

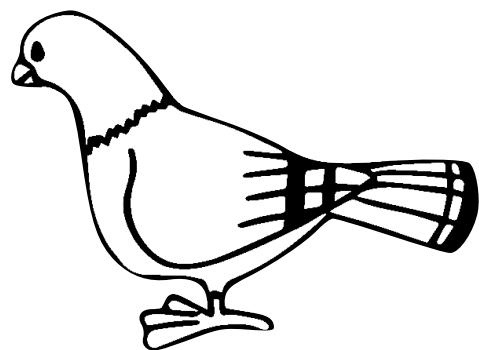
# PLUMED Masterclass

## 21.5: Replica-exchange methods

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 @BussiGio





# PLUMED

open-source  
freely-available  
C++ library

- enhanced-sampling methods
- free-energy methods
- analysis MD data



[www.plumed.org](http://www.plumed.org)



@plumed\_org

Bonomi *et al.* CPC 2009  
Tribello *et al.* CPC 2014

Gareth Tribello



Max Bonomi



Carlo Camilloni



Giovanni Bussi



Class ▲	Topic	Lecture I	Lecture II	Instructor
21.1	PLUMED syntax and analysis	January 18, 2021	January 25, 2021	M. Bonomi
21.2	Statistical errors in MD	February 1, 2021	February 8, 2021	G. Tribello
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21.8	Poster session	May 10, 2021		

# Multiple replicas

Today, we will discuss algorithms where multiple replicas are simulated

Algorithms classified based on:

- Are replicas coupled?

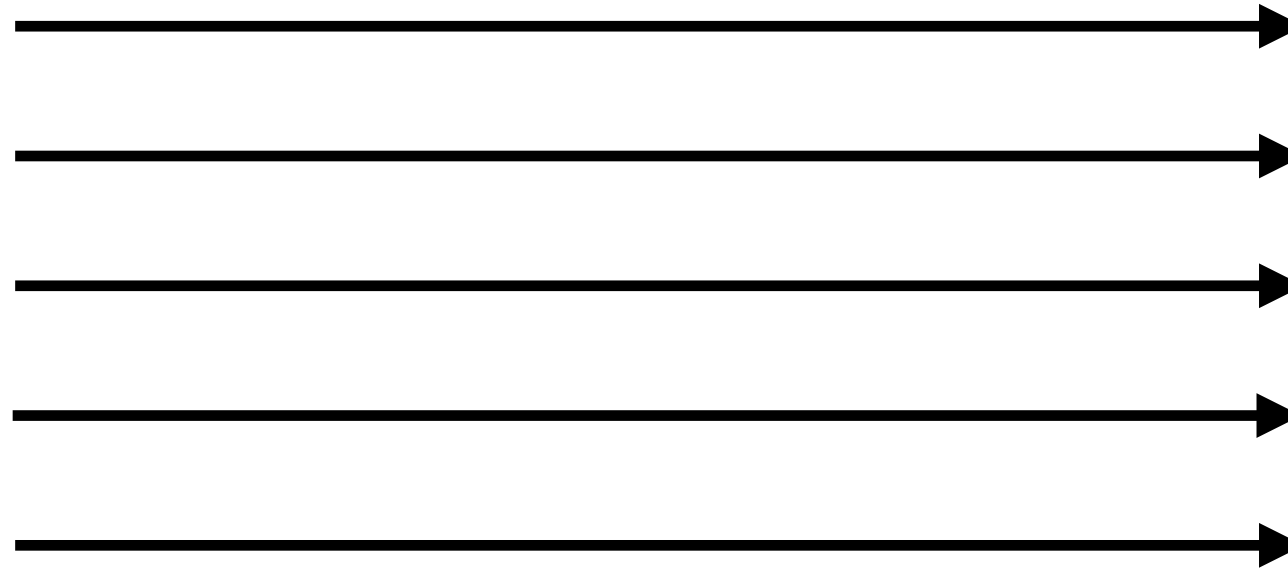
- Are simulation protocols equivalent?

(we will focus on coupled replicas with inequivalent protocols)

If simulation protocols are non-equivalent:

- How are the different protocols chosen?

# Uncoupled, equivalent replicas



Repeat the same simulation protocol N times:

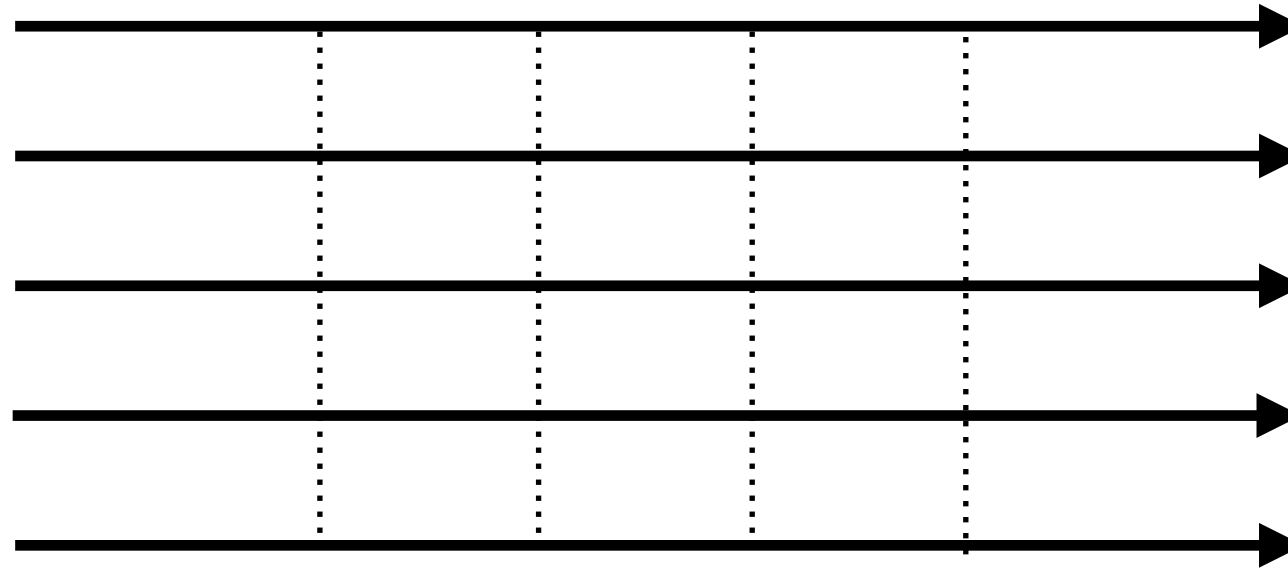
- Error estimation (cfr. Block analysis<sup>&</sup>)
- Parallelization
- Start from different states, analyse with Markov state models<sup>\*</sup>
- Steered molecular dynamics analysed with Jarzynski equality<sup>+</sup>
- ...

