Breaking time-reversal symmetry for ratchet models of molecular machines

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Biomolecular machines transduce free energy from one form to another to fulfill many important roles inside cells, with free energy dissipation required to achieve directed progress. We investigate how to break time-reversal symmetry at a given dissipation cost for sawtooth potentials, which have frequently been used to model molecular machines as ratchets. Time asymmetry increases for sawtooth potentials with higher barriers and for driving potentials of intermediate width. We unexpectedly find that symmetric sawtooth potentials maximize time asymmetry, while earlier work examining ratchet models of molecular machines required asymmetric sawtooth potentials—a distinction related to differences between autonomous and deterministic driving.

I. INTRODUCTION

Biomolecular machines perform a variety of essential tasks inside living cells [1], and inspire the development of synthetic molecular machines [2]. Molecular machines operate out of equilibrium and stochastically [3], buffeted by fluctuations at the nanoscale [4]. As with macroscopic machines, molecular machines can be designed to optimize efficiency [5–7] and speed [7–9]. However, unlike their macroscopic counterparts, design can meaningfully impact the precision of molecular machine operation [10].

Molecular machines can pay a significant fraction of their free energy budget for directed progress [11, 12]. To quantify directional behavior, Feng and Crooks [13] proposed time-reversal asymmetry, expressed as the Jensen-Shannon divergence between trajectory distributions for processes driven in forward and reverse directions.

Earlier investigations (unfolding/refolding of ribonucleic acid hairpins in experiment [13] and alanine decapeptide in molecular dynamics simulations [14]) found the trade-off between time asymmetry (seen as a potential benefit) and energy dissipation (a cost) remained near the prediction of linear-response theory [15]. For low ($0 \leq k_B T$) and high ($\geq 8k_B T$) dissipation, the linear-response prediction for time asymmetry nears the maximum possible value, while at intermediate dissipation values there is a substantial gap between the linear-response prediction and the forbidden time asymmetry, leaving room for significant improvement above linear-response behavior [16]. Understanding how molecular machines can achieve higher time asymmetry for a given dissipation cost may point towards improved design principles for molecular machines, and characteristics that could be favored by biomolecular machine evolution.

In our previous work [16], we explored how to manipulate time asymmetry for a step potential representing energy transmission, using a harmonic trap to move the system from one side of the step to the other. Intermediate step heights and protocols remaining near the step led to time asymmetries that improved most on linear response.

In this work, we investigate time asymmetry for a sawtooth potential, which is frequently used to represent a ratchet model of a molecular machine [17–29]. In contrast to step potentials, we find that high sawtooth potentials provide greater improvement over linear response. Changing from a symmetric to an asymmetric sawtooth causes time asymmetry to decrease, stemming from the greater overlap in initial equilibrium distributions for more asymmetric sawtooths.

II. METHODS

Time-reversal asymmetry $A$ (here measured in nats, $1/\ln 2$ bits) quantifies the expected information gain about whether a single observed trajectory was produced by a particular nonequilibrium process or its time reversal, assuming a 50% prior probability of the forward or reverse direction [30]. If the forward and reverse trajectory distributions are identical, then any observation provides no information on the protocol direction, defining a minimum $A = 0$. If the forward and reverse trajectory distributions are completely distinct, then any observed trajectory can be definitively assigned to the forward or reverse process, defining a maximum $A = \ln 2$ nats, amounting to one bit of information.

The Crooks fluctuation theorem [31] quantitatively describes the relative probabilities of forward and reverse trajectories solely in terms of the work required for each trajectory. This permits expression of the time asymmetry $A$ in terms of the forward and reverse work distributions [13],

$$A = \frac{1}{2} \left( \ln \frac{2}{1 + \exp(-\beta W[X|\Lambda] + \beta \Delta F)} - \ln \frac{2}{1 + \exp(-\beta W[X|\Lambda] - \beta \Delta F)} \right)_{\Lambda}. \quad (1)$$

$\Lambda$ labels a protocol, the time schedule of a controllable parameter $\lambda(t)$ over $t \in [0, \Delta t]$ for a protocol of period
Δt. The reverse protocol ˜Λ is the time-reversal of Λ, i.e.
λ(Δt − t). W[X|Λ] is the work done during protocol Λ
when the system follows trajectory X. ΔF is the free
energy change during protocol Λ, and β ≡ (k_B T)^{−1},
for Boltzmann’s constant k_B and temperature T.

