Enhanced sampling in collective variable space using the Colvars library in GROMACS

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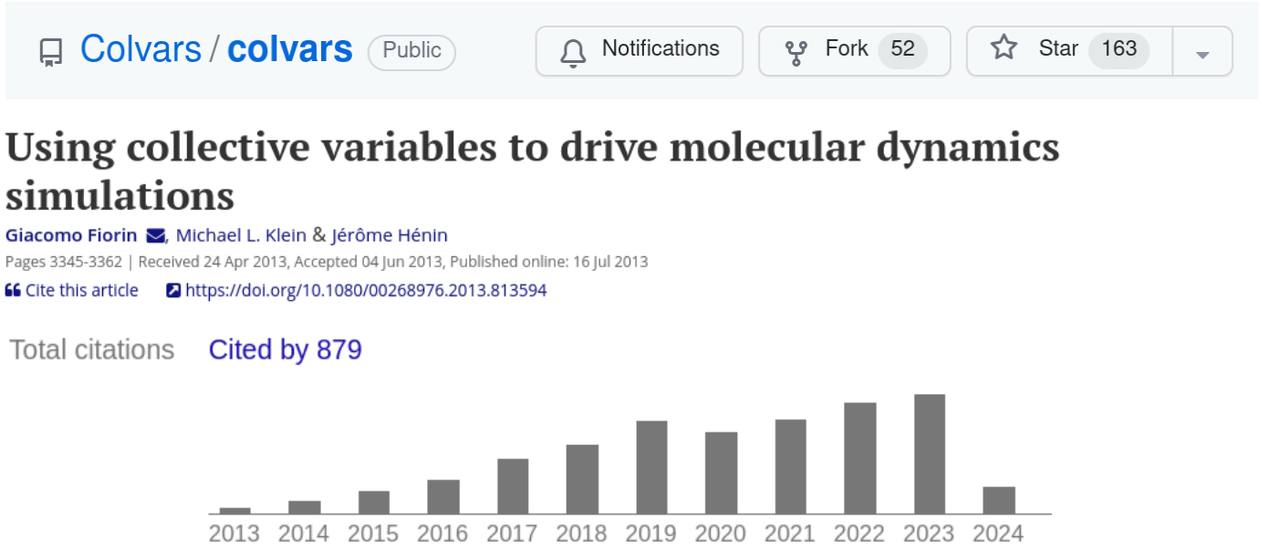
Collective variables module (Colvars)

a software library for enhanced-sampling MD simulations

"module" = it is packaged with simulation engines

https://github.com/Colvars/colvars



(additional references for features added later)

