Simulated Tempering Method in the Infinite Switch Limit with Adaptive Weight Learning

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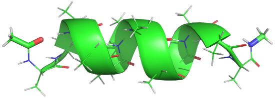
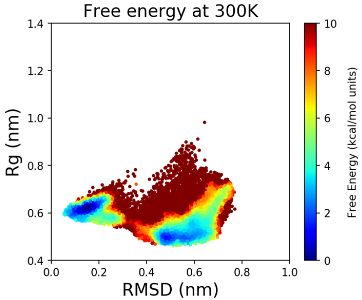




- Canonical distribution for q (positions) and p (momentum):

$$\rho_\beta(q,p) = Z^{-1}(\beta)e^{-\beta\frac{1}{2}p^T m^{-1}p - \beta V(q)}$$

where $V(q)$ is potential and $Z(\beta)$ is the normalisation constant, $\beta > 0$ reciprocal temperature

From Standard to Accelerated Sampling

- Ergodic Average of observable $A(q)$,

$$\mathbb{E}_\beta\left[A\right] = \int A(q)\rho_\beta(q,p)\,\mathrm{d}p\,\mathrm{d}q = \lim_{T\to\infty}\frac{1}{T}\int_0^T A(q(t))\,\mathrm{d}t$$

- Standard sampling methods for $\rho_\beta(q,p)$ such as e.g. Monte Carlo or Langevin Dynamics,

$$\begin{aligned} dq &= m^{-1}p\,\mathrm{d}t \\ dp &= -\nabla V(q)\,\mathrm{d}t - \gamma p\,\mathrm{d}t + \sqrt{2\gamma\beta^{-1}m}\,\mathrm{d}W \end{aligned}$$

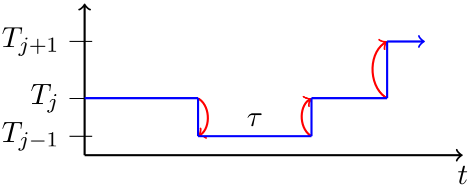
  struggle with energetic and entropic barriers

- **Accelerated sampling:** Simulated Annealing, Replica Exchange Molecular Dynamics, Simulated Tempering, Wang-Landau, Adaptive Force Biasing, Temperature-accelerated Molecular Dynamics, Hamiltonian Replica Exchange, ...

Simulated Tempering

- Temperature "ladder" with M steps, with spacing ΔT

$$T_{\min} = T_1 < \ldots < T_M = T_{\max}$$



- Let $\beta_i = (k_B T_i)^{-1}$ with assigned weight $\omega(\beta_i)$
- Switch every τ steps from $\beta_i \to \beta_j$ with probability α_{ij},

$$\alpha_{ij} = \min\{1, \frac{\omega(\beta_i)}{\omega(\beta_j)} e^{-(\beta_i - \beta_j)V(q)}\}$$

- Invariant measure with density,

$$\rho(q, p, \beta_i) = C^{-1}(\beta)\omega(\beta_i) e^{-\frac{1}{2}\beta p^T m^{-1} p - \beta_i V(q)}$$

where $C(\beta) = \sum_{i=1}^{M} \int_{\mathcal{D}\times\mathbb{R}^d} \omega(\beta_i) e^{-\frac{1}{2}\beta p^T m^{-1} p - \beta_i V(q)}\, \mathrm{d}q\, \mathrm{d}p$

Simulated Tempering Parameters

1. Choice of switch period, τ?
2. How do we justify $\omega(\beta_i) = Z_q^{-1}(\beta_i)$?

$$\mathbb{P}(\beta_i) = \frac{\omega(\beta_i)\, Z_q(\beta_i)}{\sum_{j=1}^{M} \omega(\beta_j)\, Z_q(\beta_j)}.$$

3. Can we learn $\omega(\beta_i)$ weights on-the-fly?

Remarks:

- Grid Spacing, ΔT. Is there a way to motivate the choice?
- How do we calculate an average from ρ_{β_i} i.e $\mathbb{E}_{\beta_i}[A]$?

Infinite Switch Limit of Simulated Tempering, $\tau \to 0$.

