PLUMED's collective variables in the High Throughput Molecular Dynamics analysis environment

An object model for CVs

GitHub
@tonigi
PLUMEDws2017

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Motivation

Idea – Combine PLUMED with a high-level Python-based molecular environment

Overview

1. Markov w/ large-scale MD, HTMD*
2. PLUMED-based projections: *MetricPlumed2*
3. (Not-) writing PLUMED CVs
4. Plumed-based Markov Models
5. Availability

* acellera®

Markov models from large-scale biomolecular simulations

Noe et al., Cur. Op. Str. Biol. 2014

De Fabritiis et al., PNAS 2012

Pérez-Hernández et al., JCP 2013

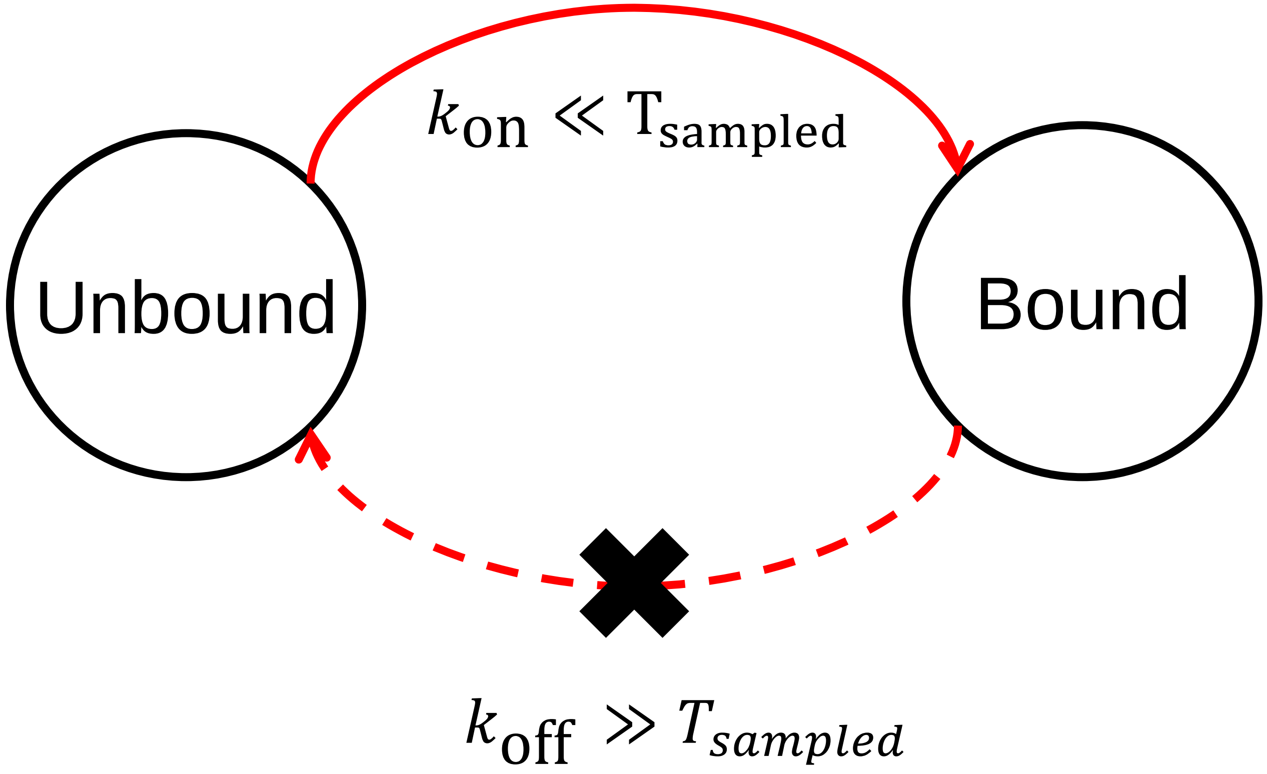
Markov Models

- Estimate $P(x_{t+\tau}|x_t)$ from observations
  - Assume discrete states, time-independent *P*
  - Need no force bias*
  - Suitable for large scale MD (…requires it)
  - Efficient use of parallel trajectories
  - Bias can be "statistic" (adaptive schemes)
- Success cases:
  - Ligand-binding kinetics (on & off)
  - Large conformational transitions
  - Protein folding...

* Not unlike forward-flux sampling

Move beyond this model…

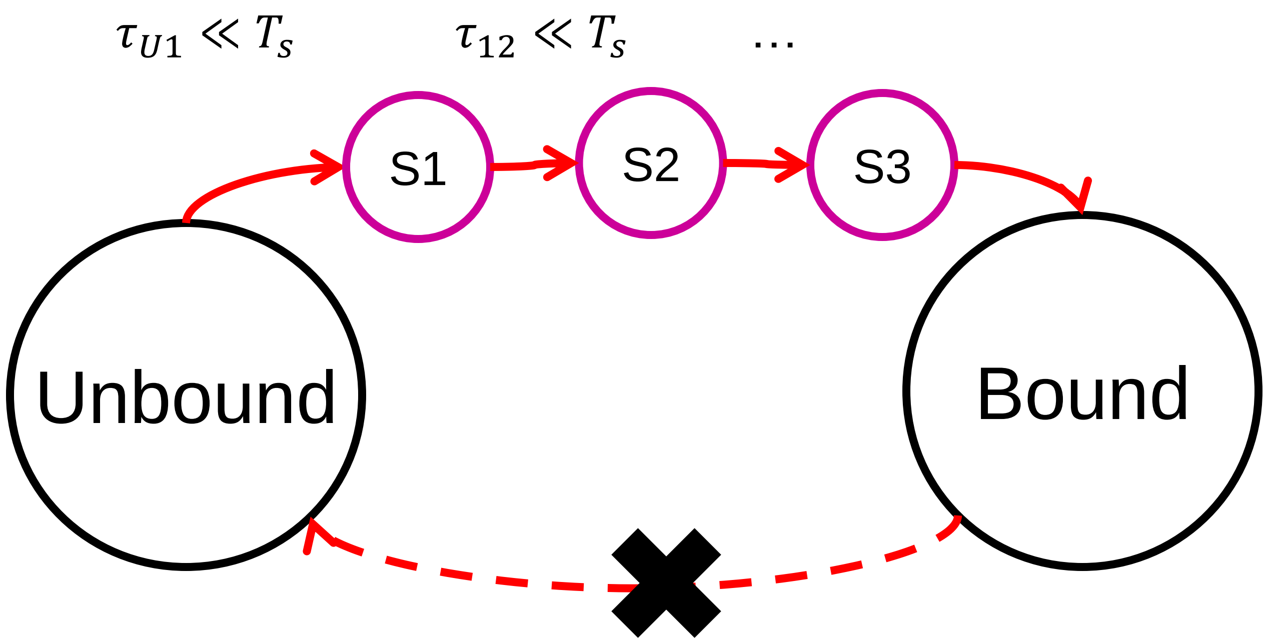
On the timescales sampled by unbiased MD…


