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Revisiting kinetic Monte Carlo algorithms for time-dependent processes: From open-loop control to feedback control

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ABSTRACT

Simulating stochastic systems with feedback control is challenging due to the complex interplay between the system's dynamics and the feedback-dependent control protocols. We present a single-step-trajectory probability analysis to time-dependent stochastic systems. Based on this analysis, we revisit several time-dependent kinetic Monte Carlo (KMC) algorithms designed for systems under open-loop-control protocols. Our analysis provides a unified alternative proof to these algorithms, summarized into a pedagogical tutorial. Moreover, with the trajectory probability analysis, we present a novel feedback-controlled KMC algorithm that accurately captures the dynamics systems controlled by an external signal based on the measurements of the system's state. Our method correctly captures the system dynamics and avoids the artificial Zeno effect that arises from incorrectly applying the direct Gillespie algorithm to feedback-controlled systems. This work provides a unified perspective on existing open-loop-control KMC algorithms and also offers a powerful and accurate tool for simulating stochastic systems with feedback control.

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I. INTRODUCTION

At the molecular scale, biological processes are complex and stochastic.^{1,2} Currently, numerical simulations contribute critical insights into the stochastic dynamics of the systems.³ One example approach involves solving for the master equation,^{4–6} constructed either through molecular dynamics simulations (e.g., via Markov state model approaches^{7–9}) or through experimental results (e.g., kinetic proofreading^{10,11}). In this case, if the system is reduced to a few state Markov network, one can numerically solve for the master equation, given the initial probability distribution and the control protocol. Another example, when the system's state space is too large, is to utilize the Gillespie algorithm¹² or kinetic Monte Carlo (KMC) simulation to obtain an ensemble of the stochastic trajectories of the process.

Numerous biological processes also respond either to external control or other coupled processes.¹³ These stochastic systems are more complex than stationary systems, as their kinetic rates change over time via open-loop (non-feedback) or closed-loop (feedback)

control. Examples of feedback controlled systems span multiple length- and timescales, from metabolic regulation^{14–16} to bacterial chemotaxis^{17,18} to cell-cycle regulation.^{19–22} Understanding feedback controlled systems is essential in unraveling their dynamics and optimizing their performance. However, it remains challenging to simulate feedback controlled stochastic systems due to the presence of in-time feedback.

Gillespie first proposed a direct KMC method that allows one to simulate the stochastic dynamics for a system that evolves under a constant set of rates.²³ Unfortunately, this method cannot be directly extended to simulate time-inhomogeneous systems, where the system's dynamical rates change over time. Naively implementing the direct KMC simulation by discretizing the simulation into a sequence of constant rate windows may lead to an incorrect underestimation of the transition frequency of the systems, which resembles the Zeno effect. In quantum mechanics, the Zeno effect describes the system dynamics being trapped into a single state due to frequent repetitive projective measurements.^{24–26}

In the past few decades, an open-loop-control KMC algorithm has been proposed to simulate various time-inhomogeneous biological systems whose kinetic rates change over time due to an open-loop (non-feedback) control protocol. These studies were presented for various biological processes, including ion channels in neurons,^{27–29} RNA folding,³⁰ and chemical reactions.^{7,31} In 2007, Anderson proposed a modified next-reaction simulation method, where the transition rate of one possible reaction could change over time due to the occurrence of another possible reaction that takes place in a shorter time.³¹ In this case, the simulation addresses the changes of the reaction rates by providing a modification to the generation of the waiting time of reactions. Later, a general class of methods^{7,27,29–31} were formulated for simulating systems with time-dependent rates. These studies address systems that fall into the category of open-loop controlled stochastic systems,³² where the system's transition rates are controlled by an external signal as a function of time according to a given protocol. However, still missing is a general theory and an algorithm for simulating feedback controlled stochastic systems, where the protocol is updated at each scheduled measurement time based on the instantaneous measurement outcome.³³ The main difficulty in developing a KMC algorithm for feedback controlled systems is that the control protocol at future times is unknown, as it depends on the results of the future measurements of the system.

In this work, we first provide an alternative derivation for the open-loop-controlled KMC, which recapitulates the methods developed in a number of existing Refs. 7, 27, and 29–31. This alternative derivation, based on single-trajectory probability analysis, lays the foundation to the development of a novel algorithm able to simulate systems under in-time feedback control. The validity and the implementation of the algorithm are demonstrated by Maxwell's feedback control refrigerator.

II. THEORY AND ALGORITHMS

A. Theory: Single-step trajectory probability

This article begins by revisiting the theoretical foundation of the open-loop-control KMC method by providing a pedagogical proof that recapitulates various versions of these algorithms.^{7,27,29–31} The theory is constructed by comparing the true probability of single-step trajectories and the simulated trajectory probability generated within one step of a modified KMC algorithm. This trajectory analysis not only provides an alternative proof for open-loop-control KMC methods described previously^{7,27,29–31} but also provides the foundation from which a closed-loop-control KMC method can be derived.

Consider a continuous-time discrete-state Markov process that is subject to an external control protocol $\lambda(t)$ as an arbitrary function of time t . The system contains a discrete number of states n_s and is initialized with probability distribution $\vec{p}(t=0)$. The dynamics of $\vec{p}(t)$ is characterized by the master equation

$$\frac{d\vec{p}}{dt} = \hat{R}(\lambda(t))\vec{p}, \quad (1)$$

where the matrix element $R_{ji}(\lambda(t))$ is the transient transition probability rate from i to j given the control parameter λ at time t . The diagonal element satisfying $R_{ii}(t) = -\sum_{j \neq i} R_{ji}(t)$ is the negative transient escape rate from state i at time t . The master equation evolution

of $\vec{p}(t)$ can also be expressed in terms of the dynamics of the i th state's probability,

$$\frac{dp_i}{dt} = \sum_{j \neq i} R_{ij}(\lambda(t))p_j(t) + R_{ii}(\lambda(t))p_i(t). \quad (2)$$

For an open-loop controlled system, the control protocol $\lambda(t)$ is externally determined. In contrast, for a closed-loop controlled system (e.g., one with a series of feedback measurements), the specific form of $\lambda(t)$ may depend on the system's state.

