3rd iCoMSE Workshop: Methods for Enhanced Sampling

Enhanced sampling molecular dynamics on HPC systems: From theory to hands-on practices

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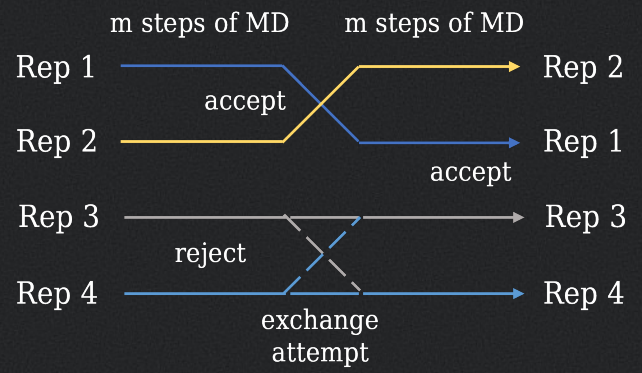

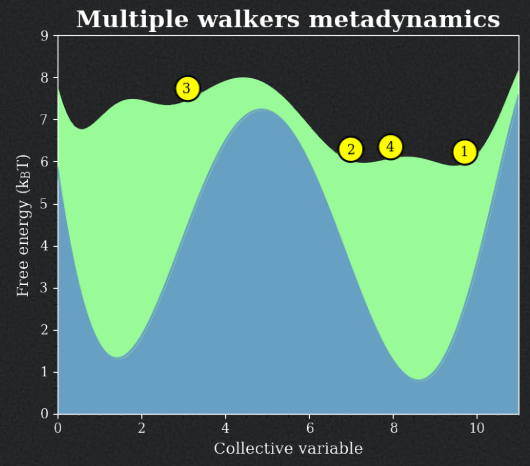

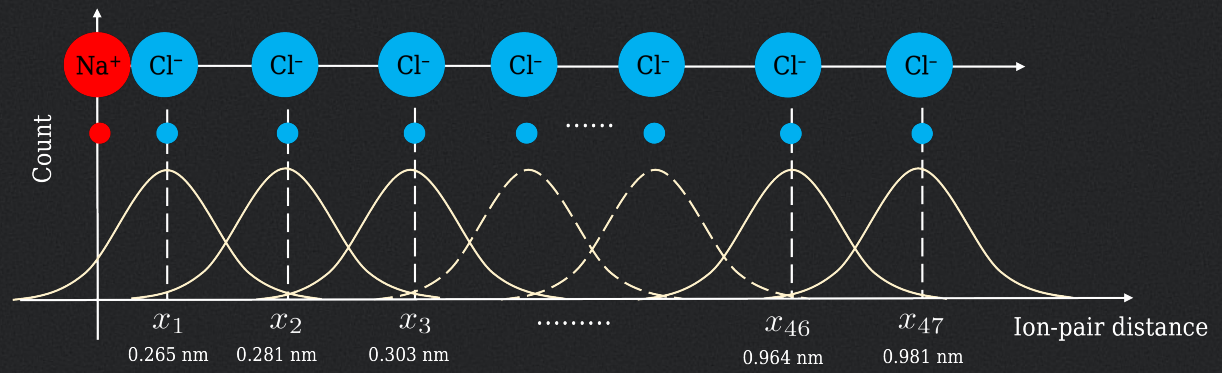

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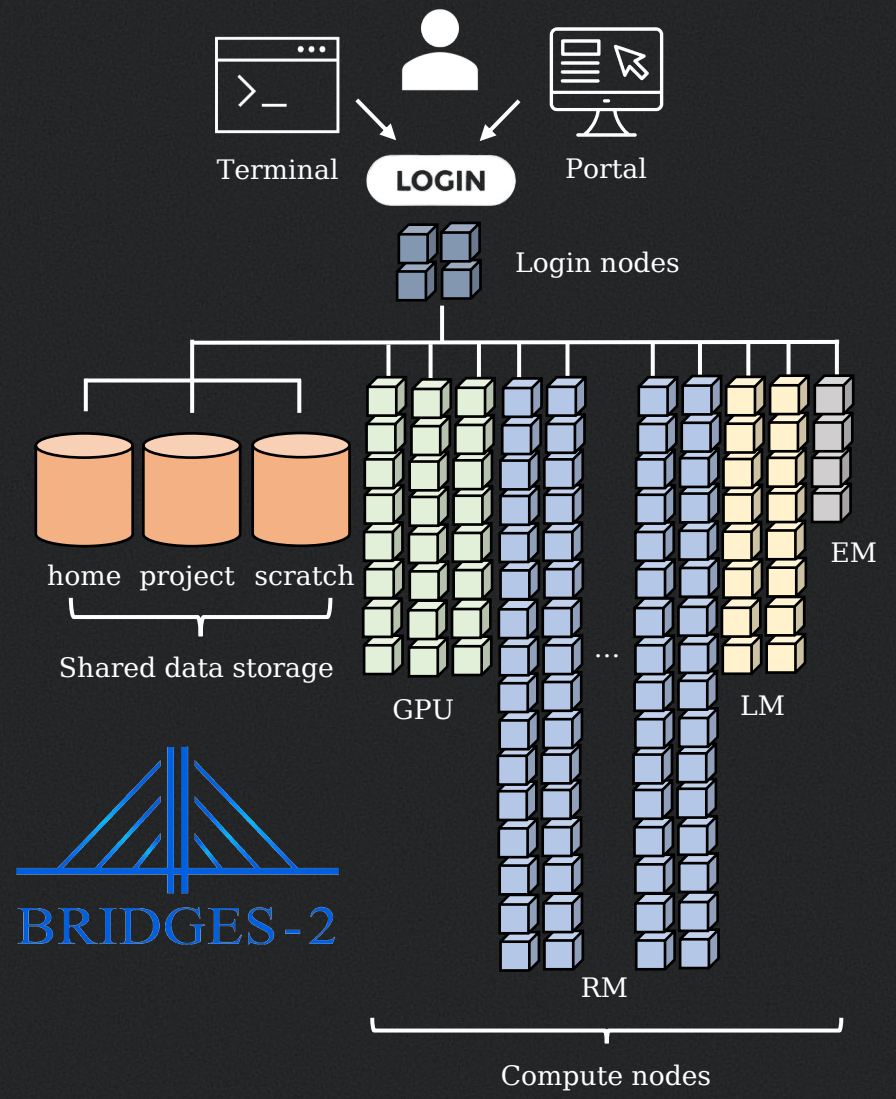
Institute of Computational Molecular Science Education

High-performance computing (HPC) systems are powerful for complex and resource-intensive tasks

- Interactive session: `interact -N 1 --ntasks-per-node=128 -p RM -p time 00:30:00`
- SLURM job submission script

