Markov state models for molecular dynamics

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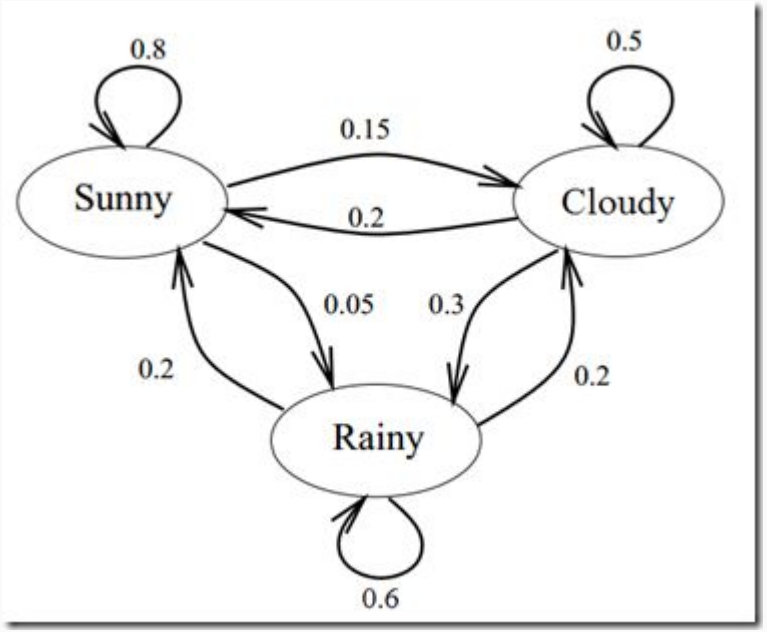
Everything you wanted to know about Markov State Models but were afraid to ask

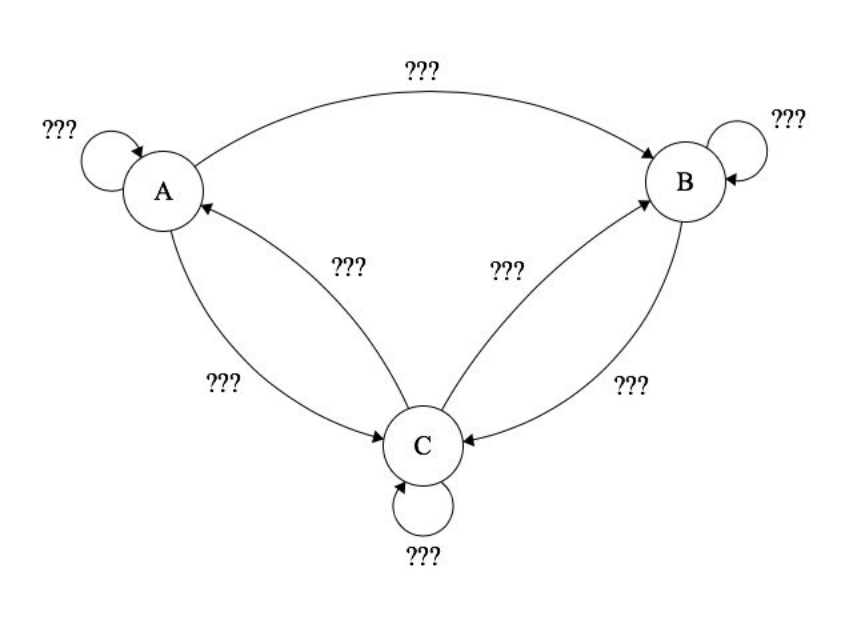
Vijay Pande, Kyle Beauchamp, Gregory Bowman

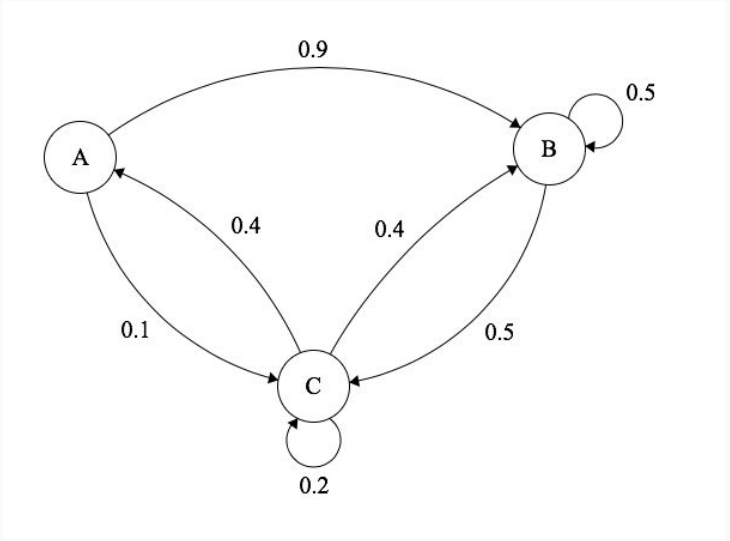
What is a Markov State Model?

