Molecular Dynamics Simulation of Met-Enkephalin Petide with Explicit Solvent

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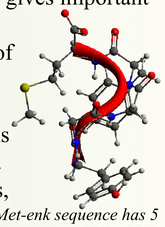
Introduction

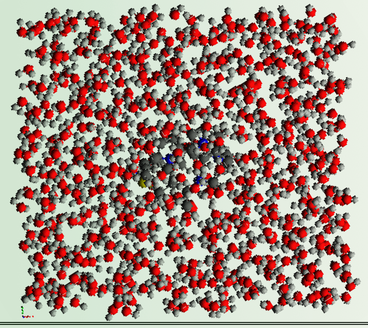
- The goal of this work is to study the the structural and dynamical characteristics of the peptide met-enkephalin (met-enk) [1]. This opiod peptide occurs naturally and is the primary endogeneous ligand of opiod receptors. It has importance in brain function and medical treatments. Therefore it is important to understand the structure which gives important information about the biological function.
- The approach is to follow in time the structural evolution of met-enk over time with molecular dynamics (MD) and to find the structures corresponding to potential energy minima of the peptide energy landscape. These simulations are done in an all-atom setting in water as explicit solvent.
- By considering the peptide surrounded by water molecules, one can explore the structures that met-enk takes on in its native physiological environment.



Met-enk sequence has 5 aminoacids: TYR, GLY, GLY, PHE,MET. In red is the ribbon visualization of the backbone between end a-carbons.

Methods

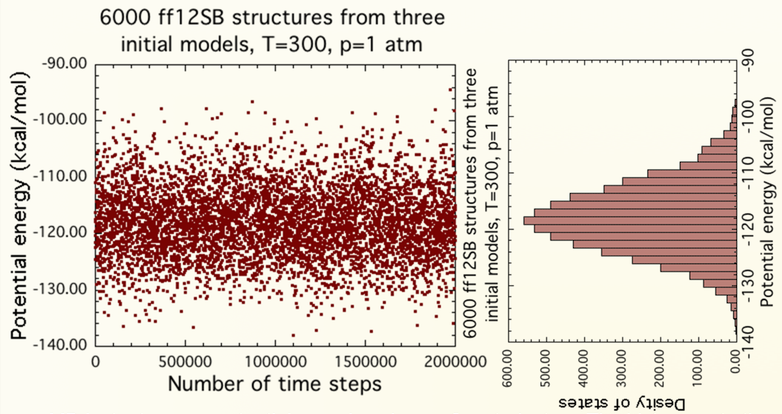
- MD simulations are carried out with the AMBER package [2] and the interaction between the atoms in the peptide and between the peptide and the water molecules were modeled with the FF12SB force field. The TIPP3 model potential was used to model the water solvent.
- MD is a powerful simulation method for solving simultaneously Hamilton's equations of motion of all atoms in the met-enk peptide and its surounding water molecules. The numerical solution corresponds to a set of 3N coupled first order ordinary differential equations (N=number of atoms). The met-enk peptide has 75 atoms, and typically the solvent box is composed of 650 water molecules.
- Periodic boundary conditions are used to simulate an extended system
- The numerical integration is done along a trajectory of several nanoseconds at constant temperature T = 300 K and pressure p = 1 atm.



Typical MD computational box containing one met-enk peptide surounded by 650 water molecules.

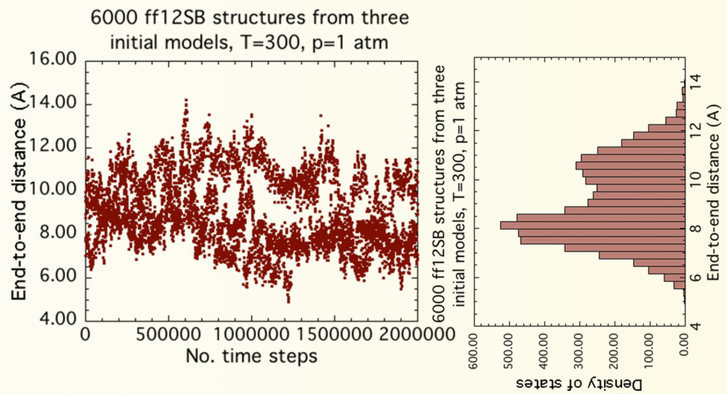
Results

- The potential energy of the system is plotted below, showing changes over time of about 20 kcal/mol. The density of the system remains at 1 gr/cm^3 along the simulation. This is an excellent result indicating that the solvent has indeed constrained the peptide motion to a fairly confined space



MD instantaneous potential energies along a 3 ps trajectory. The histogram to the right shows the gaussian density of states that is expected in thermal equilibrium.

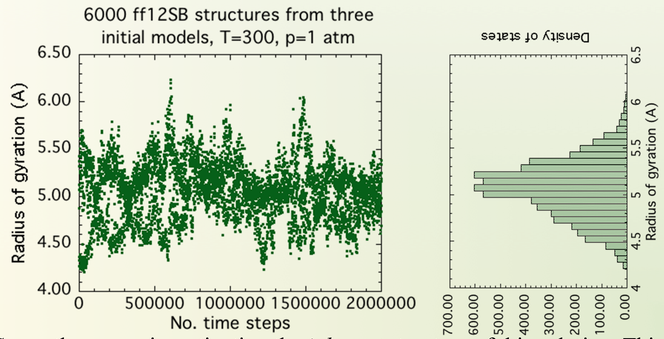
- The backbone end-to-end distance of met-enk changes over time showing that three main structures evolve and transition between them as a function of time



MD instantaneous end-to-end distance along a 3 ps trajectory. The histogram shows the overlap of 3 structures.

Conclusions

- We demonstrate that the presence of the solvent is crucial to keep the peptide encaged into a fairly globular shape where the phenyl groups shield the structure from the solvent. The result is a consequence of a smart strategy to build initially a well solvated peptide at the right density , pressure, and temperature. Our findings are more robust that any other previous simulation.
- We determine the radius of gyration as a function of time for several initial conditions as shown below. This result served as feedback for determining the constrain imposed to the basin hoping determination [3] of peptide minima explained in another poster.



- Currently we are investigating the *inherent* structure of this solution. This means, we are collecting the minima in conformation space above which each of our instantaneous structures was moving [4].
- We will be mapping these minima with density functional theory calculations to assert their validity from first principles.

References

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