Metadynamics

Practical introduction with PLUMED
University of Padova

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Overview

Morning

1. Installing software
2. Alanine dipeptide (Ala2) without Metadynamics
3. Overview of Metadynamics
4. Accelerated sampling with Metadynamics

Afternoon

5. Postprocessing
6. Metainference (experimental restraints) + Metadynamics on a real-world system

Getting settled

These instructions assume you're using Linux or a Unix-like system like MacOS.

1. Install anaconda (if you haven't already): https://www.anaconda.com/products/distribution
2. Create a new environment for our simulations:

```
conda create --name metad-class
conda activate metad-class
```

3. Install GROMACS (MD code) and PLUMED (Plugin for enhanced sampling), this will also install MPI, this means we can run multi-replica simulations:

```
conda install --strict-channel-priority -c plumed/label/
  masterclass-2022 -c conda-forge plumed gromacs
```

4. Test the installation:

```
gmx_mpi mdrun -h 2> /dev/null | grep -q plumed && echo ok
plumed --has-mpi && echo ok
```

Getting settled

Installing python libraries for analysis:

```
conda install jupyter numpy matplotlib
conda install -c conda-forge blas
```

Get the material (including these slides):

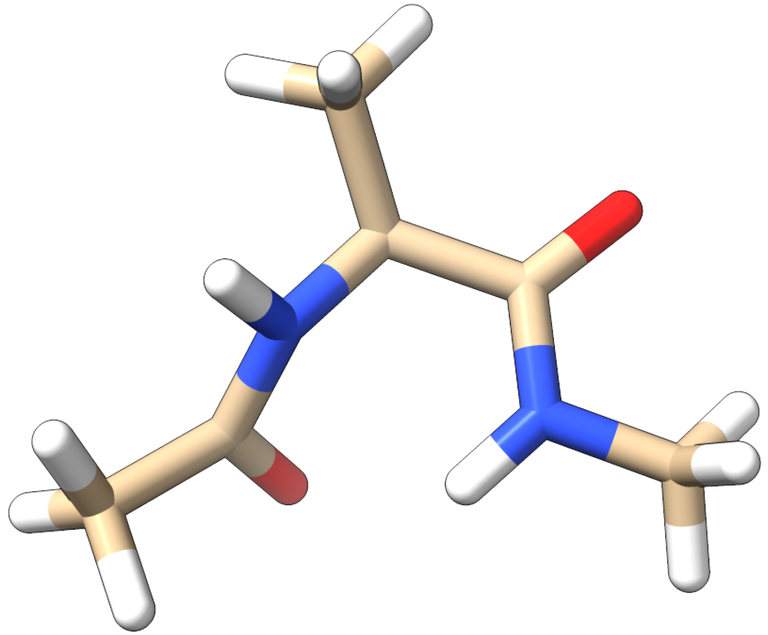
```
$ git clone github.com/tlhr/metad-course
```

Archive contents:

```
(plumed-class) $ ls -lh
total 0
drwxr-xr-x@  6 thomas  staff   192B 28 Apr 15:53 1-aladi-vanilla/
drwxr-xr-x@ 18 thomas  staff   576B 28 Apr 15:54 2-aladi-metad/
drwxr-xr-x   8 thomas  staff   256B 28 Apr 15:55 3-aladi-metad2d/
drwxr-xr-x@ 29 thomas  staff   928B 28 Apr 18:25 4-egaw-mm/
```

Alanine dipeptide

No metadynamics (1-aladi-vanilla)



Running:

```
gmx_mpi mdrun -s topol.tpr -v -nsteps 5000000
```

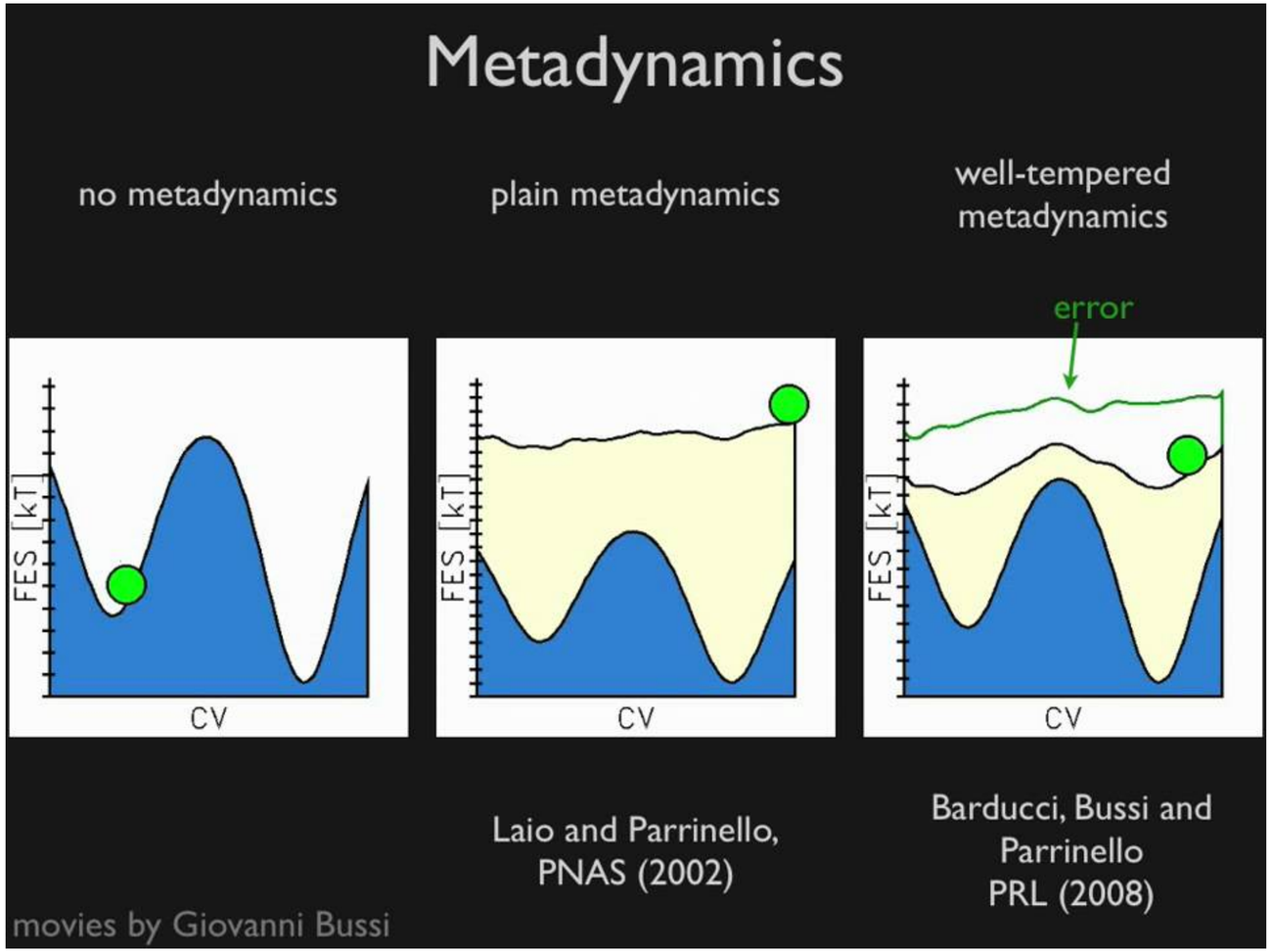
Output:

```
$ ls -lh
total 224
-rw-------@ 1 thomas  staff   1.5K 27 Apr 19:38 confout.gro
-rw-------@ 1 thomas  staff   1.7K 27 Apr 19:19 diala.pdb
-rw-------@ 1 thomas  staff    11K 27 Apr 19:38 ener.edr
-rw-------@ 1 thomas  staff    20K 27 Apr 19:38 md.log
-rw-------@ 1 thomas  staff   2.1K 27 Apr 19:38 state.cpt
-rw-------@ 1 thomas  staff   9.6K 27 Apr 19:13 topol.tpr
-rw-------@ 1 thomas  staff    34K 27 Apr 19:38 traj_comp.xtc
```

Final structure
Structure (included in tpr)
Energy over time
Logfile
Checkpoint
Run input file
Trajectory

