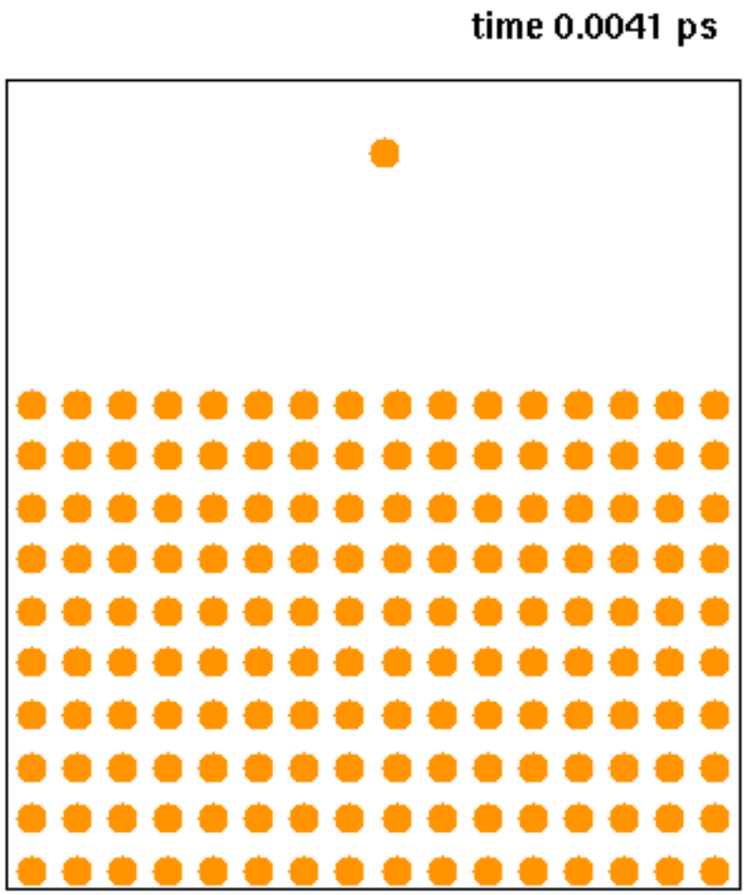
PLUMED
An introduction

Giovanni Bussi
Statistical and Biological Physics Sector
SISSA, Trieste, Italy

bussi@sissa.it
www.sissa.it/~bussi
srnas.sissa.it

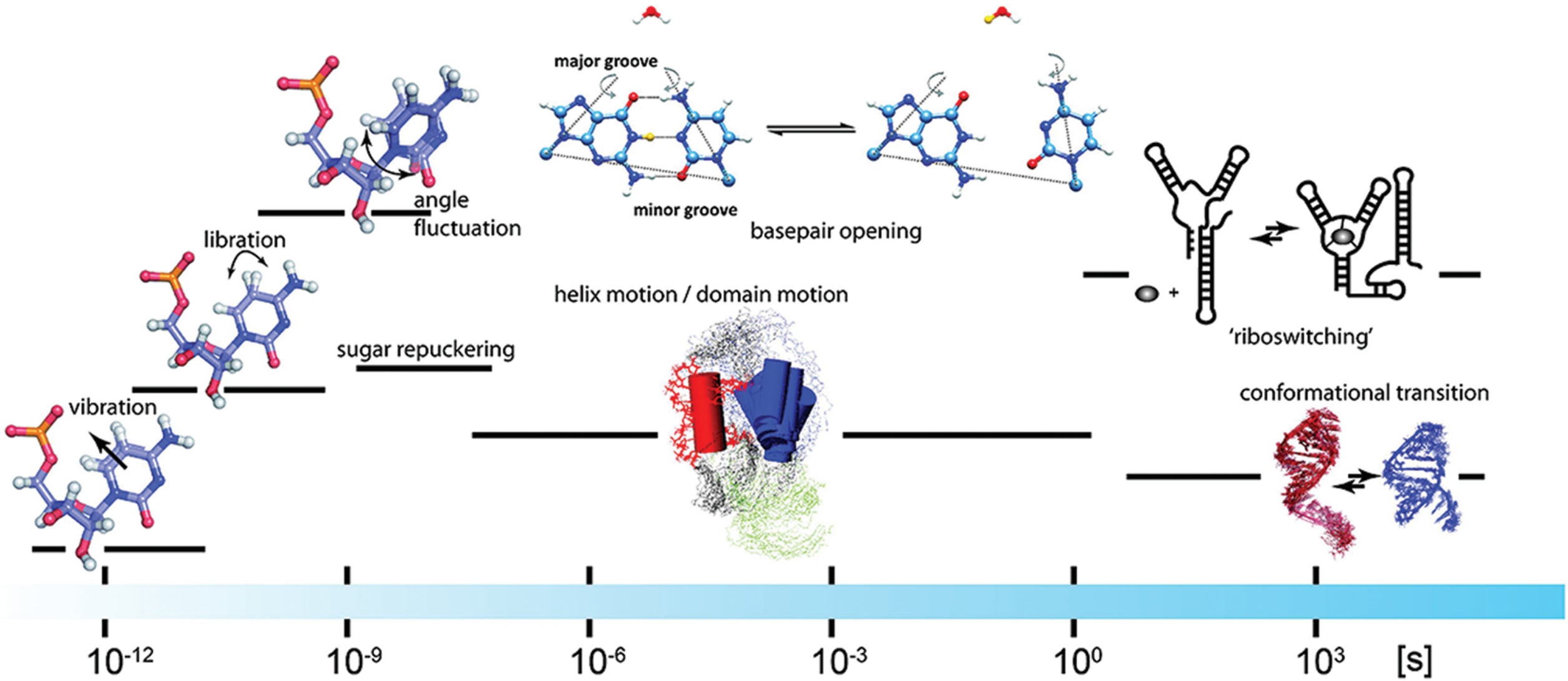
Molecular dynamics



Molecular dynamics (MD) is a form of computer simulation wherein atoms and molecules are allowed to interact for a period of time under known laws of physics, giving a view of the motion of the atoms

http://en.wikipedia.org/wiki/Molecular_dynamics

Timescales for, e.g., RNA dynamics

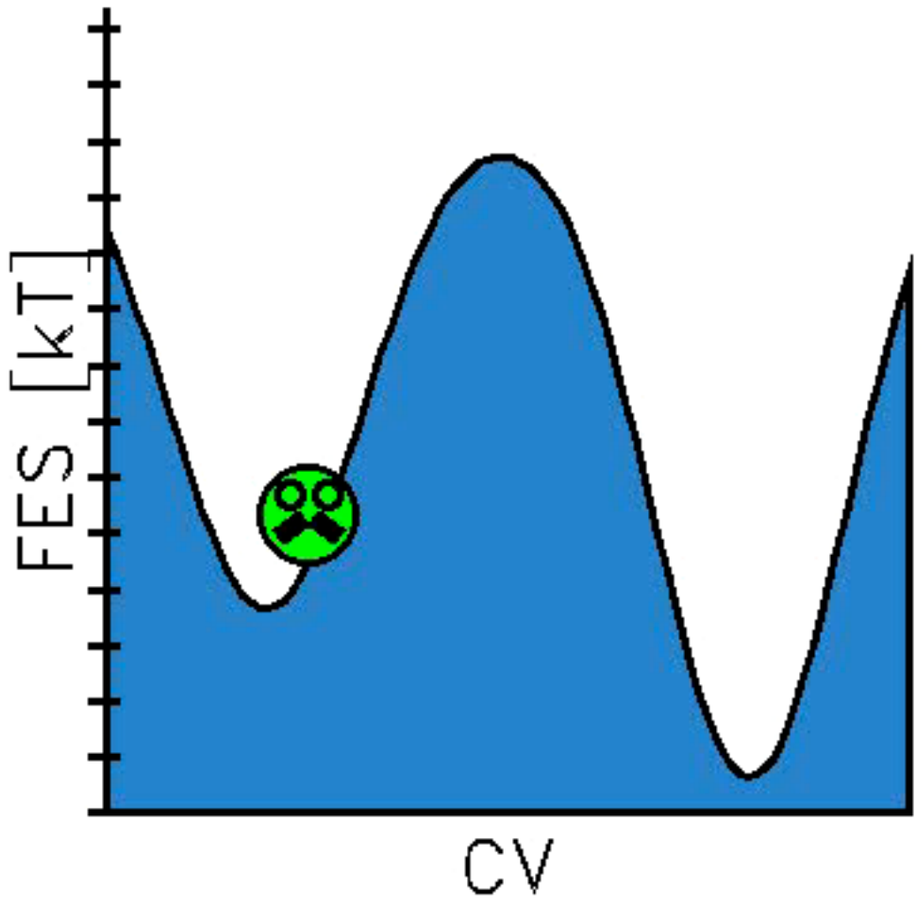


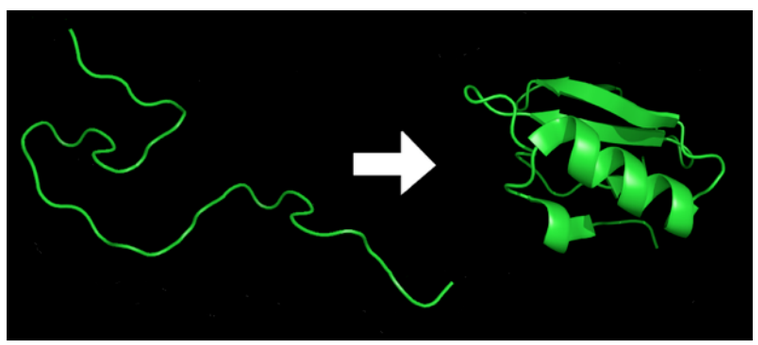
GROMACS ANTON

(normal computer) (special computer)

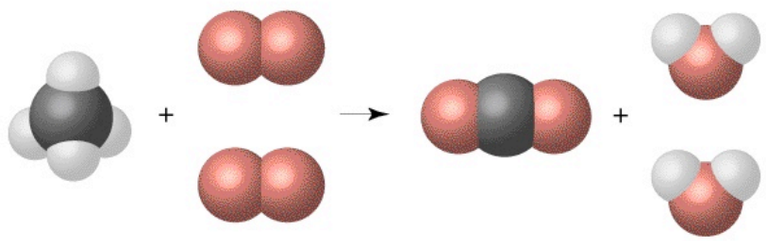
adapted from Rinnenthal, Buck, Ferner, Wacker, Fuertig, and Schwalbe Chem Res 44, 1292 (2011)

Rare events

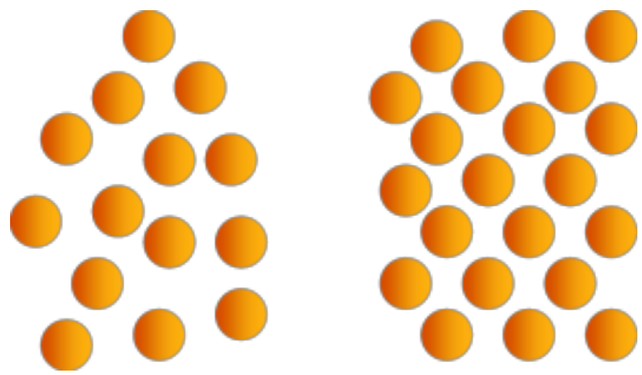




protein/RNA
folding/rearrangement

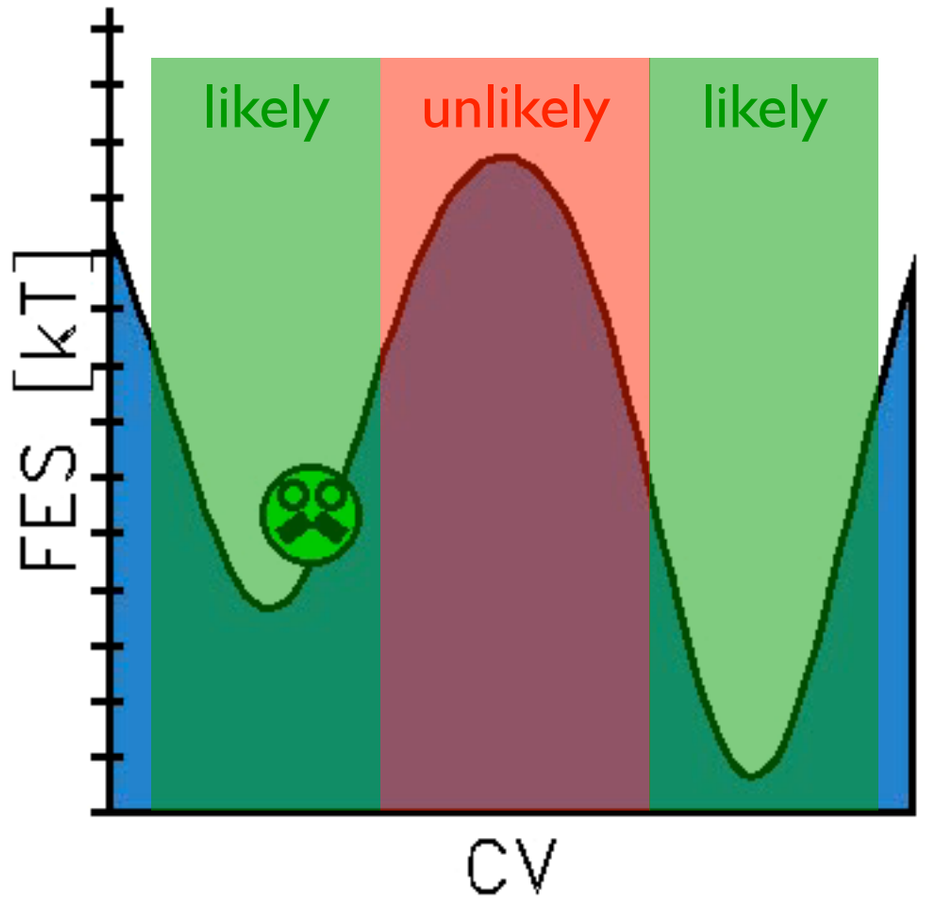


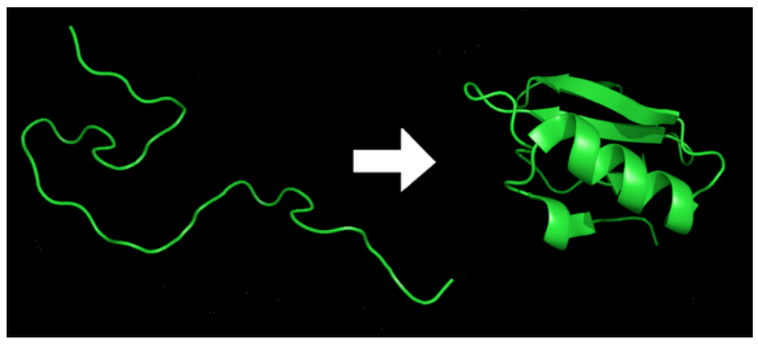
chemical reactions



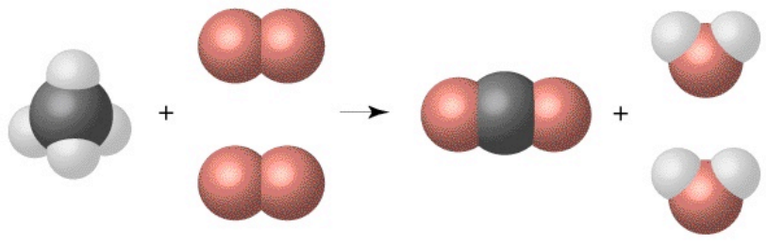
phase transitions

Rare events

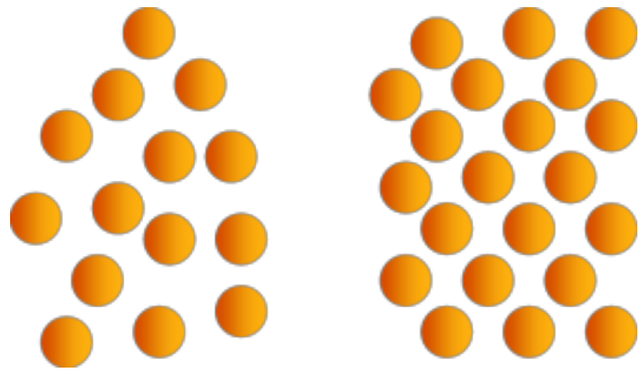




protein/RNA
folding/rearrangement



chemical reactions



phase transitions

Agenda

Tackling rare events

Introduction to PLUMED

Sample applications & recent developments

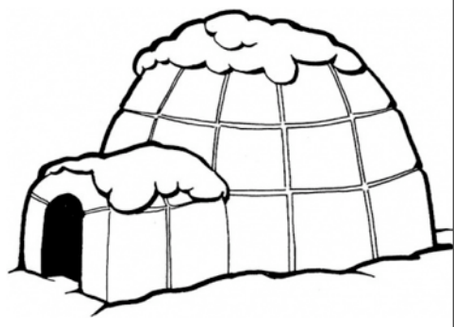
Tackling rare events

<u>Brute force</u>:
very long simulations
distributed computing
...

Tackling rare events

<u>Brute force</u>:
very long simulations
distributed computing
...

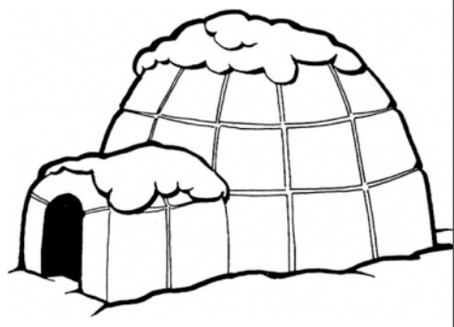
<u>Based on annealing</u>:
simulated annealing
parallel tempering
simulated tempering
...



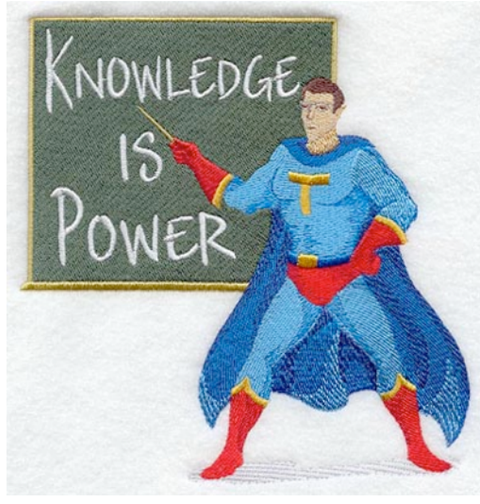
Tackling rare events

<u>Brute force</u>:
very long simulations
distributed computing
...

<u>Based on annealing</u>:
simulated annealing
parallel tempering
simulated tempering
...



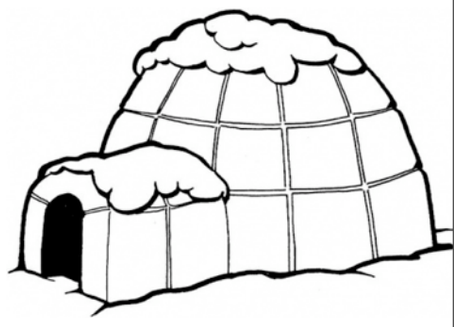
<u>Based on *a priori* physical insight</u>:
umbrella sampling
steered MD
metadynamics
adiabatic free-energy, temperature accelerated MD
...



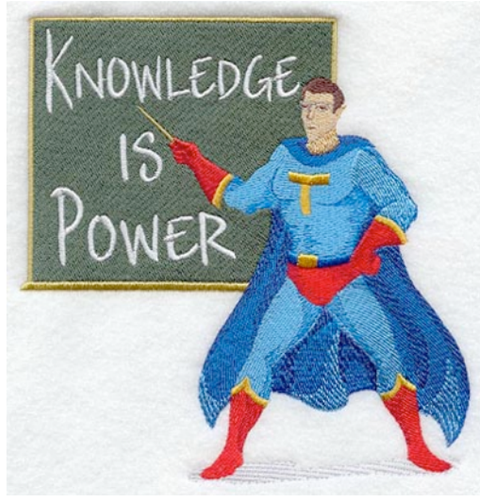
Tackling rare events

<u>Brute force</u>:
very long simulations
distributed computing
...

<u>Based on annealing</u>:
simulated annealing
parallel tempering
simulated tempering
...

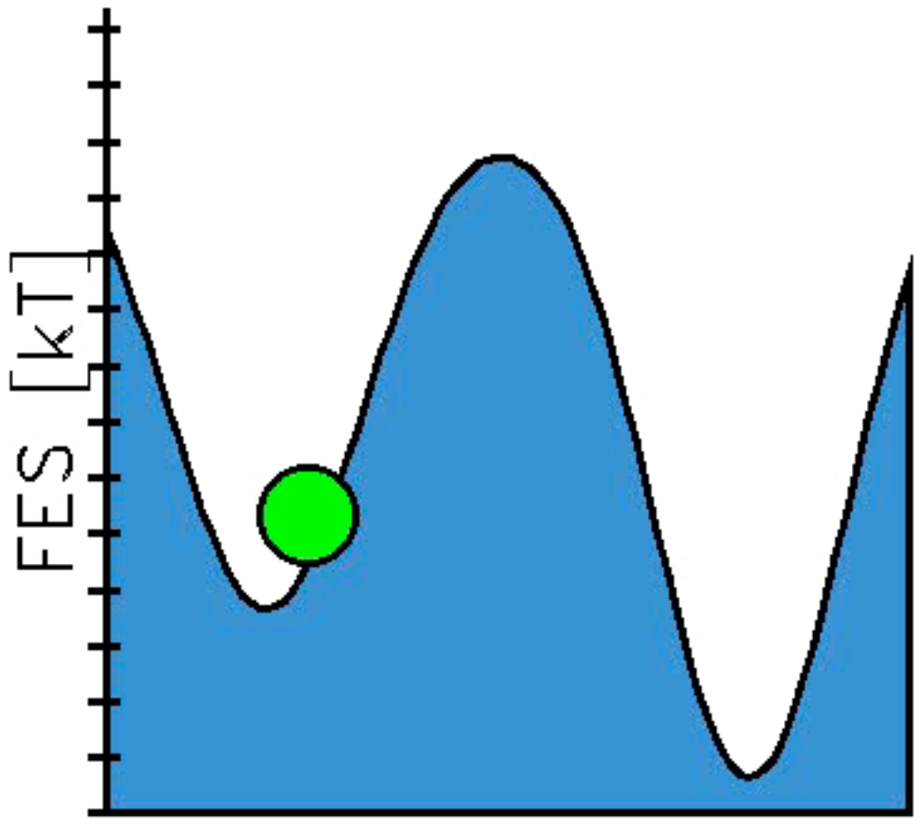


<u>Based on *a priori* physical insight</u>:
umbrella sampling
steered MD
metadynamics
adiabatic free-energy, temperature accelerated MD
...