Each individual step of a KMC simulation is concerned with only generating the next stochastic event (i.e., evolving to state x_{k+1} at time t_{k+1} from the previous state x_k and time t_k). This event can be expressed as a single-step trajectory $X_{\text{single}} = (x_k, t_k, x', t')$ given the previous step. The conditional probability for this single-step trajectory can be written as

$$p[x', t' | x_k, t_k] = e^{\int_{t_k}^{t'} R_{x_k x_k}(t) dt} R_{x' x_k}(t'), \quad (3)$$

which is also a joint probability distribution of the next event's time t' and state x' . This formula is true for any Markov dynamics regardless of whether the dynamical rates are constants or the rates change over time. We show below that, in the case of time-independent or time-dependent rates, the direct Gillespie algorithm or an open-loop-control KMC algorithm, respectively, can correctly capture the dynamics.

1. Time-independent rates

In the case where the dynamics of the system are constant over time,³⁴ the direct Gillespie algorithm²³ is sufficient. From a probability theory perspective, the single-step transition probability of the next state x' and next time t' can be factored into the product of two statistically independent distributions and can be generated separately from their own probability distributions $P_x(x')$ and $P_t(t')$,

$$p[x', t' | x_k, t_k] = P_t(t') \cdot P_x(x'), \quad t' > t_k, \quad x' \neq x_k \\ = e^{(t' - t_k) \cdot R_{x_k x_k}} \cdot R_{x' x_k}. \quad (4)$$

In this case, the direct KMC²³ is carried out by generating the next transition time t' according to $P_t(t') \propto e^{R_{x_k x_k} \cdot (t' - t_k)}$ and generating the next state x' according to the state probability $P_x(x') \propto R_{x' x_k}$.

2. Time-dependent rates

If the rates change over time, the direct KMC approach²³ fails to generate the correct dynamics since the next event's time and state are statistically correlated. In this case, we can still factorize the joint probability of t' and x' , $P(x', t') \equiv p[x', t' | x_k, t_k]$, as the product of two probability distributions,

$$P(x', t') = P_t^{\text{marg}}(t') \cdot P_x^{\text{cond}}(x' | t'), \quad (5)$$

where the marginal distribution of the transition time t' (given the previous x_k and t_k) is denoted by

$$P_t^{\text{marg}}(t') = \sum_{x' \neq x_k} p[x', t' | x_k, t_k] \\ = -e^{\int_{t_k}^{t'} R_{x_k x_k}(t) dt} \cdot R_{x_k x_k}(t') \quad (6)$$

and the conditional probability distribution of the next state x' conditioned on the transition time being t' is

$$P_x^{\text{cond}}(x'|t') = \frac{R_{x'x_k}(t')}{-R_{x_kx_k}(t')}. \quad (7)$$

In this case, a modified KMC algorithm should be capable of faithfully generating the stochastic trajectory. In one simulation step of the modified KMC algorithm, one first generates the next transition's time $t' = t^*$ according to Eq. (6) and then generates the next state x' according to Eq. (7) given the proposed time $t' = t^*$. One can verify that the generated pair of x' and t' follows the true single-step trajectory probability distribution [Eq. (3)]. This analysis is applicable to arbitrary time-dependent processes, where the system's rates change over time due to either (1) open-loop control according to a scheduled protocol^{7,27,29–31} or (2) closed-loop control with a series of feedback measurements.

B. Review of open-loop-control KMC: General algorithm

Here, we review the open-loop-control KMC methods previously described in Refs. 7, 27, and 29–31. This review also serves as an alternative derivation and justification of these algorithms in the language of single-step trajectory generation introduced in Sec. II A. The representation of the single-step trajectory probability as the product of a marginal probability and a conditional probability, Eq. (5), allows one to separately generate the next transition's time t' and state x' , even when the time dependence of the system's rate creates a statistical correlation between t' and x' .

1. Generating transition time t'

The random generation of transition time $t' > t_k$ according to the marginal probability density in Eq. (6) can be realized by first obtaining the cumulative density function,

$$\text{c.d.f.}(t') = 1 - e^{-\int_{t_k}^{t'} R_{xx}(t) dt}, \quad (8)$$

and then generating a random number u following a uniform distribution between 0 and 1, and finally solving for t^* according to the following equation:

$$u = \text{c.d.f.}(t^*) = 1 - e^{-\int_{t_k}^{t^*} R_{xx}(t) dt}. \quad (9)$$

Or equivalently, for a random number $v = 1 - u$ also following a uniform distribution between 0 and 1, one can solve t^* as the root of the following equation:

$$\ln(v) = H(t^*), \quad t^* \in (t_k, \infty), \quad (10)$$

where

$$H(t^*) = \int_{t_k}^{t^*} R_{xx}(t) dt, \quad t^* \in (t_k, \infty) \quad (11)$$

and $R_{xx}(t)$ is the negative escape rate from state x at arbitrary time t .

2. Generating the next state x'

Once the transition time t^* is generated, the selection of the next state x' is straightforward—the new state's probability is proportional to their transient transition rates evaluated at the chosen

ALGORITHM 1. Open-loop-control KMC.

- 1: The starting time of the current simulation step is t with the starting state x .
- 2: Generate the list of all possible states that the system can jump to, and evaluate the time-dependent escape rate from state x as $-R_{xx} = \sum_{x' \neq x} R_{x'x}(t)$, where the summation takes all possible new states x' into consideration.
- 3: Generate a random number $v \in (0, 1]$ following a uniform distribution. Obtain the next event time t^* by solving for $t^* > t$ from Eq. (10).
- 4: Given the proposed transition time t^* , propose the transition event (e.g., to state x') with the probability proportional to their transient transition rates $p(x') \propto R_{x'x}(t^*)$ [Eq. (7)].
- 5: Update the system state to x' and time to t^* . Continue the iteration by going to step 2.

transition time t^* , as defined in Eq. (7). This resembles the state generation in the direct KMC method, with the only difference being the probability to jump to state x' here is proportional to the transient rate $R_{x'x_k}(t^*)$ evaluated at the chosen time t^* .

