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RESEARCH ARTICLE

Linear response theory and optimal control for a molecular system under nonequilibrium conditions

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In this paper, we propose a straightforward generalization of linear response theory on a finite time-horizon to systems in nonequilibrium that are subject to external forcing. We briefly revisit the standard linear response result for equilibrium systems, where we consider Langevin dynamics as a special case, and then give an alternative derivation using a change-of-measure argument that does not rely on any stationarity or reversibility assumption. This procedure easily enables us to calculate the second order correction to the linear response formula (which may or may not be useful in practice). Furthermore, we outline how the novel nonequilibrium linear response formula can be used to compute optimal controls of molecular systems for cases in which one wants to steer the system to maximize a certain target expectation value. We illustrate our approach with simple numerical examples.

1. Introduction

Standard molecular dynamics simulations are dealing with systems in thermal equilibrium; in this case they are tuned to the canonical or Boltzmann distribution in the sense that either (1) if one starts from this distribution it remains invariant under the dynamics or (2) if one generates a very long trajectory it samples state space with respect this distribution, that is, every possible state of the molecular system under consideration is visited according to the probability given by it. Obviously, this allows to compute equilibrium expectation values with respect to the canonical distribution simply be computing long trajectories.

Often, however, one is interested in knowing about the response of the molecular system to perturbation out of equilibrium. The standard linear response formula allows to answer this question, at least partially. In the standard setting it gives us the first order of the change to an equilibrium expectation value as resulting from the nonequilibrium perturbation. Here, first order means first order in the size of the perturbation. This linear response formula has a long history of extensions and generalizations; see, e.g., [1, 2] and the references therein. In some sense it has become one of the cornerstones of modern statistical physics since it can be related to the fluctuation dissipation theorem (FDT) which roughly states that for appropriate systems in statistical equilibrium, the average response to small external perturbations can be calculated through the knowledge of suitable correlation functions of the unperturbed statistical system. Linear response formulas on the infinite time-horizon have been shown to hold under rather mild assumptions even for nonequilibrium systems that possess a unique invariant measure [3].

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There is an increasing number of articles in the literature that report on applications of molecular dynamics to nonequilibrium settings. There are many generalization to so-called nonequilibrium steady states based on the generality of the FDT [4], but despite its wide use, we are not aware of a linear response formula for equilibrium or nonequilibrium (i.e. irreversible) systems that does not rely on any kind of stationarity assumption. We will provide such a formula for the case that the underlying dynamics can be described by Langevin dynamics that may not have an invariant measure. Furthermore, we will provide a formula for the second order response of a nonequilibrium Langevin system subject to a small perturbation.

Instead of applying this theory to a molecular system we will go one step further. We will outline how the novel nonequilibrium linear response formula can be used to compute the optimal control of molecular systems. In optimal control one seeks the optimal way to perturb a molecular system, such that a certain target expectation value (e.g. population of certain states) is maximized under constraints on the energy of the control. In general, the control drives the molecular system under control out of equilibrium. Thus, the nonequilibrium linear response formula can be used to find the optimal correction of the present control regarding the expectation value of interest.

The outline of the article is as follows: First, we will review the derivation of finite time-horizon linear response formulas for general diffusion processes and diffusions of Langevin type. Next, we will show how to derive first and second order response formulas for genuine nonequilibrium systems and how to apply these formula to the computation of optimal controls. Finally, we will validate the nonequilibrium linear response formula and its use for optimal control for simple test cases. This numerical experiments will also outline that the use of the linear response formula is imperative for numerical efficiency and allows to extend the applicability of linear response theory to stronger perturbations.

2. Linear response

In this section, we first want to give a simple and formal derivation of the linear response for equilibrium and nonequilibrium systems. To this end we consider a general Itô stochastic differential equation of the form

$$dX_t = (b(X_t, t) + \varepsilon v_t)dt + a(X_t)dB_t\,, \quad t \geq 0\,, \tag{1}$$

where $X_t \in \mathbf{R}^d$, $b(\cdot,\cdot)$ is a smooth time-dependent vector field, $a(\cdot)$ a smooth field of $d \times n$ matrices and B_t is standard Brownian motion in $\mathbf{R}^n$. Here $v_t \in \mathbf{R}^d$ is any given driving force applied to the system, typically an affine function of the form $v_t = c(X_t)u(t)$, with $c(\cdot) \in \mathbf{R}^{d\times k}$ and a bounded measurable function $u\colon [0,\infty) \to \mathbf{R}^k$ such that (1) has a strong solution for all $t > 0$ whenever $\varepsilon > 0$ is sufficiently small. When (1) without the perturbation εv is considered, we write

