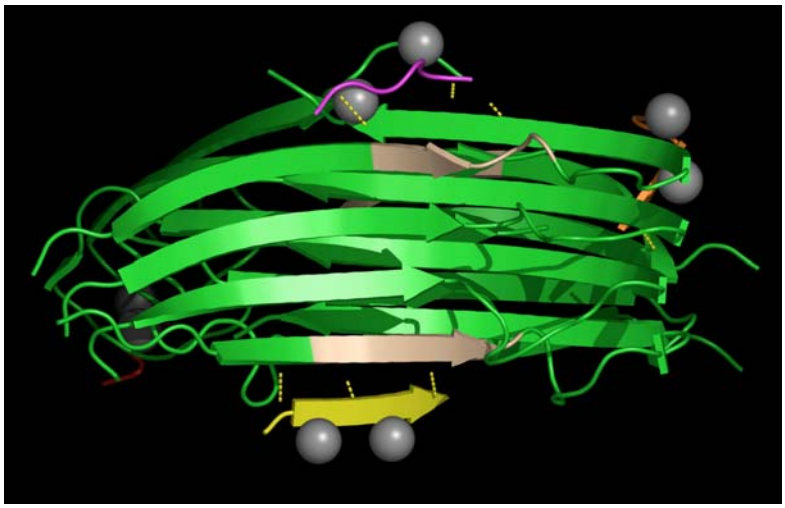
Interactions of the inhibitor with the full length Aβ(1-40) peptide.

INITIAL CONFIGURATION

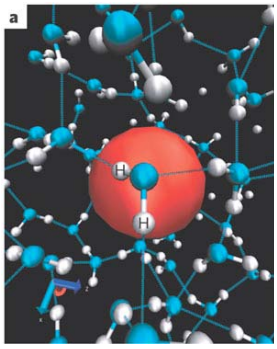


Interactions of the inhibitor with the full length Aβ(1-40) peptide.

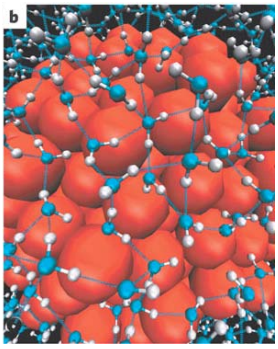
AFTER 100 NS



Hydrophobicity on different length scales: Role of Water in Peptide Aggregation



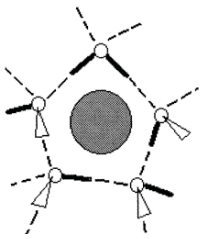
Small solute (methane)



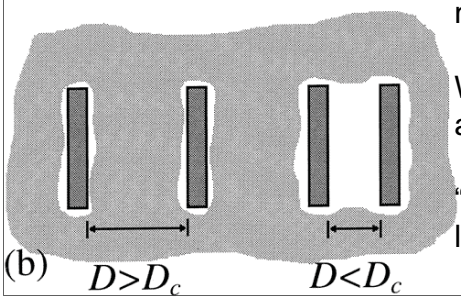
Large solute (cluster of methane)

Chandler, Nature (2005) 437, 640

Hydrophobic species do not hydrogen bond with water: regions of excluded volume



Small solute: water can reorganize without sacrificing H-bonds



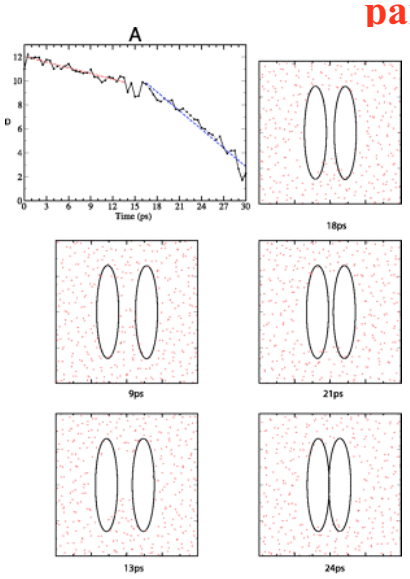
Large solute: Impossible to maintain full H-bond network

Water moves away from solute and creates interface around it

"Drying" leads to attraction of large hydrophobic surfaces

LUM et al., J. PHYS. CHEM. B. 1999 (103) 4570

Drying induced collapse of hydrophobic particles



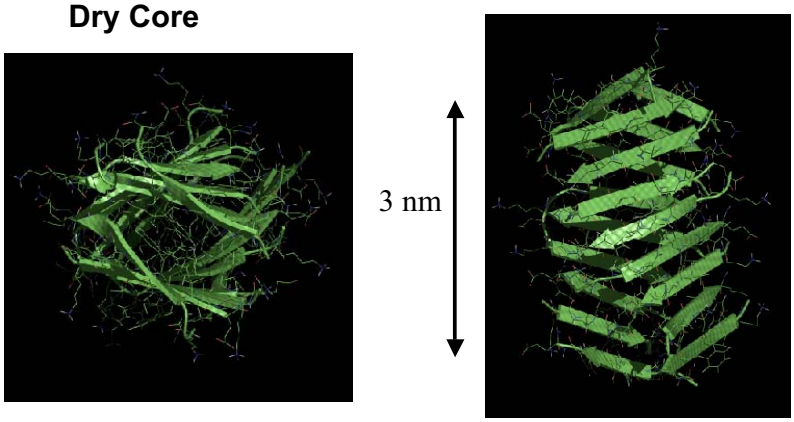
Critical distance for dewetting reduced when solute-water attractive forces present

Berne and co-workers PNAS 2003 100: 11953-11958

IS THERE A DRYING TRANSITION FOR AGGREGATION?