Dissipation h is the average excess work for an equal
weighting of forward and reverse protocols, and hence
equals the average work because the equilibrium free
energy changes during Λ and ˜Λ cancel [13]:

\[ h[Λ] \equiv \frac{1}{2} \left( \beta(\Delta W[X|Λ])_Λ + \beta(\Delta W[X|Λ])_Λ \right). \]  \hspace{1cm} (2)

Time asymmetry is mathematically upper bounded by
A ≤ h/4 and A ≤ ln[2/(1 + e^{−h})] [13, 32]. A sys-
tem which remains near equilibrium responds linearly
to small perturbations [33] – for a driven ensemble in this
linear-response regime, the work distribution is Gaussian,
and the Crooks fluctuation theorem imposes a connec-
tion between the mean and variance of the work [13, 34],

\[ \langle W \rangle = \frac{1}{2} \sigma_W^2. \]

We investigate time asymmetry and dissipation with
an overdamped system of diffusivity D on a potential
landscape \( E[x, x_{trap}(t)] = E_{trap}[x, x_{trap}(t)] + E_r(x) \). The
first component is a quadratic trap, \( E_{trap}[x, x_{trap}(t)] = \frac{1}{2} k[x - x_{trap}(t)]^2 \), with a time-dependent minimum \( \lambda(t) = x_{trap}(t) \) as the control parameter. The second component \( E_r(x) \) is a time-independent periodic sawtooth (ratchet)
potential (Fig. 1) that enables directional motion for sim-
ple models of molecular machines [17, 29].

\[ E_r(x) = \begin{cases} \Delta E_r \frac{x \mod \ell}{\ell_1}, & \text{if } 0 < x \mod \ell \leq \ell_1 \\ \Delta E_r \left(1 - \frac{x \mod \ell}{\ell_2}\right), & \text{if } \ell_1 < x \mod \ell \leq \ell , \end{cases} \]  \hspace{1cm} (3)

with \( \ell = \ell_1 + \ell_2 \) the period over which the sawtooth
repeats, and \( \Delta E_r \) the barrier height. The periodicity
of \( E_r(x) \) represents a cyclical molecular machine, with
\( \Delta F = 0 \) over a cycle. \( E, k, x, \) and \( \Delta E_r \) are nondimen-
sionalized by \( k_B T \) and the period \( \ell \) (see Appendix A for
details).

For each protocol, the trap translates at a constant
velocity \( u = 1/\Delta t \) from \( x_{trap} = 0 \) to \( x_{trap} = 1 \) for the
forward protocol, and in the opposite direction for the
reverse protocol. The system begins in equilibrium and
diffuses as the trap translates. Appendix B provides fur-
ther simulation details.

For a given spring constant \( k \), ratchet height \( \Delta E_r \), saw-
tooth lengths \( \ell_1 \) and \( \ell_2 \), and trap speed \( u \), work distributions
are compiled from many repetitions of forward and
reverse protocols, from which a single time asymme-
try vs. dissipation, with each curve generated by para-
metrically varying the trap speed. Distinct curves are
for various ratchet heights \( \Delta E_r \) and spring constants
\( k \). For each curve, both the time asymmetry and dis-
sipation are negligible for low trap speed \( u \) (bottom left of
Fig. 2a panels). A slow-moving trap allows the sys-
tem to stay near equilibrium, leading to forward and re-
verse work distributions with similar shapes, widths,
and mean work magnitudes (Fig. 2a, far left panel). These
near-equilibrium trajectories are well-described by lin-
ear response, hence staying near the linear-response time
asymmetry-dissipation curve.

As \( u \) increases (left to right in Fig. 2a), the forward
and reverse work distributions become non-Gaussian and
more separated, leading to less overlap and causing both
time asymmetry and dissipation to increase. For these
higher trap speeds, the system departs from linear
response (highest dissipations in each panel of Fig. 2a).

