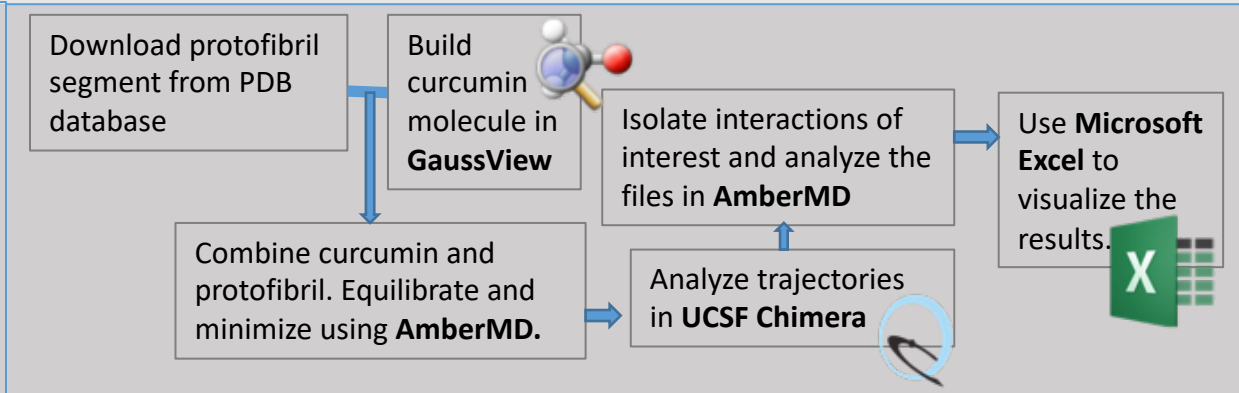
Understanding the influence of curcumin on Amyloid-β aggregation at the molecular scale

Angelina J Malagodi[1], Tye D Martin[2], David Whitten[2], Eva Y Chi Professor[2], Deborah Evans[3]

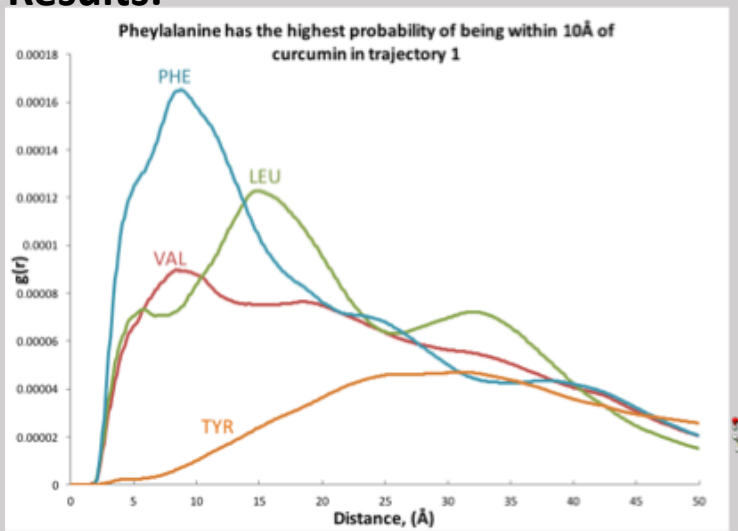
1. Macalester College.2. Dept. of Biomedical Engineering, University of New Mexico. 3. Dept. of Chemistry and the Nanoscience and Microsystems Engineering Program (NSMS), University of New Mexico.

Problem: Alzheimer's disease currently accounts for 60 – 80% of all dementia cases, and is the 3rd leading cause of elderly death. The progression of Alzheimer's is characterized by the amyloid plaques and tau proteins. Currently, there are no accessible medication or therapies to cure the disease.

Goal: Use Molecular Dynamic (MD) simulations to gain molecular level insight of interactions between curcumin and Aβ.

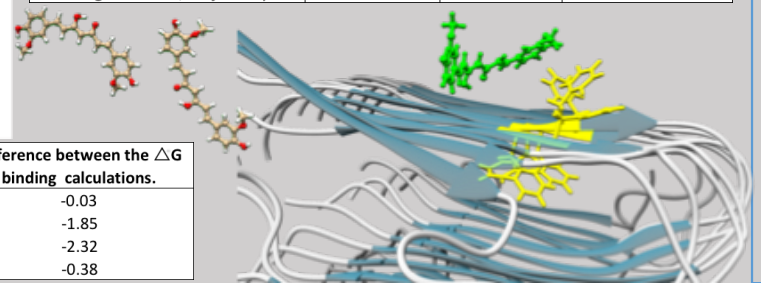


Results:



Binding energies between curcumin without protofibril	△G binding (kcal/mol)
complex 1	-10.0545
complex 2	-10.0054
complex 3	-10.6576
complex 4	-10.2894
complex 5	-9.8615