$k_{\mathrm{on}} \ll \mathrm{T}_{\mathrm{sampled}}$
Unbound
Bound
$k_{\mathrm{off}} \gg T_{sampled}$

k_{on} - estimated counting events vs sampled time

Idea

- We introduce several *intermediate steps*

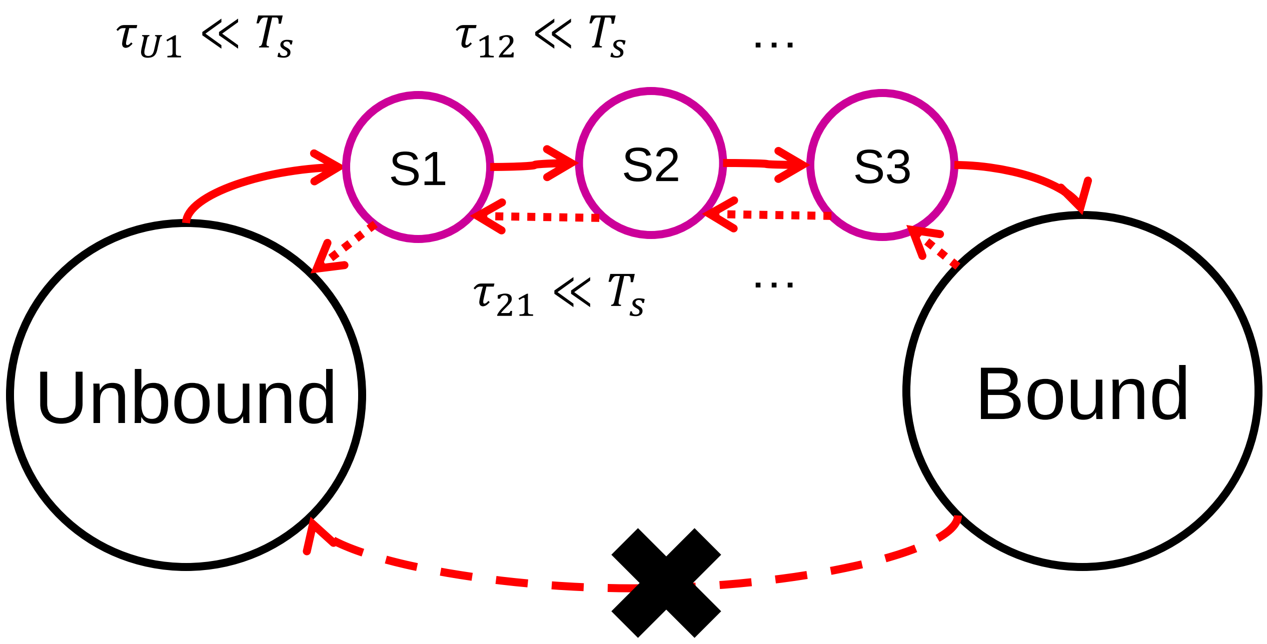


k_{on} - reconstructed combining rates of intermediate steps

Buch et al., PNAS 2012

Idea

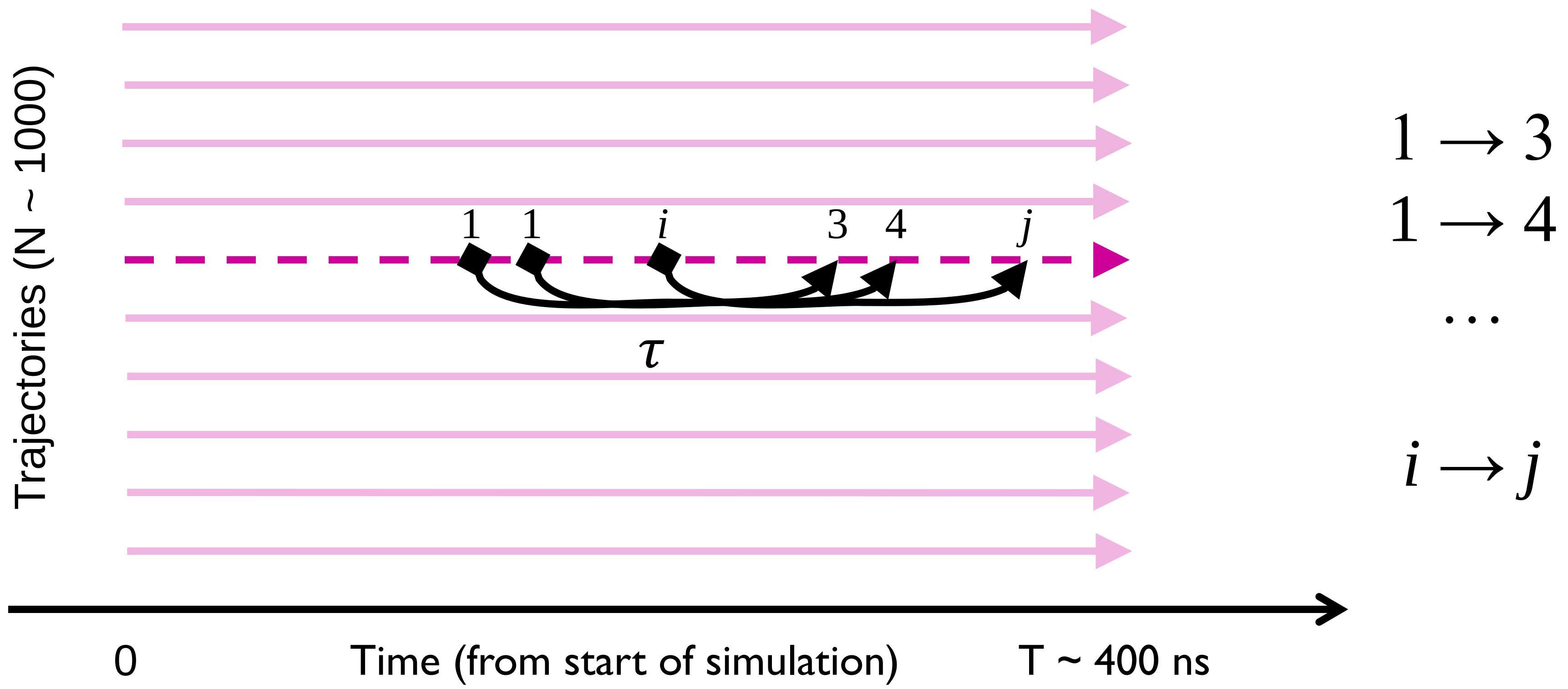
- We introduce several *intermediate steps*



k_{on} - reconstructed combining rates of intermediates steps

k_{off} - may be also reconstructed, if states are fine-grained!