Pulling

Steered MD



Reaction coordinate
(AKA Collective Variable)

Pulling to accelerate rare events
CV can be any possible function of the microscopic coordinates

Grubmuller, Heymann, and Tavan, Science (1996)
Jarzynsky, PRL (1997)

Filling

Metadynamics

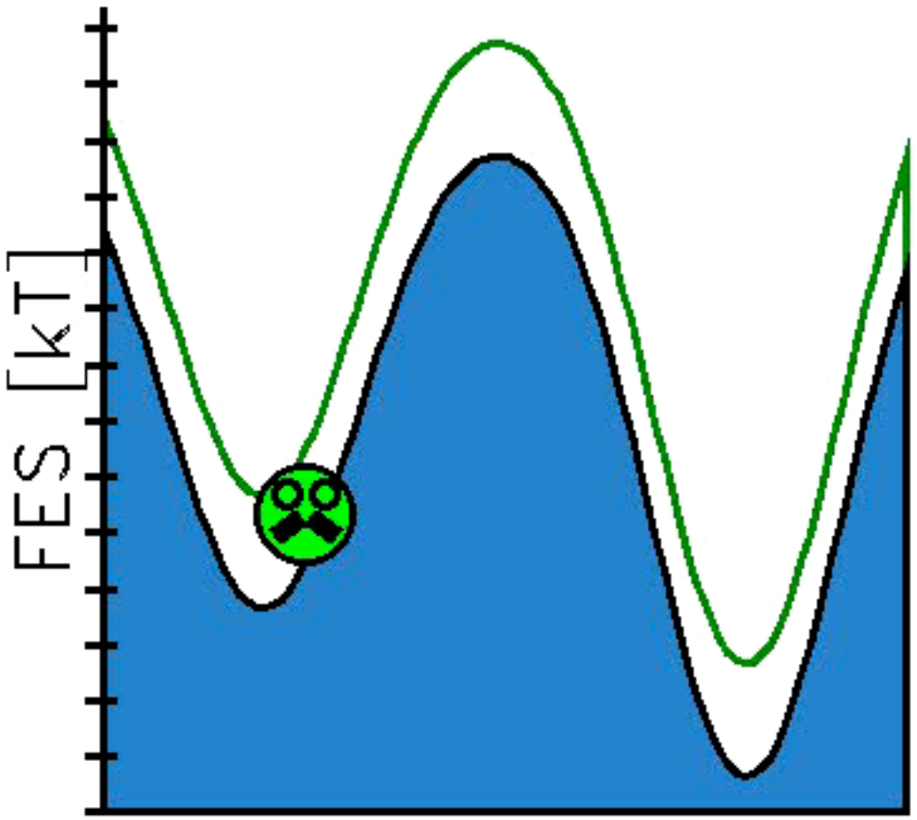
Reaction coordinate
(AKA Collective Variable)

Fill wells in free-energy landscape, then reconstruct it!

Laio and Parrinello, PNAS (2002)
Barducci, Bussi, and Parrinello, PRL (2008)

Filling

Metadynamics



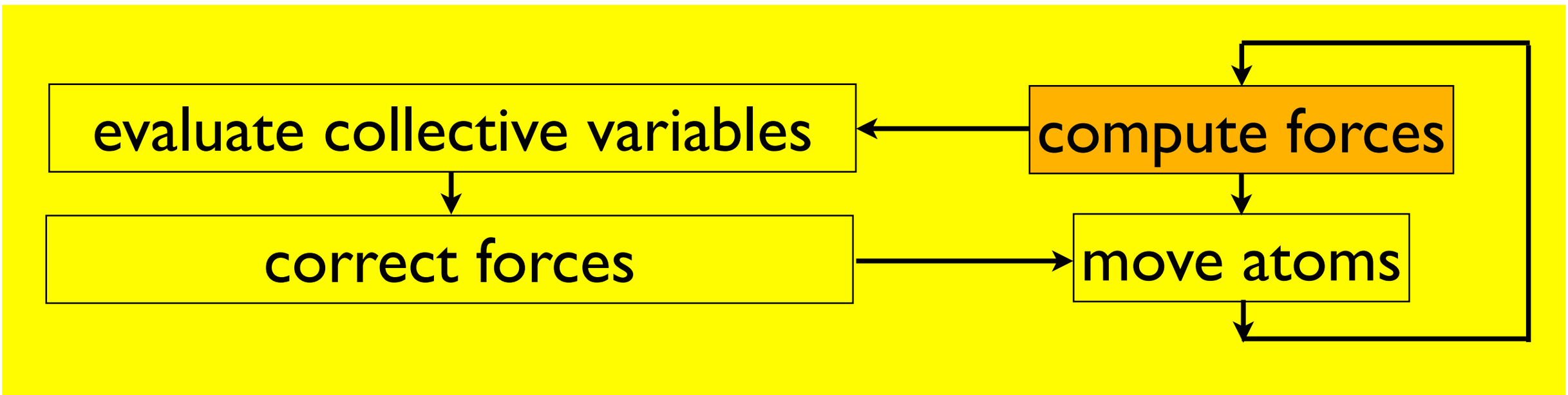
Reaction coordinate
(AKA Collective Variable)

Fill wells in free-energy landscape, then reconstruct it!

Laio and Parrinello, PNAS (2002)
Barducci, Bussi, and Parrinello, PRL (2008)

Actual implementation

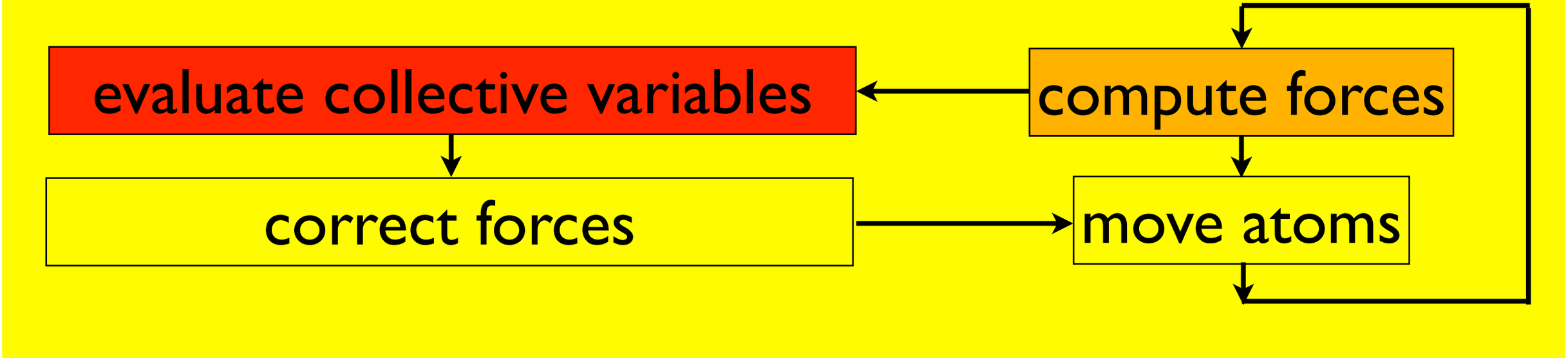
depending on physical problem/type of machine/...



Actual implementation

depending on the physical problem: distances, angles, ...

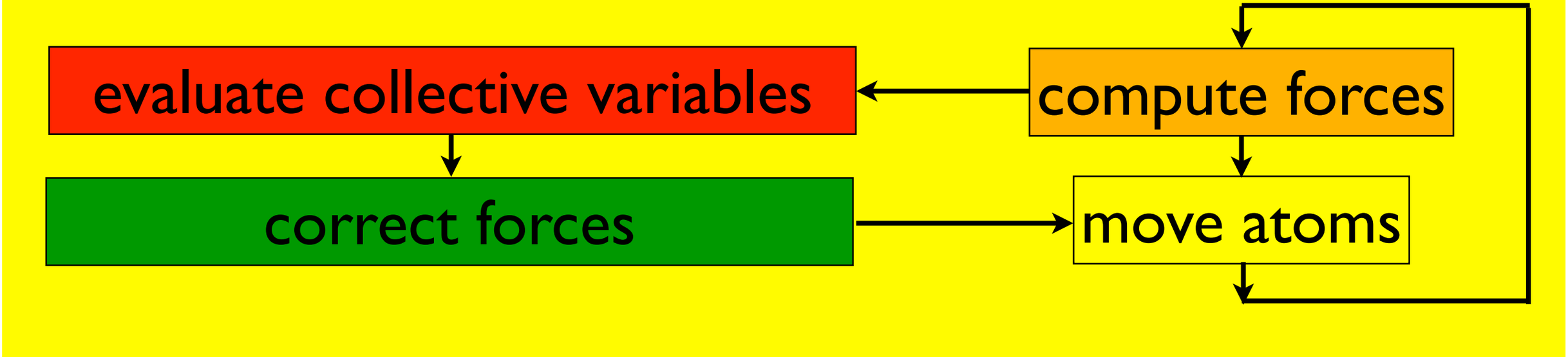
depending on physical problem/type of machine/...



Actual implementation

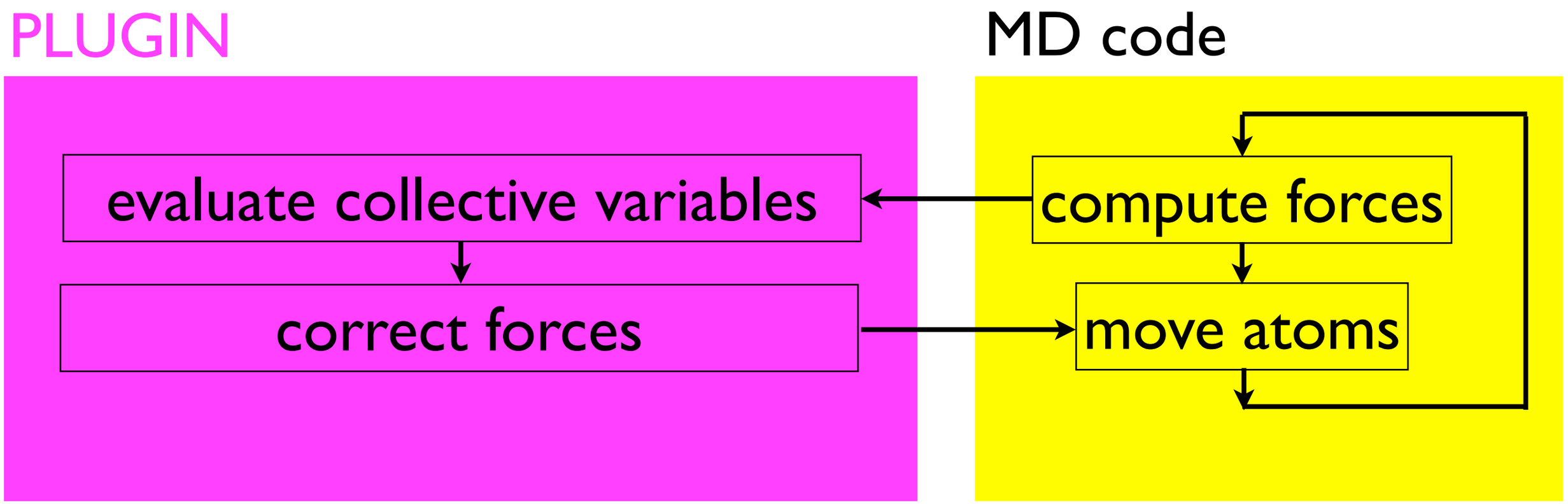
depending on the physical problem:
distances, angles, ...

depending on physical
problem/type of machine/...



several possible algorithms
e.g. steered MD, metadynamics, ...

PLUMED (born 2008)



Bonomi, Branduardi, Bussi, Camilloni, Provasi, Raiteri,
Donadio, Marinelli, Pietrucci, Broglia, and Parrinello, CPC (2008)

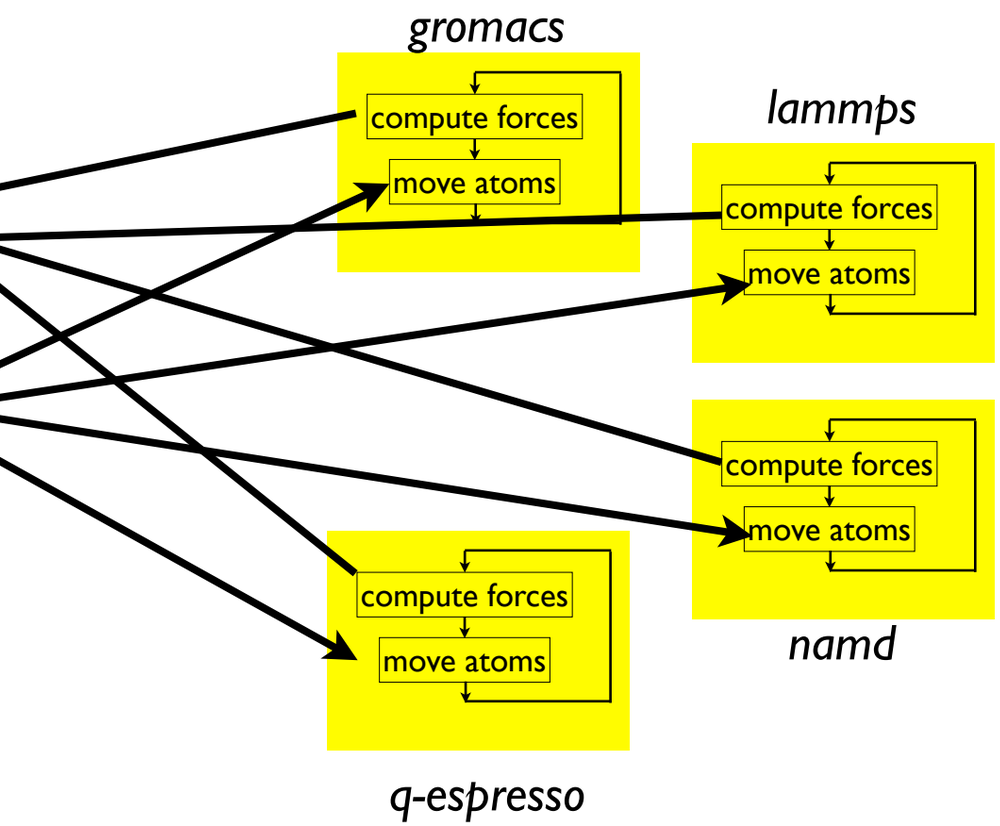
PLUMED (born 2008)

PLUGIN

evaluate collective variables

correct forces

MD codes



One open source pluging
for several MD codes!

Bonomi, Branduardi, Bussi, Camilloni, Provasi, Raiteri,
Donadio, Marinelli, Pietrucci, Broglia, and Parrinello, CPC (2009)

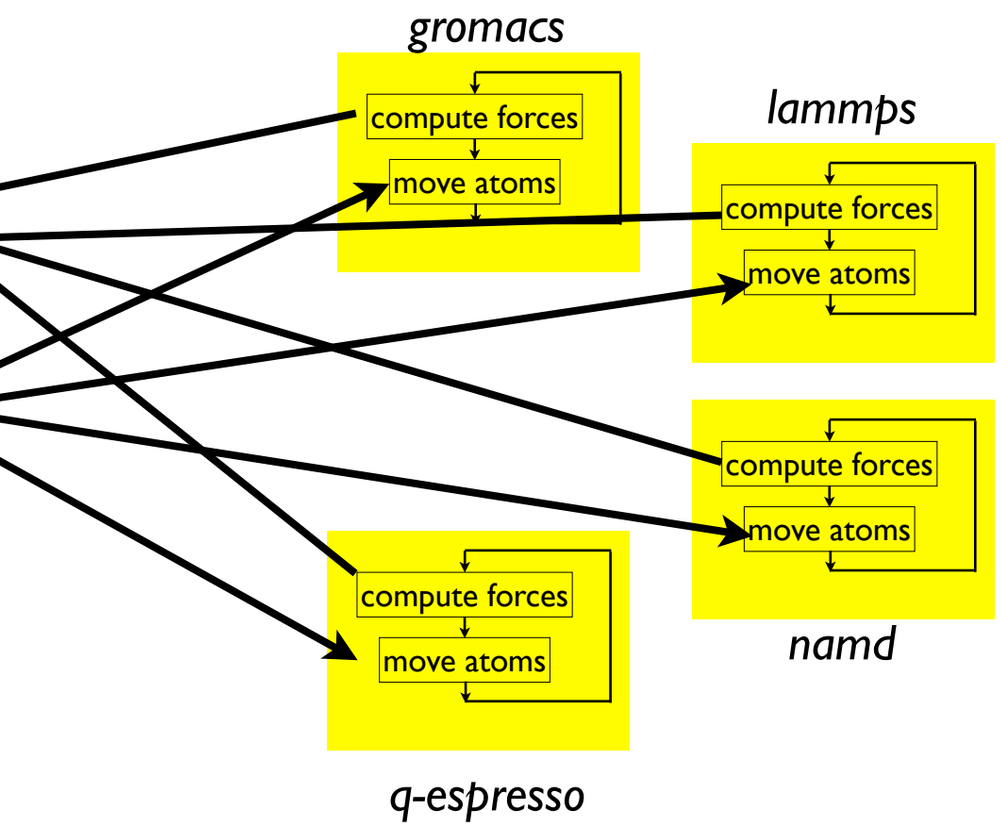
PLUMED (born 2008)

PLUGIN

evaluate collective variables

correct forces

MD codes



One open source pluging
for several MD codes!

Why **PLUMED**?

Bonomi, Branduardi, Bussi, Camilloni, Provasi, Raiteri,
Donadio, Marinelli, Pietrucci, Broglia, and Parrinello, CPC (2009)

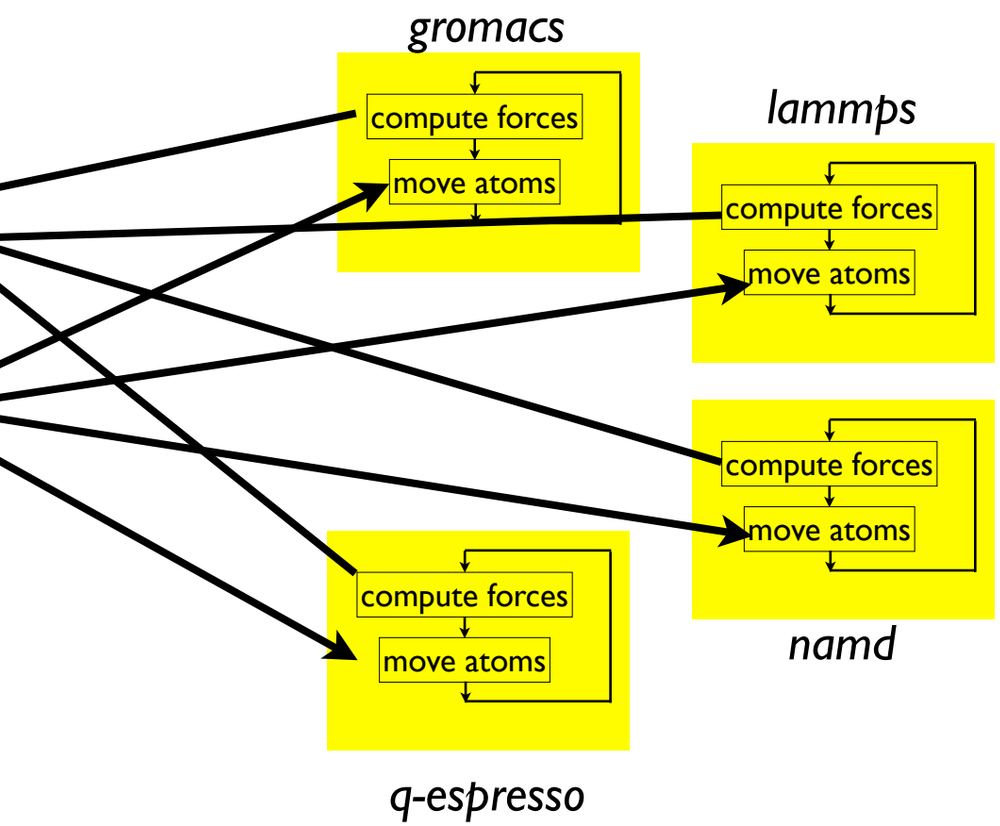
PLUMED (born 2008)

PLUGIN

evaluate collective variables

correct forces

MD codes



One open source pluging
for several MD codes!

PLUgin for **ME**ta**D**ynamics

Why **PLUMED**?

Bonomi, Branduardi, Bussi, Camilloni, Provasi, Raiteri,
Donadio, Marinelli, Pietrucci, Broglia, and Parrinello, CPC (2009)

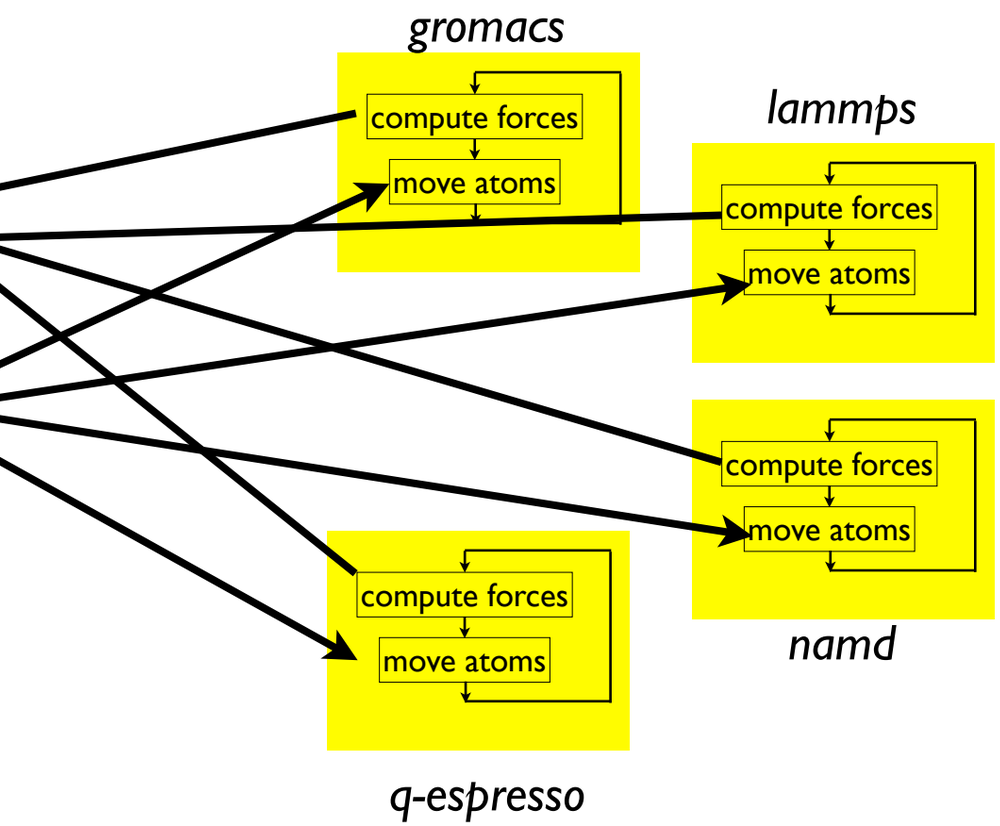
PLUMED (born 2008)

PLUGIN

evaluate collective variables

correct forces

MD codes



One open source pluging
for several MD codes!

