Metadynamics: Improved Methodology and a Proof of Convergence

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Background

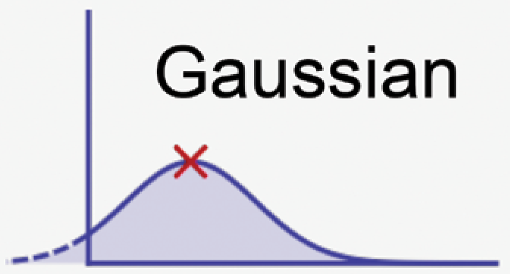
Metadynamics:

- Goal: predict millisecond or minute timescale behavior from nanosecond simulations
- Means: add "hills" of bias at successively sampled points to enhance exploration

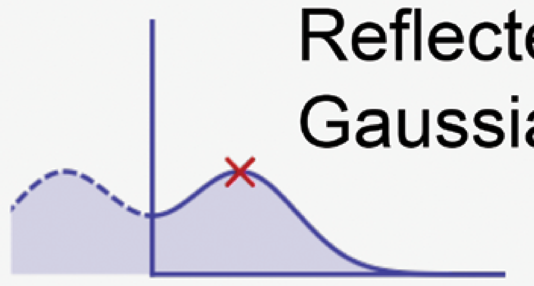
State coordinate : s Bias: $V(s,t)$

First design concern: **hill shape**

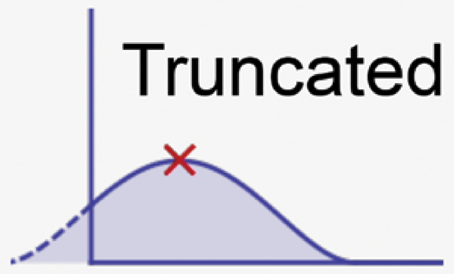
Gaussian



Reflected Gaussian



Truncated



A hill deposited at s' (red x) has shape $G(s,s')$

Choose shape based on short time and length scale, **local** dynamics

Second design concern: **hill size**

Well-tempered metadynamics: shrink new hills set near old ones (WTMetaD, no tempering: UTMetaD)

Hills now: $\exp\left(-\frac{V(s',t)}{\Delta T}\right) G(s,s')$

Set the parameter ΔT based on the **overall total** energy scale

Size must go to zero to converge … but not too fast.

More Robust Metadynamics

Motivation

Well-tempered metadynamics forced one to **choose between** exploration and convergence.

- At low ΔT, slow escape
- At high ΔT, slow convergence

An **ideal rule** would

- Not shrink hills until all basins have been escaped
- Then shrink hills aggressively

Transition Tempering

In a case with two basins, **an effective near-ideal** is:

$$\exp\left(-\frac{V^{\ddagger}(t)}{\Delta T}\right)G(s,s')$$

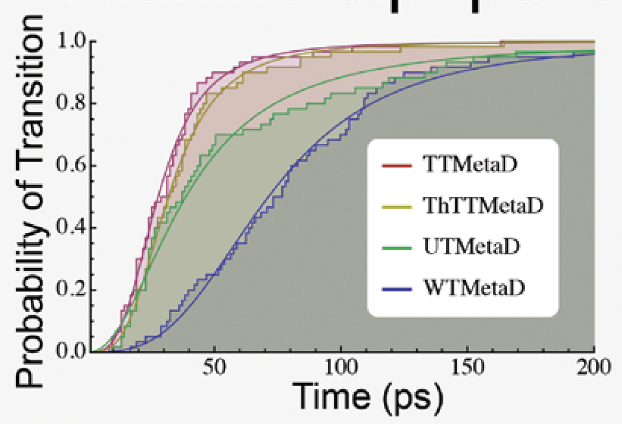
for $V^{\ddagger}(t)$ the bias at the barrier state between them.

This barrier position can be estimated on the fly; this rule eliminates the tradeoff.

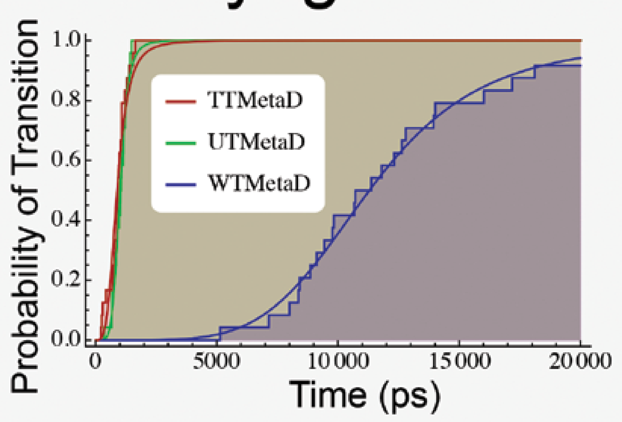
Performance

Fast exploration:

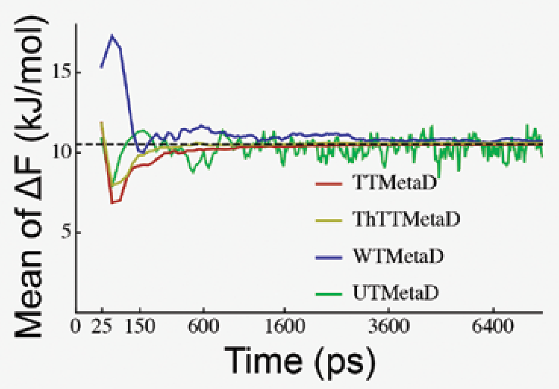
Alanine dipeptide

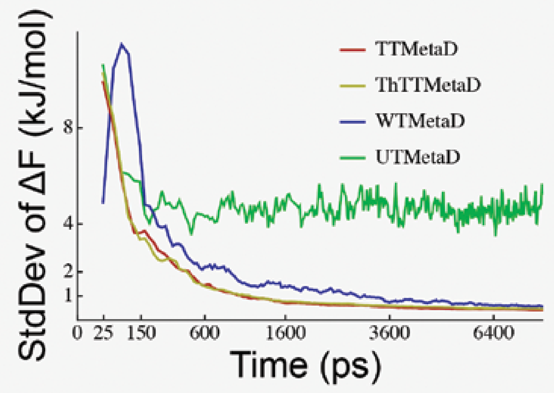


Myoglobin



Improved accuracy: (alanine dipeptide)





JFD, GR, MP, GAV, JCTC July 2014

Proof of Convergence

Context

History-dependent biasing is both non-Markovian and non-equilibrium, a challenge for intuition and analytical methods

Though introduced in 2002, metadynamics lacked a clear, rigorous justification in stat mech

Widespread uncertainty about the bases for such methods impeded progress in the field

Proof Method

1. Prove that the limit points of the stochastic iteration are the same as those of a quasi-equilibrium ODE
2. Prove that the ODE has a unique limit point corresponding to the desired final state

Implications

- New design constraints for hill shape based on positivity
- Hill size must decay exponentially with the overall bias level for convergence
- Timescale separation is not essential: works on non-Markovian CVs very well
- Studied CVs must equilibrate quickly (correlations O(1/t)) and must not jam (responses O(1/t))

JFD, MP, and GAV, PRL June 2014

Current Work

Self-limiting metadynamics with **specified, bounded exploration**

New ways to use metadynamics to calculate **transition rates** efficiently