- Follows same large deviation approach as for REMD by Dupuis et. al. [1] [2]
- ST in $\tau \to 0$ limit for some continuous $\beta_c \in [\beta_{\min}, \beta_{\max}]$ is equivalent to sampling the averaged potential [3],

$$\bar{V}(q) = -\beta^{-1} \log \int_{\beta_{\min}}^{\beta_{\max}} \omega(\beta_c) e^{-\beta_c V(q)} d\beta_c$$

for some prior known weights $\omega(\beta_c)$.

[1] **Dupuis et. al.** 2012.
[2] **Plattner et. al** 2011.
[3] **A.M. et. al.** 2018.

Outline of $\tau \to 0$ Results

- The rate functional $\mathbb{P}(\nu_T \approx \mu) \asymp \exp\left[-T^{-1} I_\tau(\mu)\right]$ of the ergodic dynamics is a monotonically decreasing function of τ, i.e if

$$\tau < \tau' \implies I_\tau(\mu) \geq I_{\tau'}(\mu)$$

For faster convergence to μ, let $\tau \to 0$.

- The dynamical equations in $\tau \to 0$ limit,

$$\begin{aligned} \mathrm{d}q &= m^{-1} p \,\mathrm{d}t, \\ \mathrm{d}p &= -\beta^{-1} \bar{\beta}(V(q)) \nabla V \,\mathrm{d}t - \gamma p \,\mathrm{d}t + \sqrt{2\gamma\beta^{-1} m^{-1}} \,\mathrm{d}W_p \end{aligned}$$

which implies that we have averaged potential,

$$\bar{V}(q) = -\beta^{-1} \log \int_{\beta_{\min}}^{\beta_{\max}} \omega(\beta_c) e^{-\beta_c V(q)} d\beta_c$$

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Justification of $\omega(\beta) \propto Z_q^{-1}(\beta)$.

Overview of $\omega(\beta) \propto Z_q^{-1}(\beta)$

- The density function of $V(q)$

$$\bar{\rho}(E) = \frac{\int_{\beta_{\min}}^{\beta_{\max}} e^{-\beta_c E}\omega(\beta_c)\,\mathrm{d}\beta_c}{\int_{\beta_{\min}}^{\beta_{\max}} Z_q(\beta_c)\omega(\beta_c)\,\mathrm{d}\beta_c}\,\Omega(E),$$

where $\Omega(E) = \int_{\mathcal{D}} \delta(V(q) - E)\,\mathrm{d}q$.

- In that large system size limit,

$$\bar{\rho}(E) \asymp 1$$

when $\omega(\beta) \propto Z_q^{-1}(\beta)$.

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$$\mathbb{P}(\beta_i) = \frac{\omega(\beta_i)\, Z_q(\beta_i)}{\sum_{j=1}^{M} \omega(\beta_j)\, Z_q(\beta_j)}.$$

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Adaptive $\omega(\beta_c)$ adjustment as we learn $Z_q(\beta_c)$.

Outline of $\omega(\beta_c)$ Adjustment Results: part 1

- For $\beta_c \in [\beta_{\min}, \beta_{\max}]$ we can construct

$$z(t,\beta_c) = \frac{1}{t}\int_0^t \frac{e^{-\beta_c V(q(s))}}{\int_{\beta_{\min}}^{\beta_{\max}} \omega(\beta_c')e^{-\beta_c' V(q(s))}\,\mathrm{d}\beta_c'}\,\mathrm{d}s$$

  which can be calculated for all $t > 0$.

- In the limit as $t \to \infty$,

$$\lim_{t\to\infty} z(t,\beta_c) = \frac{Z_q(\beta_c)}{\int_{\beta_{\min}}^{\beta_{\max}} Z_q(\beta_c')\omega(\beta_c')\,\mathrm{d}\beta_c'},$$

- This implies that we learn ratios of $Z_q(\beta_c)$ regardless of knowledge of $\omega(\beta_c)$,

$$\lim_{t\to\infty} \frac{z(t,\beta_c)}{z(t,\beta_c')} = \frac{Z_q(\beta_c)}{Z_q(\beta_c')}$$

- Define $z(t, \beta_c)$ as,

$$z(t,\beta_c) = \frac{1}{t}\int_0^t \frac{e^{-\beta_c V(q(s))}}{\int_{\beta_{\min}}^{\beta_{\max}} \omega(\beta_c')e^{-\beta_c' V(q(s))}\,\mathrm{d}\beta_c'}\,\mathrm{d}s$$

- Adjusting the weights according to,

$$\kappa\dot{\omega}(t,\beta_c) = z^{-1}(t,\beta_c) - \lambda(t)\omega(t,\beta),\ \text{with}\ \lambda(t) = \int_{\beta_{\min}}^{\beta_{\max}} z^{-1}(t,\beta_c)\,\mathrm{d}\beta_c$$

will ensure that $\omega(t, \beta_c) \propto Z_q^{-1}(\beta_c)$ as $t \to \infty$.