- Way of modeling a random process
- Markov Assumption
  - Next state is determined only by current state



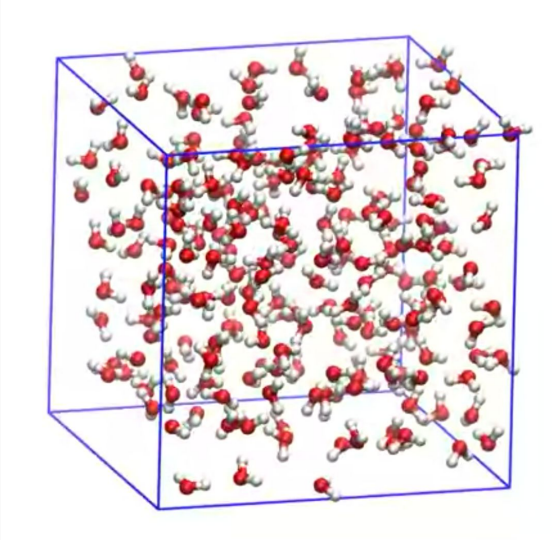
Transition probabilities





Applications

- Protein folding
- **Molecular Dynamics**
- Speech recognition
- Self-driving cars
- Gene prediction
- Machine translation
- Part-of-speech tagging



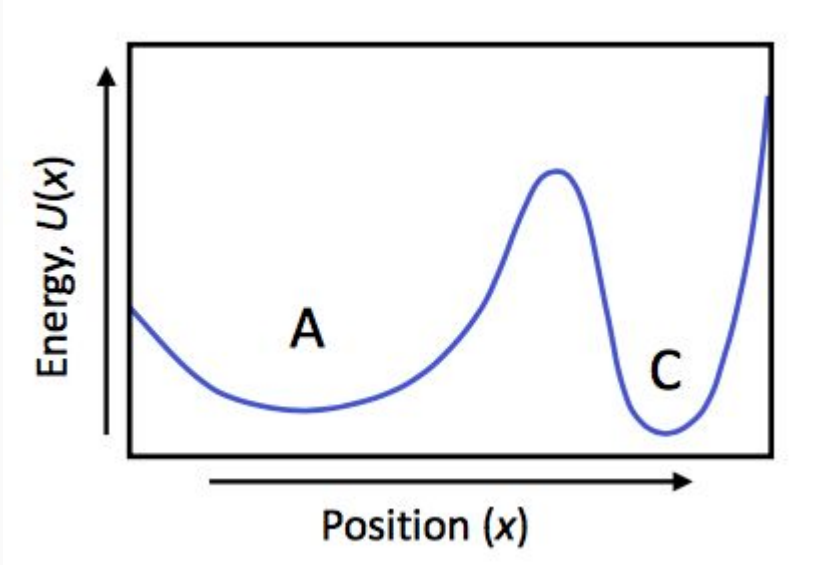
Challenges in Molecular Dynamics

- Computationally Intensive
  - Relevant simulation timescales milliseconds - seconds

- Force Fields are limited
- Analysis of simulation data
  - Trajectories

Building an MSM for MD

- Choose Markov states to correspond to kinetic macrostates
  - Similar conformations clustered to groups with a representative energy
- Build transitions matrix based on MD probabilities of state changes
  - Frequentist and Bayesian approaches



Molecular Dynamics with MSM’s

- N states with transition probabilities between them
  - N ~ thousands to millions
  - Large number of states gives more accurate representation
- Define states in a physically meaningful way
- Build the transition matrix efficiently
- Start with some initial data set
  - e.g. a molecular dynamics simulation

Adaptive Sampling

- Often there is not enough simulation data to immediately build an accurate Model
  - Need to perform more simulations to get novel data
- Use transition probability matrix to select macrostate to start simulation in
  - Statistical analysis to run simulations to generate the most data
- Significantly improves efficiency

Caveats

- Sampling is *still* a challenge
  - Long-timescale events are out of reach
- Limited by force fields
- State decomposition is difficult
  - Complex systems require more than just kinetic approaches
    - e.g. knots, topological effects
- Need new metrics for structural similarity

Questions?

