# Modeling of Alzheimer's Disease (AD) inducing Protein Amyloid-beta (Aβ) in 3D

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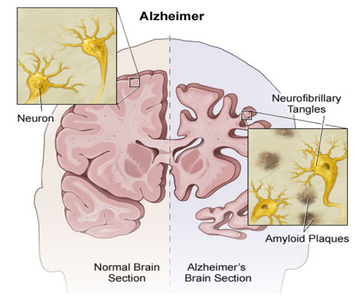
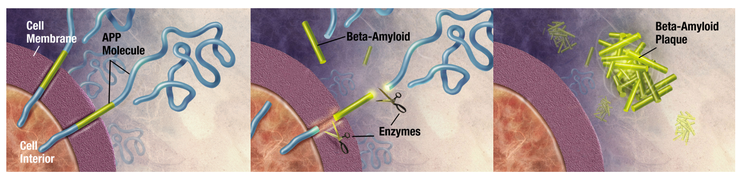
## Overview

Alzheimer's disease is a form of dementia affecting mainly the elderly. Symptoms are loss of short term memory in the early stages up to shut down of basic bodily functions leading to death in the final stages. There is currently no treatment for the prevention or delay of AD, with medication manly focusing on suppressing AD symptoms. The disease is caused by the protein fragment Amyloid-beta, clustering together with other fragments inside of the brain and forming a Plaque at Neurons, leading to their cell death! The main structure of Amyloid-beta is known and can be further investigated using Molecular dynamics (MD) simulations. MD uses classical mechanics to numerically analise protein structures , which allows one to investigate structural changes to the protein.

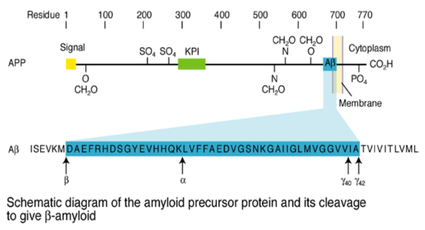



## Alzheimer's Disease, APP and Aβ

APP stands for Amyloid Precursor Protein, it's actual use is unknown but it is widely suggested to have a repairing function for neurons in the brain. Aβ is formed when an enzyme, (secretase) cuts APP. The accumulation and mis-folding of Aβ leads to plaque formation.



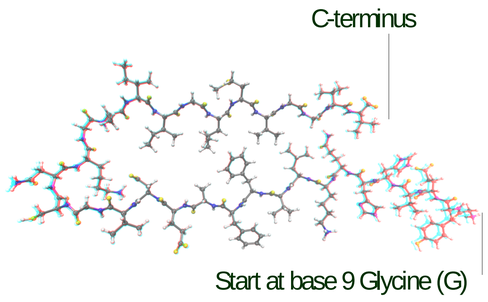

Cleavage of APP at the N and C terminus by alpha and gamma secretase forms Aβ. The sequence of letters stand for amino acids, basic building blocks of proteins.

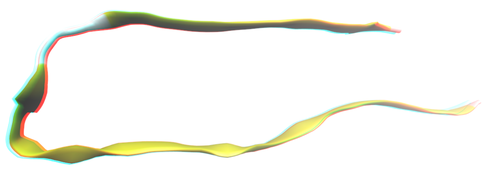


Schematic diagram of the amyloid precursor protein and its cleavage to give β-amyloid

### Amyloid-beta (Aβ) 40:

This protein fragment contains 40 amino acids, ending in Valine (V) at the C-terminus. For the simulation, base 1 – 8 at the N-terminus were omitted.