Trajectories → States → Markov state model



$$N\left(X_{t-\tau} \xrightarrow{\text{lag } \tau} X_t\right) \Rightarrow$$

$$P_{ij} = P(X_t = j \mid X_{t-\tau} = i)$$

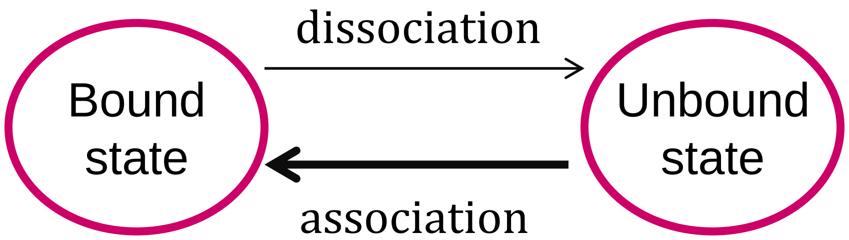
P_{ij} = Time-independent probability to change state from i to j at each point in time (constant)

Why do we care?

1. Thanks to memoryless-ness and homogeneity assumptions, one can accumulate counts from **different** trajectories in the **same** matrix.

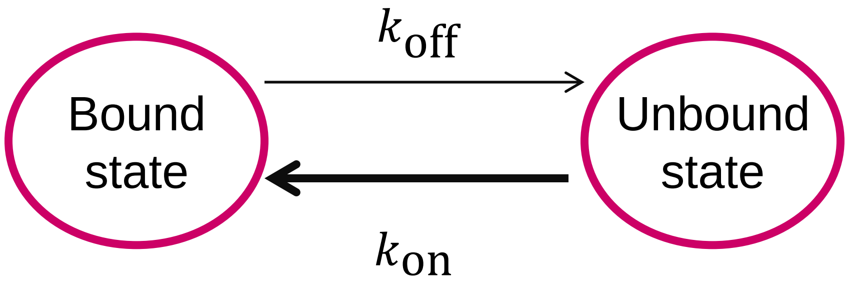
2. Because equilibrium probabilities *are* the free energy of binding (ΔG), an important determinant of drug potency.

$$K_D = \frac{p_U}{p_B} = \exp\frac{-\Delta G}{RT} \quad \left(\propto \frac{[P][L]}{[PL]}\right)$$



3. Because **mean-first-passage times** correspond to inter-state kinetics...

$$K_D = \frac{k_{\text{off}}}{k_{\text{on}}} \propto \frac{\tau_{\text{on}}}{\tau_{\text{off}}} \sim \frac{t_U^{(B)}}{t_B^{(U)}}$$



Code by yourself, or…

- Building matrices builds on non-trivial algorithms (MLE of reversible process, bootstrapping, convergence, …)
- Extraction of observables from *large* amounts of trajectories
- → Strongly motivated analysis frameworks, e.g. MSMBuilder, PyEMMA, **HTMD***

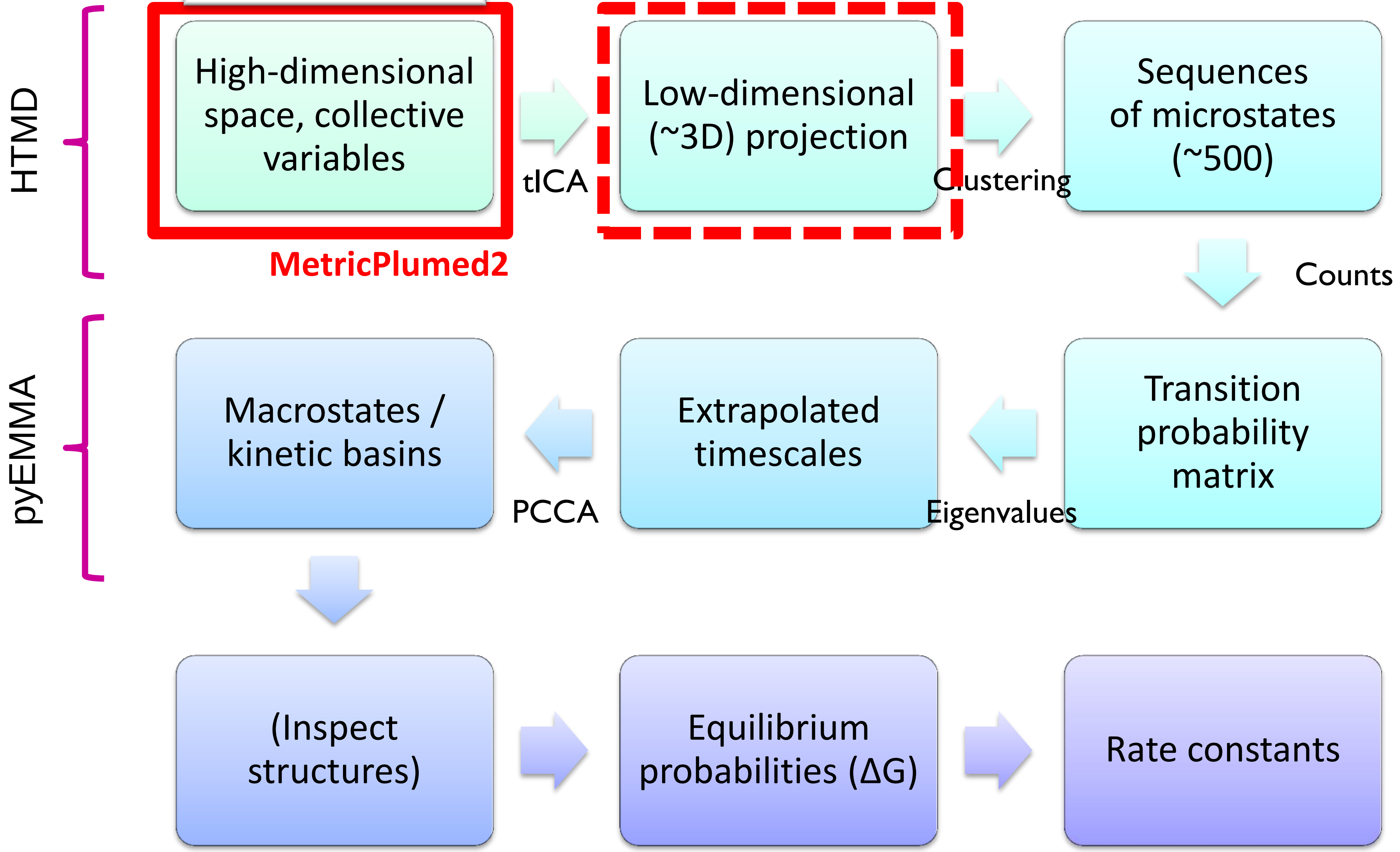
* Deals with *building, run and analysis*; we'll only see the latter