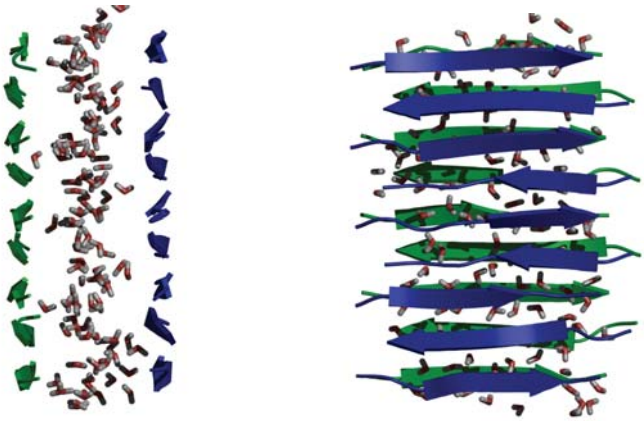
Aβ(16-22) PROTOFILAMENT: All interior side chains (leu^{17}, phe^{19}, ala^{21}) are hydrophobic

Dry Core

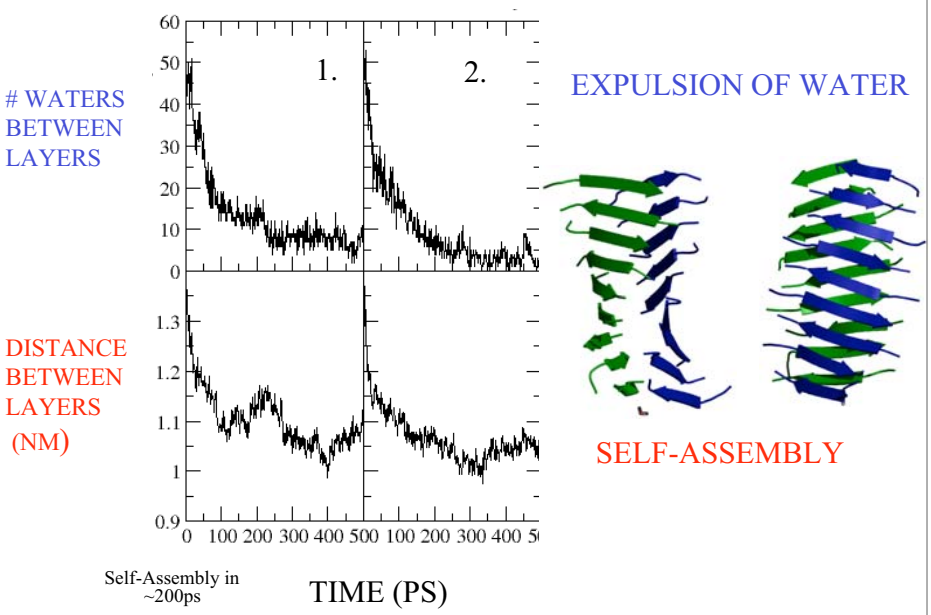


Initial Structure:

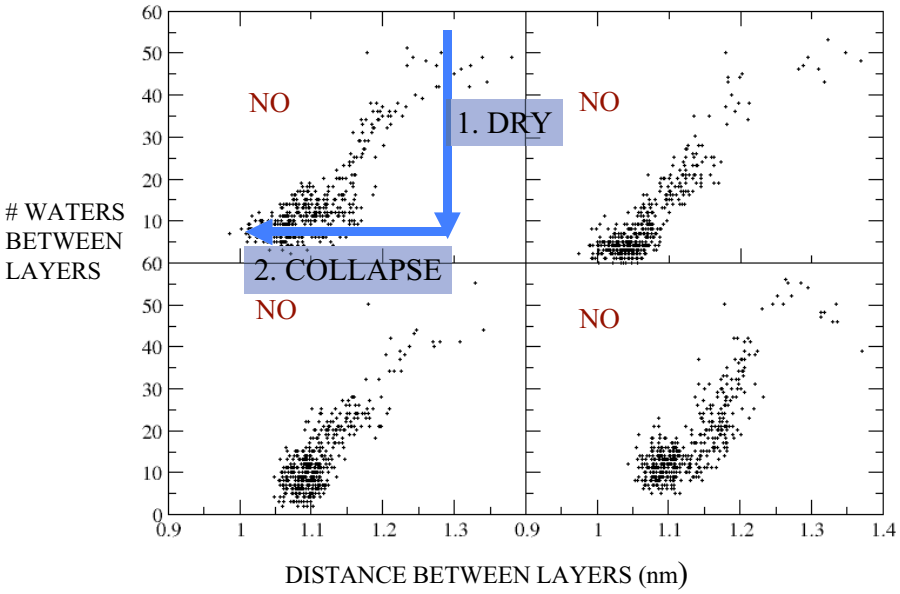
D_C=1.38nm



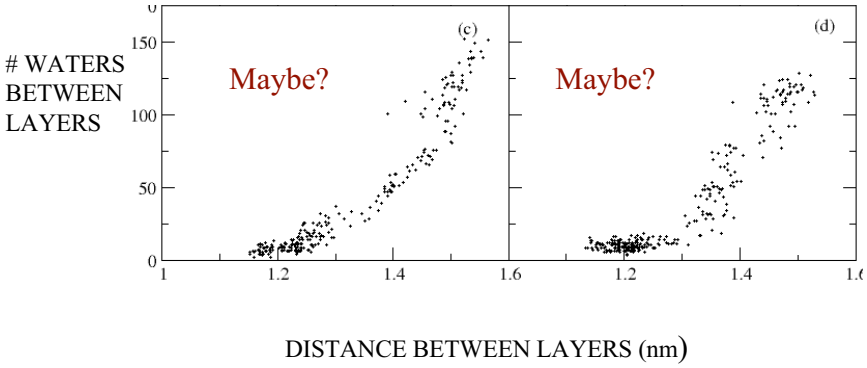
MD SIMULATIONS ($D < D_c$)

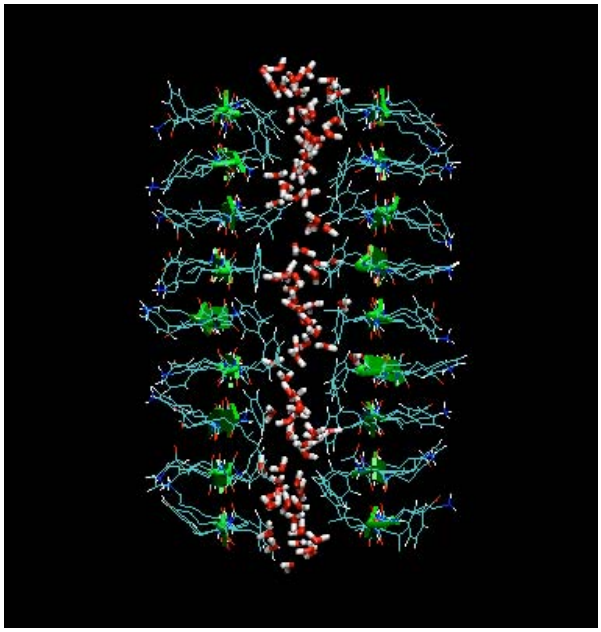


IS THERE A DRYING TRANSITION?



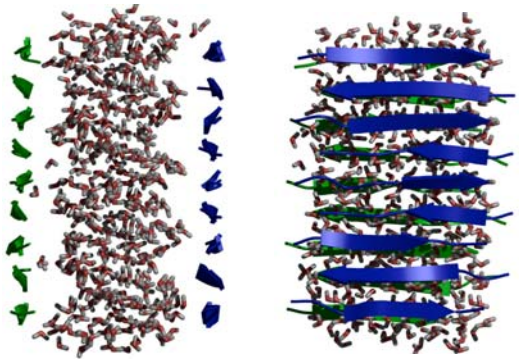
IS THERE A DRYING TRANSITION?





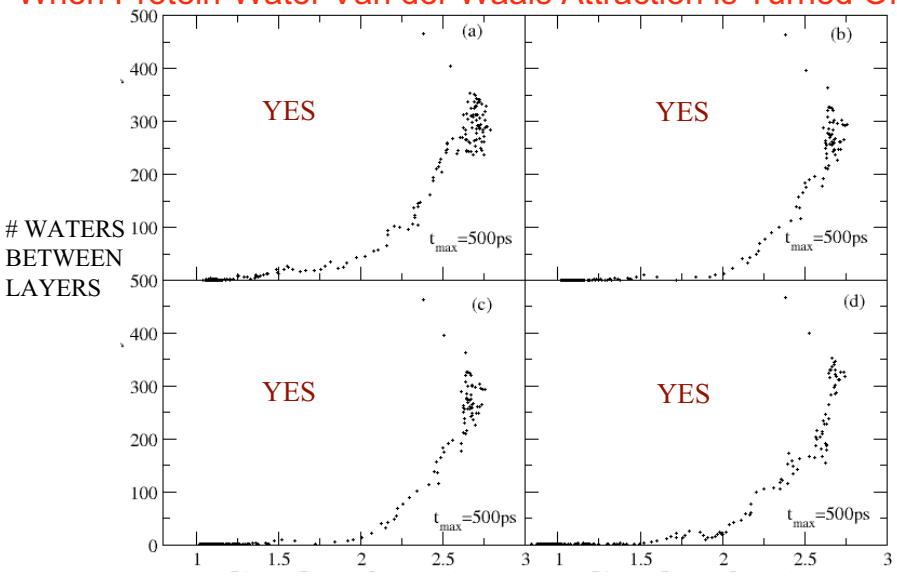
Turn off Van der Waals attraction between water and protein