2006: in-house code

2008: packaged with NAMD

2012: packaged with LAMMPS

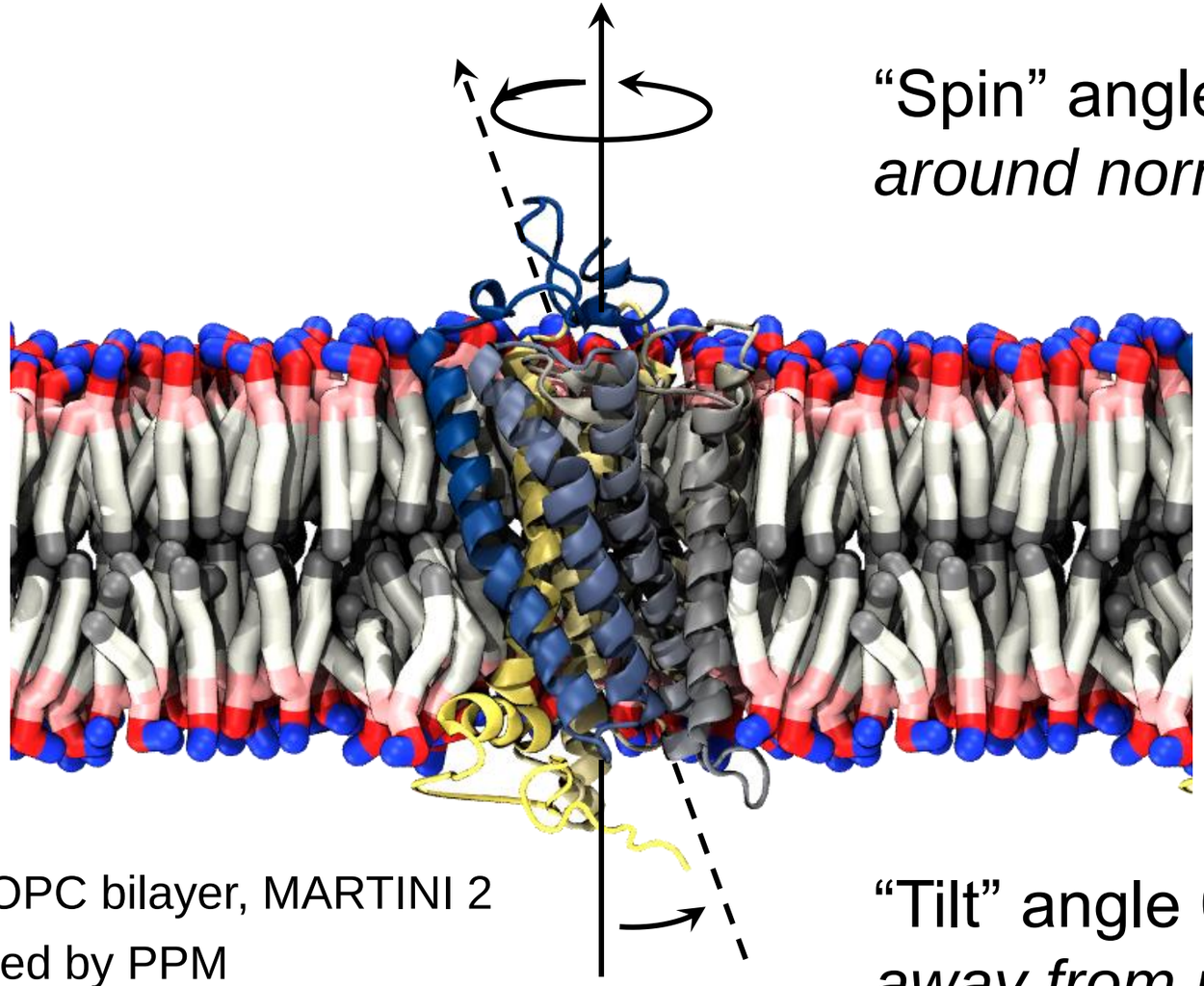
2014: packaged with VMD

2021: Dashboard (GUI plugin)

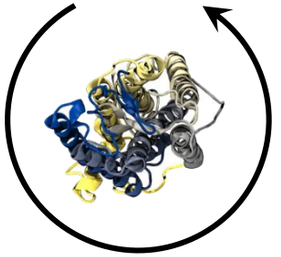
2023: packaged with Tinker-HP

2024: packaged with GROMACS

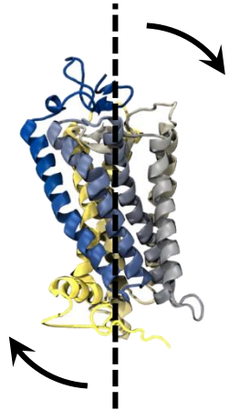
Example: whole-body rotations of a membrane protein



“Spin” angle φ:
around normal axis



“Tilt” angle θ:
away from normal

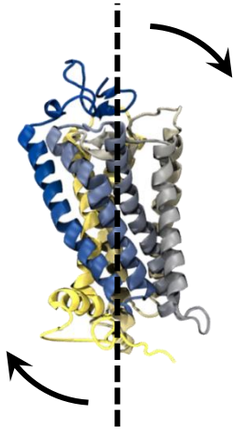


Rhodopsin (1F88) in POPC bilayer, MARTINI 2

Initial orientation modeled by PPM
(sources: OPM, EncoMPASS)

