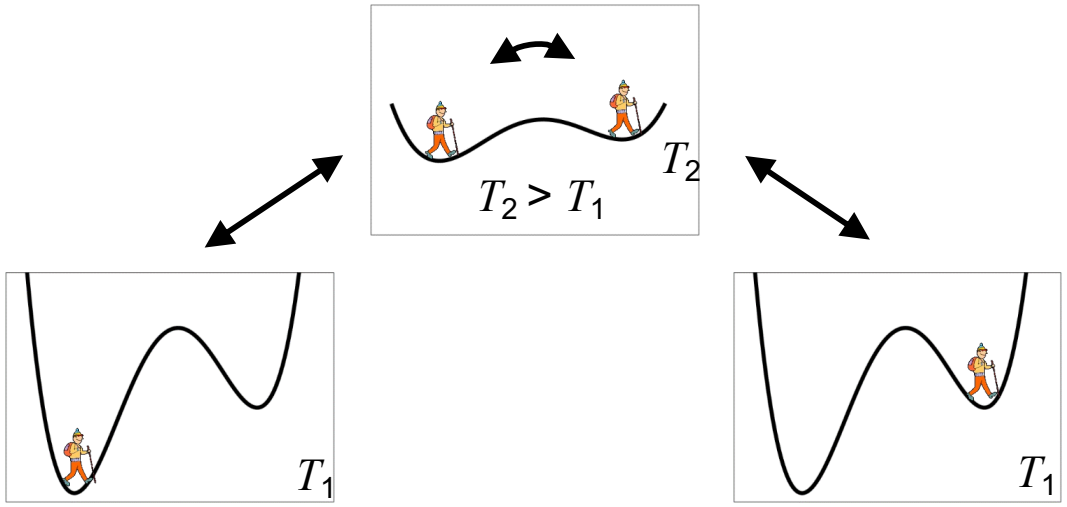
Enhanced sampling with TSS

- Times Square Sampling (TSS) is an enhanced sampling approach related to simulated (Hamiltonian) tempering
- TSS has built-in online free energy estimators