Why **PLUMED**?

PLUgin for **ME**ta**D**ynamics

PLUgin for free-energy **ME**tho**D**s

Bonomi, Branduardi, Bussi, Camilloni, Provasi, Raiteri,
Donadio, Marinelli, Pietrucci, Broglia, and Parrinello, CPC (2009)

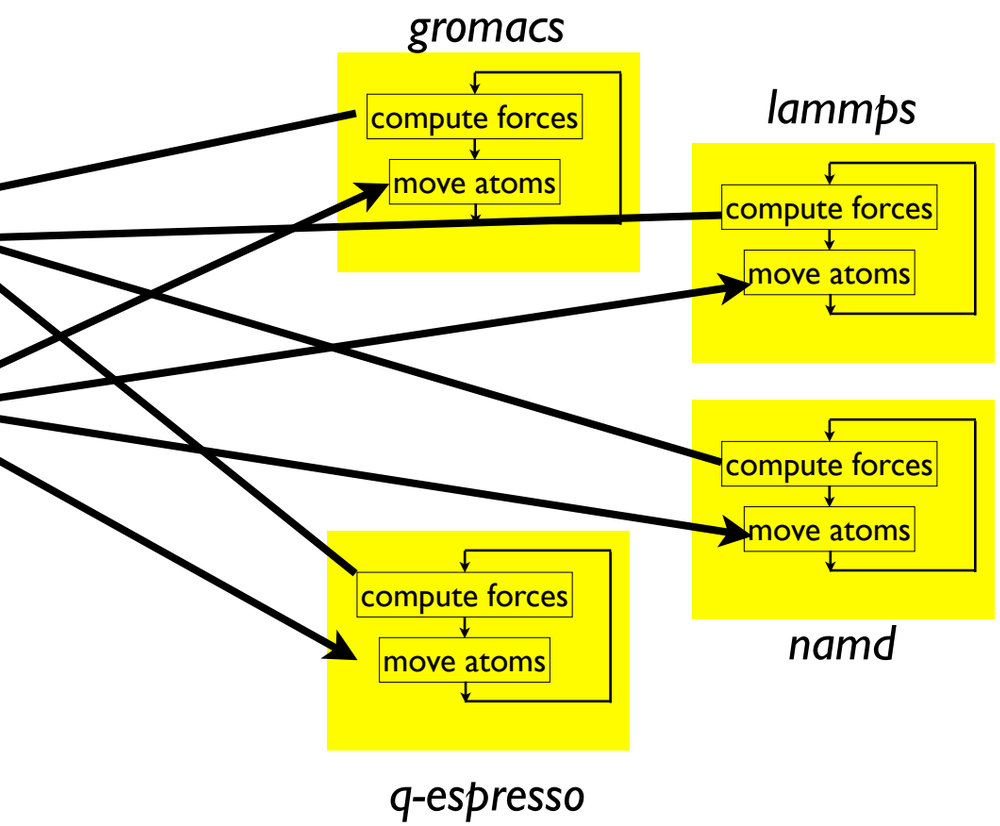
PLUMED (born 2008)

PLUGIN

evaluate collective variables

correct forces

MD codes



One open source pluging
for several MD codes!

Why **PLUMED**?

PLUgin for **ME**ta**D**ynamics

PLUgin for free-energy **ME**tho**D**s

PLUgin for **M**ol**E**cular **D**ynamics

Bonomi, Branduardi, Bussi, Camilloni, Provasi, Raiteri,
Donadio, Marinelli, Pietrucci, Broglia, and Parrinello, CPC (2009)

History

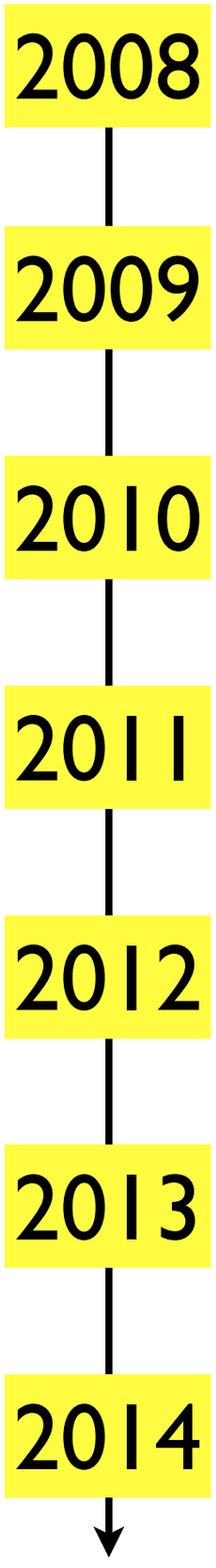
PLUMED 1.x

1.0

1.1

1.2 *CECAM tutorial*

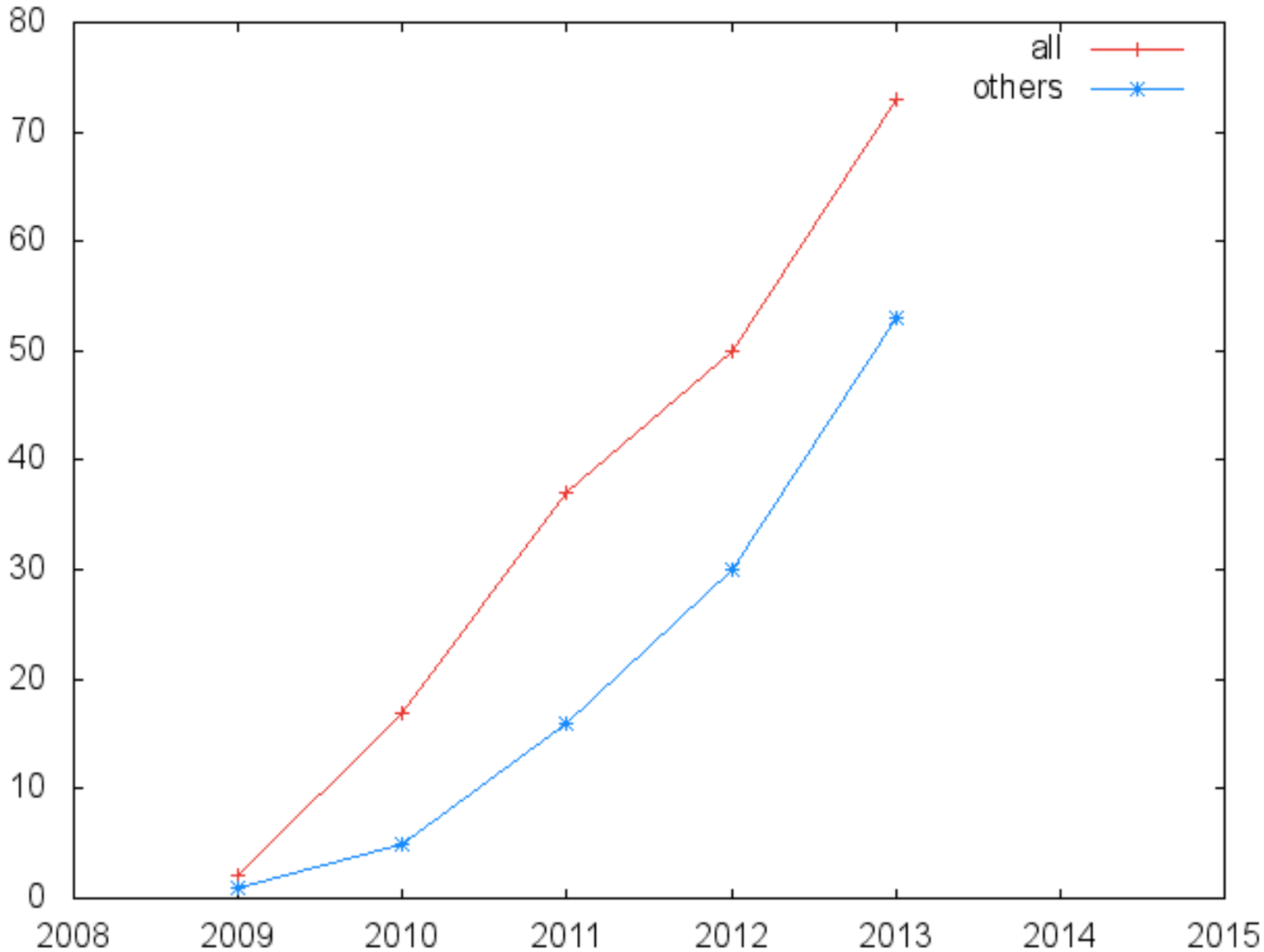
1.3



History

PLUMED 1.x		2008	PLUMED 2.x
1.0		2009	
1.1		2010	
1.2	*CECAM tutorial*	2011	development started
1.3		2012	*user meeting* beta
		2013	2.0
		2014	*CECAM tutorial+ user meeting* 2.1

A quickly growing community



Number of "external" users grows rapidly

all: ISI citations to Bonomi et al CPC (2009)
others: without authors of first paper + Laio and Gervasio

What can you do with PLUMED?

Analyze trajectories[$]

```
# using plumed as a standalone tool
plumed driver --igro traj.gro --plumed plumed.dat
```

Analyze simulations on the fly*

```
# e.g. using gromacs:
mdrun -plumed plumed.dat
```

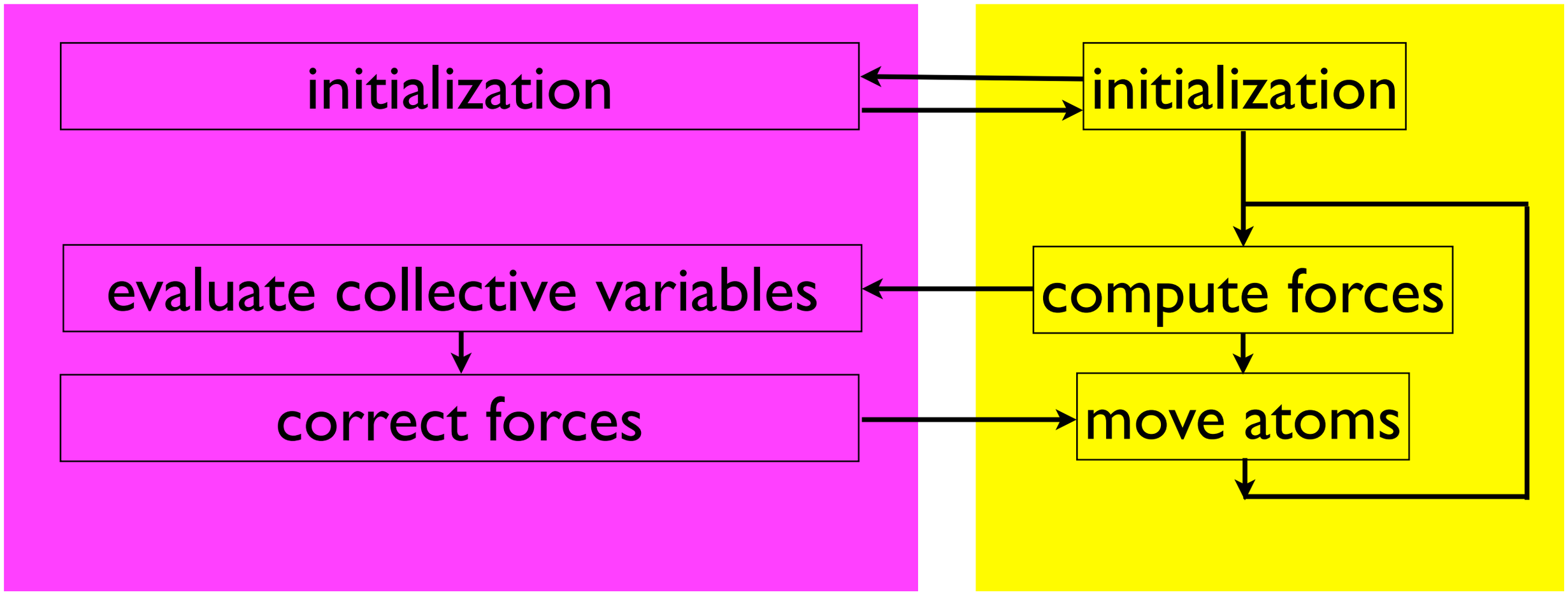
Bias simulations on the fly*

```
# e.g. using gromacs:
mdrun -plumed plumed.dat
```

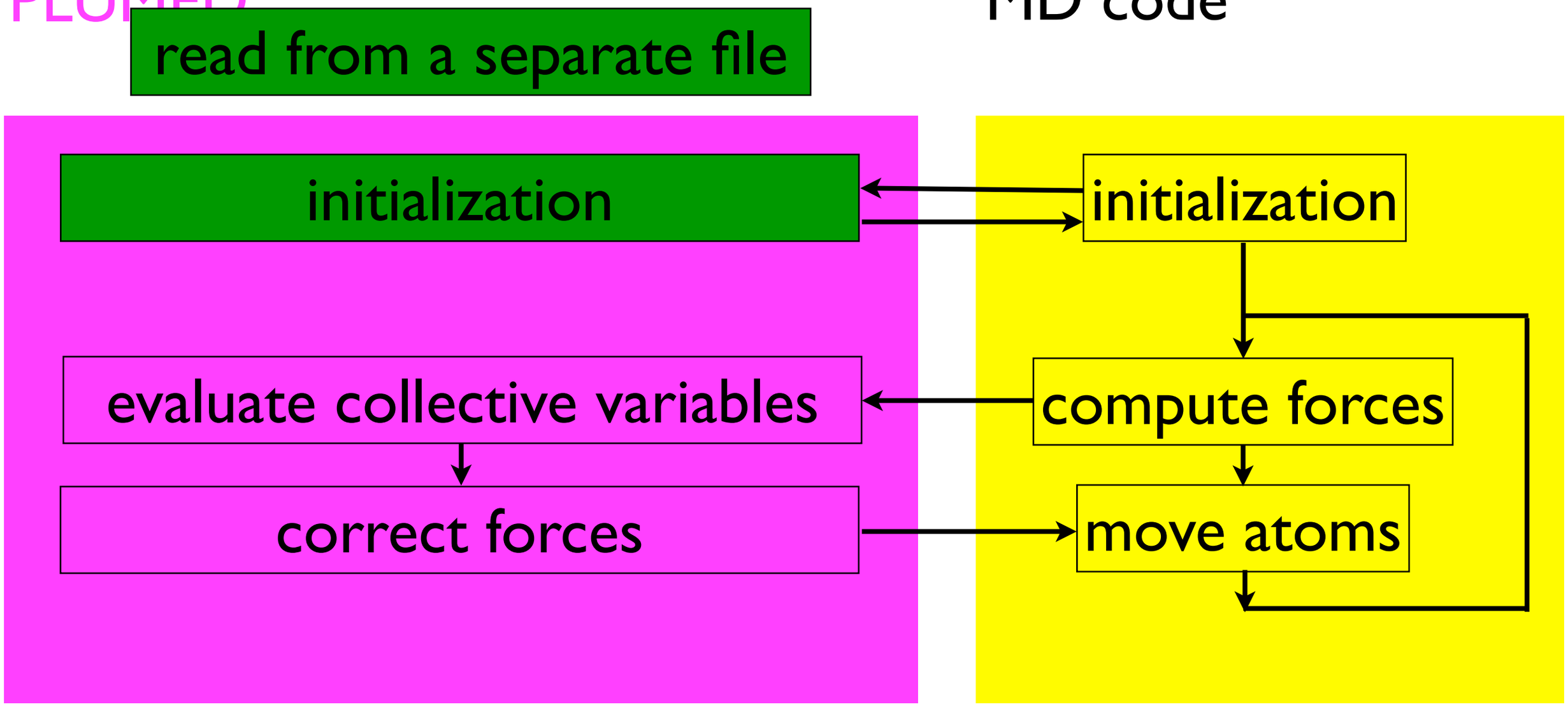
[$]from command line or from VMD - Giorgino, CPC (2014), http://github.com/tonigi/vmd_plumed

*used in combination with a supported MD engine, e.g. GROMACS, NAMD, LAMMPS, Q-ESPRESSO, AMBER + others

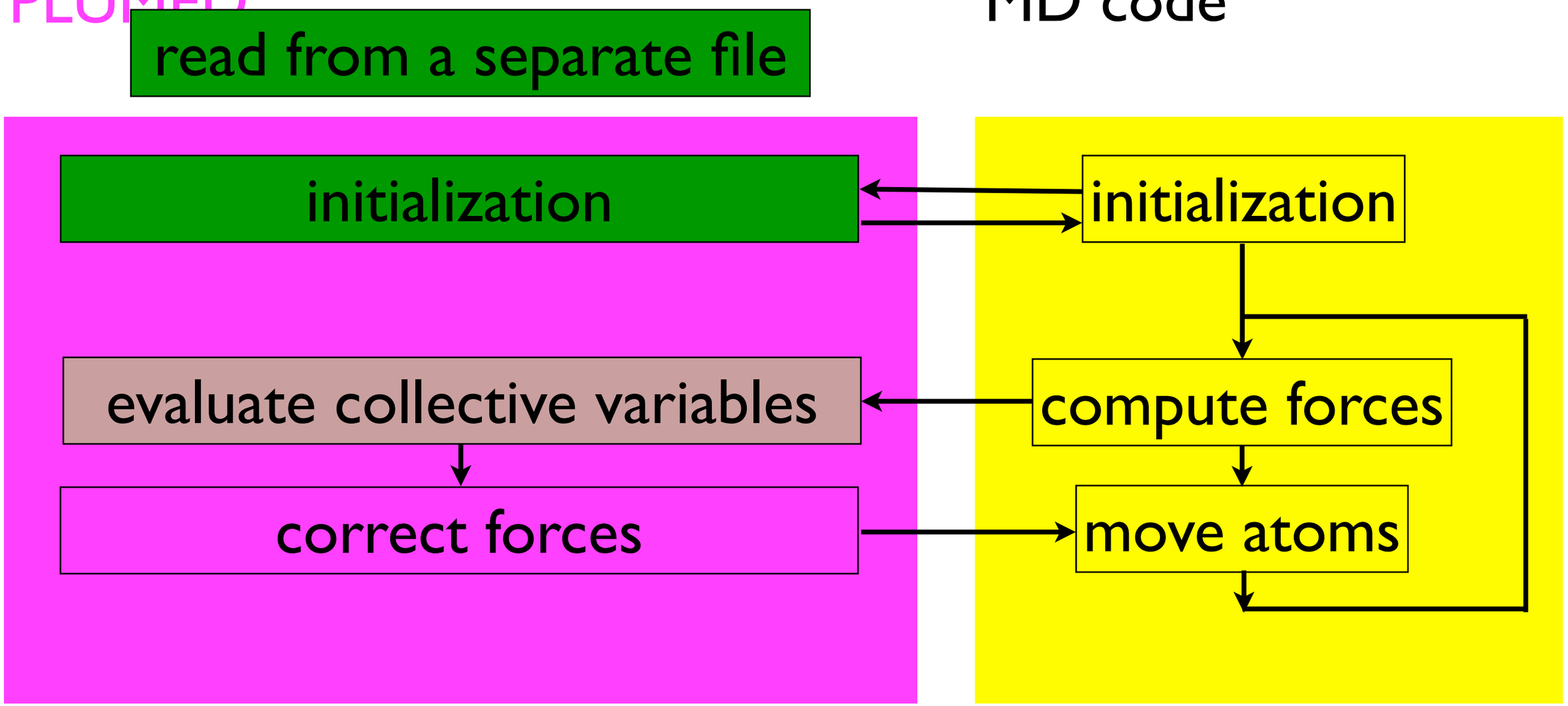
PLUMED+MD


PLUMED
MD code
initialization
initialization
evaluate collective variables
compute forces
correct forces
move atoms

PLUMED+MD


PLUMED
MD code
read from a separate file
initialization
initialization
evaluate collective variables
compute forces
correct forces
move atoms

PLUMED+MD



also derivatives w.r.t. atom positions

PLUMED+MD

PLUMED

MD code

read from a separate file

initialization

evaluate collective variables

correct forces

initialization

compute forces

move atoms

also derivatives w.r.t. atom positions

sometime using history-dependent schemes

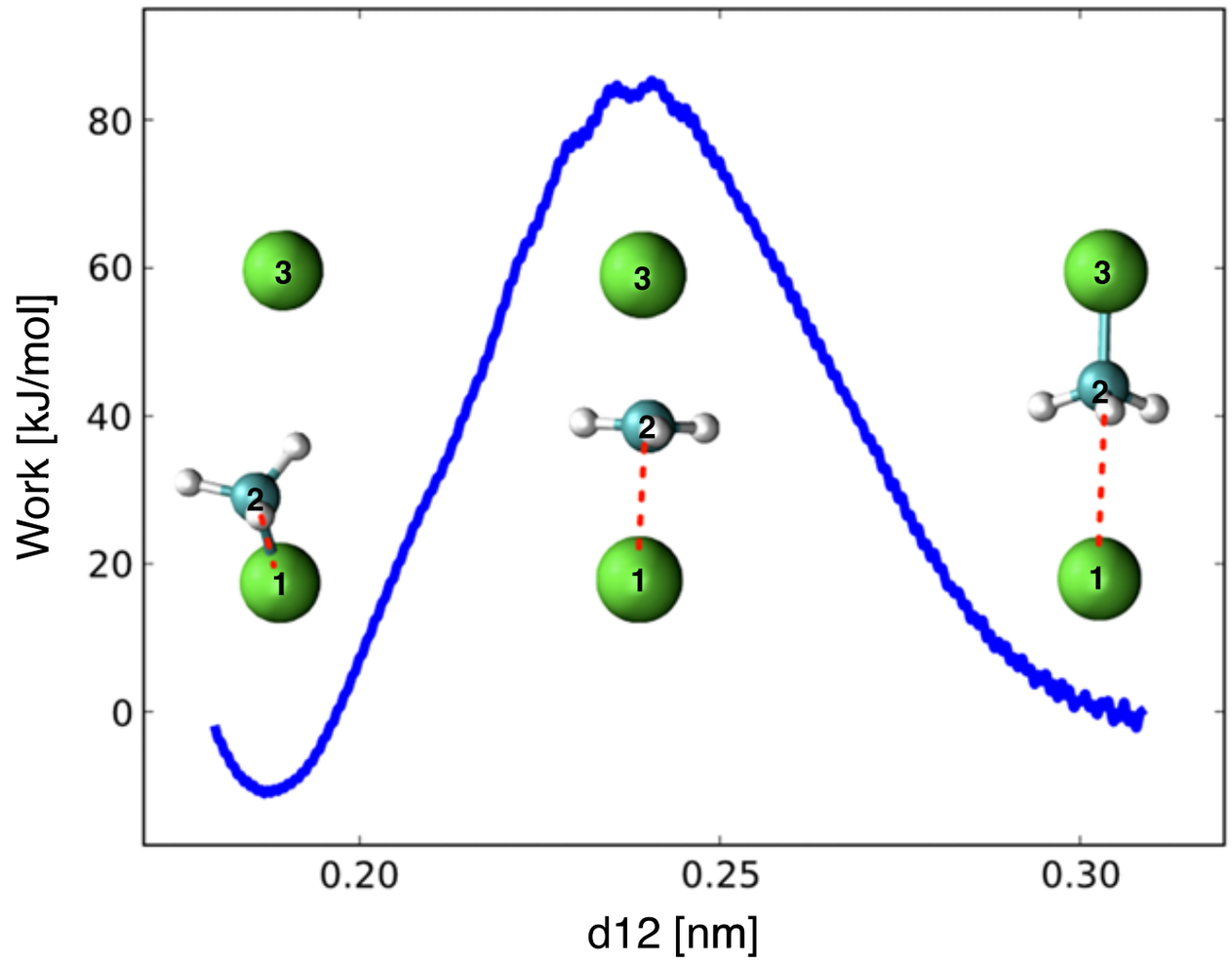
plumed.dat file

```
# Compute distances, angles, torsions, ...
c1: COM ATOMS=1-10
c2: COM ATOMS=30-40
d1: DISTANCE ATOMS=c1,c2 COMPONENTS
f1: COMBINE ARG=d1.x,d1.y,d1.z POWERS=2,2,2
a1: ANGLE ATOMS=14,15,16
t1: TORSION ATOMS=20,c1,c2,23

# Perform a metadynamics simulation
b1: METAD ARG=f1,a1 PACE=20 HEIGHT=0.5 SIGMA=0.05,0.1

# Limit the exploration to a relevant region
b2: UPPER_WALL ARG=d1.z AT=1.0 KAPPA=0.1

# Print the result
PRINT ARG=a1,t1,b1.bias,b2.bias FILE=colvar STRIDE=100
```

Syntax has changed from 1.3 to 2.0 release - much more flexible now

Example: SN2 reaction

SN2 reaction with density functional theory (QESPRESSO). Compute Cl-C distance and bias it with a moving restraint.