Harrigan, Biophys J 2017; Scherer, JCTC 2015; Doerr, JCTC 2016

Markov Workflow Overview

- Start in an arbitrary space, high dimensional
  - **This is what Plumed addresses well…**
  - …and the motivation of this talk
- Reduce dimension, try to preserve "slow" DOF (e.g. use tICA)
  - MM have this problem in common with metadynamics
- Compute transition matrix at several lag times
  - Cluster, eigenvectors, convergence, etc.
- If bad projection, **do not resimulate**: pick new projections, **re-calculate CVs** and model

Typ M analysis


HTMD
High-dimensional space, collective variables
MetricPlumed2
tICA
Low-dimensional (~3D) projection
Clustering
Sequences of microstates (~500)
Counts
pyEMMA
Transition probability matrix
Eigenvalues
Extrapolated timescales
PCCA
Macrostates / kinetic basins
(Inspect structures)
Equilibrium probabilities (ΔG)
Rate constants

The MetricPlumed2 object model

Basic Usage (1 trajectory)

- Install HTMD via *conda* (see website)
- Start Python and import packages

```
from htmd import *                         # Experimental, so...
from htmd.projections.metricplumed2 import *
                                           # Check ...
htmd.projections.metricplumed2._getPlumedRoot()
```

- Instantiate *MetricPlumed2* objects
- Then `metric.project(molecule)`

MetricPlumed2 – string form

- Pass METAINP as strings:

```
metric = MetricPlumed2(['d1: DISTANCE ATOMS=1,200',
                        'd2: DISTANCE ATOMS=5,6'])
mol=Molecule(“1KDX”)                                # 17 frames
metric.project(mol)
    array([[ 22.44125175,   2.80880904],
           [ 21.7255497 ,   2.9548099 ],
           [ 22.68965721,   2.99287391], …
```

- **Note** CVs are strings; atoms are inconveniently selected as serials. Solution in next slides.

Object-oriented CV creation (1)

- Instead of strings, we can build and pass *PlumedCV* objects. Construct with the following arguments, in order…
  1. CV name (DISTANCE, GYRATION,…)
  2. unique label (default autogenerated)
  3. CV arguments, as Python named arguments

```
gyr1 = PlumedCV("GYRATION", "gyr1", ATOMS="10-20", TYPE="RADIUS")
str(gyr1)
    'rgyr: GYRATION ATOMS=10-20 TYPE=RADIUS'
```

Object-oriented CV creation (2)

- *Atom groups* and *centers of masses* are also objects. They can be passed *in lieu* of atom indices or lists.
- *PlumedGroup* and *PlumedCOM* constructors:
  1. the molecule corresponding to the system
  2. the group label
  3. an atom selection (VMD syntax)

```
protCA = PlumedCOM(m, "protCA", "chain A and name CA")
lig    = PlumedCOM(m, "lig",    "resname BEN and noh")
dCAlig = PlumedCV("DISTANCE", "dCAlig", ATOMS=[protCA,lig])
```

CV dependencies

- Note dependencies between CVs; e.g.
  - `dCAlig: DISTANCE ATOMS=protCA,lig`
  - `COMBINE ARG=dCAlig POWERS=2.0`
- *Topological sort** ensures correct evaluation

```
dCAlig2=PlumedCV("COMBINE",     ARG=[dCAlig],
                 POWERS="2.0", label="dCAlig2")
myDistMetric=MetricPlumed2(dCAlig2)
print(myDistMetric)
    protCA: COM ATOMS=2,10,17,21,25,37,44,50...
    lig: COM ATOMS=1632,1633,1634,1635,1636,1637,...
    dist: DISTANCE ATOMS=protCA,lig
    dCAlig2: COMBINE ARG=dist POWERS=2.0
```

* and deduplication

Multi-trajectory usage

- Instantiate *MetricXXX* objects
  - `myPlumedMetric = MetricPlumed2(…)`
- Create a *simlist* object
  - `slist = simlist( […], ‘name.pdb’)`
- Put it in a *Metric* object
  - `metr = Metric(slist)`
  - `metr.set(myPlumedMetric)`
- .project() – yields a *MetricData* object
  - `data = metr.project()`