At higher trap speeds, individual system trajectories
can be roughly categorized as either crossing from the
initial side to the far side of the sawtooth potential bar-
tier, or remaining on the initial side without crossing the
barrier. In Fig. 2b with \( u = 0.625 \), there are two compo-
nents comprising the work distributions, corresponding
to these two trajectory categories. The wide ‘crossing’
components, at low work magnitude, represent systems
that cross to the far side of the barrier, thus staying closer
to \( x_{trap} \), such that the trap does less work on the system.
The narrow ‘non-crossing’ peaks, at higher work magni-
tude, are for systems that ‘get stuck’ and do not cross
to the far side of the barrier, keeping the system further
from \( x_{trap} \) and increasing the work done by the trap on
the system.

As the trap speed \( u \) increases further, the system is
more likely to remain stuck on the initial side of the
barrier, shifting probability from the crossing compo-
nent to the non-crossing component (Fig. 2a, \( u = 5 \) and
\( u = 2 \times 10^4 \)). At the highest trap speeds, the protocol

FIG. 1. Sawtooth energy landscape model. The poten-
tial landscape is composed of a time-dependent quadratic
trap, \( E_{trap}[x, x_{trap}(t)] = \frac{1}{2} k[x - x_{trap}(t)]^2 \) (red); and a time-


dependent sawtooth potential \( E_r(x) \) (blue) from Eq. (3).

When the sawtooth is asymmetric, the gradual (\( \ell_1 > 0.5 \)) and
steep (\( \ell_1 < 0.5 \)) sides of the sawtooth are indicated.
duration is insufficient for substantial system diffusion, so the system never crosses to the far side of the barrier.

As trap speed $u$ increases (Fig. 2b, left to right), work distributions depart from Gaussian distributions, gaining the secondary components discussed in the preceding paragraphs. These components, with less overlap than the Gaussian work distributions of linear response, cause time asymmetries above linear response, as shown in Fig. 2c.

For higher barrier $\Delta E_r$, time asymmetry $A$ is higher at a given dissipation (Fig. 2h). Figure 2g shows work distributions for increasing barrier height $\Delta E_r$. As $\Delta E_r$ increases, the system is less likely to cross from the initial to the far side of the barrier, which narrows the work distributions and decreases their overlap, producing higher time asymmetries.

Maximum dissipation is achieved with the fastest trap speeds, approaching instantaneous trap movement, such that the system is unable to substantially diffuse over the protocol duration. For a system effectively frozen in its initial position (drawn from the initial equilibrium ensemble), the maximum dissipation $h_{\text{max}} = 1/2k$ (shown as a vertical dashed line in Fig. 2h) equals the energy change in changing the trap from $x_{\text{trap}} = 0$ to $x_{\text{trap}} = 1$, averaged over the equilibrium distribution given $x_{\text{trap}} = 0$ (see Appendix C).

Figure 3 shows time asymmetry $A$ relative to linear-response time asymmetry $A_{\text{LR}}$ at the same dissipation, $A_{\text{rel}}(h) \equiv A(h) - A_{\text{LR}}(h)$, for two speeds $u$ as spring constant $k$ and barrier height $\Delta E_r$ are varied. The dependence of $A_{\text{rel}}$ on $k$ and $\Delta E_r$ is unchanged across a wide range of $u$. $A_{\text{rel}} \approx 0$ if either $k$ or $\Delta E_r$ are small. $A_{\text{rel}}$ sharply increases to substantial positive values at $\Delta E_r \approx 5$ or at $k \approx 10$.

For larger $\Delta E_r$, there is an optimum $k \approx 18$ which maximizes $A_{\text{rel}}$ (Fig. 3). At low and high dissipation, linear-response time asymmetry nears the maximum possible time asymmetry, limiting $A_{\text{rel}}$. At intermediate
dissipation, there is substantial room between linear response and forbidden time asymmetries, permitting larger \( A_{rel} \). Intermediate \( k \) values select these intermediate dissipation values that permit large \( A_{rel} \).

After an initial sharp increase of \( A_{rel} \) at \( \Delta E_r \approx 5 \), \( A_{rel} \) plateaus with further increases of \( \Delta E_r \). This plateau underlies the diminishing returns in increasing time asymmetry for increasing \( \Delta E_r \) in Fig. 2a, caused once \( \Delta E_r \) is sufficiently large to prevent nearly all system trajectories from crossing the barrier.

