

Designing, Implementing and Optimizing Collective Variables in VMD and NAMD

Jérôme Hénin

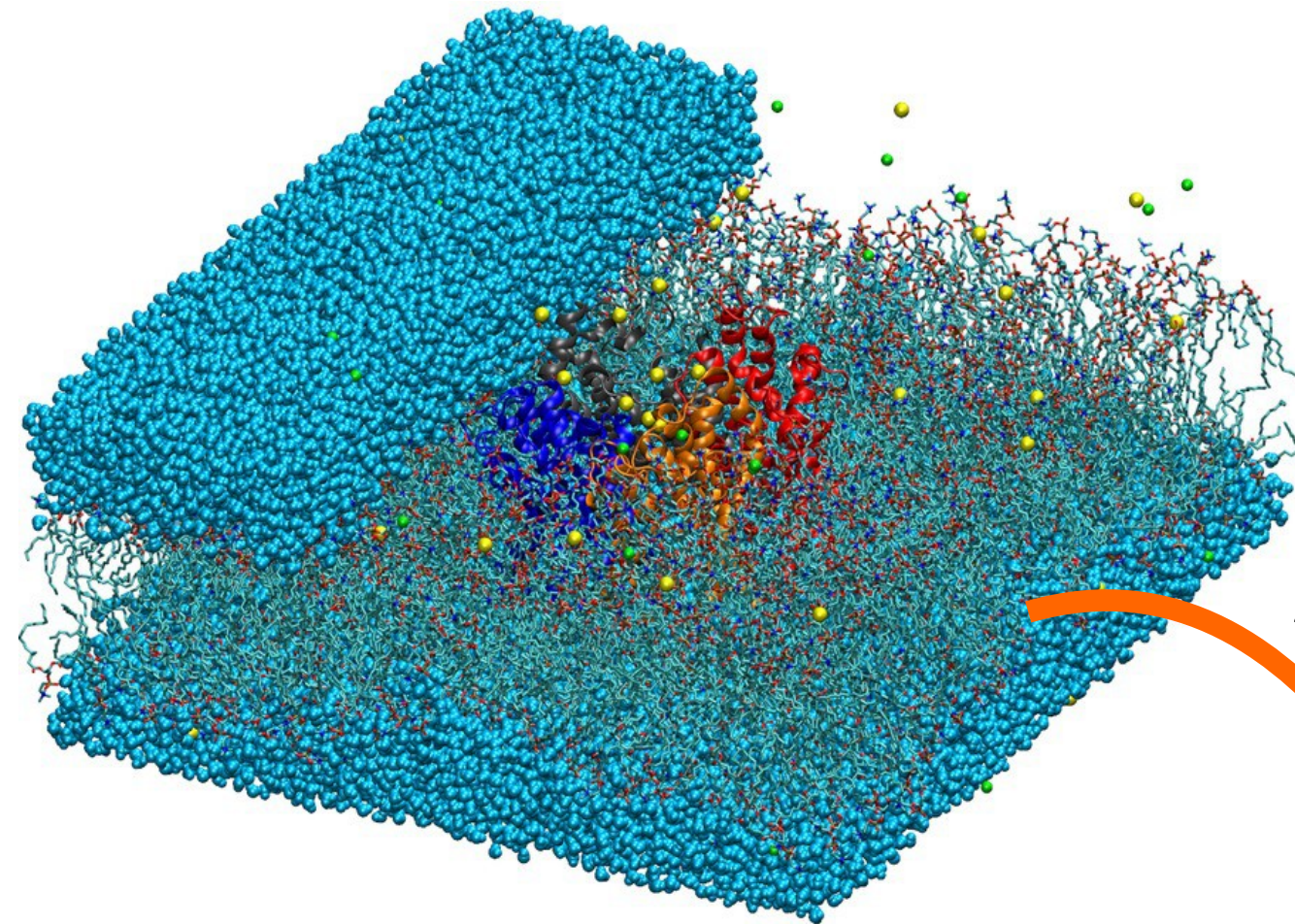


Enhanced Sampling
and Free-Energy Calculations
Urbana, 12 September 2018

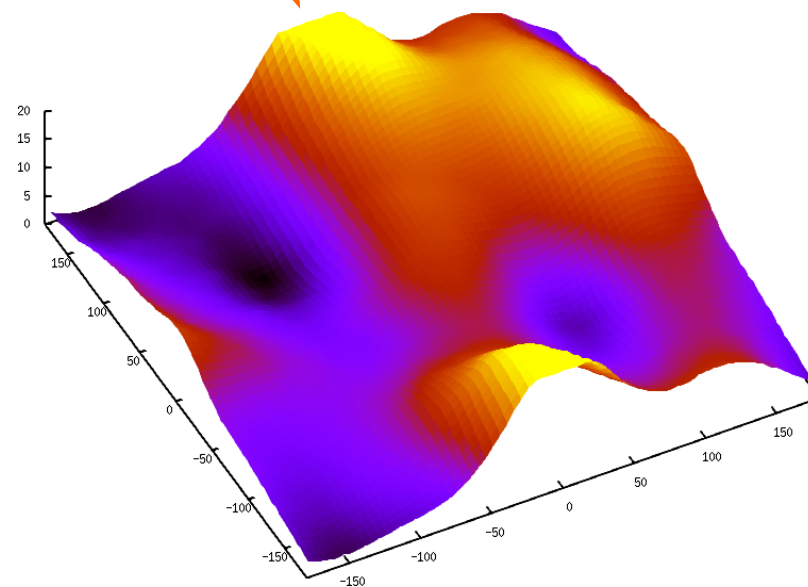
IBPC

How to:

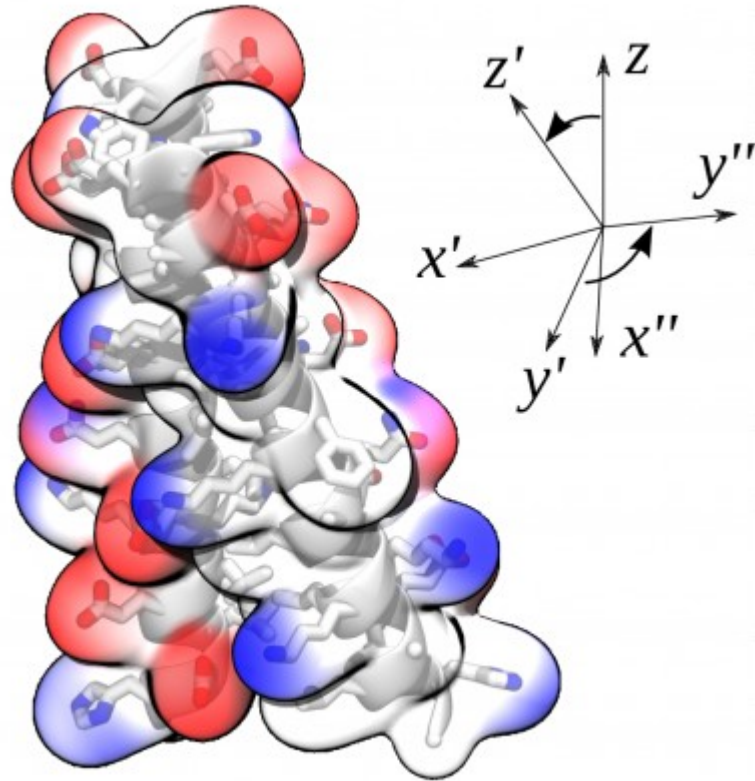
- define colvars?
- analyze colvars?
- choose colvars?
- bias colvars?



??