Metadynamics

Conceptual overview



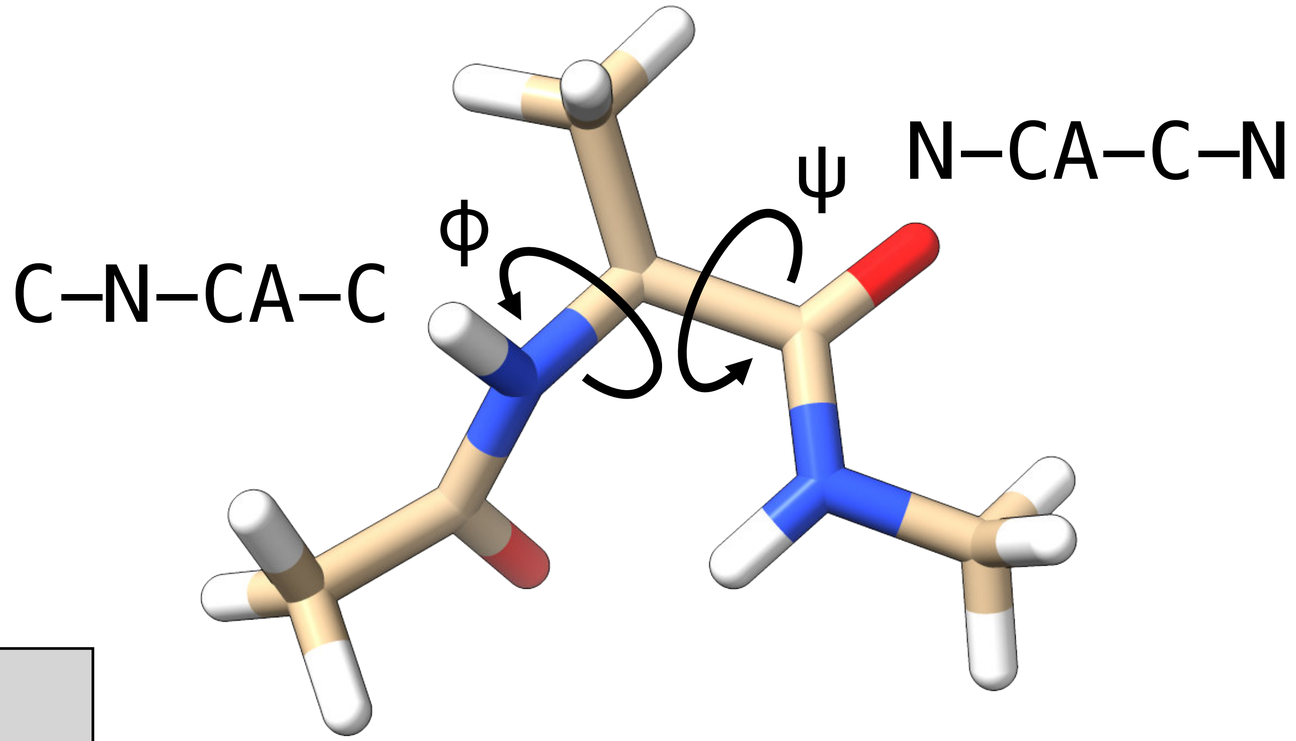
Update potential with Gaussian hill:

$$\dot{V}_{\mathrm{MetaD}}(s,t) = \omega \exp\left[-\sum_{\alpha=1}^{N_{\mathrm{CV}}} \frac{(s_\alpha - s_\alpha(t))^2}{2\sigma_\alpha^2}\right]$$

$$\dot{V}_{\mathrm{WTMetaD}}(s,t) = \omega \exp\left[-\frac{V(s(t),t)}{k_{\mathrm{B}}\Delta T}\right] \exp\left[-\sum_{\alpha=1}^{N_{\mathrm{CV}}} \frac{(s_\alpha - s_\alpha(t))^2}{2\sigma_\alpha^2}\right]$$

Alanine dipeptide

No metadynamics



PLUMED syntax:

```
label: ACTION FOO=3.14 BAR=blah
```

PLUMED input (`plumed.dat`):

```
phi: TORSION ATOMS=????
psi: TORSION ATOMS=????

PRINT ARG=phi,psi FILE=COLVAR STRIDE=1
```

Analysis:

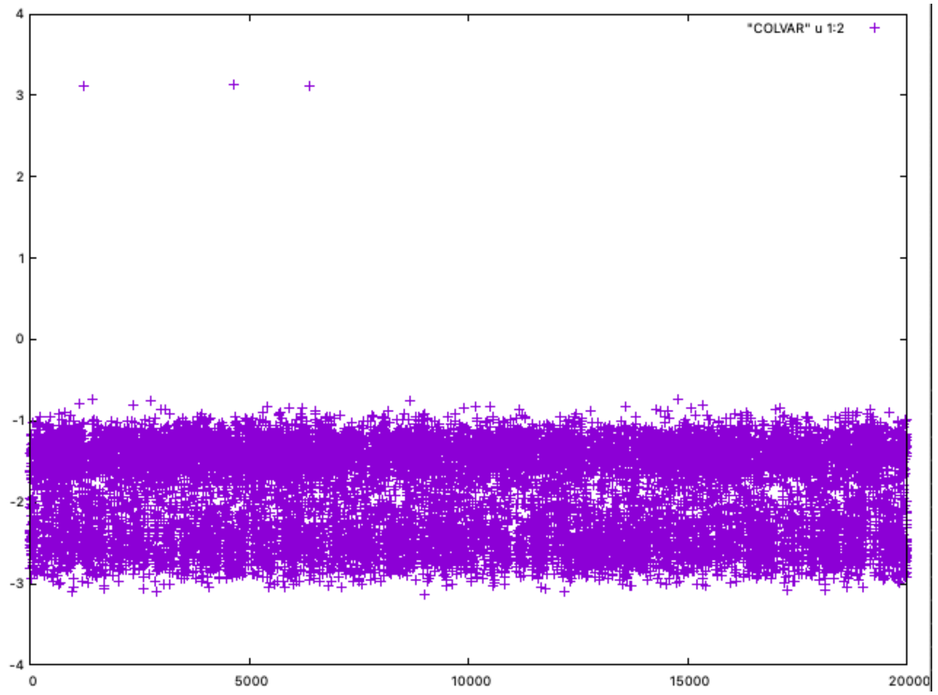
```
plumed driver --plumed plumed.dat --mf_xtc traj_comp.xtc
```

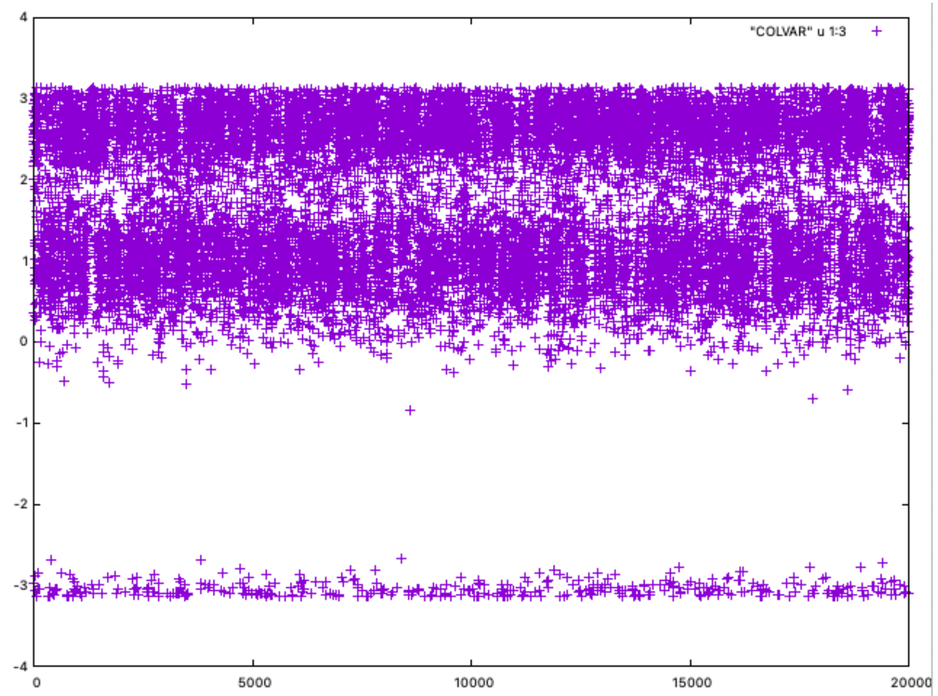
Alanine dipeptide

No metadynamics

Plotting CV over time:

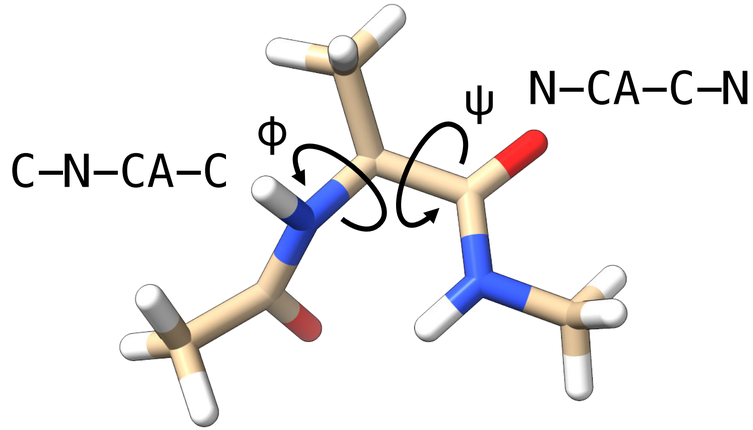
```
gnuplot
plot “COLVAR” u 1:2
replot “COLVAR” u 1:3
```





Alanine dipeptide

Metadynamics (2-aladi-metad)



PLUMED input (plumed.dat):

```
phi: TORSION ATOMS=5,7,9,15
psi: TORSION ATOMS=7,9,15,17

metad: METAD ...
    ARG=phi
    PACE=500 HEIGHT=1.2 BIASFACTOR=8
    # Choose sigma based on fluctuations in unbiased run (1/2 or 1/3)
    SIGMA=????
    FILE=HILLS GRID_MIN=-pi GRID_MAX=pi
...

PRINT ARG=phi,psi,metad.bias FILE=COLVAR STRIDE=100
```

Running:

```
gmx_mpi mdrun -s topol.tpr -v -nsteps 5000000 -plumed plumed.dat
```

Detour: Parallel-bias metadynamics

Biasing many collective variables at once

Problem: Depositing a high-dimensional Gaussian falls victim to the curse of dimensionality

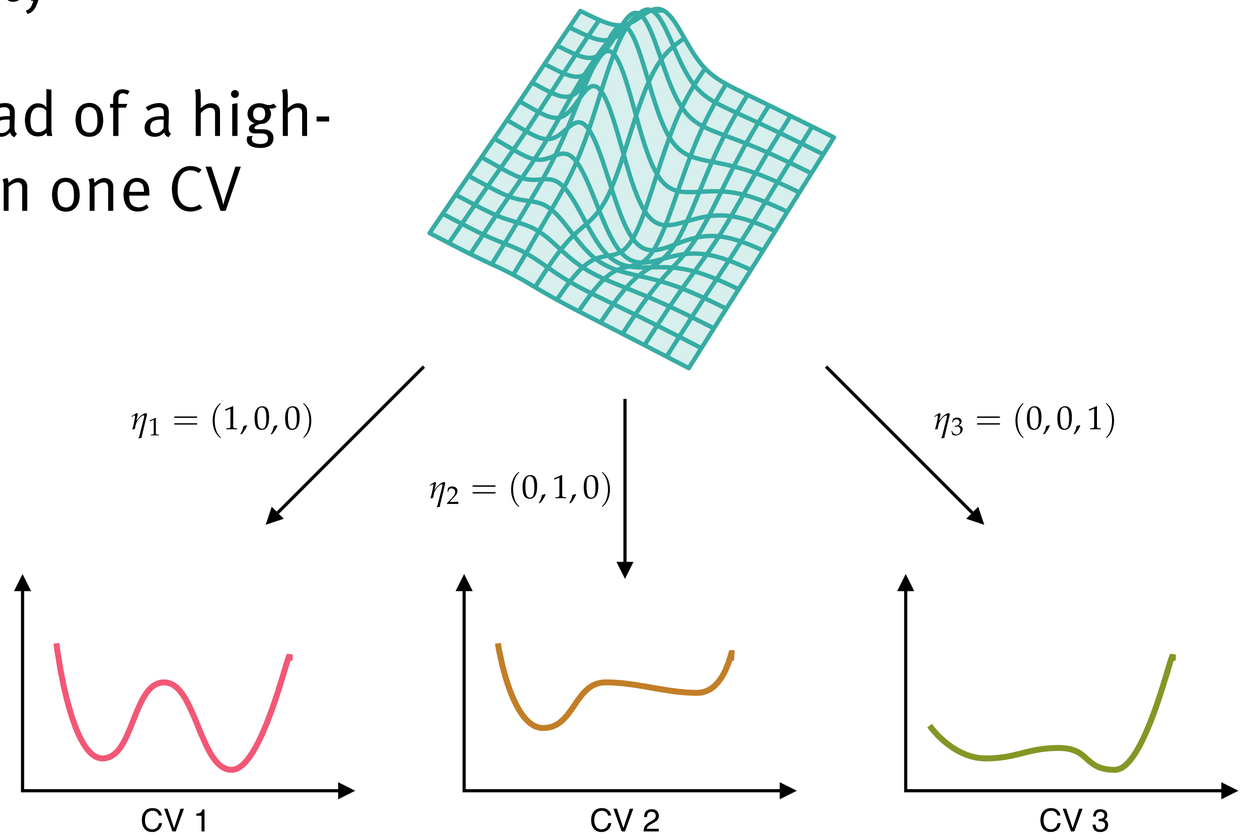
Idea: deposit many 1D-Gaussians instead of a high-dimensional Gaussian, scale the bias on one CV based on the bias on the others

$$V_{\mathrm{PB}}(\boldsymbol{S},t) = -\frac{1}{\beta}\log\left[\sum_{S\in\boldsymbol{S}}\exp(-\beta V_{\mathrm{G}}(S,t))\right]$$

$$V_{\mathrm{G}}(S_i,t) = k_{\mathrm{B}}\Delta T_i \log\left[1+\frac{\omega_i N(S_i,\boldsymbol{\eta}=\boldsymbol{e}_i,t)}{k_{\mathrm{B}}\Delta T_i}\right]$$

$$\omega_i(t) = \omega_i \exp\left(-\frac{V_{\mathrm{G}}(S_i,t)}{k_{\mathrm{B}}\Delta T_i}\right) P(\boldsymbol{\eta}_i \mid \boldsymbol{R})$$

$$P(\boldsymbol{\eta}_i \mid \boldsymbol{R}) = \frac{\exp(-\beta V_{\mathrm{G}}(S_i,t))}{\sum_i \exp(-\beta V_{\mathrm{G}}(S_i,t))}$$



Alanine dipeptide

Metadynamics postprocessing

Plotting CV over time:

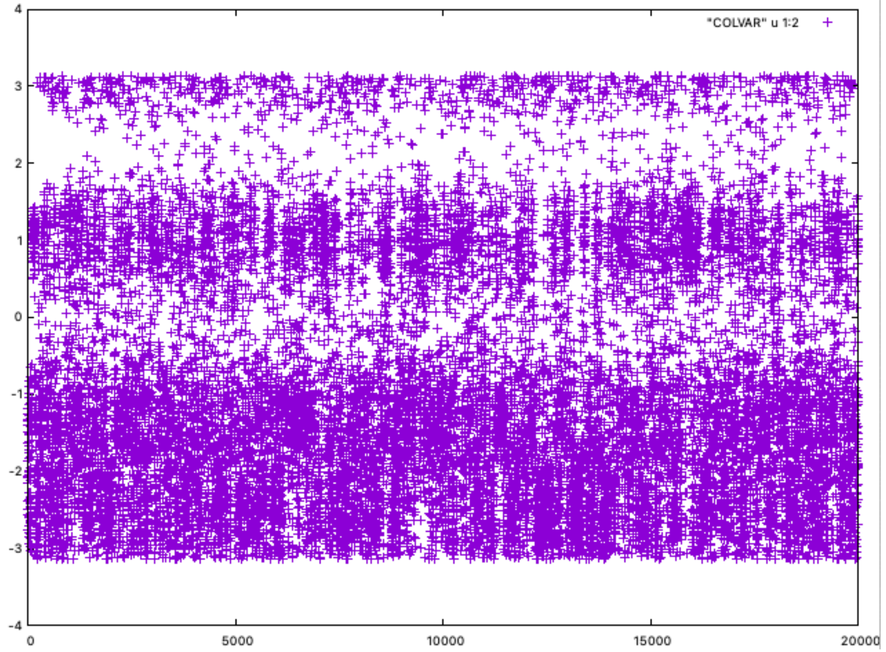
```
gnuplot
plot “COLVAR” u 1:2
replot “COLVAR” u 1:3
```