### B. Asymmetric ratchets

We now explore asymmetric ratchets with \( \ell_1 \neq \ell_2 \). Figure 3 shows time asymmetry vs. dissipation for various sawtooth potentials. Potentials with \( \ell_1 = 0.5 \pm \delta \), for a given \( \delta \in [0, 0.5] \), will yield the same time asymmetry, because time asymmetry does not depend on which work distribution is labeled forward and which is labeled reverse. Accordingly, we increase \( \ell_1 \) from 0.5 towards 1 to explore the effect of an asymmetric potential. Although one might naively expect that an asymmetric barrier would increase the distinction between forward and reverse trajectory distributions and thus increase time asymmetry, we find that time asymmetry \( A \) at a given dissipation decreases as the asymmetry of the potential increases.

To understand the time asymmetry decrease as \( \ell_1 \) increases, Fig. 4 compares work distributions for symmetric (\( \ell_1 = \ell_2 \)) and asymmetric (\( \ell_1 \neq \ell_2 \)) potentials. For slow trap speed, the work distributions for symmetric and asymmetric ratchets are similar and appear Gaussian (Fig. 5 far left). As trap speed increases, the work distributions for symmetric and asymmetric ratchets become distinct.

A symmetric sawtooth potential and an intermediate trap speed (Fig. 5, middle) lead to non-Gaussian forward and reverse work distributions, with a clear peak corresponding to trajectories that do not cross the barrier, and a tail of trajectories that cross the barrier. For a comparable asymmetric ratchet, the forward and reverse work distributions are not symmetric (Fig. 5, middle). The forward-protocol peak is wider, as \( \ell_1 > 0.5 \) allows the system during the forward protocol to slowly climb up the gradual potential slope (Fig. 1). The primary reverse-protocol peak is narrower, as the system is stuck on the low side of a steep cliff; a secondary component of the reverse-protocol work distribution occurs at the same work value as the forward-protocol peak, due to trajectories which stay on the gradually sloped side of the sawtooth. The overlap of the forward-protocol peak and reverse-protocol secondary component decreases the time asymmetry compared to the symmetric work distributions. Compared to symmetric potentials, asymmetric sawtooth potentials increase the probability that the system is on the gradual side of the ratchet potential (independent of whether the trap starts on the steep or gradual side), leading to more similar trajectories overall, and thus more difficulty in distinguishing between the forward and reverse protocols.

Fast driving of a symmetric ratchet produces forward and reverse work distributions composed of single, symmetric, non-Gaussian peaks (Fig. 5, right). For asymmetric potentials, the work distribution peaks nearly recapitulate the sawtooth potential shape, with one side rising gradually and the other quite steeply (Fig. 5b, right). The work distributions for both symmetric and asymmetric potentials are caused by the initial equilibrium distributions, as there is insufficient time for substantial system diffusion. In addition to the primary peak in each distribution, there is a much smaller secondary component at more positive work values — the reverse-protocol secondary component overlaps with the forward-
FIG. 5. Work distributions for forward (black) and reverse (red) protocols with a) symmetric sawtooth potentials ($\ell_1 = \ell_2 = 0.5$), or b) asymmetric sawtooth potentials ($\ell_1 = 0.99$ and $\ell_2 = 0.01$). Driving speed increases from left to right panels. Spring constant $k = 8$ and barrier height $\Delta E_r = 4$. Distributions are over $5 \times 10^4$ samples.

protocol primary peak. As for intermediate speeds, the greater overlap of the work distributions for the asymmetric sawtooth leads to a lower time asymmetry. The cause of this greater overlap in work distributions is a greater overlap in initial equilibrium positions: a system with a trap which begins the protocol centered on the steep side of the potential (reverse protocol) has a non-vanishing equilibrium probability to be on the gradual side of the potential.

Overall, in an asymmetric ratchet the system is more likely to be in the same initial equilibrium position during forward and reverse protocols, compared to symmetric ratchets. Slower protocols that allow time for diffusion eliminate this difference in overlap of initial positions reflected in the work distributions.