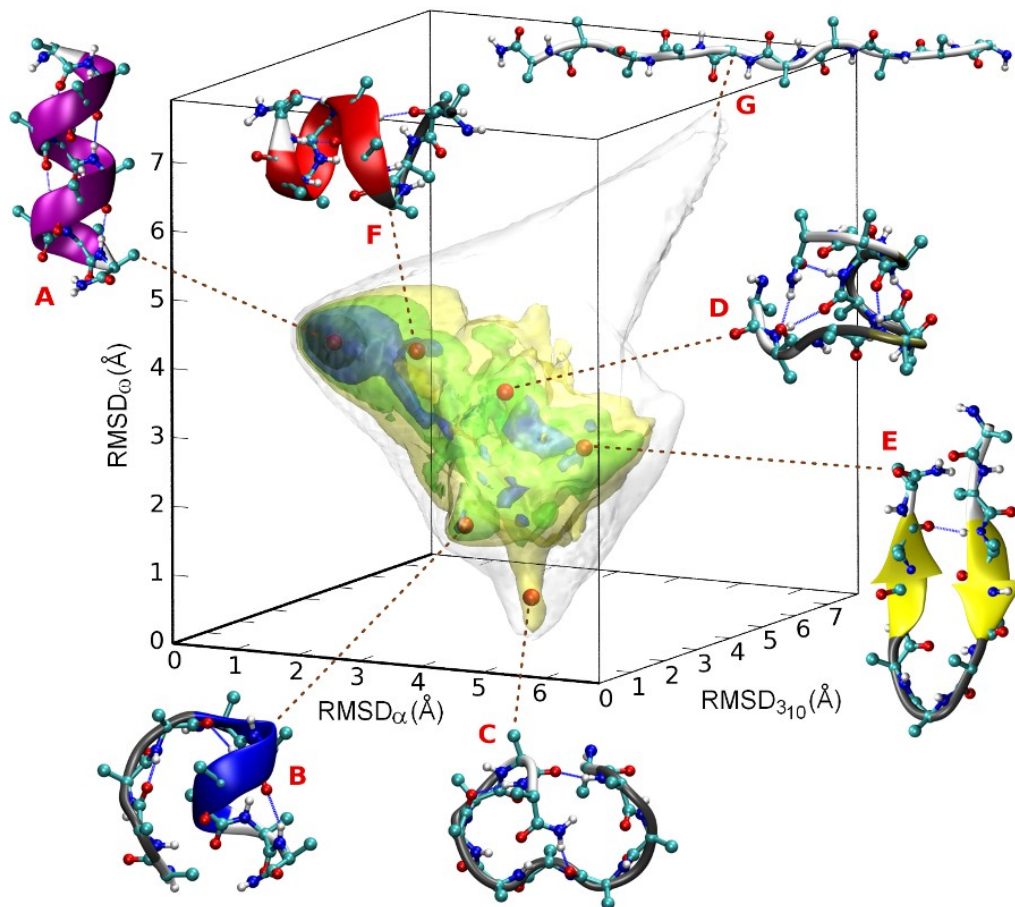
Collective Variables Module



Giacomo Fiorin
Temple University

Versatile biases in generalized coordinates

- arbitrary dimension
- run-time combination of variables
- many variables available
- time-dependent biases
- → adaptive free energy methods (metadynamics, ABF)
- included in **NAMD**, **LAMMPS**, **VMD**
- extensible through **C++** or **Tcl**

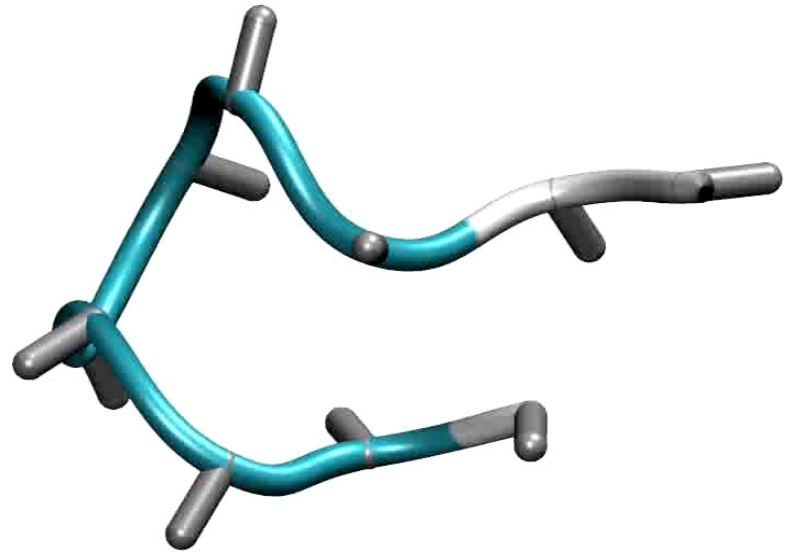


Example Targeted MD

colvar simulation = **collective variable** + **bias**

```
colvar {  
  name RMSD  
  
  rmsd {  
    atoms {  
      atomsFile beta.pdb  
      atomsCol 0  
    }  
    refPositionsFile beta.pdb  
  }  
}
```

```
harmonic {  
  colvars RMSD  
  
  centers 5.3  
  targetCenters 0.0  
  targetNumSteps 200000  
  forceConstant 100.  
}
```



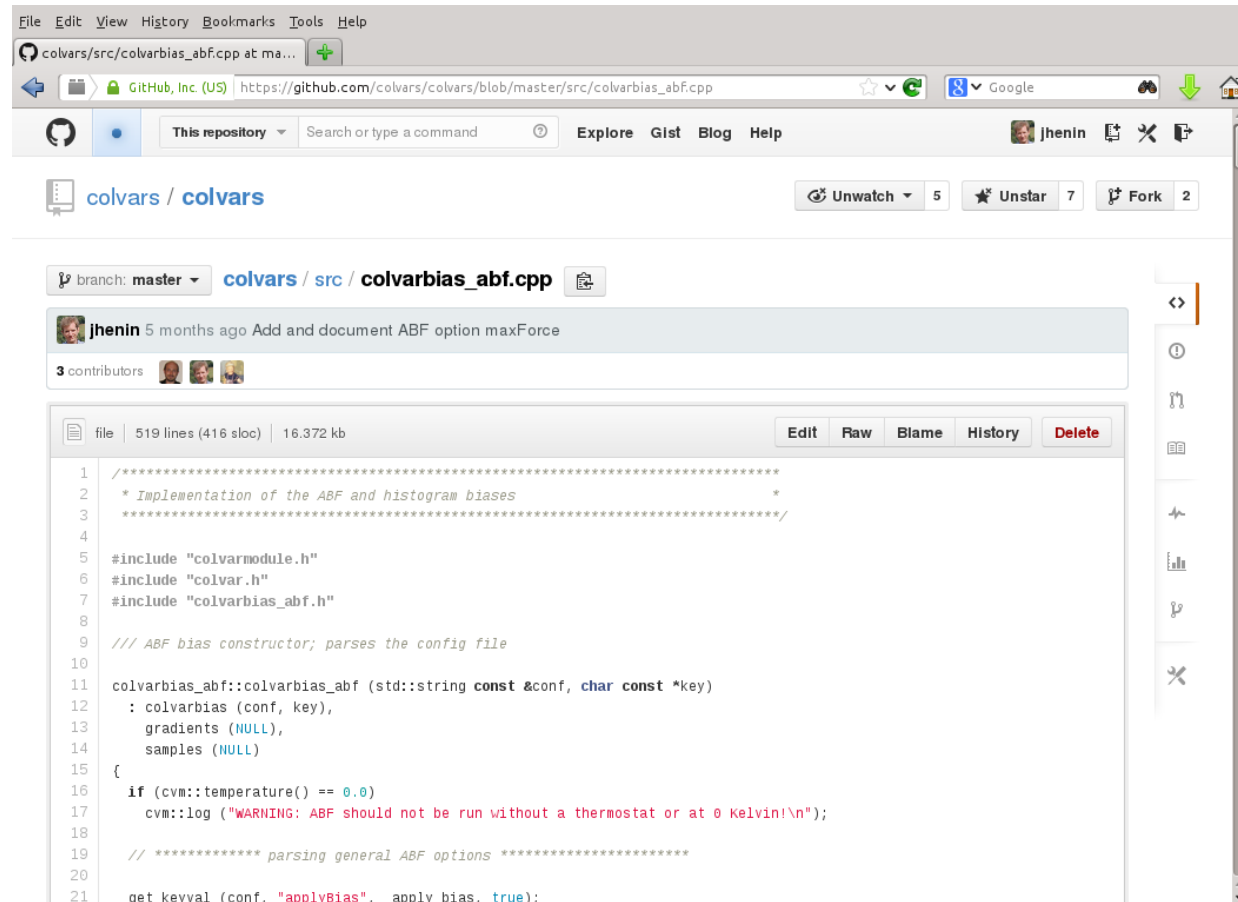
Getting Colvars 1: with precompiled binaries

- recent versions of NAMD and VMD include Colvars
 - 1) Download NAMD or VMD binaries
 - 2) use Colvars
 - 3) ...
 - 4) Profit!

