# Aggregation phenomena relevant to Alzheimer's Disease: Statistical physics approach

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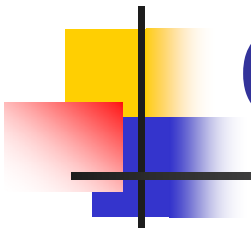


# Outline

- Alzheimer's disease & Aβ-protein
- Simulation of Aβ-proteins folding and aggregation

# Alzheimer's disease is related to Amyloid β-proteins(Aβ)

- Over 50%  for the people over 85 years old
- Increasing forgetfulness, etc.
- Clinically, a dementia characterized by fibril made of amyloid β-proteins(Aβ) and tangles made of τ-protein in brain
- Amyloid β-proteins(Aβ) come in two forms:
  - Aβ40: $^{1}$DAEFR $^{6}$HDSGY $^{11}$EVHHQ $^{16}$KLVFF $^{21}$AEDVG $^{26}$SNKGA $^{31}$IIGLM $^{36}$VGGVV
  - Aβ42: $^{1}$DAEFR $^{6}$HDSGY $^{11}$EVHHQ $^{16}$KLVFF $^{21}$AEDVG $^{26}$SNKGA $^{31}$IIGLM $^{36}$VGGVV $^{41}$I$^{42}$A

- Oligomers of Aβ-40 and Aβ-42 are neurotoxic
- Oligomers of Aβ-42 are more neurotoxic than that of Aβ-40

# What did we do? Why?

- We used "**Discrete Molecular Dynamics**" for the study of oligomerization of Aβ-40 and Aβ-42 in atomic detail

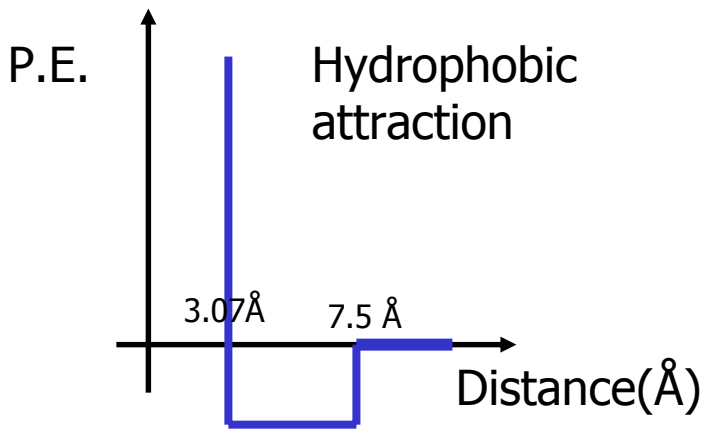
- Why?
  - Experiment cannot show how Aβ-40 protein and Aβ-42 protein oligomerize in atomic detail
  - Conventional molecular dynamics cannot study oligomerization (too much CPU time)

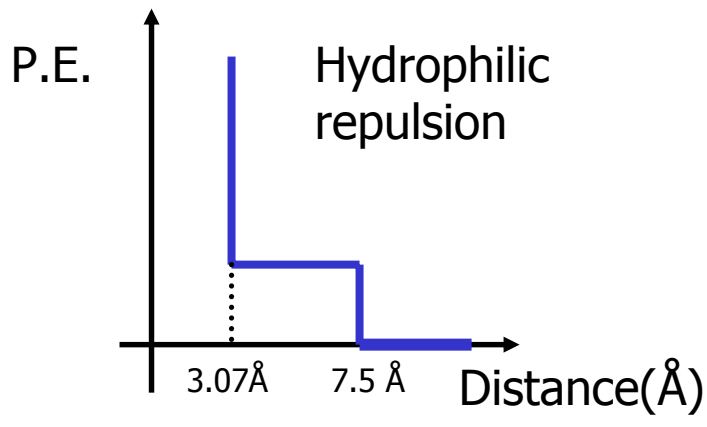
# Discrete Molecular Dynamics(DMD)

