Markov-state modeling of biomolecular systems II

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Plan of the practice

1. We compute a MSM of a "toy model": trajectory in a 1-D potential (R language).
2. Move to a realistic trajectory set: prothrombin:inhibitor binding
   a. PLUMED projection
   b. build a simple MSM in R like before

Instructions

- Connect as usual to 159.149.160.118
- `. /tmp/go-markov`
- This will copy the exercise files in your directory, `$HOME/practice`

1. Toy model in 1D

- Start the R environment
- See the "*Markov From Scratch*" document
- Data file needed: data1.csv.gz
  - data10.csv.gz is also available for experimenting, see comments

```
$ zless data1.csv.gz
2.3000000000000000e+01
2.3000000000000000e+01
2.4000000000000000e+01
2.5000000000000000e+01
2.6000000000000000e+01
2.6000000000000000e+01
2.6000000000000000e+01
```

Prothrombin:ligand example

- This is a large, realistic simulation set
  - From htmd.org: Ligand Binding Analysis
  - 3 GB (don't download today)
  - 852 trajectories (in 3 groups)
  - 852 x 20 ns ≈ 17 μs
- See the *MarkovOnLargeDataset* document
- Files in `/mnt/scratch/shared/markov/binding/`

MarkovOnLargeDataset

- It is an R notebook similar to the 1-D example. However…
- The original space is high-dimensional. So
  1. Project it with a PLUMED script: Protein-Ligand vector after alignment
  2. Convert the 3D projection to discrete states with a *k-means* clustering algorithm

Using PLUMED for projections

- We need to extract from *each frame of each trajectory* a limited number of values (projection, or metric)
- Must be orientation-independent (align)
- PLUMED may be used for the task
  - protein-ligand-vector.plumed
  - project-with-plumed.sh
- Results: metric.dat

protein-ligand-vector.plumed

```
UNITS LENGTH=A

FIT_TO_TEMPLATE STRIDE=1 REFERENCE=reference.pdb TYPE=OPTIMAL

# These are the serial numbers of protein CA's
prot: CENTER ...
ATOMS={   5,   20,   30,   42,   52,   59,   78,  110,  116,  135,  155,
        170,  192,  214,  225,  244,  259,  271,  293,  307,  322,  346,
                                                    . . .
       4229, 4253, 4272, 4294, 4316, 4340, 4359, 4376, 4398, 4414, 4433,
       4445, 4462
       }
...

# This is "resname MOL and noh" (inhibitors's heavy atoms)
ligand: CENTER ATOMS=4481,4484,4487,4490,4493,4496,4497,4498,4501

pl: DISTANCE ATOMS=prot,ligand COMPONENTS

PRINT ARG=pl.*
```

project-with-plumed.sh

Computes the metric over all the trajectories

(You don't actually have to run this. The results are already in **metrics.dat**)

```
#!/bin/bash

# This file computes the PLUMED metric indicated in $script
# on all of the trajectory files in $indir. The results
# are printed in stdout.

# You only need to run this file if you change the definition
# of the metric. The current results are in metric.dat

script=$HOME/practice/protein_ligand_vector.plumed
indir=/mnt/scratch/shared/markov/binding/1/filtered

# Loop over all files ending by .xtc
for tj in `find $indir -name \*.xtc -and -not -name .\*`; do
  # Output file name
  outname=`basename $tj`
  echo Running plumed on $tj >&2
  plumed driver --plumed $script \
    --pdb $indir/filtered.pdb \
    --mf_xtc $tj | \
       egrep "^ " | sed "s+^+$outname+"
done
```

```
project-with-plumed.sh > newmetric.dat
```