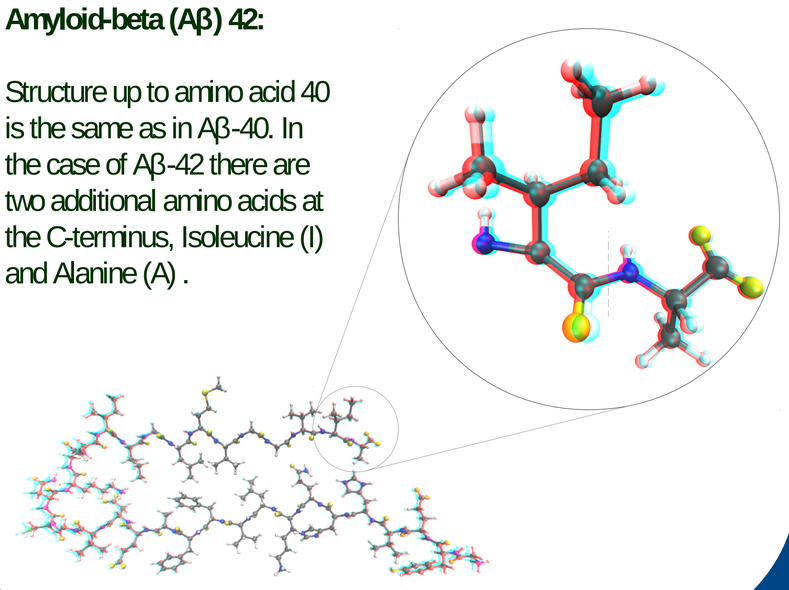


This is the same molecule as above using a secondary structure representation. The arrows display bet-sheets which are associated with forming fibrils (plaque).

### Amyloid-beta (Aβ) 42:

Structure up to amino acid 40 is the same as in Aβ-40. In the case of Aβ-42 there are two additional amino acids at the C-terminus, Isoleucine (I) and Alanine (A) .



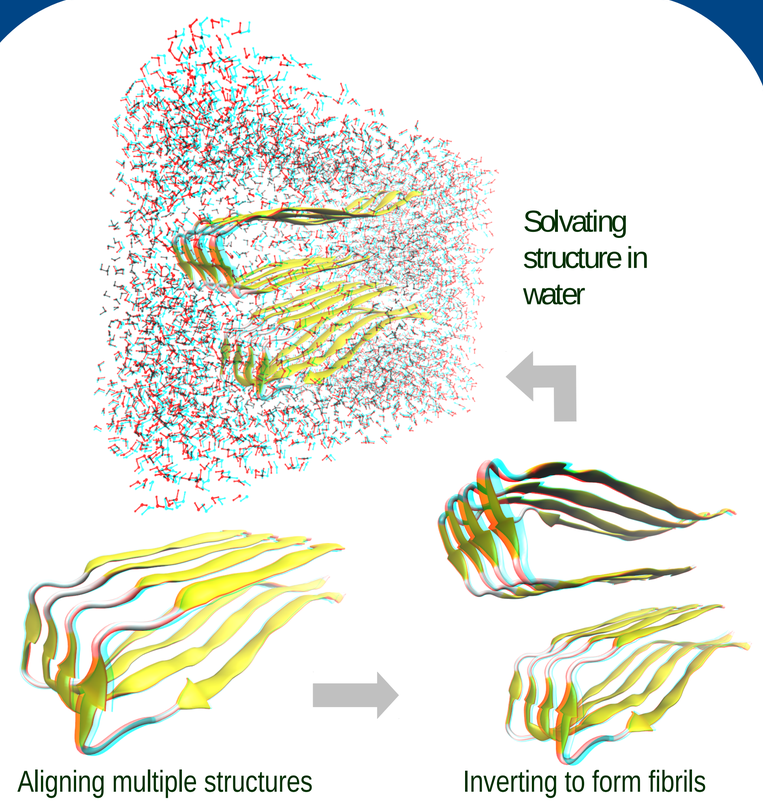
## The Project

**What is to be investigated?**

- Amyloid-beta 40 and Amyloid-beta 42, in an ensemble of up to 8 molecules aligned in such a way to resemble plaque.

**What are the predicted observations?**

- Experimental investigation of Amyloid-beta 42 shows an increased toxicity due to the formation of larger Amyloid-beta plaques. Hence a lower computational potential or rmsd value (see on the right) should be computed for Aβ-42 permitting the formation of more stable ensembles.
- Experimental data suggest that the salt bridge (ionic bond between two amino acids) is shifted in the case of Aβ-42. If this shift is reasonable and might even contribute to the greater stability can be investigated using MD.