Getting Colvars 2: source repository

- public repository on GitHub <http://github.com/Colvars/colvars>
- always up-to-date code
- documentation
- automated regression tests

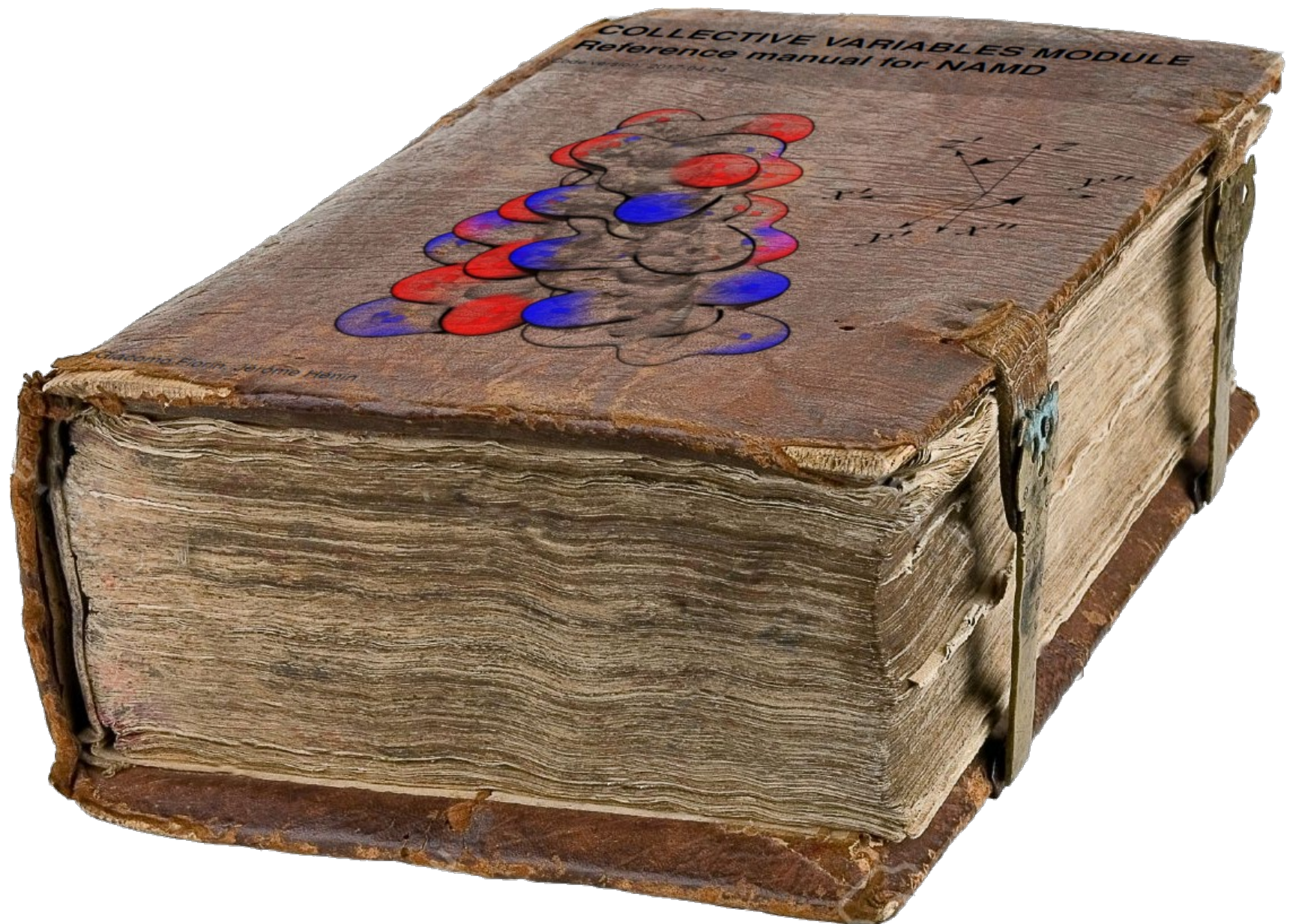
- [issue tracker](#)
- we rely on [user feedback](#)



The screenshot shows a web browser displaying the GitHub repository for 'colvars/colvars'. The page is for the file 'colvars/src/colvarbias_abf.cpp' at the master branch. The commit message is 'jhenin 5 months ago Add and document ABF option maxForce'. The file is 16.372 kb and contains 519 lines of code. The code is shown in a monospaced font with syntax highlighting. The code includes headers for 'colvarmodule.h', 'colvar.h', and 'colvarbias_abf.h'. It defines a constructor for 'colvarbias_abf' that takes a configuration string and a key. The constructor initializes 'gradients' and 'samples' to NULL. It also includes a warning message: 'WARNING: ABF should not be run without a thermostat or at 0 Kelvin!'. The code ends with a call to 'get_keyval' to parse the 'applyBias' option.

```
1  /*****
2  * Implementation of the ABF and histogram biases
3  *****/
4
5  #include "colvarmodule.h"
6  #include "colvar.h"
7  #include "colvarbias_abf.h"
8
9  /// ABF bias constructor; parses the config file
10
11  colvarbias_abf::colvarbias_abf (std::string const &conf, char const *key)
12  : colvarbias (conf, key),
13    gradients (NULL),
14    samples (NULL)
15  {
16    if (cvm::temperature() == 0.0)
17      cvm::log ("WARNING: ABF should not be run without a thermostat or at 0 Kelvin!\n");
18
19    // ***** parsing general ABF options *****
20
21    get_keyval (conf, "applyBias", apply_bias, true);
```

Where can I find documentation?



Information 1: reference manuals

- Colvars chapter in the NAMD and VMD user guides
- available as online HTML at <http://colvars.github.io>
- details in reference publication (Open Access)

Molecular Physics, 2013

Vol. 111, Nos. 22–23, 3345–3362, <http://dx.doi.org/10.1080/00268976.2013.813594>



INVITED ARTICLE

Using collective variables to drive molecular dynamics simulations

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A software framework is introduced that facilitates the application of biasing algorithms to collective variables of the type commonly employed to drive massively parallel molecular dynamics (MD) simulations. The modular framework that is presented enables one to combine existing collective variables into new ones, and combine any chosen collective variable with available biasing methods. The latter include the classic time-dependent biases referred to as steered MD and targeted MD, the temperature-accelerated MD algorithm, as well as the adaptive free-energy biases called metadynamics and adaptive biasing force. The present modular software is extensible, and portable between commonly used MD simulation engines.

Keywords: molecular dynamics simulation; collective variable; free-energy calculation; adaptive bias; sampling

Information 2: online examples

- Simple, runnable examples:

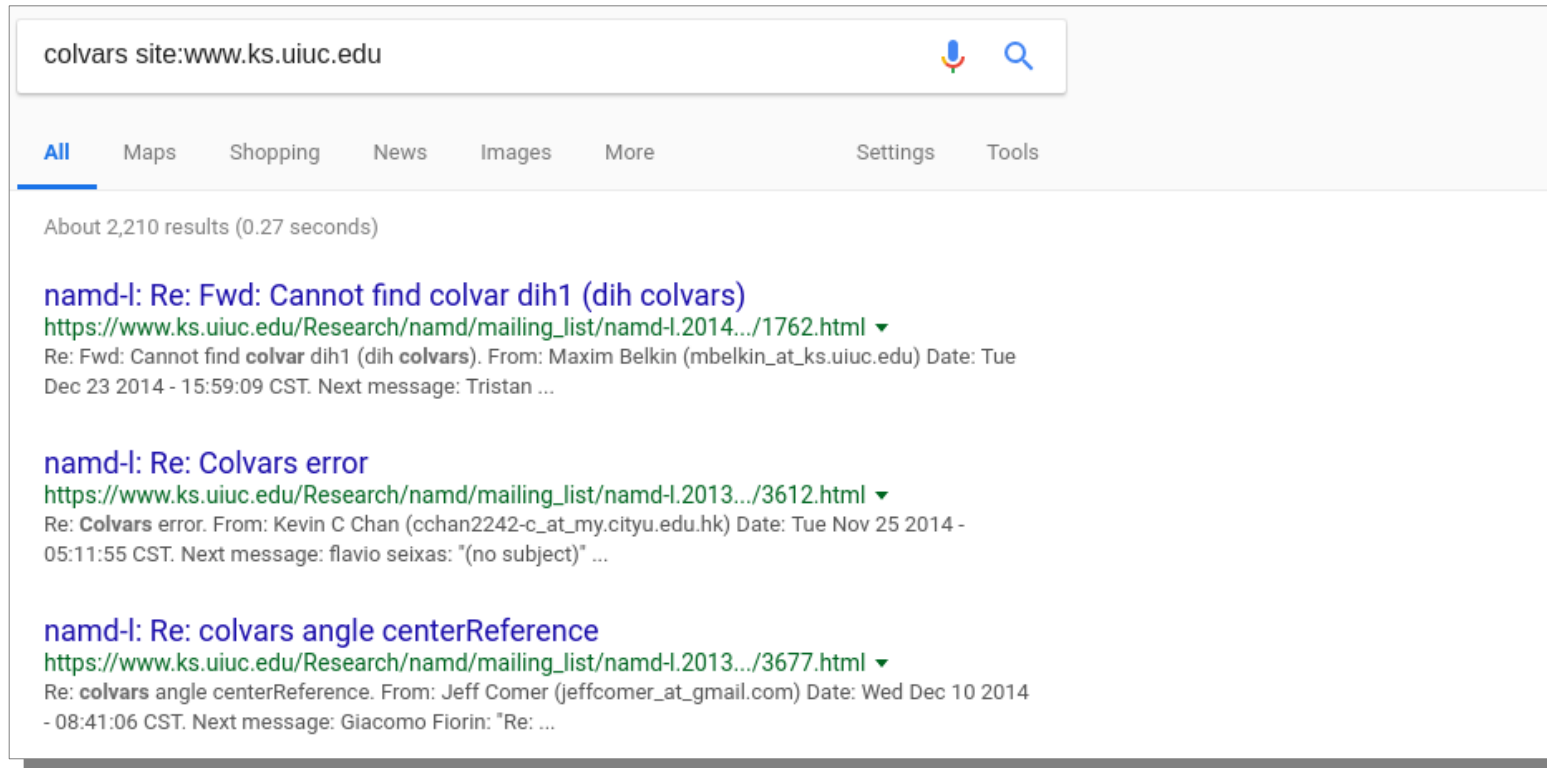
<http://github.com/Colvars/examples>

- Various advanced examples used in Colvars publication

<http://github.com/Colvars/colvars/tree/master/examples>

Information 3: mailing lists

- NAMD and VMD mailing lists offer **searchable archives**



The screenshot shows a Google search interface with the query 'colvars site:www.ks.uiuc.edu'. The search results are filtered to 'All' and show approximately 2,210 results. Three search results are visible, each with a blue title, a green URL, and a snippet of text.