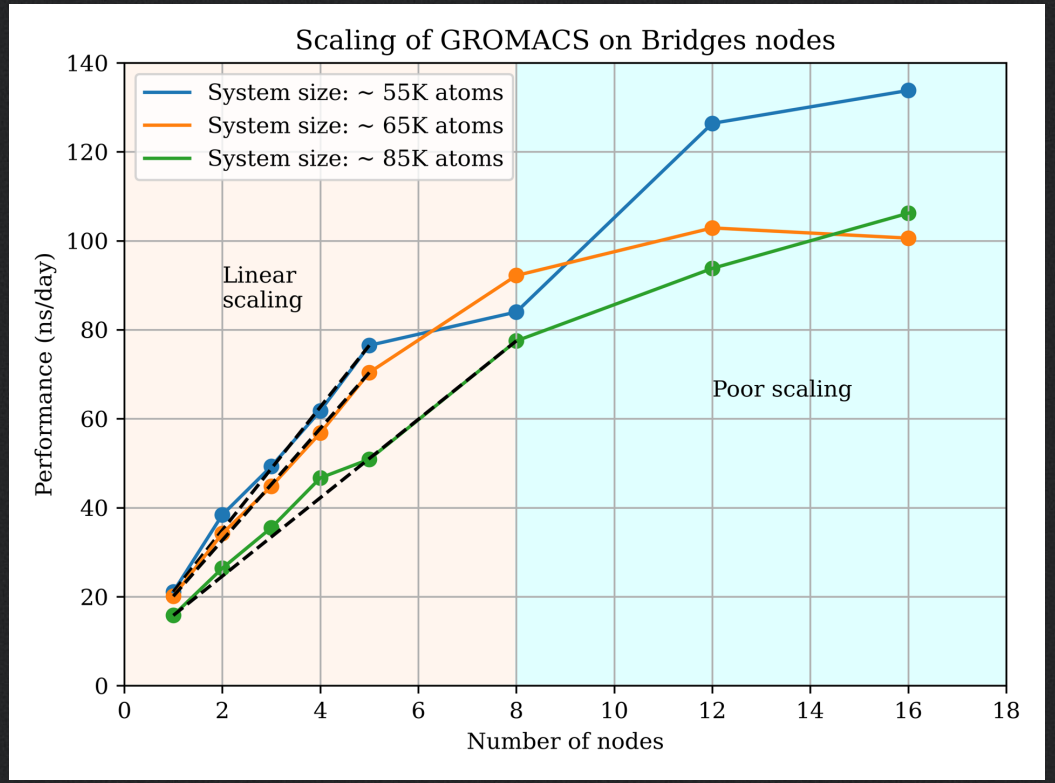
```
#!/bin/sh
#SBATCH --job-name MD_simulation
#SBATCH -N 1
#SBATCH -p RM
#SBATCH -t 2:00:00
#SBATCH --ntasks-per-node=64

module load gromacs
module load openmpi/3.1.6-gcc10.2.0

mpirun -np 16 gmx_mpi mdrun -deffnm md
```



It is important to make the best use of computational resources when running simulations in parallel

- Parallelization can be performed across
  - ✓ Multiple cores in a single node using multiple threads (e.g. OpenMP thread)
  - ✓ Multiple nodes using multiple MPI processes by OpenMPI (launched by `mpirun` or `mpiexec`)

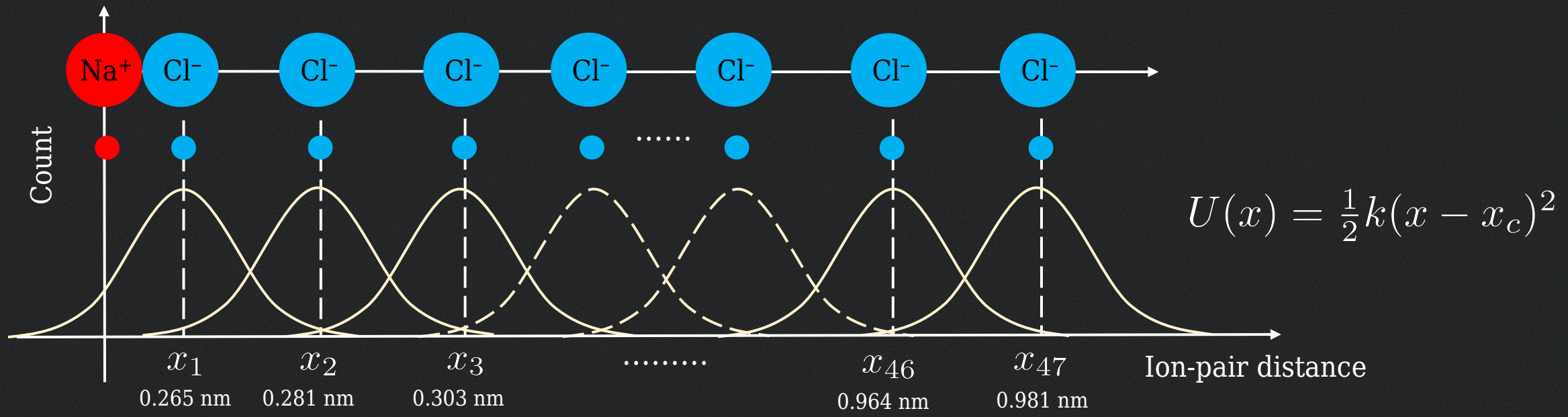
Communications take time!



👷 **Hands-on exercise 1**
Running uncoupled MD simulations in parallel

Umbrella sampling runs simulations at different values of CV

- Pulling simulation: Fix Na^+ and pull Cl^- away to generate states of different CV values.
- Production runs: Fix the whole ion-pair and perform the simulations under restraint.
- A reasonable force constant should ensure overlap between states.



