SI Appendix

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Here we extend our derivation of RENS to allow for stochastic updates in the system's evolution. For specificity, we assume that our dynamics are given by Eq. 13 of the paper, in conjunction with the Andersen thermostat. For these dynamics we define reduced work by Eq. A-8 below, and we argue that with this definition detailed balance is satisfied, i.e. that $\mathcal{R}_A$ and $\mathcal{R}_B$ sample their respective equilibrium distributions.

In the Andersen thermostating scheme, the momenta of randomly selected particles are re-assigned from a Maxwell-Boltmann distribution. To keep our analysis simple, we will at first assume a single Andersen update at time $t = s$ during the work simulation, and we will use the notation

$$\gamma_A : x_0 \longrightarrow x_s \Longrightarrow x'_s \longrightarrow x_\tau \tag{A-1}$$

to denote a work simulation in replica A. The notation is interpreted as follows. The trajectory evolves deterministically (Eq. 13) from $t = 0$ to $t = s$. Then the momentum of the i'th particle (selected randomly) is replaced by a new momentum sampled from the Maxwell-Boltzmann distribution: $\mathbf{p}_i \Rightarrow \mathbf{p}'_i$, where $p_{\mathrm{MB}}(\mathbf{p}'_i; \lambda^A_s) \propto \exp[-p'^2_i/2m_i k_B T_{\lambda^A_s}]$. Finally, deterministic evolution continues from $t = s$ to $t = \tau$. In replica B we generate a trajectory

$$\gamma_B : y_\tau \longleftarrow y'_{\tau-s} \Longleftarrow y_{\tau-s} \longleftarrow y_0 \,, \tag{A-2}$$

with a similar interpretation. Since the protocols for varying λ in the two replicas are related by time-reversal, $\lambda^A_t = \lambda^B_{\tau-t}$, the Andersen updates in Eqs. A-1 and A-2 occur at the same value of work parameter, which we will denote λ^*.

The probability to generate a particular trajectory γ_A in $\mathcal{R}_A$, conditioned on the initial state x_0, can be written as

$$\pi_A[\gamma_A] = \pi_A(x_0 \to x_s) \cdot \pi_A(x_s \Rightarrow x'_s) \cdot \pi_A(x'_s \to x_\tau) \,. \tag{A-3}$$

The first and third factors are analogous to Eq. 7a, and describe evolution during the two deterministic intervals; and

$$\pi_A(x_s \Rightarrow x'_s) \propto \exp(-p'^2_i/2m_i k_B T_{\lambda^*}) \,. \tag{A-4}$$

Similar expressions hold for $\pi_B[\gamma_B]$.

Now consider a particular trajectory γ_A in $\mathcal{R}_A$ (Eq. A-1), along with the time-reversed version of that trajectory, which we denote

$$\bar{\gamma}_B : \bar{x}_0 \longleftarrow \bar{x}_s \Longleftarrow \bar{x}'_s \longleftarrow \bar{x}_\tau \,. \tag{A-5}$$

The conditional probabilities for these two trajectories are related as follows:

$$\pi_A[\gamma_A] = \frac{\pi_B[\bar{\gamma}_B]}{J_A} \, \frac{\pi_A(x_s \Rightarrow x'_s)}{\pi_B(\bar{x}_s \Leftarrow \bar{x}'_s)} = \pi_B[\bar{\gamma}_B] \, e^{-q_A[\gamma_A]} \,, \tag{A-6}$$

where

$$q_A[\gamma_A] = h(x'_s; \lambda^*) - h(x_s; \lambda^*) + \ln J_A \tag{A-7}$$

and $J_A = (T_B/T_A)^{N/2}$. In Eq. A-6, the factor $\pi_B[\bar{\gamma}_B]/J_A$ was obtained as in Eq. 10a; and the remaining factor was evaluated using Eq. A-4. Here N denotes the number of degrees of freedom in the system, not the number of particles.

The quantity $h(x'_s; \lambda^*) - h(x_s; \lambda^*)$ in Eq. A-7 is the change in h that accompanies the Andersen update $\mathbf{p}_i \Rightarrow \mathbf{p}'_i$. Interpreting $q_A[\gamma_A]$ as the reduced heat absorbed by the system during the trajectory γ_A, we define the reduced work:

$$w_A[\gamma_A] = h(x_\tau; \lambda_\tau) - h(x_0; \lambda_0) - q_A[\gamma_A]. \tag{A-8}$$

Eqs. A-6 and A-8 are analogues of Eqs. 10 and 4 of the main text, and Eq. A-6 is equivalent to Crooks's result, Eq. 9 of Ref. [18]. With these equations – and similar ones for a trajectory γ_B generated in $\mathcal{R}_B$ (Eq. A-2) – we now establish detailed balance for the joint transition $(x, y) \to (y', x')$, in a manner analogous to Eq. 12 of the main text:

$$\begin{aligned} P(y', x'|x, y) &= \pi_A[\gamma_A] \, \pi_B[\gamma_B] \, \alpha[\gamma_A, \gamma_B] \\ &= \pi_B[\bar{\gamma}_B] \, \pi_A[\bar{\gamma}_A] \, e^{-q_A[\gamma_A] - q_B[\gamma_B]} \, \alpha[\bar{\gamma}_A, \bar{\gamma}_B] \, e^{-w_A[\gamma_A] - w_B[\gamma_B]} \\ &= P(\bar{x}, \bar{y}|\bar{y}', \bar{x}') \, e^{-h_A(y') - h_B(x') + h_A(x) + h_B(y)} \,. \end{aligned} \tag{A-9}$$

Here, γ_A is the unique trajectory that starts at x_0 and ends at x_τ, and similarly for γ_B; and $\alpha = \min\{1, e^{-w}\}$ where $w = w_A + w_B$.