IV. DISCUSSION

We have investigated the tradeoffs of time asymmetry and dissipation for driven systems diffusing in sawtooth potentials, which are frequently used as simple ratchet models for molecular machines [17–29]. Accordingly, we explored the effect of sawtooth potential (height and asymmetry) and protocol (speed and driving strength) characteristics on time asymmetry.

For high barriers and intermediate spring constants, high trap velocities lead to time asymmetries well above linear response for a sawtooth potential (Fig. 2a). The barrier is difficult to cross in either direction (as the system must climb the barrier), such that for fast protocols the system rarely crosses the barrier during the entire protocol. This finding suggests molecular machines could gain a higher time asymmetry by proceeding through much of each cycle rapidly, consistent with recent work describing the kinesin cycle with slow transitions following rapid events, such as ATP isomerization following ATP binding [35], diffusive search for a forward microtubule binding site following neck linker docking [35], and ADP release following binding of the kinesin head to the microtubule [36, 37].

Increasing the barrier height of a sawtooth potential increases time asymmetry for a given dissipation, until the barrier is sufficiently high that the system rarely crosses the barrier (Figs. 2 and 3). The probability of crossing the barrier decreases as the barrier height increases, leading to more distinct forward and reverse trajectory distributions.

The linear-response relationship between time asymmetry and dissipation holds for slow processes that allow the system to stay near equilibrium [34]. To assess performance for driving the system over a sawtooth potential, we compared time asymmetries to linear-response behavior at the same dissipation (Fig. 3), finding a clear optimum spring constant which maximizes the improvement over linear response. At this optimum spring constant, relatively fast protocols produce dissipation in the range ($1k_B T \lesssim h \lesssim 6k_B T$) at which linear-response time asymmetry is far below forbidden time asymmetries. This optimum spring constant suggests that molecular machines may benefit from states that are not too tightly or loosely constrained, aligning with the somewhat constrained dispersion of position distributions for states of both kinesin [35] and F$_1$-ATPase [38].
When driving over a step potential [16], there also is an optimal spring constant that maximizes time asymmetry relative to linear response. However, driving over steps exhibits increased time asymmetry for intermediate step heights, while driving over ratchets maximizes time asymmetry for large barrier heights. Sawtooth and step potentials are similar in that climbing either a sufficiently high barrier or step can cause the system to ‘get stuck’, leading to distinct trajectory distributions for forward and reverse protocols. However, moving the trap from the beginning to the end of the protocol for a step potential changes the equilibrium energy, while for a sawtooth potential the equilibrium energy remains unchanged. For a sufficiently large step, although the trap may be located on the high side of the step, the most equilibrium probability will be on the low side of the step, allowing very similar trajectories for forward and reverse protocols; this is not possible for a sawtooth potential. This contrast between large steps and sawtooth barriers—regarding how equilibrium probability is located—causes time asymmetry to be maximal for intermediate step heights but for large sawtooth barriers.

Previous work has focused on the effect of barrier shape on transition characteristics and molecular machine behavior [7][9]. Accordingly, we examined how an asymmetric sawtooth potential (with a barrier unevenly spaced between neighboring states) affects time asymmetry compared to a symmetric potential (barrier halfway between states). We unexpectedly found that symmetric ratchets maximize time asymmetry (Fig. 4). Symmetric ratchets maximize the distance between the sawtooth potential barrier and the closest neighboring sawtooth potential minimum, decreasing the equilibrium probability to find the system on the opposite side of the barrier from the trap. This increases the chance of distinct forward and reverse trajectories and leads to higher time asymmetries.

Our finding that time asymmetry is maximized for symmetric sawtooth potentials (Fig. 4) contrasts with previous work on ratchet potentials for molecular machines, primarily with flashing ratchets, which required an asymmetric ratchet potential to provide directed motion [17][29][25][28][24]. Our results highlight distinct strategies to optimize performance that depend on the autonomy of a molecular machine: autonomous machines [11] which ‘drive themselves’ require asymmetric potentials for directed motion, while machines with directed motion provided by an external protocol (in this paper, the imposed trap translation schedule) are free to have symmetric potentials while retaining directed motion. External driving does not imply an outside agent is providing a schedule for variation of a system parameter. A process could be considered ‘externally driven’ if a rapid change, such as ATP binding or neck-linker docking for kinesin [39], occurred spontaneously, causing a sudden change in the potential experienced by another part of the machine, thereby inducing a transition. While biomolecular machines are autonomous at the level of entire machines, current synthetic molecular machines are typically externally driven [40].