System	non mutated system	mutated system PHE	Binding Energy Differences for PHE
Configuration 2, trajectory 1	-20.9852	-17.7602	-3.225
Configuration 2, trajectory 2	-16.7395	-8.471	-8.2685
Configuration 2, trajectory 3	-16.1241	-9.3968	-6.7273



System (configuration 1, Trajectory 1)	Individual curcumin binding energy's combined	Multiple curcumin definded as a single ligand	Difference between the △G binding calculations.
combined 2/7/8/9	-11.96	-11.99	-0.03
combined 3/4/10	-63.22	-65.07	-1.85
combined 5/6	-16.08	-16.64	-2.32
combined 1/11/12	-4.53	-4.91	-0.38

Summary

-Curcumin is likely to be found near **phenylalanine** and **tyrosine**

-Probability of finding curcumin interacting with water decreases over 100ns, due to complexation of curcumin with each other and protofibril.

-Curcumin are more likely to bind to protofibril than each other

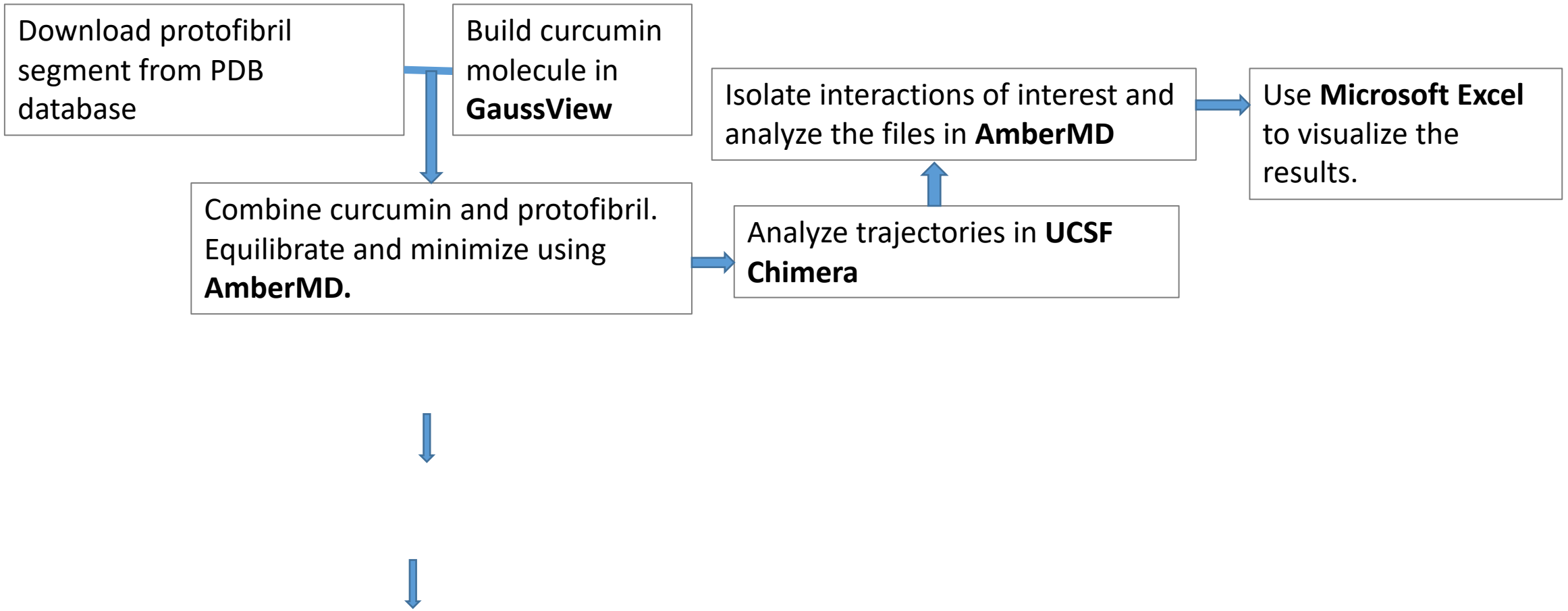
-curcumin complexation increases binding energy to protofibril

-Mutation studies on **phenylalanine** indicate that switching 4 residues to **alanine** decrease binding potential.

Future Work

-Simulate curcumin and lipid membrane interactions.

-Create and analyze system of 5 curcumin in solvate with new force field parameters and VinaDock positioning.


Download protofibril segment from PDB database
Build curcumin molecule in **GaussView**
Combine curcumin and protofibril. Equilibrate and minimize using **AmberMD.**
Analyze trajectories in **UCSF Chimera**
Isolate interactions of interest and analyze the files in **AmberMD**
Use **Microsoft Excel** to visualize the results.