D_0=2.38nm

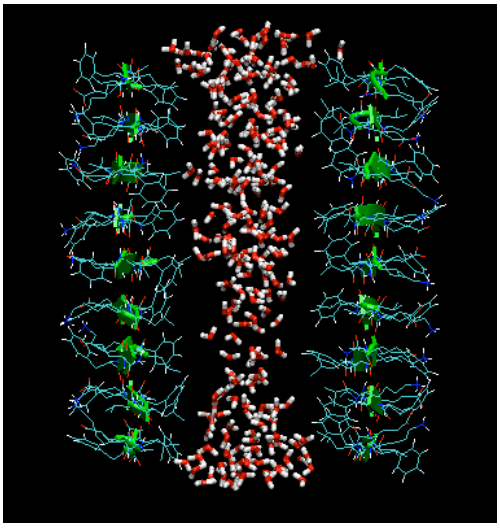


DRYING TRANSITION

When Protein-Water Van der Waals Attraction is Turned Off



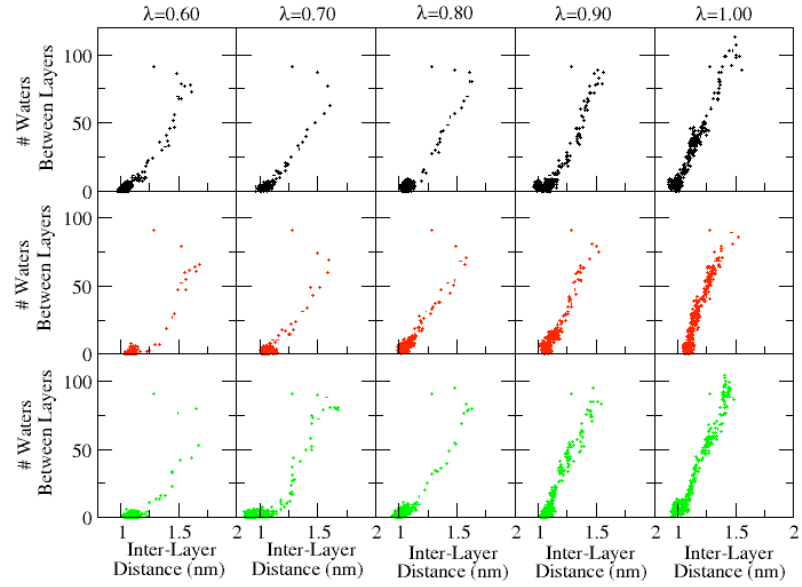
DRYING INDUCED ASSEMBLY WHEN THE PROTEIN-WATER VAN DER WAALS ATTRACTION IS TURNED OFF