To summarize, one simulation step of the open-loop-control KMC algorithm can be enumerated in Algorithm 1. Furthermore, by including appropriate approximations (see Sec. II C), one can reproduce various open-loop-control KMC algorithms previously described in Refs. 7, 27, and 29–31.

C. Piece-wise approximations to open-loop control

In practice, solving for the next event's time t^* by a given random number v and Eq. (10) for arbitrarily complex time-dependent rates may be challenging. We now briefly review a few ways to approximately solve for this integral equation. Various methods have been proposed in simulating specific biological processes.^{27–30} For illustrative purposes, we demonstrate two approximations and sketch the corresponding algorithms for: (i) piece-wise linear function approximation and (ii) piece-wise step function approximation for the escape rate $-R_{xx}(t)$.

Here, we illustrate the algorithms by focusing on one step of the simulation. Let us denote the previous state as $x_k = x$ and the previous time $t_k = t_{\text{last}}$; then, the algorithm's task is to generate the next event's time t^* and the next state x' . As illustrated in Fig. 1(a), the negative escape rate from the state x , $R_{xx}(t)$ (shown as the black curve), can be approximated by (i) a consecutive set of straight line segments (top panel), or (ii) a set of stepwise step functions (bottom panel).

1. Piece-wise linear escape rates

Let us denote each window w_i by a time interval (τ_i, τ_{i+1}) and also set the beginning of the first window at $\tau_1 = t_{\text{last}}$. The negative escape rate from state x at each window's left edge is denoted by $R_{xx}^i = -\sum_{x' \neq x} R_{x'x}(\tau_i)$. Under this assumption, the numerical integration involved in Eqs. (10) and (11) can be considered as

$$H(t^*) = A_1 + A_2 + \cdots + A_{i-1} + \int_{\tau_i}^{t^*} R_{xx}(t) dt \quad (12)$$

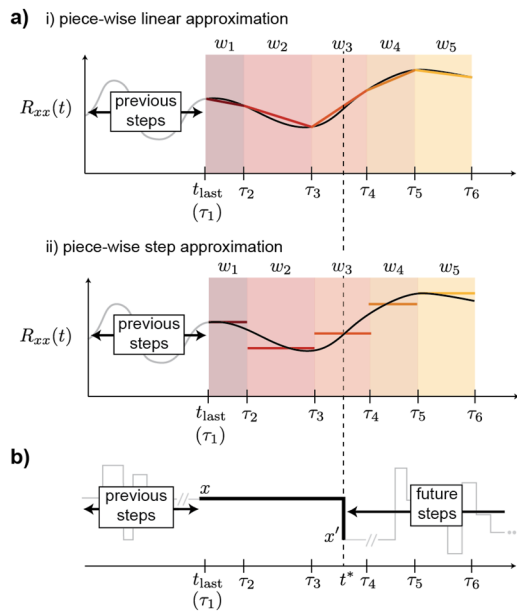


FIG. 1. Approximating open-loop protocol control. (a) Graphical representation of both (i) piece-wise linear rate function and (ii) piece-wise step-function rates. The black curve is the actual negative escape rate $R_{xx}(t)$. The approximation breaks the time into multiple windows. Each window w_i starting at time τ_i is represented by shaded regions, and the colored straight lines represent the approximated piece-wise negative escape rate. (b) Cartoon of one possible trajectory of the system. Here, the trajectory within the step of simulation is shown by the bold black lines; previous and future trajectories are shown by light gray lines. This simulation step is conditioned on the starting time t_{last} and state x and proposes to jump to a new state x' at time $t^* > t_k$.

for $\tau_i < t^* < \tau_{i+1}$. Here, the integral for each window starting from $\tau_1 = t_{\text{last}}$ is defined as

$$A_i = (\tau_{i+1} - \tau_i) R_{xx}^{\tau_i} + \frac{R_{xx}^{\tau_{i+1}} - R_{xx}^{\tau_i}}{2} (\tau_{i+1} - \tau_i). \quad (13)$$

Here, A_i is the integrated negative escape rate within the window w_i defined from τ_i to τ_{i+1} . Successive windows w_i starting from $i = 1$ will be evaluated until the j th window where the transition time is chosen, which can be identified by $\sum_{i=1}^{j-1} A_i < -\ln v < \sum_{i=1}^j A_i$. Given Eqs. (12) and (13), we can solve for t^* according to Eq. (10) in sequence, starting from $i = 1$ and continuing until the appropriate t^* can be drawn from the j th window according to³⁵

$$\sum_{i=1}^{j-1} A_i + R_{xx}^{\tau_j} (t^* - \tau_j) + \frac{R_{xx}^{\tau_{j+1}} - R_{xx}^{\tau_j}}{2(\tau_{j+1} - \tau_j)} (t^* - \tau_j)^2 = \ln v. \quad (14)$$

2. Piece-wise step-function escape rates

When the time dependent escape rate from state x is considered as a piece-wise step function, where $R_{xx}(t) = R_{xx}^{\tau_i}$ for each window $t \in (\tau_i, \tau_{i+1})$, we can determine the next event's time t^* by solving for a linear equation,

$$(t^* - \tau_k) R_{xx}^{\tau_k} + \sum_{i=1}^{k-1} B_i = \ln v, \quad (15)$$

where v is a random number uniformly distributed between 0 and 1 and the integrated negative escape rate for each window is denoted by

$$B_i = (\tau_{i+1} - \tau_i) R_{xx}^{\tau_i}. \quad (16)$$

By solving for the above equations starting from the first window, one can find the next event's time as $t^* \in (\tau_k, \tau_{k+1})$ occurring at the k th window. We demonstrate this method in a 1D lattice diffusion problem as shown in the Appendix.