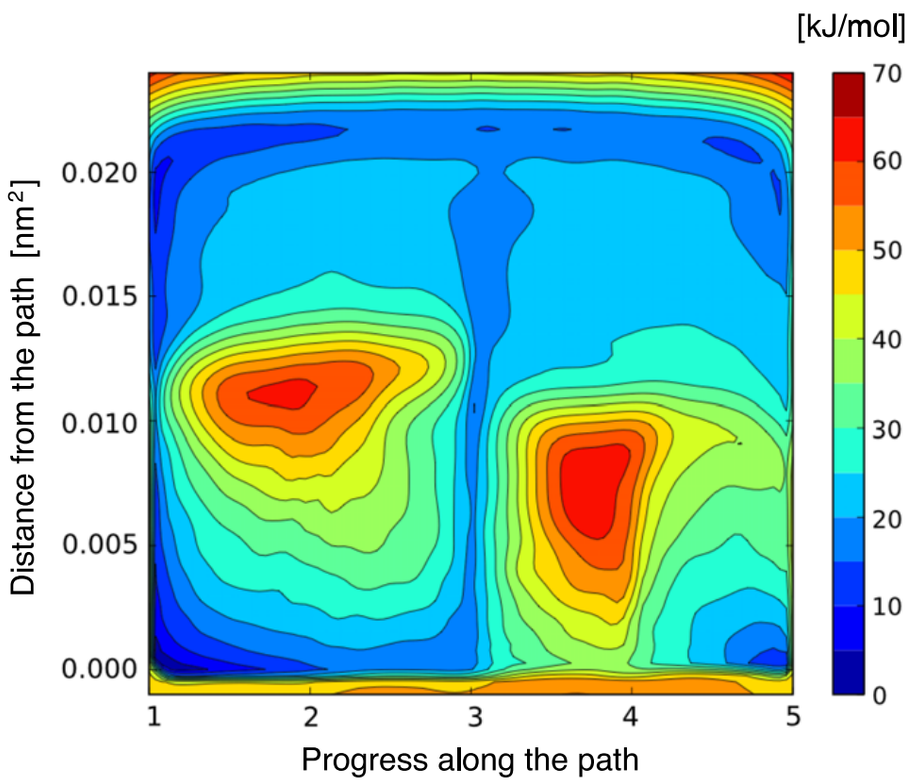



```
d12: DISTANCE ATOMS=1,2
d23: DISTANCE ATOMS=2,3
# moving restraint
MOVINGRESTRAINT ...
 ARG=d12
 STEP0=0    AT0=0.31  KAPPA0=200000.0
 STEP1=5000 AT1=0.18
 LABEL=steer
... MOVINGRESTRAINT
PRINT ...
FILE=COLVAR ARG=d12,d23,steer.d12_cntr,steer.d12_work STRIDE=1
... PRINT
```

Tribello, Bonomi, Branduardi, Camilloni, and Bussi, CPC (2014)

Example: path CV

Alanine dipeptide
Path CVs[#] + WT-MetaD[$] with adaptive Gaussians[%]
(path can be made with a single command
this is just to show input flexibility)

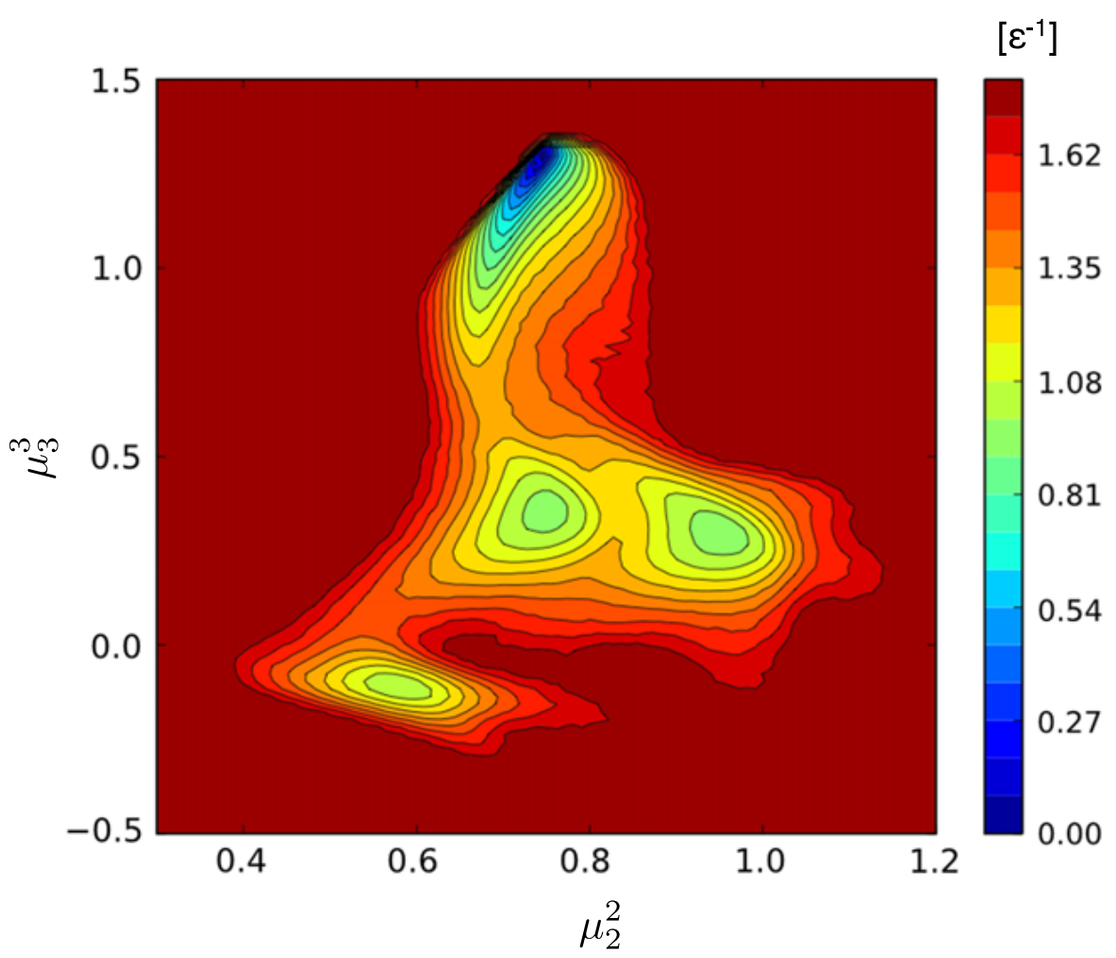



```
# just declare the RMSD^2 for five structures
t1: RMSD REFERENCE=c_1.pdb TYPE=OPTIMAL SQUARED
### ...etc for t2, t3, t4, t5 ... ###
# calculate the sum of the exp of the five RMSDs
MATHEVAL ...
 LABEL=dwn
 ARG=t1,t2,t3,t4,t5 VAR=d1,d2,d3,d4,d5
 FUNC=(exp(-770*d1)+exp(-770*d2)+exp(-770*d3)+exp(-770*d4)+exp(-770*d5))
 PERIODIC=NO
... MATHEVAL
### etc ###
# do metadynamics
METAD HEIGHT=1.2 SIGMA=0.02 PACE=60 ARG=s,z ADAPTIVE=GEOM BIASFACTOR=5 TEMP=300
```

Tribello, Bonomi, Branduardi, Camilloni, and Bussi, CPC (2014)
[#]Branduardi, Gervasio, and Parrinello, JCP (2007)
[$]Barducci, Bussi, and Parrinello, PRL (2008)
[%]Branduardi, Bussi, and Parrinello, JCTC (2012)

Example: CV distribution

Lennard-Jones cluster at high T reweighted at low T. Free energy as a function of moments of coordination number distribution*




```
COORDINATIONNUMBER ...
 SPECIES=1-7
 MOMENTS=2-3
 SWITCH={RATIONAL R_0=1.5 NN=8 MM=16}
 LABEL=c1
... COORDINATIONNUMBER
#
# calculate histograms from the moments
#
HISTOGRAM ...
 ARG=c1.moment_2,c1.moment_3 STRIDE=10
 REWEIGHT_TEMP=0.1 TEMP=0.2
 GRID_MIN=0.2,-0.5 GRID_MAX=1.2,1.7 GRID_BIN=200,440
 BANDWIDTH=0.01,0.01 KERNEL=triangular
 GRID_WSTRIDE=10000000 GRID_WFILE=histo
... HISTOGRAM
```

Tribello, Ceriotti, and Parrinello, PNAS (2010)

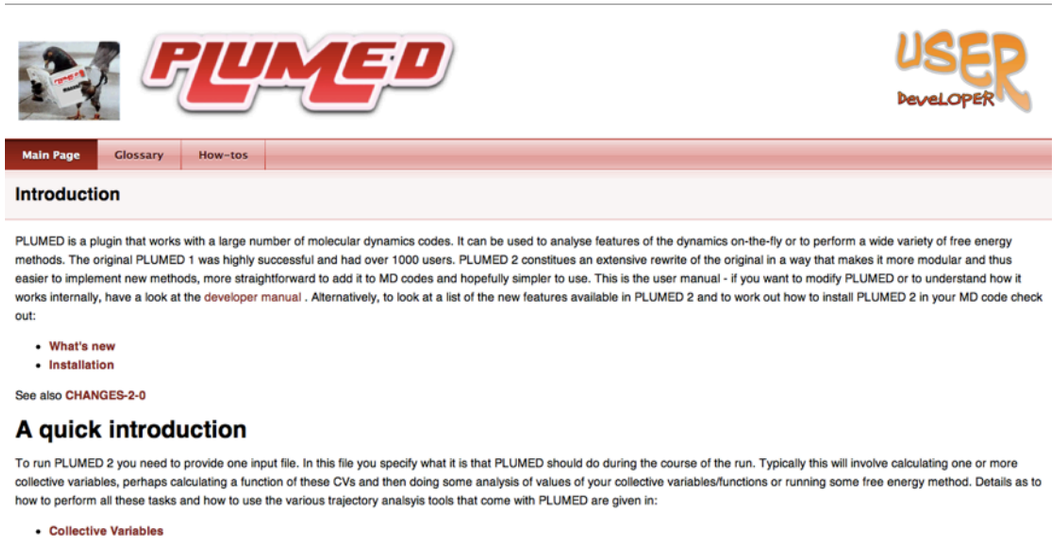
On the web

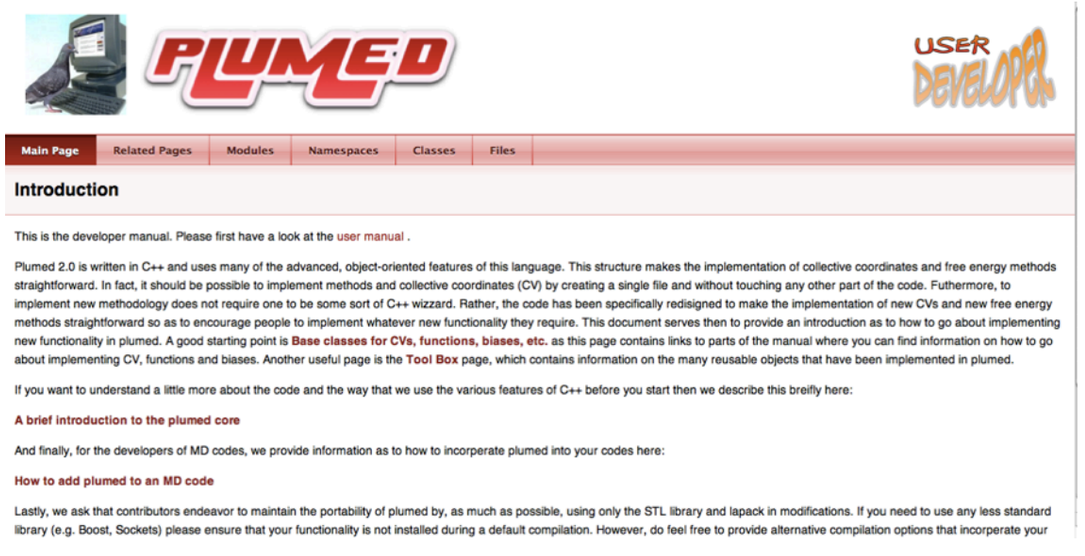
Website: http://www.plumed-code.org/

Github: http://github.com/plumed/plumed2

User & developer mailing lists

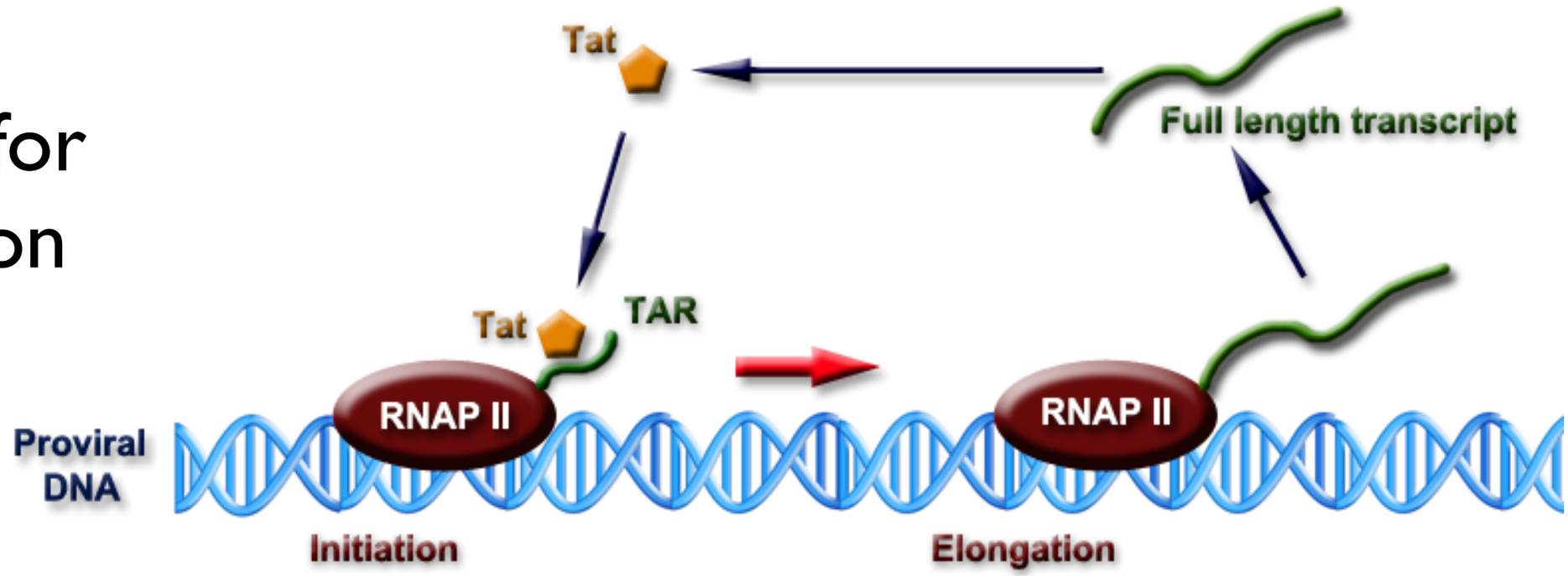
User & developer manuals + tutorials

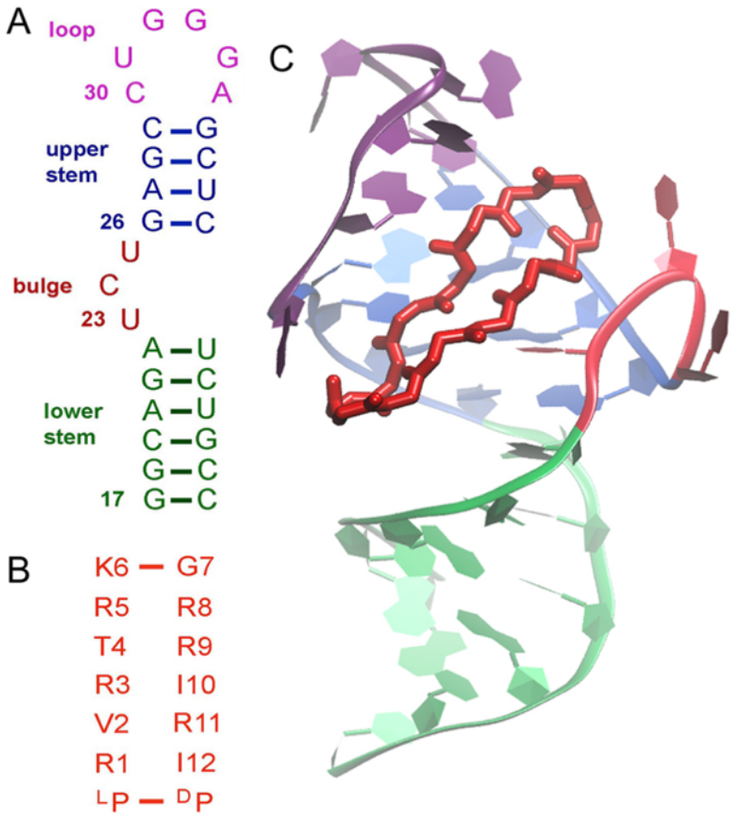




TAR-Tat binding

Crucial step for HIV replication





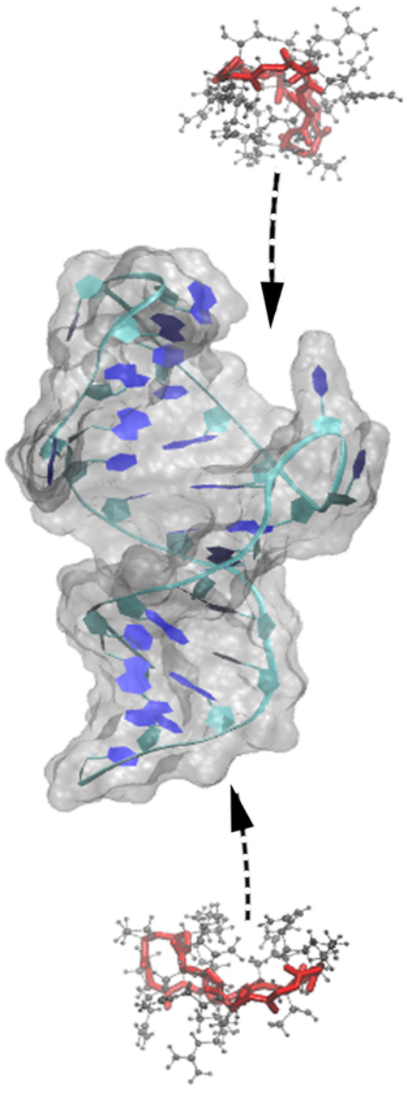
Oligopeptides mimicking TAT developed in G.Varani's lab* (UoW)

Mechanism of binding?

*Davidson et al, PNAS (2009)

Pretend binding mode is unknown

- GROMACS 4 MD code* (+PLUMED#)
- parmbsc0 force field%
- Explicit water (TIP3P$, ~12k molecules)
- Explicit counter-ions (NaCl 150mM)

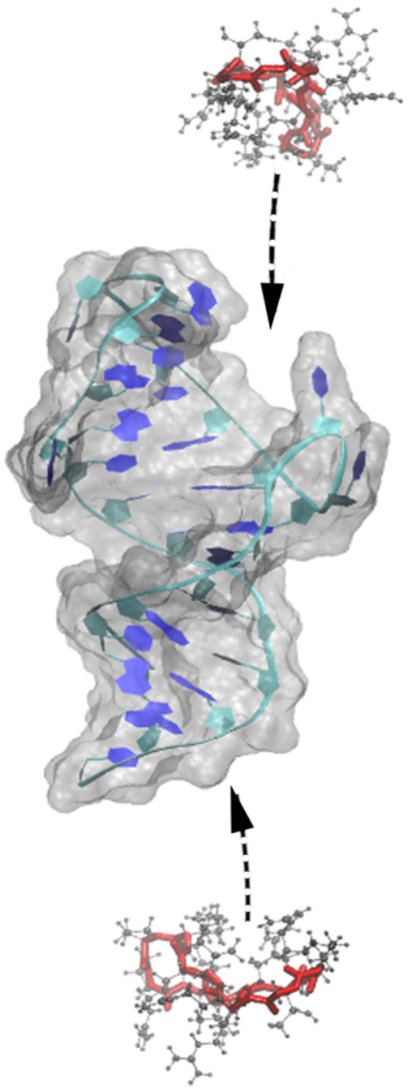


Pulling on TAR-peptide distance: problem is too complex, difficult to reach the proper binding site...