<sup>&</sup>Flyvbjerg, Petersen, JCP (1989)

<sup>\*</sup>Chodera and Noe, COSB (2014)

<sup>+</sup>Jarzynski, PRL (1997)

# Coupled, equivalent replicas



Perform N simulations simultaneously. They communicate each other, but they behave in a (statistically) identical manner:

- Replica-average methods (communicate at every step to compute averages)&
- Multiple-walkers metadynamics (share history dependent potential)\*
- Altruistic metadynamics+
- ...

&Lindorff-Larsen et al Nature (2005)

\*Raiteri et al, JPCB (2006)

+Hosek et al JPCB (2016)

# Uncoupled, non-equivalent replicas



Simulations are performed under different conditions:

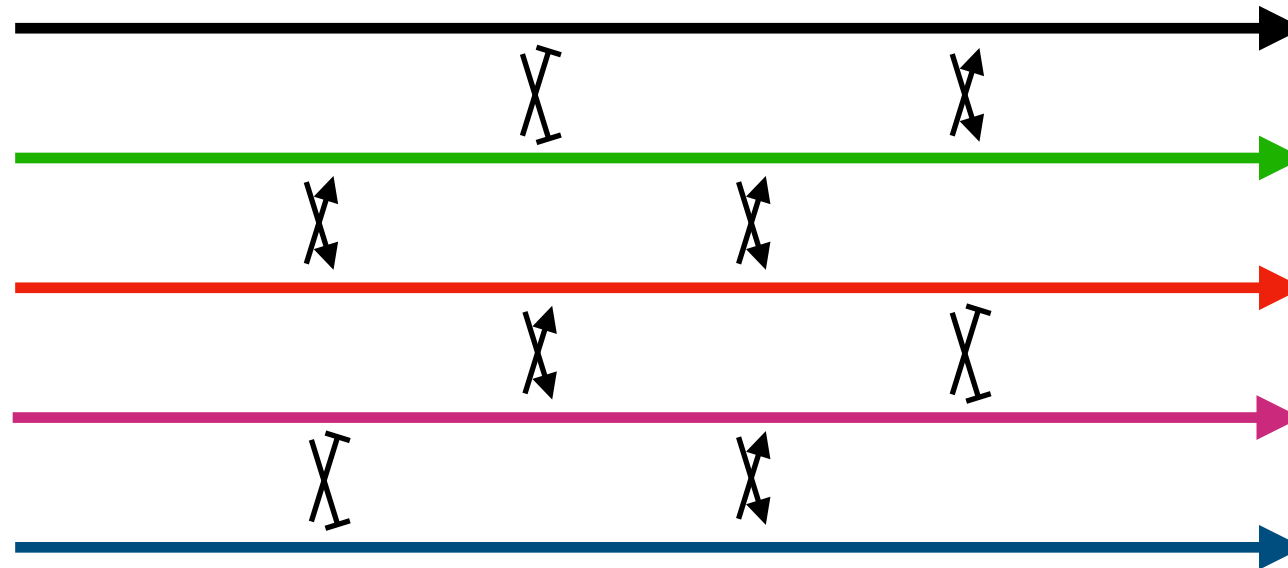
- Multiple-windows umbrella sampling<sup>&</sup>
- Alchemical transformations<sup>\*</sup>

Typically, they are combined with WHAM or related methods  
(see masterclass 21.3)

<sup>&</sup>Kumar et al JCC (1992)

<sup>\*</sup>Shirts, Mobley, and Chodera ARCC (2007)

# Coupled, non-equivalent replicas



The typical coupling is “replica exchange”: from time to time, coordinate exchanges are attempted and accepted or rejected using Metropolis Monte Carlo:

- Parallel tempering (different temperatures)&
- Hamiltonian replica exchange (different Hamiltonians)\*
- Umbrella sampling or alchemical replica exchange
- ...

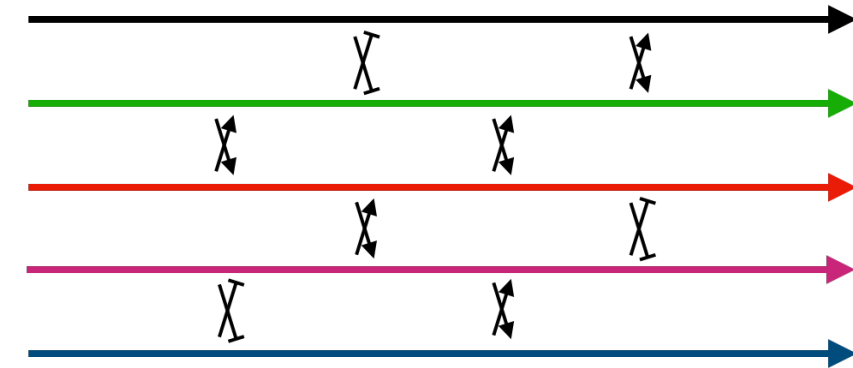
&Hansmann, CPL (1997)

\*Fukunishi et al JCP (2002)



# Replica exchange

Every  $N_x$  steps, propose a coordinate swap.  
Exchange pattern depends on chosen ensembles.