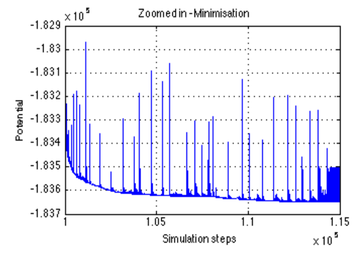



## The MD Simulation

1. **Building Aβ-40 and 42**
   - Structures of 40 and 42 were build and then duplicated, aligning them as shown above. Ensemble was then suspended in water and saved to a .pdb (protein data bank) file and a .psf (protein structure file) file.
2. **Minimisation**
   - Keeps Backbone and C-α atoms fixed in place allowing amino acids to find position of minimum potential and then releases them while temperature is set to 0 K
3. **Heating and Equilibration**
   - System is gradually heated to 300 K and all restraints are lifted
   - Protein is allowed to move freely to find lowest energy confirmation
4. **Dynamics**
   - Simulation is carried out under desired conditions (NPT ensemble)

## Analysis and Results

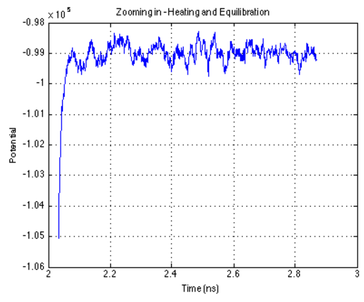
### (A) Minimisation




The minimisation graph shows how the potential gradually decreases while the temperature approaches 0K. The peaks arise from fixing and releasing the backbone and c-α.

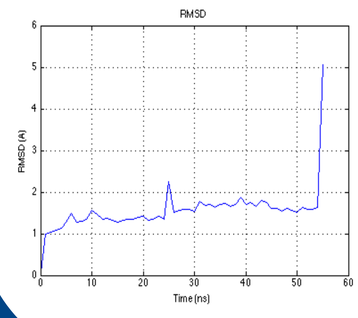
### (B) Heating and Equilibration

The graph to the right represents the increase in the potential while heating the system to 300K. After heating all restrains are removed and the protein can find a position of minimum potential. Hence a gradually decreasing vibration about a certain potential value.




### (C) RMSD

Root Mean Square Deviation (RMSD) is used to compare the two structures. It is a measure of how much each atom of the molecule moves about during the simulation. Small displacements are an indication of a stable structure and hence the possibility to form fibrils and plaque in the case of Aβ.

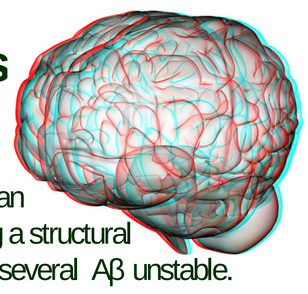



The graph to the left represents the RMSD of Aβ-40 in a simulation of 55ns. It has a minor peak at 25, indicating a slight instability. The drastic increase at the end suggests a computational error and has to be further investigated.

## Conclusions

All the simulations for Aβ-40 have been completed and the results are shown above. The simulations for Aβ-42 are still in progress, running on FIONN and SONIC (clusters). All the data is expected to be available shortly. Hence a comparison will soon be possible. Leaving us with the intermediate conclusion that the first simulation was successful!

## Benefits



Further investigation into the structure of Aβ can lead to the development of an advanced drug, which aims at inducing a structural change in Aβ, making an assemble of several Aβ unstable. Therefore no plaque formation can take place, prohibiting AD.

## The Maths behind MD Simulations (for TP's):

VMD (Visual Molecular Dynamics) is a tool to visualise different molecular structures. The above molecular structures have been rendered in different representations using VMD. Coupled with the NAMD (Nanoscale molecular Dynamics) tool, simulations can be prepared of molecules suspended in water for a certain period of time. For an accurate simulation the CHARMM – force field is utilised by NAMD. This force field computes the interactions between each atom on a completely classical basis. The term force field is misleading since calculations are actually based on approximating the following potential.

$$U_{total} = U_{bond} + U_{angle} + U_{dihedral} + U_{vdW} + U_{Coulomb}$$

Where the first three potentials describe the stretching, bending and torsion between bonded atoms. vdW stands for van der Waals interactions, which are the forces between non bonded atoms. The Coulomb terms describes the electrostatic interactions. The approximation method invoked for computation is a finite difference method (Leapfrog-Verlet).

## References

1. James C. Phillips et al, **"Scalable Molecular Dynamics with NAMD"**, J Comput Chem 2005, 26: 1781-1802.
2. Frenkel Daan, Smit Berend, **"Understanding Molecular Simulation from Algorithms and Applications "** 2002, 1996 Elsevier.
3. www.alzforum.org/mutations