*Hess, Kutzner, Van Der Spoel and Lindahl JCTC (2008)
#www.plumed-code.org
%Perez *et al*, BJ (2007)
$Jorgensen *et al*, JCP (1983)

Pretend binding mode is unknown

- GROMACS 4 MD code* (+PLUMED#)
- parmbsc0 force field%
- Explicit water (TIP3P$, ~12k molecules)
- Explicit counter-ions (NaCl 150mM)



Pulling on TAR-peptide distance: problem is too complex, difficult to reach the proper binding site...

Binding is driven by electrostatics: why not pulling the "electrostatic energy"?

Der Spoel and Lindahl JCTC (2008)
#www.plumed-code.org
%Perez *et al*, BJ (2007)
$Jorgensen *et al*, JCP (1983)

Pulling the estimated interaction energy

pulling out
(from NMR structure)

pulling in
(from unbound structure)

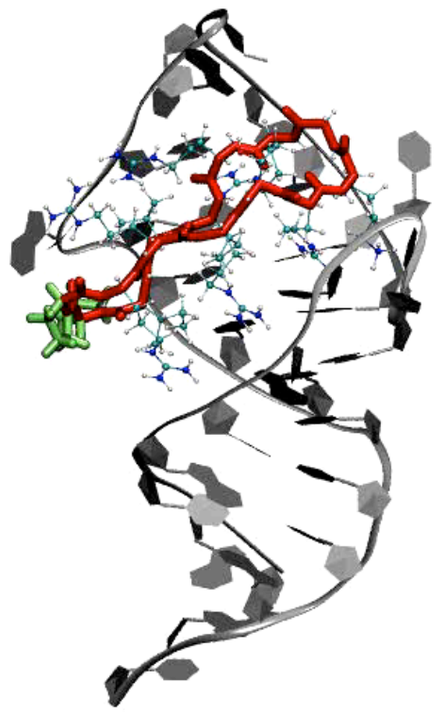
$$s = G^{DH} = \frac{1}{k_B T \epsilon_w} \sum_{j \in B} \sum_{i \in A} q_i q_j \frac{e^{-\kappa |\mathbf{r}_{ij}|}}{|\mathbf{r}_{ij}|}$$

$$V(t, s) = \frac{1}{2} k \left(s_0 + (s_1 - s_0) \frac{t}{T} - G^{DH} \right)^2$$

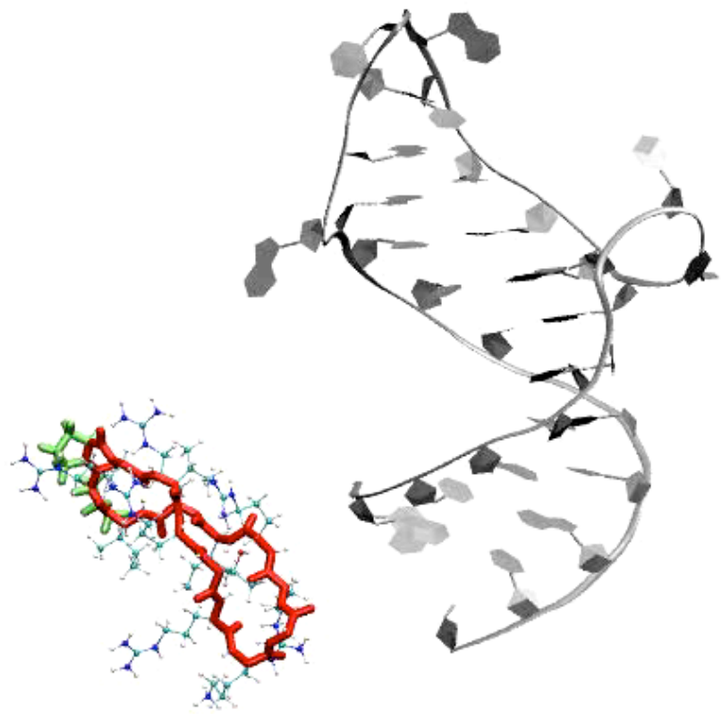
Made on
FERMI@CINECA

Pulling the estimated interaction energy

pulling out
(from NMR structure)



pulling in
(from unbound structure)



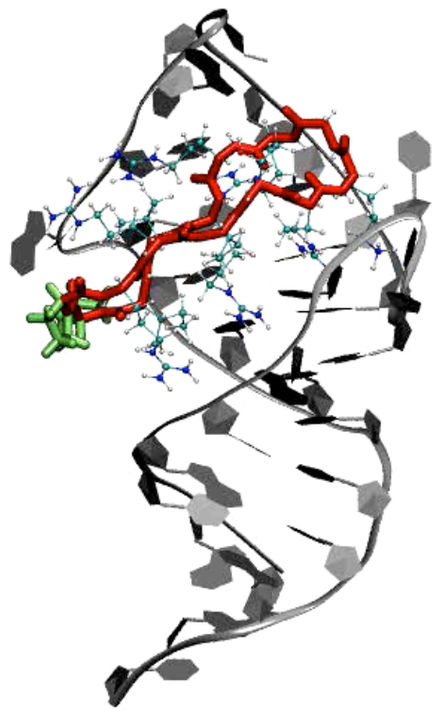
$$s = G^{DH} = \frac{1}{k_B T \epsilon_w} \sum_{j \in B} \sum_{i \in A} q_i q_j \frac{e^{-\kappa |\mathbf{r}_{ij}|}}{|\mathbf{r}_{ij}|}$$

$$V(t, s) = \frac{1}{2} k \left(s_0 + (s_1 - s_0) \frac{t}{T} - G^{DH} \right)^2$$

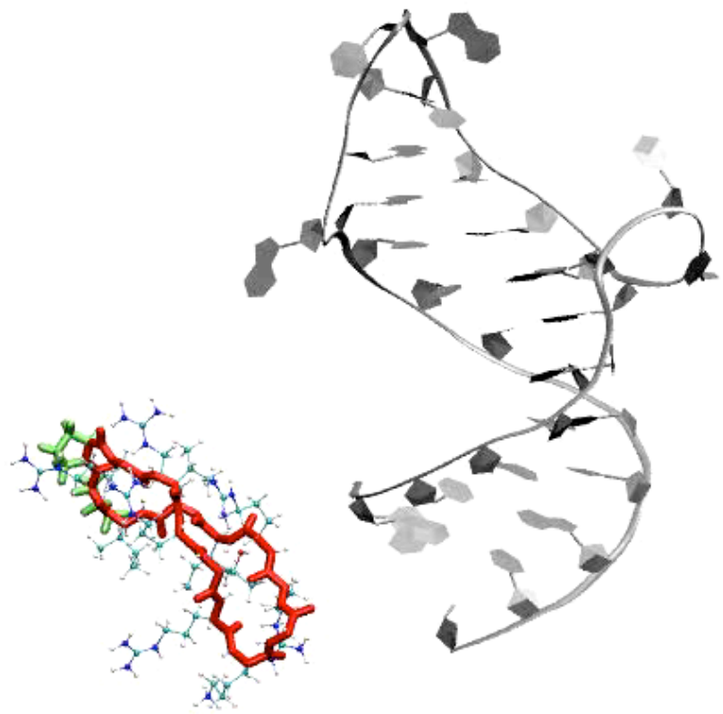
Made on
FERMI@CINECA

Pulling the estimated interaction energy

pulling out
(from NMR structure)



pulling in
(from unbound structure)

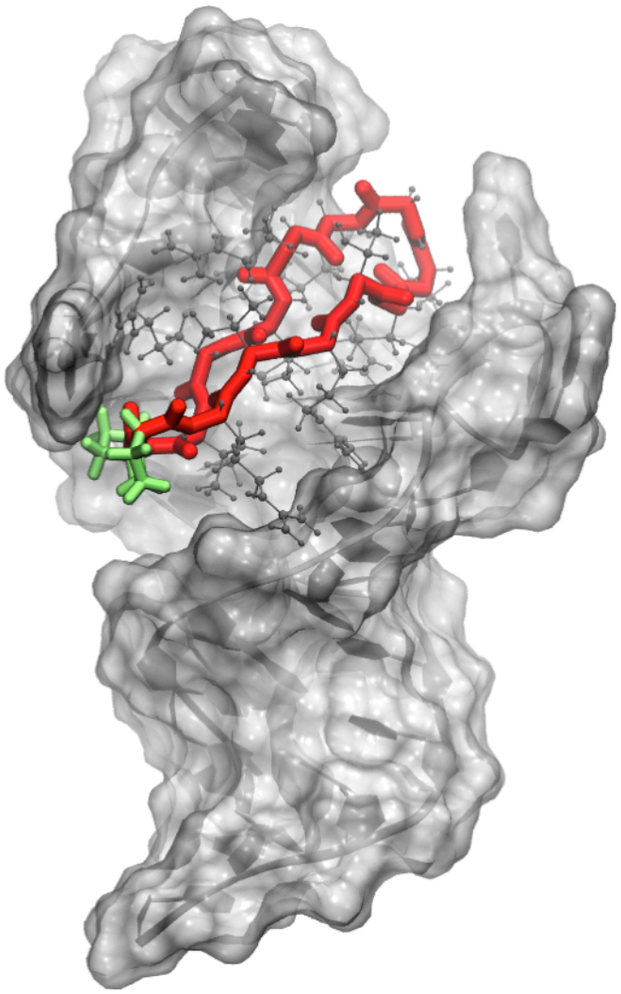


$$s = G^{DH} = \frac{1}{k_B T \epsilon_w} \sum_{j \in B} \sum_{i \in A} q_i q_j \frac{e^{-\kappa |\mathbf{r}_{ij}|}}{|\mathbf{r}_{ij}|}$$

$$V(t, s) = \frac{1}{2} k \left(s_0 + (s_1 - s_0) \frac{t}{T} - G^{DH} \right)^2$$

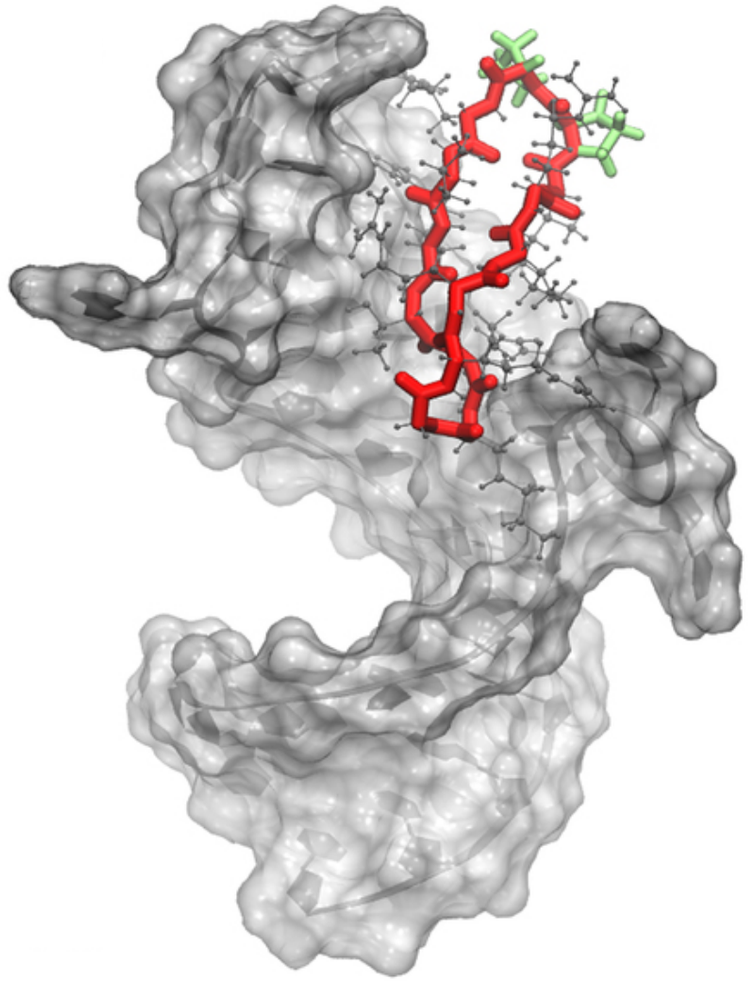
Made on
FERMI@CINECA

Comparison with NMR structure



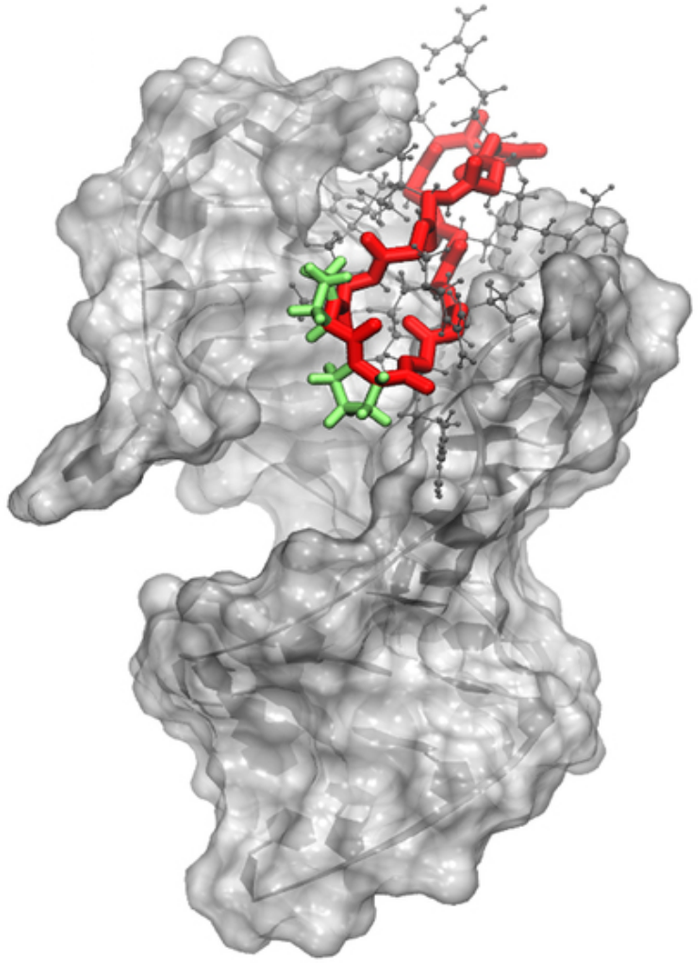
NMR*

(1)



correct pocket
inverse orientation

(2)



correct pocket
correct orientation

*Davidson et al, PNAS (2009)
Do, Carloni, Varani and Bussi, JCTC (2013)

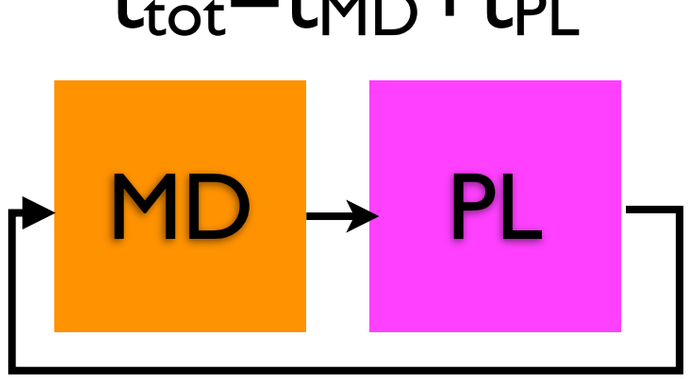
When performance is an issue

Biased sampling is expected to provide a huge speedup provided good CVs are used.

However good CVs are sometime expensive:

- Steinhardt order parameters[1]
- Path/Property maps[2]
- Secondary structure CVs[3]
- SPRINT[4]
- Sketch maps[5]
- DH-Energy[6]

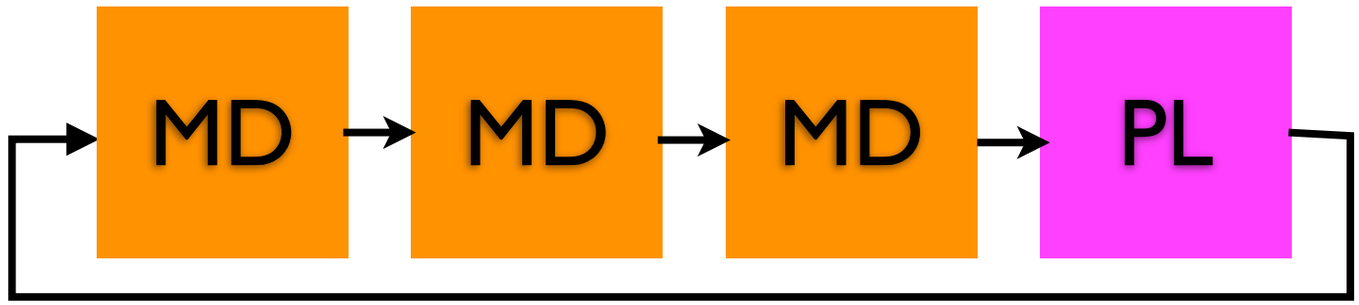
$t_{tot}=t_{MD}+t_{PL}$



[1]Steinhardt, Nelson, and Ronchetti, PRB (1983); Trudu, Donadio, and Parrinello, PRL (2006);
[2]Branduardi, Gervasio, and Parrinello, JCP (2007); Spiwok and Králová, JCP(2011);
[3]Pietrucci and Laio, JCTC (2009); [4]Pietrucci and Andreoni, PRL (2011);
[5]Tribello, Ceriotti, and Parrinello, PNAS (2012); [6]Do, Carloni, Varani, and Bussi, JCTC (2013)

Multiple time stepping

Compute PLUMED forces every *n* steps



$t_{tot}=t_{MD}+t_{PL}/n$

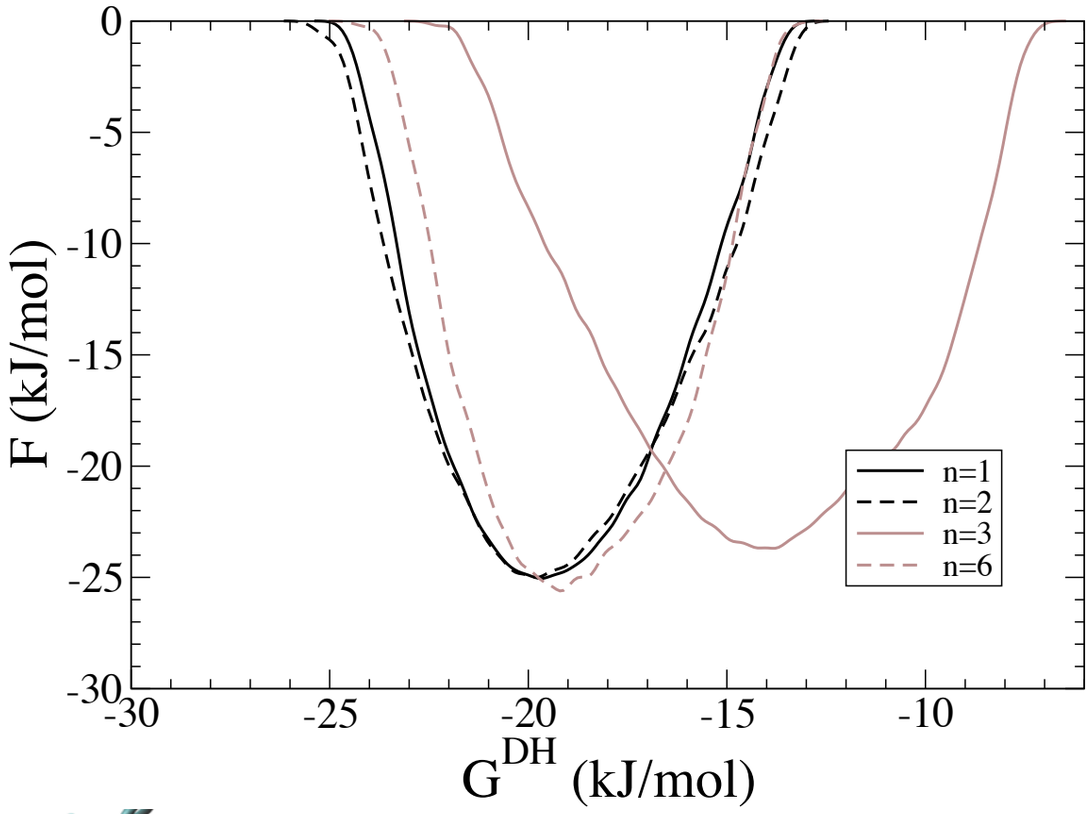
$$e^{A+B} \approx e^{\frac{A}{2}} e^{B} e^{\frac{A}{2}}$$

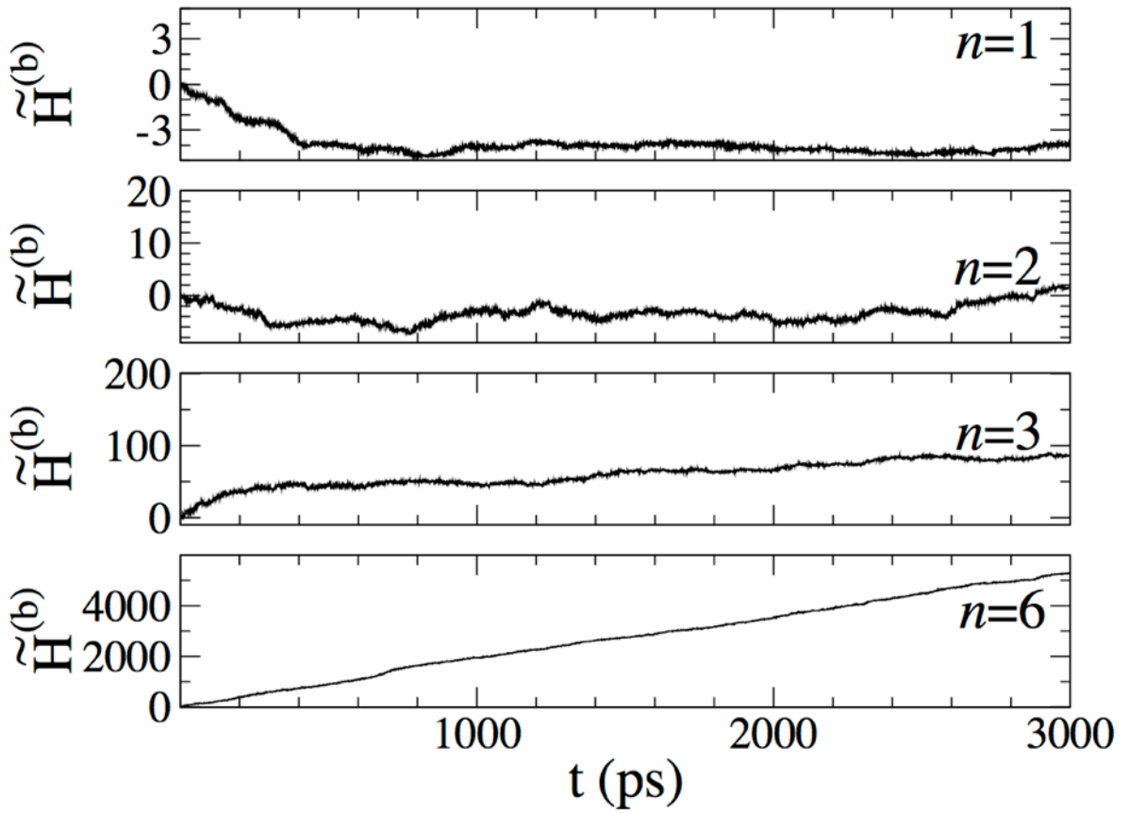
Forces from PLUMED scaled up by a factor $n^{\#}$