Defining collective variables for specific rotations

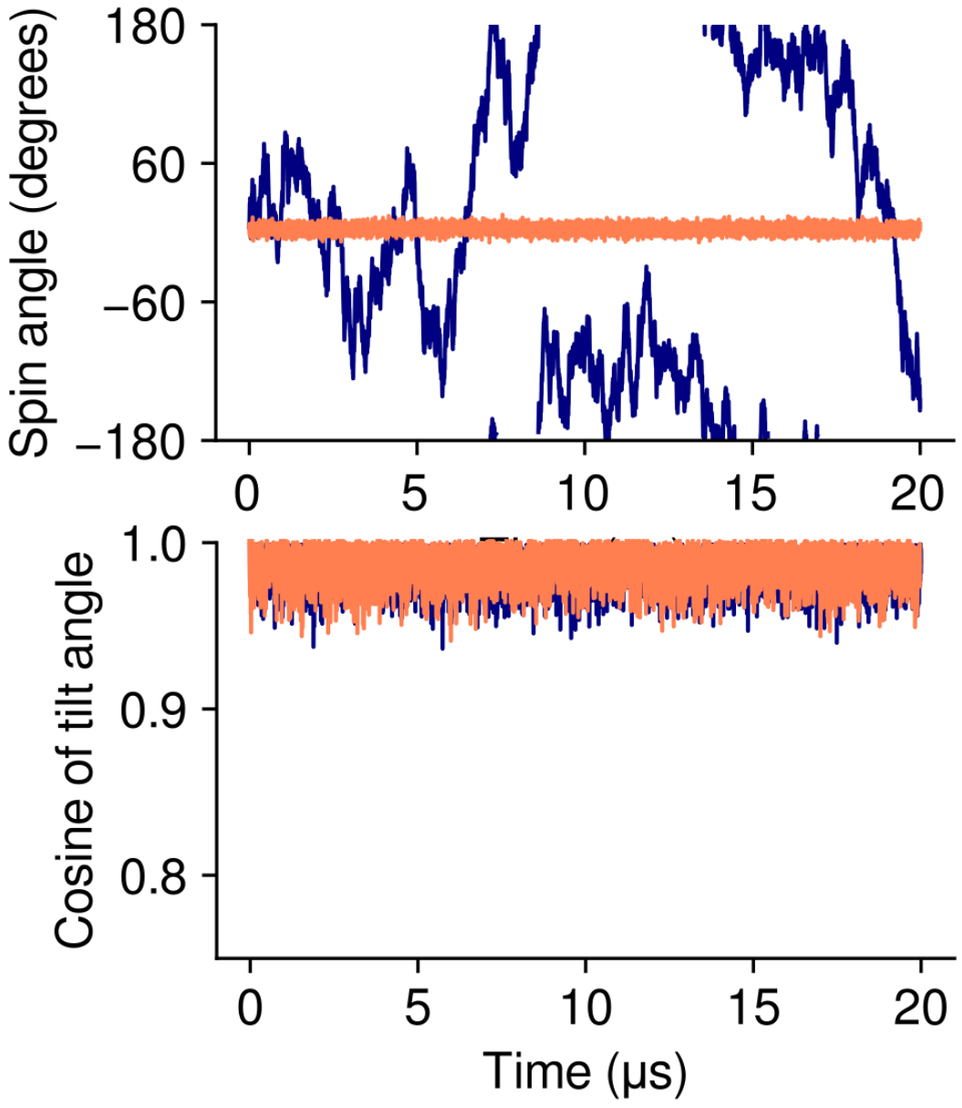
Colvars configuration file contents:

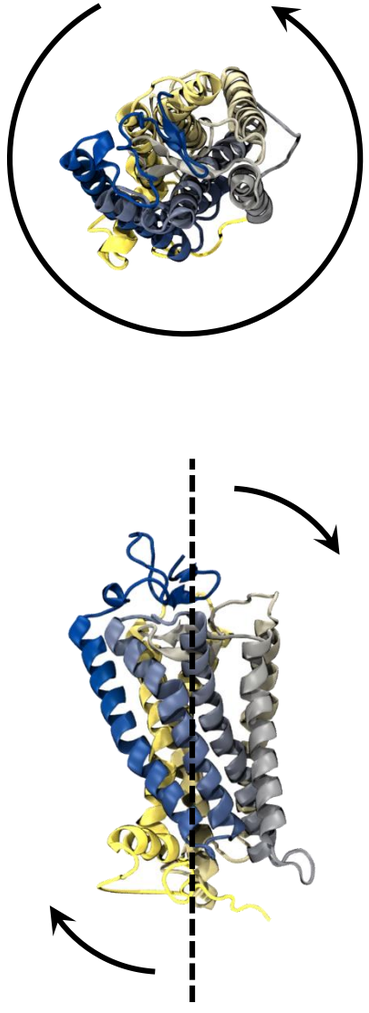


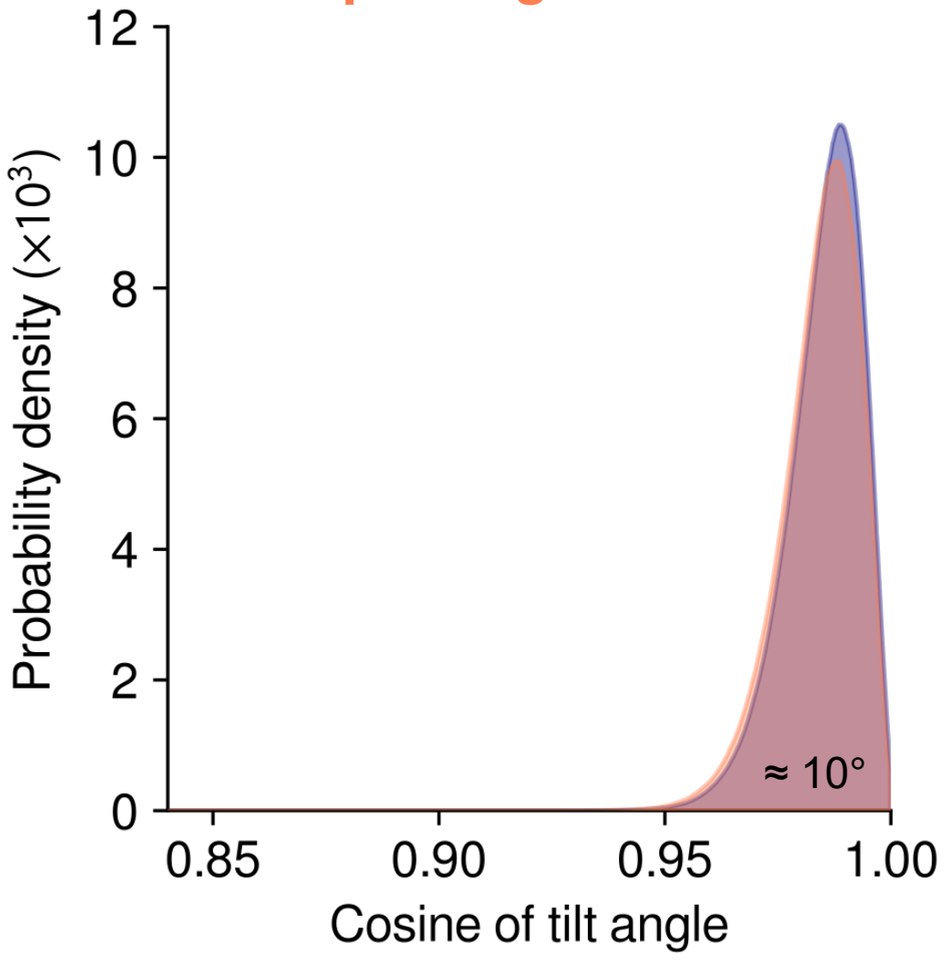
```
# Load an index file to define atom groups
# (you may load more than one...)
indexFile rhodopsin_popc_bilayer.ndx

colvar {   # define tilt, i.e. cos(θ)
    name t
    width 0.0005   # set default bin width
    tilt {         # range = [-1:1]
        atoms { indexGroup Backbone }
        refPositionsFile backbone.xyz
        axis (0.0, 0.0, 1.0)
    }
}
```

```
colvar {   # define spin angle φ
    name phi
    width 3.0     # set default bin width
    spinAngle {   # range = [-180:180]
        atoms { indexGroup Backbone }
        refPositionsFile backbone.xyz
        axis (0.0, 0.0, 1.0)
    }
}

harmonic {
    name r_phi
    colvars phi     # variable(s) to restrain
    centers 0.0
    forceConstant 2.5 # in kJ/mol/width²
    outputEnergy yes
}
```