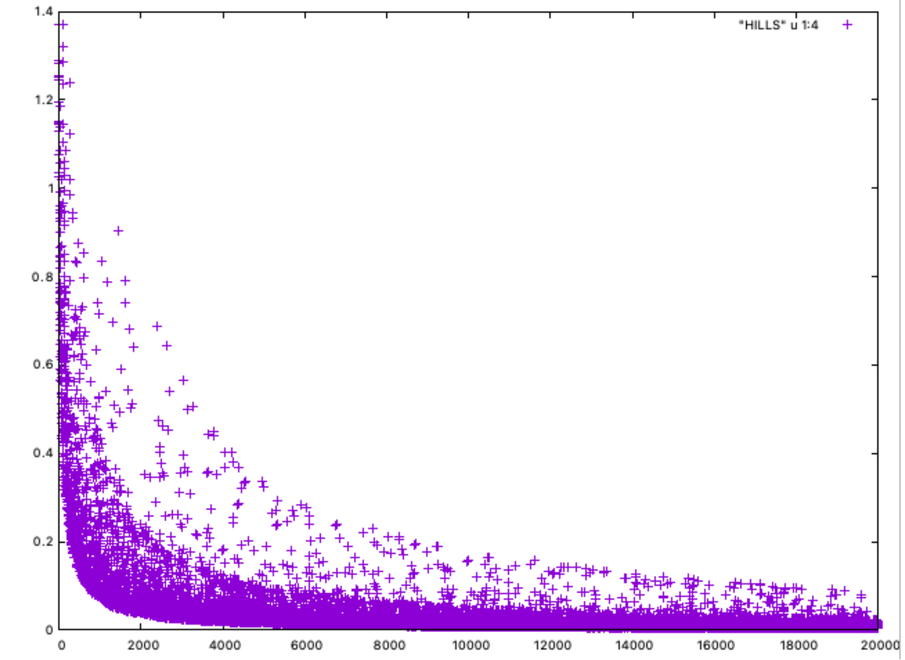
HILLS file content:

```
#! FIELDS time phi sigma_phi height biasf
#! SET multivariate false
#! SET kerneltype stretched-gaussian
#! SET min_phi -pi
#! SET max_phi pi
```

Plot the gaussian height over time:

```
gnuplot
plot “HILLS” u 1:4
```



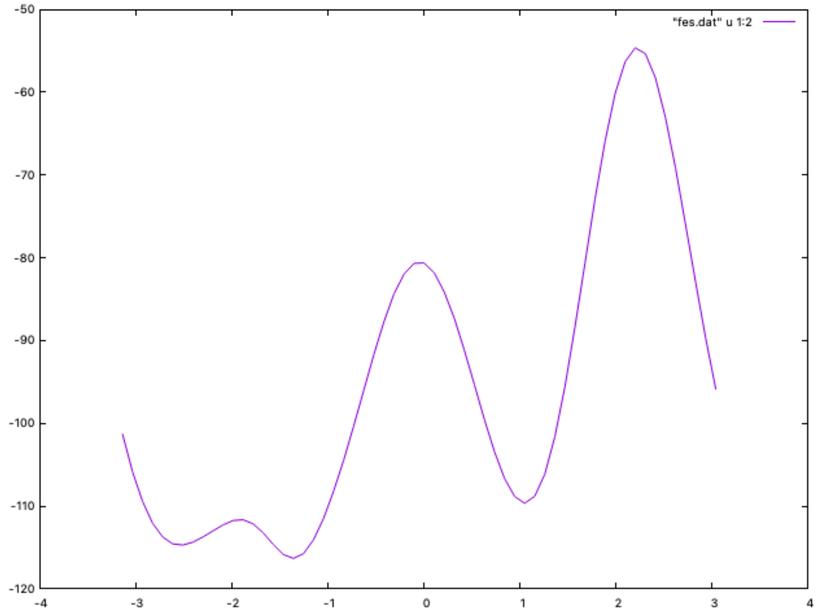


Alanine dipeptide

Metadynamics postprocessing

Estimate the free energy surface:

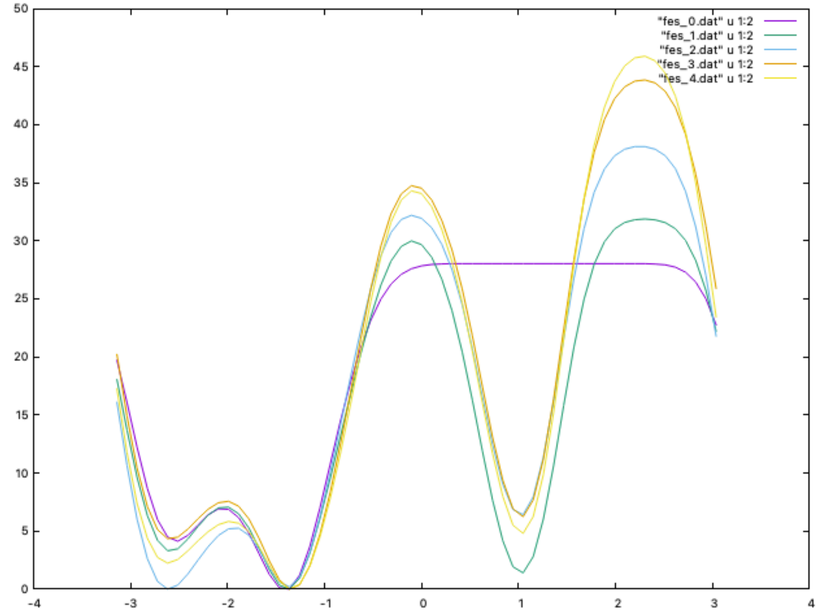
```
plumed sum_hills --hills HILLS
```



Estimate the free energy surface over time:

```
plumed sum_hills --hills HILLS --stride 100 –mintozero
# Plot the first few fes.dat files
```

Is it converged?



Alanine dipeptide

Metadynamics postprocessing

Un-biasing the simulation:

```
phi: TORSION ATOMS=5,7,9,15
psi: TORSION ATOMS=7,9,15,17

metad: METAD ...
    ARG=phi
    PACE=10000000 HEIGHT=0.0 BIASFACTOR=8
    SIGMA=???? # Use your value here!
    FILE=HILLS GRID_MIN=-pi GRID_MAX=pi
    RESTART=YES
...

PRINT ARG=phi,psi,metad.bias FILE=COLVAR_RW STRIDE=1
```

Run on the trajectory:

```
plumed driver --plumed plumed-rw.dat --mf_xtc traj_comp.xtc --kt 2.494339
```

