Modeling Binding of Amyloid Beta-42 Peptide to the Alpha 7 Nicotinic Receptor

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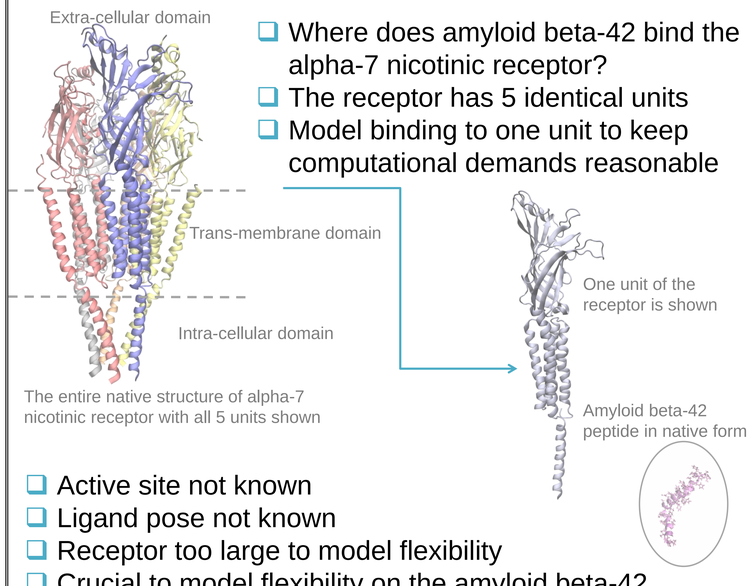
College of Science COS Undergraduate Research URC Colloquium 2014

Abstract

- There is a hypothesis that beta amyloids bind G-protein coupled receptors and so affect downstream signaling [1]
- Elucidating this will help us understand Alzheimer's
- Doing so using frameworks based on Molecular Dynamics is a computationally-expensive proposition
- We are investigating other more efficient frameworks based on conformational sampling
- Focus: amyloid beta-42 and the alpha 7 nicotinic receptor
- The study detailed here, under the supervision of two faculty, is part of a larger effort under the Mason OSCAR summer intensive program

Introduction

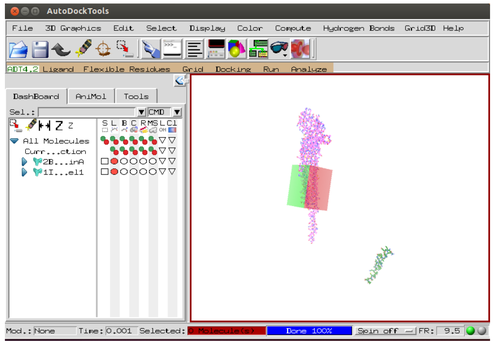


- Where does amyloid beta-42 bind the alpha-7 nicotinic receptor?
- The receptor has 5 identical units
- Model binding to one unit to keep computational demands reasonable

- Active site not known
- Ligand pose not known
- Receptor too large to model flexibility
- Crucial to model flexibility on the amyloid beta-42
- First step: model binding of native form of peptide
- Determine receptor active site and ligand pose
- Future goal: model binding of Alzheimer form

Methods

Thermodynamic treatment to predict binding site and pose



Screenshot of data preparation in Autodock Tools Interface

- We employ Autodock, a popular receptor-ligand binding package [2], to model binding of a flexible ligand (amyloid beta-42) onto a rigid receptor (unit of alpha-7 nicotinic receptor)
- Autodock tools is used first to prepare models

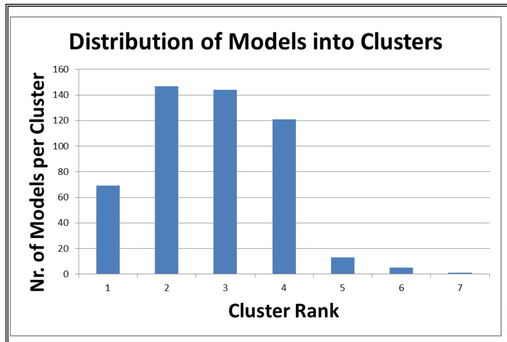
Data Preparation:

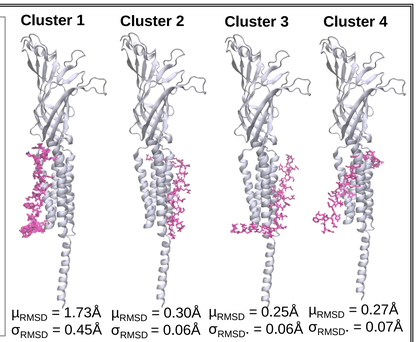
- The structure of the alpha-7 nicotinic receptor is obtained from the entry with id 2BG9 in the Protein Data Bank (PDB)
- Chain A is extracted from this structure
- Autodock tools functionality is used to add hydrogens, compute hydrogen bonding and charges
- The structure of the amyloid beta-42 peptide undergoes a similar preparation, specifying all its backbone angles as flexible
- Its structure is originally extracted from Model 1 in the entry with PDB id 1IYT (native form of peptide)
- The region likely to contain the binding site is defined through a grid (shown above) encapsulating the trans-membrane region (based on agonist and antagonist binding to the receptor)

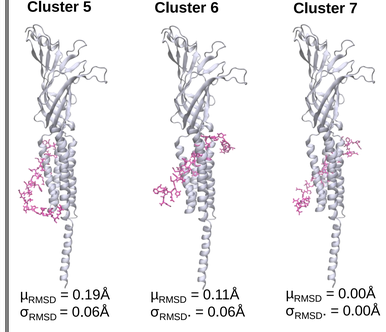
Experimental Setup:

- Autodock 4.2 is used to run a Lamarckian evolutionary algorithm that evolves a population of 150 ligand poses and configurations, using both mutation and crossover
- The algorithm is run 500 times to obtain 500 different lowest-energy binding poses and configurations of the ligand
- The latter are clustered to identify the most populous ones
- The entire process takes about 4 days on a single CPU

Results and Conclusions







Conclusions:

- In clusters 4-7 the ligand penetrates the unit, which is unlikely given the other four units in the full receptor
- Clusters 2 and 3 represent the widest energy basins
- Given its lower rank (by binding energy), cluster 2 can be offered as a prediction

Future Work:

- Model the kinetics of the binding process with efficient robotics-inspired methods developed in the Shehu lab [4]
- Expand the treatment to the Alzheimer form of the peptide
- These efforts will further elucidate possible interactions of amyloid beta-42 with other GPCRs studied in the Kabbani lab [5] and spur studies on therapeutics for Alzheimer's disease

References and Acknowledgements

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Acknowledgements: Continuing work on this project will be funded as part of an OSCAR Summer Intensive Award to Herath Pilapitiya. The author is indebted to Daniel Veltri for providing seminal instruction on receptor and ligand structures, as well as how to tame Autodock.