Simulated Tempering Parameters

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$$\mathbb{P}(\beta_i) = \frac{\omega(\beta_i)\, Z_q(\beta_i)}{\sum_{j=1}^{M} \omega(\beta_j)\, Z_q(\beta_j)}.$$

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Grid Spacing

- The equations of motion are,

$$
\begin{aligned}
\mathrm{d}q =& m^{-1} p \,\mathrm{d}t, \\
\mathrm{d}p =& -\beta^{-1}\hat{\beta}(t, V(q))\nabla V \,\mathrm{d}t - \gamma p \,\mathrm{d}t + \sqrt{2\gamma\beta^{-1} m}\,\mathrm{d}W_p
\end{aligned}
$$

- We need to calculate the following force re-scaling

$$
\hat{\beta}(t, V(q)) = \frac{\int_{\beta_{\min}}^{\beta_{\max}} \beta_c \,\omega(t, \beta_c)\, e^{-\beta_c V(q)} \,\mathrm{d}\beta_c}{\int_{\beta_{\min}}^{\beta_{\max}} \omega(t, \beta_c)\, e^{-\beta_c V(q)} \,\mathrm{d}\beta_c}
$$

- We therefore discretise $[\beta_{\min}, \beta_{\max}]$ with the aim of calculating $\hat{\beta}(t, V(q))$

Calculating Averages

- In standard Simulated Tempering

$$\mathbb{E}_{\beta_c}[A] = \lim_{T\to\infty} \frac{1}{T} \int_0^T A(q(t))\mathbb{1}_{\beta_c}\,\mathrm{d}t$$

- We instead use a reweighting of the entire trajectory (importance sampling),

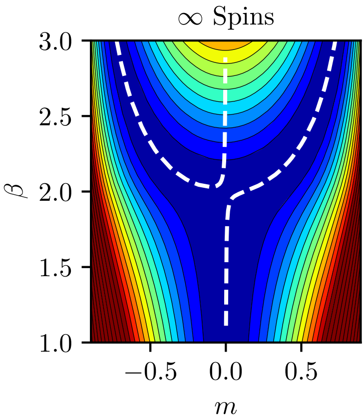
$$\mathbb{E}_{\beta_c}[A] = \lim_{T\to\infty} \frac{1}{T} \int_0^T A(q(t))W_{\beta_c}(t, q(t))\,\mathrm{d}t$$

where,

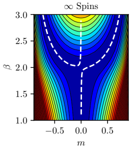
$$W_{\beta_c}(t,q) = \frac{z^{-1}(t,\beta_c)}{\int_{\beta_{\min}}^{\beta_{\max}} \omega(t,\beta_c')e^{-(\beta_c'-\beta_c)V(q)}d\beta_c'}$$

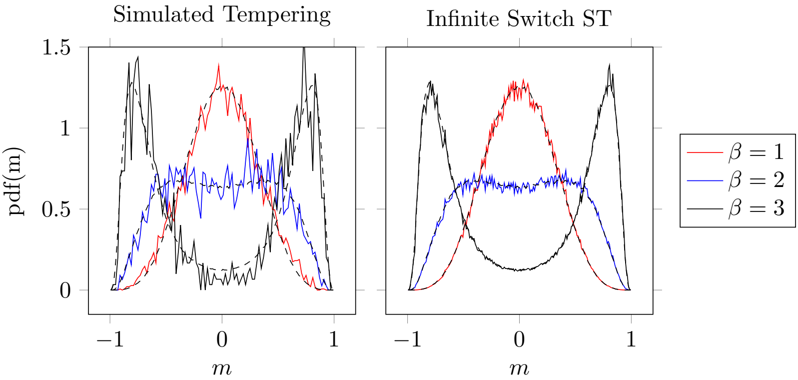
where $z(t,\beta_c)$ is the estimate of $Z_q(\beta_c)$ at time t.