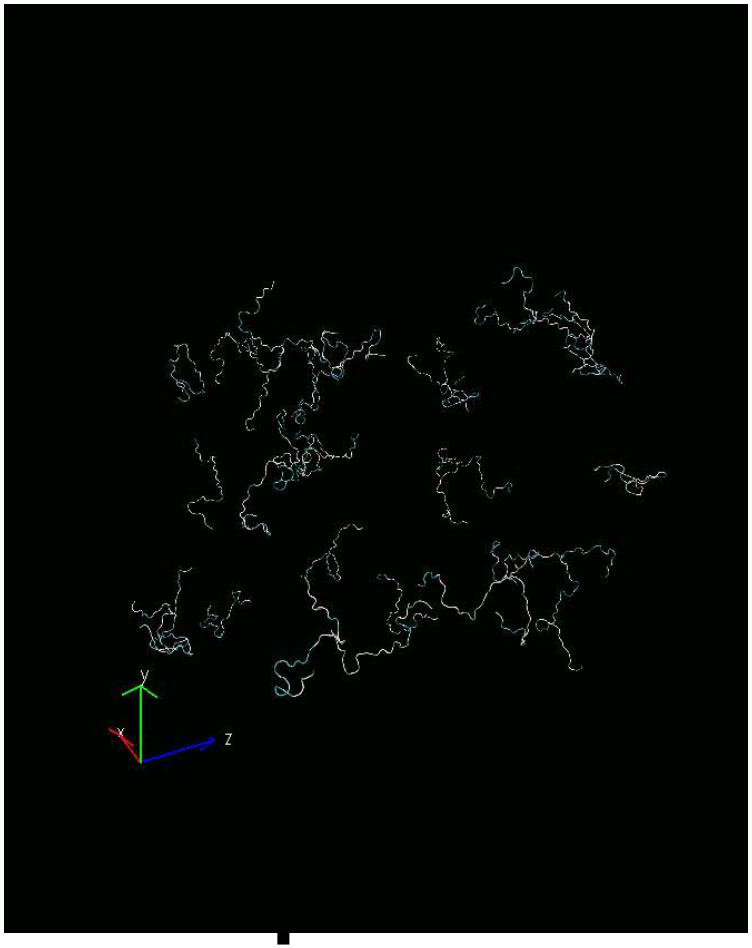
- Conventional Molecular Dynamics
- Discrete Molecular Dynamics

# DMD with hydrophobic interaction

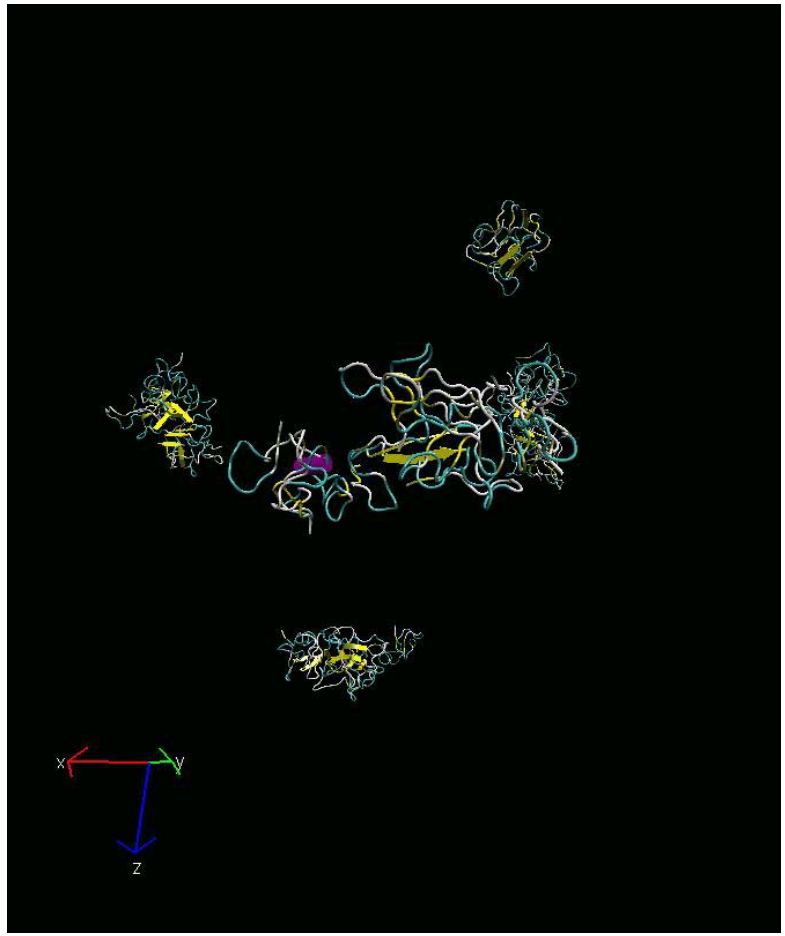
- Hydrophobicity is the driving force of the protein folding and aggregation
- Hydrophobicity appears as "the effective attraction" between hydrophobic particles
- Hydrophilicity appears as "the effective repulsion" between hydrophilic particles