Markov state models of biomolecular conformational dynamics

Chodera et al., 2014

Adithya Ganesh

Markov Chain Simulation

- Markov Chain simulation
  - http://setosa.io/blog/2014/07/26/markov-chains/index.html

Recent theoretical advances

- Old approach
  - Maximizing “metastability” -- quantity related to *lifetime* of states
- Recent advances
  - Formulate analysis as an eigenvalue problem
- Key intuition
  - Eigenvector with eigenvalue 1 → steady state!

$$\boldsymbol{\pi}^\top \mathbf{P} = \boldsymbol{\pi}^\top .$$

Markov Chain Eigenvector Simulation

- **Key intuition**
  - Eigenvector (with $\lambda = 1$)$\rightarrow$ steady state
- Simulation
  - http://setosa.io/ev/eigenvectors-and-eigenvalues/
- PageRank
  - *“The $25,000,000,000 Eigenvector - The Linear Algebra Behind Google”*
    - https://www.rose-hulman.edu/~bryan/googleFinalVersionFixed.pdf
  - A very similar Markov chain problem
    - Obtain transition probabilities by observing which pages link to others
    - Eigenvectors give you the steady state “page ranks”

EMMA Python package -- demo

Raw simulated trajectory

↓

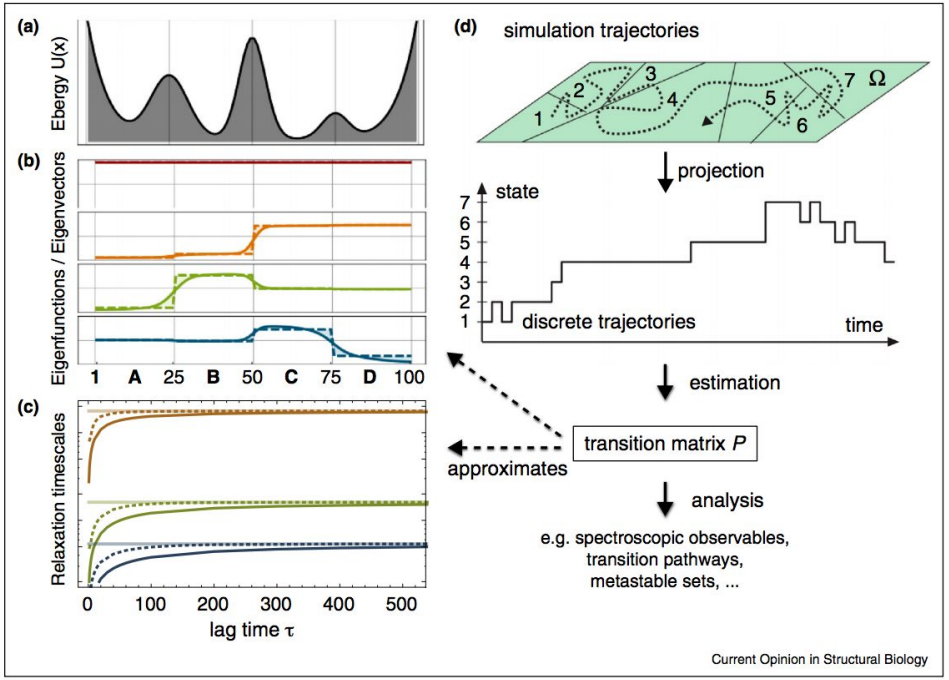
“Compressed” Trajectory (TICA projection)

↓

Clustering (K-means)

↓

Estimate MSM + visualize states



Questions?

HTMD: High-Throughput Molecular Dynamics for Molecular Discovery

Motivation

- Molecular dynamics simulations (MD) come with several limitations:
  - Data analysis
  - Reproducibility
  - Accuracy of force fields
  - Time sampling limitations
- Necessity of a more standardized methodology

High-Throughput Molecular Dynamics (HTMD)

- Programmable workspace for simulation based molecular discovery
- Python
- VMD

Integrated Platform

- Structure Manipulation
- System Building
- Molecular Simulation
- Adaptive Sampling
- Projecting and Clustering
- Markov State Models (MSMs)