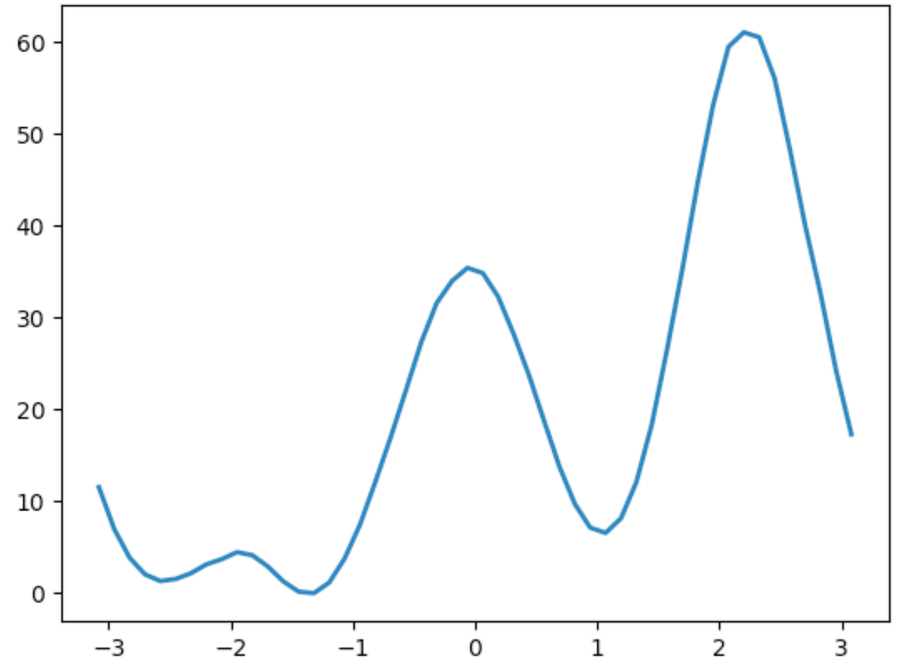
Alanine dipeptide

Metadynamics postprocessing

Calculating weights:

$$w \propto \exp\left[\frac{V_{\mathrm{MetaD}}(s)}{k_{\mathrm{B}}T}\right]$$

```
import numpy as np

bias = np.loadtxt("COLVAR_RW")[:, -1]
weights = np.exp(bias / 2.494339)
weights /= weights.sum()
```

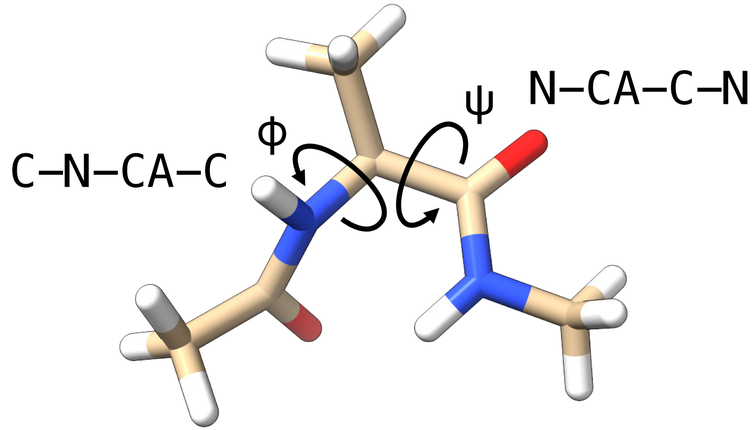


Creating a 1D free energy surface:

```
import matplotlib.pyplot as plt

phi, psi = np.loadtxt("COLVAR_RW")[:, [1, 2]].T
hist, edges = np.histogram(phi, bins=50, range=(-np.pi, np.pi),
                           density=True, weights=weights)
x = 0.5 * (edges[:-1] + edges[1:])
F = -2.494339 * np.log(hist)
F -= F.min()
plt.plot(x, F); plt.show()
```

Alanine dipeptide

2D Metadynamics (3-aladi-metad2d)



PLUMED input (`plumed.dat`):

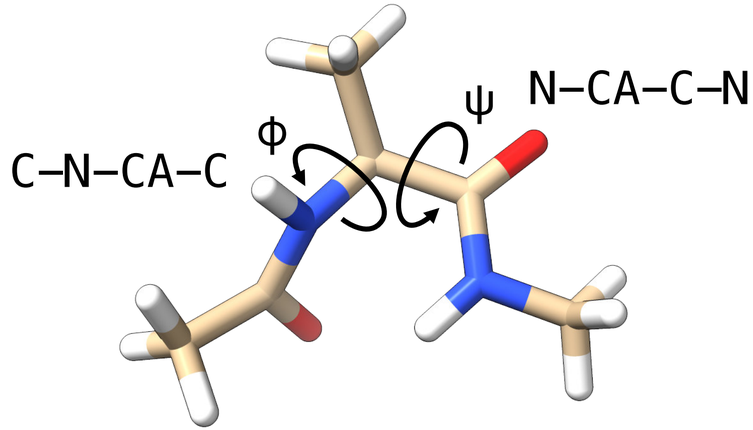
```
phi: TORSION ATOMS=5,7,9,15
psi: TORSION ATOMS=7,9,15,17

metad: METAD ...
    ARG=phi,psi
    PACE=500 HEIGHT=1.2 BIASFACTOR=14
    # Choose sigma based on fluctuations in unbiased run (1/2 or 1/3)
    SIGMA=????,????
    FILE=HILLS GRID_MIN=-pi,-pi GRID_MAX=pi,pi
...

PRINT ARG=phi,psi,metad.bias FILE=COLVAR STRIDE=100
```

Running:

```
gmx_mpi mdrun -s topol.tpr -v -nsteps 5000000 -plumed plumed.dat
```

Alanine dipeptide

2D Metadynamics postprocessing



PLUMED input (`plumed.dat`):

```
phi: TORSION ATOMS=5,7,9,15
psi: TORSION ATOMS=7,9,15,17

metad: METAD ...
    ARG=phi,psi
    PACE=10000000 HEIGHT=0.0 BIASFACTOR=14
    # Choose previous values
    SIGMA=????,????
    FILE=HILLS GRID_MIN=-pi,-pi GRID_MAX=pi,-pi
    RESTART=YES
...

PRINT ARG=phi,psi,metad.bias FILE=COLVAR_RW STRIDE=100
```

Running:

```
plumed driver --plumed plumed-rw.dat --mf_xtc traj_comp.xtc --kt 2.494339
```

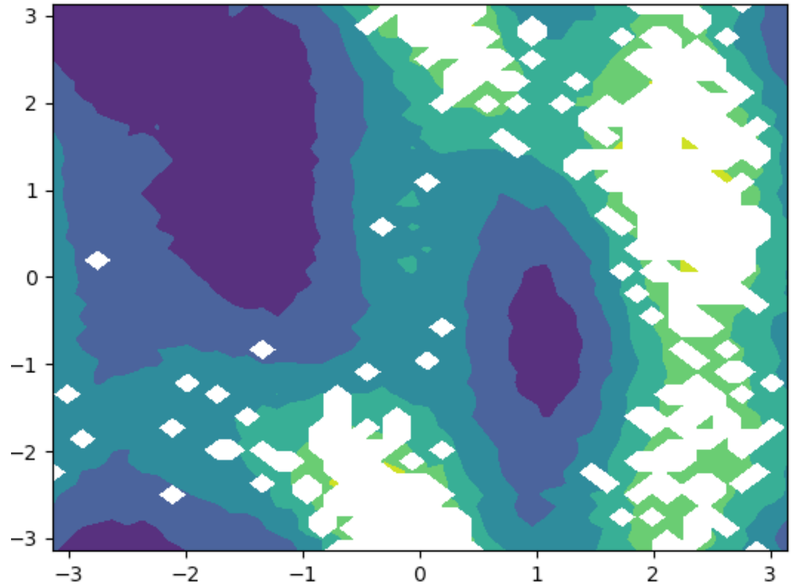
Alanine dipeptide

2D Metadynamics postprocessing

Calculate weights as before $w \propto \exp\left[\frac{V_{\mathrm{MetaD}}(s)}{k_{\mathrm{B}}T}\right]$