Acceptance:

$$\alpha = \min \left( 1, \frac{P_i(x_j)P_j(x_i)}{P_i(x_i)P_j(x_j)} \right)$$

Different temperatures

$$\alpha = \min \left( 1, e^{\Delta\beta\Delta U} \right)$$

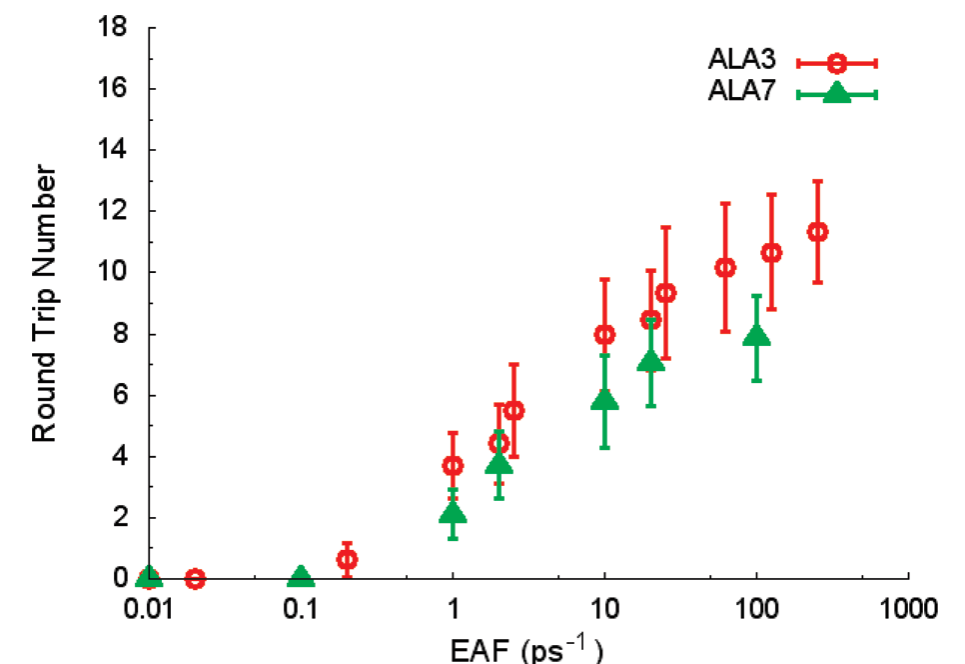
Different potentials

$$\alpha = \min \left( 1, e^{-\beta(U_i(x_j)+U_j(x_i)-U_i(x_i)-U_j(x_j))} \right)$$

The method is an *equilibrium* method. Since exchanges satisfy detailed balance, there's no need to equilibrate after an exchange has been accepted.

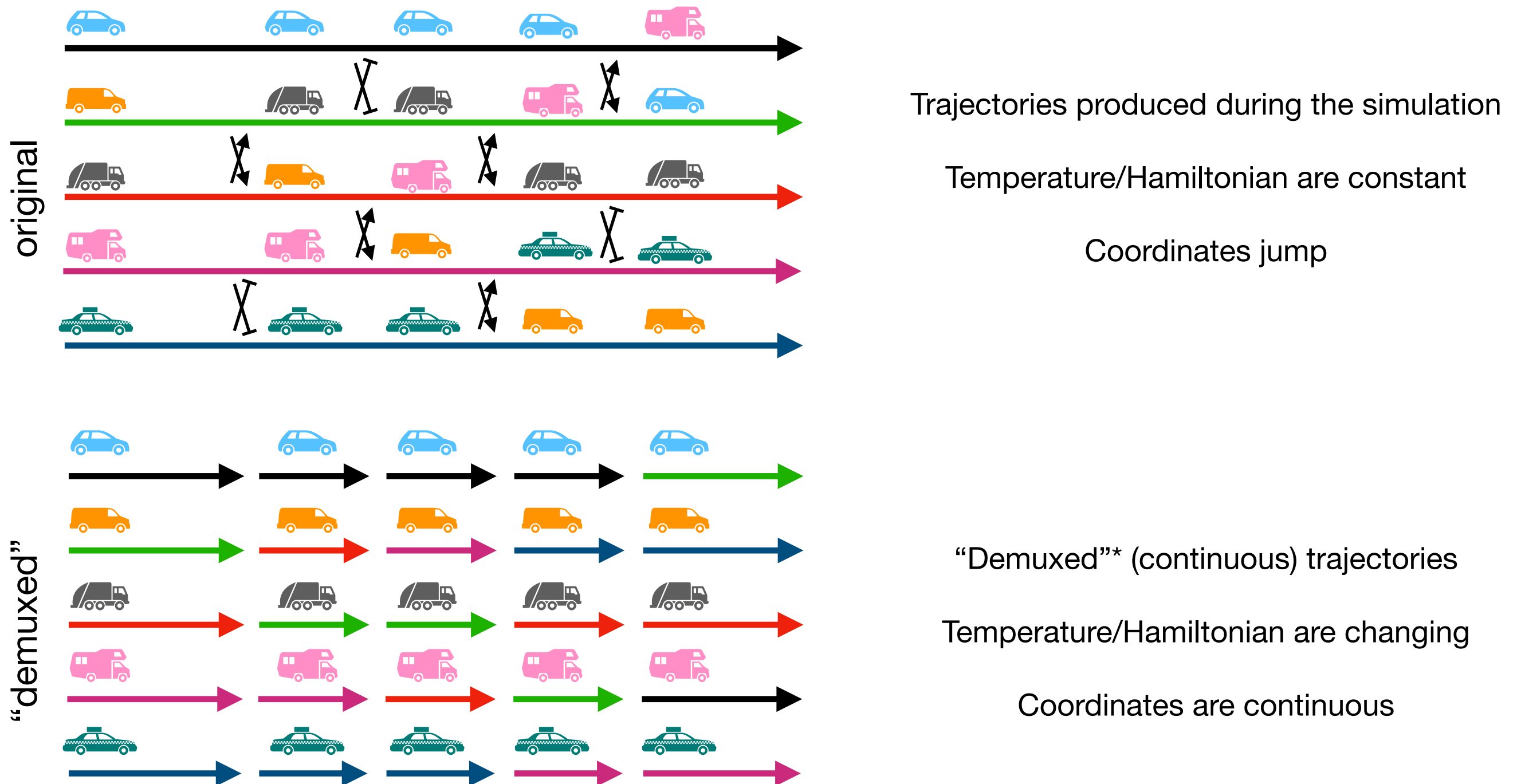
$N_x$  can be as small as one wishes. In most cases, the smallest the better\* (though one should balance with computational overhead).