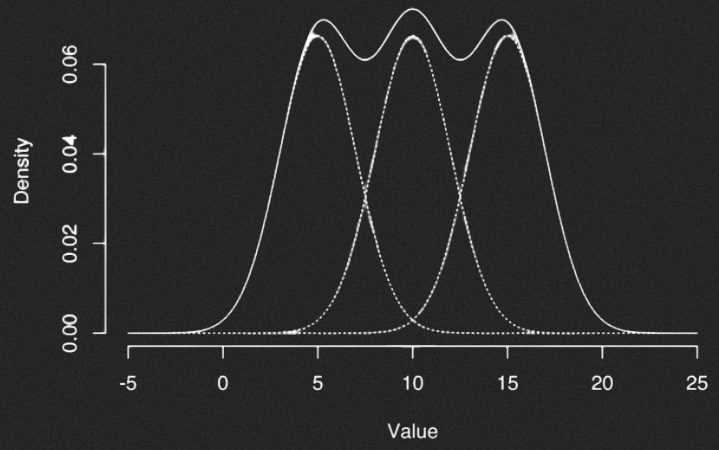
We can use MBAR to recover the free energy profile along the CV of interest from umbrella sampling

- Possible methods: WHAM, TI, BAR, MBAR and even more!
- Protocol of using MBAR
  - ✓ Decorrelate the time series of the collective variables.

$$g = 1 + 2\tau,\ \tau = \sum_{t=1}^{n-1}\left(1 - \frac{t}{n}\right)\left(\frac{\langle x_i x_{i+1}\rangle - \langle x\rangle^2}{\mathrm{var}(x)}\right)$$

  - ✓ Reweight from the mixture distribution.

$$F_i = -\frac{1}{\beta}\ln\sum_{j=1}^{K}\sum_{n=1}^{N_j}\frac{\exp(-\beta U_i^{(b)}(x_{jn}))}{N_k \exp(\beta(F_k - U_k^{(b)}(x_{jn}))}$$