Curie Weiss Magnet – mean field Isings model

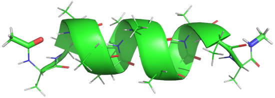


Curie Weiss Magnet





Numerical Experiments: Part 2, Alanine-12

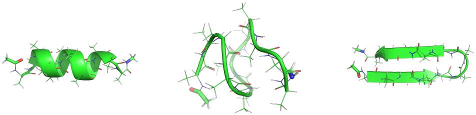


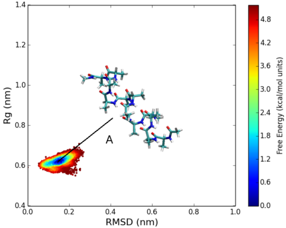
- Molecular Integration Simulation Toolkit (MIST) [4] integrates with `Amber 14, GROMACS 5.0.2, NAMD-Lite 2.0.3, LAMMPS`
- In vacuum, using Gromacs with MIST[5]
- Measure RMSD and radius of gyration, r_g, from initial helix state

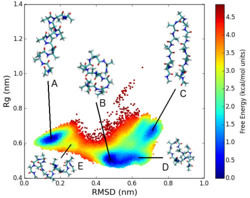
[4] **Bethune et. al.** *MIST: A Simple and Efficient Molecular Dynamics Abstraction Library for Integrator Development*, **Computer Physics Communications** , 2018

[5] https://bitbucket.org/extasy-project/mist/wiki/Home

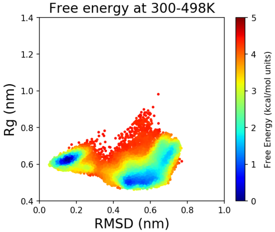
Alanine-12: LD vs ST vs ISST





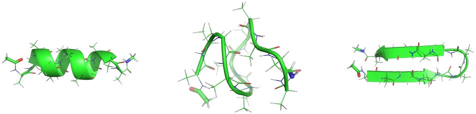


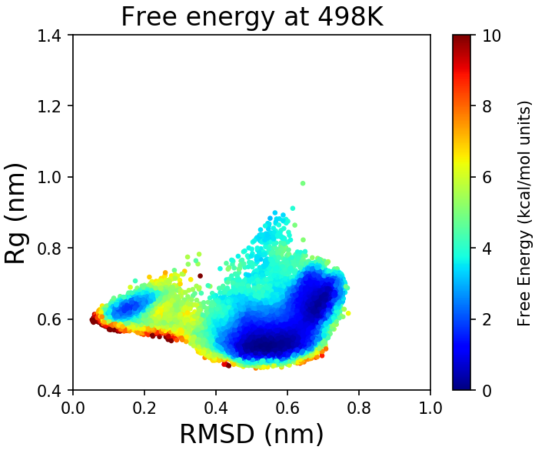
(b) Simulated Tempering 300-450K [6]