Much smaller than “autocorrelation time” is usually not giving much advantage.



\*Sindhikara et al JCTC (2010)

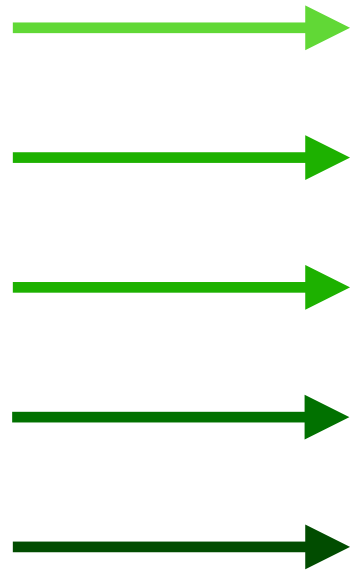
# “Demuxing” trajectories



\*name borrowed from the [demux.pl](#) tool in GROMACS

# Rationale for choosing the ensembles

Bridging

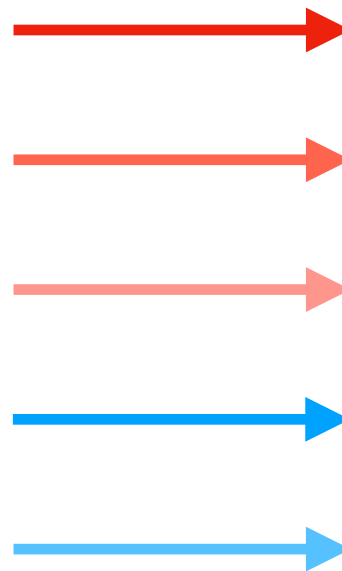


Bring system  
from A to B  
(or C/D/etc)