Running
DMD
Simulation

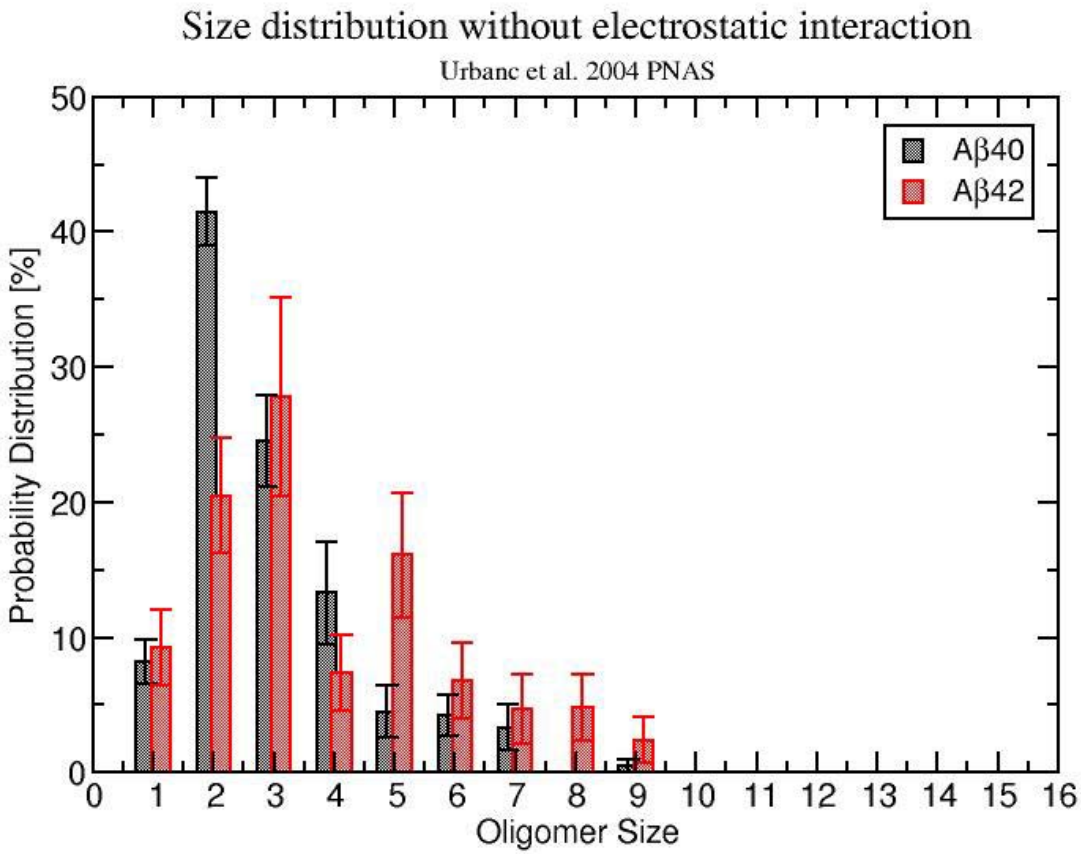


Prepare 8 sets of 32 proteins
for each Aβ40 and Aβ42

Get 8 trajectories
for each Aβ40 and Aβ42

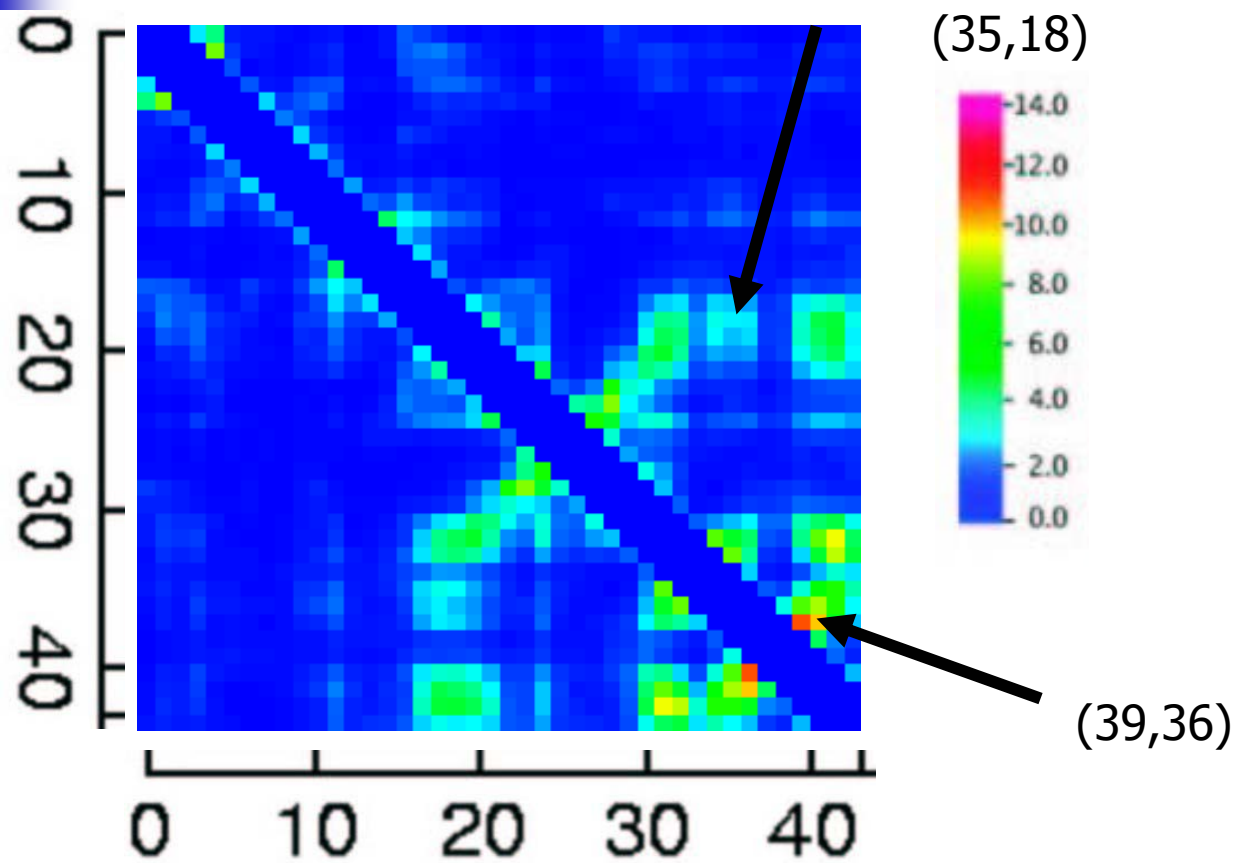