In obtaining this result we have made the simplifying assumptions that (i) only a single Andersen update is made during the work simulation, and (ii) Eq. 13 gives the deterministic portion of the dynamics. We now sketch a derivation for the more general case in which K Andersen updates are performed, at times $s_1, \cdots s_K$, and the evolution between these updates is deterministic and time-reversal symmetric (in the sense discussed in the text), but otherwise quite general. Under these assumptions we can obtain the following expression for the relative probabilities of generating γ_A in $\mathcal{R}_A$ and its time-reverse $\bar{\gamma}_B$ in $\mathcal{R}_B$:

$$\pi_A[\gamma_A] = \pi_B[\bar{\gamma}_B]\, e^{-q_A[\gamma_A]}\,, \tag{A-10}$$

where

$$q_A[\gamma_A] = \ln J_A[\gamma_A] + \sum_{k=1}^{K} \left[h(x'_{s_k}; \lambda^A_{s_k}) - h(x_{s_k}; \lambda^A_{s_k})\right] \tag{A-11}$$

and J_A is the product of Jacobians along the deterministic intervals of the trajectory:

$$J_A[\gamma_A] = \left|\frac{\partial x_\tau}{\partial x'_{s_K}}\right| \cdot \left|\frac{\partial x_{s_K}}{\partial x'_{s_{K-1}}}\right| \cdots \left|\frac{\partial x_{s_1}}{\partial x_0}\right|\,. \tag{A-12}$$

(As with Eqs. 10 and A-6, Eq. A-10 corresponds to Eq. 9 of Ref. [18].) We then define reduced work as in Eq. A-8.

Since there now exist multiple trajectories that that connect given initial and final points, the transition probability P will be given by an integral over all intermediate points:

$$P(y', x'|x, y) = \int \mathcal{D}'\gamma_A \int \mathcal{D}'\gamma_B \;\pi_A[\gamma_A]\, \pi_B[\gamma_B]\, \alpha[\gamma_A, \gamma_B] \tag{A-13}$$

where $\int \mathcal{D}'\gamma_A = \int dx_{s_1} \int dx'_{s_1} \cdots \int dx_{s_K} \int dx'_{s_K}$, and γ_A begins and ends in the fixed configurations $x_0 = x$ and $x_\tau = x'$. Analogous comments apply to $\int \mathcal{D}'\gamma_B$.

Eq. A-13 is a path-integral expression for the transition probability for the trial move $(x, y) \to (y', x')$. Writing the corresponding expression for the reverse trial move, $(\bar{x}, \bar{y}) \leftarrow (\bar{y}', \bar{x}')$, we get

$$\begin{aligned}
P(\bar{x}, \bar{y}|\bar{y}', \bar{x}') &= \int \mathcal{D}'\bar{\gamma}_A \int \mathcal{D}'\bar{\gamma}_B \;\; \pi_A[\bar{\gamma}_A]\, \pi_B[\bar{\gamma}_B]\, \alpha[\bar{\gamma}_A, \bar{\gamma}_B] \\
&= \int \mathcal{D}'\gamma_A \int \mathcal{D}'\gamma_B \;\; \pi_B[\gamma_B]\, \pi_A[\gamma_A]\, e^{q_A[\gamma_A]+q_B[\gamma_B]}\, \alpha[\gamma_A, \gamma_B]\, e^{w_A[\gamma_A]+w_B[\gamma_B]} \\
&= e^{h_A(y')+h_B(x')-h_A(x)-h_B(y)} \int \mathcal{D}'\gamma_A \int \mathcal{D}'\gamma_B \;\; \pi_B[\gamma_B]\, \pi_A[\gamma_A]\, \alpha[\gamma_A, \gamma_B] \\
&= e^{h_A(y')+h_B(x')-h_A(x)-h_B(y)}\, P(y', x'|x, y)
\end{aligned} \tag{A-14}$$

Here we have used Eqs. A-8 and A-10, along with the correspondence between a trajectory and its time-reversed twin ($\mathcal{D}'\bar{\gamma}_A = \mathcal{D}'\gamma_B$, etc.).

This derivation can be generalized further by replacing the Andersen updates with any stochastic moves that satisfy detailed balance (for instance Metropolis Monte Carlo moves). Eqs. A-10 - A-14 remain unchanged under these quite general conditions, and therefore RENS remains valid.