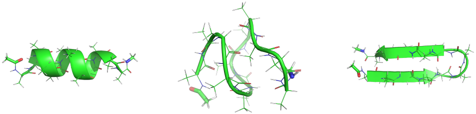


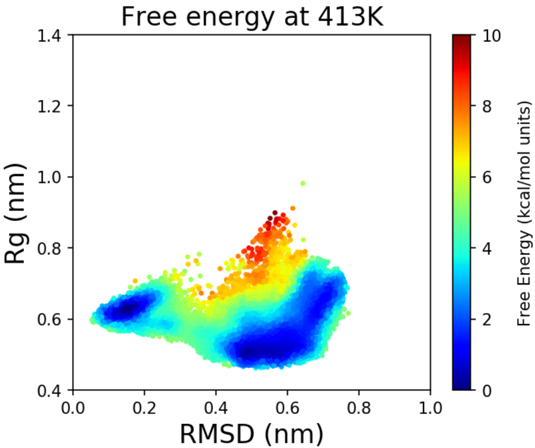
[6] **Bethune et. al.**, 2018

Alanine-12: ISST

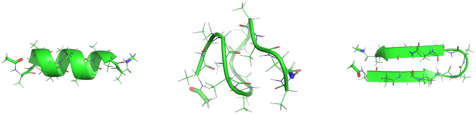


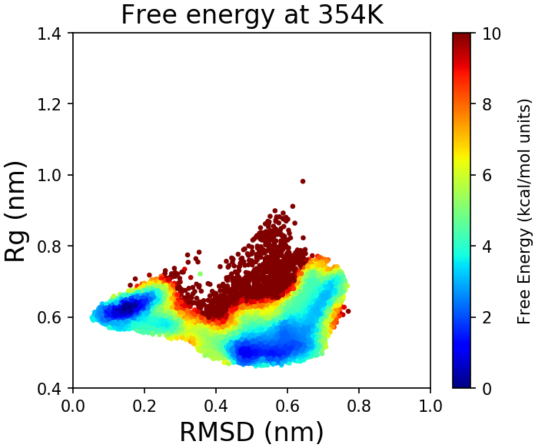




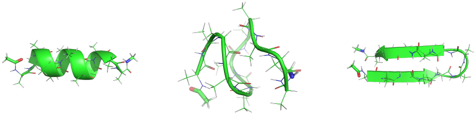

Free energy at 413K
Rg (nm)
1.4
1.2
1.0
0.8
0.6
0.4
0.0
0.2
0.4
0.6
0.8
1.0
RMSD (nm)
10
8
6
4
2
0
Free Energy (kcal/mol units)

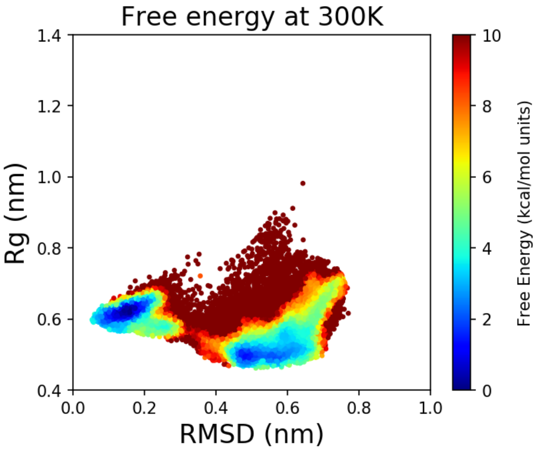
Alanine-12: ISST



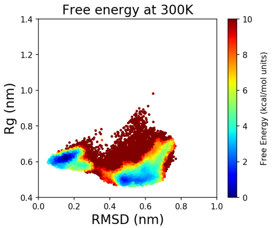


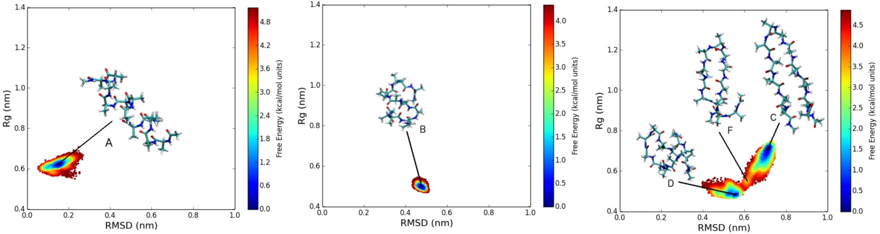
Alanine-12: ISST





Alanine-12: LD vs ISST





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[7] **Bethune et. al.**, 2018

Conclusions

- Operate ST in the Infinite Switch limit, with adaptive weight learning – without temperature being a dynamical variable [8]
- We have presented work on MD, future work is looking into applying the method in data science and ML
- We have implemented the method in MIST and it is available to download at https://bitbucket.org/extasy-project/mist/wiki/Home

[8] Anton Martinsson, Jianfeng Lu, Ben Leimkuhler, Eric Vanden-Eijnden, *Simulated Tempering Method in the Infinite Switch Limit with Adaptive Weight Learning*, **to appear in JSTAT**, 2018

Paul Dupuis, Yufei Liu, Nuria Plattner, and J. D. Doll.
On the Infinite Swapping Limit for Parallel Tempering.
Multiscale Modeling & Simulation, 10(3):986–1022, 2012.

Nuria Plattner, J D Doll, Paul Dupuis, Hui Wang, Yufei Liu, and J E Gubernatis.
An infinite swapping approach to the rare-event sampling problem.
The Journal of chemical physics, 135(13):134111, oct 2011.

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