Replica exchange  
recommended

Usually, exchanges between adjacent pairs

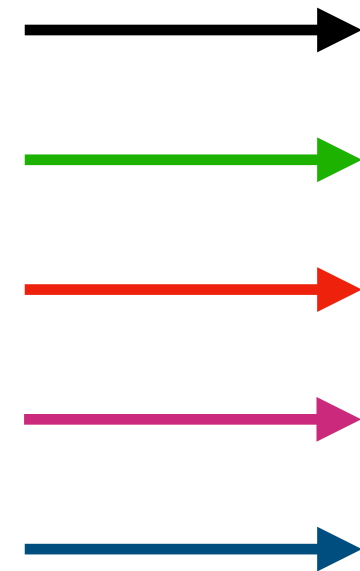
Tempering



Bring system from  
ergodic to non-ergodic

Replica exchange required

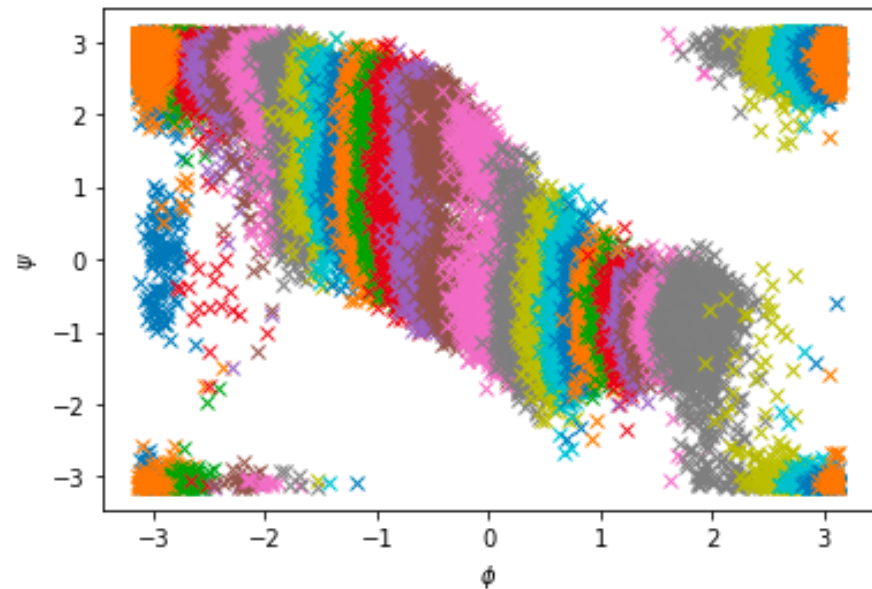
Mixed



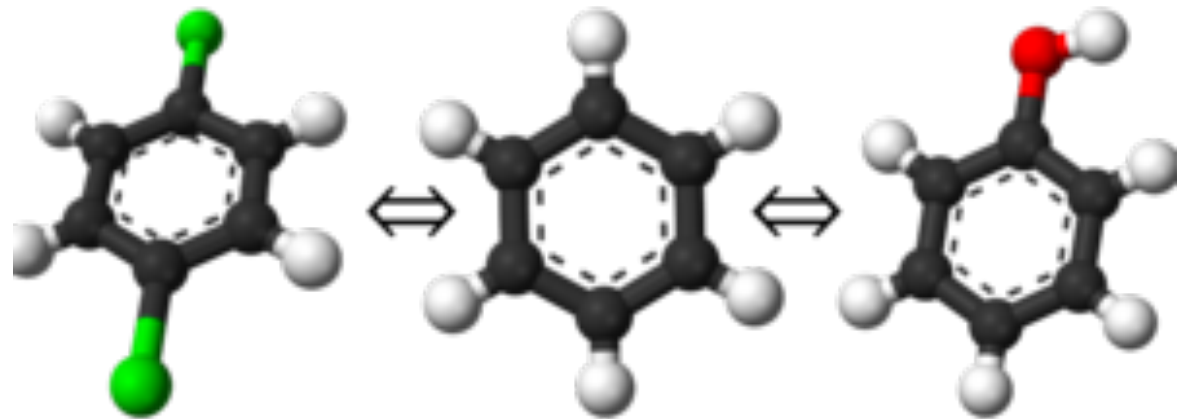
Mix different  
simulations

Exchanges between  
random pairs

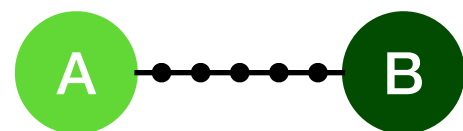
# “Bridging” between states



Restrains at intermediate positions  
(to enhance sampling)

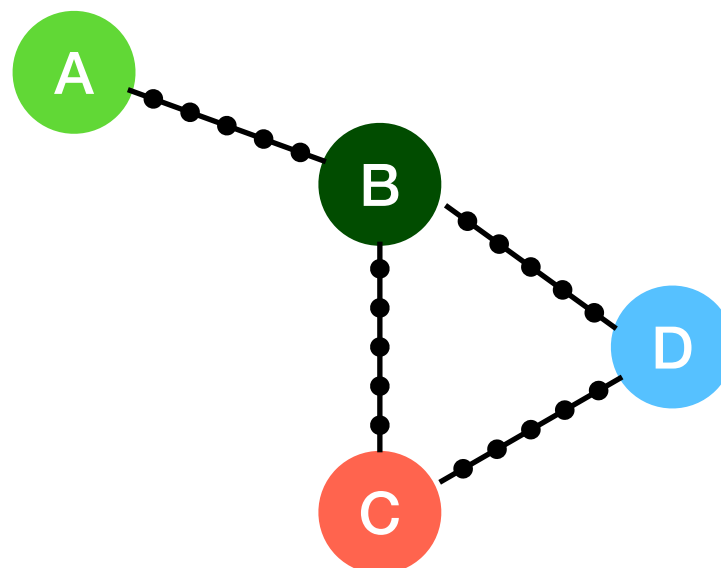


Alchemically changes  
(to compute FE differences)