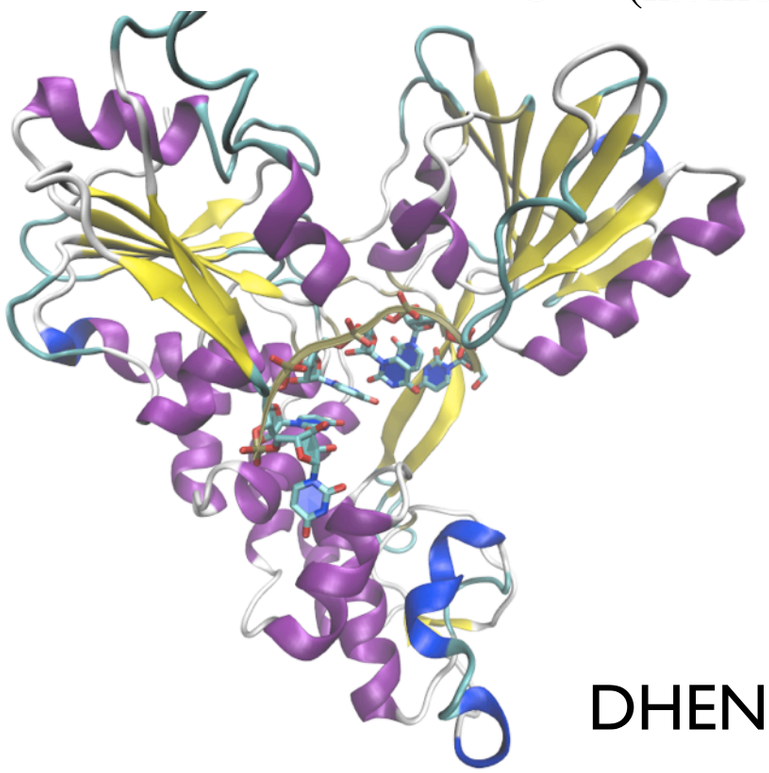
Reversible trajectories

[#]Tuckerman, Berne, and Martyna, JCP (1992); Sexton and Weingarten, Nucl. Phys. B (1992)

RNA/protein complex





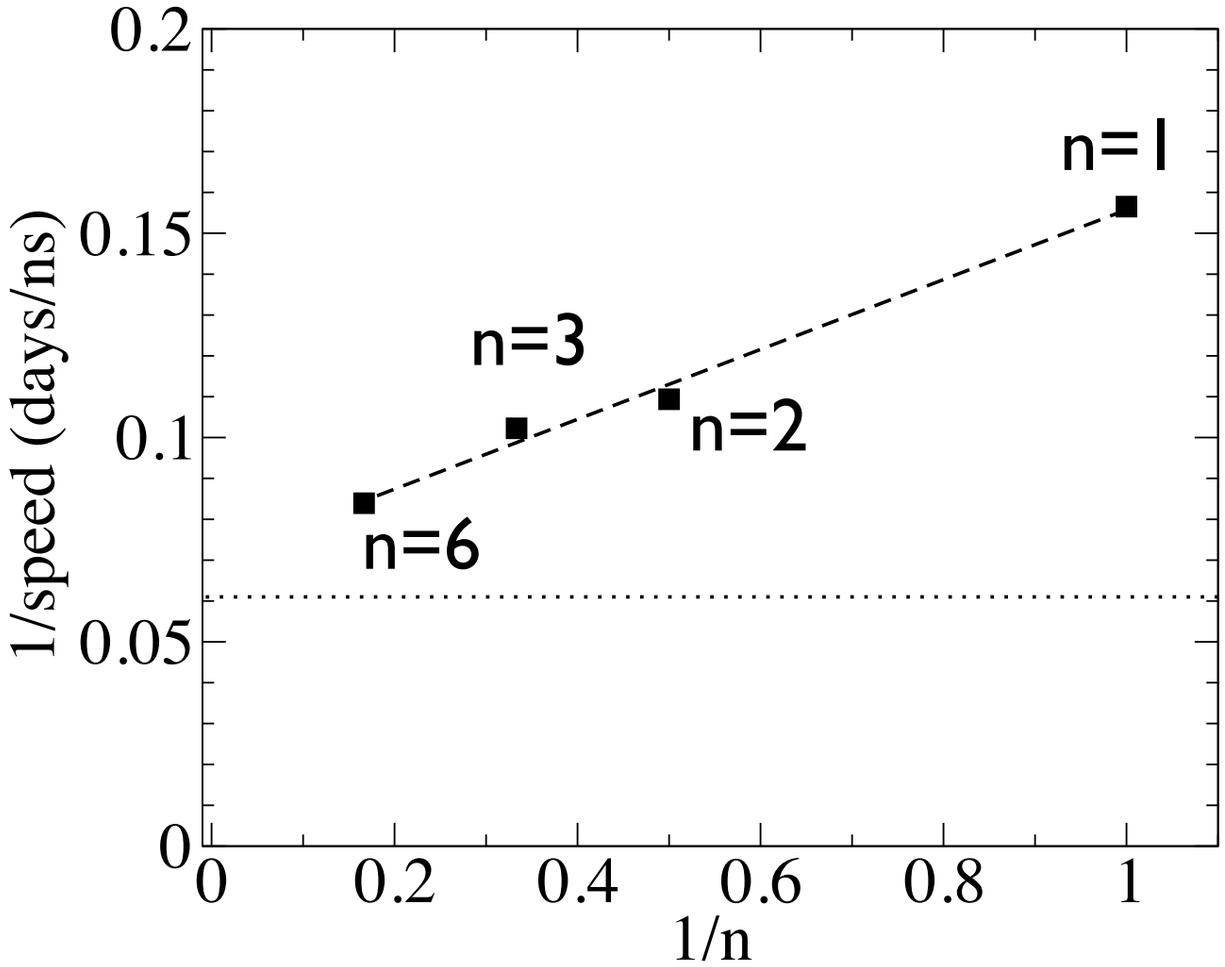


MetaD on RNA/protein interaction

$$G^{DH} = \frac{1}{k_B T \epsilon_w} \sum_{i \in \text{prot}} \sum_{j \in \text{RNA}} q_i q_j \frac{e^{-\kappa |\mathbf{r}_{ij}|}}{|\mathbf{r}_{ij}|}$$

DHENERGY as introduced in Do, Carloni, Varani, and Bussi JCTC (2013)
Ferrarotti, Bottaro, Perez-Villa, and Bussi, submitted

Overall speedup



← GROMACS-only speed

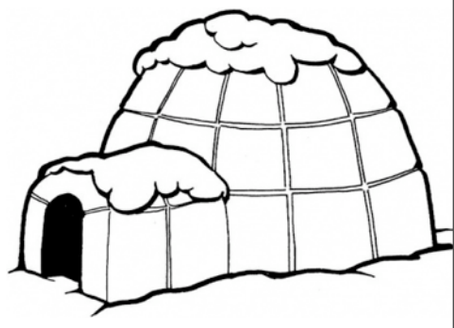
PLUMED overhead can be decreased by a factor *n*
Even *n*=2 can be interesting!

Ferrarotti, Bottaro, Perez-Villa, and Bussi, submitted

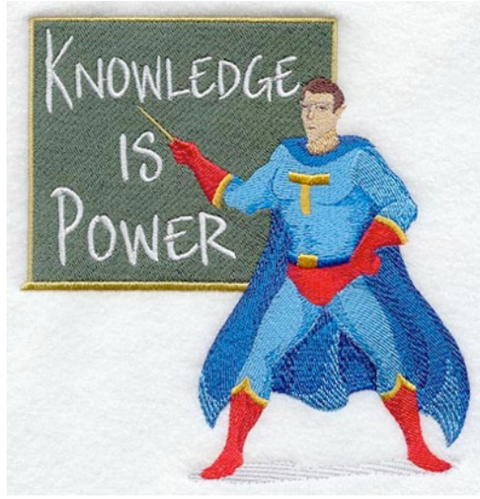
Tackling rare events

<u>Brute force</u>:
very long simulations
distributed computing
...

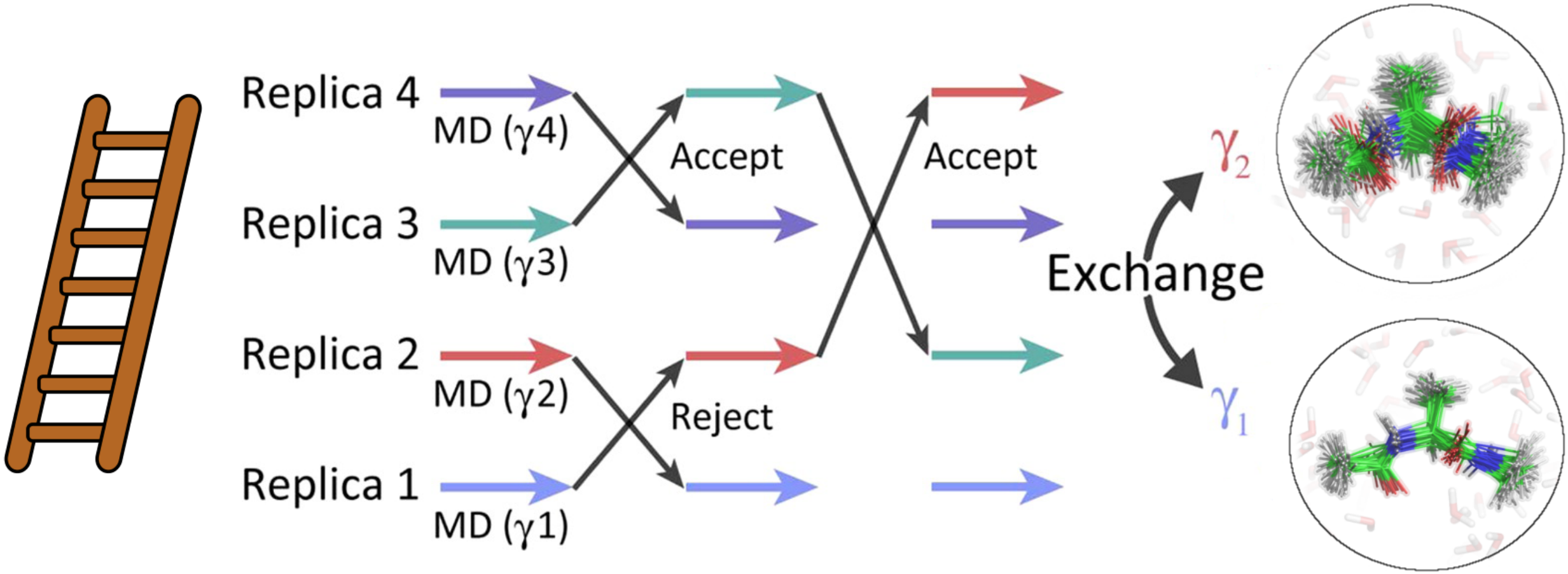
<u>Based on annealing</u>:
simulated annealing
parallel tempering
simulated tempering
...



<u>Based on *a priori* physical insight</u>:
umbrella sampling
steered MD
metadynamics
adiabatic free-energy, temperature accelerated MD
...



Replica exchange

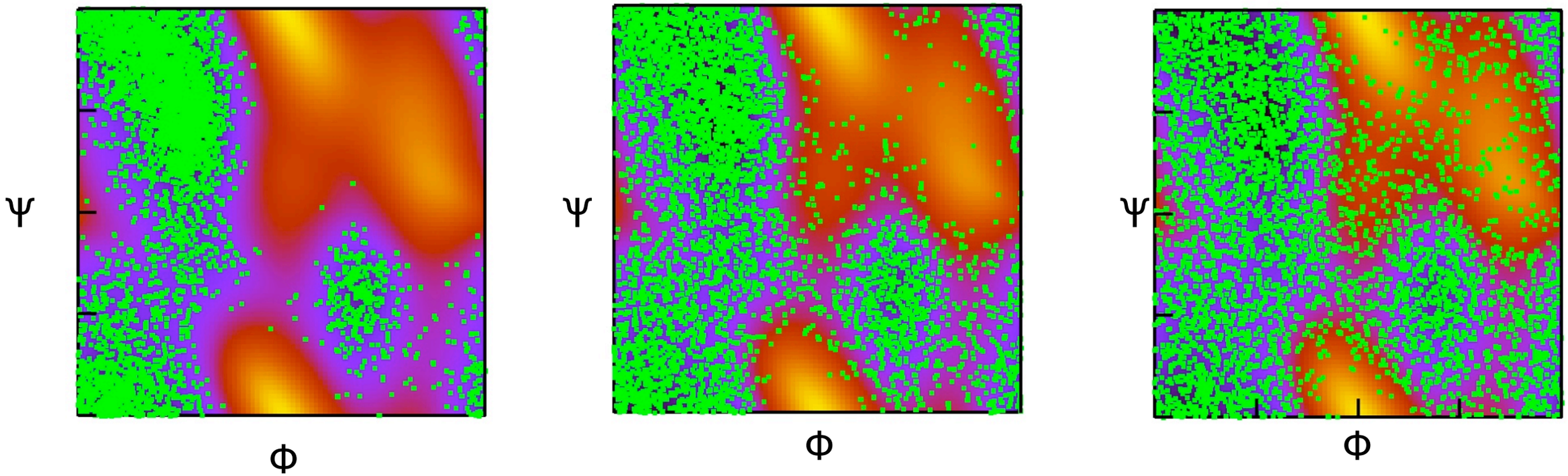


Ladder of replicas:

- "reference" replica
- "ergodic" replica
- as many as needed in the middle (depends on "how different")

In parallel tempering, "ergodic" means "high T"

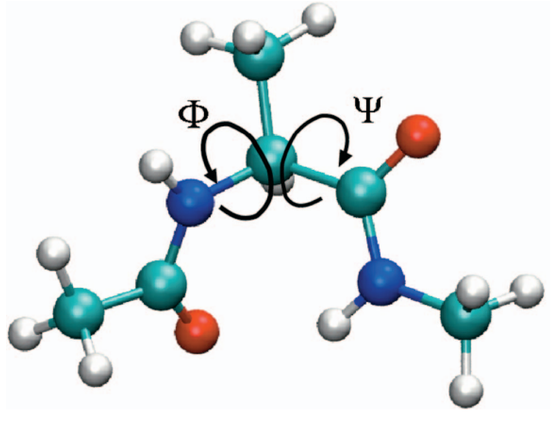
MetaD used to "increase T"



ΔT=600K ΔT=1800K ΔT=4200K

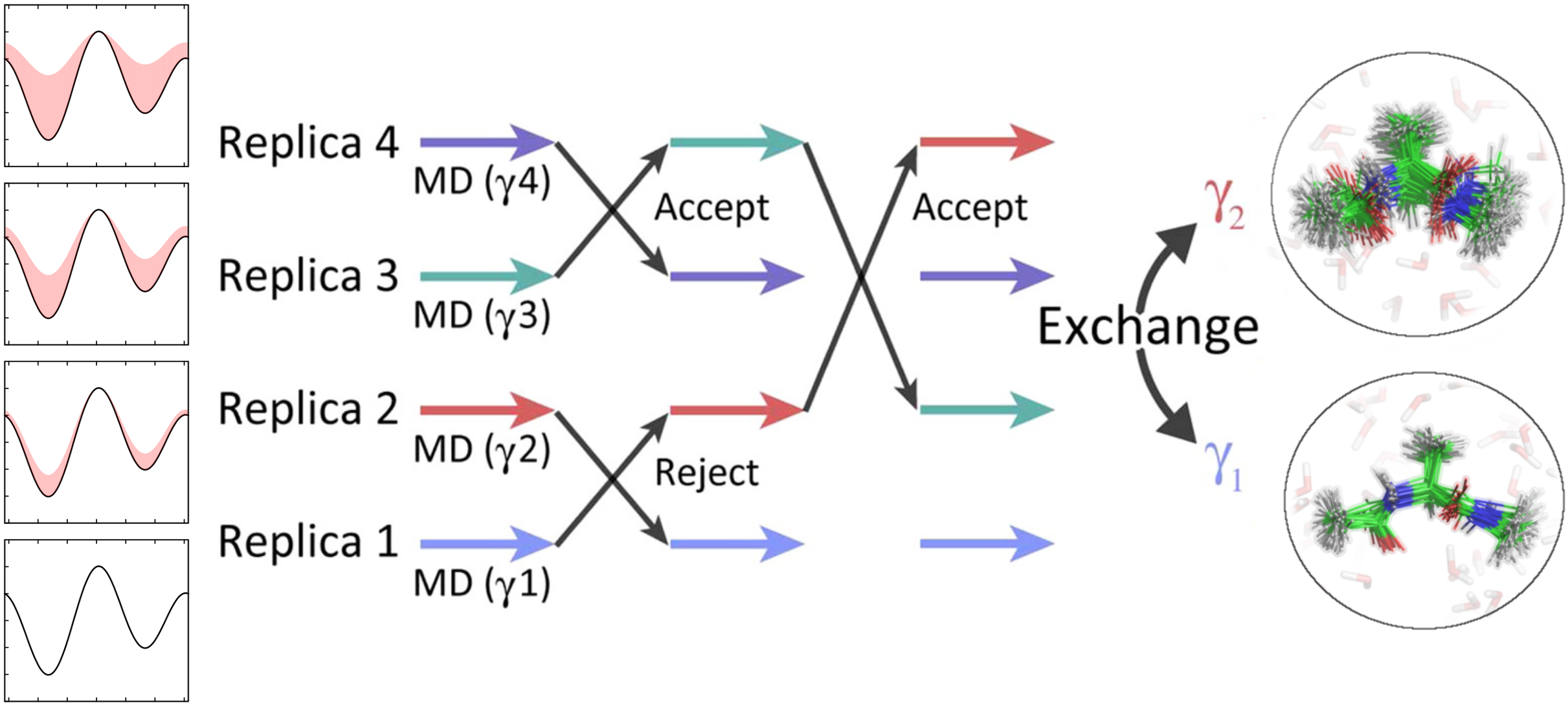
time is spent on the desired region exp(-F/(T+ΔT))

ΔT tunes the explored region



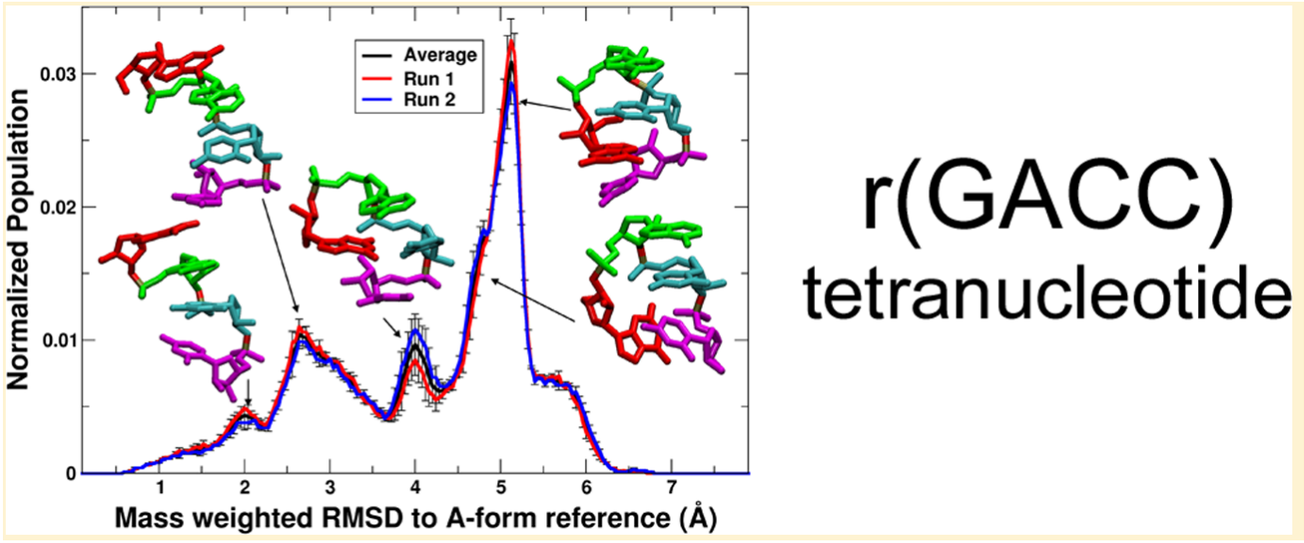
(initial rate ω= ΔT/τ=2.4 kcal/mol/ps)