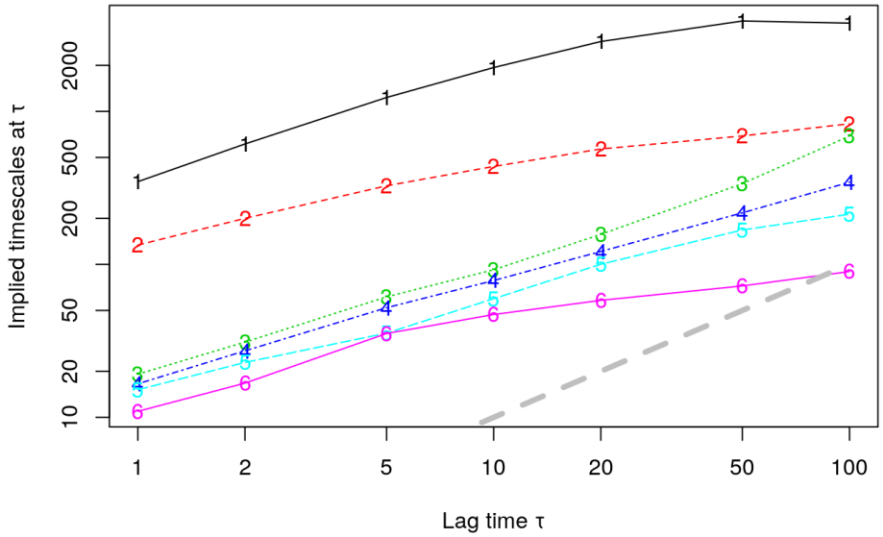
metric.dat

Results of the projection are in metric.dat.
This will be read in by R.

```
(htmd) tonigiorgino@monaco:~/practice$ head metrics.dat
e36s5_e27s3f37-....xtc 0.000000 -0.224091 -11.886612 1.973588
e36s5_e27s3f37-....xtc 1.000000 -0.413809 -12.038901 1.644167
e36s5_e27s3f37-....xtc 2.000000 -0.532973 -12.323975 2.144003
e36s5_e27s3f37-....xtc 3.000000 -0.300480 -11.363546 1.903810
e36s5_e27s3f37-....xtc 4.000000 -0.433555 -11.792027 2.057442
. . .
e24s3_e21s4f177-....xtc 196.000000 8.976495 -10.536748 2.060360
e24s3_e21s4f177-....xtc 197.000000 9.262883 -11.399111 2.169123
e24s3_e21s4f177-....xtc 198.000000 8.517335 -12.355884 2.464811
e24s3_e21s4f177-....xtc 199.000000 8.496182 -12.325769 1.489607
```

Where to go from here (I)

- We are starting to see convergence, but not quite. Try better metrics to improve Markovianity.
- Explore the most stable states
- Explore major relaxation modes



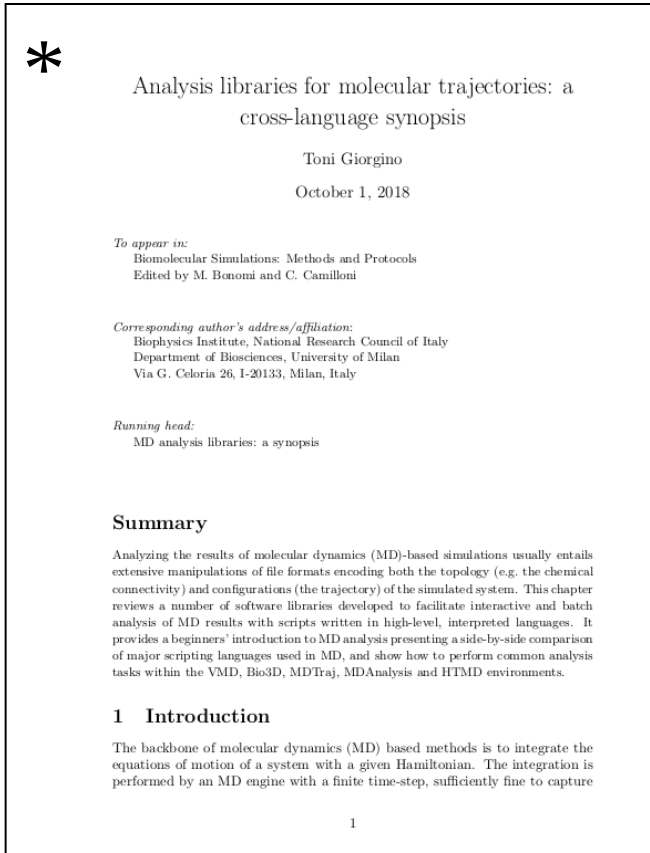
Where to go from here (II)

- Try the other split of the dataset. (1 vs 2 vs 3). Are they independent?
- Use all of them together.
- Try the other systems in
  `/mnt/scratch/shared/markov/villin`
  `/mnt/scratch/shared/markov/cxcl12`
  - Familiarize with the PDB
  - Devise a reasonable metric

Where to go from here (III)

- R is fine, but there are specialized environments for MD analysis
  - HTMD, MdAnalysis, MdTraj, Bio3D, … *
  - Most are Python based
- HTMD provides:
  - Molecule/trajectory visualization
  - Markov Modeling (etc)

*



Analysis libraries for molecular trajectories: a cross-language synopsis

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Running head:
MD analysis libraries: a synopsis

Summary

Analyzing the results of molecular dynamics (MD)-based simulations usually entails extensive manipulations of file formats encoding both the topology (e.g. the chemical connectivity) and configurations (the trajectory) of the simulated system. This chapter reviews a number of software libraries developed to facilitate interactive and batch analysis of MD results with scripts written in high-level, interpreted languages. It provides a beginners' introduction to MD analysis presenting a side-by-side comparison of major scripting languages used in MD, and show how to perform common analysis tasks within the VMD, Bio3D, MDTraj, MDAnalysis and HTMD environments.

1 Introduction

The backbone of molecular dynamics (MD) based methods is to integrate the equations of motion of a system with a given Hamiltonian. The integration is performed by an MD engine with a finite time-step, sufficiently fine to capture

1

Python Notebooks

- Start with "nb" (it's a shortcut).
  - Open the address shown in your browser, like http://159.149.160.118:8889/?token=8499de73866d18c …
- You will see an interactive Python (*jupyter*) Notebook.