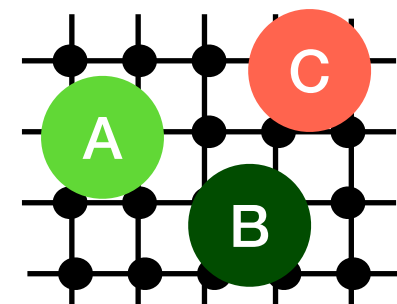


Two end states

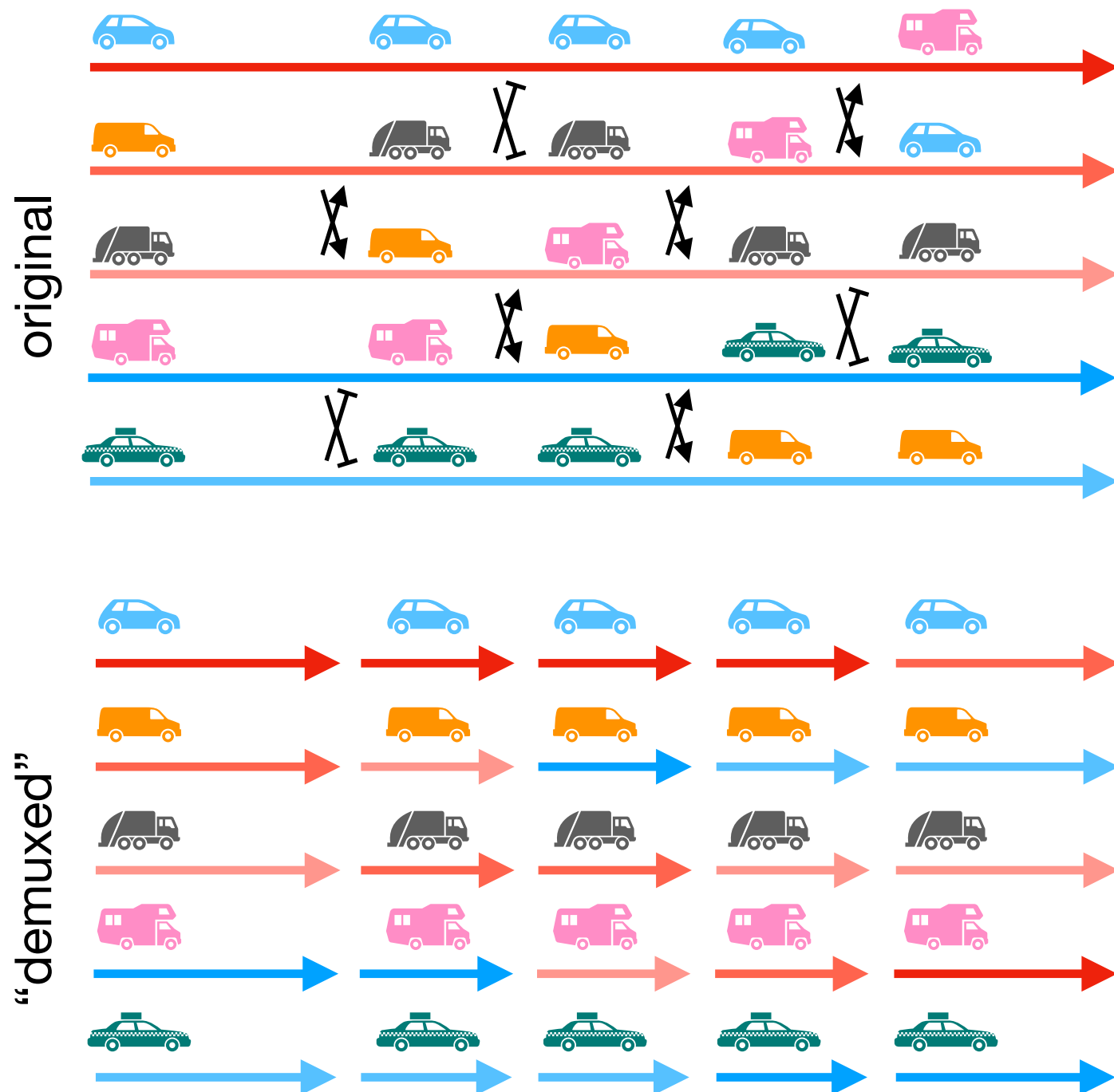
Network of states



Grid (2D/3D)



# Tempering methods



Demux replicas follow an annealing procedure<sup>#</sup> (temperature increases then decreases)

Often, only lower replica is analysed, but it is possible to use WHAM

It is possible to scale Hamiltonian (e.g. REST2, partial tempering)<sup>\*</sup> or to add index-dependent biases<sup>&</sup>

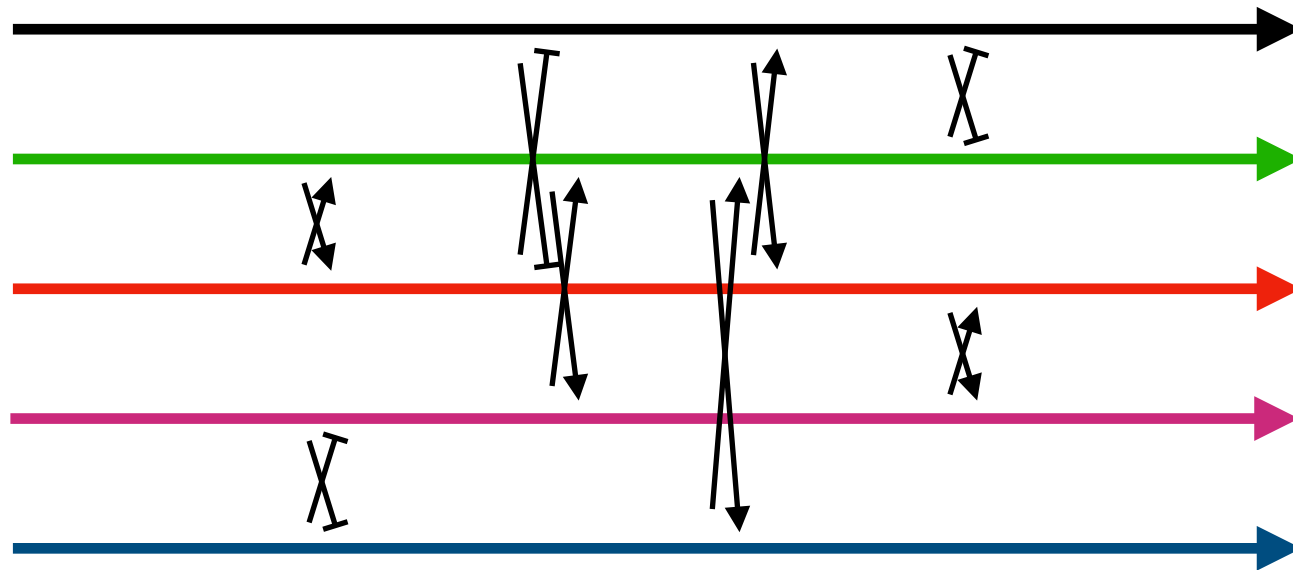
Entropic barriers are not affected by raised temperature

<sup>#</sup>Kirkpatrick et al, Science (1983)

<sup>\*</sup>Wang et al JPCB (2011); Bussi Mol Phys (2014)

<sup>&</sup>Curuksu and Zacharias, JCP (2009); Gil-Ley and Bussi JCTC (2015)

# Mixed ensembles - bias exchange metadynamics



$$\alpha = \min \left( 1, e^{-\beta(U_i(x_j) + U_j(x_i) - U_i(x_i) - U_j(x_j))} \right)$$

Each replica runs a metadynamics on one CV

Optionally, a neutral replica (no metadynamics) is included

Sampling enhanced if one of the CVs can approximately single-out a transition state