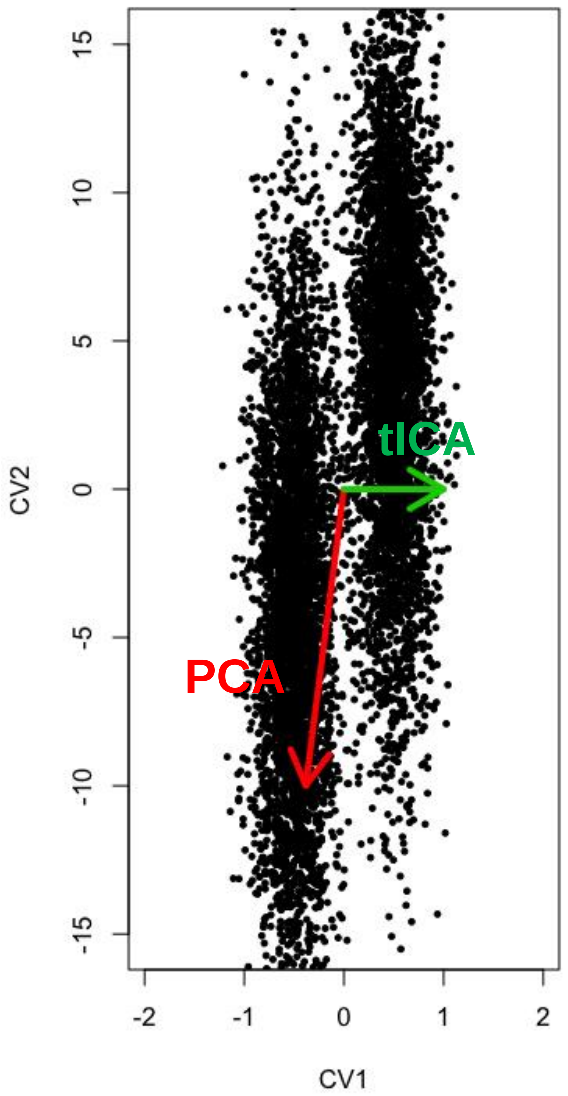
Time-lagged independent component analysis

- A low-dimensional projection on the "slow" DOF (based on lagged autocorrelation)
- Instantiate a *TICA* object

```
tica = TICA(data, 2,
                units='ns')
```

- Reduce to 3 dimensions

```
dataTica = tica.project(3)
```



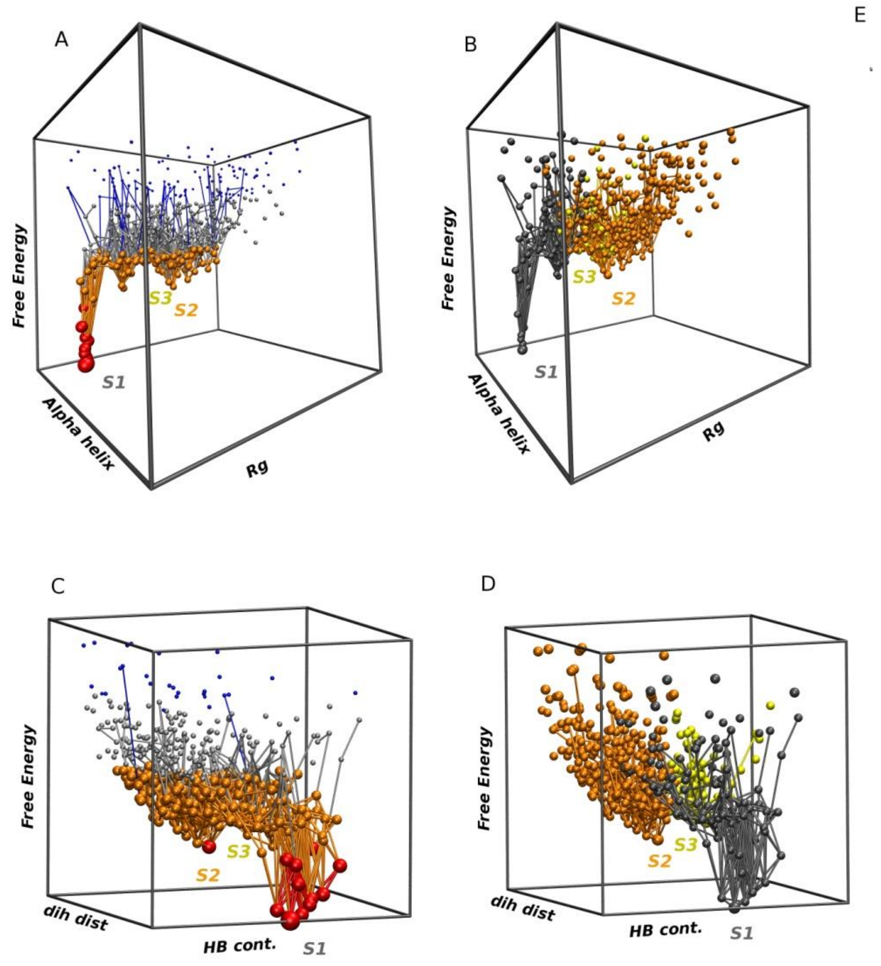
J. Chem. Phys. 139, 015102 (2013).

Discretization

- Clustering gets you discrete states
  - `data.cluster(MiniBatchKMeans(n_clusters=100))`
- Model built here
  - `model=Model(data)`
- Eigenvalues = relaxation timescales
  - `model.plotTimescales()`
- Macrostates
  - `model.markovModel(2,4,units="ns")`
  - `model.eqDistribution()`

Examples

Villin headpiece example (1)