Scale the Van der Waals Attraction

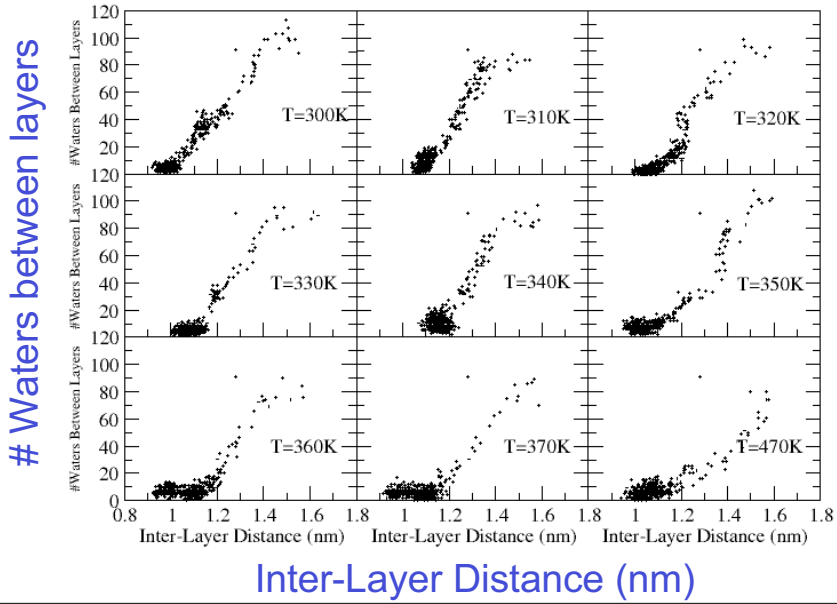
D_0=1.28nm

Drying occurs when up to ~70-90% of protein-water vdw attraction is present



Full Potential: Temperature Dependence

D_0=1.28nm

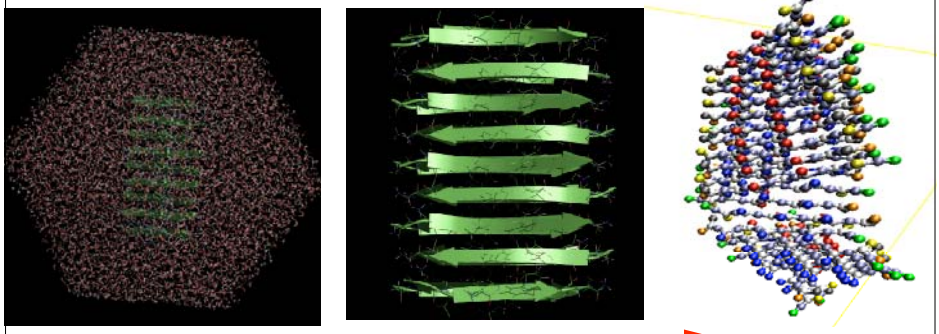


TYPES OF SIMULATIONS

All-atom: (MD) With EXPLICIT Solvent

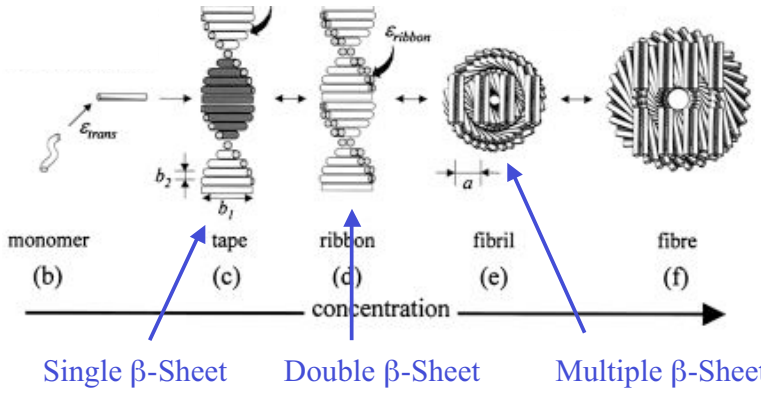
All-atom: IMPLICITsolvent

Off-lattice minimalist: Langevin dynamics



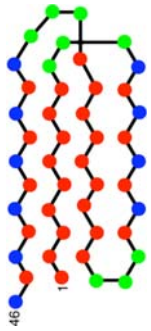
COARSE GRAINING

Hierarchical Peptide Self-Assembly



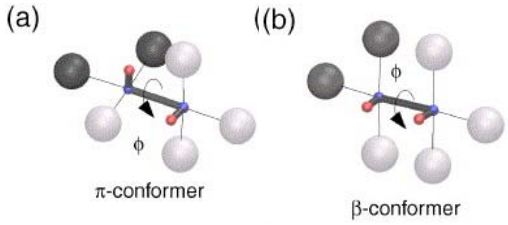
A. Aggeli et al. (2001) PNAS 98(21), 11857-11862.

Single-Bead Models

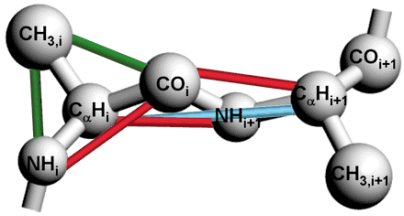


Missing:
. Side chains
. Hydrogen bonding
. Chirality

Multiple Bead Models

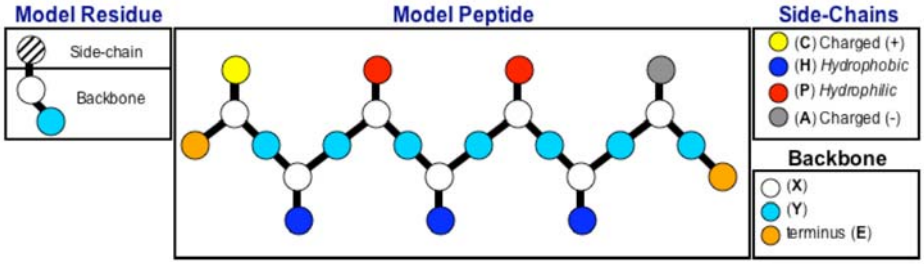


Caflisch and co-workers (2006) JMB 360,882-892.



Hall and co-workers (2004) PNAS 101, 16180-16185.