Analysis is done using WHAM<sup>#</sup>

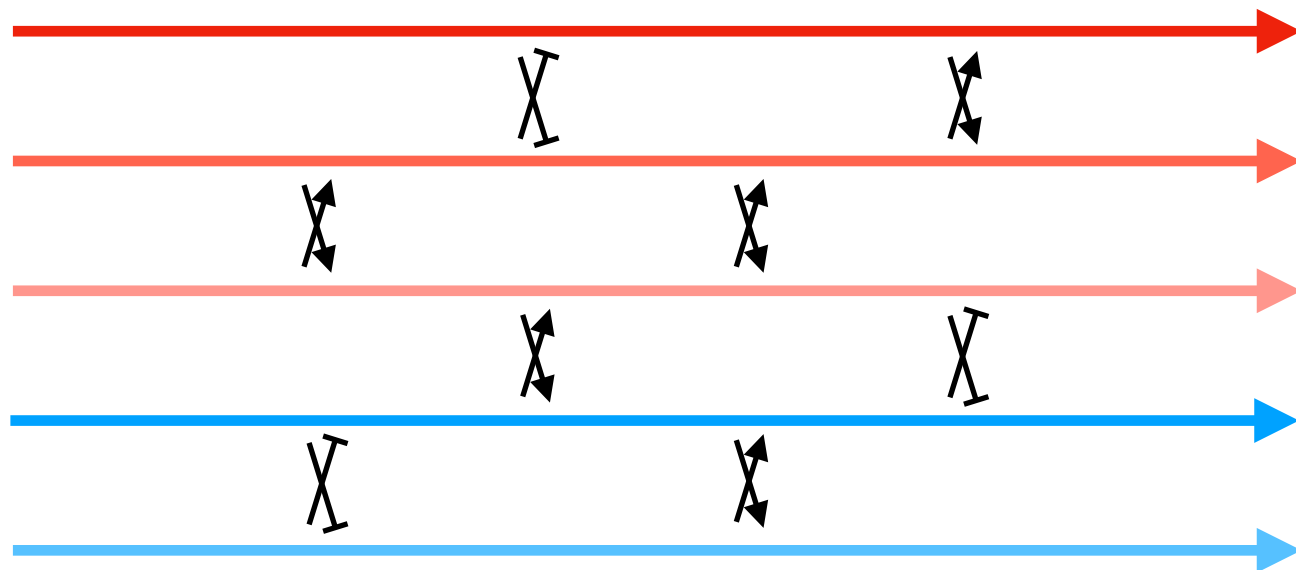
Too frequent exchanges might lead to suboptimal performance (empirical)<sup>\*</sup>

Piana and Laio, JPCB (2007)

<sup>#</sup>Marinelli et al PCB (2009); also binless, see tutorial

<sup>\*</sup>Cossio et al, JPCB (2010)

# Parallel-tempering + metadynamics



Each replica runs a metadynamics on the same CVs, but at a different T

Usually, Gaussian height chosen proportional to temperature T

Parallel tempering enhances all transitions (but requires many replicas!)

Metadynamics enhances selected transitions

Parallel tempering can be replaced with REST2<sup>#</sup>

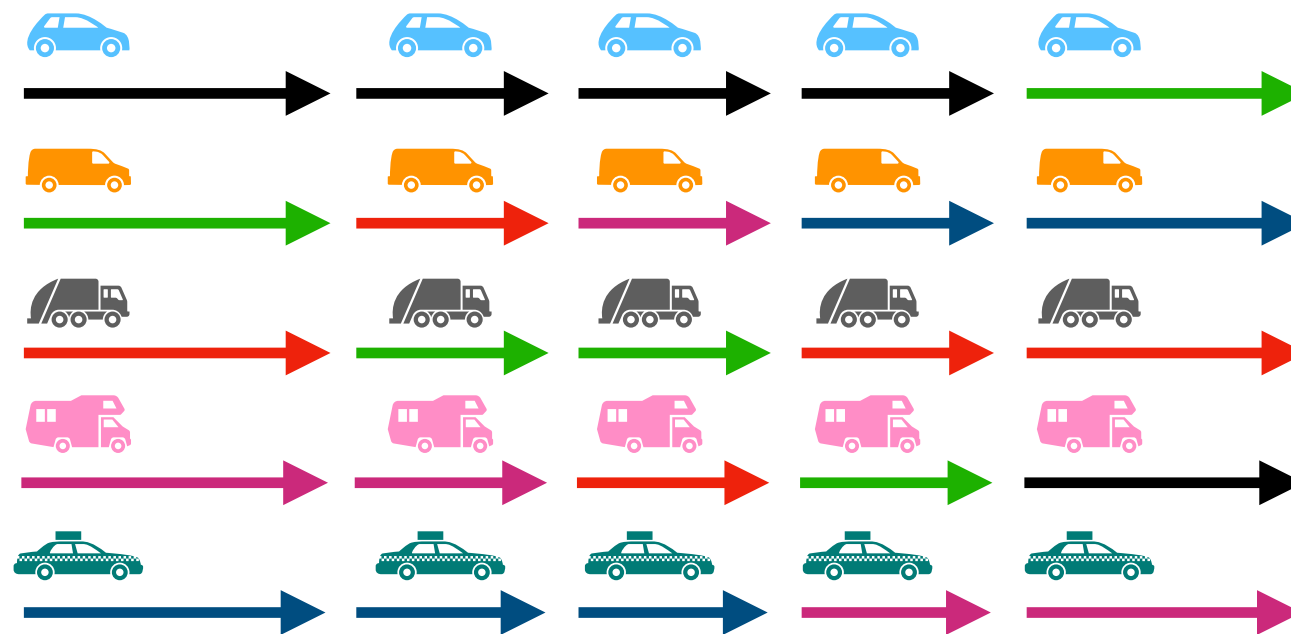
Metadynamics might be used to balance states (not enhance transitions)\*

Bussi et al, JACS (2006)

<sup>#</sup>Camilloni et al, Proteins (2008)

\*Bottaro et al, JPCL (2016)

# Pay attention to block analysis



Original (discontinuous) trajectories might contain long-time correlation that are difficult to detect. The same conformation might appear again in a given replica after some time spent in other replicas.

