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GROMACS

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PLUMED Masterclass

22.10: Hamiltonian Replica Exchange (GROMACS + PLUMED)

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@BussiGio

See also Masterclass 21.5!
(Simulations with multiple replicas)

SISSA

Enhanced sampling

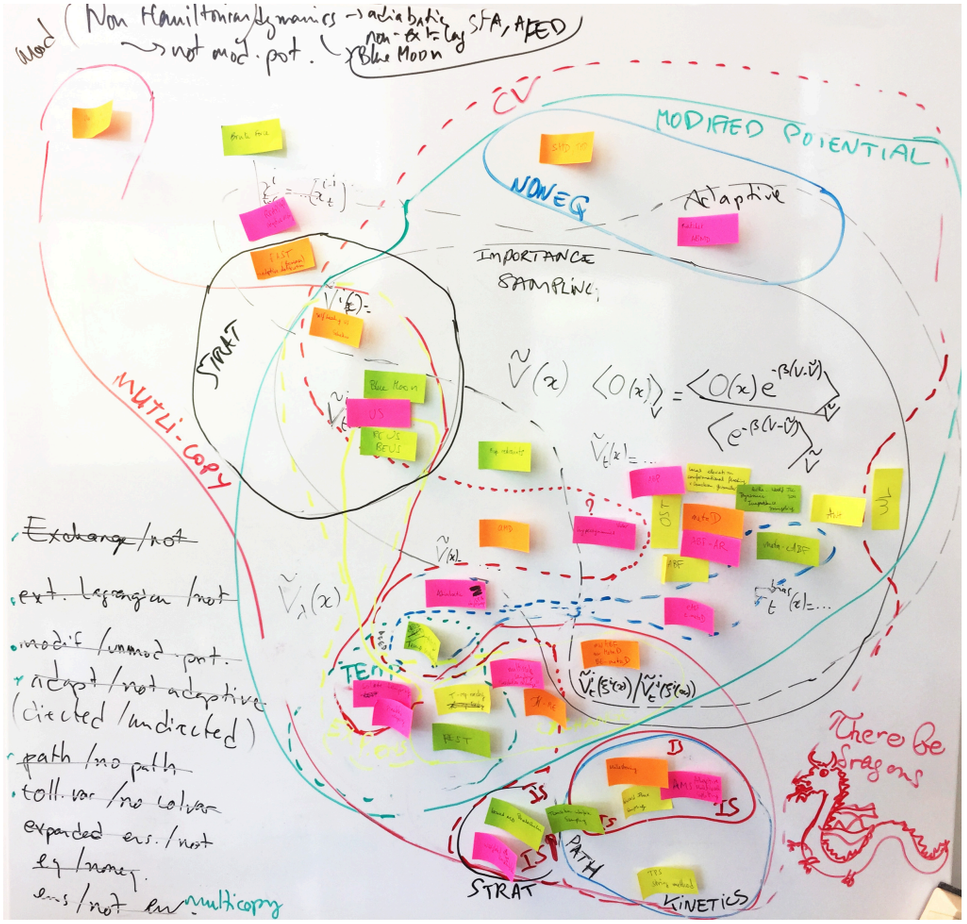
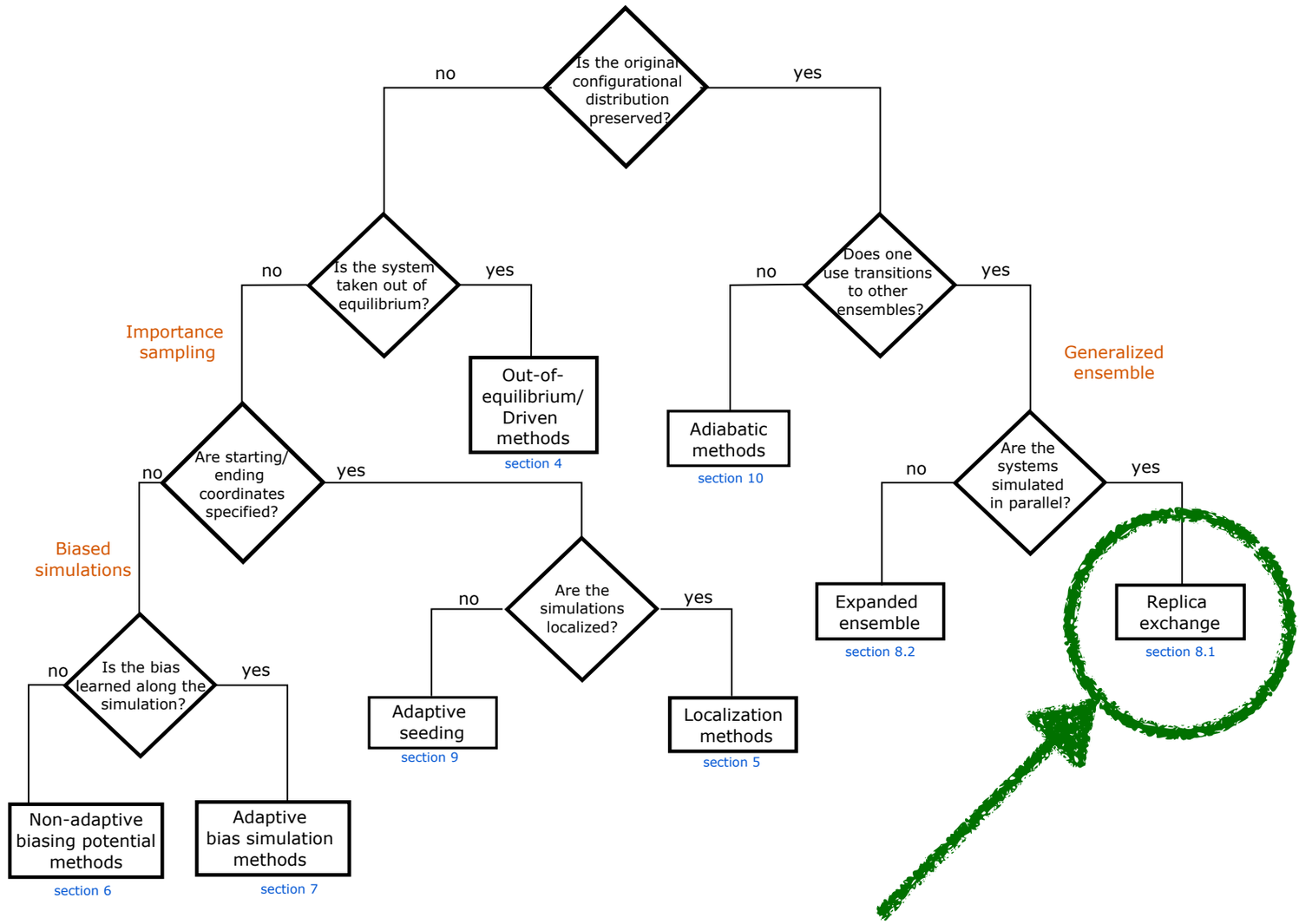
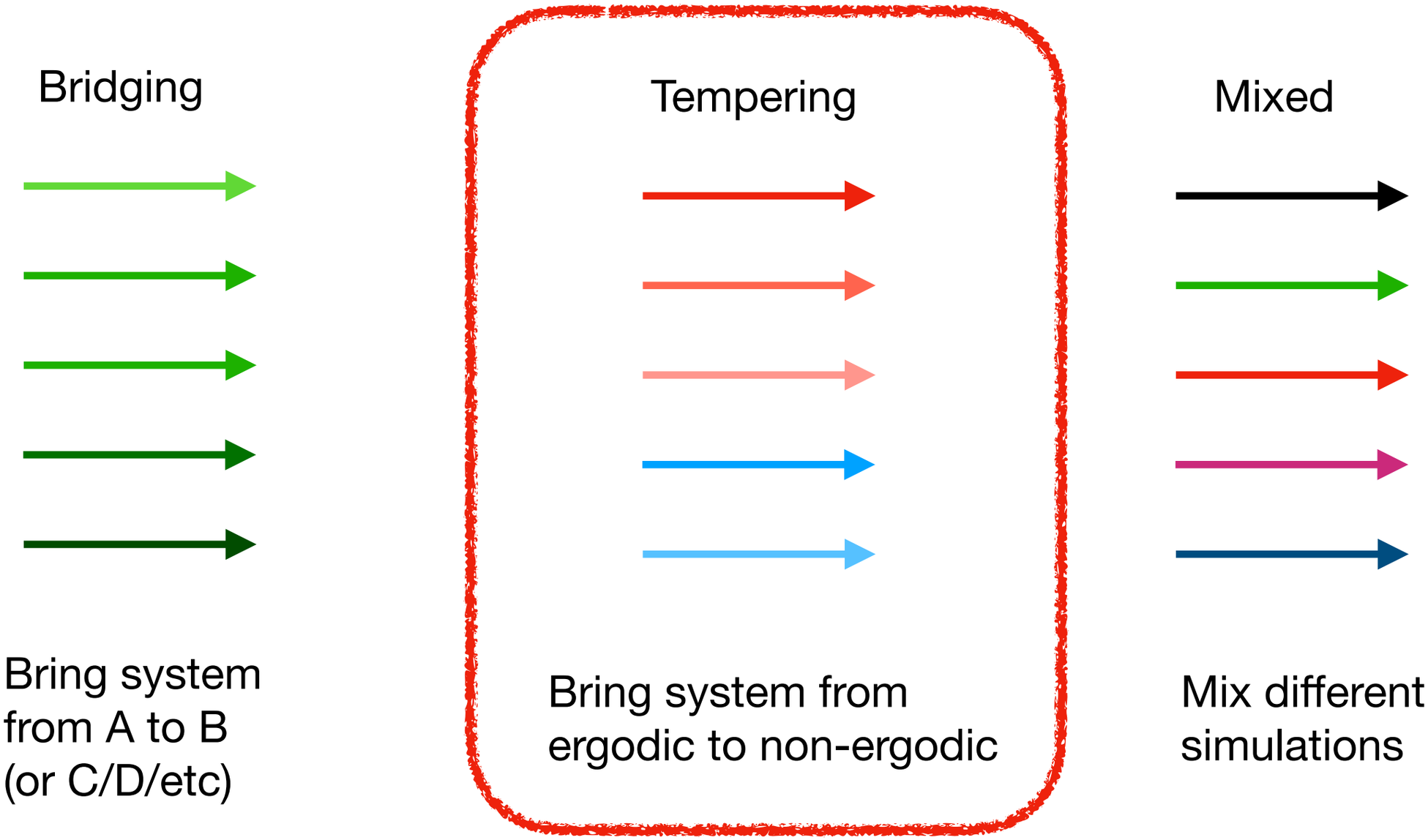