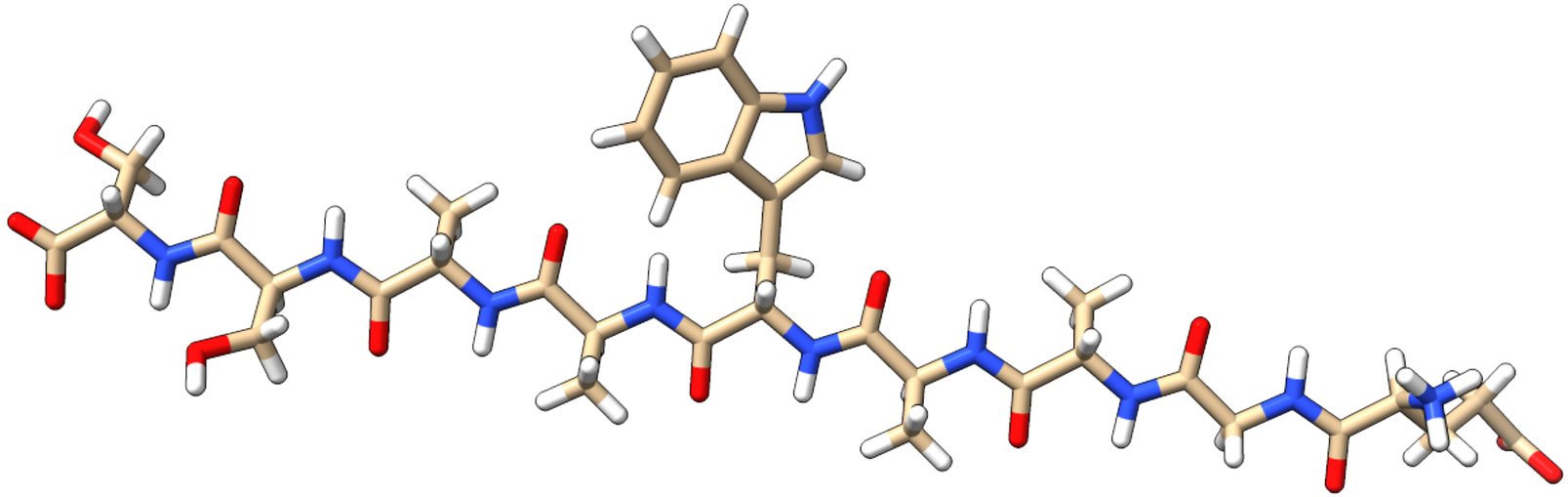
Create a 2D free energy surface:

```
import matplotlib.pyplot as plt

phi, psi = np.loadtxt("COLVAR_RW")[:, [1, 2]].T
hist, edges = np.histogram2d(
    phi, psi, bins=50, density=True, weights=weights,
    range=((-np.pi, np.pi), (-np.pi, np.pi)))
xx, yy = np.mgrid[-np.pi:np.pi:50j, -np.pi:np.pi:50j]
F = -2.494339 * np.log(hist)
F -= F.min()
plt.contourf(xx, yy, F); plt.show()
```



Real system: EGAAWAASS peptide

Metadynamics + experimental restraints (`4-egaw-mm`)



Enhance sampling with metadynamics, and add experimental restraints (from NMR) to improve accuracy

Real system: EGAAWAASS peptide

Metadynamics + experimental restraints

To apply restraints we need a *forward model* mapping from our structure (XYZ coordinates) to our experimental observable (typically a scalar):

$$f : \text{Structure} \to \mathbb{R}$$

Use the *Karplus* relation to go from dihedral angles to J-coupling:

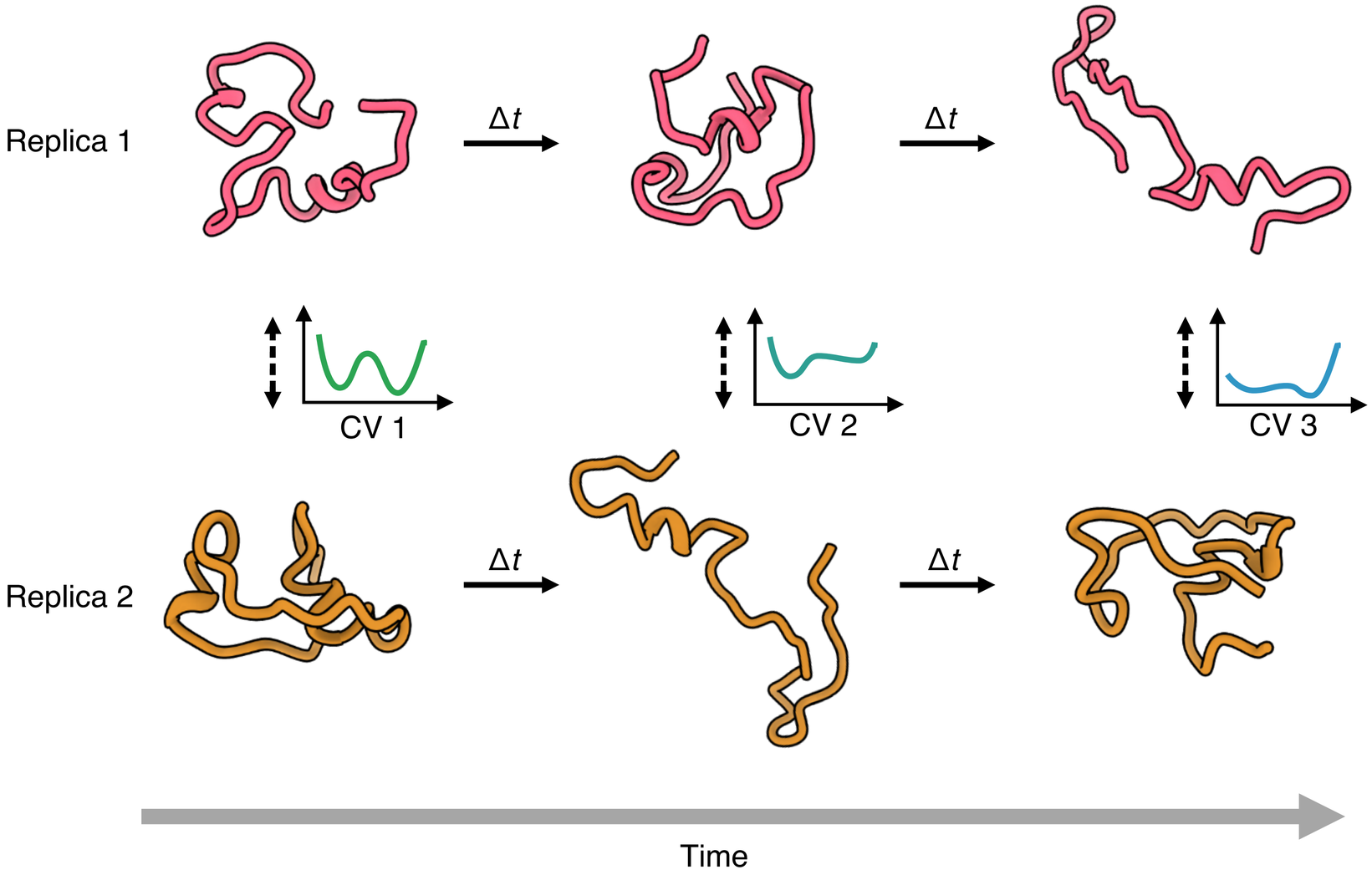
$$^3J(\theta) = A\cos^2(\theta + \Delta\theta) + B\cos(\theta + \Delta\theta) + C$$

Then apply a restraint in form of a harmonic potential:

$$V(X, \sigma \mid d) \propto \frac{(f(X) - d)^2}{\sigma^2}$$

Real system: EGAAWAASS peptide

Intro to multi-replica simulations

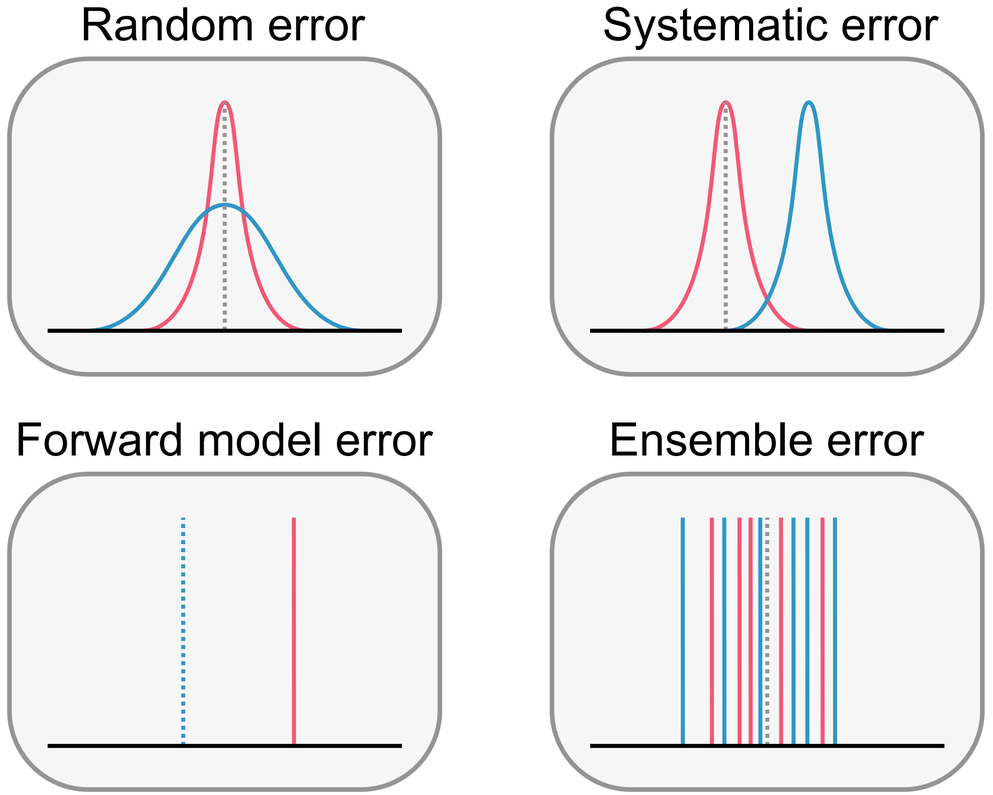


Real system: EGAAWAASS peptide

Metainference

$$V_{\mathrm{MI}}(\boldsymbol{X},\sigma \mid \boldsymbol{d}) = \sum_{r=1}^{N_{\mathrm{r}}} \left\{ V_{\mathrm{FF}}(X_r) + k_{\mathrm{B}}T \sum_{i=1}^{N_{\mathrm{d}}} \left[\frac{(\langle f_i(\boldsymbol{X}) \rangle - d_i)^2}{2\sigma_{r,i}^2} + \frac{1}{2}\ln(2\pi\sigma_{r,i}^2) + \frac{1}{2}\ln\left(\frac{\sigma_{r,i}^2}{2}\right) \right] \right\}$$

$\boldsymbol{X} = [X_r]$	Ensemble of conformations
$\sigma = [\sigma_{r,i}]$	Errors
$\boldsymbol{d} = [d_i]$	Datapoints
$f(X)$	Forward model
N_{d}	Number of datapoints
N_{r}	Number of replicas



Real system: EGAAWAASS peptide

Metadynamics + experimental restraints

Forward model in PLUMED (H^{α}–N, based on Ψ dihedrals):

```
JCOUPLING ...
    TYPE=HAN
    ATOMS1=@psi-2 COUPLING1=-0.49
    ATOMS2=@psi-4 COUPLING2=-0.54
    ATOMS3=@psi-5 COUPLING3=-0.53
    ATOMS4=@psi-7 COUPLING4=-0.39
    ATOMS5=@psi-8 COUPLING5=-0.39
    LABEL=jhan
...
```

$$^{3}J(\theta) = A\cos^{2}(\theta + \Delta\theta) + B\cos(\theta + \Delta\theta) + C$$

Real system: EGAAWAASS peptide

Metadynamics + experimental restraints

Ensemble-averaged statistics:

```
ENSEMBLE ...
    ARG=(jhan\.j-.*),pb.bias REWEIGHT
    LABEL=ens
... ENSEMBLE

STATS ...
    ARG=(ens\.jhan\.j-.*) PARARG=(jhan\.exp-.*)
    LABEL=jhanst
... STATS

PRINT ARG=jhanst.* STRIDE=2000 FILE=../STATS.J
```

Weighted instantaneous ensemble average

$$w(s_r,t) = \exp\left(\frac{V(s_r,t)}{k_\mathrm{B}T}\right)\left[\sum_{j=1}^{N_\mathrm{replica}} \exp\left(\frac{V(s_j,t)}{k_\mathrm{B}T}\right)\right]^{-1}$$

Statistics (e.g. correlation of forward model with experimental value)

Print to file

Real system: EGAAWAASS peptide

Metadynamics + experimental restraints

Ensemble-averaged restraints with error-accounting:

```
METAINFERENCE ...
    ARG=(jhan\.j-.*),(jhahn\.j-.*),pb.bias
    PARARG=(jhan\.exp-.*),(jhahn\.exp-.*)
    NOISETYPE=MGAUSS REWEIGHT OPTSIGMAMEAN=SEM AVERAGING=200
    SIGMA0=5.0 SIGMA_MIN=0.0001 SIGMA_MAX=15.0 DSIGMA=0.1
    WRITE_STRIDE=10000
    LABEL=byj
...
```

$$V_{\mathrm{MI}}(\boldsymbol{X},\sigma \mid \boldsymbol{d}) = \sum_{r=1}^{N_{\mathrm{r}}} \left\{ V_{\mathrm{FF}}(X_r) + k_{\mathrm{B}}T \sum_{i=1}^{N_{\mathrm{d}}} \left[\frac{(\langle f_i(\boldsymbol{X}) \rangle - d_i)^2}{2\sigma_{r,i}^2} + \frac{1}{2}\ln(2\pi\sigma_{r,i}^2) + \frac{1}{2}\ln\left(\frac{\sigma_{r,i}^2}{2}\right) \right] \right\}$$

$$\sigma_{r,i}^2 = (\sigma_{r,i}^{\mathrm{B}})^2 + (\sigma_i^{\mathrm{SEM}})^2$$

Sampled by Monte Carlo

Estimated based on windowed average (AVERAGING)

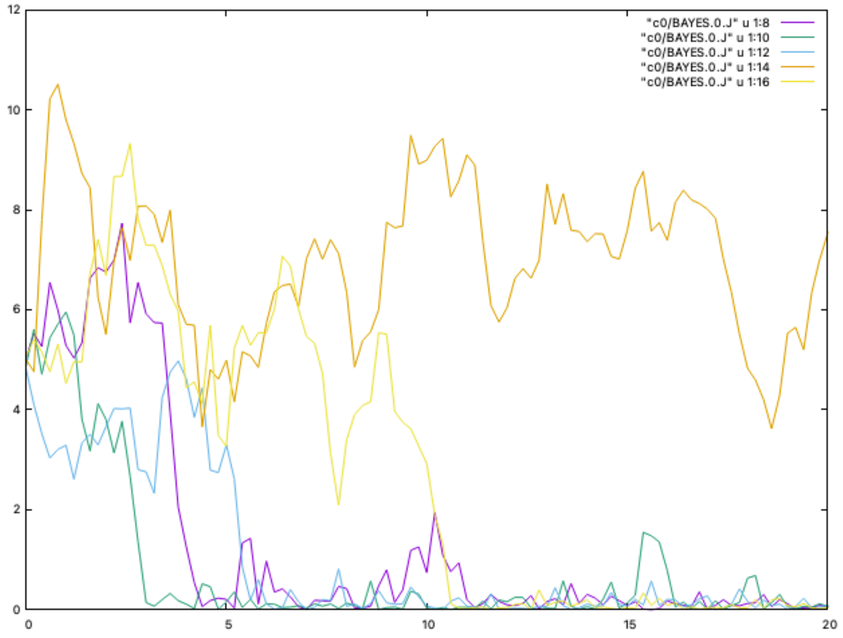
Real system: EGAAWAASS peptide

Metadynamics + experimental restraints

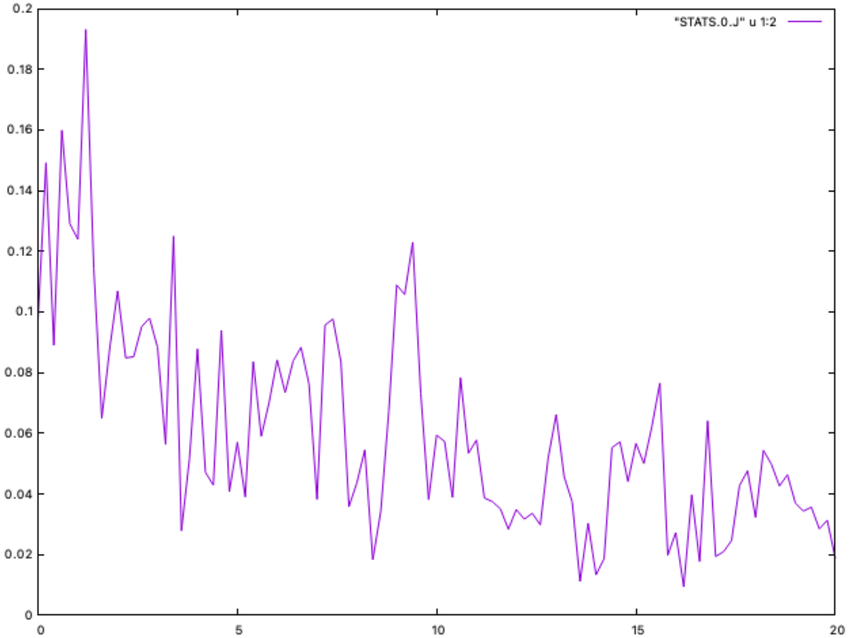
Running in multi-replica mode (requires at least 4 cores):

```
mpirun -np 4 gmx_mpi mdrun -s topol -plumed ../plumed.dat
-multidir c? -v -nsteps 10000
```

