Structural Analysis and Dynamics of the Met-Enkephalin Peptide

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Background

- The met-enkephalin (met-enk) peptide is a naturally occurring opiod that mediates pain and opiate dependence by interacting with opioid receptors [1].
- Our objective is to map the structure space accessed by met-enk to complement observations in the wet laboratory via two routes:

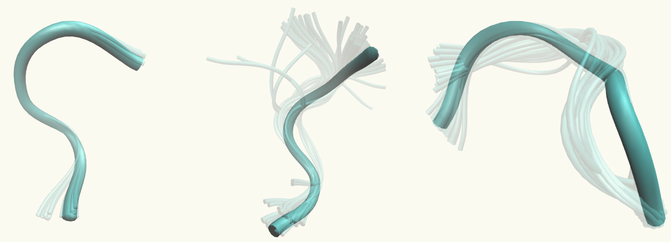
1) A dynamical study following the peptide time evolution of the for several nanoseconds with an atomistic description of the molecular interactions in explicit water solvent.

2) An evolutionary algorithm initiated from the met-enk sequence to sample minima of the potential energy in an ab-initio setting.

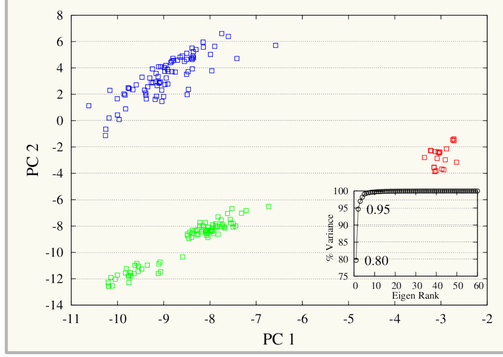
- A linear embedding shows that the two modeling settings explore a similar structure space. The diversity of this space suggests that met-enk exhibits high physiological structural flexibility.

PCA-based Structural Analysis

- A novel similarity analysis [3] between the torsion angles of the NMR experimental structures shows that met-enk prefers three structures in aqueous solution as shown below:



Clustering of 180 NMR experimental models of met-enk. Each structure shows the first model drawn opaque with a superposition of the others drawn transparent. Only backbones are shown.

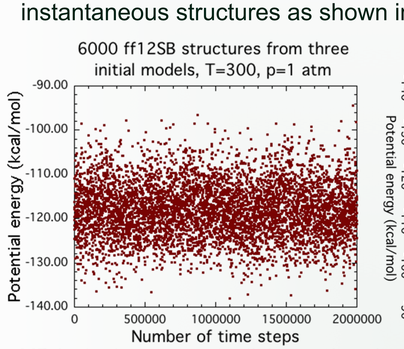


- Using Principal Component Analysis (PCA) [2], we map backbone structures in the plane of the two principal components PC1 and PC2
- Shown left are the projections of the NMR experimental structures

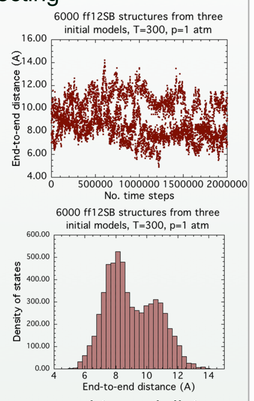
Structure and Dynamics Modeling

Molecular Dynamics Modeling

- Molecular dynamics (MD) simulations are conducted using the AMBER package [3] and the FF12SB force field with explicit water as solvent. The peptide dynamics is followed for several nanoseconds, collecting instantaneous structures as shown in the figures below.



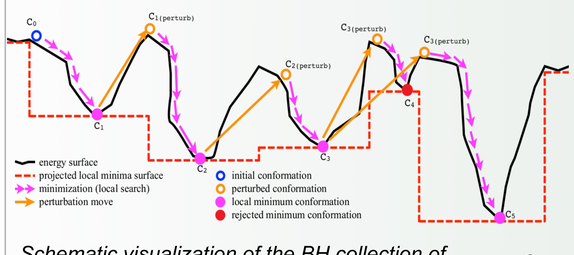
MD instantaneous potential energies along a 3 ps trajectory. The histogram to the right shows the gaussian density of states that is expected in thermal equilibrium.



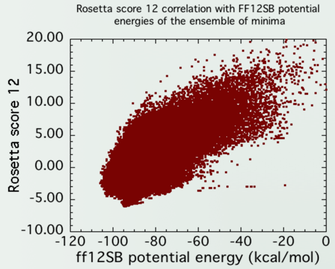
MD instantaneous end-to-end distance along a 3 ps trajectory. The histogram shows the overlap of 3 structures.

Ab-initio Structure Sampling

- Basin Hopping (BH) [4], an evolutionary algorithm, is initiated from a linear conformation of met-enk. BH iterates between perturbations and minimizations.
- Structural perturbations assign random backbone angles phi/psi.
- Minimization of the BH structures is carried out with the Relax protocol in the Rosetta package, using the all-atom score12 function.
- An ensemble of 100,000 minimized conformations is collected.



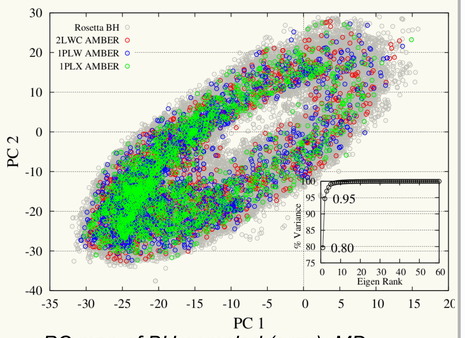
Schematic visualization of the BH collection of minima to build the ensemble of structures.



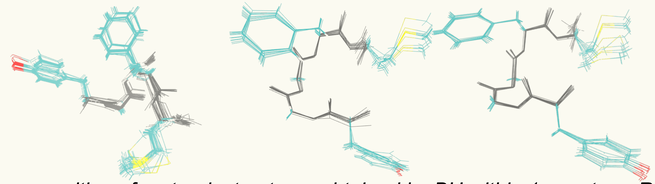
Correlation between Rosetta and Amber potential energies, when calculating AMBER energies of BH-sampled minima.

Discussion and Conclusions

- BH reproduces wet-lab structures and the MD structures.
- BH and MD explore similar structure space for the met-enk backbone.
- Main structural diversity is based on the motion of the side chains.
- PCA shows excellent superposition between the MD, ab-initio, and experimental structures in a the planar map of the two principal components as shown on the right.



PC map of BH-sampled (gray), MD, (green), and experimental (red) structures.



3D superposition of met-enk structures obtained by BH within 1 angstrom RMSD of wet-lab structures, indicating that BH reproduces the wet-lab structures.

- The MD results suggest that met-enk is quite flexible in solvents that emulate appropriately simulated physiological conditions.
- Current efforts focus on finding the thermodynamic variables [5] of the structural transitions enabling the met-enk peptide to change between the three conformations unveiled in this work.

References

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Acknowledgement: Supported by the Thomas F. and Kate Miller Jeffress Memorial Trust Award

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