Figure 2. Early attempt at listing and classifying existing enhanced sampling schemes.



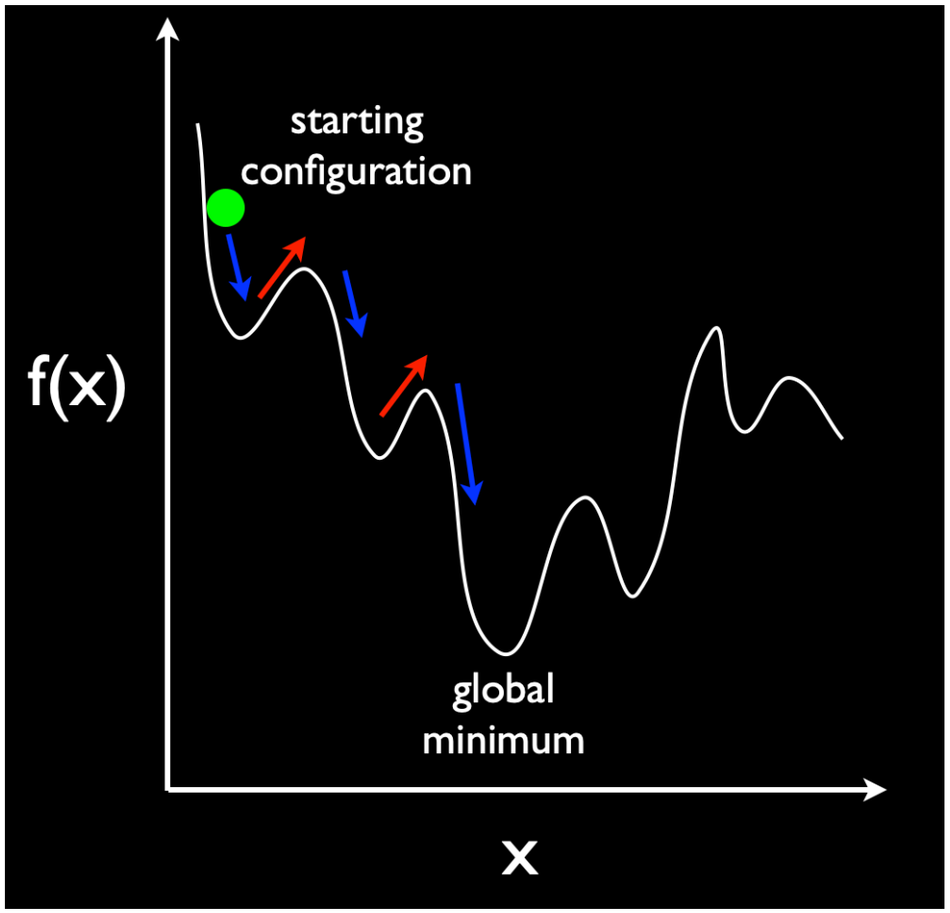
Henin et al, arXiv (2022)