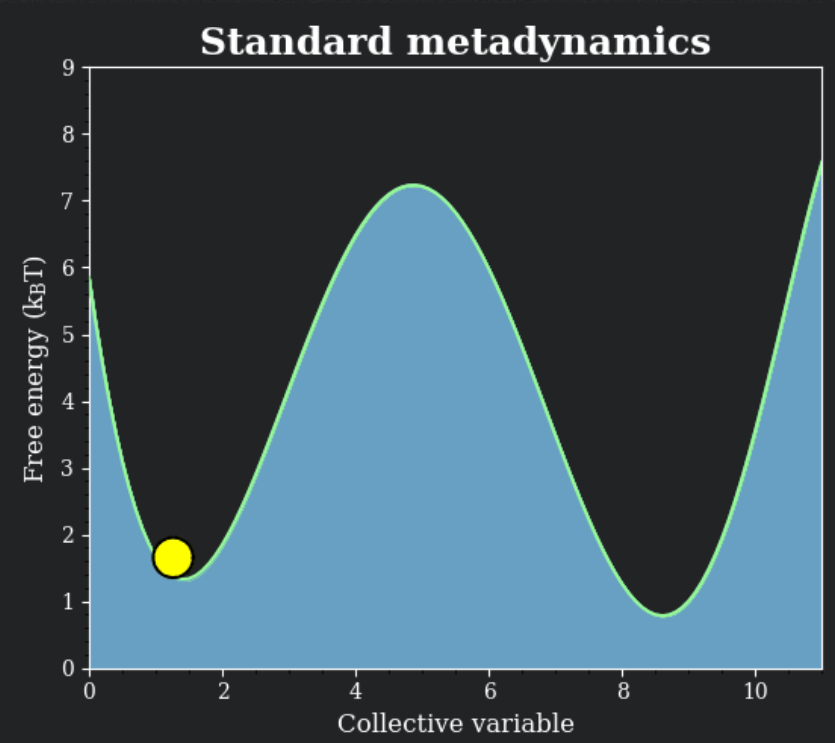
👨‍💻 **Hands-on exercise 2**

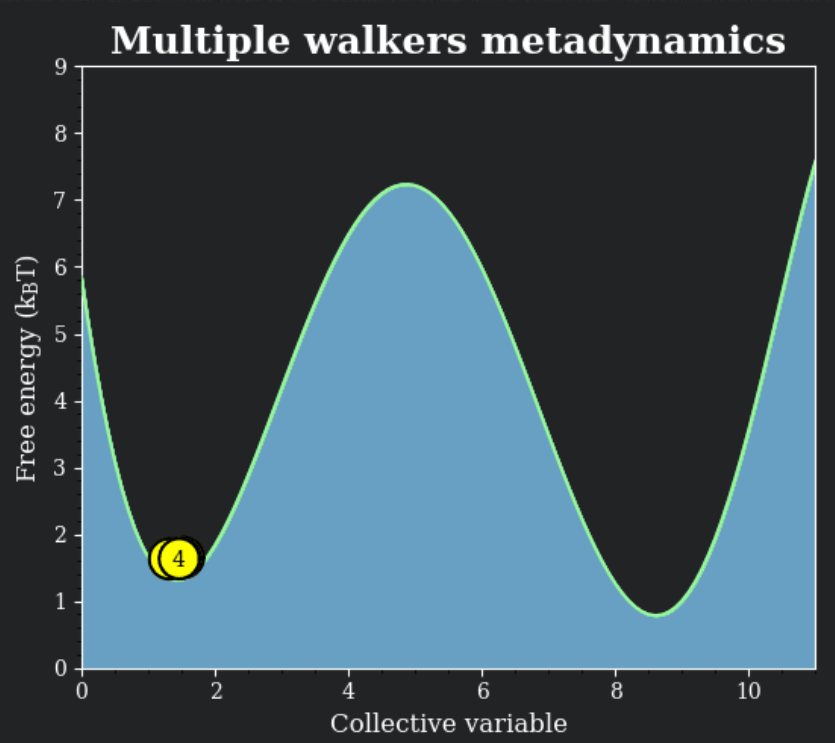
Perform and analyze umbrella sampling

The convergence of metadynamics can be sped up by running multiple walkers sampling the same free energy surface

- In multiple walkers metadynamics, the deposited bias