Restraining “spin” while preserving “tilt” motions



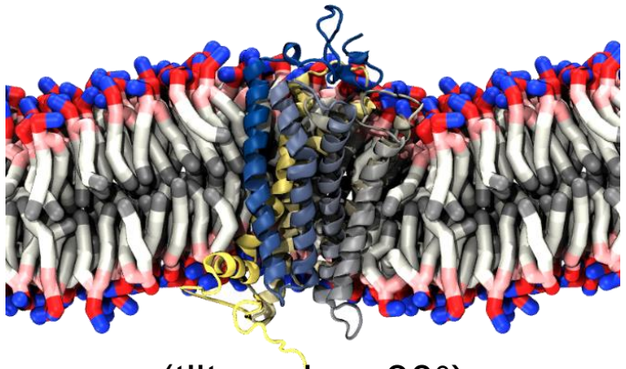




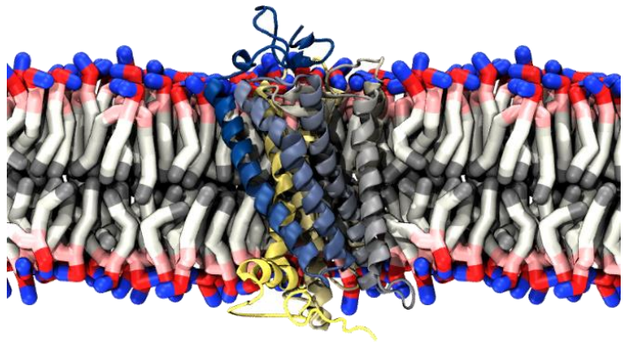
Elucidate membrane-related driving forces

Adding enhanced sampling:

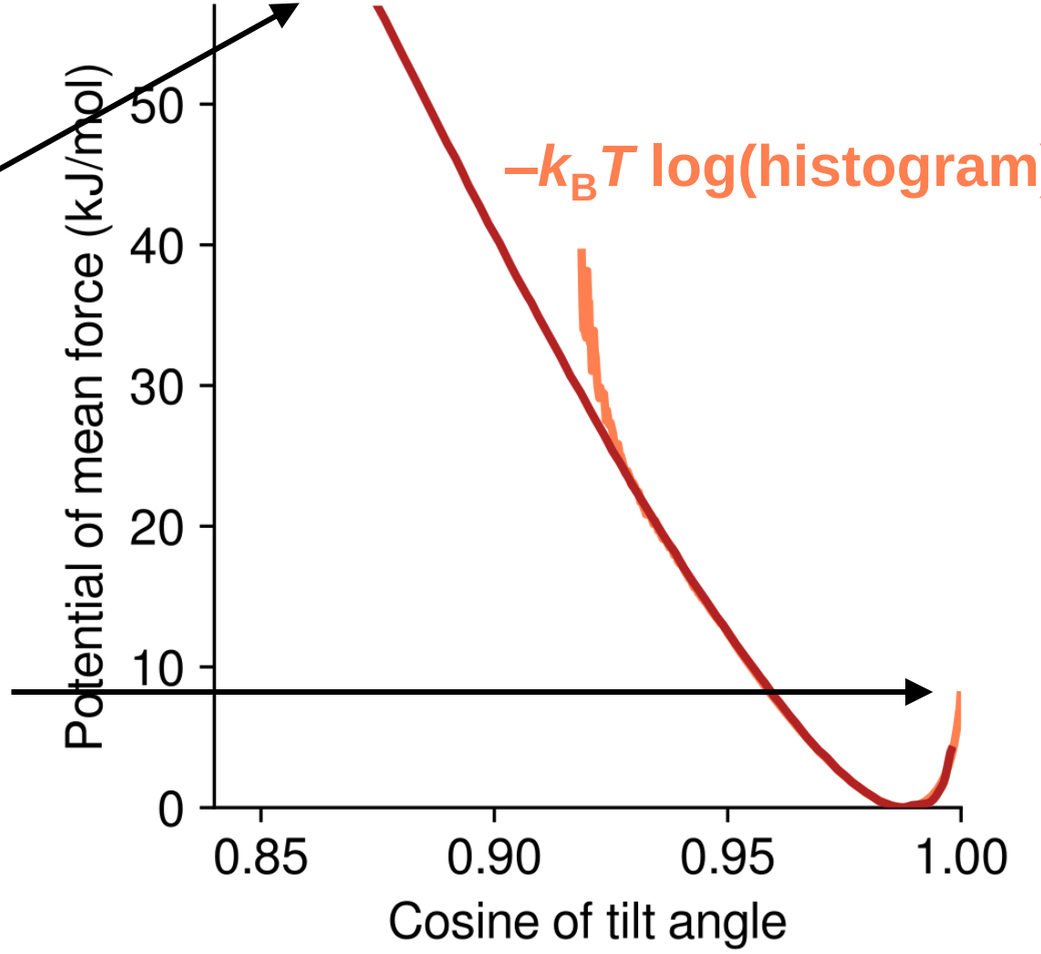
```
metadynamics {
    name mtd
    colvars t     # run metadynamics on tilt
    newHillFrequency 1000   # number of steps
    hillWeight 0.002        # in kJ/mol
    gaussianSigmas 0.001    # best if ≥ bin width
}
```



(tilt angle ≈ 30°)



(tilt angle ≈ 0°)



Sampling schemes supported (GROMACS 2024)

Harmonic restraints
umbrella sampling (Torrie and Valleau, 1977), steered MD (Grubmuller *et al*, 1996), wall restraints

Adaptive biasing force (ABF) (Darve and Pohorille, 2001)
extended-system ABF (Lesage *et al*, 2017)

Metadynamics
classic (Laio and Parrinello, 2002), multiple-walkers (Raiteri *et al*, 2006), well-tempered (Barducci *et al*, 2008), ensemble-biased (Marinelli and Faraldo-Gomez, 2015)

Advanced restraints
linear (Pitera and Chodera, 2012), adaptive linear bias (White and Voth, 2014), histogram restraint (Shen *et al*, 2015)

Analysis methods (no applied forces)
histograms, correlation functions

Collective variable types supported (GROMACS 2024)

DISTANCES

distance: distance btw two groups
distanceZ: distance along axis
distanceXY: distance on plane
distanceVec: distance vector (3D)
distanceDir: distance unit vector
distanceInv: mean distance

ANGLES

angle: angle btw three groups
dipoleAngle: angle from dipole vector
dihedral: torsional angle btw four groups
polarTheta: polar angle (spherical coords)
polarPhi: azimuthal angle (spher coords)

COLLECTIVE METRICS

rmsd: root mean square displacement
eigenvector: projection on a given vector
gyration: radius of gyration
inertia: total moment of inertia
inertiaZ: same around chosen axis
dipoleMagnitude: magnitude of moment
neuralNetwork: dense NN in CV space