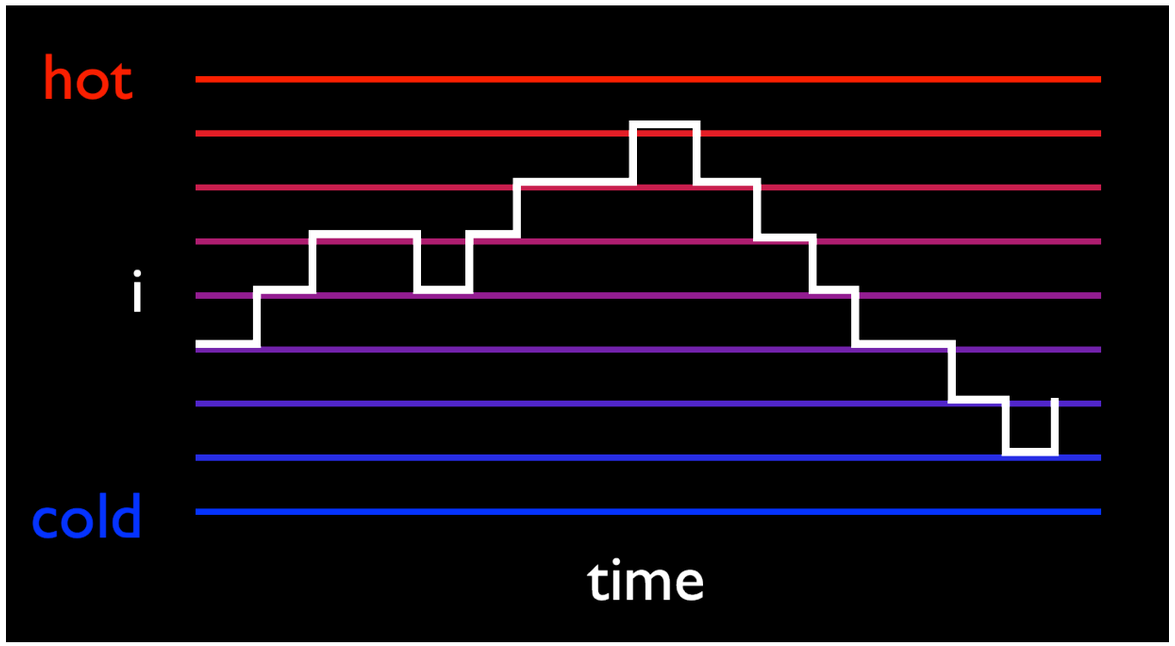
Rationale for choosing the ensembles

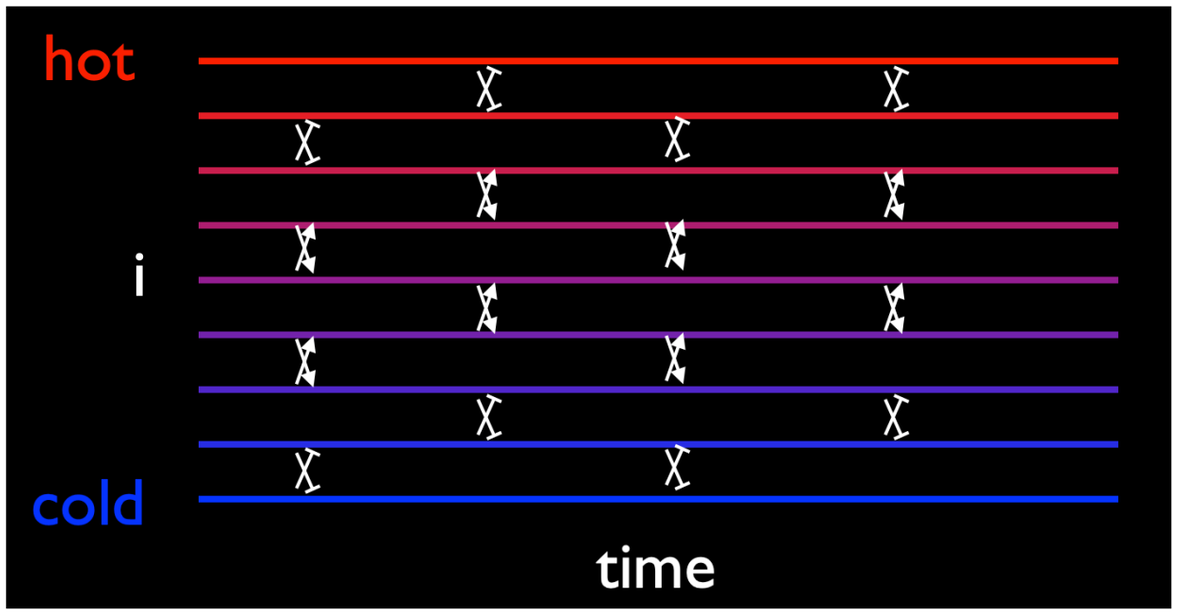


From Masterclass 21.5

Simulated annealing, simulated tempering, and parallel tempering (T-REMD)







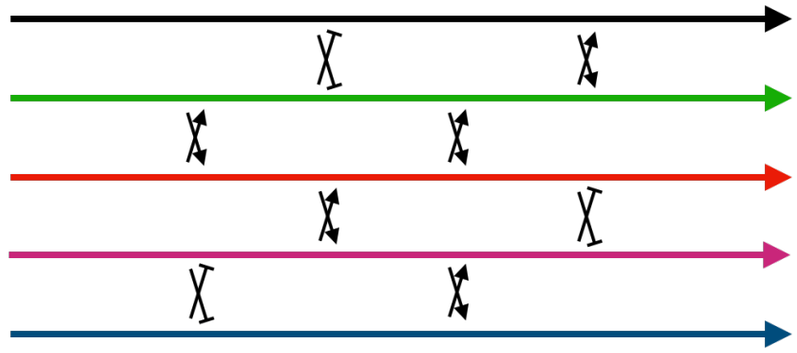
Kirkpatrick et al, Science (1983)

Marinari and Parisi, EPL (1992)

Hansmann, CPL (1997)

Sugita and Okamoto, CPL (1999)

Replica exchange



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

Acceptance:

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

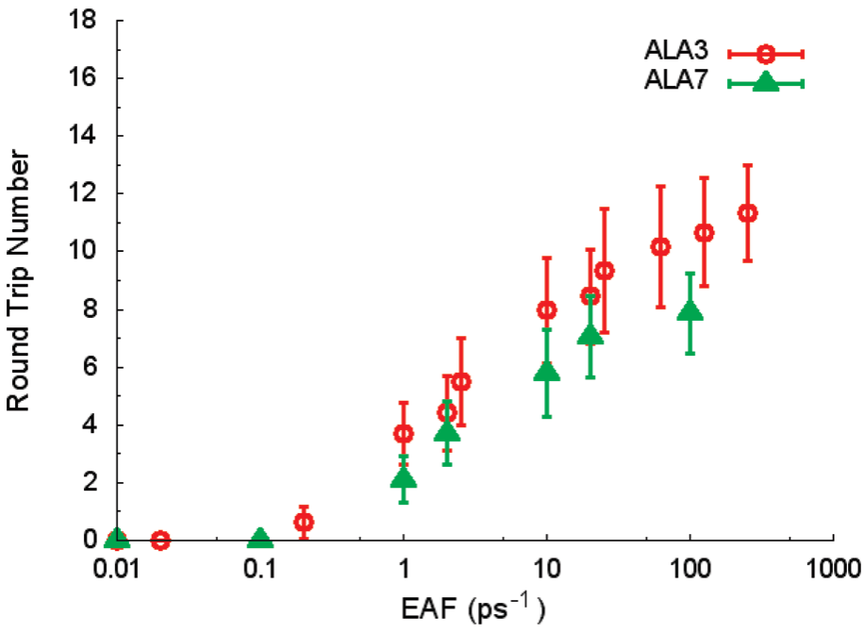
Different temperatures $\alpha = \min\left(1, e^{\Delta\beta\Delta U}\right)$

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.

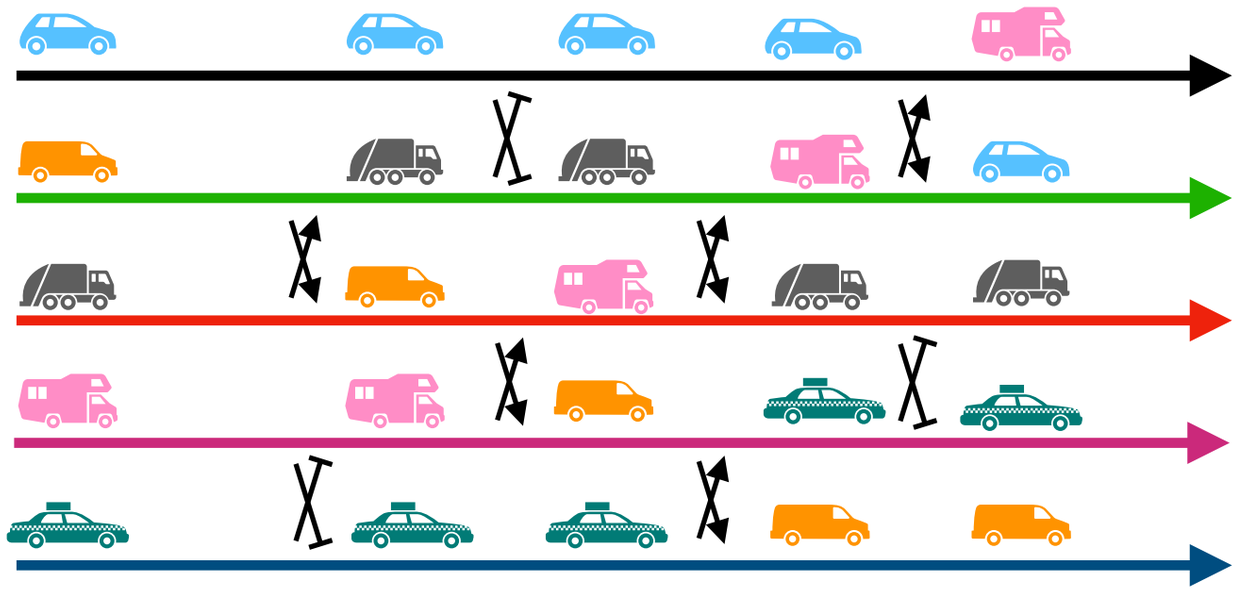


*Sindhikara et al JCTC (2010)