(Hamiltonian) replica exchange

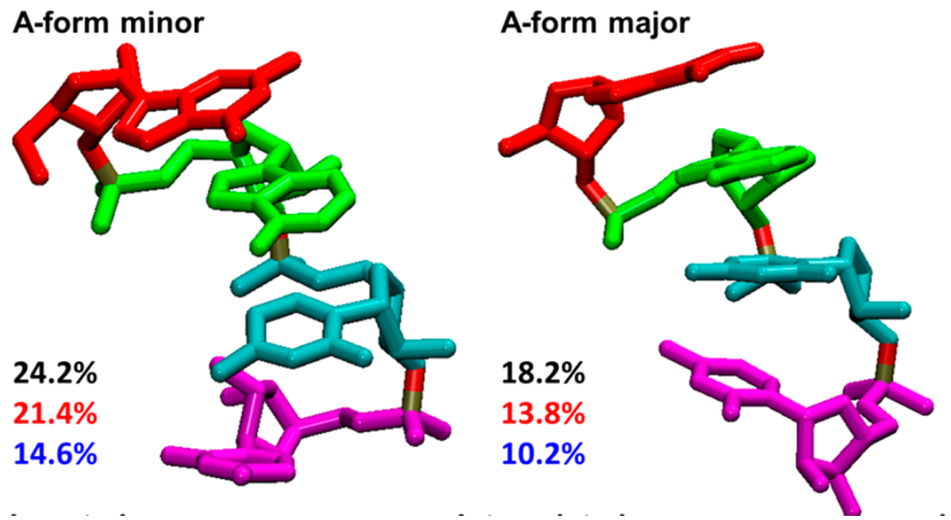


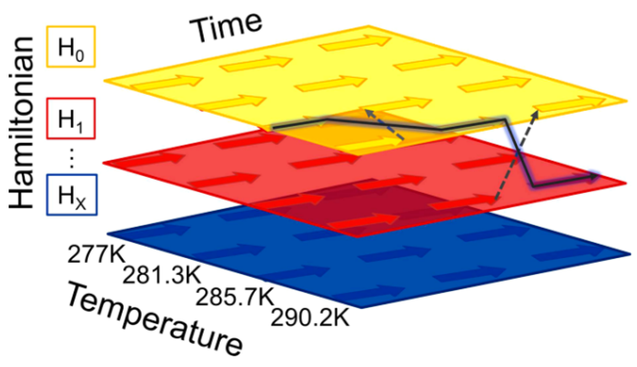
- Replicas with different value of $(T+\Delta T)=\gamma T$

GACC tetranucleotide



r(GACC)
tetranucleotide





24 (T-REMD) x 8 (H-REMD) replicas
≈60μs total

In comparison with poly-peptides, roughly 3x complexity per residue

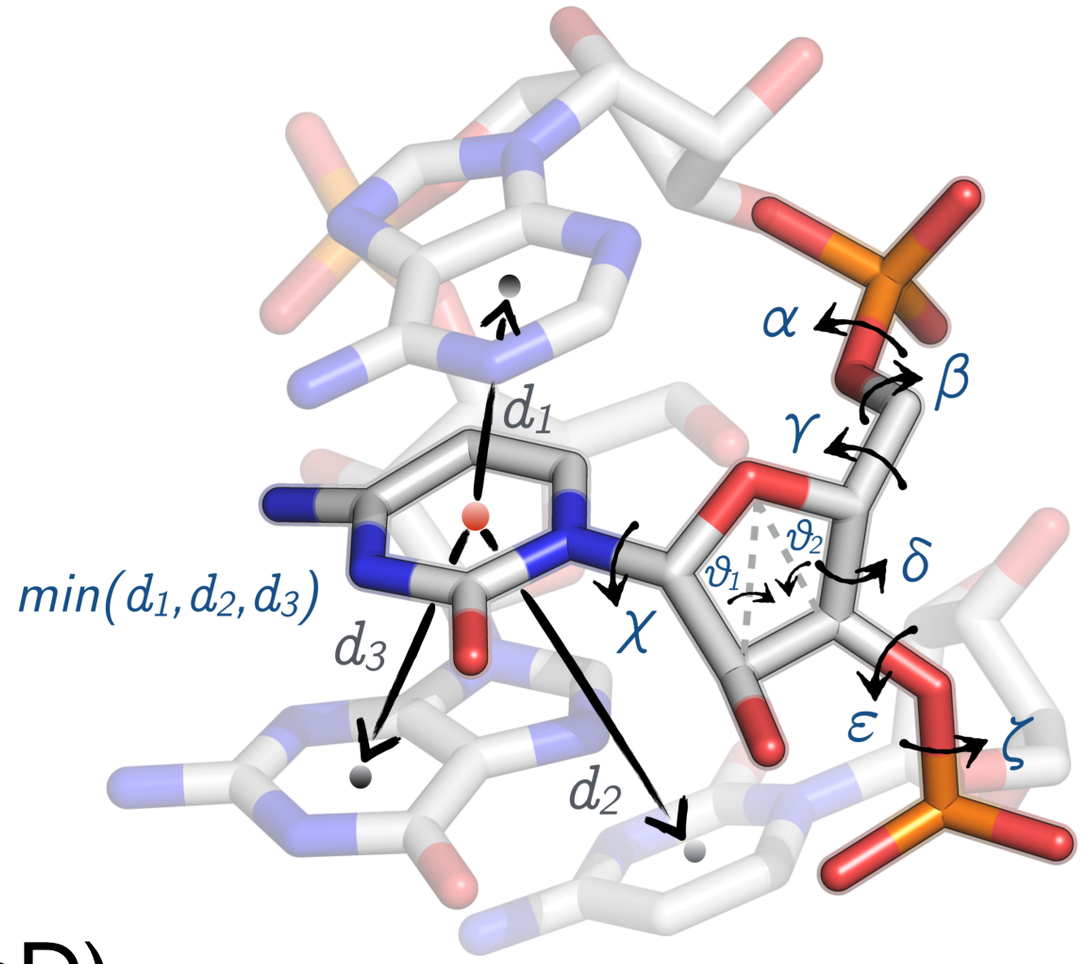
Bergonzo, Henriksen, Roe, Swails, Roitberg, and Cheatham, JCTC (2014)

GACC tetranucleotide

Amber99-chiOL[#]
TIP-3P water[%]
GROMACS 4.6[$]
PLUMED 2.0[@]

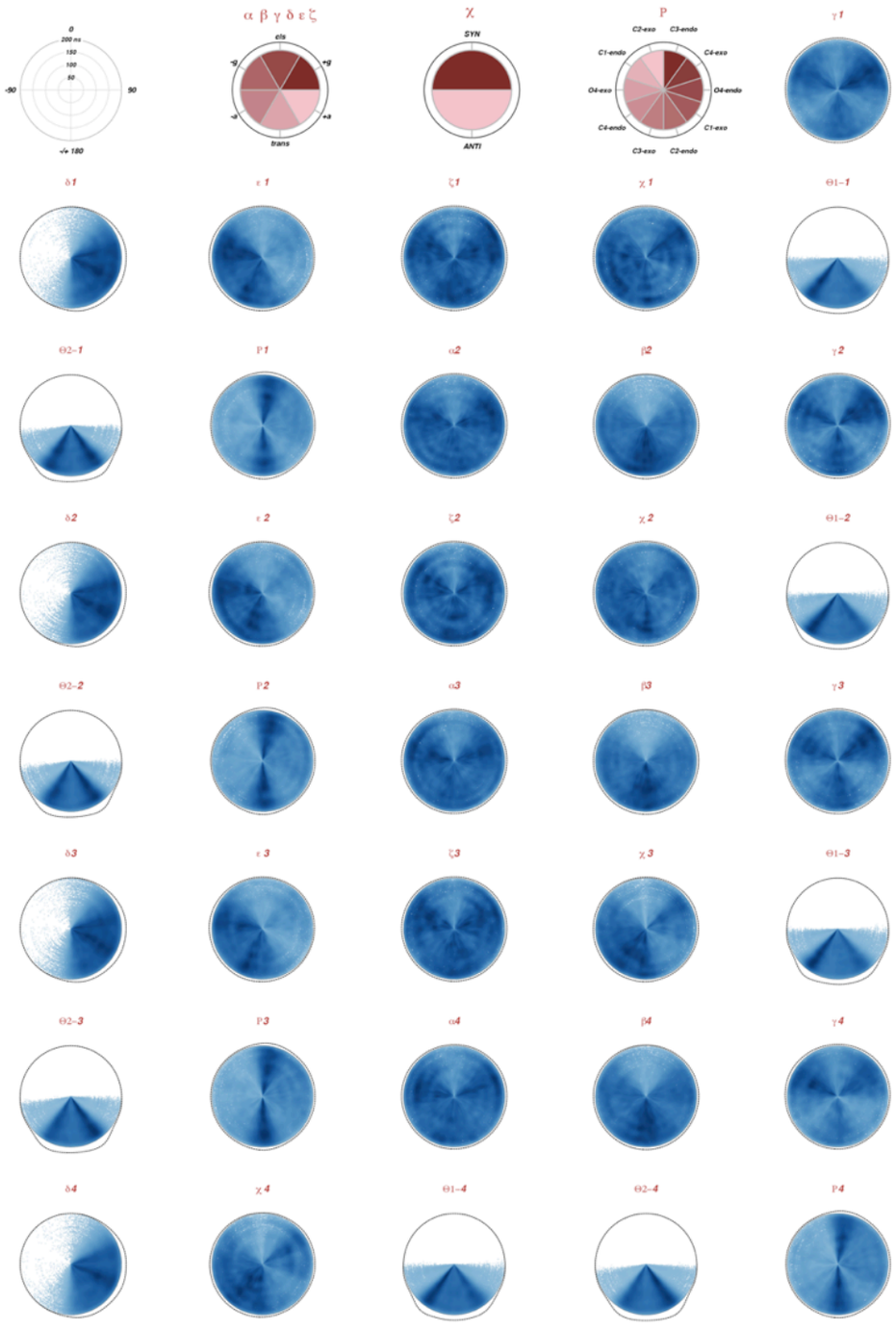
Each nucleotide:
7 backbone dihedrals
puckering
minimum distance from other bases
(total 28x1D+4x2D concurrent MetaD)

16 replicas
γ=1-4
α≈40%-70%

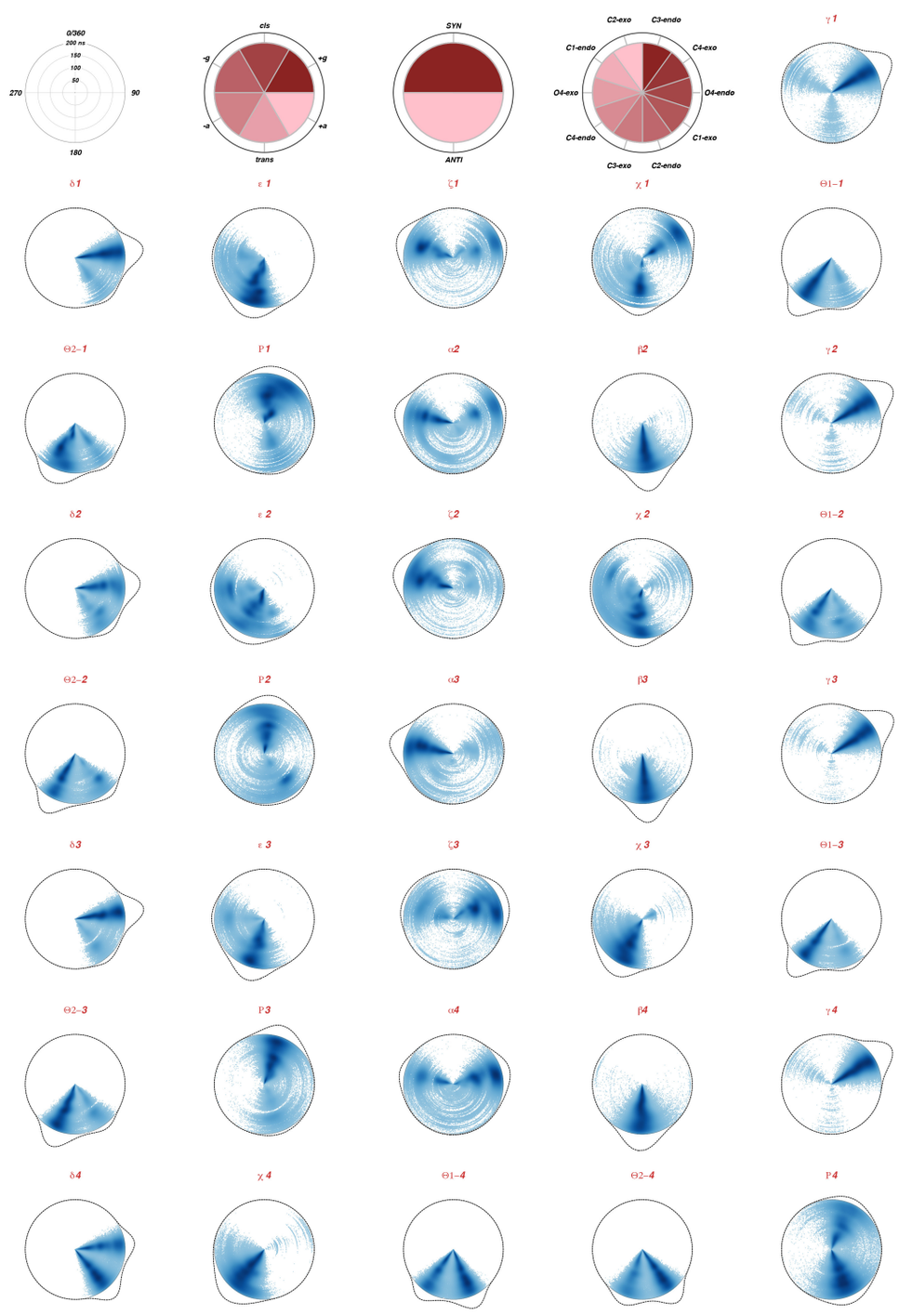


[#]Zgarbova et al, JCTC (2010)
[%] Jorgensen et al, JCP (1983)
[$]Hess et al, JCTC (2008)
[@]Tribello et al, CPC (2014)

Dihedral distribution

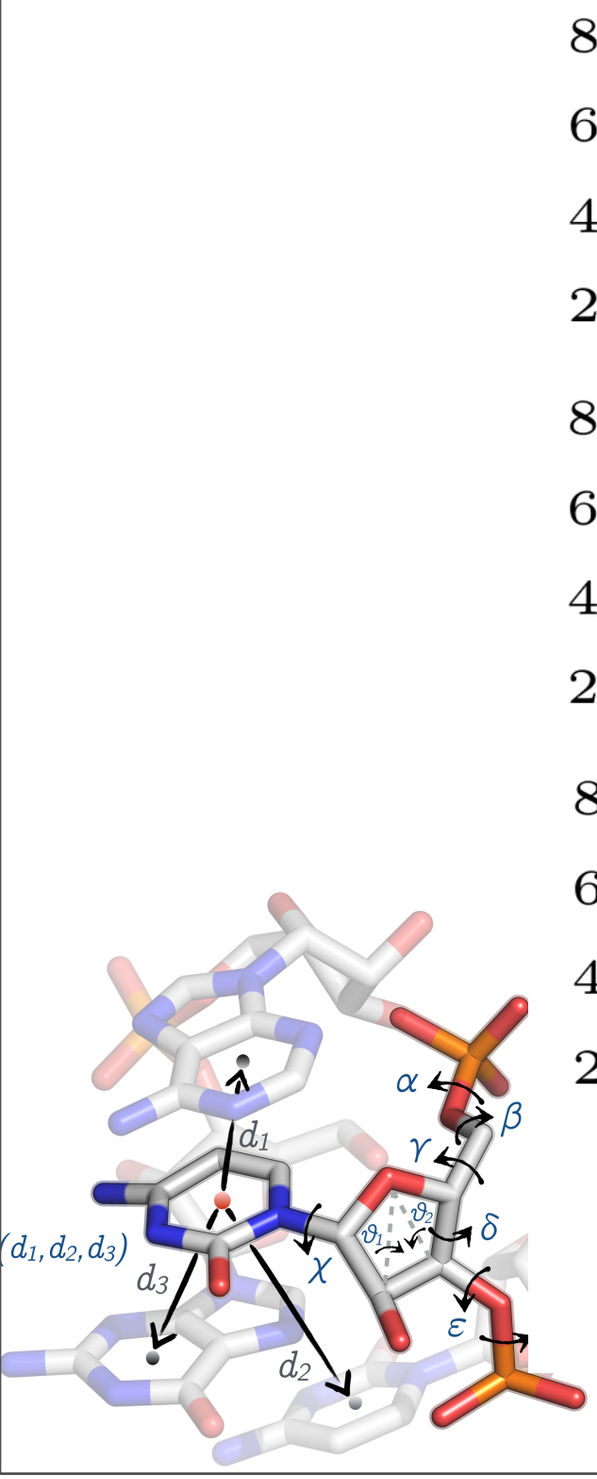


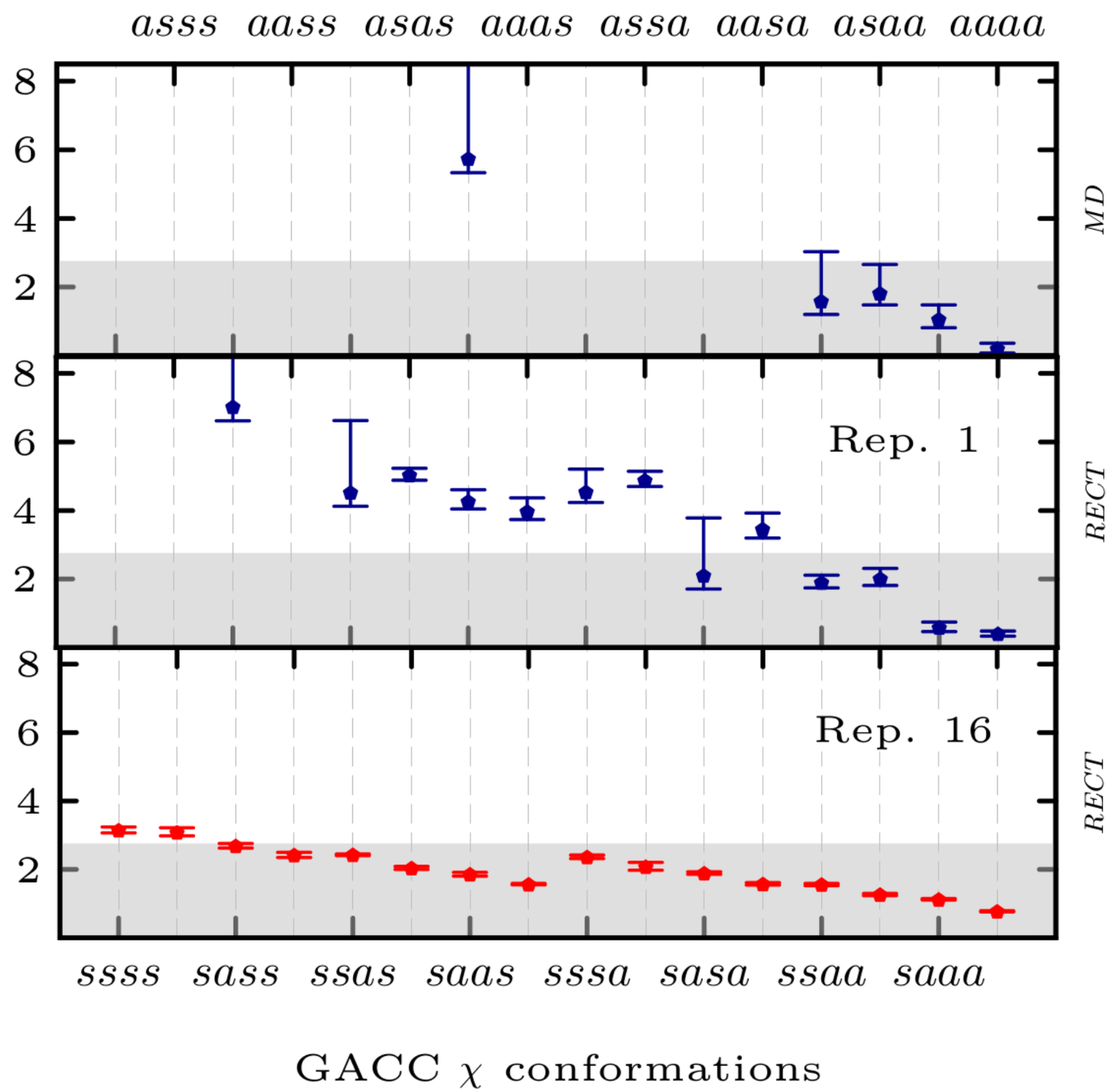
highest replica
(biased)



lowest replica
(un biased)

Relative stability of rotamers





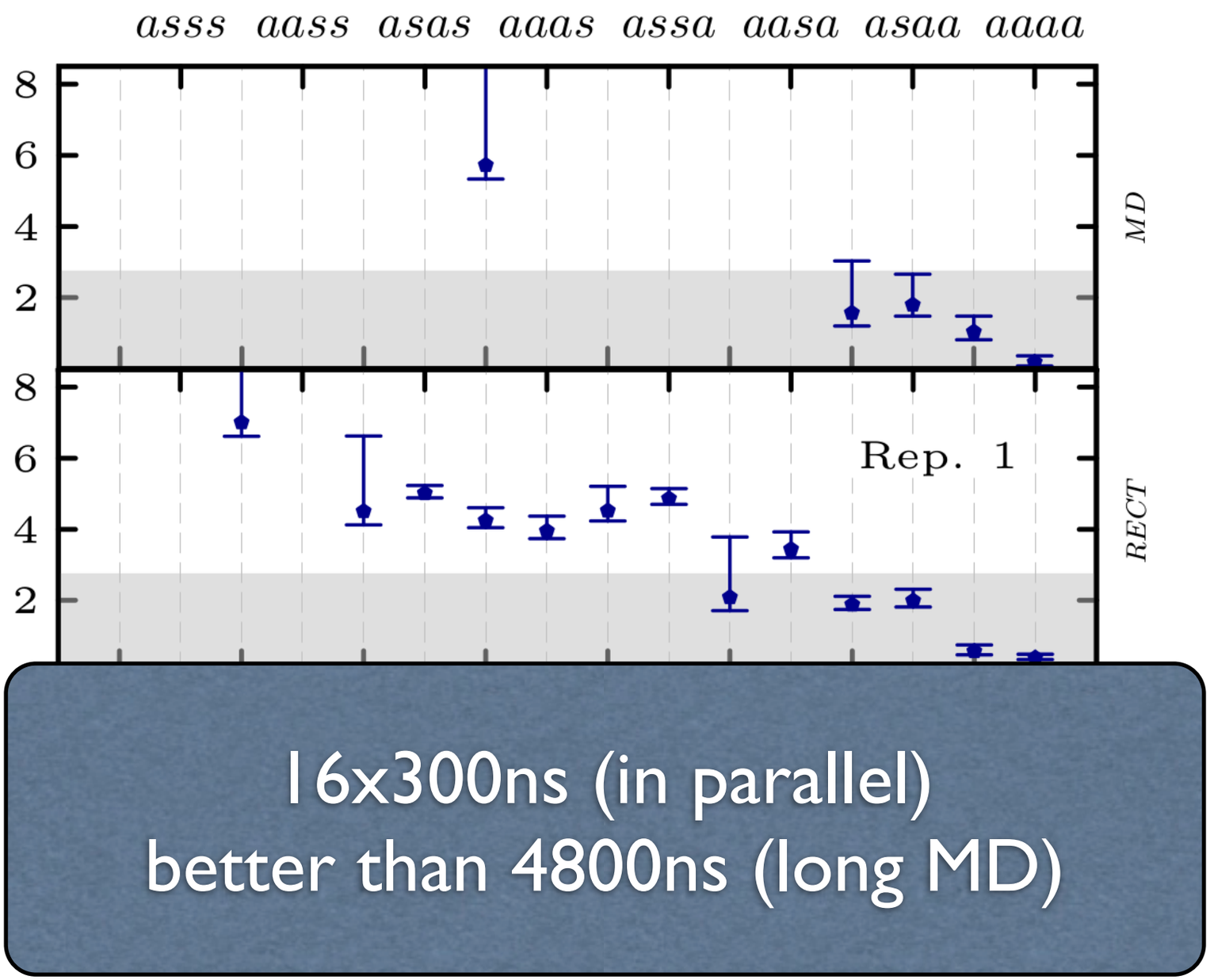
long MD

Replica 1 (unbiased)