CONTACTS

coordNum: coordination # btw two groups
selfCoordNum: coord # within group
hBond: coord # btw two atoms

ROTATIONS

orientation: full rotation from ref. coords
orientationAngle: angle of same
orientationProj: cosine of orientationAngle
spinAngle: angle of rotation around axis
tilt: cosine of rotation away from axis
eulerPhi: roll angle
eulerTheta: pitch angle
eulerPsi: yaw angle

PATH CVs (arithmetic and geometric)

aspath: progress along Cartesian path
azpath: distance from same
aspathCV: progress along CV path
azpathCV: distance from same
gspath: progress along Cartesian path
gzpath: distance from same
gspathCV: progress along CV path
gzpathCV: distance from same

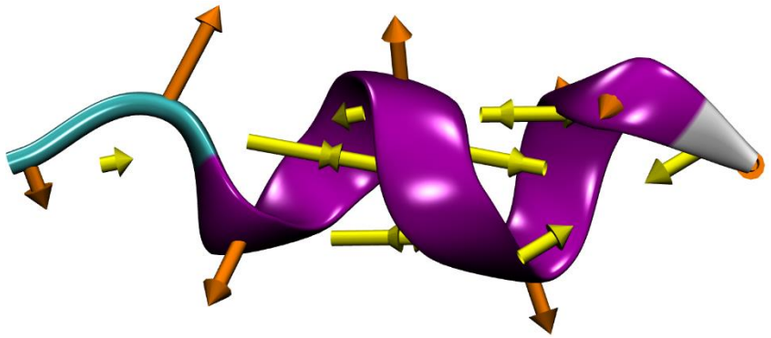
(Not included: variable types supported in other MD engines or code versions)

Following the Colvars development

Not included (yet) in GROMACS:

- customFunction (define new CVs using Lepton)
- protein secondary structure CVs
- speedup by removing duplicate computation
- multiple-walkers ABF
- *…other cool stuff*

```
colvar {
  name custom
  customFunction cos(phi1 + phi2)
  dihedral {
    name phi1
    ...
  }
  dihedral {
    name phi2
    ...
  }
}
```



“Unofficial” devel releases → https://github.com/Colvars/gromacs

Design and usage of Colvars with GROMACS

GROMACS - Colvars interface design

Features:

- Compatible with most GROMACS classical integrators, GPU scheme
- Validate input at pre-processor time and bundle everything in the TPR
- Use GROMACS checkpointing