From Masterclass 21.5

“Demuxing” trajectories

original

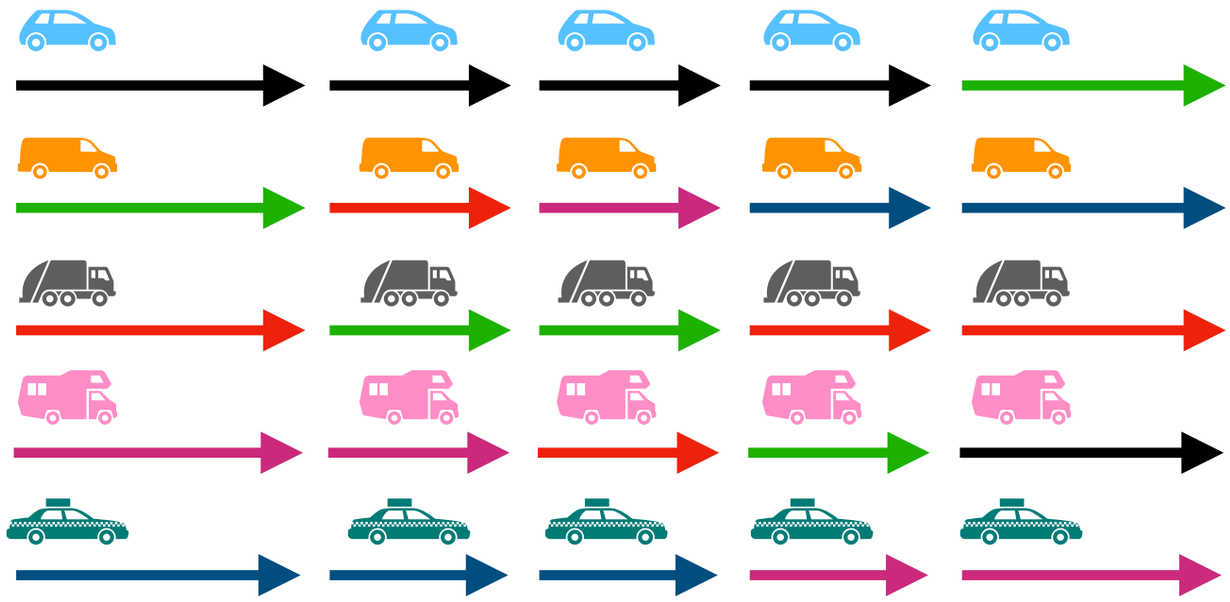


Trajectories produced during the simulation

Temperature/Hamiltonian are constant

Coordinates jump

“demuxed”



“Demuxed”* (continuous) trajectories

Temperature/Hamiltonian are changing

Coordinates are continuous

*name borrowed from the demux.pl tool in GROMACS

From Masterclass 21.5

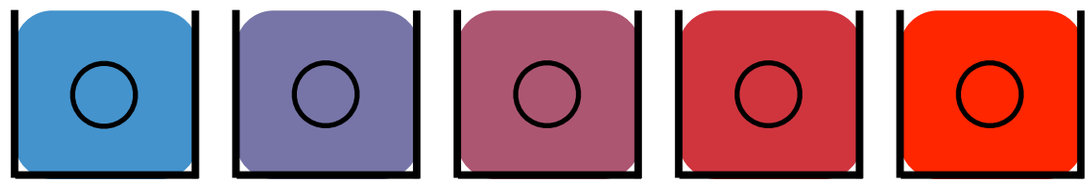
Increase temperature vs decrease energy

Canonical ensemble $P(q;\lambda) \propto e^{-\frac{U(q)}{(\lambda T)}} = e^{-\frac{(U(q)/\lambda)}{T}}$

Energy is extensive $U(q) = U_1(q) + U_2(q)$

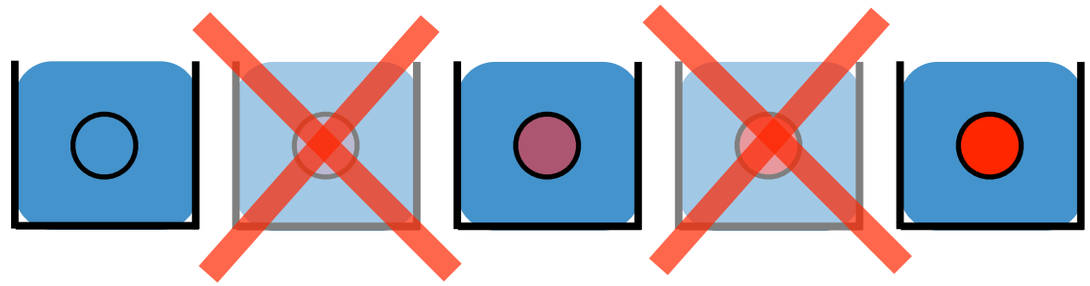
"Selective" heating $P(q;\lambda) \propto e^{-\frac{U_1(q)+U_2(q)/\lambda}{T}}$