Geometry and Force Field



$$H = \sum_{bonds} K_b(b-b_0)^2 + \sum_{angles} K_\theta(\theta-\theta_0)^2 + \\ + \sum_{dihedrals} K_\chi(1+cos(n\chi+\delta)) + \\ + \sum_{nonbonded} 4\epsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right] + \frac{q_1 q_2}{\varepsilon r}$$

G. Bellesia et J.E. Shea (2007) J. Chem. Phys. In Press

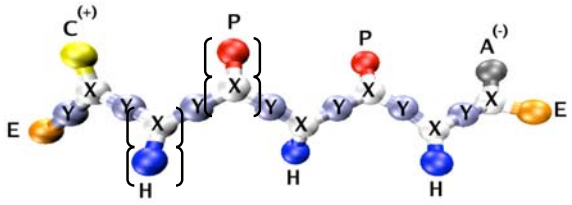
β–sheet assembly (tapes)

Modeling the H-bond:

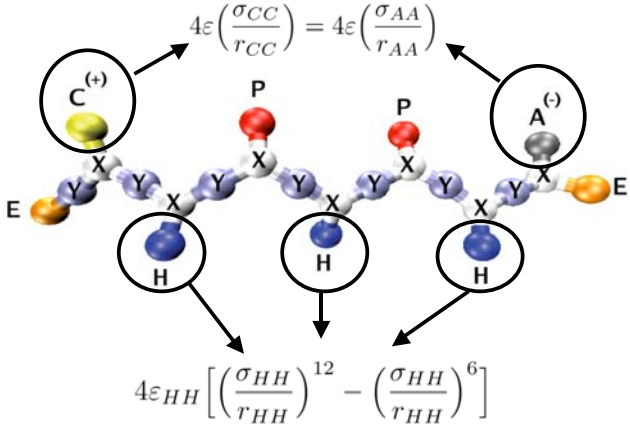
combination of LJ terms

Introducing chirality:

$$K_\chi(1 + cos(n\chi + \delta)), \delta \neq k\pi, k = \pm 0, 1, 2, 3...$$



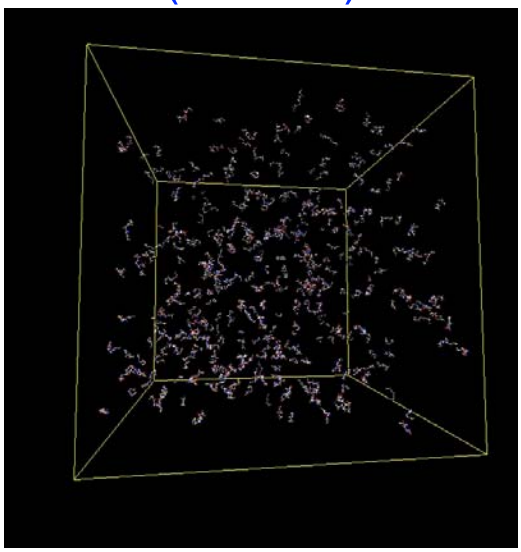
Double Tapes and Protofibrils

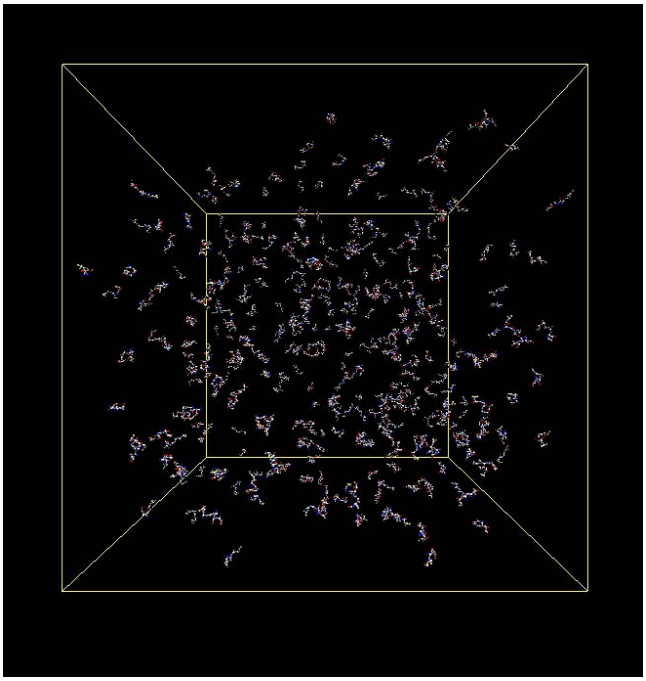


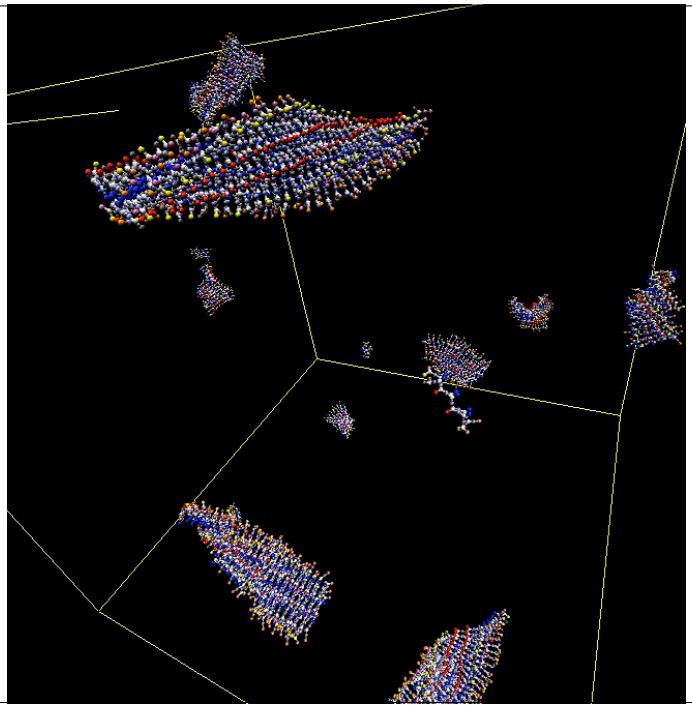
H	ε_{HH}	σ_{AA}=σ_{CC}
S1	1.0	4.0
S2	2.0	4.0
S3	3.0	4.0

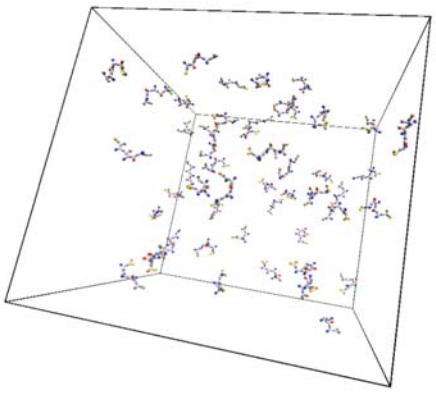
H	ε_{HH}	σ_{AA}=σ_{CC}
S1b	1.0	2.0
S2b	2.0	2.0
S3b	3.0	2.0

400 peptides - Langevin Dynamics (H=S3b)





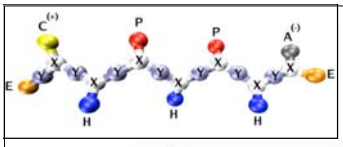




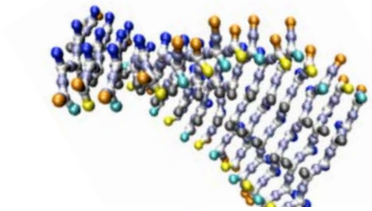
50 peptides

Replica Exchange Langevin Dynamics, PBC

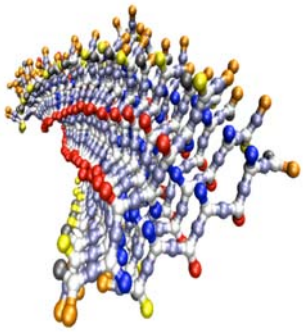
500 ns



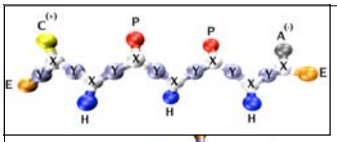
Hamiltonians S1-S3: Big charged groups (C and A)



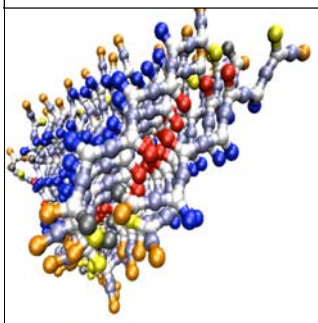
Tape



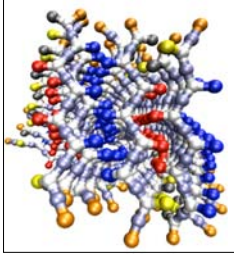
Ribbon(A): HHH-HHH interface

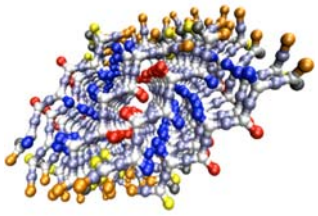


Hamiltonians S1b-S3b: Small charged groups (C and A)