Replica 16 (biased)

Gil-Ley and Bussi, submitted

Relative stability of rotamers

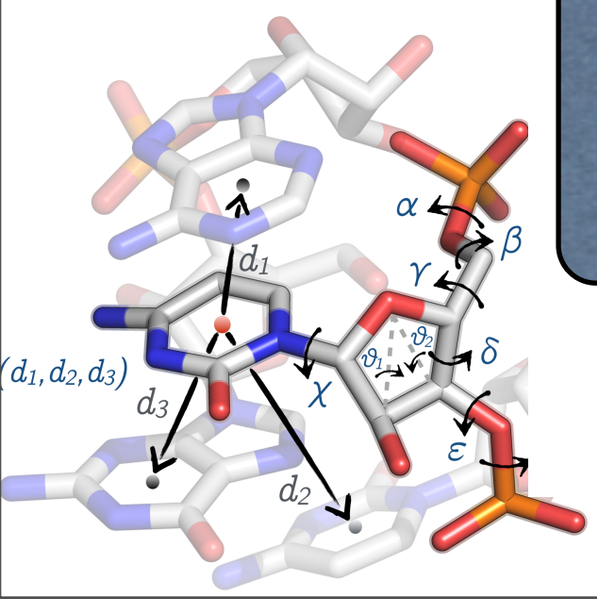


long MD

Replica 1 (unbiased)

16x300ns (in parallel)
better than 4800ns (long MD)

Replica 16 (biased)



Gil-Ley and Bussi, submitted

Take home message

PLUMED: an open source plugin for molecular dynamics

A posteriori/on-the-fly analysis of MD

Many CVs and biasing methods (metadynamics *et al*)

Compatible with several MD engines

http://www.plumed-code.org

Acknowledgements

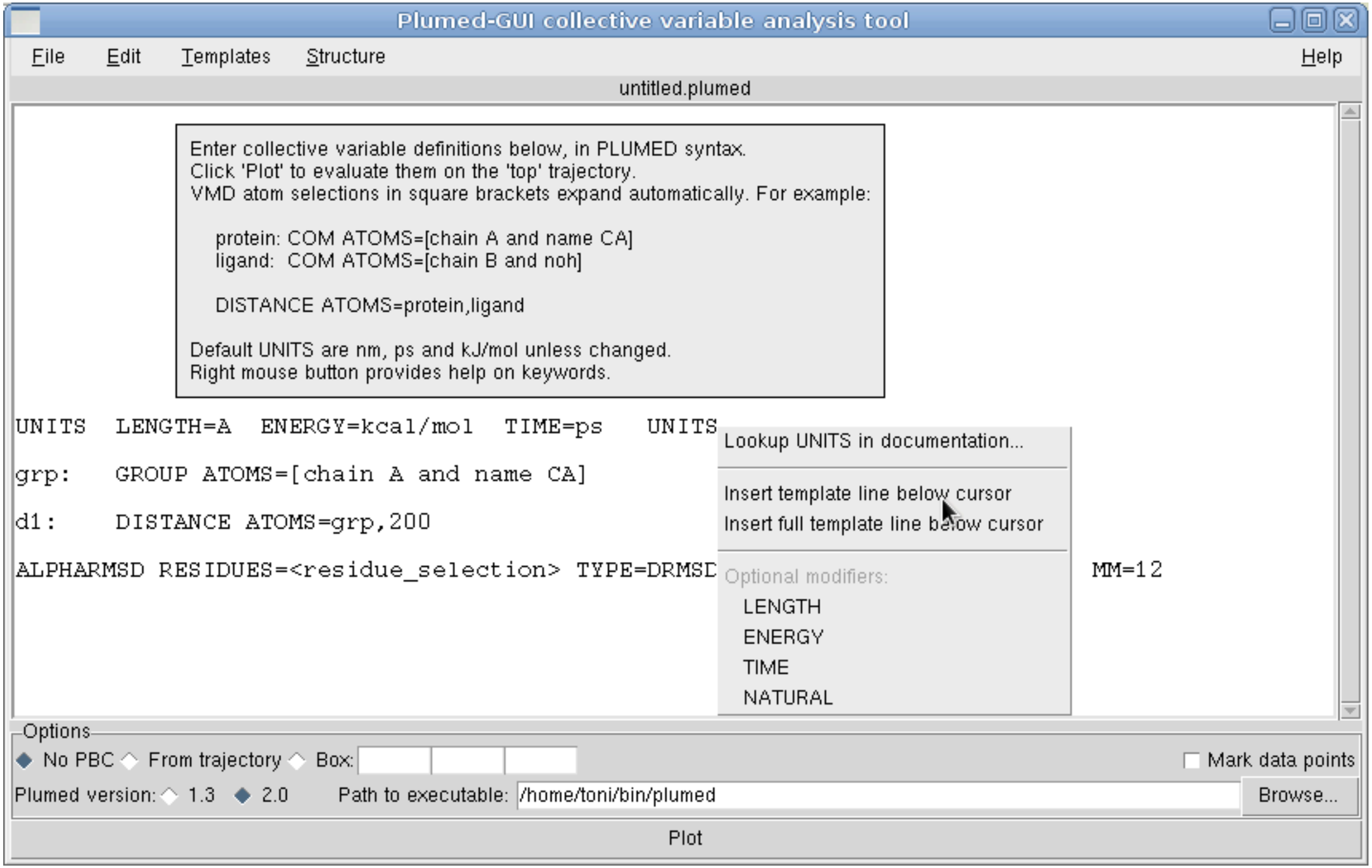
Andrea Perez-Villa
Sandro Bottaro
Alejandro Gil-Ley

Marco Jacopo Ferrarotti
Do Trang

PLUMED developers:
Gareth Tribello
Max Bonomi
Davide Branduardi
Carlo Camilloni

ERC for funding
CINECA for computing time

PLUMED+VMD (GUI)



http://www.ks.uiuc.edu/Research/vmd

Giorgino, CPC (2014) - see http://github.com/tonigi/vmd_plumed

Supported MD codes

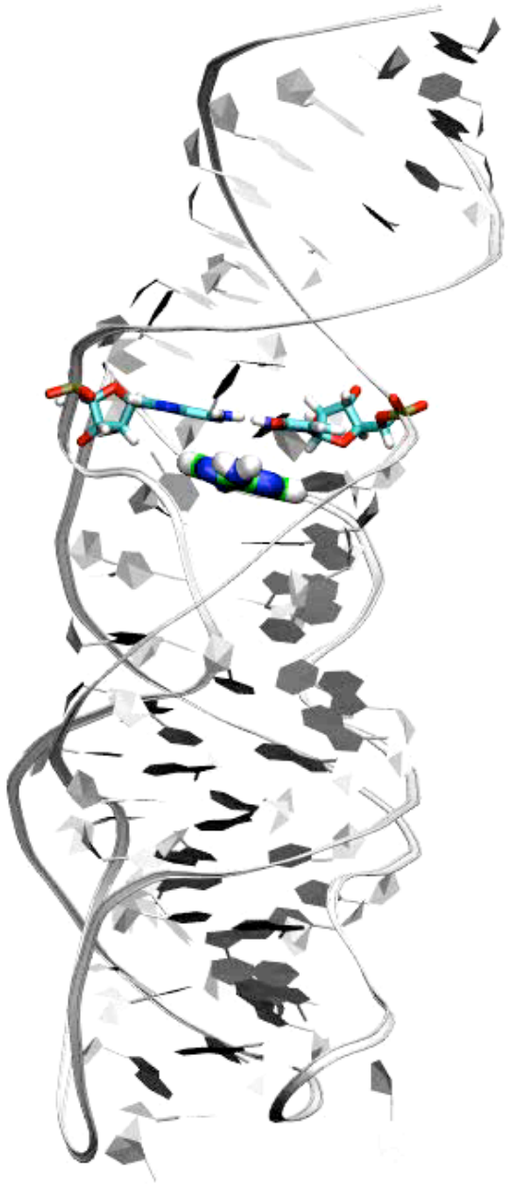
GROMACS - fast, tuned for biomolecules, open source
NAMD - fast, tuned for biomolecules, scalable
LAMMPS - very general and scalable, open source
QuantumESPRESSO - DFT, open source
AMBER/sander, many force methods (QMMM, semi-empirical,...)

+ some code has PLUMED support out-of-the-box

PLUMED is a library with a documented API
thus, you can easily add your own code!

http://www.gromacs.org
http://www.ks.uiuc.edu/Research/namd
http://lammps.sandia.gov
http://www.quantum-espresso.org
http://ambermd.org

Molecular Dynamics



$$E_{\text{total}} = \sum_{\text{bonds}} k_{\text{b}}\left(\ell - \ell_0\right)^2 + \sum_{\text{angles}} k_{\text{a}}\left(\theta - \theta_0\right)^2$$

$$+ \sum_{\text{torsions}} \frac{1}{2} V_{\text{n}}[1 + \cos(n\omega - \gamma)]^2$$

$$+ \sum_{j=1}^{N-1} \sum_{i=j+1}^{N} \left\{ \varepsilon_{i,j} \left[\left(\frac{r_{0ij}}{r_{ij}} \right)^{12} - 2\left(\frac{r_{0ij}}{r_{ij}} \right)^{6} \right] + \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \right\}$$

Classical empirical force field:

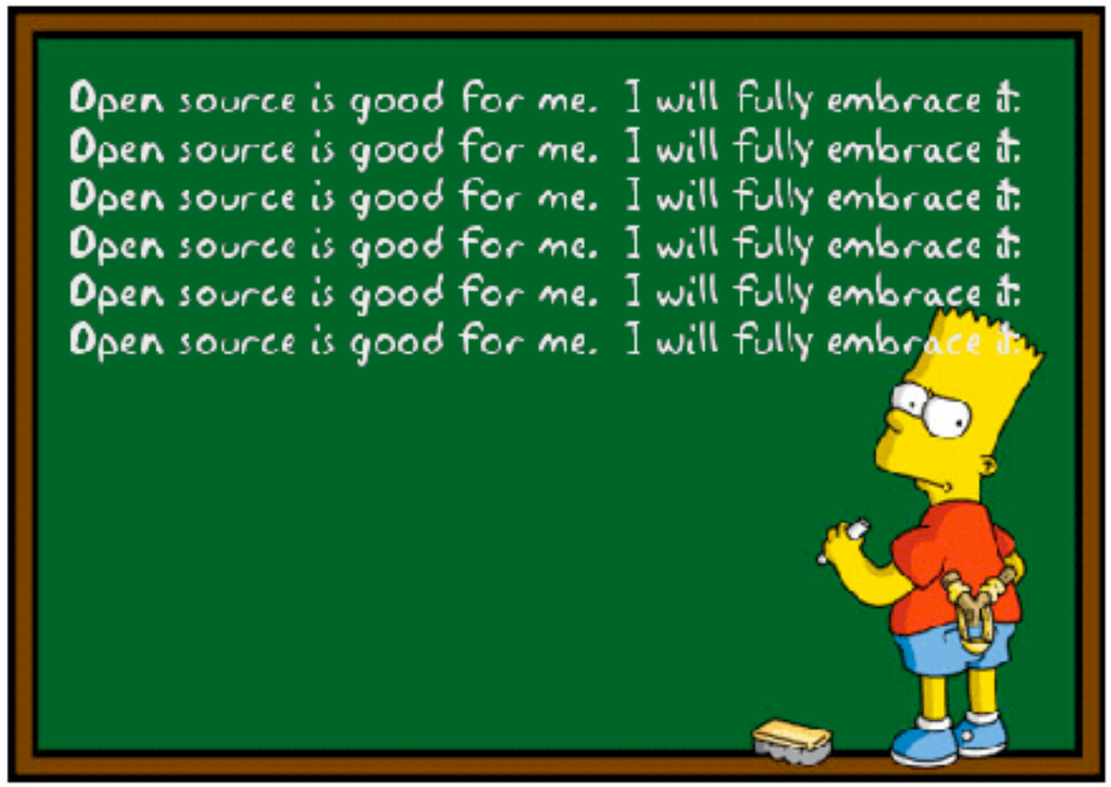
- Chemically motivated interactions
- Atomistic detail
- Water and ions explicitly modeled
- No polarization, no chemical reactions

Large computers required

5-100 ns/day

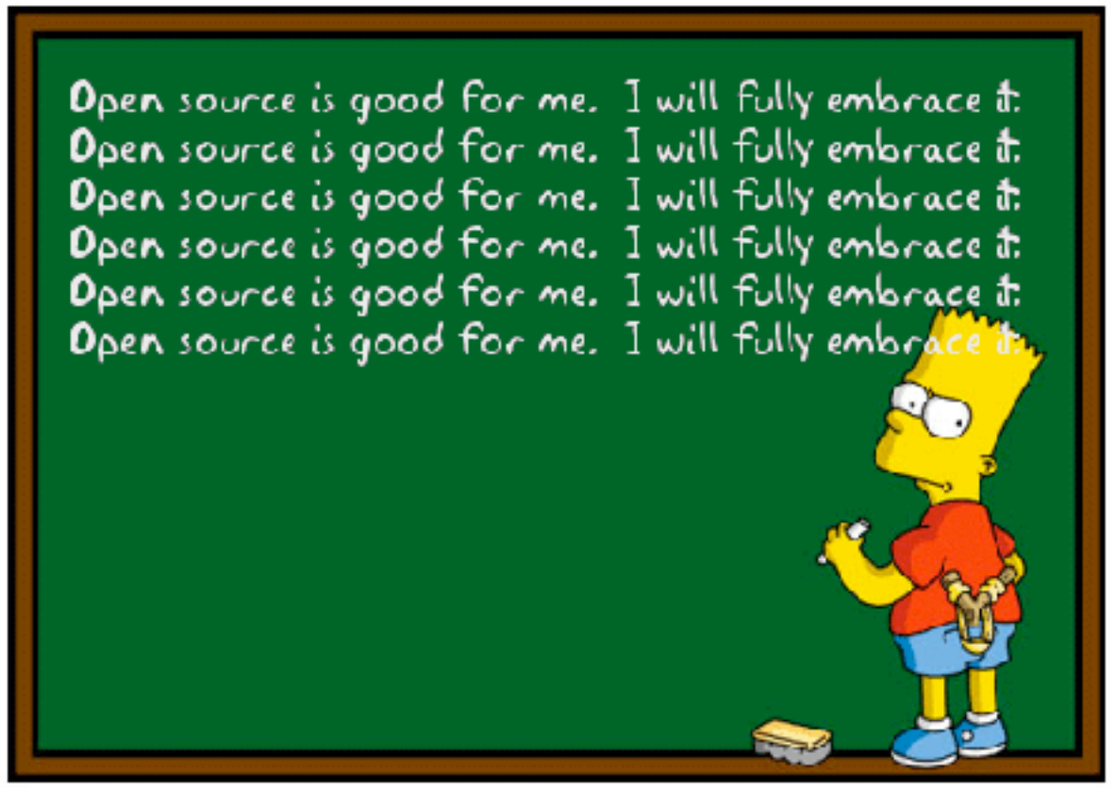
Open source philosophy

Do you want to contribute:
- reaction coordinates?
- free energy methods?
- source code cleaning?
- write documentation?
- port to other MD code?



Open source philosophy

Do you want to contribute:
- reaction coordinates?
- free energy methods?
- source code cleaning?
- write documentation?
- port to other MD code?

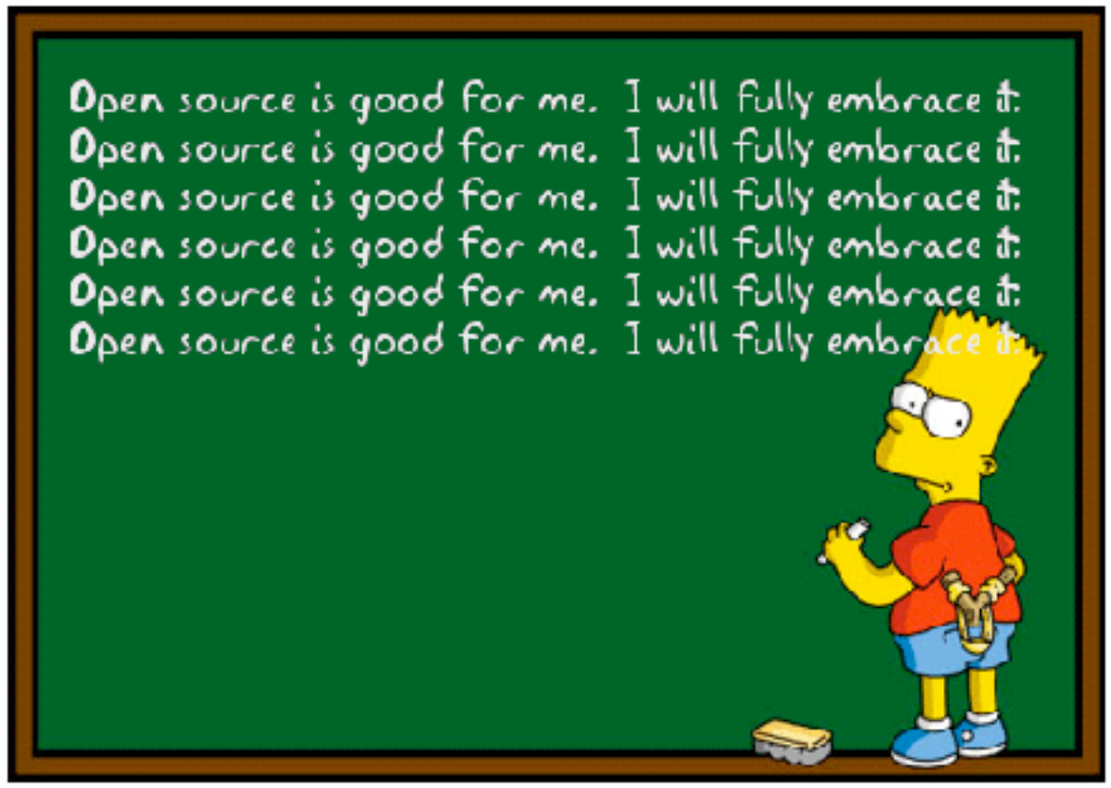


Your code will be available for free, forever (also to you!)

Your method/coordinate will be usable by many people immediately

Open source philosophy

Do you want to contribute:
- reaction coordinates?
- free energy methods?
- source code cleaning?
- write documentation?
- port to other MD code?

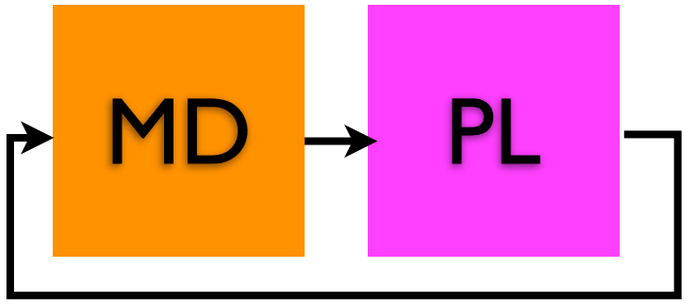


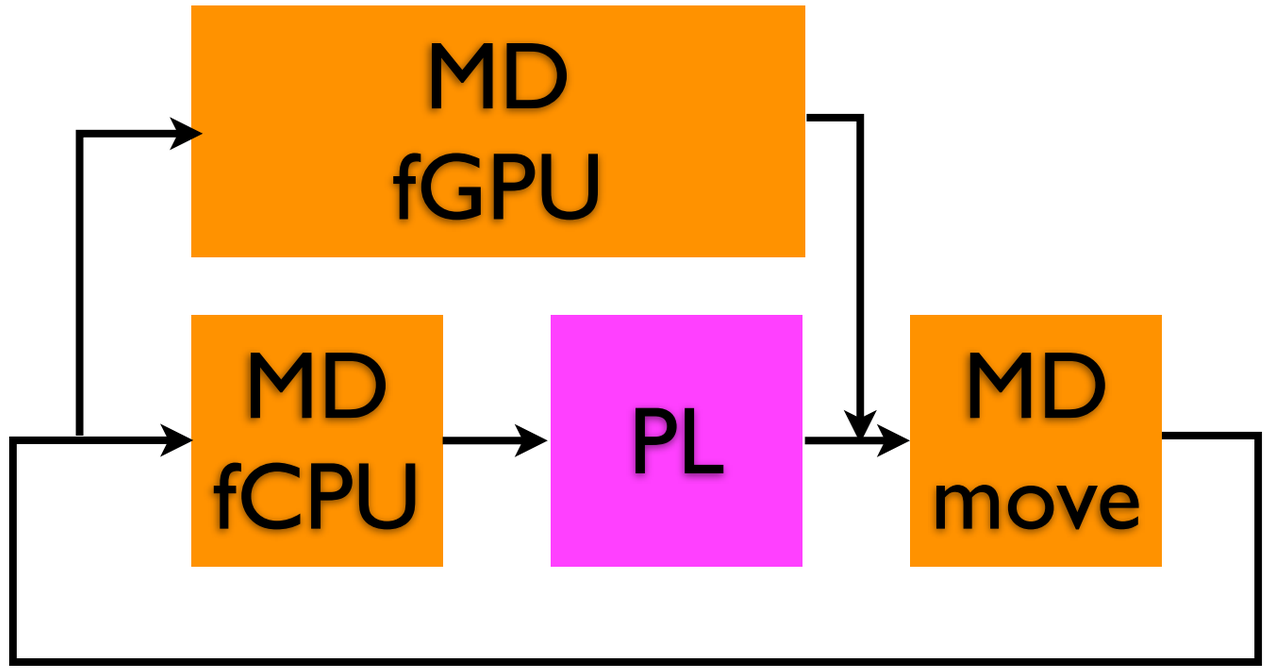
Your code will be available for free, forever (also to you!)

Your method/coordinate will be usable by many people immediately *

*this is good for citations, too!

GPUs (gromacs)





Load balancing shifts load to GPU
when PLUMED is too expensive