Splitting factors [9] are thought to reflect the barrier asymmetry for a molecular machine transition [8], analogous to how the distance to the transition state affects unfolding rates [11]. Splitting factors have been estimated for a variety of biomolecular machines, and their values indicate that barriers between molecular machine states range from symmetric to very asymmetric [9], suggesting that evolution could steer biomolecular machines towards symmetric potentials.

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Appendix A: Nondimensionalization

The system energy $E'$ at position $x'$ in a quadratic trap with spring constant $k'$ centered at $x' = x'_{\text{trap}}$ with sawtooth barrier height $\Delta E'_r$ is

$$E' = \frac{1}{2} k' (x' - x'_{\text{trap}})^2 + \frac{\Delta E'_r x'}{\ell'_1} . \quad (A1)$$

for $x' < \ell'_1$. We nondimensionalize all quantities using energy scale $H$ and length scale $\ell$:

$$\frac{E'}{H} = \frac{1}{2} k \ell^2 \frac{(x' - x'_{\text{trap}})^2}{\ell^2} + \frac{\Delta E'_r x'}{H \ell} . \quad (A2)$$

We set $E = E'/H$, $k = k' \ell^2/H$, $x = x'/\ell$, $\Delta E_r = \Delta E'_r/H$, $\ell_1 = \ell_1'/\ell$, and $\ell_2 = \ell_2'/\ell$. We choose $H = k_B T$, so that all energies are in units of $k_B T$. $\ell$ is chosen so that $\ell_1 + \ell_2 = 1$, i.e. the nondimensionalized period of the sawtooth is one. The same nondimensionalization applies for positions $x' > \ell'_1$. We also nondimensionalize all times by timescale $\tau$ chosen so that dimensionless diffusivity $D$ is unity.

Appendix B: Simulation details

The system moves on a one-dimensional spatial lattice with spacing $\delta x = 0.01$, with each sawtooth repeat $\ell = 1$ in length. Each timestep $\delta t$, the system randomly attempts to move either left or right, with moves accepted...
Appendix C: Instantaneous trap translation

The system is on an infinitely repeating static sawtooth potential (sawtooth period is one) and initially the trap is centered at $x_{\text{trap}} = 0$. The energy at position $x$ is $E(x, x_{\text{trap}}(t)) = E_{\text{trap}}[x, x_{\text{trap}}(t)] + E_r(x)$. If the trap moves instantaneously, the system does not move. When $x_{\text{trap}}$ is increased by one (the sawtooth period),

$$\Delta E_r = 0 ,$$

and $\Delta E_{\text{trap}}(x) = k(\frac{1}{2} - x)$. The mean work done by this instantaneous trap movement, the maximum that can be achieved for a monotonic protocol connecting the control-parameter endpoints, is

$$\langle W \rangle_{\text{max}} = \frac{1}{Z} \int_{-\infty}^{\infty} \Delta E_{\text{trap}}(x) e^{-\frac{E[x, x_{\text{trap}}=0]}{k}} dx ,$$

where $Z \equiv \int_{-\infty}^{\infty} e^{-\frac{E[x, x_{\text{trap}}=0]}{k}} dx$. For a symmetric sawtooth potential, the $O(x)$ term in Eq. (2) does not contribute to the integral, because the integral bounds are symmetric about $x = 0$ and $k x e^{-\frac{E[x, x_{\text{trap}}=0]}{k}}$ is overall an odd function of $x$. Therefore $\langle W \rangle_{\text{max}} = \frac{1}{2} k$. The same result is found for instantaneous trap translation from $x = 1$ to $x = 0$ (reversing the protocol). Thus, using Eq. 2 the maximum dissipation is $h_{\text{max}} = \langle W \rangle_{\text{max}} = \frac{1}{2} k$.

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