

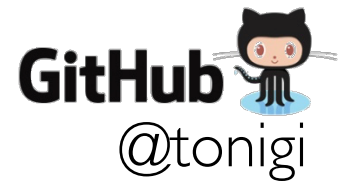
Markov-state modeling of biomolecular systems II



Toni Giorgino

National Research Council of Italy

toni.giorgino@cnr.it



Structural Bioinformatics @ UniMi
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Plan of the practice

1. We compute a MSM of a “toy model”:
trajectory in a I-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

I. Toy model in ID

- 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
2.3000000000000000000000e+01
2.3000000000000000000000e+01
2.4000000000000000000000e+01
2.5000000000000000000000e+01
2.6000000000000000000000e+01
2.6000000000000000000000e+01
2.6000000000000000000000e+01
```

Prothrombin:ligand example

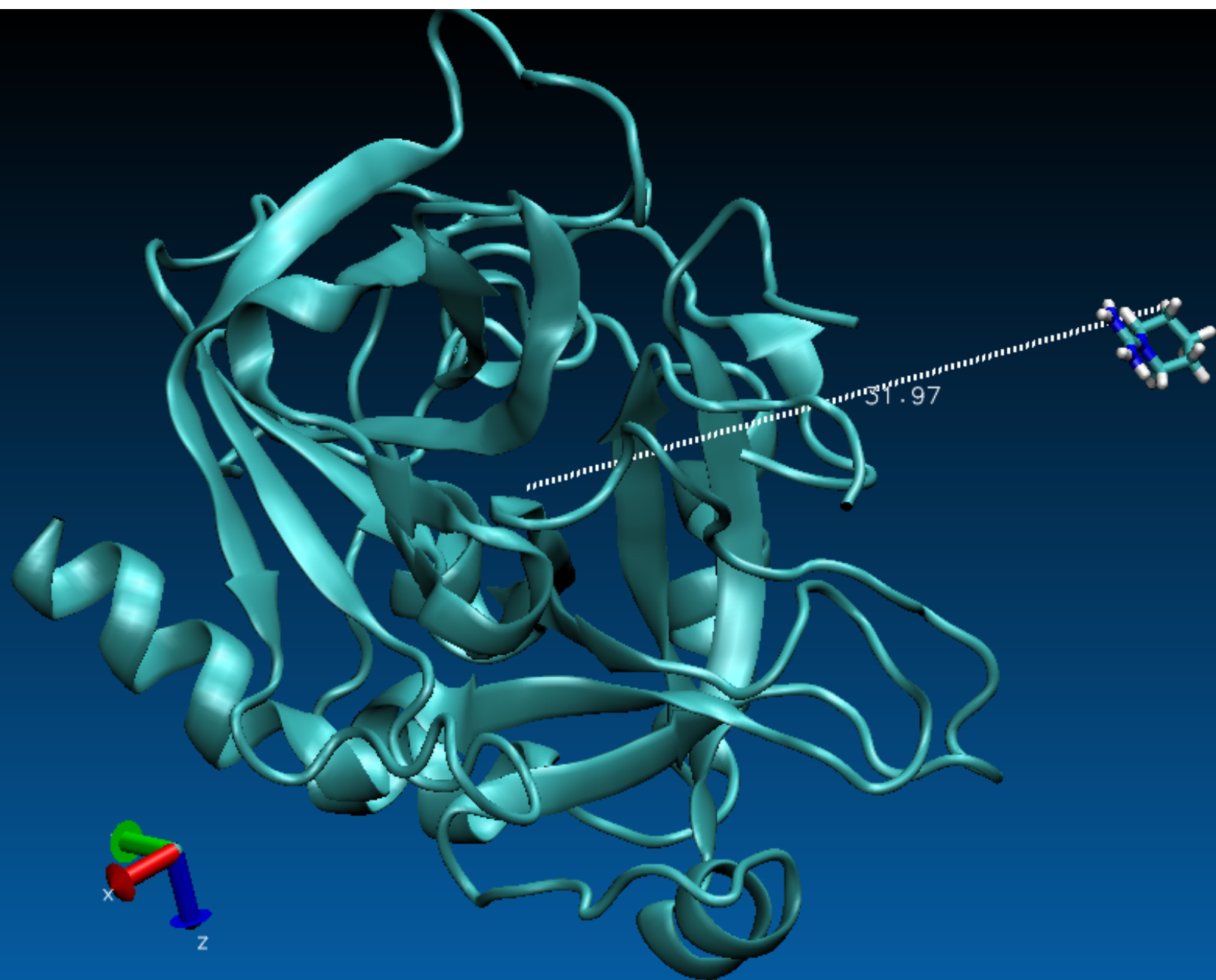
- This is a large, realistic simulation set
 - From htmd.org: [Ligand Binding Analysis](#)
 - 3 GB (don't download today)
 - 852 trajectories (in 3 groups)
 - $852 \times 20 \text{ ns} \approx 17 \mu\text{s}$
- See the [MarkovOnLargeDataset](#) document
- Files in `/mnt/scratch/shared/markov/binding/`

MarkovOnLargeDataset

- It is an R notebook similar to the I-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
```