**Finally, Statistical analysis**

# Simulation results (1) Oligomer Size distribution



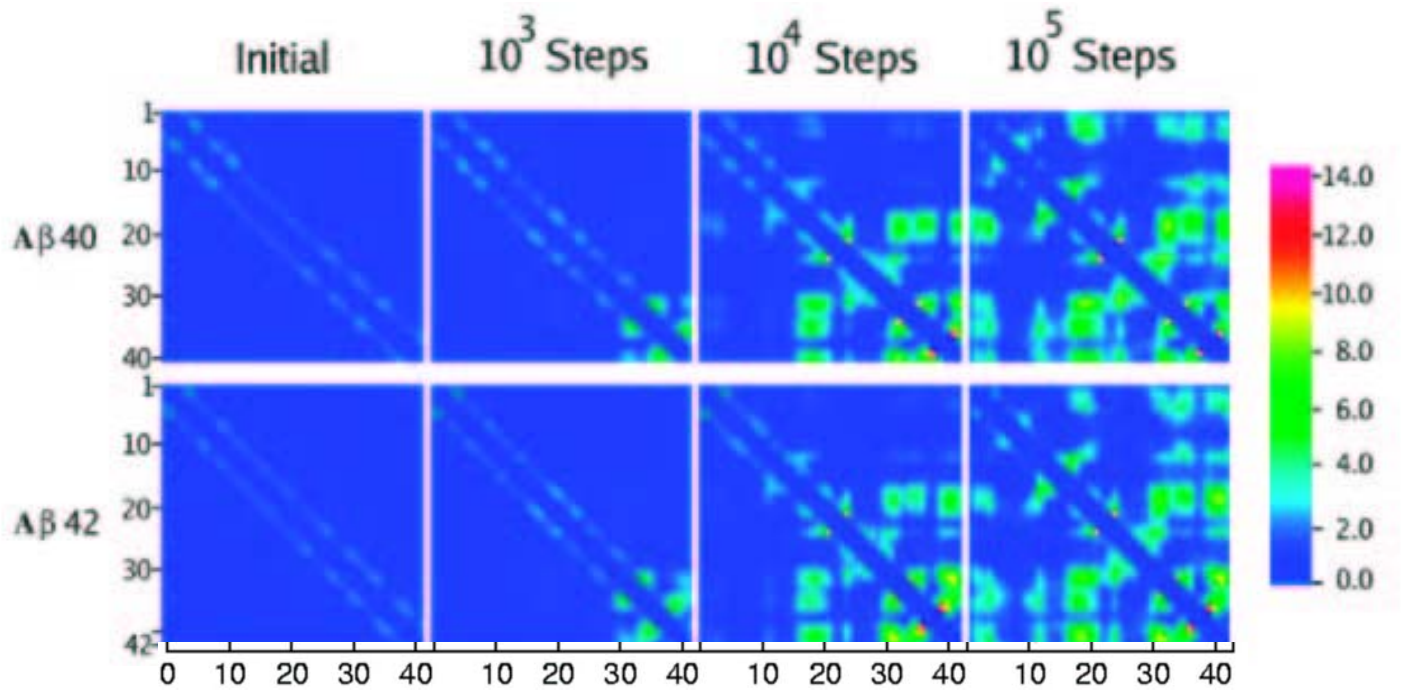

Ref) Bital et al. (2003) Proc. Natl. Acad. Sci. USA 100(1) 330-5

# How to read a contact map




[1]DAEFR [6]HDSGY [11]EVHHQ [16]KLVFF [21]AEDVG [26]SNKGA [31]I I GLM [36]VGGVV [41]I [42]A

# Simulation results(2)
## How “monomers” fold as time goes on

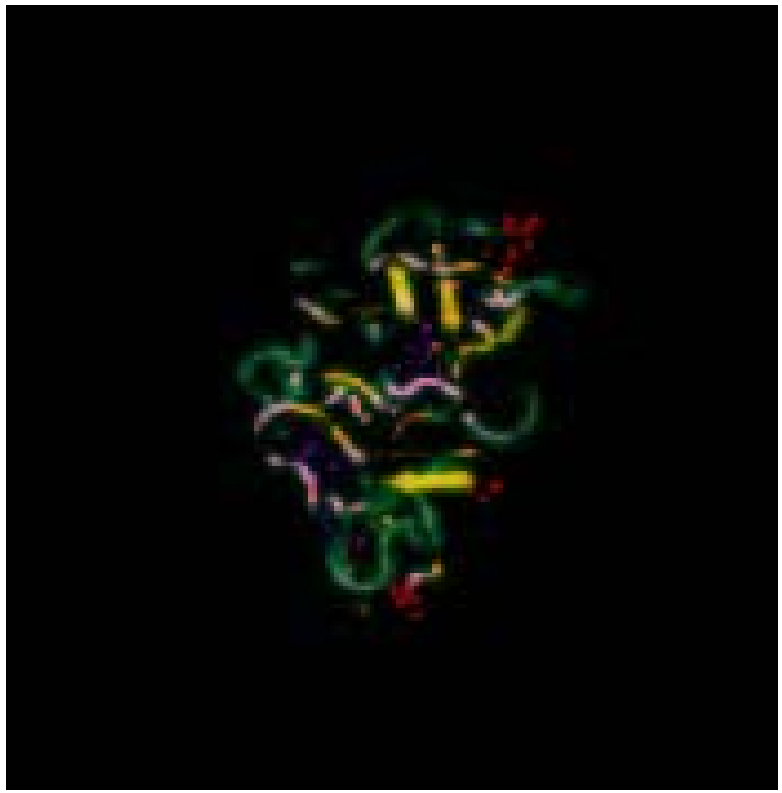



$^{1}$DAEFR $^{6}$HDSGY $^{11}$EVHHQ $^{16}$KLVFF $^{21}$AEDVG $^{26}$SNKGA $^{31}$I I GLM $^{36}$VGGVV $^{41}$I $^{42}$A

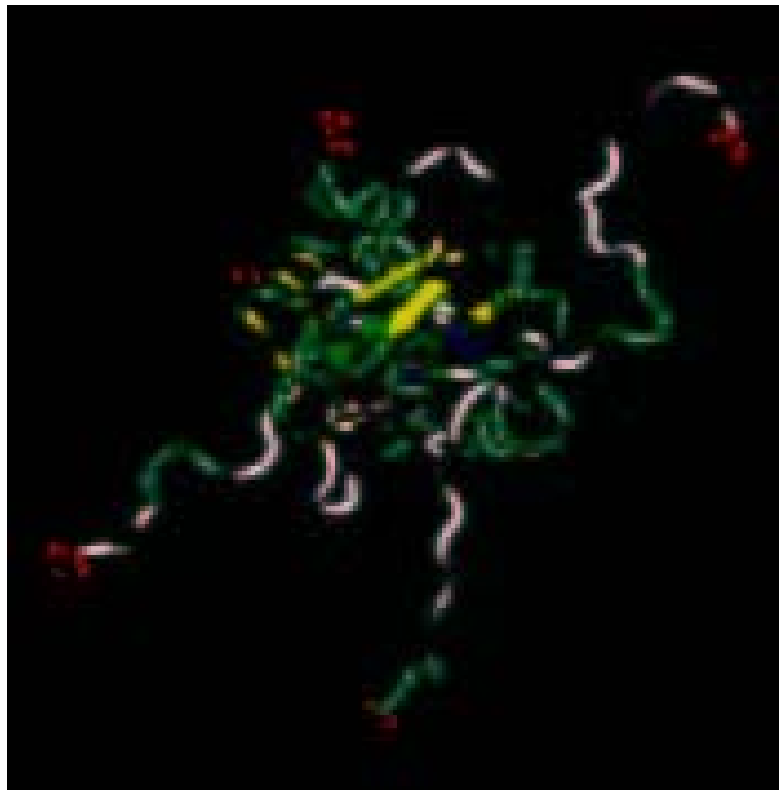
**Monomers fold from “C terminal region”(Around 40 or 42) to “N terminal region”(around 1)**

