Using Spectral Clustering to Sample Molecular States and Pathways

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Motivation

- **Molecular Dynamics (MD) simulations** are quintessential tools for exploring the state space of bio-molecules.
- However, exploring the state space is hindered by **timescale barrier** (i.e., temporal gap between simulation that requires a time step in fs and biological systems with timescales of ms).
- Hence, **enhanced sampling techniques** are used to explore the state space in a clever way.
- **Concurrent Adaptive Sampling (CAS) algorithm** uses a large number of short simulations or "walkers" with probabilities or "weights" to explore the state space.
- **Reducing the number of walkers by clustering** these walkers when there are too many walkers in the simulation can **speed up the overall sampling**.

Methodology

CAS Algorithm

- Walkers are binned to newly created circular microstates or "balls" and within each ball, walkers are split and/or merged so that each ball ends up with the same number of walkers. This is done to constantly observe all states irrespective of their energy barriers.
- As the walkers explore the state space, the number of balls grows very quickly. When the total number of balls reaches a certain threshold, balls are clustered into a set number of macrostates.

Spectral Clustering

- Cluster balls based on normalized second eigenvector of the state transition matrix (i.e., probability changes in state space) and ball distance information using k-means.

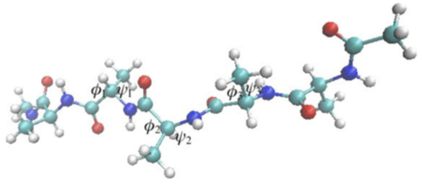
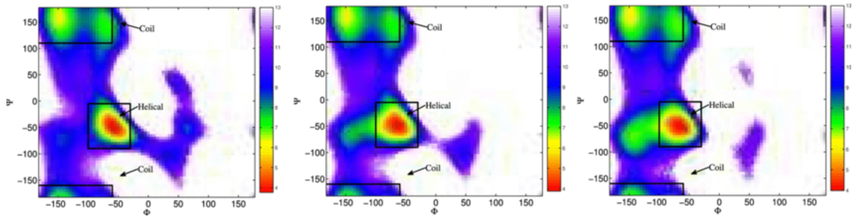
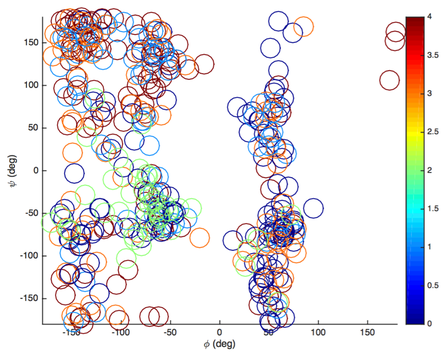


Fig 1. Penta-alanine and its 3 reference Ramachandran plots for each middle ϕ, ψ pair

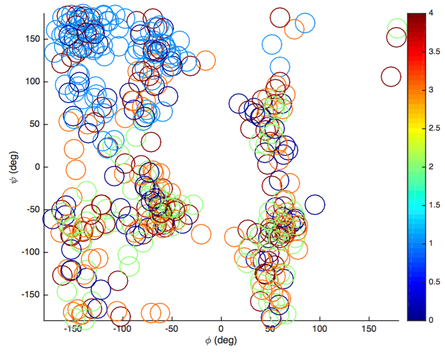


Results

- **Model of interest**: penta-alanine, which has a 6-dimensional state space described by 3 pairs of dihedral angles ϕ, ψ.
- First, we clustered just based on the normalized second eigenvector, which gave the following results:

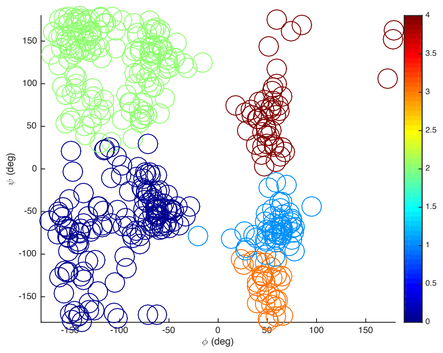


- Then, we decided to cluster based on the normalized second eigenvector **and** ball distance information:

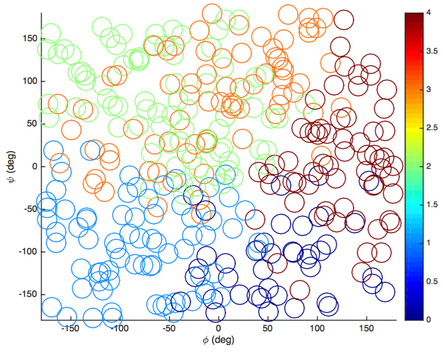


Results

- If we cluster based on the **first 2 ball coordinates rather than all 6**, we get clusters representing important metastable regions in Fig 1:



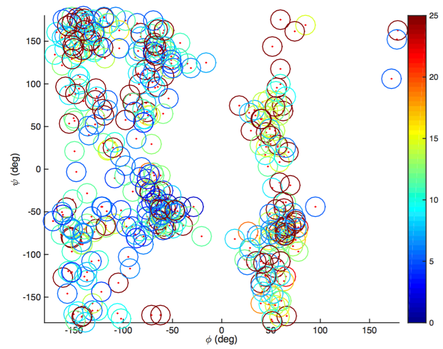
- To further demonstrate that our clustering actually does a good job, we depict the **feature space onto the first two principal components**:



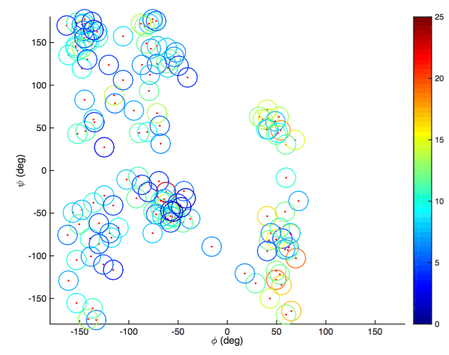
- We can see that the clusters are well-separated from PCA, but it is unclear which balls correspond to which physical state in the Ramachandran plot.

Results

- Before clustering:



- After clustering:



- **Conclusion**: We can successfully cluster microstates into physically meaningful and well-separated macrostates and speed up the simulation by reducing "redundant" states and without sacrificing accuracy/precision.
- **Future Work**: Increase time step of the simulation to get better sampled transition matrices. Run simulations further to collect mean first passage time statistics.