D. Closed-loop feedback controlled systems: General algorithm

Consider a feedback control scheme where a scheduled series of measurements will be taken at a set of observation time points $\tau_1, \dots, \tau_i, \tau_{i+1}, \dots, \tau_{i+k}, \dots$ [see Fig. 2(a)]. At each observation time τ_j , the measurement outcome is determined by the transient state of the stochastic system: $m_j = x(\tau_j)$.³⁴ Immediately, the measurement outcome updates the system's kinetic rates via a rapid feedback control mechanism. Let us denote the control signal as an explicit function of time $\lambda(t)$, which can be represented by a piece-wise function where each piece is defined for the time between two consecutive measurements and is determined by all previous measurement outcomes. The actual protocol can be piece-wise constant (see an illustrative example in Secs. II E and III A), or, in more general cases, could be a solution of an ODE parameterized by the measurement outcomes at each feedback measurement. The general algorithm proposed here is applicable to arbitrary functional forms of the control protocol.

The key to correctly simulate the feedback controlled system is to recognize that, when carrying out each step of a KMC simulation, one only needs to predict the next transition event given the present

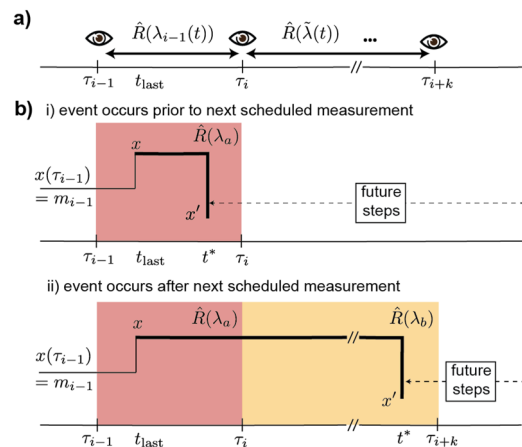


FIG. 2. Closed-loop control protocol. (a) Graphical representation of a series of scheduled measurements occurring at $\tau_{i-1}, \tau_i, \dots, \tau_{i+k}$. (b) Two types of single-step trajectories illustrated in the piece-wise step-function feedback control: (i) the next event occurs prior to the next scheduled measurement evolved using the determined protocol based on the last measurement $R_{xx}(\lambda_a)$ or (ii) event occurs after the k additional measurements, and the rate is projected by fixing the future measurements to be state x resulting in control signal being λ_b , and the escape rate is $R_{xx}(\lambda_b)$.

state and the transition rates set by the control protocol. Now, consider a system placed at state x and time t_{last} set by the previous step of simulation. Without losing generality, let us consider the current time as $\tau_{i-1} < t_{\text{last}} < \tau_i$ so that the current system has gone through the $(i-1)$ th measurement and the very next feedback measurement (the i th measurement) will occur at a future time τ_i .

To carry out the present simulation step and predict the next transition time t^* and next state x' , there are only two possible scenarios to consider, which are separated by a milestone time—the immediate next measurement time, τ_i . The two scenarios are the following: (i) the next event takes place at a time before the milestone time [$t^* < \tau_i$, Fig. 2(b-i)] or (ii) the next event takes place at any time after the milestone time [$t^* > \tau_i$, Fig. 2(b-ii)]. The milestone time τ_i is highlighted by the color scheme transition from red to yellow in Fig. 2(b-ii).

In the first case, one does not need to consider the control protocol after the next measurement and only needs to consider the protocol before τ_i . For this case, the control protocol for any $t < \tau_i$ is fully determined without any ambiguity, given the historical trajectory of the simulation. This pre-milestone part of control protocol before τ_i can be generally represented by the following function and is fully determined:

$$\lambda(t) = \begin{cases} \lambda_1(t; m_1), & \tau_1 \leq t < \tau_2, \\ \vdots \\ \lambda_{i-1}(t; m_1, \dots, m_{i-1}), & \tau_{i-1} \leq t < \tau_i, \end{cases} \quad (17)$$

where λ_j denotes the control protocol for time window $\tau_j < t \leq \tau_{j+1}$, and its functional form can be impacted by all the previous measurement results m_1, m_2, \dots, m_j through any prescribed feedback mechanisms. Here, j must be smaller than i .

In the second case, we need to treat the system with a step-wise protocol where the system still evolves according to the pre-milestone protocol [Eq. (17)] up to the milestone time τ_i , and then the protocol is updated to a future post-milestone protocol. It may appear that the post-milestone protocols (for $t > \tau_i$) cannot be fully determined due to the ambiguity of the future system states. However, as we have argued, each step of the KMC simulation involves the generation of a single step trajectory that starts at (x, t_{last}) , remains at state x , and only jumps to an unknown state x' at a future unknown transition time t^* . Thus, for any unknown transition time $t^* > \tau_i$ larger than the milestone time, each futuristic feedback measurement according to the trajectory under consideration will return a measurement outcome based on the system state x . In other words, the post-milestone protocol for any future $t \geq \tau_i$ is denoted by

$$\tilde{\lambda}(t) = \begin{cases} \tilde{\lambda}_i(t; m_1, \dots, m_{i-1}, x), & \tau_i \leq t < \tau_{i+1}, \\ \tilde{\lambda}_{i+1}(t; m_1, \dots, m_{i-1}, x, x), & \tau_{i+1} \leq t < \tau_{i+2}, \\ \tilde{\lambda}_{i+2}(t; m_1, \dots, m_{i-1}, x, x, x), & \tau_{i+2} \leq t < \tau_{i+3}, \\ \vdots \end{cases} \quad (18)$$

which is determined without ambiguity because all future measurements must detect the system at the current state x (i.e., $m_i, m_{i+1}, m_{i+2}, \dots = x$). In this argument, all futuristic protocols are then determined by the combination of the historical measurement outcomes and the asserted futuristic measurement outcomes, $m_1, m_2, \dots, m_{i-2}, m_{i-1}, x, x, x, \dots$.