is shared between replicas so each replica is aware of the whole history of the bias.

Hands-on exercise 3





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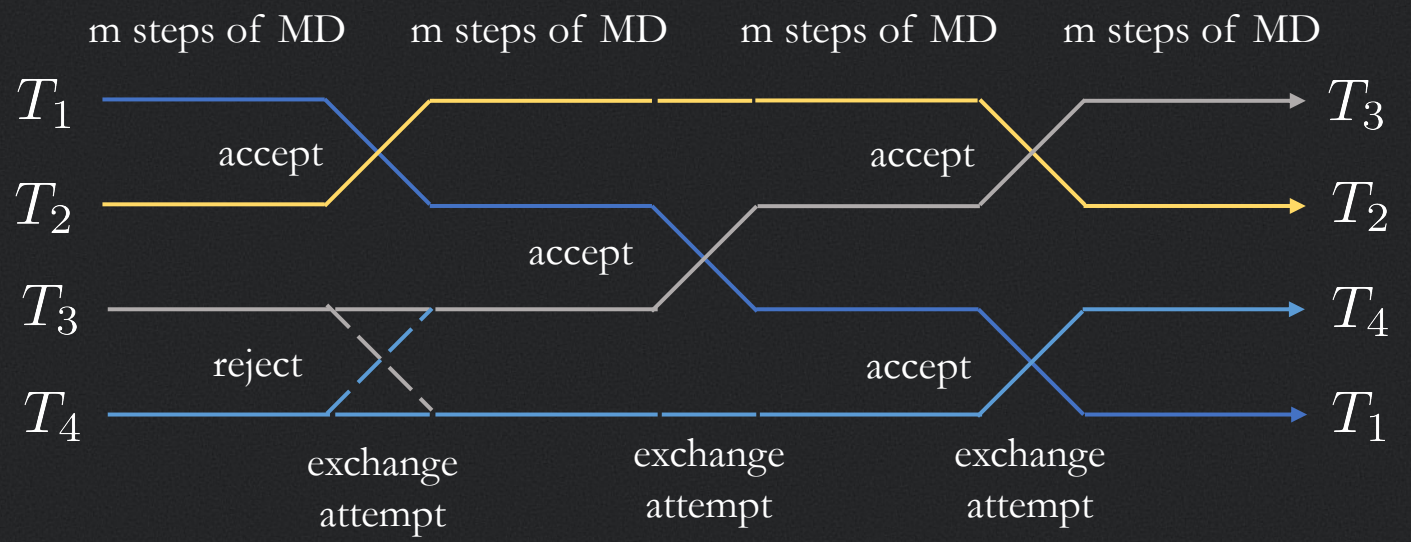
Temperature replica exchange periodically exchange coordinates for simulations at different different temperatures