2. METHODS

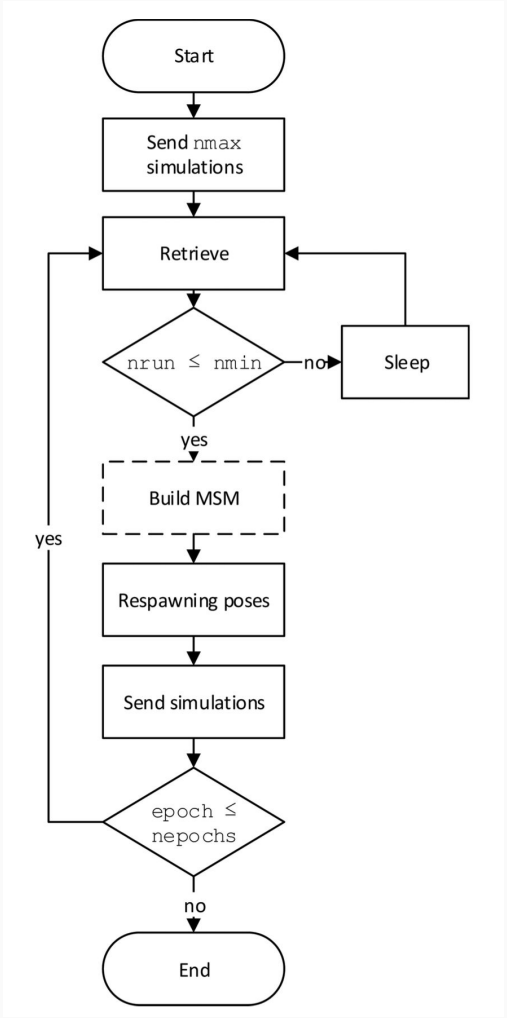
2.1. Integrated Platform for Molecular Modeling.

Listing 1: Manipulating molecular structures.

```
# Download the PDB structure of Barnase
mol = Molecule('2F4Y')
# Set the chain ID of Barnase to 'Y'
mol.set('chain', 'Y', sel='protein')
# Remove the carbon alpha of residue 15
mol.remove('residue 15 and name CA')
# Append Barstar to Barnase
mol.append(Molecule('2HXX'))
# Visualize in VMD or NGL
mol.view()
# Solvate in water box
solvate(mol, minmax=[[-50, -50, -50],
                     [50 ,  50,  50]])
```

Adaptive Sampling

- Efficient and intelligent sampling of conformational space
- From previous simulation knowledge, it identifies conformational subspaces that are under-sampled



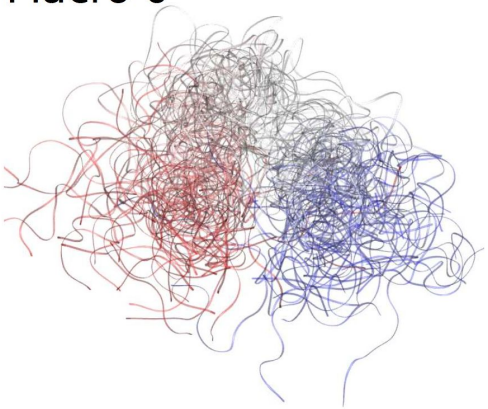
Protein Folding Analysis

```
# Collect and link simulation files
sims = simlist(glob('data/*/'),
    glob('input/*/structure.pdb'))
# Calculate protein contact maps
met = Metric(sims)
met.projection( MetricSelfDistance(
    'protein and name CA',
    metric='contacts') )
data = met.project()
# Project on slowest 10 TICA dimensions
tica = TICA(data, 20)
dataTica = tica.project(10)
# Cluster data with kmeans
dataTica.cluster(
    MiniBatchKMeans(n_clusters=1000))
# Link a model with the data
model = Model(dataTica)
# Calculate the Markov model
model.markovModel(300, 4)
# Macrostates equilibrium distribution
model.eqDistribution()
# Visualize the macrostates in VMD
model.viewStates()
# Calculate the kinetics
kin = Kinetics(model, temperature=360)
kin.getRates()
```