parallel tempering

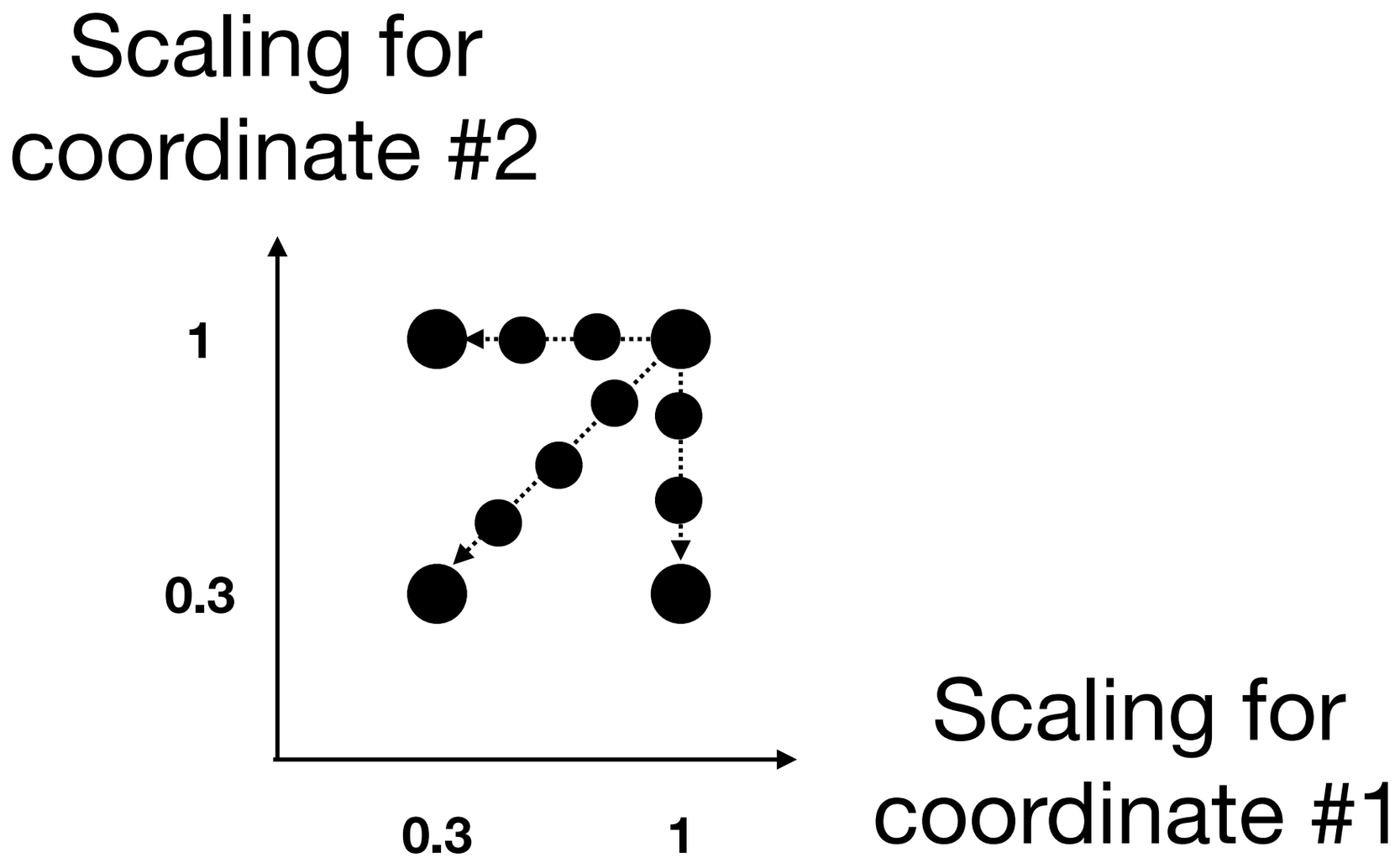


vs

solute tempering



Understanding the scaling of N replica vs system size



Diagonal length proportional to sqrt(N)

Solute tempering aka REST2

THE JOURNAL OF PHYSICAL CHEMISTRY B

ARTICLE

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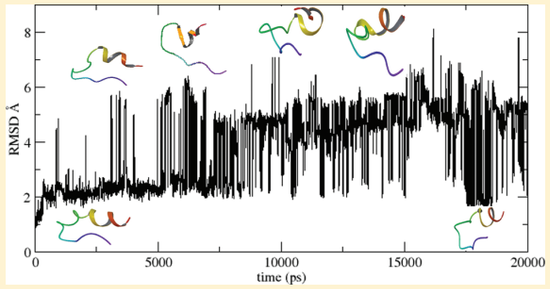
Replica Exchange with Solute Scaling: A More Efficient Version of Replica Exchange with Solute Tempering (REST2)

Lingle Wang, Richard A. Friesner, and B. J. Berne*

Department of Chemistry, Columbia University, 3000 Broadway, New York, New York 10027, United States

ABSTRACT: A small change in the Hamiltonian scaling in Replica Exchange with Solute Tempering (REST) is found to improve its sampling efficiency greatly, especially for the sampling of aqueous protein solutions in which there are large-scale solute conformation changes. Like the original REST (REST1), the new version (which we call REST2) also bypasses the poor scaling with system size of the standard Temperature Replica Exchange Method (TREM), reducing the number of replicas (parallel processes) from what must be used in TREM. This reduction is accomplished by deforming the Hamiltonian function for each replica in such a way that the acceptance probability for the exchange of replica configurations does not depend on the number of explicit water molecules in the system. For proof of concept, REST2 is compared with TREM and with REST1 for the folding of the trpcage and β-hairpin in water. The comparisons confirm that REST2 greatly reduces the number of CPUs required by regular replica exchange and greatly increases the sampling efficiency over REST1. This method reduces the CPU time required for calculating thermodynamic averages and for the ab initio folding of proteins in explicit water.



$$E_m^{\mathrm{REST2}}(X) = \frac{\beta_m}{\beta_0} E_{\mathrm{p}}(X) + \sqrt{\frac{\beta_m}{\beta_0}} E_{\mathrm{pw}}(X) + E_{\mathrm{ww}}(X)$$

See Liu et al PNAS (2005) for REST1
Wang et al, JPCB (2011)

JCTC Journal of Chemical Theory and Computation

A Novel Hamiltonian Replica Exchange MD Protocol to Enhance Protein Conformational Space Sampling

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Institut für Biochemie, Eidgenössische Technische Hochschule ETH-Zurich, Schafmattstrasse 18, 8093 Zurich, Switzerland, and Institut de Chimie Moléculaire et Biologique, BCH-LCBC, Ecole Polytechnique Fédérale de Lausanne, 1015 Lausanne, Switzerland

Received October 13, 2005

Abstract: Limited searching in the conformational space is one of the major obstacles for investigating protein dynamics by numerical approaches. For this reason, classical all-atom molecular dynamics (MD) simulations of proteins tend to be confined to local energy minima, particularly when the bulk solvent is treated explicitly. To overcome this problem, we have developed a novel replica exchange protocol that uses modified force-field parameters to treat interparticle nonbonded potentials within the protein and between protein and solvent atoms, leaving unperturbed those relative to solvent−solvent interactions. We have tested the new protocol on the 18-residue-long tip of the P domain of calreticulin in an explicit solvent. With only eight replicas, we have been able to considerably enhance the conformational space sampled during a 100 ns simulation, compared to as many parallel classical molecular dynamics simulations of the same length or to a single one lasting 450 ns. A direct comparison between the various simulations has been possible thanks to the implementation of the weighted histogram analysis method, by which conformations simulated with modified force-field parameters can be assigned different weights. Interatom, inter-residue distances in the structural ensembles obtained with our novel replica exchange approach and by classical MD simulations compare equally well with those derived from NMR data. Rare events, such as unfolding and refolding, occur with reasonable statistical frequency. Visiting of conformations characterized by very small Boltzmann weights is also possible. Despite their low probability, such regions of the conformational space may play an important role in the search for local potential-energy minima and in dynamically controlled functions.

$$E_k(\mathbf{q}) = V_{\mathrm{u}}(\mathbf{q}) + f_k V_1(\mathbf{q}) + f_k^2 V_2(\mathbf{q})$$

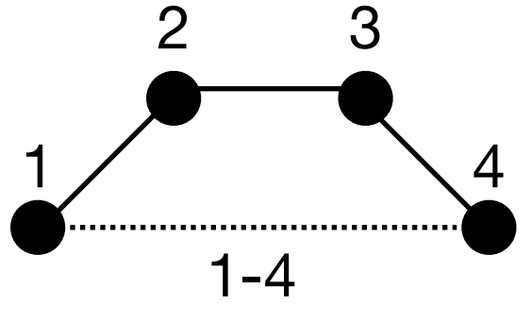
Affentranger et al, JCTC (2006)