- The sampling alternates between the configurational and temperature space.
- At higher temperature, it is easier to cross the free energy barrier.
- Useful for estimating free energy or heat capacity as a function of temperature

Transition probability

$$w(X \to X') = \begin{cases} 1, & \text{for } \Delta \leq 0 \\ \exp(-\Delta), & \text{for } \Delta > 0 \end{cases}$$

$$\Delta \equiv (\beta_m - \beta_n)(U(q^{[i]}) - U(q^{[j]}))$$



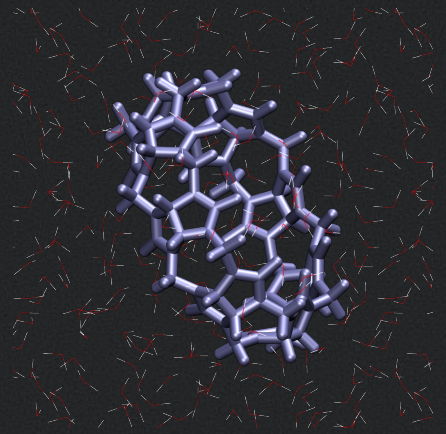
Alchemical intermediate states are useful for calculating solvation free energy, binding free energy, and mutation free energy

- An alchemical intermediate state is defined by a vector of coupling parameters.

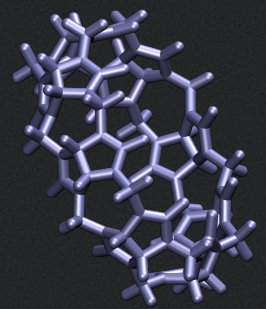
`; lambda-states`	`= 1`	`2`	`3`	`4`	`5`	`6`	`7`	`8`	`9`
`coul-lambdas`	`= 0.00`	`0.25`	`0.50`	`0.75`	`1.00`	`1.00`	`1.00`	`1.00`	`1.00`
`vdw-lambdas`	`= 0.00`	`0.00`	`0.00`	`0.00`	`0.00`	`0.25`	`0.50`	`0.75`	`1.00`
$\vec{\lambda}_i = (\lambda_{\mathrm{vdW},\,i}, \lambda_{\mathrm{coul},\,i})$	$\vec{\lambda}_1$	$\vec{\lambda}_2$	$\vec{\lambda}_3$	$\vec{\lambda}_4$	$\vec{\lambda}_5$	$\vec{\lambda}_6$	$\vec{\lambda}_7$	$\vec{\lambda}_8$	$\vec{\lambda}_9$

$\vec{\lambda}_1 = (0.0, 0.0)$

Fully coupled (interactions on)