Per-datapoint sigma over time

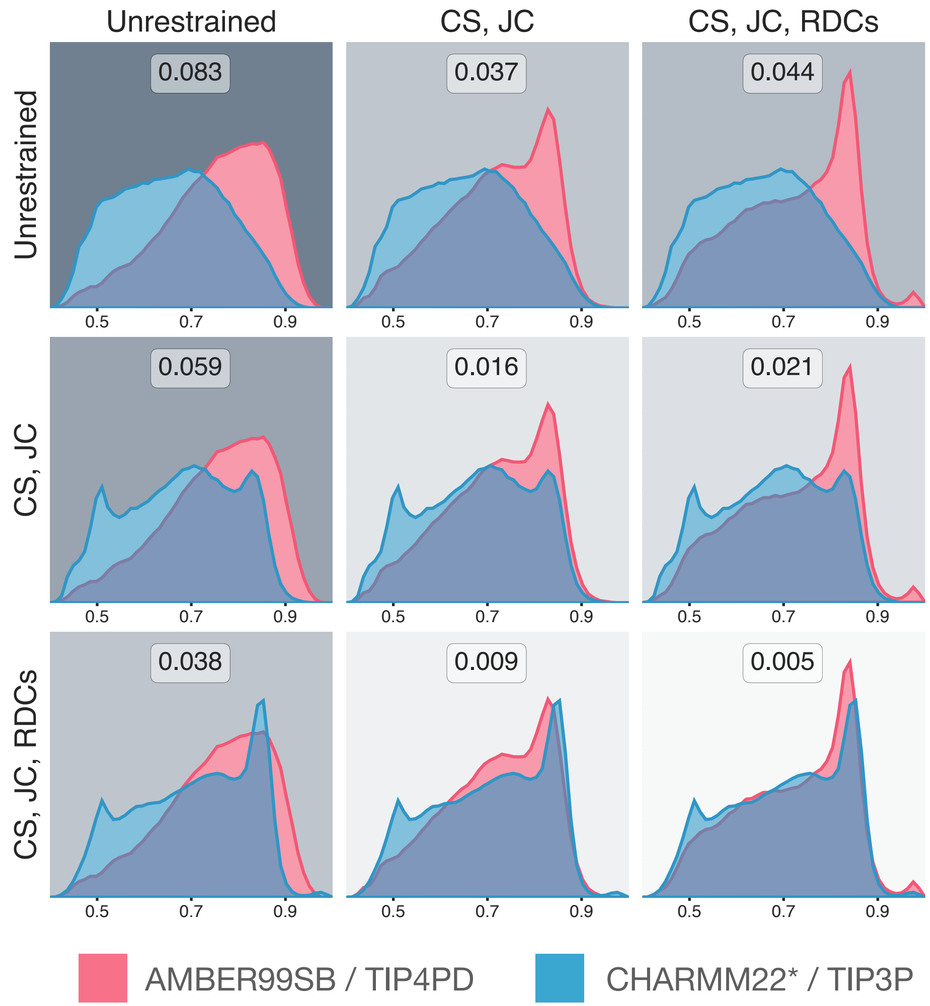


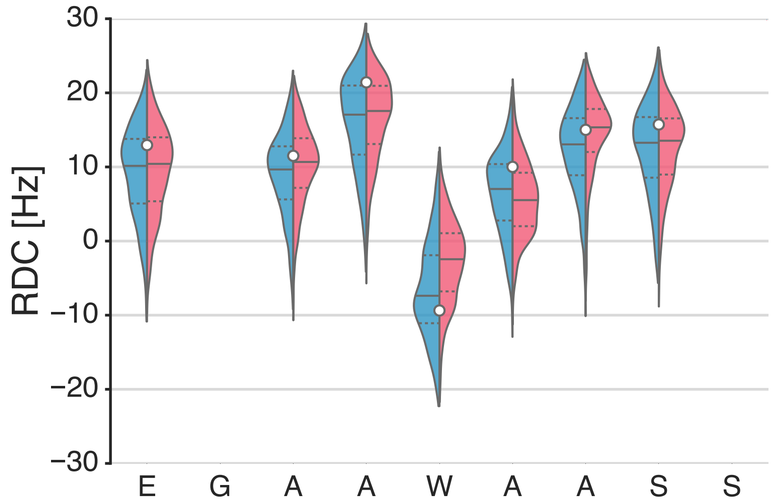
Squared deviation over time

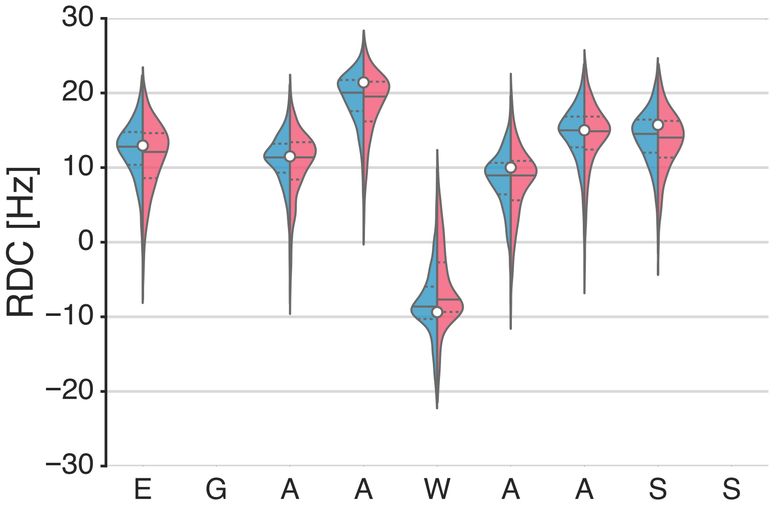


Real system: EGAAWAASS peptide

Metadynamics + experimental restraints







Useful resources

- GROMACS
  - Simple tutorial: http://www.mdtutorials.com/gmx/lysozyme/
  - User guide: https://manual.gromacs.org/documentation/current/user-guide/index.html
- PLUMED
  - Brief intro: https://www.plumed.org/doc-v2.8/user-doc/html/master-_i_s_d_d-1.html
  - Metadynamics: https://www.plumed.org/doc-v2.8/user-doc/html/master-_i_s_d_d-2.html
  - Metainference: https://www.plumed.org/doc-v2.8/user-doc/html/isdb-1.html
  - Reference: https://www.plumed.org/doc-v2.8/user-doc/html/index.html
- Python
  - Standard library: https://docs.python.org/3/
  - Numpy: https://numpy.org/doc/stable/

Relevant papers / books

- Metadynamics
  - How-to guide — Bussi & Branduardi
  - Well-tempered metadynamics — Barducci 2008
  - Parallel-bias metadynamics — Pfaendtner & Bonomi 2015
  - Adaptive gaussians — Branduardi 2012
- Forward models
  - J-couplings — Karplus 1963
  - 3-J coupling *A*, *B*, *C* parameters — Pérez 2001
- Metainference
  - Original method — Bonomi & Camilloni 2015
  - With metadynamics — Bonomi & Camilloni 2016
  - Practical guide on the EGAAWAASS peptide