colvars site:www.ks.uiuc.edu

All Maps Shopping News Images More Settings Tools

About 2,210 results (0.27 seconds)

namd-l: Re: Fwd: Cannot find colvar dih1 (dih colvars)
https://www.ks.uiuc.edu/Research/namd/mailling_list/namd-l.2014.../1762.html ▼
Re: Fwd: Cannot find colvar dih1 (dih colvars). From: Maxim Belkin (mbelkin_at_ks.uiuc.edu) Date: Tue Dec 23 2014 - 15:59:09 CST. Next message: Tristan ...

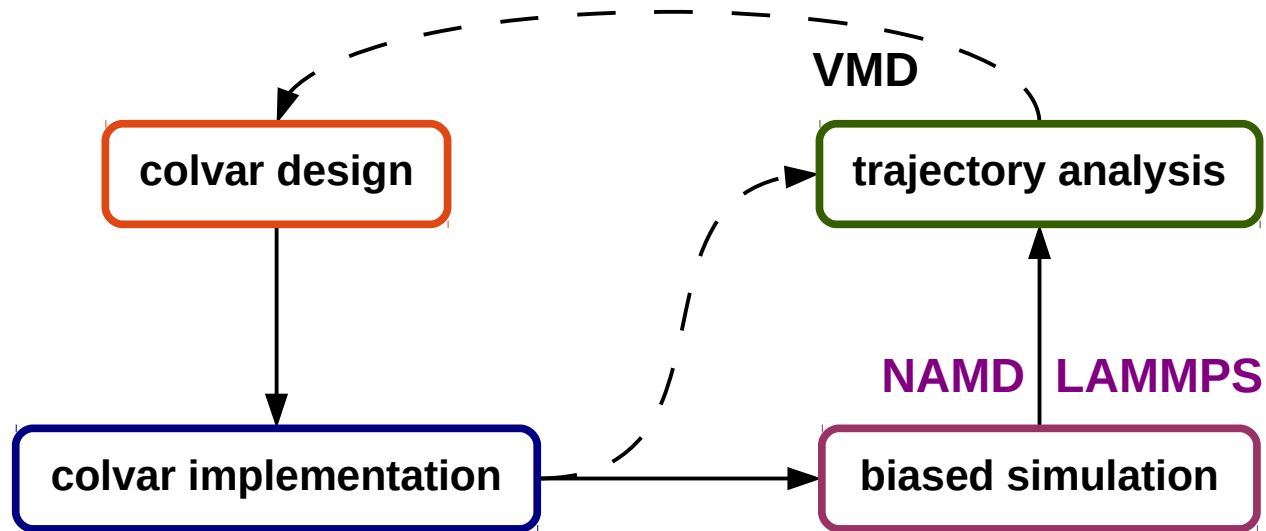
namd-l: Re: Colvars error
https://www.ks.uiuc.edu/Research/namd/mailling_list/namd-l.2013.../3612.html ▼
Re: Colvars error. From: Kevin C Chan (cchan2242-c_at_my.cityu.edu.hk) Date: Tue Nov 25 2014 - 05:11:55 CST. Next message: flavio seixas: "(no subject)" ...

namd-l: Re: colvars angle centerReference
https://www.ks.uiuc.edu/Research/namd/mailling_list/namd-l.2013.../3677.html ▼
Re: colvars angle centerReference. From: Jeff Comer (jeffcomer_at_gmail.com) Date: Wed Dec 10 2014 - 08:41:06 CST. Next message: Giacomo Fiorin: "Re: ...

- if the answer is not there, send a precise question to the **most relevant mailing list** (namd-l or vmd-l)

A tour of Colvars features

Collective variable modeling workflow



basis functions
(aka components)

$$\xi(x) = \zeta(x)$$

polynomials

$$\xi(x) = \sum_{i=1}^n c_i \zeta_i(x)^{p_i}$$

custom functions

$$\xi(x) = f_{\text{user}}(\zeta_1(x), \dots, \zeta_n(x))$$

- classic algorithms
- adaptive sampling
- multiple-walker sampling
- scripted biases

Components (basis functions)

distances	distance	center-of-mass distance between two groups
	distanceZ	projection of a distance vector on an axis
	distanceXY	modulus of the projection of a distance vector on a plane
	distanceVec	distance vector between two groups
	distanceDir	distance unit vector between two groups
raw data	distanceInv	mean distance between two groups of atoms
	distancePairs	set of pairwise distances between two groups
	cartesian	vector of atomic Cartesian coordinates
angles	angle	angle between three groups
	dipoleAngle	angle between two groups and dipole of a third group
	dihedral	torsional angle between four groups
	polarTheta	polar angle in spherical coordinates
	polarPhi	azimuthal angle in spherical coordinates
coordination	coordNum	coordination number between two groups
	selfCoordNum	coordination number between atoms within a group
	hBond	hydrogen bond between two atoms
collective	rmsd	root mean square displacement (RMSD) from reference positions
	rmsd-based	path collective variables
	eigenvector	projection of the atomic coordinates on a vector
	gyration	radius of gyration of a group of atoms
	inertia	total moment of inertia of a group of atoms
orientation	inertiaZ	total moment of inertia of a group of atoms around a chosen axis
	orientation	orientation from reference coordinates
	orientationAngle	angle of rotation from reference coordinates
	orientationProj	cosine of the angle of rotation from reference coordinates
	spinAngle	angle of rotation around a given axis
protein structure	tilt	cosine of the rotation orthogonal to a given axis
	alpha	α -helix content of a protein segment
	dihedralPC	protein dihedral principal component

Write your own colvar (WYOC): Custom functions with the Lepton library

Combine **existing basis functions** with **custom expressions**

```
colvar {
  name myVariable

  # This is a 2-vector function of a 4-vector
  customFunction x - r1
  customFunction cos(x) + r1 + r2 + r3

  distance {
    name x
    group1 { atomNumbers 4 }
    group2 { atomNumbers 99 }
  }
  distanceVec {
    name r
    group1 { atomNumbers 50 }
    group2 { atomNumbers 60 }
  }
}

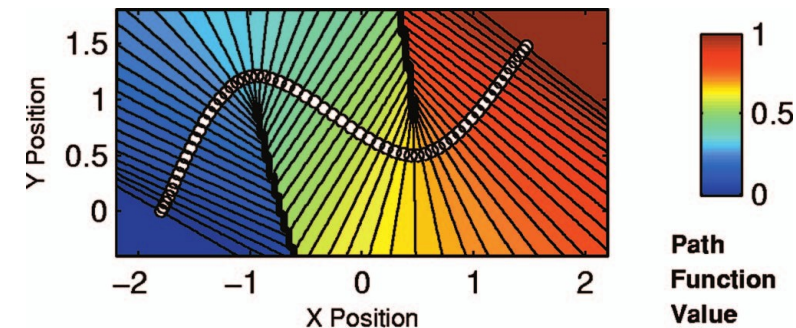
harmonic {
  colvars myVariable
  centers (20, -5)
  forceConstant 100
}
```

Scripted function: path collective variables

```
colvar {
  name s
  rmsd {
    atoms { atomNumbers { 10 20 30 } }
    repositionsfile string-1.pdb ;# coordinates of the first bead
    componentExp 1 ;# index of the first bead
  }
  rmsd {
    atoms { atomNumbers { 10 20 30 } }
    repositionsfile string-2.pdb ;# coordinates of the second bead
    componentExp 2 ;# index of the second bead
  }
  scriptedFunction pathCV
}
```

```
proc calc_pathCV { args } {
  global pathCVlambda; global pathCVu; global pathCVv
  set N [llength $args]
  set i 0; set u 0.0; set v 0.0
  foreach x $args {
    set u [expr {$u + $i * exp(-$lambda * $x * $x)}]
    set v [expr {$v + exp(-$lambda * $x * $x)}]
    incr i
  }
  return [expr {1.0 / ($N - 1.0) * $u / $v}]
}
```