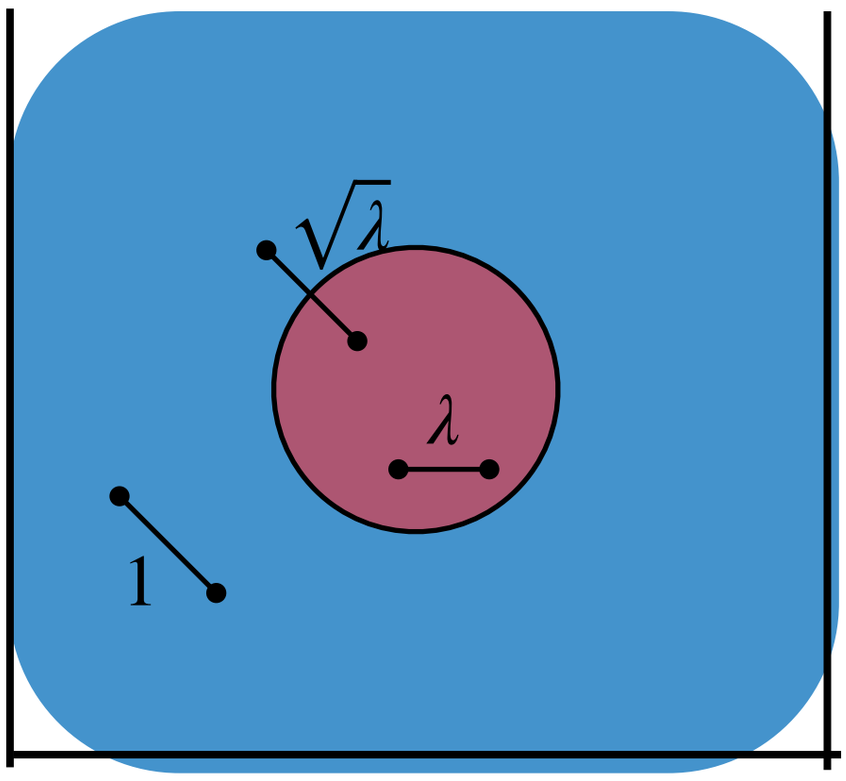
Multiple topologies

$$E = \sum_{bonds} \frac{1}{2} k_b (r - r_0)^2 + \sum_{angles} \frac{1}{2} k_a (a - a_0)^2 +$$

$$\sum_{torsions} \sum_{n} \frac{V_n}{2} (1 + \cos(n\phi - \delta)) +$$

$$\sum_{LJ} 4\varepsilon_{ij} \left(\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right) + \sum_{electrostatics} \frac{q_i q_j}{r_{ij}}$$





$$\epsilon_i' = \lambda \epsilon_i \qquad \epsilon_{ij}' = \sqrt{\epsilon_i \epsilon_j} = \sqrt{\lambda_i \lambda_j} \epsilon_{ij}$$

$$q_i' = \sqrt{\lambda} q_i \qquad q_i' q_j' = \sqrt{\lambda_i \lambda_j} q_i q_j$$

$V_n' = \lambda V_n$ If 1-4 are in hot region

$V_n' = \sqrt{\lambda} V_n$ If 1 and 4 are in hot/cold region

Bonds and bends not scaled (in this implementation)

Implementation in GROMACS

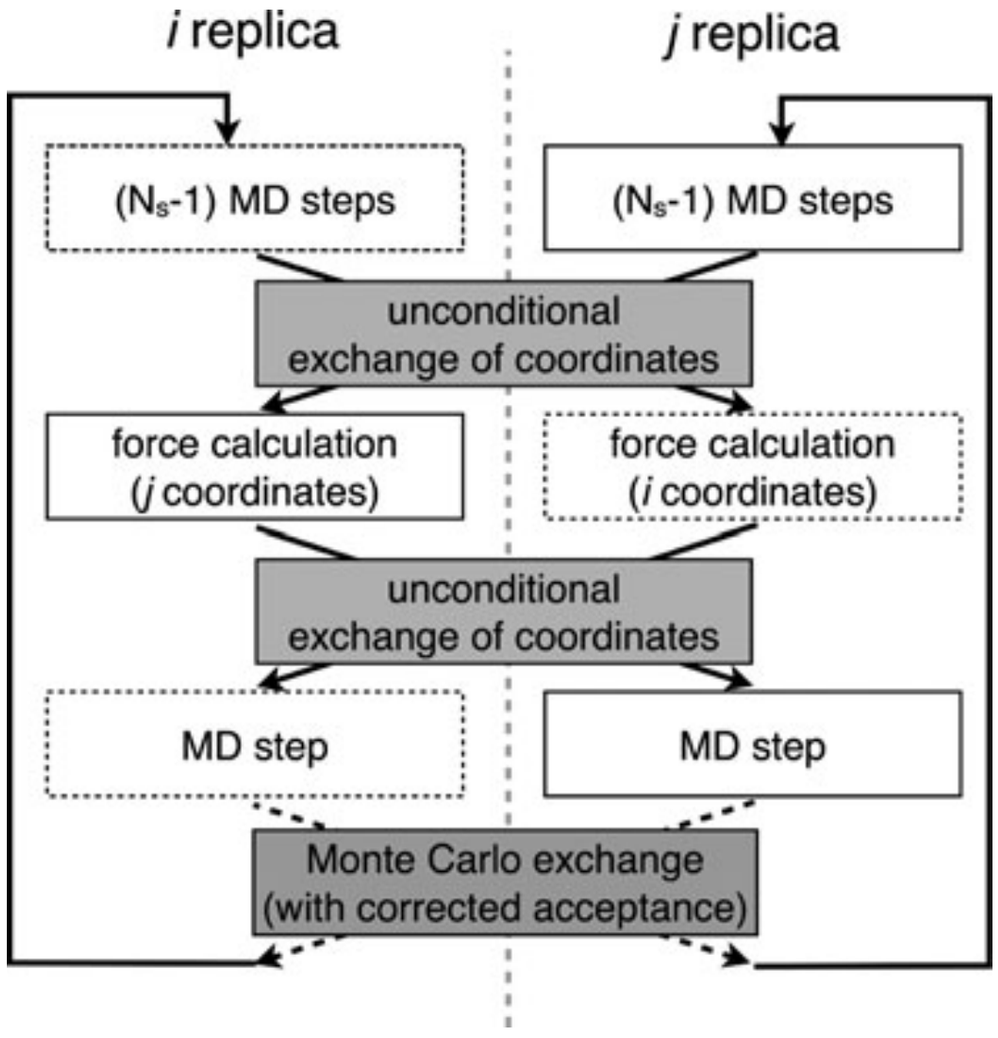


Figure 1. Flowchart of our HREX implementation. After having performed $N_s - 1$ molecular dynamics steps, a coordinate swap is carried out. Then, the energy is recomputed and coordinates are swapped again. At this point, a further MD step is done and a real exchange is attempted with a corrected Monte Carlo acceptance (Equation (1)).

Arbitrary force fields

Identical masses
(velocities are not scaled!)

Bussi Mol Phys (2014)

Example: alanine dipeptide in water

As a first test case, we focused on alanine dipeptide, a standard benchmark for enhanced sampling methods. The low-energy conformations of this system can be described using the two dihedral angles of the Ramachandran plot, ϕ and ψ. Transitions between conformations $C_{7\mathrm{eq}}(\phi = -80^\circ, \psi = 75^\circ)$ and $C_{7\mathrm{ax}}(\phi = 75^\circ, \psi = -75^\circ)$ are hindered by large free-energy barriers. An alanine dipeptide molecule modeled with Amber99sb force field [30] was solvated in a box containing approximately 700 TIP3P water molecules [31]. All bonds were kept rigid [32,33] and equations of motion were integrated using a time step of 2 fs. Long-range electrostatics was treated using particle-mesh Ewald [34] and temperature was controlled by stochastic velocity rescaling [35].