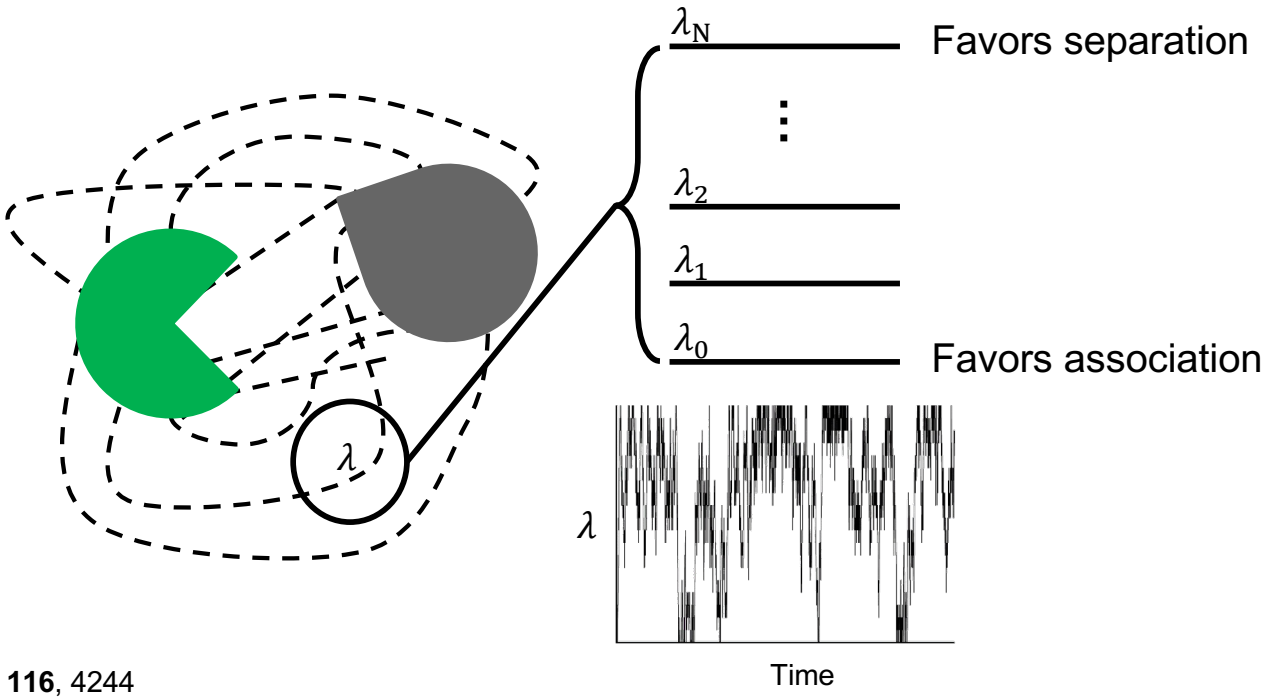


Times Square Sampling: An Adaptive Algorithm for Free Energy Estimation

Cristian Predescu, Michael Snarski, Avi Robinson-Mosher, Duluxan Sritharan, Tamas Szalay & **David E. Shaw**