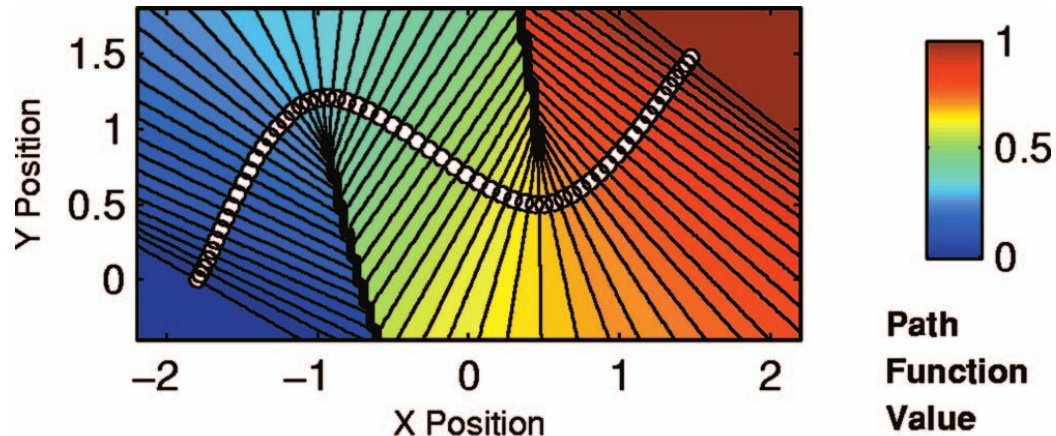
```
proc calc_pathCV_gradient { args } {
  global pathCVlambda; global pathCVu; global pathCVv
  set N [llength $args]
  set grad {} ; set i 0
  foreach x $args {
    set uprime [expr {-2.0 * $i * $lambda * $x * exp(-$lambda*$x*$x)}]
    set vprime [expr {-2.0 * $lambda * $x * exp(-$lambda*$x*$x)}]
    incr i
    lappend grad [expr {1.0/($N-1.0)*($uprime*$v - $vprime*$u)/($v*$v)}]
  }
  return $grad
}
```



$$s(\mathbf{R}) = \frac{1}{P-1} \frac{\sum_{i=1}^P (i-1) e^{-\lambda(\mathbf{R} - \mathbf{R}(i))^2}}{\sum_{i=1}^P e^{-\lambda(\mathbf{R} - \mathbf{R}(i))^2}}$$

Branduardi et al. JCP 2007

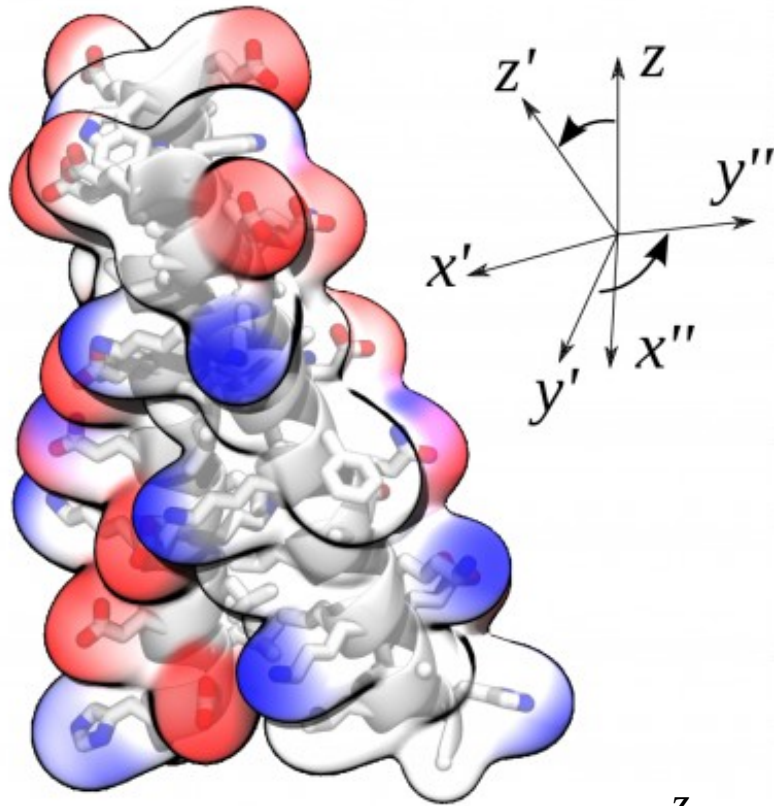
Optimization: dynamic colvar components



$$s(\mathbf{R}) = \frac{1}{P-1} \frac{\sum_{i=1}^P (i-1) e^{-\lambda(\mathbf{R} - \mathbf{R}(i))^2}}{\sum_{i=1}^P e^{-\lambda(\mathbf{R} - \mathbf{R}(i))^2}}$$

- path collective variables
 - depends on RMSD from all images on a discrete path – **expensive**
 - dominated by a few terms nearby images
- Colvars implementation is a Tcl-scripted coordinate
 - each RMSD is a colvar component (cvc)
- scripting command `cvcflags` is used to limit calculation to relevant RMSDs

Describing “soft-body” rotations



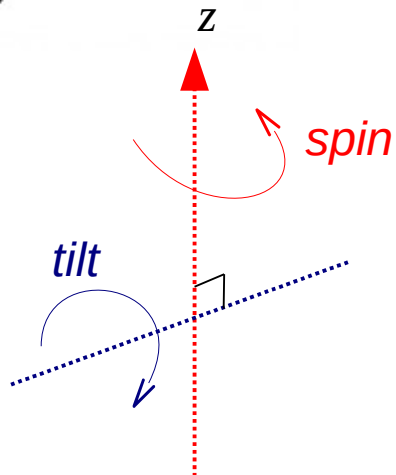
Problem

describe collective rotation of *flexible* objects

- least-squares fit, minimizing

$$d^2 = (R(X) - X^0)^2$$

- solved as eigenproblem with quaternion representation of rotations
- use **optimal rotation as coordinate**

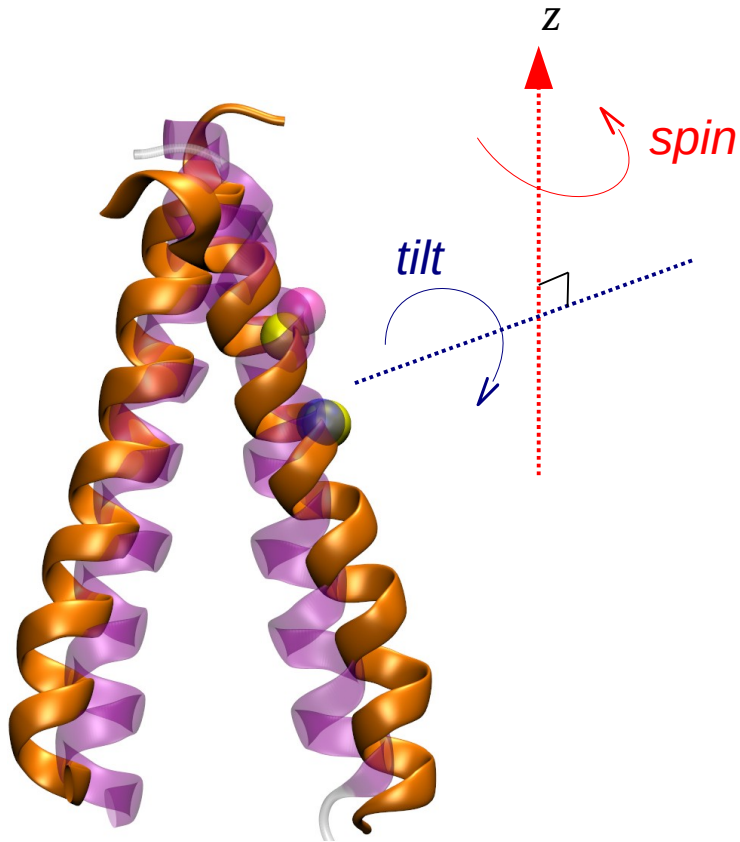


- preferred axis z
- rotation decomposed into *spin* and *tilt*
- gives two rotation angles

Local frames of reference

- all coordinates based on atom groups
- atom groups can **center and rotate themselves transparently** to fit reference positions, working in a separate frame of reference
 - **centerReference** translation
 - **rotateReference** best-fit rotation
 - contribution of rotation to the gradients is calculated