ΔG_{solv}



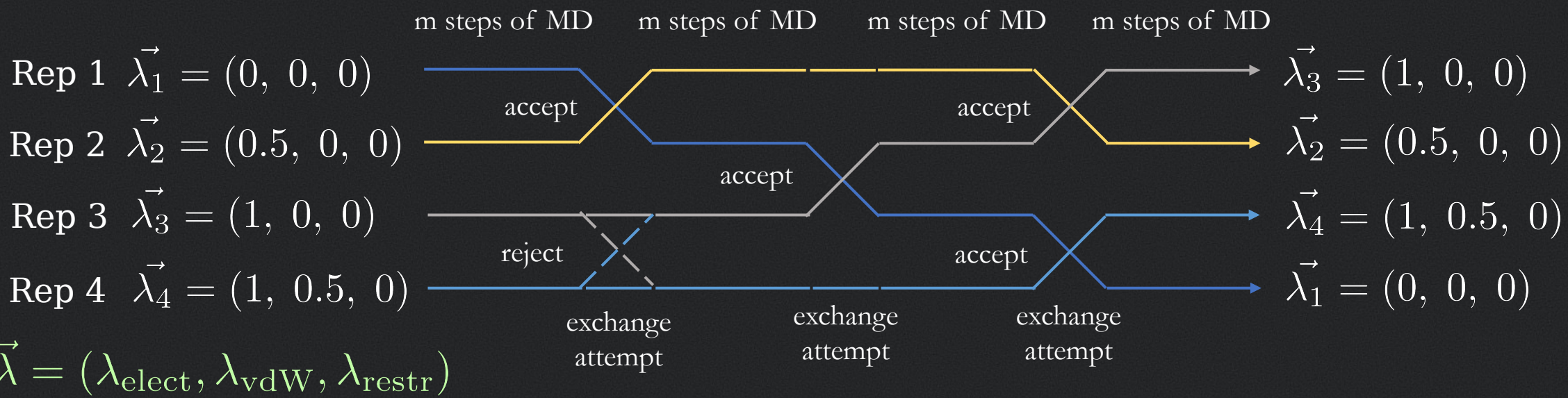
$\vec{\lambda}_9 = (1.0, 1.0)$

Fully decoupled (interactions off)

Hamiltonian replica exchange generalizes the ensemble with the alchemical direction

- Hamiltonian replica exchange (HREX) alternates the sampling between the coordinate and the alchemical space.

Hands-on exercise 4



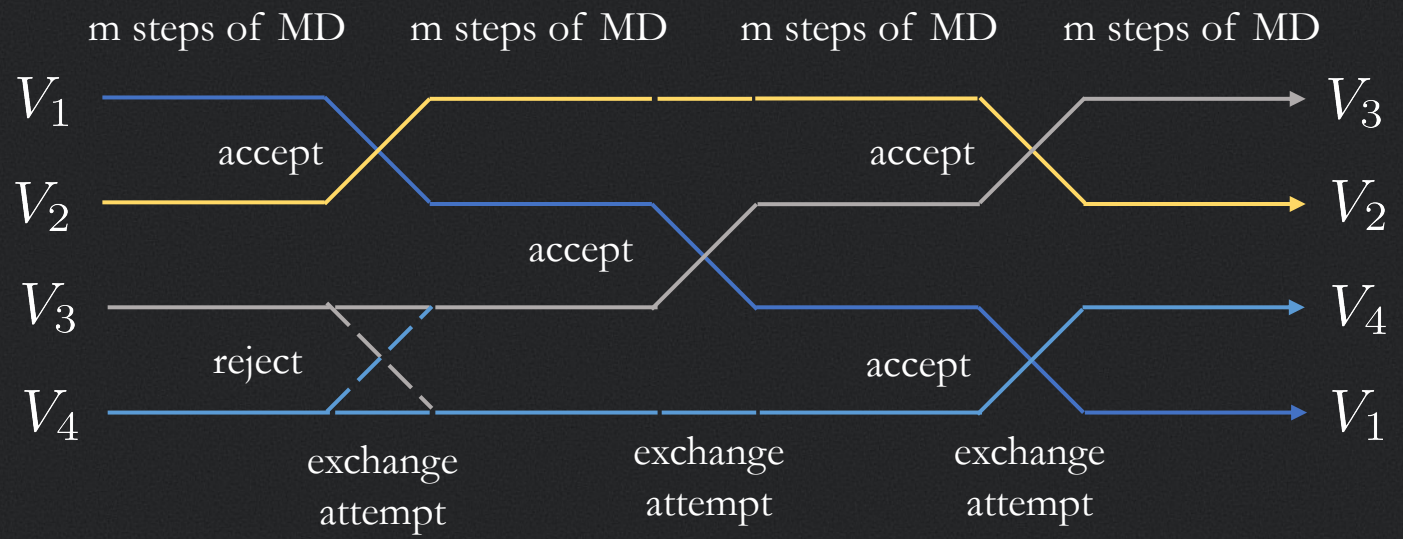
$\vec{\lambda} = (\lambda_{\text{elect}}, \lambda_{\text{vdW}}, \lambda_{\text{restr}})$