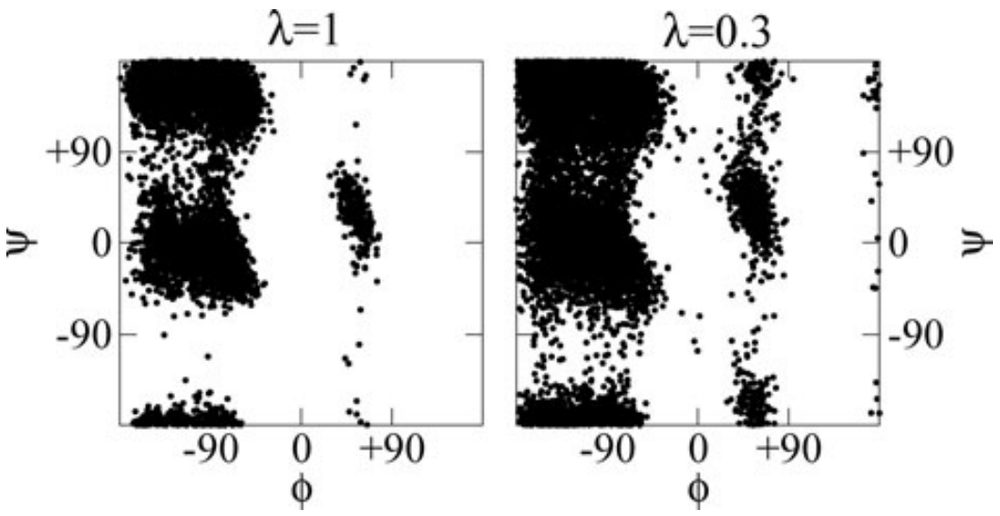


Figure 2. Conformational space explored for alanine dipeptide by first ($\lambda = 1$, left) and last ($\lambda = 0.3$, right) replicas. It can be seen that the conformational space explored by the last replica is larger.

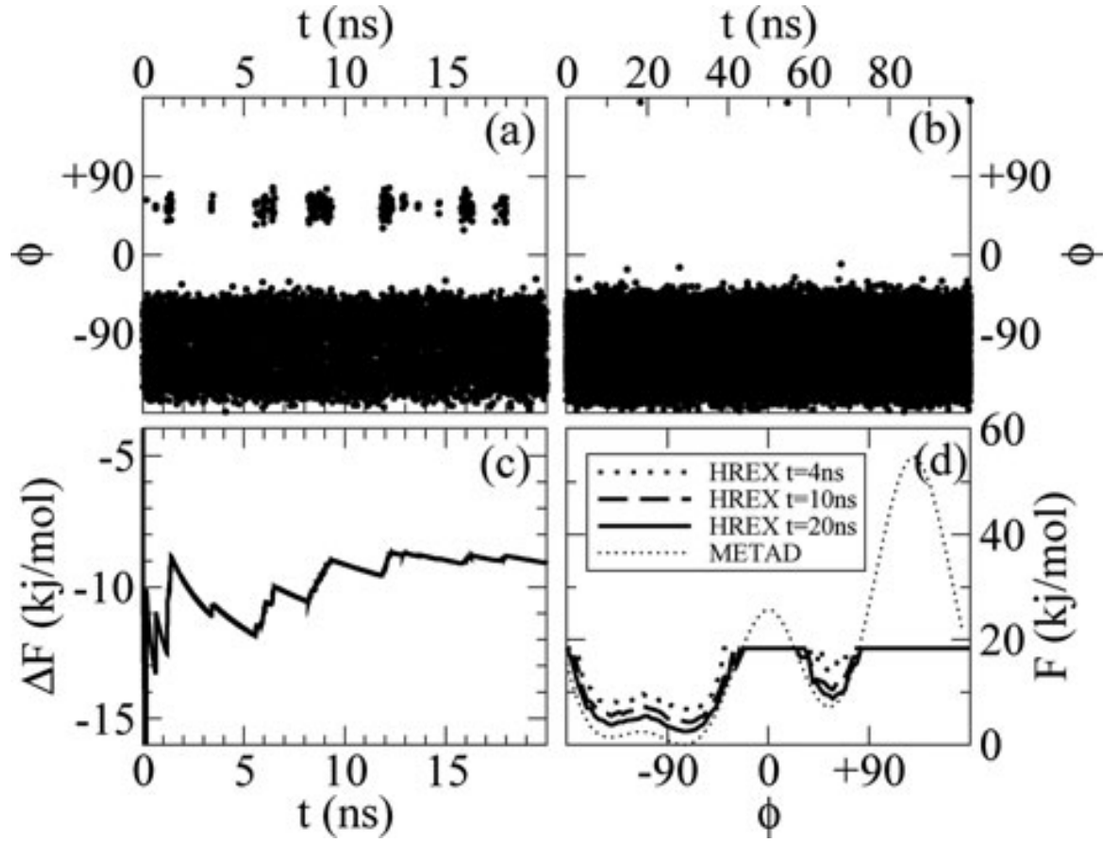
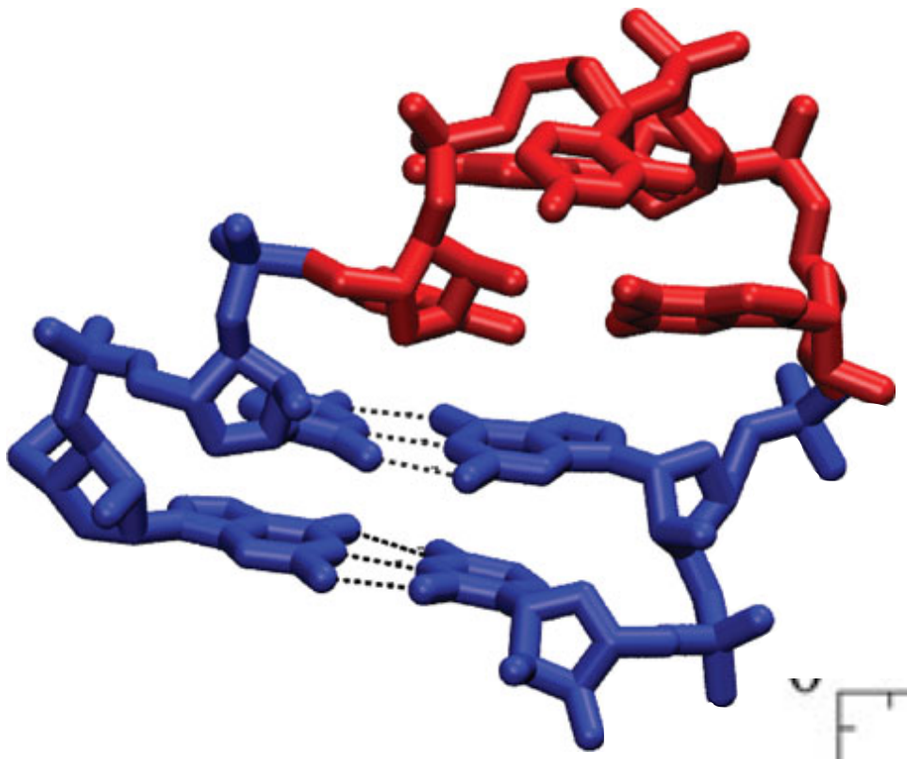
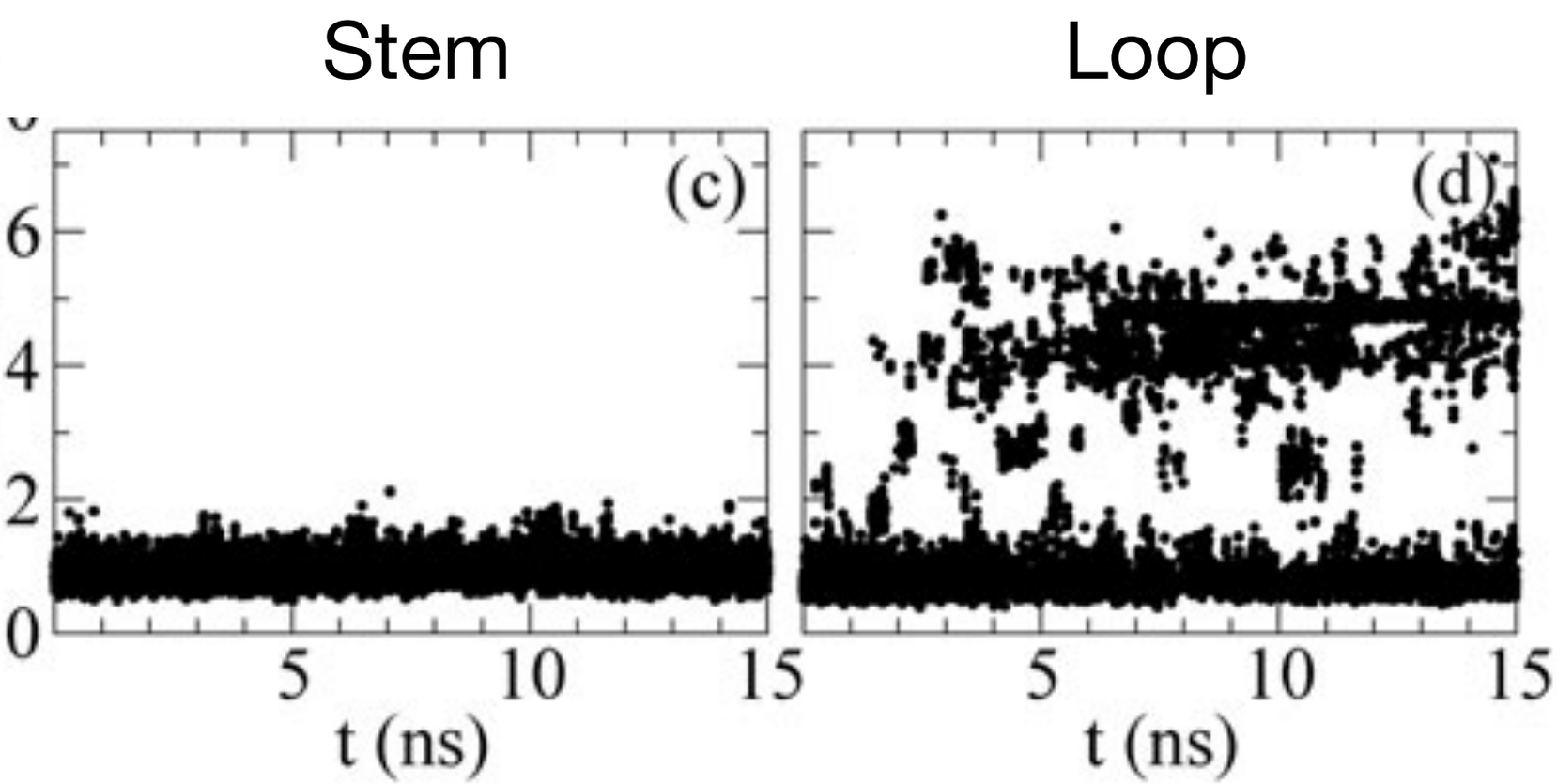