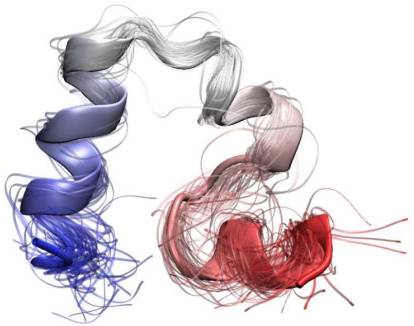
Protein Folding Analysis

The 4 macrostates produced by the Markov state model of Villin

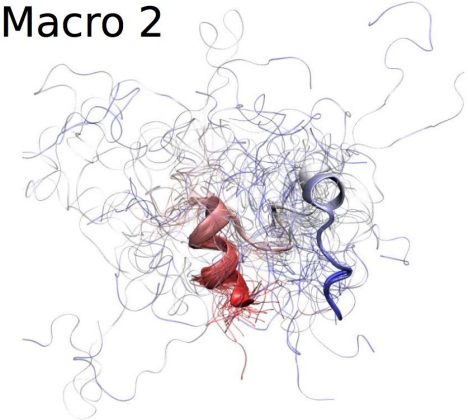
Macro 0



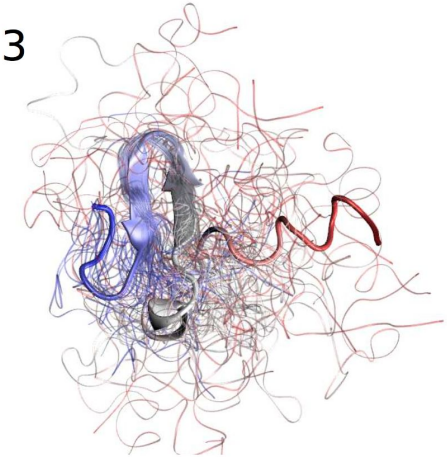
Macro 1



Macro 2

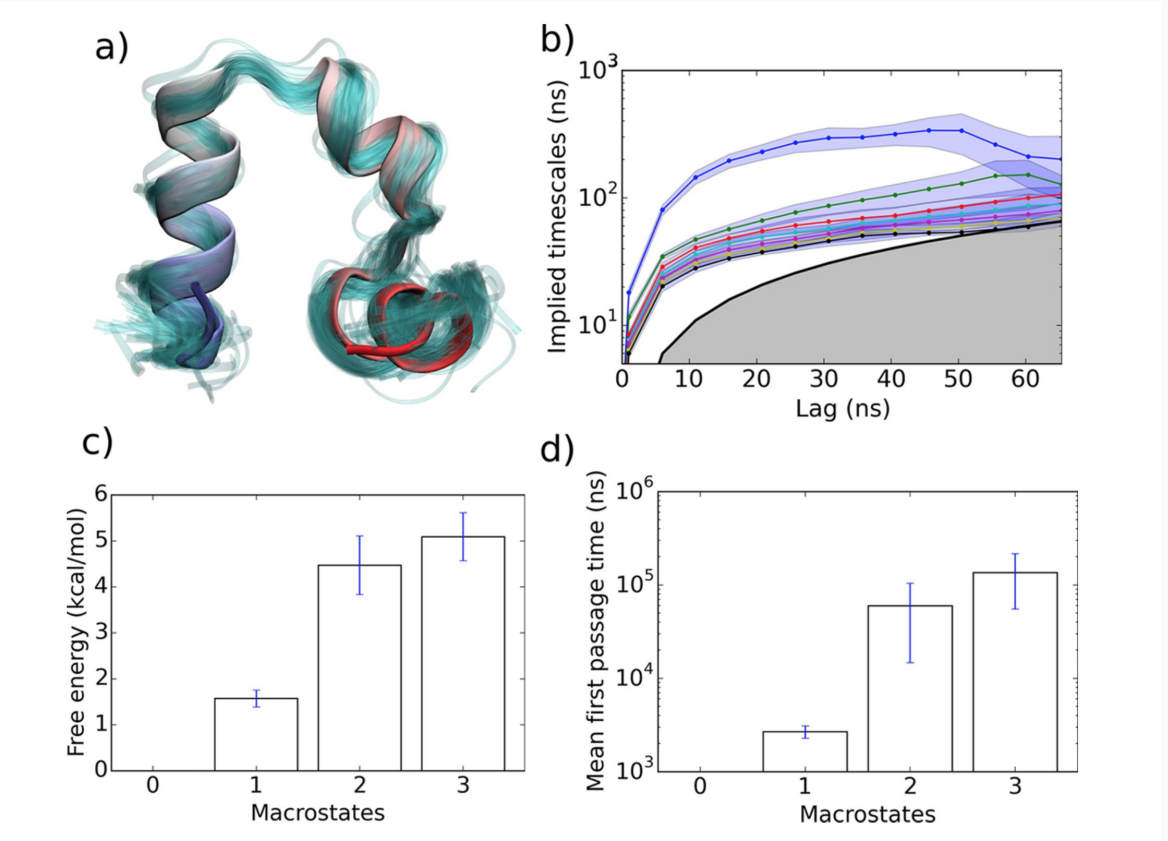


Macro 3



Questions?

Protein Folding Analysis



Adaptive Sampling Protein Folding