In summary, through our single-step trajectory probability argument introduced in Sec. II A, we are able to assert a fully determined protocol for a feedback control system. This determined protocol combines Eq. (17), the pre-milestone protocol $\lambda(t)$ for $t < \tau_i$, which is fully determined by historical feedback measurements, and Eq. (18), the futuristic post-milestone protocol $\tilde{\lambda}(t)$ for $t > \tau_i$, which appears to be unknown due to the future feedback measurement outcomes. As a result, even for closed-loop controlled systems, one can utilize an open-loop-control KMC algorithm^{7,27,29–31} reviewed in Sec. II B to generate the next transition event according to the correct probability distribution [Eqs. (5)–(7)]. This general algorithm is shown in Algorithm 2. For illustrative purposes, the following demonstrates a simple application of the proposed feedback-control KMC algorithm.

E. Application: Piece-wise-constant feedback control

Here, we demonstrate the proposed new algorithm with a general yet simple scenario. In this example, the rates within each measurement window remain constant and are instantaneously updated

ALGORITHM 2. Closed-loop-control KMC.

- 1: In the current simulation step, the last transition event takes place between the $(i-1)$ th and i th measurement $\tau_{i-1} < t < \tau_i$, and landing at the present state x ; the control protocol $\lambda(t)$ can be determined up to $t < \tau_i$ [see Eq. (17)] with the last measurement outcome being $m_{i-1} = x(\tau_{i-1})$. (See Fig. 2.)
- 2: To project future control protocols for $t \geq \tau_i$, take the current state x for all future measurements. The projected control protocols are written in Eq. (18).
- 3: Generate the list of all possible states that the system can jump to from the current state x , and evaluate the time-dependent escape rate from state x as $-R_{xx}(t) = \sum_{x' \neq x} R_{x'x}(t)$. These time-dependent rates $R_{x'x}(\lambda(t))$ are determined by the protocol $\lambda(t)$. The control protocol is described by the combination of the deterministic part for $t < \tau_i$ [Eq. (17)] and the projected part for $t \geq \tau_i$ [Eqs. (17) and (18)].
- 4: Generate a random number $v \in (0, 1]$ following a uniform distribution. Obtain the next event time t^* by solving for $t^* > t$ from Eq. (10), where $H(t^*)$ is defined by Eq. (11), where the rates $R_{xx}(\lambda(t))$ are dictated by the protocols defined in Eqs. (17) and (18).
- 5: Given the proposed transition time t^* , propose the transition event (e.g., to state x') with the probability proportional to their transient transition rates [Eq. (7)]. If $t^* < \tau_i$, the transient rates are determined by the deterministic protocol from Eq. (17). If $t^* > \tau_i$, the rates are determined by the projected protocol from Eq. (18).
- 6: Update the system time to t^* and state to x' . If the time duration between t and t^* includes one or more scheduled feedback measurements, also record measurement results of state x .
- 7: Continue the iteration by returning to step 2.

based on each measurement. For more complicated feedback control regimes (e.g., the control protocol evolves deterministically in time according to differential equations parameterized by historical measurement outcomes), one can simply extend this algorithm in accordance with the general feedback controlled KMC algorithm described in Algorithm 2.

We here describe a model algorithm where the control parameter $\lambda(t)$ between two consecutive measurement events is always maintained at a constant value. In this case, both the determined protocol $\lambda_{i-1}(t) = \lambda_a, t_{\text{last}} < t < \tau_i$, and the projected protocol $\tilde{\lambda}(t) = \lambda_b, t > \tau_i$, are piece-wise constants. Therefore, the escape rate from state x is a piece-wise constant function with only two pieces [see Fig. 2(b)],

$$R_{xx}(\lambda(t)) = \begin{cases} R_{xx}(\lambda_a), & t_{\text{last}} \leq t < \tau_i, \\ R_{xx}(\lambda_b), & t \geq \tau_i. \end{cases} \quad (19)$$

In this case, the simulation chooses the next event's occurrence time by solving for the solution of the piece-wise function,

$$\ln(v) = \begin{cases} R_{xx}(\lambda_a)(t^* - t_{\text{last}}), & t < \tau_i, \\ R_{xx}(\lambda_b)(t^* - \tau_i) + R_{xx}(\lambda_a)(\tau_i - t_{\text{last}}), & t \geq \tau_i, \end{cases} \quad (20)$$

where v is a uniformly distributed random number between 0 and 1, and the *r.h.s* of the equation is defined by Eq. (11). There are two types of possible simulation outcomes of the single-step trajectories. At possibility no.1 [top panel of Fig. 2(b)], when the next event occurs before the next measurement, $t_{\text{last}} < t^* < \tau_i$, the dynamical rates remain unchanged throughout the time, and the rates were determined by the last measurement outcome $m_{i-1} = x(\tau_{i-1})$ [see the red shaded regions in Fig. 2(b)]. At possibility no.2 [bottom panel of Fig. 2(b)], when the next event occurs after k more future measurements $\tau_{i+k-1} < t^* < \tau_{i+k}$, for $k = 1, 2, \dots$, the dynamics are initially governed by the old rates $\hat{R}(\lambda_a)$ before the i th measurement and then by a new rate $\hat{R}(\lambda_b)$ after τ_i [see the yellow shaded regions in Fig. 2(b)]. We demonstrate this method in a two-state refrigerator model in Sec. III A.

III. RESULTS AND DISCUSSION

A. Demonstration: 2-State feedback control Maxwell's refrigerator

To demonstrate the new feedback controlled KMC algorithm proposed in Sec. II D, we utilize an example feedback control system whose behavior can be solved analytically. Feedback control systems have been extensively studied in various stochastic systems.^{32,37–46} Here, we choose to simulate the stochastic trajectories of a 2-state refrigerator inspired by Ref. 47.

Consider a 2-level system coupled to a heat bath. The ground state level's energy is $E_0 = 0$, and the excited level's energy is controlled externally by a binary toggle switch. At control A, the excited state energy is $E_1^A = 1$; at control condition B, $E_1^B = \epsilon > 1$. The feedback control is facilitated by a periodic sequence of instantaneous measurements to the system's state at times $\tau_i = i/\nu$, where ν is the measurement frequency. If the measurement detects the system at the ground state "0," the control is switched to B, and if excited state "1," control is A [see Fig. 3(a)].