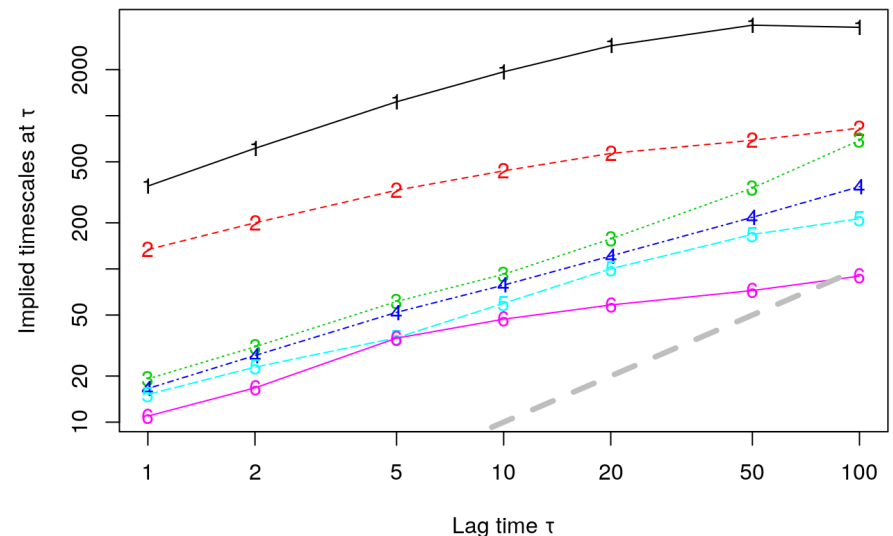
metric.dat

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 *specialized* environments for MD analysis are more productive
 - HTMD^o, MdAnalysis, MdTraj, Bio3D, ... *
 - Most are Python based
- ^o It does:
 - Molecule/trajectory visualization
 - Markov Modeling (etc)



Analysis libraries for molecular trajectories: a cross-language synopsis

Toni Giorgino

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To appear in:

Biomolecular Simulations: Methods and Protocols
Edited by M. Bonomi and C. Camilloni

Corresponding author's address/affiliation:

Biophysics Institute, National Research Council of Italy
Department of Biosciences, University of Milan
Via G. Celoria 26, I-20133, Milan, Italy

Running head:

MD analysis libraries: a synopsis

Summary

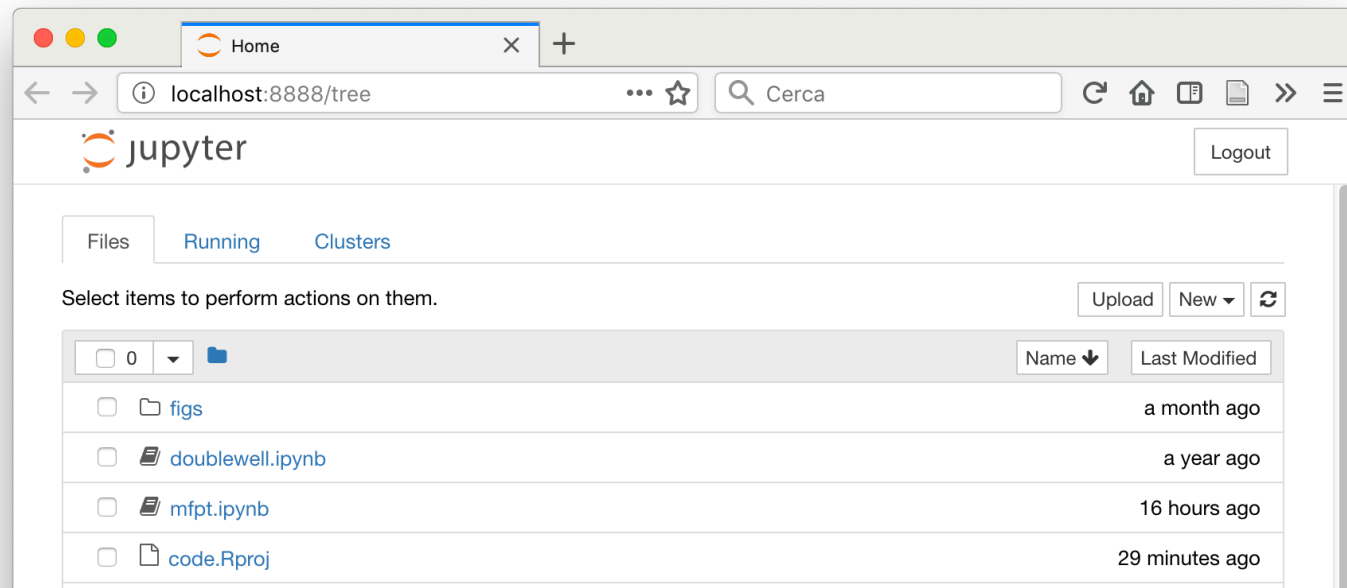
Analyzing the results of molecular dynamics (MD)-based simulations usually entails extensive manipulations of file formats encoding both the topology (e.g. the chemical connectivity) and configurations (the trajectory) of the simulated system. This chapter reviews a number of software libraries developed 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

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.



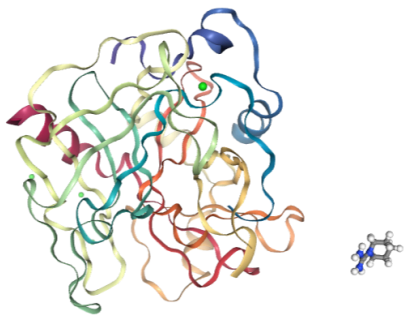
Python Notebooks

Home 5_ligand-binding-analysis 4_Python_HTMD_introduction

jupyter 4_Python_HTMD_introduction Last Checkpoint: 17 ore fa (unsaved changes) Logout

File Edit View Insert Cell Kernel Widgets Help Trusted Python 3

In [4]: `n=Molecule("/mnt/scratch/shared/markov/binding/1/filtered/filtered.pdb")`
`n.view()`
`G13 "HG21" "HG22" "HG23")`



In [5]: `n.sequence()`

Python Notebooks (MSM)