Replica exchange umbrella sampling is a special case of Hamiltonian replica exchange

- In Hamiltonian replica exchange, we have $U_\lambda(q) = U_0(q) + \lambda V(q)$
- In replica exchange umbrella sampling, we have $U_\lambda(q) = U_0(q) + \sum_{l=1}^{L} \lambda^{(l)} V_l(q)$

👨‍💻 **Hands-on exercise 5**

Perform and analyze REUS



We can exchange coordinates between simulations at any different thermodynamic states as long as there is overlap!

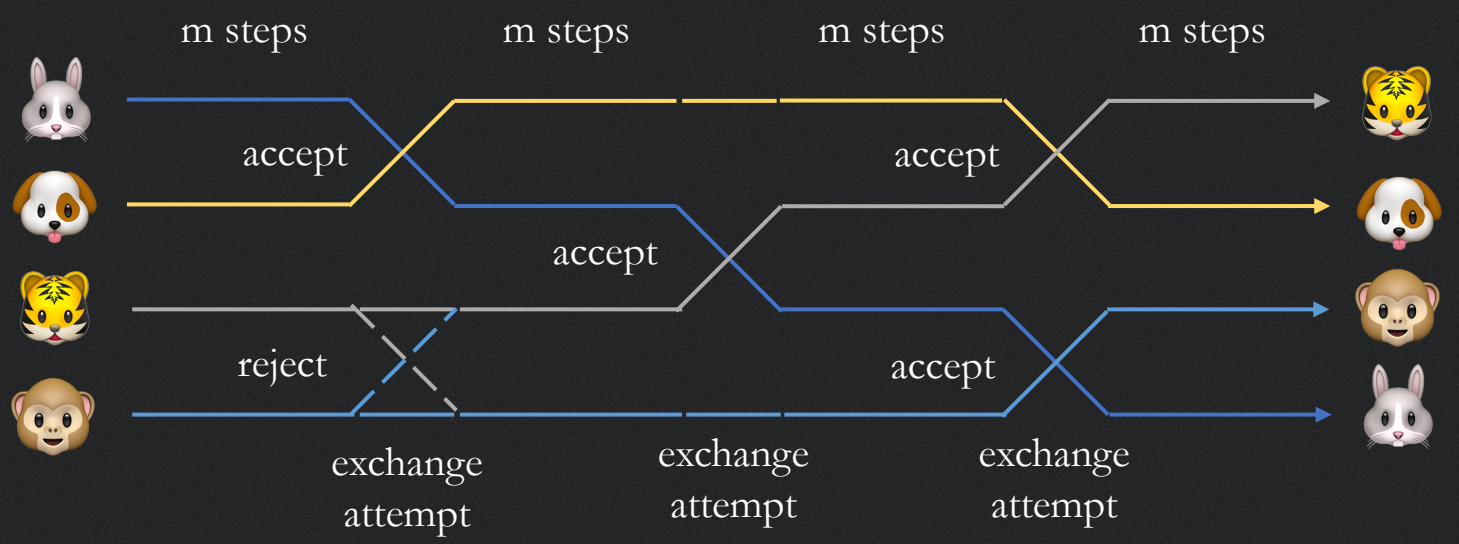
$$\Delta = \min\left(1, \exp\left[\left(\beta_1 - \beta_2\right)\left(\beta_1(U_1(x_2) - U_1(x_1)) + \beta_2(U_2(x_1) - U_2(x_2))\right)\right]\right)$$

Hamiltonian + temperature

$$\Delta = \min\left(1, \exp\left[\left(\beta_1 - \beta_2\right)\left(U_1 - U_2\right) + \left(\beta_1 P_1 - \beta_2 P_2\right)\left(V_1 - V_2\right)\right]\right)$$

REMD in NPT ensemble

- Bias-exchange MetaD
- Parallel-tempering MetaD
- Ensemble of expanded ensemble (EEXE)



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