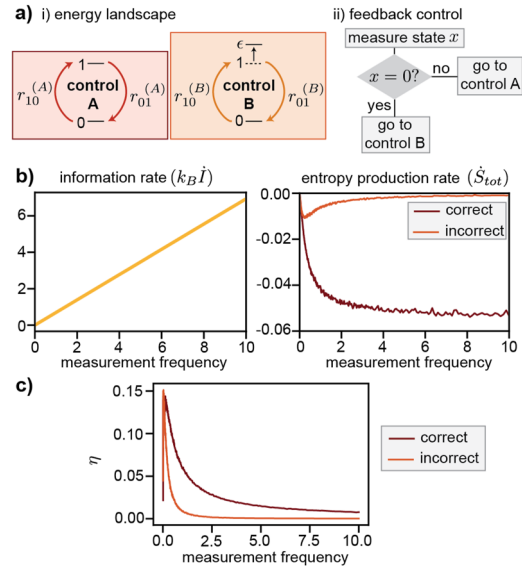


FIG. 3. Two-state refrigerator through periodic feedback control. (a) (i) Design of energy landscape of a two-state system in two different conditions and (ii) feedback control decision occurring at each measurement time. (b) Time-averaged thermodynamic properties of the refrigerator including (left) information rate and (right) entropy production rate computed under different feedback measurement frequencies. To demonstrate the artificial Zeno effect, both the correct feedback controlled KMC method (correct) and a naively implemented direct KMC method (incorrect) are shown. (c) System's thermodynamic efficiency ($\eta \leq 1$) calculated under different feedback control frequencies with both the correct and the incorrect algorithms.

This system falls into the category of the stepwise constant feedback control scenario (discussed in Secs. II E). In this case, the system evolves either according to the transition rates set by control condition A or by condition B. At each instantaneous time, the transition rates take the Arrhenius form $R_{ij} = e^{B_{ij} - E_j}$, where we have taken the unit such that the inverse temperature $\beta = 1/(k_B T) = 1$. In our demonstration, we set the barrier for the transition to $B_{ij} = 2$ and set the energies according to $E_1^A = 1$ and $E_1^B = \epsilon = 1.5$. Under this feedback control, it was shown that the system behaves as a refrigerator, constantly drawing energy from the heat bath and performs work against the external control. This refrigerator does not require energy expenditure but rather operates at the cost of information obtained via the measurements. For a comprehensive overview of the definition of heat and work in the stochastic systems, refer to Ref. 48. For the connection between information and thermodynamic entropy, a few representative studies can be found in Refs. 43, 46 and 49–56.

At each stochastic transition from the ground state to the excited state, the system draws from the heat bath energy $Q_{\text{sys}} = 1$ (for control A) or $Q_{\text{sys}} = \epsilon$ (for control B). At the transition from the excited state to the ground state, the system's heat gain is $Q_{\text{sys}} = -1$ (for control A) and $Q_{\text{sys}} = -\epsilon$ (for control B). At any scheduled measurement causing a control switch from A to B (the system is at the ground state), there is no work or heat exchange ($W = 0, Q = 0$). At the scheduled measurement causing a control switch from B to A, the system performs positive work to the controller $W_{\text{ext}} = \epsilon - 1$, and

there is no heat exchange $Q = 0$ within the instantaneous measurement time. By counting the frequencies of the stochastic transitions of the system (0 to 1 or 1 to 0) under different control conditions A and B, respectively, one can calculate the average heat rate (the average heat drawn by the system per unit time).

By implementing the feedback controlled KMC algorithm, we are able to obtain an ensemble of 100 statistically independent stochastic trajectories from such a feedback controlled refrigerator. Each trajectory is of time length 500, and we exclude the initial relaxation period of length 100 from statistics. From the trajectory, one can compute the bath's entropy change rate, which is equal to the total entropy change rate of the system and the bath,

$$\dot{S}_{tot} = \frac{J_{0 \rightarrow 1}^A \cdot (E_0 - E_1^A) + J_{0 \rightarrow 1}^B \cdot (E_0 - E_1^B)}{T}, \quad (21)$$

where the net transition current J is defined by the difference between the detailed currents,

$$J_{0 \rightarrow 1}^A = j_{0 \rightarrow 1}^A - j_{1 \rightarrow 0}^A, \quad (22)$$

$$J_{0 \rightarrow 1}^B = j_{0 \rightarrow 1}^B - j_{1 \rightarrow 0}^B. \quad (23)$$

Furthermore, since each measurement is binary, one can calculate the information rate simply by multiplying the information per measurement with the measurement frequency: $k_B \dot{I} = \nu \ln 2$. Finally, we also computed the efficiency of the refrigerator as the entropy decrease rate over the information gain rate,

$$\eta = \frac{-\dot{S}_{tot}}{k_B \dot{I}} \leq 1, \quad (24)$$

which characterizes the system's ability to decrease entropy at the expenditure of information change. Notice that according to the generalized second law of thermodynamics $\dot{S}_{tot} + k_B \dot{I} \geq 0$,^{43–46} the efficiency must be lower than or equal to 1. The simulation results for a range of measurement frequencies are shown in Figs. 3(b) and 3(c).