$$dx_t = b(x_t, t)dt + a(x_t)dB_t\,, \quad t \geq 0\,. \tag{2}$$

2.1. *Small perturbations from equilibrium: Langevin dynamics*

We consider the equilibrium and nonequilibrium case separately and start with the equilibrium case (see, e.g., [5, 6]). To begin with, we assume that the perturbation-free part of the infinitesimal generator

$$\mathcal{A}^\varepsilon = \mathcal{A}_0 + \varepsilon\mathcal{A}_1\,,$$

of (1) with

$$\mathcal{A}_0 = \frac{1}{2} aa^T : \nabla^2 + b \cdot \nabla \,, \quad \mathcal{A}_1 = v \cdot \nabla$$

has an isolated eigenvalue 0 corresponding to the unique invariant measure $d\mu_\infty = \rho_\infty dx$. We denote by $\mathcal{A}_0^*$ and $\mathcal{A}_1^*$ the formal adjoints in L^2, e.g., $\mathcal{A}_1^* \phi = -\nabla(v\phi)$.

Now let $f : \mathbf{R}^{2n} \to \mathbf{R}$ be any integrable function and let $\rho^\varepsilon = \rho^\varepsilon(x,t)$ denote the probability density of X_t, at time $t > 0$, assuming that $X_0 = x$ was distributed according to $\rho^\varepsilon(x,0) = \rho_\infty(x)$. We define the expectation with respect to ρ^ε as

$$\mathbf{E}_{\rho^\varepsilon}[f] = \int_{\mathbf{R}^{2n}} f(x) \rho^\varepsilon(x,t)\, dx \,.$$

A classical result, that is usually derived using a formal expansion of the solution to the Fokker-Planck equation in powers of ε using the ansatz

$$\rho^\varepsilon(x,t) = \rho_0(x,t) + \varepsilon \rho_1(x,t) + \ldots$$

with

$$\rho^\varepsilon(x,0) = \rho_\infty \,, \text{ i.e. } \rho_0(x,0) = \rho_\infty \text{ and } \rho_i(x,0) = 0 \text{ for } i > 0,$$

then states that (see, e.g., [6, 7])

$$\lim_{\varepsilon \to 0} \frac{\mathbf{E}_{\rho^\varepsilon}[f] - \mathbf{E}_{\rho^0}[f]}{\varepsilon} = \int_{\mathbf{R}^{2n}} f(x) \left(\int_0^t e^{\mathcal{A}_0^*(t-s)} \mathcal{A}_1^*(s) \rho_\infty(x)\, ds \right) dx \,. \tag{3}$$

Green-Kubo relations

Specifically, we are interested in the case that (1) has the form of a second-order Langevin equation, in which case $d = 2n$ and

$$b(x,t) = (J - R)\nabla H(x) \,, \quad a = \sqrt{2\beta^{-1}} R^{1/2} \,, \tag{4}$$

with $J = -J^T$ the canonical $2n \times 2n$ symplectic matrix,

$$J = \begin{pmatrix} 0 & I_{n\times n} \\ -I_{n\times n} & 0 \end{pmatrix},$$

$R = R^T \geq 0$ the positive semidefinite $2n \times 2n$ friction matrix

$$R = \begin{pmatrix} 0\ 0 \\ 0\ \gamma \end{pmatrix},$$

for $\gamma \in \mathbf{R}^{n\times n}$ symmetric positive definite, and

$$H : \mathbf{R}^{2n} \to \mathbf{R} \,, \quad H(x) = \frac{1}{2}|p|^2 + U(q) \quad (x = (q,p))$$

the Hamiltonian of the system. We assume that the potential U is bounded from below. Then, under some mild growth conditions on U for $|q| \to \infty$ (see, e.g., [8]),

the unperturbed dynamics has a unique invariant measure with density

$$\rho_\infty(x) = \frac{1}{Z}\exp(-\beta H(x))\,, \quad Z = \int_{\mathbf{R}^{2n}} \exp(-\beta H(x))\,dx\,.$$