# Simulation results (3) “Pentamers” of Aβ-40 and Aβ-42

Aβ-40



Aβ-42



**“N terminal”(Around 1) of Aβ42 is more stretched than that of Aβ40**

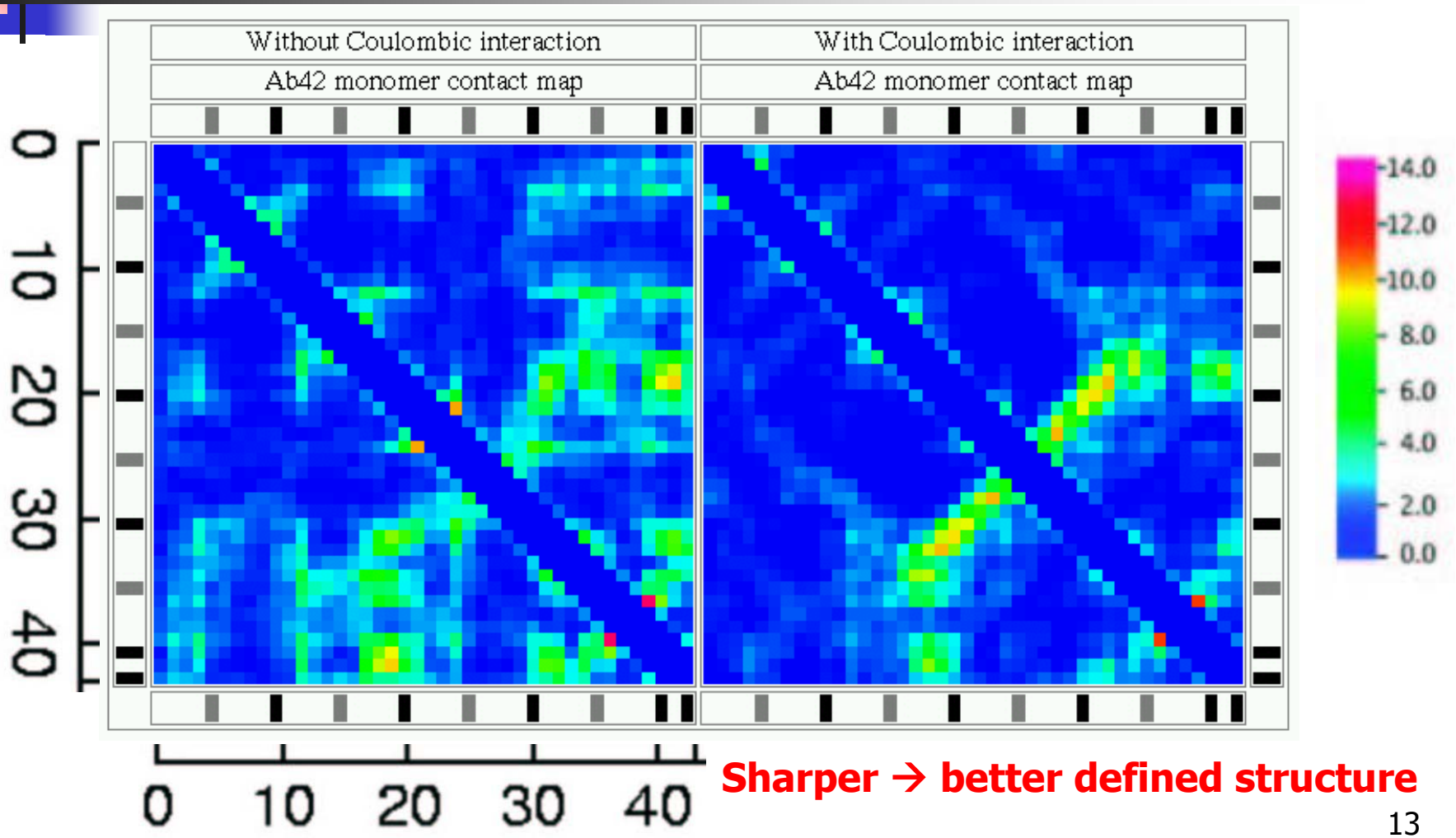
Ref) Urbanc B, Cruz L,Yun S, Buldyrev SV, Bitan G, Teplow DB, Stanley HE, (2004) Proc. Natl. Acad. Sci. USA 101 17345-17350

# Ongoing work: Adding Coulombic interaction

- Some amino acids are charged.
- Negatively charged amino acids: **$D^-$**, **$E^-$**
- Positively charged amino acids: **$R^+$**, **$K^+$**

$^{1}$**D$^-$**A**E$^-$**F**R$^+$** $^{6}$H**D$^-$**SGY $^{11}$**E$^-$**VHHQ $^{16}$**K$^+$**LVFF $^{21}$A**E$^-$D$^-$**VG $^{26}$SN**K$^+$**GA $^{31}$I I GLM $^{36}$VGGVV $^{41}$I $^{42}$A

# Analysis ongoing:
# When electrostatic interaction is added




**Sharper → better defined structure**

# Conclusions

- "Monomers" fold from C terminal to N terminal
- N terminals of Aβ-42 oligomers are more stretched out than those of Aβ-40 oligomers
- Simulation shows there is a significant difference between aggregation of Aβ-40 and Aβ-42
- Simulation gives insights why Aβ-40 and Aβ-42 aggregate differently;
  - Reason; The hydrophobicity of 41th and 42th amino acids causes the structural difference in folding