One can verify the proposed feedback controlled KMC by comparing its result to the analytical solution of the system. In the limit of the infinitely high frequency measurements, $\nu \gg 1$, one can obtain an effective constant rate matrix of the system and analytically obtain its average heat rate and entropy change rate. Due to infinitely frequent measurements, the system's transition rate from state 1 to 0 is always equal to $R_{01}^{\text{eff}} = R_{01}^A = e^{-1}$ and the system's transition rate from state 0 to 1 is always equal to $R_{10}^{\text{eff}} = R_{10}^B = e^{-2}$. As a result, the effective rate matrix under infinite frequency feedback control is

$$\hat{R}^{\text{eff}} = \begin{bmatrix} -e^{-2} & e^{-1} \\ e^{-2} & -e^{-1} \end{bmatrix}. \quad (25)$$

The steady state probability for this system can be written as $(p_0^{\text{ss}}, p_1^{\text{ss}}) = (\frac{e}{1+e}, \frac{1}{1+e})$. This allows us to compute the detailed transition current from 0 to 1 as $\frac{e}{1+e} e^{-2}$, and current from 1 to 0 as $\frac{1}{1+e} e^{-1}$. Due to the frequent measurement, each transition from 0 to 1 must occur under control B, which takes energy ϵ from the bath, and each transition from 1 to 0 must occur under control A, which deposits energy 1 into the bath. As a result, for a system at the steady state (no system

entropy change), the total entropy change of the system and the bath is purely the bath entropy change with the rate

$$\lim_{\nu \rightarrow \infty} \dot{S}_{tot} = \frac{j_{1 \rightarrow 0}^A \cdot 1 + j_{0 \rightarrow 1}^B \cdot (-\epsilon)}{T} \approx -0.049\,469\,009\,9, \quad (26)$$

where the detailed steady-state currents are

$$j_{1 \rightarrow 0}^A = R_{01}^{\text{eff}} \cdot p_1^{\text{ss}} = R_{01}^A \cdot p_1^{\text{ss}}, \quad (27)$$

$$j_{0 \rightarrow 1}^B = R_{10}^{\text{eff}} \cdot p_0^{\text{ss}} = R_{10}^B \cdot p_0^{\text{ss}}. \quad (28)$$

From Fig. 3, one can verify that the entropy change rate at a high frequency limit obtained from our proposed feedback controlled KMC algorithm matches well with the analytical result in Eq. (26).

B. Discussion: Avoiding artificial Zeno effect

This work proposed a new algorithm to simulate systems under feedback control. Here, we illustrate that for systems with time-dependent control (both open-loop and closed-loop), the direct implementation of the original Gillespie algorithm¹² can lead to erroneous results, where the system's dynamics appears to be immobilized due to frequent changes of the external control parameter or frequent feedback controls. We name this erroneous result the artificial Zeno effect. This effect appears to resemble the quantum Zeno effect⁵⁷ but is fundamentally different—the former is an artificial numerical error, and the latter is a true physical phenomenon.

In the quantum Zeno effect,⁵⁷ frequent projective measurements may reset the system's wave function into an eigenstate and, in the limit of infinitely high measurement frequency, the system's wave function is frozen at the eigenstate and the system appears to be non-evolving. In contrast, classical stochastic systems, where the measurement does not directly impact the system's state,³⁵ should not have any Zeno effect. The artificial Zeno effect is a numerical error only when one naively implements the direct KMC algorithm in a piece-wise manner for time-dependent systems.

For illustrative purposes, we first demonstrate the erroneous artificial Zeno effect in the feedback control system discussed in Fig. 3. In the Appendix, this discussion has been extended to open-loop controlled time-dependent systems (Fig. 4).

For the feedback controlled system, one naïve way to implement the original Gillespie algorithm¹² is to reset the KMC simulation at each measurement time point. Specifically, one may perform a constant-rate KMC simulation for each measurement time window. Consider a system at state x at time $\tau_{i-1} < t < \tau_i$. If the direct KMC approach proposes the next transition's time to be $t^* > \tau_i$, one simply evolves the system time to $t' = \tau_i$ while maintaining the system state to be x and then starts another step of the direct KMC simulation, with the initial state x and initial time τ_i . This approach appears to be valid, since the predicted time t^* is indeed longer than the time of the next measurement, and the system should not change until after the next measurement. However, this direct implementation of the KMC method leads to wrong results that can become obvious by considering the infinitely frequent measurement limit, where the time until the next measurement approaches 0 and the chance that the direct KMC proposes a t^* before the next measurement becomes zero. Thus, the simulation is frozen to state x . This

artificial Zeno effect becomes more prominent for higher frequency measurements.

To illustrate this mistake, we implement the above direct KMC simulation for the Maxwell's refrigerator discussed in Sec. III A and show that the artificial Zeno effect significantly underestimates the transition events of the systems dynamics, resulting in an underestimation of the refrigerator's entropy decreasing rate and thermodynamic efficiency [see Figs. 3(b) and 3(c)].

For a feedback controlled system where one measures and acquires system's states at a scheduled sequence of times, plainly restarting the clock of the KMC simulation from the measured state to simulate the dynamics of the system will lead to an artificial Zeno effect. The closed-loop-control algorithm demonstrated here avoids this pitfall and preserves the correct dynamics. In the Appendix, we show that similar mistakes may occur in open-loop-control systems only if one overlooks previously introduced algorithms.^{7,27,29–31}

IV. CONCLUSION

In conclusion, we here propose a new method to simulate stochastic trajectories of systems experiencing feedback control. This new method is derived based on a general single-step trajectory probability analysis. This analysis can be used to derive and recapitulate several previously proposed open-loop-control KMC algorithms for non-feedback control systems whose rates change in time under a given protocol. Then, we demonstrate that feedback controlled systems can be simulated by combining a pre-milestone control protocol and a post-milestone control protocol. This allows us to perform a time-dependent KMC simulation for feedback controlled systems with a modified open-loop-control KMC algorithm. We validate our claims using the simulation of a two-state feedback control Maxwell's refrigerator. Our correct algorithm provides the true dynamics of the system. The simulation results are compared with the analytical results obtained in the infinitely frequent controlled scenarios, and the numerical results are in perfect agreement with the analytical result. Furthermore, the new modified KMC algorithms avoid the artificial Zeno effect, where a wrong implementation of the direct KMC may lead to an erroneous underestimation of the frequency of transitions.