“Demuxed” (continuous) trajectories are more smooth. My recommendation:

- Check that they display transitions
- Difference between them might suggest problems
- Can be used as quasi-independent blocks (see tutorial)



# Multiple replicas with plumed + gromacs

attention to shell globbing

```
mpiexec -np 8 gmx_mpi mdrun -multidir  
dir? dir?? -plumed ../plumed.dat
```

```
# a single plumed file  
plumed.dat  
dir0/topol.tpr  
dir1/topol.tpr  
...  
dir15/topol.tpr
```

topol.tpr might be generated with:

- different initial coordinates
- different temperatures/pressure
- different lambdas (alchemical)

If bias potential for different replicas is different, it will affect acceptance

NB also with a single file it could be different, e.g. depending on history of each replica!

```
mpiexec -np 8 gmx_mpi mdrun -multidir  
dir? dir?? -plumed plumed.dat
```

```
# separate plumed files
```

```
dir0/topol.tpr dir0/plumed.dat  
dir1/topol.tpr dir1/plumed.dat  
...  
dir15/topol.tpr dir15/plumed.dat
```

(for codes without multidir, use  
plumed.0.dat, plumed.1.dat, etc.)

output files will be suffixed in both cases  
(e.g. colvar.0.dat, colvar.1.dat)

$$\alpha = \min \left( 1, e^{\Delta\beta\Delta U - (\beta_i V_i(x_j) + \beta_j V_j(x_i) - \beta_i V_i(x_i) - \beta_j V_j(x_j))} \right)$$

# Use a single plumed.dat when possible

```
# replicas run metadynamics with height proportional to T  
# (as in parallel-tempering metadynamics)
```

```
phi: TORSION ATOMS=5,6,7,8  
METAD ARG=phi TAU=2.0 SIGMA=0.3 # TAU instead of HEIGHT
```

Use “@replicas:” syntax to make small variations

```
# replicas have restraints at different positions  
# (as in multiple windows umbrella sampling)
```

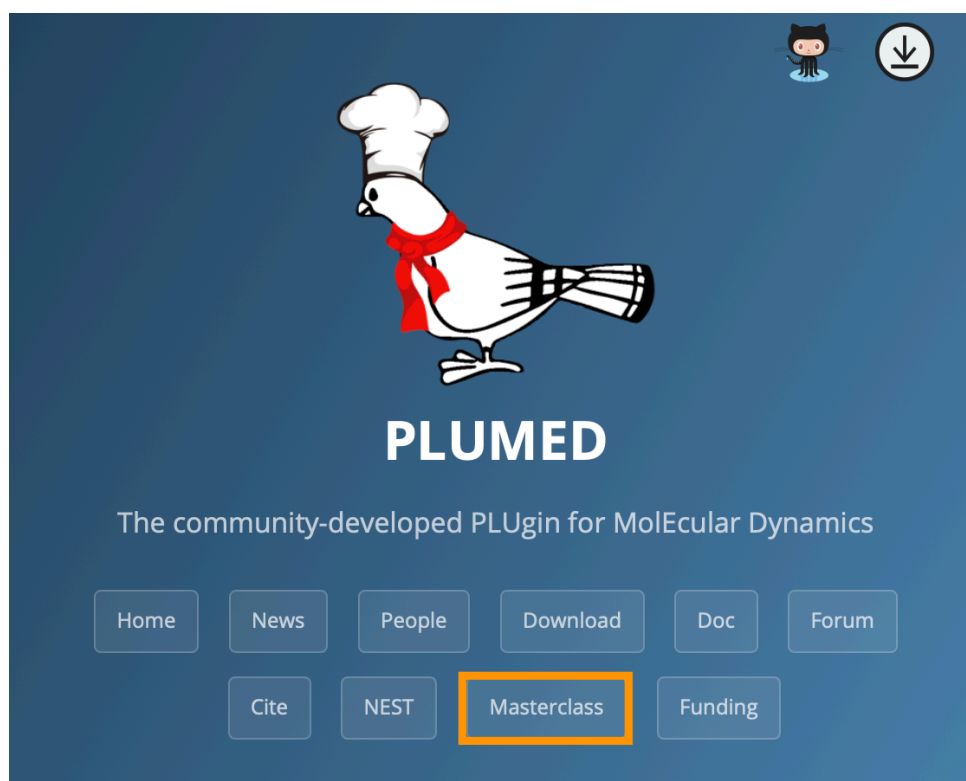
```
phi: TORSION ATOMS=5,6,7,8  
RESTRAINT ARG=phi KAPPA=100 AT=@replicas:1.0,1.5,2.0,2.5
```

```
# replicas run metadynamics on different collective variables  
# (as in bias-exchange metadynamics)
```

```
d: DISTANCE ATOMS=1,2  
phi: TORSION ATOMS=5,6,7,8  
METAD ARG=@replicas:d,phi HEIGHT=1.0 SIGMA=@replicas:0.1,0.3
```

In any case, maximum flexibility with separate plumed.dat files

# Instructions



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1. Go to [www.plumed.org](http://www.plumed.org)
2. Click on the **Masterclass** tab
3. Click on the **Topic** of class 21.5
4. 1 week to complete the exercises
5. Questions/discussions on Slack channel [masterclass-21-5](#)
6. Lecture I and II available on **YouTube**