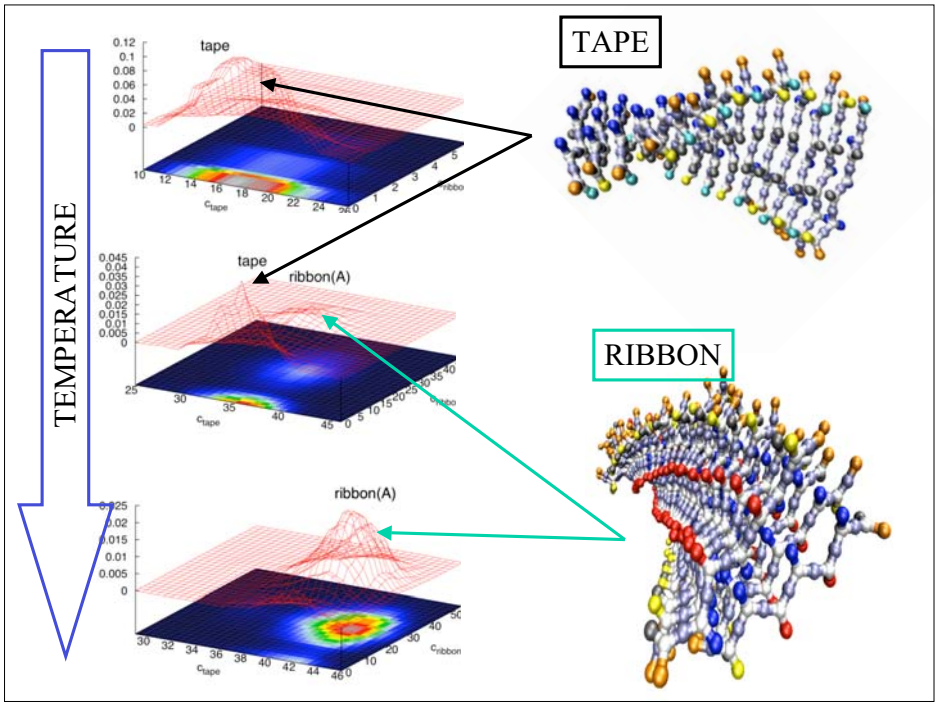


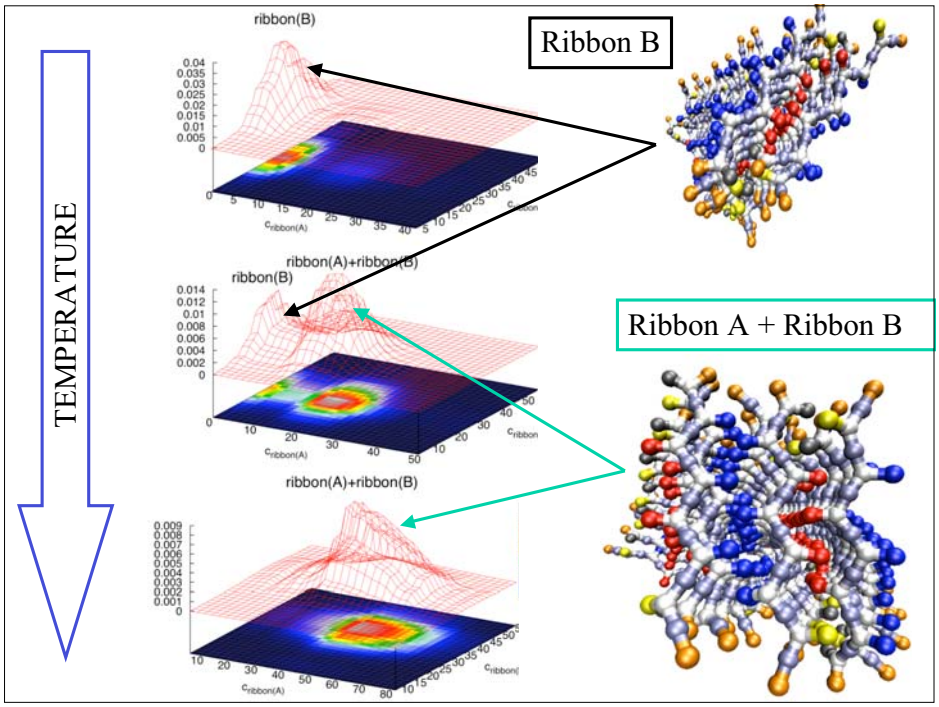
Ribbon(B) CPPA-CPPA interface



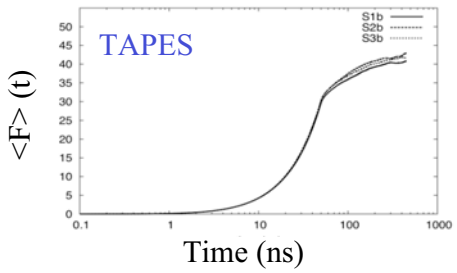


Triple and Quadruple Ribbons: Mixed(A) and (B)

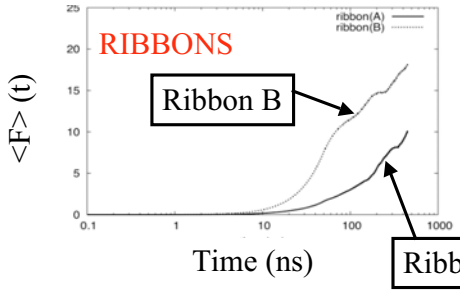

TEMPERATURE
tape
TAPE
tape
ribbon(A)
RIBBON
ribbon(A)


TEMPERATURE
ribbon(B)
Ribbon B
ribbon(A)+ribbon(B)
ribbon(B)
Ribbon A + Ribbon B
ribbon(A)+ribbon(B)

Kinetics of Assembly



No real lag time



"Nucleation-Growth"

Ribbon B template for Ribbon A

Ribbon A