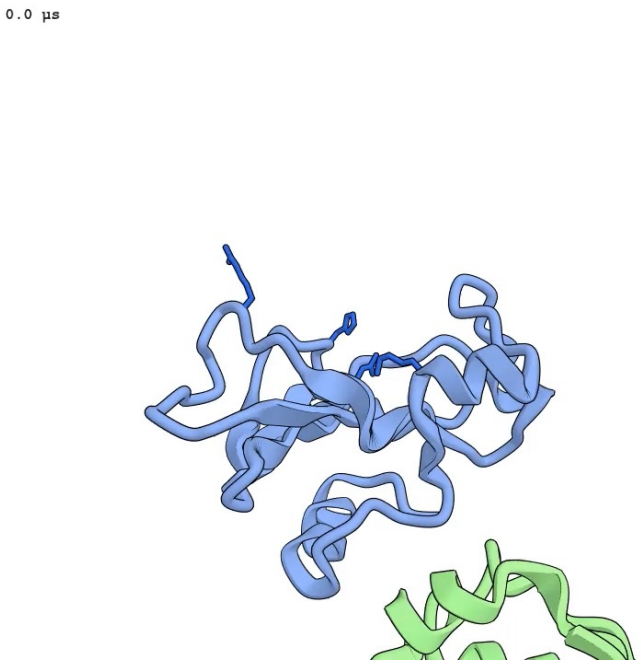
https://github.com/DEShawResearch/tss

Tempered binding



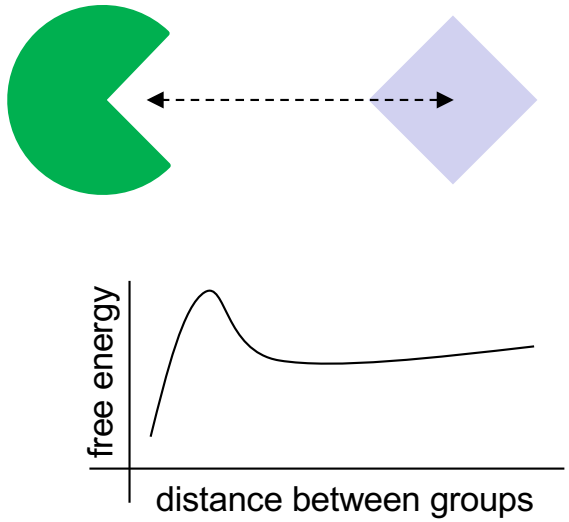
PNAS (2019), **116**, 4244

Tempered binding speeds up escape from metastable traps

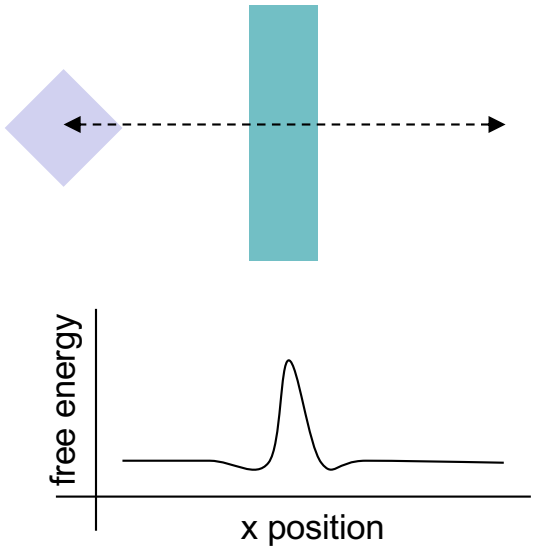


Tempering restraints on atom group centers

Relative position

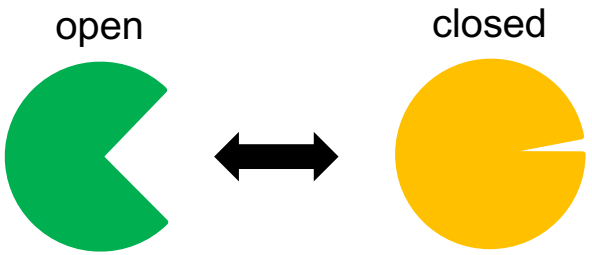


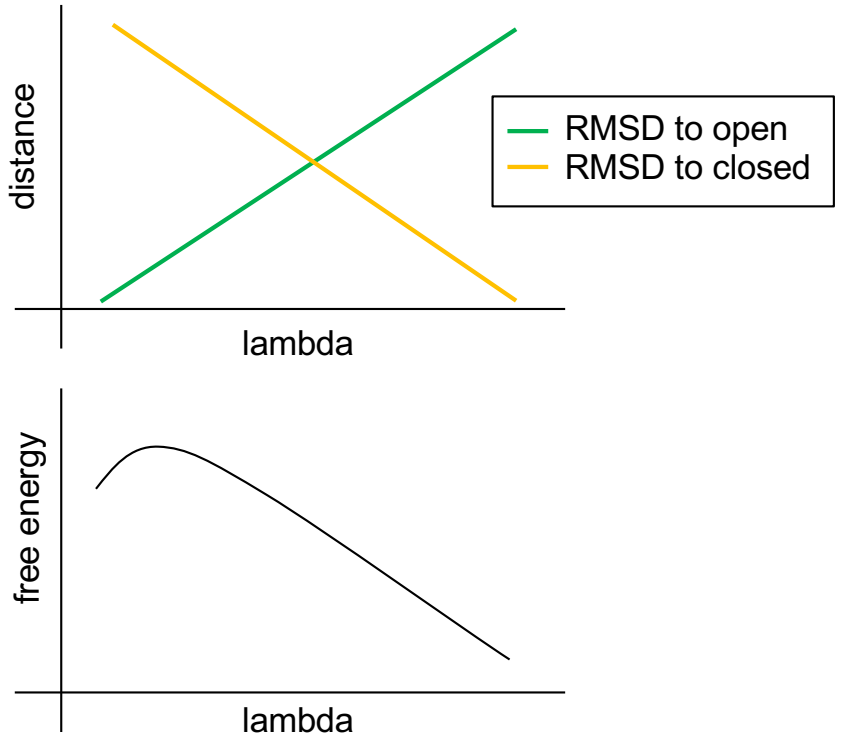
Absolute position



Tempering root mean square distance (RMSD) to reference structure

Example: computing free energy difference between conformations





Available forms of enhanced sampling

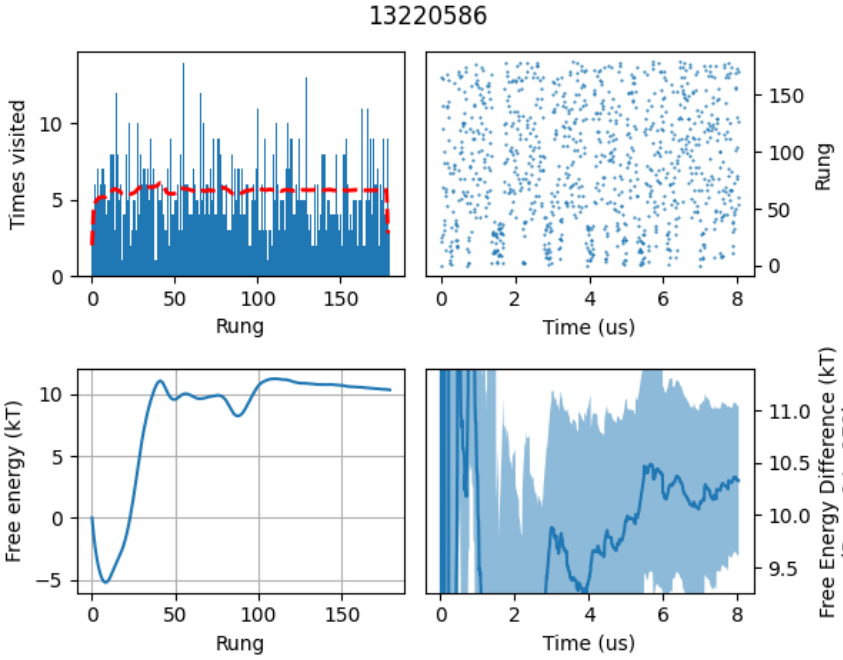
1. Simulated tempering (temperature tempering with adaptive weighting)