Application 1: internal rotations in a dimer



To describe *relative* rotation of one helix

- fit pair of objects, minimizing

$$d_{AB}^2 = \left(R_{AB}(X_{AB}) - X_{AB}^0 \right)^2$$

- fit of one object A, relative to pair

$$d_A^2 = \left(R_A \circ \tilde{R}_{AB}(X_A) - X_A^0 \right)^2$$

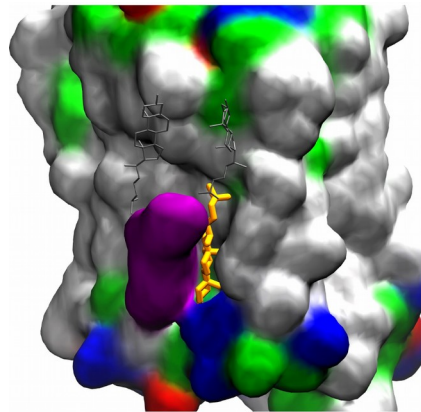
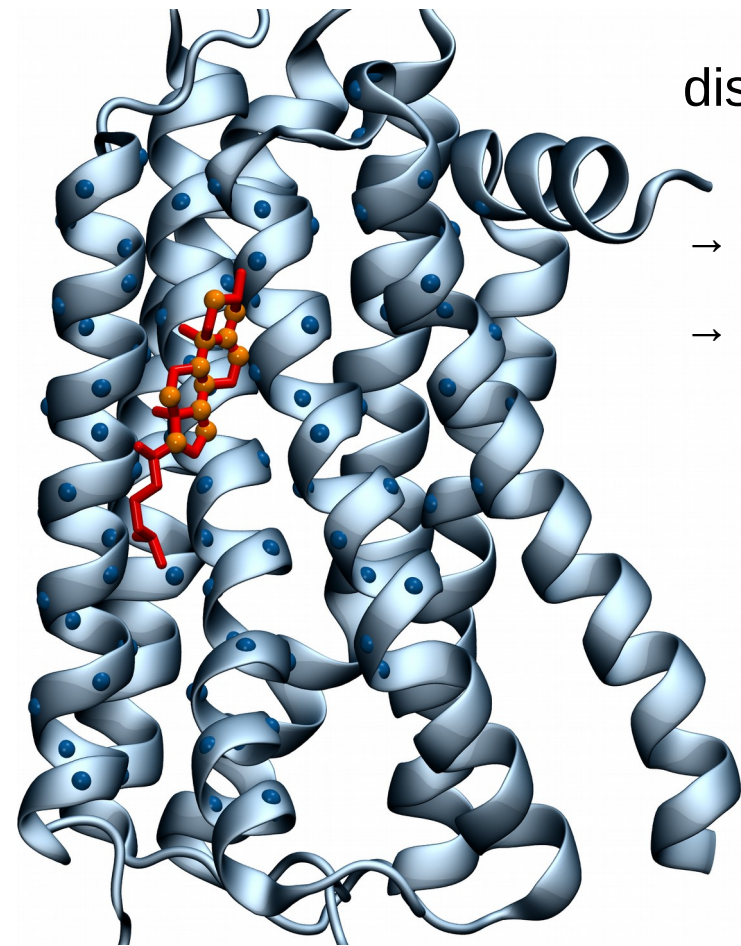
- rotation R_A split into *spin* and *tilt*
- gives two internal rotation angles
- defined at run-time, no coding needed

Application 2: ligand binding coordinate

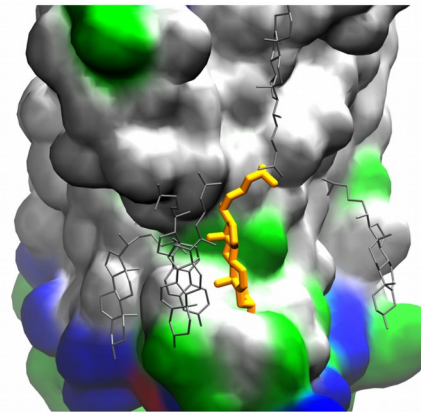
distance to bound configuration (DBC)

= ligand RMSD in *receptor's frame of reference*

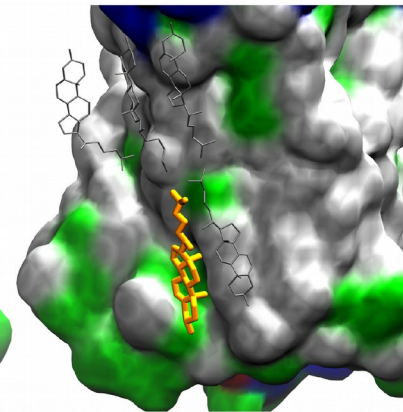
- captures **ligand** position, orientation and conformation
- independent of **receptor** position, orientation, and conformation



β 2-Adrenergic
3D4S
 $x_{50} = 10^{-9}$



5-HT2B
4NC3
 $x_{50} = 10^{-2}$

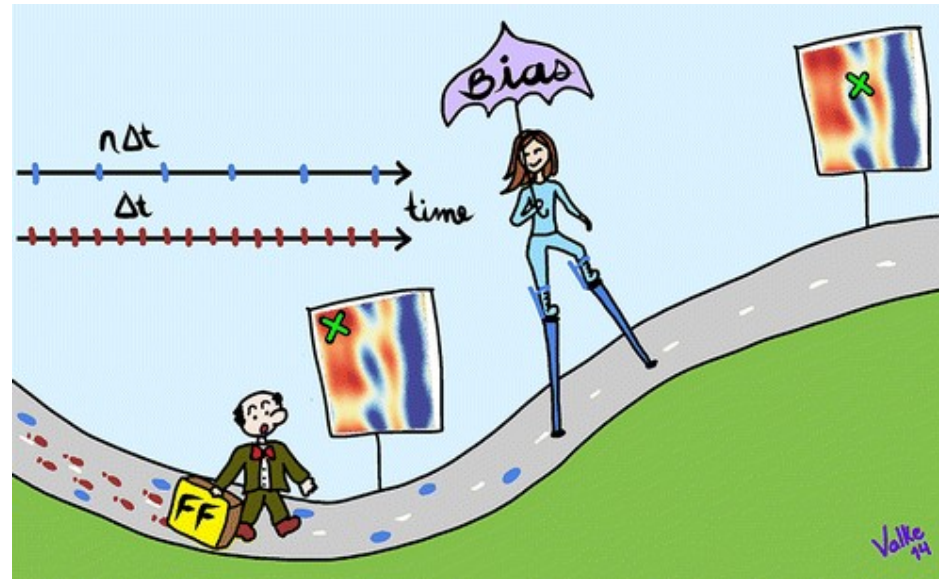


μ -Opioid
5C1M
 $x_{50} = 0.7$

GPCR-cholesterol binding affinities

Brannigan, Hénin & coworkers, in press

Multiple time-step colvars



- Bussi and coworkers (Ferrarotti et al. 2014)
- colvar forces are *slow forces*
- colvars can be coarse-grained in time
- biasing forces on colvars integrated at coarse time using impulses as in r-RESPA
- extended-Lagrangian case *explicit* coarse-time dynamics

Write your own bias (WYOB)

Adiabatic Bias MD (Marchi et al. 1999) pushes a variable with a “ratchet potential” that follows the variables high-water mark (highest level reached)

In a few lines of Tcl/Colvars:

```
proc calc_colvar_forces { ts } {
  if { $ts == 0 } {
    set max [cv colvar $cvname value]
  }

  set x [cv colvar $cvname value]
  if { $x > $max } {
    if { $x <= $xmax } { set max $x }           ;# above high-water mark?
    ;# then raise it
  } else {
    cv colvar $cvname addforce [expr { $k * ($max - $x) } ] ;# else apply bias
  }
}
```

(<https://github.com/Colvars/colvars/blob/master/colvartools/abmd.tcl>)

The Colvars Dashboard in VMD

https://raw.githubusercontent.com/Colvars/colvars/dashboard/vmd/scripts/cv_dashboard.tcl

The screenshot displays the VMD (Visual Molecular Dynamics) interface with three main windows:

- VMD 1.9.4a12 OpenGL Display <2>**: Shows a ribbon representation of a protein structure with a small molecule (ligand) bound in the center.
- Colvars dashboard <2>**: A control panel for collective variables. It includes buttons for "Load config file", "Save colvars config", and "Reset Colvars Module". A table shows the current values for defined colvars:

Colvars	Values
distance1	7.502
distance2	6.485
distance_vector	(6.422 0.7442 0.5078)

Buttons for "Edit [dbl-click]", "Interactive plot", "New", "Refresh table", and "Delete" are also present. The "Frame:" field shows 2279, and a "Track" checkbox is checked.
- MultiPlot**: A trajectory plot titled "Colvars trajectory [left-click, keyb arrows (+ Shift/Ctr) to navigate & zoom, v/h to fit vert/horizontally]". The y-axis is labeled "Value" and ranges from -15 to 35. The x-axis is labeled "Frame" and ranges from 2250 to 2850. A legend identifies five data series: distance1 (black), distance2 (red), distance_vector_1 (green), distance_vector_2 (blue), and distance_vector_3 (magenta). A vertical blue line is drawn at frame 2300, and a horizontal dashed line is at value 0.

