# Conformational Sampling and Principal Component Analysis of the Met-Enkephalin Peptide

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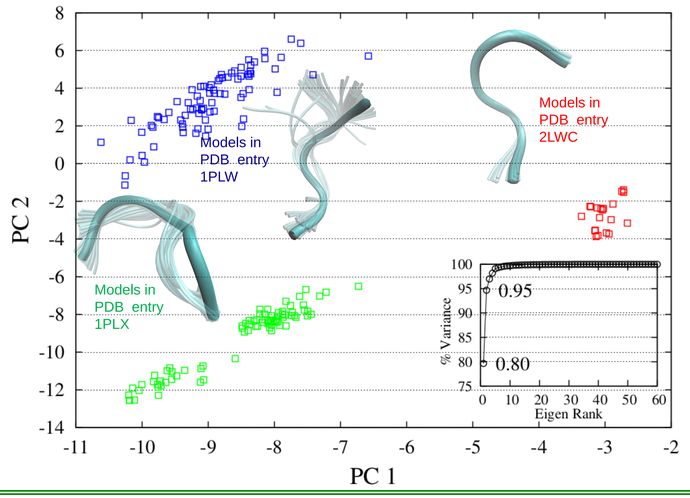
## Abstract

- Met-enkephalin (met-enk) is a naturally-occurring opiod that mediates pain and opiate dependence by interacting with opioid receptors [1].
- It flexes its structure to bind different opioid receptors.
- Wet-laboratory techniques have revealed a few structural states of met-enk [2].
- Research Objective: provide a comprehensive view of the structure space of met-enk through a variety of computational techniques.
- Project team of two faculty and three undergraduate student researchers.
- **My role**: structure ensemble analysis through linear dimensionality reduction techniques and conformational search exploration based on evolutionary algorithms.

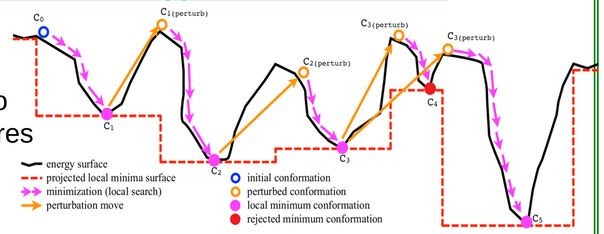
## Methodology

- Using Principal Component Analysis (PCA) [3], we project wet-lab backbone structures of met-enk on the plane of the two top principal components.




## Methodology Continued

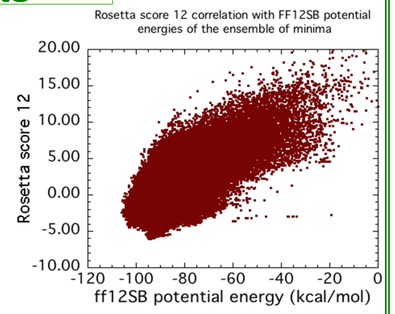
- Basin Hopping (BH) algorithm to compute structures de novo

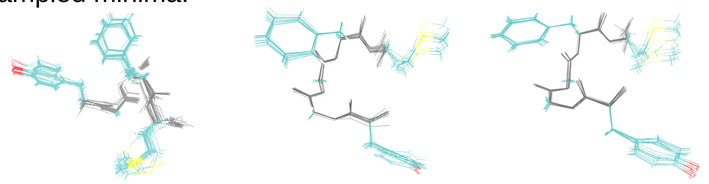



- Input: sequence of met-enk tyr-gly-gly-phe-met.
- Conformations are minima obtained after series of perturbations and minimizations.
- Perturbation: assign phi and psi angles of a randomly selected amino acid some value sampled over [-π, π).
- Minimization: add side chains and minimize using simulated annealing through the Rosetta Relax protocol.
- Analysis: compare ensemble to wet-lab structures and those obtained via Molecular Dynamics (led by M. Namazi).

## Results

- Good correlation between Rosetta and Amber potential energies, when calculating AMBER energies of BH-sampled minima conformations.
- Conformations of all-atom lRMSD < 1Å from the wet-lab models found in the ensemble of BH-sampled minima.

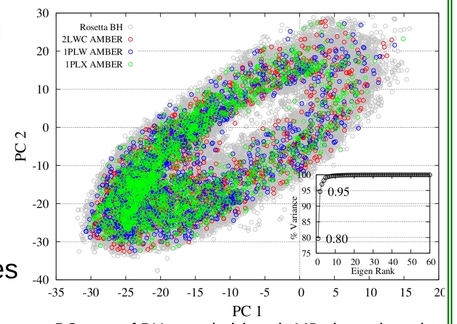


Less than 1A lRMSD conformations from model 1 in 2LWC (left), 1PLW (middle) and 1PLX (right) are shown, superimposed over model 1 of each respective PDB entry

## Discussions and Conclusions

- PCA analysis of we-lab, BH- and MD-obtained structures shows:
  - BH and MD explore similar structure space for the met-enk backbone.
  - Explore larger structure space than obtained experimentally
  - Large concentration of structures in the bottom left quadrant




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

- BH reproduces wet-lab structures and the MD structures
- MD exploration broad and not limited to experimental structures
- Overall shape of PC map indicates that PCs capture a backbone angle or a combination of angles
- Molecular Dynamics results suggest that met-enk is quite flexible in solvents that emulate appropriately simulated physiological conditions.
- Future work will focus on employing additional Monte-Carlo based structure exploration algorithms developed in the Blaisten-Barojas lab [5] and connectivity mapping with robotics-inspired techniques developed in the Shehu lab [6].

## References

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