2. Tempered binding
3. Restraints between centers of mass of groups of atoms
4. Restraints on the RMSD (root mean squared deviation) of a group of atoms with respect to a given reference structure

For (3) and (4), equilibria and spring constants can be either:

1. Controlled according to a fixed schedule
2. Controlled adaptively by TSS to implement a form of umbrella sampling

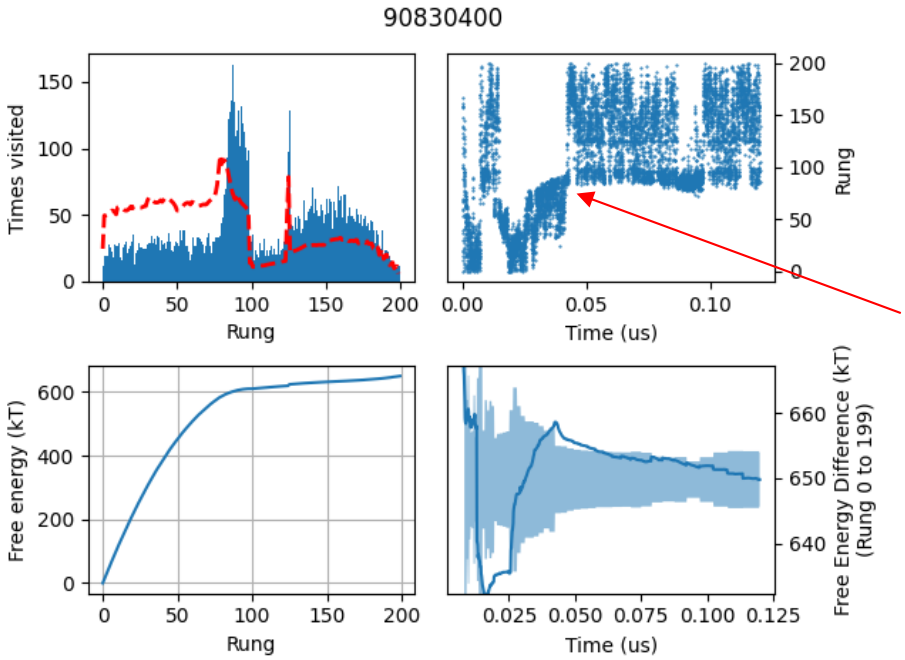
Analyzing enhanced sampling runs

```
$ pytss_psc plot_basic /path/to/workdir
```



https://anton-docs.psc.edu/DESRES/adaptive_enhanced_sampling.html

Troubleshooting poor enhanced sampling runs



Focus on barriers

Use trajectory to examine changes across barriers