At the bottom, the **Colvar config editor** window shows the configuration for the "distance2" colvar:

```
colvar {
  name distance2
  distance {
    forceNoPBC
    group1 {
      psfSegID XP1 XP1 XP1 XP1 XP1
      atomNameResidueRange CA 48-58
      atomNameResidueRange CA 91-94
      atomNameResidueRange CA 101-112
      atomNameResidueRange CA 148-153
      atomNameResidueRange CA 160-165
      atomNameResidueRange CA 183-188
    }
    group2 {
      psfSegID LIG
      atomNumbers 3260 3263 3266 3267 3268 3270 3271 3272 3273 3274 3275 3276
    }
  }
}
```

Buttons for "Apply [Ctrl-s]" and "Cancel" are at the bottom of the editor.

Practical tricks

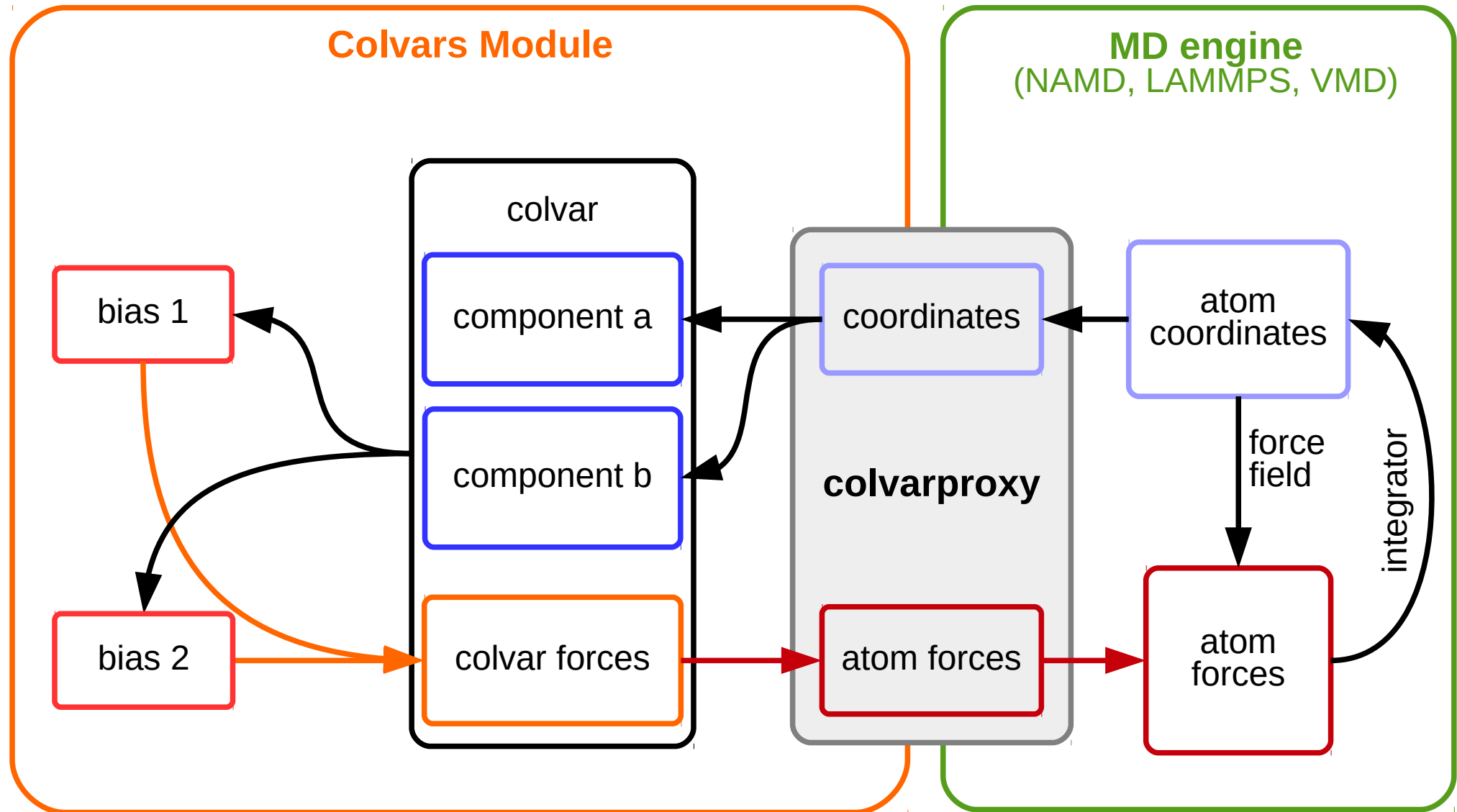
- the Colvars module can read multiple configuration files / strings
 - colvarsConfig <file> (*NAMD only*)
 - cv configfile <file>
 - cv config “<config string>”
- → you can split your input files to reuse common parts
- e.g. one file for variables only, one for biases
- config for variables can be written by [Colvars Dashboard](#) in VMD (does not handle biases)
- depending on workflow, most **convenient definition of atom groups**:
 - index file (see tma-aco/Common/write_index_file.tcl)
 - PDB files with flags
 - atom ID lists from VMD selections (Colvars Dashboard)

Performance-tuning tricks

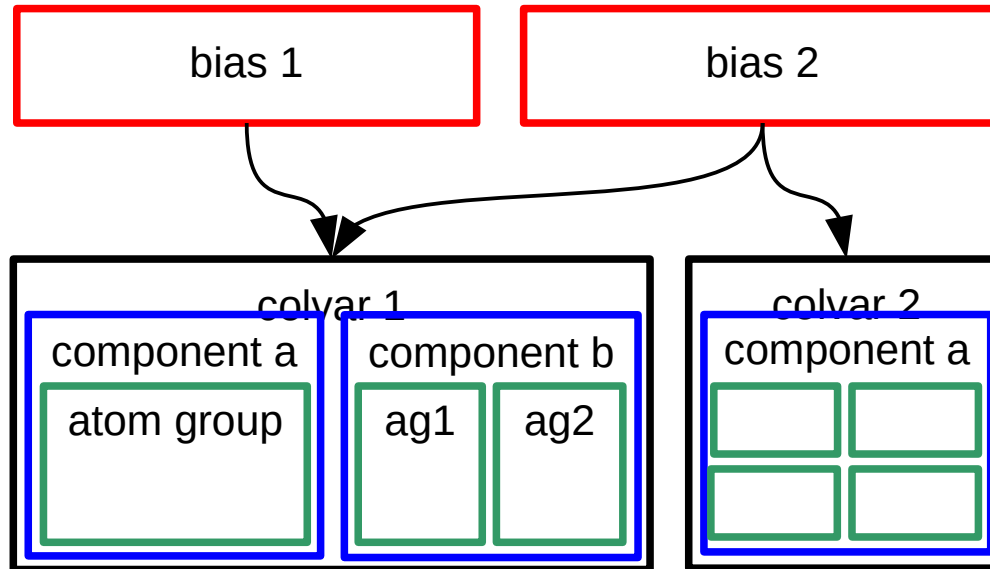
- NAMD is highly parallelized
- Colvars is only partially parallelized → can be a bottleneck
- benchmark your own system and colvars on production hardware
- optimizations:
 - use no more atoms than necessary (eg. RMSD on alpha carbons)
 - variables that depend on **centers of mass** scale better
 - have multiple colvars? Make sure **SMP** feature is enabled
 - use **multiple-timestep** colvars if possible
(first, test carefully for physical consistency; fullElectFreq is often safe)
 - if not all variables are needed at all times, write script setting **cvcflags**
(see pathCV example), or even creating or deleting colvars on-the-fly

under the hood: a developer's view

Interface with MD engines: the *colvarproxy* class



The dependency problem in a modular code



- hierarchy of objects

- objects have many features that can be combined
- modular combinations are key to functionality
- originally dependencies implemented as control structures in the code
- very hard to maintain there are more use cases than we can think of