Figure 3. Convergence of HREX for alanine dipeptide. The angle ϕ for (a) replica at $\lambda = 1$ and (b) for a longer, serial simulation. (c) Estimate of the free-energy difference between $C_{7\mathrm{eq}}$ and $C_{7\mathrm{ax}}$ as a function of the simulated time per replica, obtained from analysing the replica at $\lambda = 1$. (d) Free-energy landscape as a function of dihedral angle ϕ, as obtained from HREX, compared with a reference metadynamics calculation. Results for HREX are shown for different simulation lengths (simulated time per replica equal to 4, 10 and 20 ns, as indicated), whereas metadynamics profile has been obtained from a single 10-ns simulation.

Bussi Mol Phys (2014)

Example: "partial tempering" on a RNA tetraloop





Bussi Mol Phys (2014)

Advanced use

Mixing temperature and Hamiltonian changes

Results

We explore the multidimensional free energy landscapes of diversely complex proteins using the REHT method and compare its efficiency with that of the state-of-the-art REST2[11] simulations. Toward this, we exploited the HREX module of PLUMED, originally developed for performing the Hamiltonian replica exchange simulations[19]. The module is very flexible and allows for simultaneous use of different bias in the replicas such as the Hamiltonian, collective variable, temperature and pre

3. Aβ42 at the gold/water interface [ABAU-HTREMD]: HT-REMD simulation spanning temperatures between 300 K and 450 K over a cumulative period of 20 μs using 128 replicas initialized from the final structures of the adsorption trajectories. The gold/protein interactions were scaled starting from replica 20 (*i.e.* at 320 K) following the scheme reported in ref. 42. The scaling factor spanned between 1 and 0.6, thus, in the last replica, the gold/protein interactions are scaled by a factor of 0.6.

Combination with m

Hamiltonian replica exchange in GROMACS: a flexible implementation

G Bussi - Molecular Physics, 2014 - Taylor & Francis

A simple and general implementation of Hamiltonian replica exchange for the popular **molecular** dynamics software GROMACS is presented. In this implementation, arbitrarily different …

☆ Salva Cita Citato da 185 Articoli correlati Tutte e 9 le versioni Web of Science: 127

$$- \beta_j \big(V_j(s(X_j)) - V_j(s(X_i))\big).$$

Bellucci et al Nanoscale (2017)
Appadurai et al, Nat Commun (2021)

Camilloni et al, Proteins (2008)

Constructing multiple topologies

```
# create a “self contained” top file
gmx grompp -pp processed.top

# edit to select “hot” atoms (add _ to atom names)
vi processed.top

# use this tool distributed with plumed to scale hot atoms
plumed partial_tempering 0.5 < processed.top > scaled0.5.top

# !!! double check carefully the resulting topology !!!
```

WARNING: the partial_tempering script tries to understand as much as possible of gromacs top files, but might fail! E.g., CHARMM CMAPs are tricky to scale (see PLUMED mailing list)

You can use your own tools to generate scaled topologies

Multiple replicas with plumed + gromacs

attention to shell globbing

mpiexec -np 16 gmx_mpi mdrun -multidir dir? dir??
-plumed ../plumed.dat -replex 200 -hrex

```
# a single plumed file (likely empty?)
# see in masterclass 21.5 how to have one plumed.dat file
# per replica
plumed.dat
dir0/topol.tpr
dir1/topol.tpr
…
dir15/topol.tpr
```

topol.tpr might be generated with:

- different initial coordinates
- different temperatures/pressure (be careful with pressure, not really tested)
- different lambdas (alchemical) (not really tested)
- different force-field parameters (but identical masses)

Instructions

22.06	EDS module + Coarse-Grained directed simulations	April 26, 2022	May 2, 2022	G. Hocky A. White
22.07	Learning and enhancing fluctuations along information bottleneck for automated enhanced sampling	May 9, 2022	May 16, 2022	P. Tiwary
22.08	Modelling Concentration-Driven processes with PLUMED	May 23, 2022	June 1, 2022	M. Salvalaglio
22.09	Using path collective variables to find reaction mechanisms in complex free energy landscapes	June 6, 2022	June 13, 2022	B. Ensing
22.10	Hamiltonian replica exchange with PLUMED and GROMACS	June 21, 2022	June 27, 2022	G. Bussi

1. Go to www.plumed.org
2. Click on the Masterclass tab
3. Click on the Topic of class 22.10
4. 1 week to complete the exercises
5. Questions/discussions on Slack channel masterclass-22-10
6. Lecture I and II available on YouTube