In this case, the linear response result (3) can be recast in form of the better known Green-Kubo formula [9]. Assuming that the forcing is of the form $v_t = Cu(t)$ with $u\colon [0,\infty) \to \mathbf{R}^n$ and $C \in \mathbf{R}^{2n\times n}$ being any suitable given time-dependent function, the above expression can be recast as

$$\lim_{\varepsilon\to 0} \frac{\mathbf{E}_{\rho^\varepsilon}[f] - \mathbf{E}_{\rho^0}[f]}{\varepsilon} = \beta \int_0^t F(t-s)u(s)\,ds \tag{5}$$

where

$$F(t) = -\int_{\mathbf{R}^{2n}} \mathbf{E}_x[f(x_t)]C^T\nabla H(x)\rho_\infty(x)\,dx$$

is the response function and the expectation under the integral is taken over all realization of the equilibrium process (2) starting from $x_0 = x$. In other words:

$$\mathbf{E}_{\rho^\varepsilon}[f] \approx \mathbf{E}_{\rho_\infty}[f] + \varepsilon\beta \int_0^t F(t-s)u(s)\,ds\,,$$

where we have used the fact that $\rho^0(x,t) = \rho_\infty(x)$ for all $t \geq 0$.

Remark. Ciccotti and Jacucci have pointed out that the equilibrium linear response can also be calculated by a direct nonequilibrium simulation of the perturbed process, and this nonequilibrium approach has a smaller statistical uncertainty in comparison with the standard Green-Kubo fomula [10].

Remark. It is possible to extend the above framework to the case of observables that are functionals of the path, i.e. to functions the form

$$\varphi^\varepsilon(x,t) = \mathbf{E}_x\left[\int_0^t f(X_s)ds\right]\,,$$

where the expectation is over all realizations of the *nonequilibrium* process X_t with initial condition $X_0 = x$. In this case a linear response result can be obtained by expanding the solution of the Kolmogorov backward equation

$$\frac{\partial\varphi^\varepsilon}{\partial t} = \mathcal{A}^\varepsilon\varphi^\varepsilon - f\,, \quad \varphi^\varepsilon(x,0) = 0\,,$$

rather than the Fokker-Planck equation, where the equivalence between the solution of the backward equation and the conditional expectation of the path functional follows from the Feynman-Kac formula [11, Thm. 1.3.17].

2.2. *Nonequilibrium response theory: controlled Langevin dynamics*

The derivation of the classical response result heavily relies on the fact that the unperturbed system has a unique equilibrium distribution, which requires that

the generator of the process has certain spectral properties; cf. [3, 12]. Moreover the usual perturbation argument does not provide a framework, under which the second and even higher order responses can easily be derived. Here we propose an alternative derivation of the linear response result, that is based on a change of drift in the corresponding SDE and which allows for an easy generalization of the above linear response result to nonequilibrium systems.

Girsanov transformation

We will briefly review the idea of the change of drift via Girsanov transformations; for details we refer to the textbook [13]. To this end, let $x_t = x_t(\omega)$ and $X_t = X_t(\omega)$ be the solutions of our generic stochastic differential equations

$$dx_t = b(x_t, t)dt + a(x_t)dB_t\,, \quad 0 \le t \le T \tag{6a}$$

$$dX_t = (b(X_t, t) + \varepsilon v_t)dt + a(X_t)dB_t\,, \quad 0 \le t \le T \tag{6b}$$

for $T < \infty$ and deterministic initial conditions

$$x_0(\omega) = X_0(\omega) = x \quad \text{(almost surely)}\,.$$

Suppose that there exists an auxiliary stochastic process $\xi_t \in \mathbf{R}^n$ such that

$$a(X_t)\xi_t = v_t\,. \tag{7}$$

The auxiliary variable ξ will be called *control variable*. We define

$$W_t = \varepsilon \int_0^t \xi_s\, ds + B_t\,, \quad 0 \le t \le T\,,$$

which allows us to rewrite (6b) as

$$dX_t = b(X_t, t)dt + a(X_t)dW_t \tag{8}$$

It follows from the Girsanov theorem [13, Thm. 8.6.8], sometimes also called *Cameron-Martin-Girsanov theorem* [14], that W_t is again a Brownian motion under a new probability measure that has a density with respect to the Gaussian probability measure that is generated by the Brownian motion B_t. Specifically, let P denote the law of the Brownian motion B_t and define a new probability measure Q on the space of continuous trajectories by

$$dQ = M_T dP$$

with

$$M_t = \exp\left(-\varepsilon \int_0^t \xi_s \cdot dB_s - \frac{\varepsilon^2}{2}\int_0^t |\xi_s|^2 ds\right)\,, \quad 0 \le t \le T\,. \tag{9}$$