Draft dependency tree

cvm scripts

bias

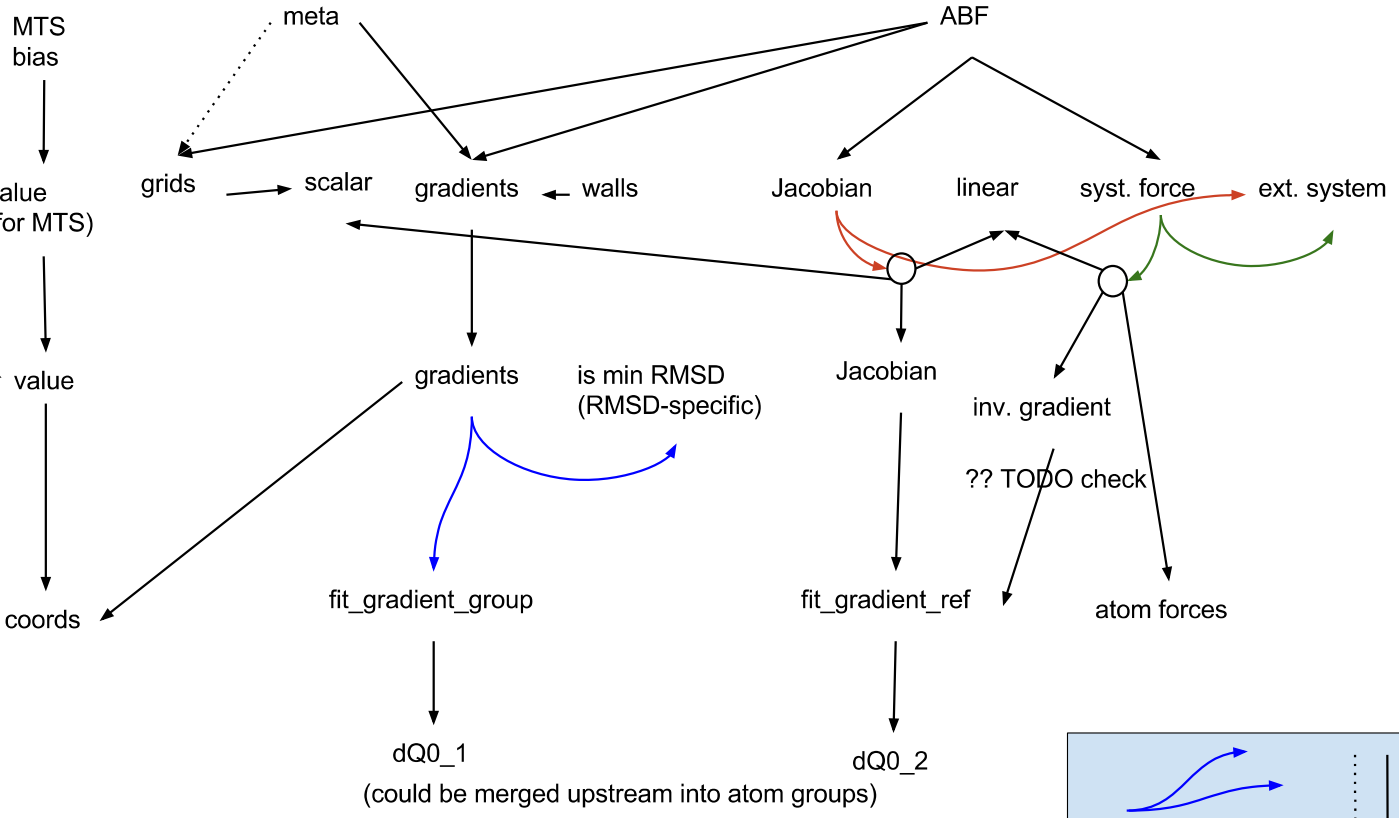
variable-cvc colvar (eg path)

value

coords

group

group.rotation



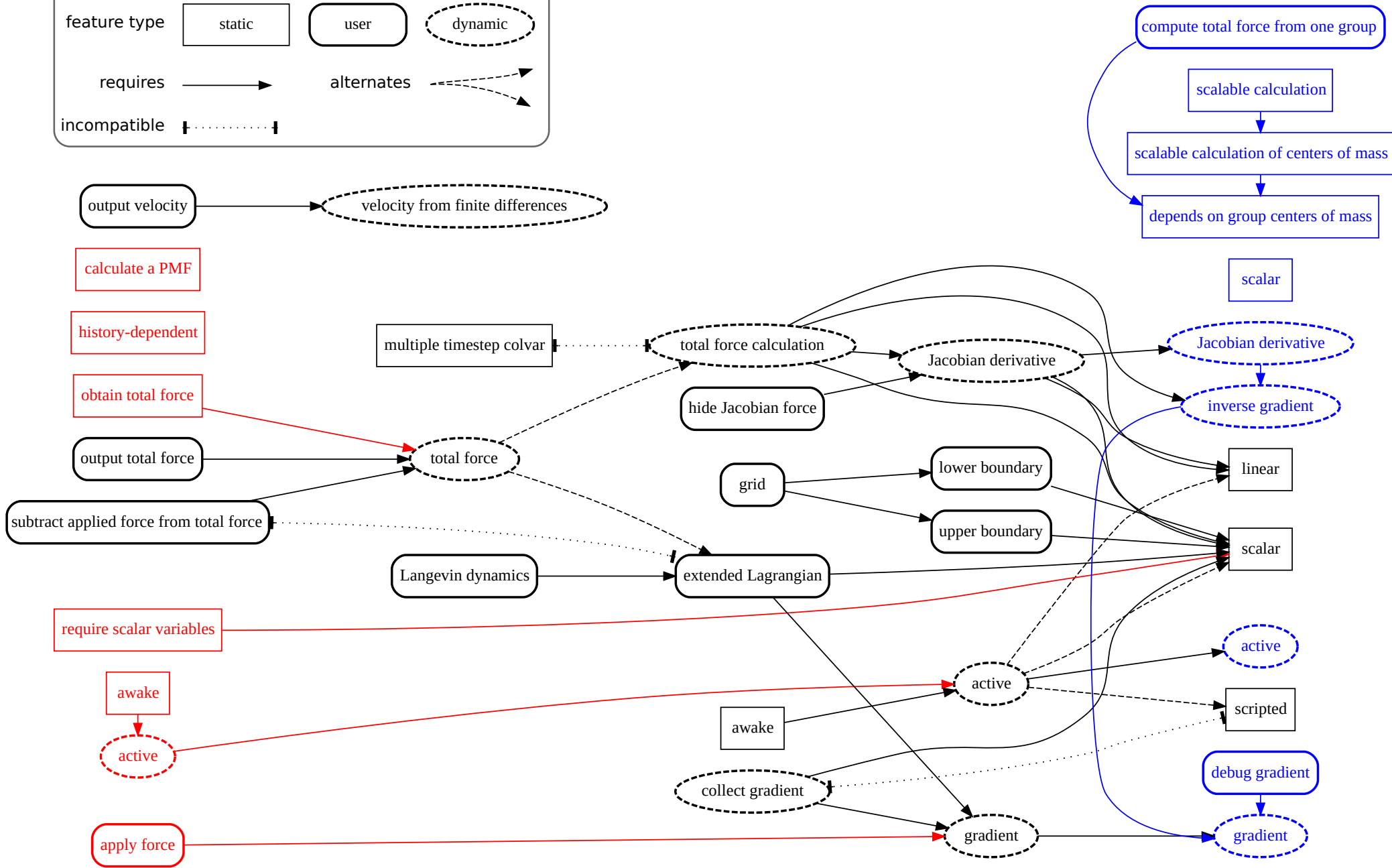
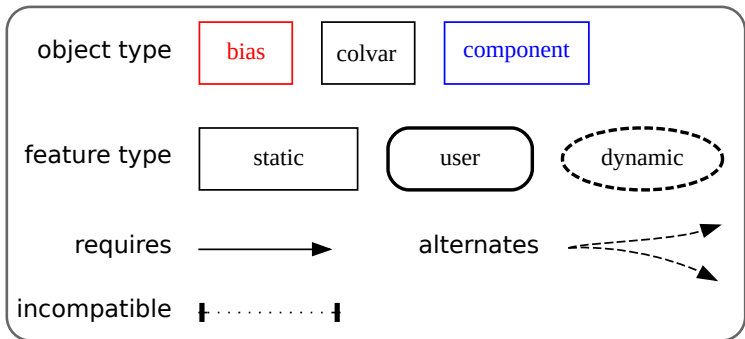
alternate requires

(occasional) requires

combined requires

Current dependency tree

(generated from the code)



(See Mr. Coffin's Grant) The creation of officers has
it has been withheld - Indeed, it has been a long
time since any noteworthy Grant had a line to you
shall I according to the usual style, or formality of your
phrase give an apology for my long delay in answering
know you will say 'tis needless, come promptly & willingly
pardon humbly to write whatever my capricious
imagination may suggestly present
me to you it should be a letter of praise
I might say it is a letter of praise
to raise the
fury of your
to my
and
some
with the idea of

W. Martin
Manila

May 21 1862
Franklin Dec 10 1862

For instructions how to apply
to your & I am in haste

W. Martin
Manila

Be a most truly reliable
to the Major-General
Papers & Papers
Army & Army

Dear Quarters
Washington Virginia
Dec 10 1862

W. Martin
Manila

W. Martin
Manila

W. Martin
Manila



W. Martin
Manila