The algorithms described herein can find broad applicability in a number of fields, particularly in biological systems that experience rapid fluctuations in local environments and frequent feedback control via interaction with surroundings. Multiple processes—such as neurophysiology,⁵⁹ transcriptional regulation,⁶⁰ circadian clocks,⁶¹ and metabolic regulation⁶²—are examples of such systems beyond the scope of analytical solutions. A KMC algorithm to treat these feedback controlled systems would allow the relevant dynamics to be sampled and captured. Even though the example provided in Fig. 3 is a binary state model that is analytically solvable, the algorithm can be directly applied to complex systems that are not analytically solvable (see Secs. II E). If the system's control protocol follows complex rules, one can still apply the general algorithm by making necessary approximations on the control protocol similar to those sketched in Secs. II C. While rapid feedback control or complex dynamics may pose challenges by increasing the computational cost of these simulations, our derivation provides a flexible path to tackling these problems. We believe that the relevant non-equilibrium behavior and thermodynamic quantities in a wide variety of feedback

controlled chemical and biological system, such as reaction turnover rates, binding affinity, or assembly properties, can be accurately captured by using the new algorithm.

SUPPLEMENTARY MATERIAL

Numerical simulation codes can be found in the [supplementary material](#).

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

Supraja S. Chittari: Data curation (equal); Funding acquisition (equal); Methodology (equal); Writing – original draft (equal). **Zhiyue Lu:** Conceptualization (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Supervision (equal); Writing – original draft (equal); Writing – review & editing (equal).

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

APPENDIX: ZENO-EFFECT IN OPEN-LOOP-CONTROL KMC

If one overlooks the existing open-loop-control KMC methods^{7,27,29–31} and approximates the control protocol by piecewise functions, it is possible that an artificial Zeno effect similar to Fig. 3 appears. Below, we demonstrate a comparison between the correct method^{7,27,29–31} and the erroneous result.

Let us consider a diffusion process on a 1-dimension lattice, where random walkers experience biased transitions. The initial states of all random walkers are placed at position 0. Under a periodic switch between controls *A* and *B*, the system evolves under two sets of rates with control period set to $2\tau = 0.02$ [see Fig. 4(a)]. In condition *A*, the transition rate for moving right is $r_+^A = 0.4$ and for moving left is $r_-^A = 0.1$ [Fig. 4(a), left panel]. Conversely, in condition *B*, these rates are $r_+^B = 0.2$ and $r_-^B = 0.1$. As the environment oscillates rapidly between conditions *A* and *B*, the system experiences alternating transition rates [Fig. 4(a), right panel]. To accurately

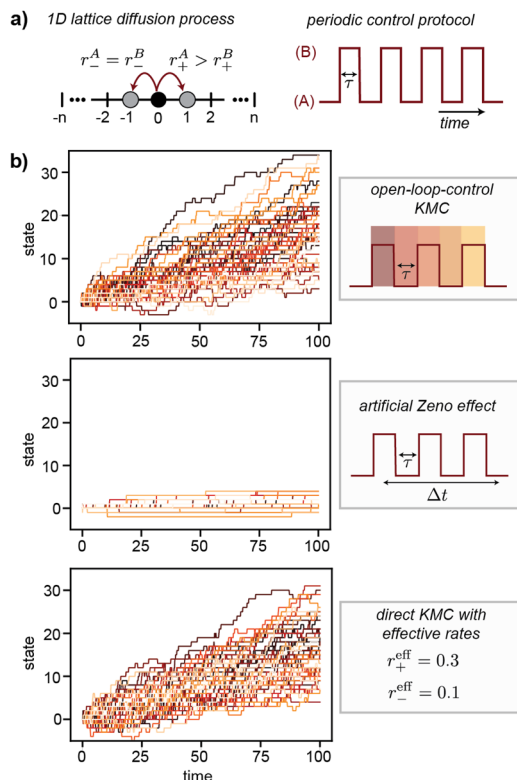


FIG. 4. Diffusion along a 1D lattice. (a) (Left panel) Schematic of the diffusion processes with jumping rates to the right and left direction denoted as $r_+^{A/B}$ and $r_-^{A/B}$. The control condition is denoted by A and B. (Right panel) Periodic control protocol with period 2τ . (b) Simulated diffusion trajectories using (top panel) averaged rate dynamics in traditional KMC, (center panel) individual rate dynamics using incorrectly applied KMC due to timescale mismatch between τ and time for each move Δt , (bottom panel) individual rate dynamics correctly simulated using the KMC described herein.

simulate this scenario, we employ the correct open-loop-control KMC method to generate a set of trajectories representative of the random walker's behavior [see Fig. 4(b), top panel]. To illustrate the erroneous artificial Zeno effect, we perform a piece-wise direct KMC simulation and find that the artificial Zeno effects significantly slowed down the system's diffusion, and the random walkers are mostly frozen without many transitions [see Fig. 4(b), middle panel]. In the end, to verify the validity of the open-loop-control KMC, we include an alternative way to obtain the true dynamics of random workers: by acknowledging that the control switch frequency is much greater than the diffusion rates, $\nu = 1/(2\tau) = 50 \gg r_{+/-}^{A/B}$, one can show that this system evolves under effective dynamics with constant rates.^{63,64} In this case, the system's dynamics can be generated by a direct KMC simulation under the effective rates, shown in Fig. 4(b) bottom panel. We verify that under the rapid oscillation limit, the effective dynamics and the dynamics generated by the open-loop-feedback KMC agree with each other. However, the naïve implementation of direct KMC to time-dependent dynamics results in a significant slowdown of the dynamics (i.e., the artificial Zeno effect).

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- ³⁴Here constant rate over time is used to describe the time period between two consecutive stochastic events. Naturally, when the system state changes after the next event, the possible transitions and their rates are naturally updated.
- ³⁵In practical implementation of the numerical code, when $q_i \approx q_{i-1}$, the quadratic equation reduces to the linear, which can be solved from Eq. (15).
- ³⁶Here the measurement of the system may not be as detailed as the specific state that the system is in. It is possible that a subset of states will give a same measurement outcome (i.e., coarse-grained measurement). The method can be applied to both cases.
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