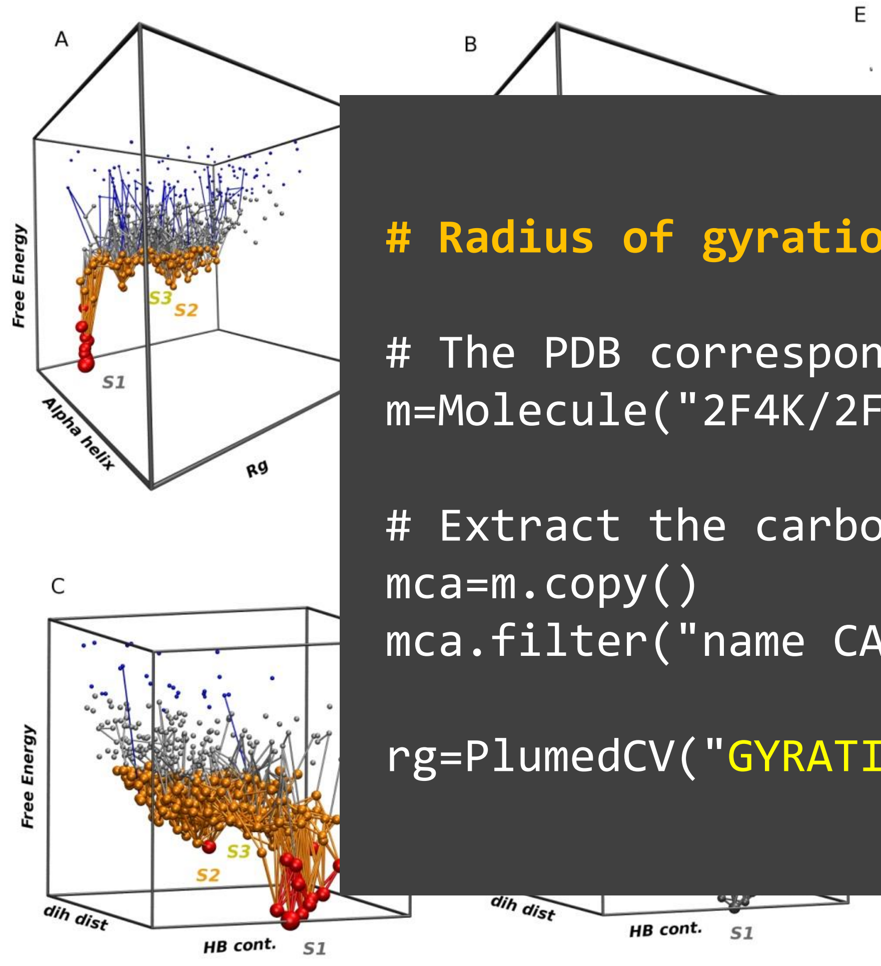


"The collective variables employed were the content of α-helix, the radius of gyration, […] and the number of hydrophobic contacts.

The number of hydrophobic contacts was computed […] between all the possible hydrophobic residues side-chain pairs" *

* Giorgino, Laio, Rodriguez CPC 2017

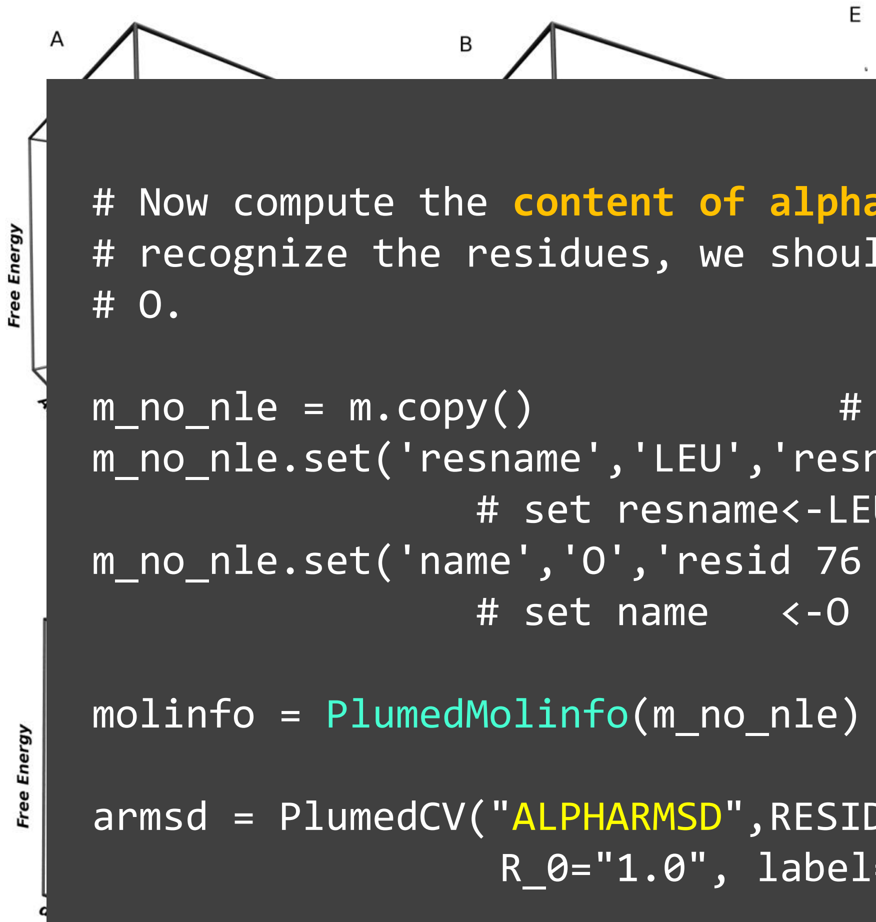
Villin headpiece example (I)



```
# Radius of gyration of Cα

# The PDB corresponding to the structure
m=Molecule("2F4K/2F4k-0.pdb")

# Extract the carbon-alpha atoms only
mca=m.copy()
mca.filter("name CA")

rg=PlumedCV("GYRATION",ATOMS=mca,label="rg")
```

Giorgino, Laio, Rodriguez CPC 2017

Villin headpiece example (2)



```
# Now compute the content of alpha-helix. For PLUMED's MOLINFO to
# recognize the residues, we should rename NLE as LEU, and OT1 as
# O.

m_no_nle = m.copy()                  # Work on a copy
m_no_nle.set('resname','LEU','resname NLE')
                # set resname<-LEU where resname==NLE
m_no_nle.set('name','O','resid 76 and name OT1')
                # set name   <-O   where resid==76 and name==OT1

molinfo = PlumedMolinfo(m_no_nle)

armsd = PlumedCV("ALPHARMSD",RESIDUES="42-76",
                 R_0="1.0", label="armsd")
```