# Primary structure of Aβ(1-42)

$^{1}D^{-}AE^{-}FR^{+}$ $^{6}HD^{-}SGY$ $^{11}E^{-}VHHQ$ $^{16}K^{+}LVFF$

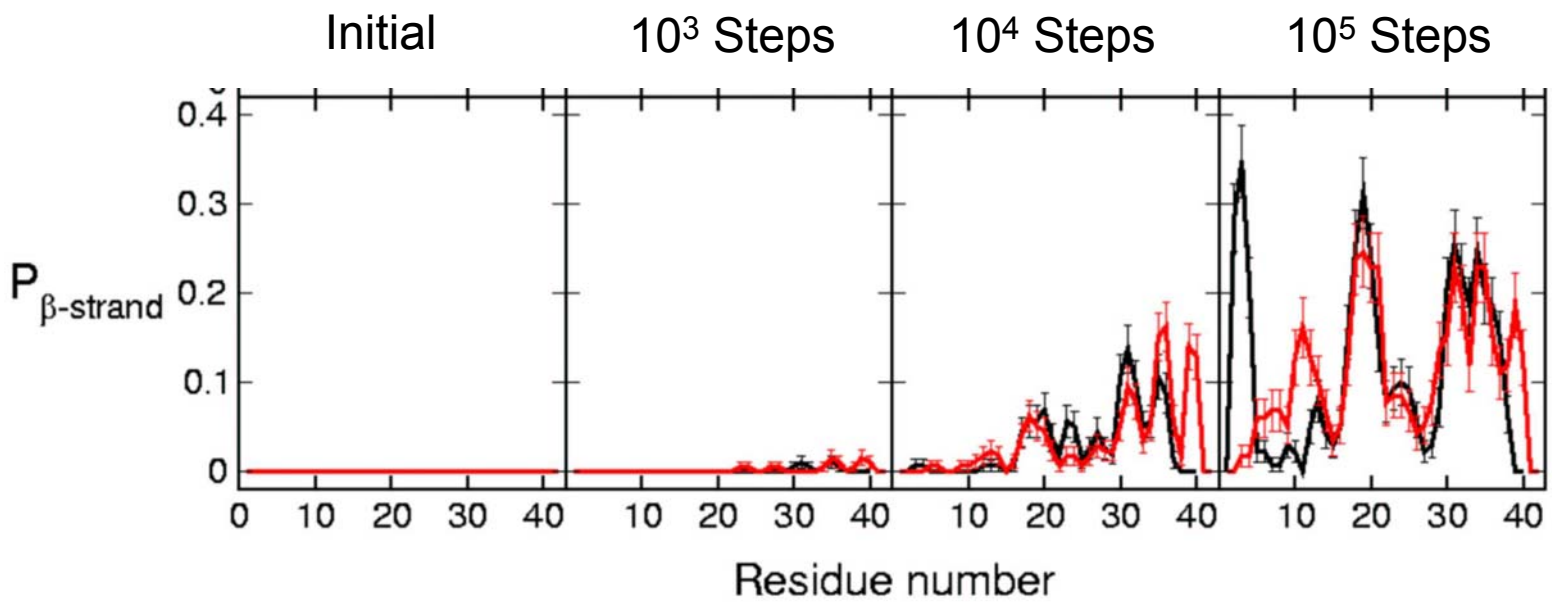
$^{21}AE^{-}D^{-}VG$ $^{26}SNK^{+}GA$ $^{31}IIGLM$ $^{36}VGGVV$

$\{^{41}I\,^{42}A\}$

- *(Hydrophobic)*
  *I:Ile V:Val L:Leu F:Phe C:Cys M:Met A: Ala*
- (Neutral in hydrophobicity)
  S:Ser T:Thr W:Trp P:Pro Y:Tyr G:Gly
- (Hydrophilic)
  $R^{+}$:Arg $K^{+}$:Lys $D^{-}$:Asp $E^{-}$:Glu N:Asn Q:Gln H:His

# Simulation additional results

## Prediction of secondary structure of monomers (no electrostatic interaction)




Black: Aβ40

Red: Aβ42