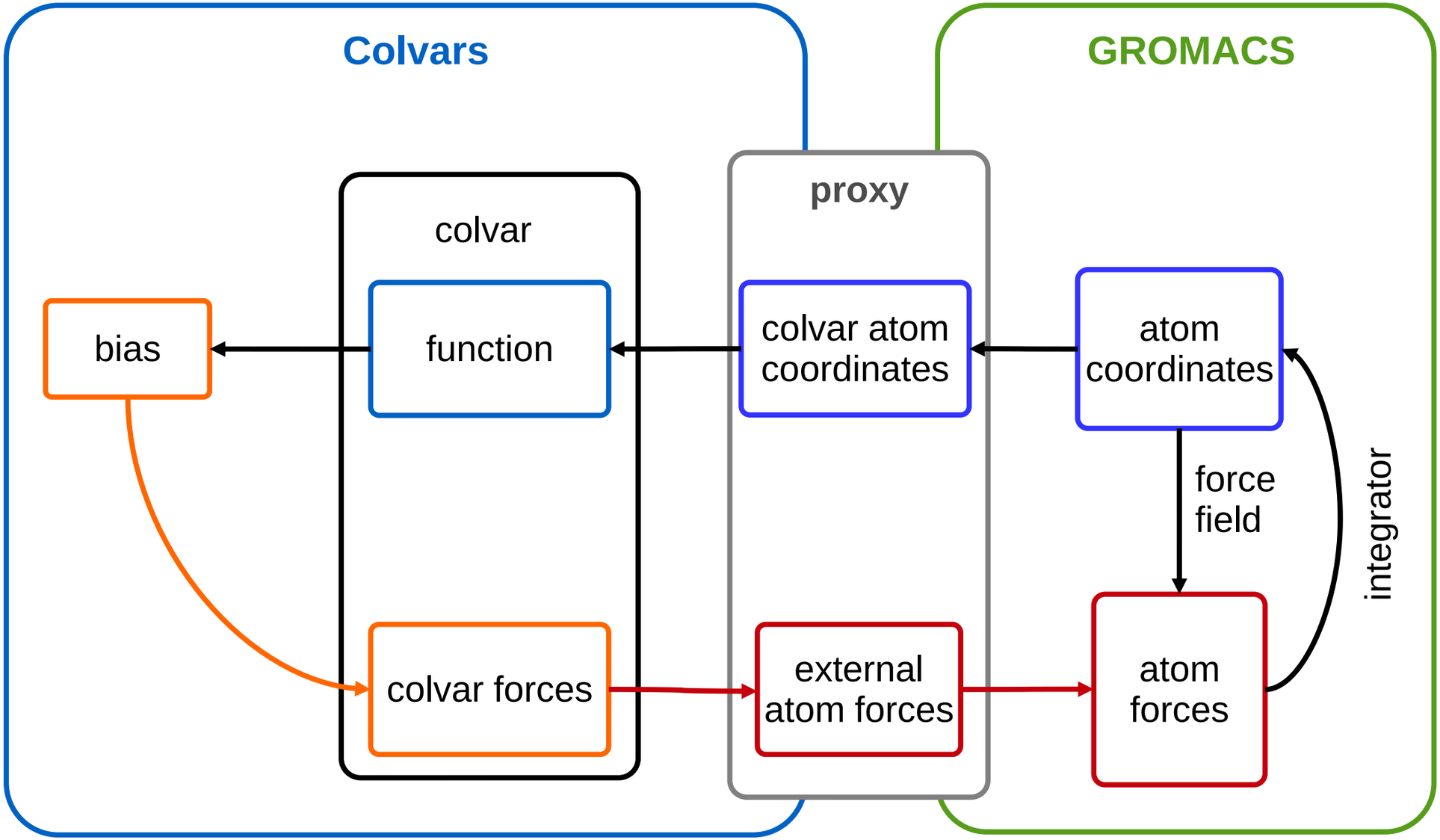
Known limitations:

- Colvars computation performed on main CPU node only

Documentation:

https://manual.gromacs.org/2024.1/reference-manual/special/colvars.html
https://colvars.github.io/gromacs-2024/colvars-refman-gromacs.html

GROMACS - Colvars interface design



Setting up a GROMACS - Colvars simulation

New mdp options:

```
;       example.mdp
...
        colvars-active = true               # Activate Colvars
        colvars-configfile = colvars.inp # Name of configuration file
```

Pre-processing:

```
gmx grompp -f example.mdp -p system.top -c system.gro -o test.tpr
```

Colvars config file and all its dependencies (e.g. coordinates for RMSDs, index files) are embedded in the .tpr file

Running the simulation - additional outputs

Standard *mdrun* command line:

```
gmx mdrun -s test.tpr -deffnm md [...]
```

Colvars produces its own output files:

- .colvars.traj -> trajectory of the collective variable(s)
- .pmf, .count, etc -> additional files depending of the feature(s) used.

The prefix of the Colvars output files is the same as the .edr prefix

Restart/Continuation:

- All colvars information are stored in the .cpt file. (text version is also produced with the name .colvars.state).

```
gmx mdrun -s test.tpr -cpi md.cpt -deffnm md [...]
```

Live demo: Colvars Dashboard in VMD

Thank you

to everyone who contributed code through GitHub:

to all members of the GROMACS team (especially Magnus and Berk)

to our fantastic colleagues in Bethesda and in Paris

to BioExcel for hosting us

…and *to you* for listening and trying it out!