Giorgino, Laio, Rodriguez CPC 2017

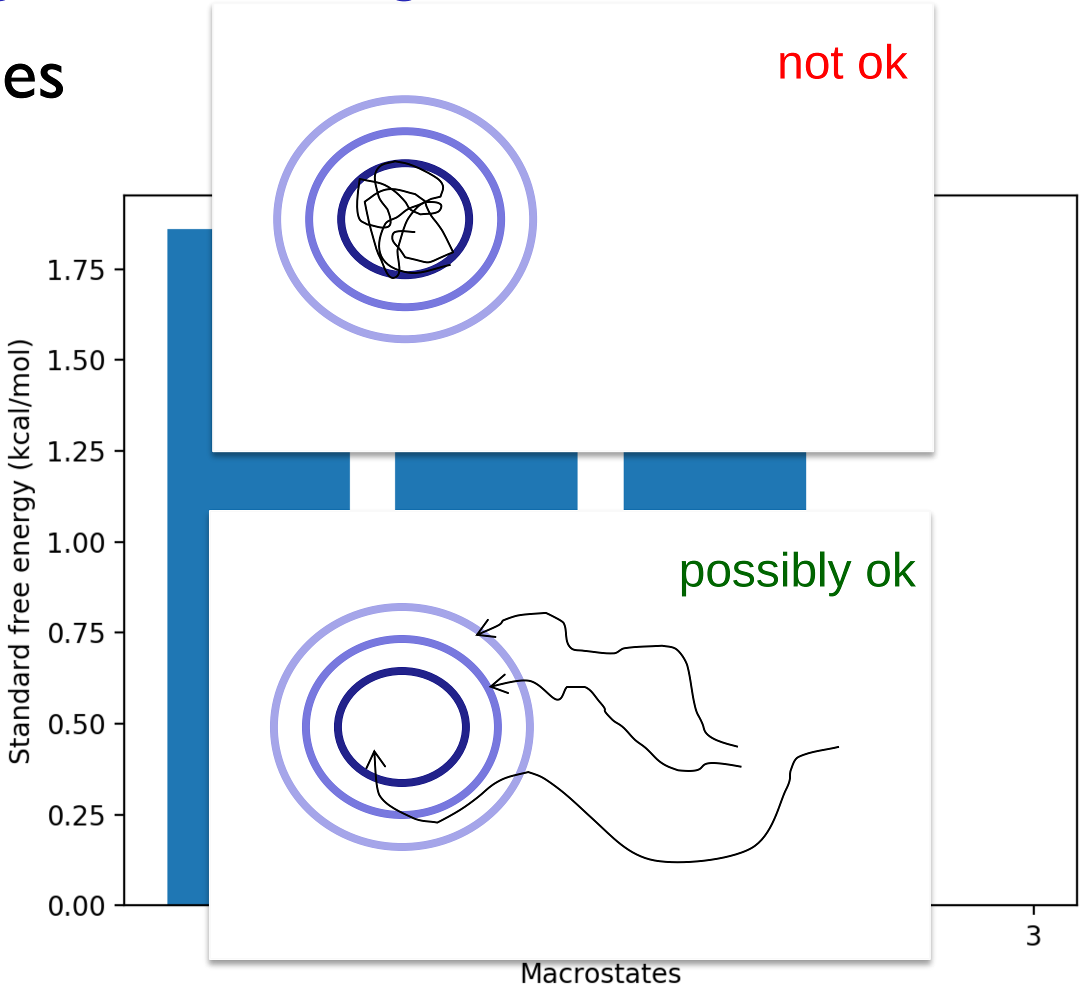
```
# Number of hydrophobic contacts - i.e. coordination number (3.5 A)
# of heavy atoms in the sidechains of hydrophobic residues.

# First, make a group for each hydrophobic sidechain […]
for resid in hyd_resid:
    pg.append(PlumedGroup(m,
                          "hg_{}".format(i),
                          "resid {} and not name N CA C O and noh".
                                 format(resid)))

# Second, form COORDINATION CVs between all the pairs. (17*16/2=136 pairs).
for g1 in range(ngroups):
    for g2 in range(g1+1,ngroups):
        group_pairs.append(PlumedCV("COORDINATION",
                                    GROUPA=pg[g1],
                                    GROUPB=pg[g2],
                                    R_0="3.5",
                                    label="c_{}".format(i)))

# Third, sum all contacts counted above
hydrophobic_contacts_sum = PlumedCV("COMBINE", ARG=group_pairs,
                                         PERIODIC="NO", label="hbc")
```

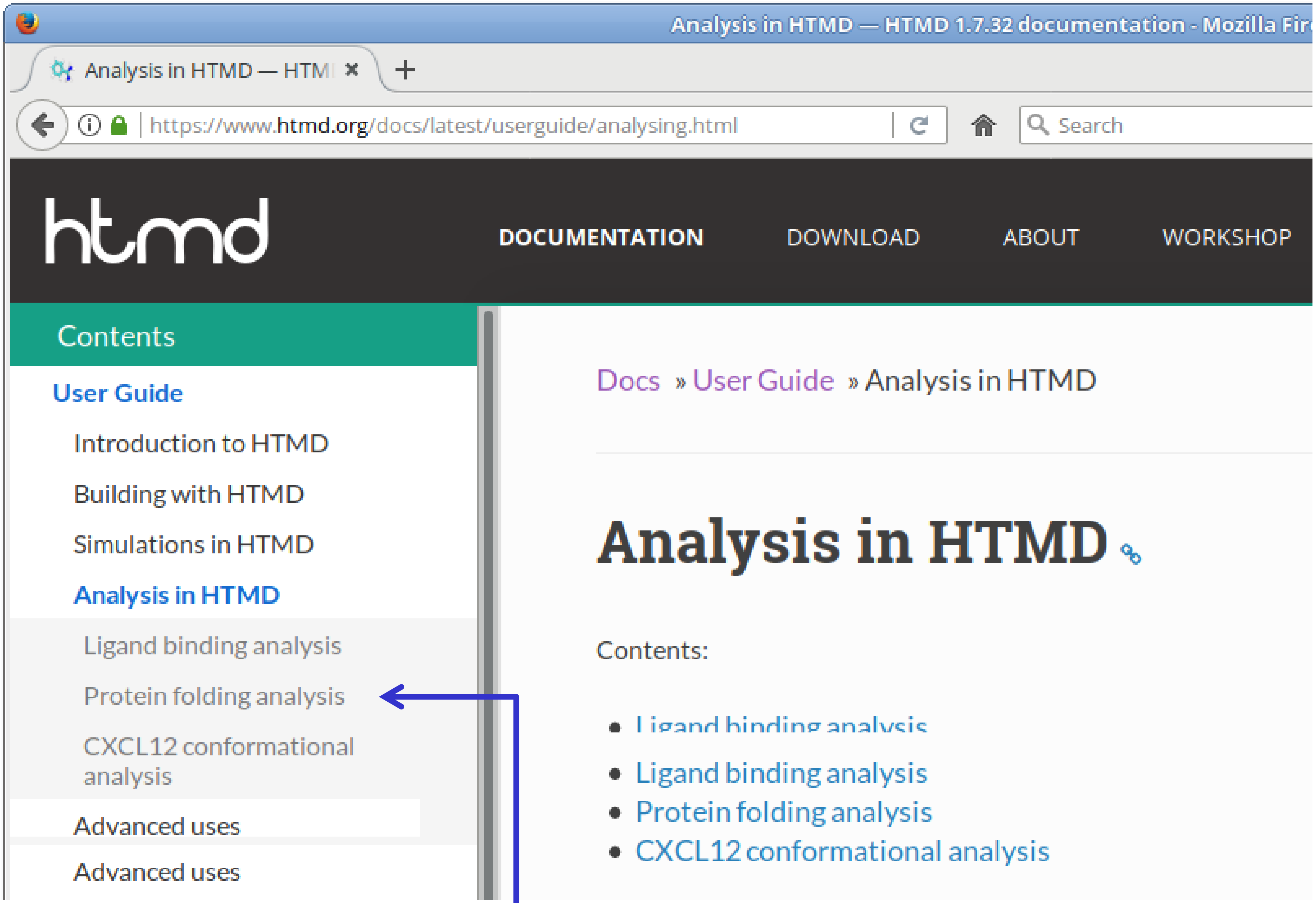
Outputs…

```
MOLINFO STRUCTURE=/var/folders/qz/7p0f8wdj4zdd8nwxm89xzhy80000gn/T/tmp8zgqt19m.pdb
armsd: ALPHARMSD RESIDUES=42-76 R_0=1.0
lab_1: GROUP ATOMS=5,24,35,47,62,74,94,116,126,142,162,169,186,200,224,235,245,265,275,289,310,322,341,365,384,401,418,436,455,474,496,511,533,540,562
rg: GYRATION ATOMS=lab_1
hg_15: GROUP ATOMS=542,545,547,551
hg_16: GROUP ATOMS=558,559,564,567,568,570,572,574,576
hg_14: GROUP ATOMS=457,460,463,466
hg_13: GROUP ATOMS=438,441,443,447
hg_12: GROUP ATOMS=367,370,373,376
hg_11: GROUP ATOMS=343,346,347,349,351,352,353,355,357,359
hg_10: GROUP ATOMS=324,327,329,333
hg_9: GROUP ATOMS=291,294,296,300
hg_8: GROUP ATOMS=267
hg_7: GROUP ATOMS=247,250,251,253,255,257,259
hg_6: GROUP ATOMS=237
hg_5: GROUP ATOMS=171,174,177,178
hg_4: GROUP ATOMS=144,147,148,150,152,154,156
hg_3: GROUP ATOMS=128,130,134
hg_2: GROUP ATOMS=118
hg_1: GROUP ATOMS=76,79,80,82,84,86,88
hg_0: GROUP ATOMS=7,10,12,16
c_1: COORDINATION GROUPA=hg_0 GROUPB=hg_1 R_0=3.5
c_2: COORDINATION GROUPA=hg_0 GROUPB=hg_2 R_0=3.5
c_3: COORDINATION GROUPA=hg_0 GROUPB=hg_3 R_0=3.5
c_4: COORDINATION GROUPA=hg_0 GROUPB=hg_4 R_0=3.5
c_5: COORDINATION GROUPA=hg_0 GROUPB=hg_5 R_0=3.5

[…]

c_130: COORDINATION GROUPA=hg_12 GROUPB=hg_16 R_0=3.5
c_131: COORDINATION GROUPA=hg_13 GROUPB=hg_14 R_0=3.5
c_132: COORDINATION GROUPA=hg_13 GROUPB=hg_15 R_0=3.5
c_133: COORDINATION GROUPA=hg_13 GROUPB=hg_16 R_0=3.5
c_134: COORDINATION GROUPA=hg_14 GROUPB=hg_15 R_0=3.5
c_135: COORDINATION GROUPA=hg_14 GROUPB=hg_16 R_0=3.5
c_136: COORDINATION GROUPA=hg_15 GROUPB=hg_16 R_0=3.5
hbc: COMBINE
ARG=c_1,c_2,c_3,c_4,c_5,c_6,c_7,c_8,c_9,c_10,c_11,c_12,c_13,c_14,c_15,c_16,c_17,c_18,c_19,c_20,c_21,c_22,c_23,c_24,c_25,c_26,c_27,c_28,c_29,c_30,c_31,c_32,c_33,
c_34,c_35,c_36,c_37,c_38,c_39,c_40,c_41,c_42,c_43,c_44,c_45,c_46,c_47,c_48,c_49,c_50,c_51,c_52,c_53,c_54,c_55,c_56,c_57,c_58,c_59,c_60,c_61,c_62,c_63,c_64,c_65,
c_66,c_67,c_68,c_69,c_70,c_71,c_72,c_73,c_74,c_75,c_76,c_77,c_78,c_79,c_80,c_81,c_82,c_83,c_84,c_85,c_86,c_87,c_88,c_89,c_90,c_91,c_92,c_93,c_94,c_95,c_96,c_97,
c_98,c_99,c_100,c_101,c_102,c_103,c_104,c_105,c_106,c_107,c_108,c_109,c_110,c_111,c_112,c_113,c_114,c_115,c_116,c_117,c_118,c_119,c_120,c_121,c_122,c_123,c_124,
c_125,c_126,c_127,c_128,c_129,c_130,c_131,c_132,c_133,c_134,c_135,c_136 PERIODIC=NO
# Rendered PlumedStatement
```

No free lunch demo: 1μs Ace-Ala3-Nme

- Part of examples at: github.com/tonigi/PLUMEDws2017
- 6 Ramachandran angles
- The system is trapped
- How to «shoot» trajectories:
  - «bathtub» not ok
  - «shower» maybe
  - adaptive spawning
  - or your favourite string-like method





Analysis in HTMD — HTMD 1.7.32 documentation - Mozilla Fir

Analysis in HTMD — HTMI

https://www.htmd.org/docs/latest/userguide/analysing.html

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htmd

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Protein folding analysis

CXCL12 conformational analysis

Advanced uses

Advanced uses

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Analysis in HTMD

Contents:

- Ligand binding analysis
- Ligand binding analysis
- Protein folding analysis
- CXCL12 conformational analysis

Each come with 2GB (200 μs) of trajectories

- Still preliminary. To try out:
  1. Get HTMD
  2. If needed, use branch toni-devel-plumed from GitHub and set `PYTHONPATH`
- Examples at github.com/toni/PLUMEDws2017
- Implementation
  - `plumed` invoked externally (I/O via XTC)
  - Poor diagnostics; in case of error, inputs are kept in a directory
  - Parallelized, if multiple trajectories

In summary

- *MetricPlumed2* gets:
  - Sophisticated CVs, courtesy of Plumed, and
  - A Markov "workflow", courtesy of HTMD
  - METAINP files written instantiating objects
- Use cases
  - CV-based Markov-type calculations
  - Scripted analysis (meta-generation of CVs)
  - Bonus: Python-based notebooks generally readable (and reproducible)

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