Technical details aside, the Girsanov theorem implies that W_t for any functional

$$\varphi(\omega) = \int_0^T f((X_s(\omega))\, ds + g(X_T(\omega))$$

that is integrable with respect to ν, we have the identity[1]

$$\mathbf{E}_P[\varphi] := \int_\Omega \varphi(\omega)\, dP(\omega) = \int_\Omega \varphi(\omega) M_T^{-1}(\omega)\, dQ(\omega) =: \mathbf{E}_Q[M_T^{-1}\varphi]\,.$$

where

$$M_T^{-1} = \exp\left(\varepsilon \int_0^T \xi_s \cdot dW_s - \frac{\varepsilon^2}{2}\int_0^T |\xi_s|^2 ds\right)$$

is the density of P relative to Q. Note that the expectation on the right hand side corresponds to the unperturbed dynamics, because W_t is a standard Brownian motion under Q, and the expectation is over all realizations of (8) starting from $X_0 = x$. On the other hand, X_t under P corresponds to the perturbed dynamics, which should become clear upon comparing equations (6b) and (8).

Remark. A quick-and-dirty derivation of the above change-of-measure formula can be easily obtained, if the noise covariance $a(\cdot)a(\cdot)^T$ has full rank with bounded inverse. Then, using Euler's method for (6), it follows that (9) is basically the likelihood ratio between the time-discrete path densities of (6b) and (6a). Another route to the same result is by using the Onsager-Machlup functional [15] for $(X_t)_{0\le t\le T}$ and $(x_t)_{0\le t\le T}$; then M_T is found as the likelihood ratio of the two densities.

An alternative linear response formula

Linearization of M_T^{-1} about $\varepsilon = 0$, assuming that the control has bounded variance, yields the alternative linear response formula

$$\lim_{\varepsilon\to 0} \frac{\mathbf{E}_{P_x^\varepsilon}[\varphi] - \mathbf{E}_{P_x^0}[\varphi]}{\varepsilon} = \mathbf{E}_{P_x^0}\left[\varphi \int_0^T \xi_s \cdot dB_s\right]\,, \tag{10}$$

where, in analogy with the previous linear response formula, P_x^ε and P_x^0 denote the path probability measures of perturbed and unperturbed paths—i.e. the trajectories obtained from (6b) and (6a)—with deterministic initial condition. The path measure P_x^ε should not be confused with the phase space density $\rho^\varepsilon(x,t)$ in Section 2.1 that solves the Fokker Planck equation. Note moreover that φ on the right hand side of (10) is understood as a functional of $(x_t)_{0\le t\le T}$, i.e. the solution to (6a) with initial condition $x_0 = x$, with ξ_t being the solution to $a(x_t)\xi_t = v_t$.

By averaging the the initial values x on both sides of (10) over any given initial distribution, one obtains an analogous formula for distributed initial conditions. Note that φ and B_t are not independent, hence the product of φ and the integral over the Brownian motion does not average to zero in general.

[1] One of the omitted technical details is Novikov's condition [13, pp. 162] that guarantees that $(M_t)_{0\le t\le T}$ is a Martingale, which by $\mathbf{E}_Q[1] = \mathbf{E}_P[M_T] = 1$ implies normalizability of the new probability measure Q.

Remark. By formally expanding M_T^{-1} up to second order we get an analogous second order response formula:

$$\begin{aligned}\mathbf{E}_{P_x^\varepsilon}[f] \approx \mathbf{E}_{P_x^0}[\varphi] + \varepsilon \mathbf{E}_{P_x^0}\left[\varphi \int_0^T \xi_s \cdot dB_s\right] \\ + \frac{\varepsilon^2}{2}\mathbf{E}_{P_x^0}\left[\varphi\left\{\left(\int_0^T \xi_s \cdot dW_s\right)^2 - \int_0^T |\xi_s|^2\, ds\right\}\right].\end{aligned} \tag{11}$$

Nonequilibrium Langevin Dynamics

We now link our previous considerations with the previous case and consider a nonequilibrium Langevin equation. Specifically, we add a non-gradient perturbation to the drift (4) of the previous Langevin equation, i.e., we set

$$b(x,t) = (J-R)\nabla H(x) + c(x)u(t)\,, \quad a(x) = \sqrt{2\beta^{-1}}R^{1/2} \tag{12}$$

with the definitions of J, R and H unchanged, $u \in \mathbf{R}^n$ being some bounded measurable control, and $c(\cdot) \in \mathbf{R}^{2n\times n}$ given by

$$c(x) = \begin{pmatrix} 0 \\ D(x) \end{pmatrix}$$

The matrix $D(\cdot) \in \mathbf{R}^{n\times n}$ must be chosen such that c satisfies the Fredholm alternative $\mathrm{range}(c(\cdot)) \perp \ker((a(\cdot))^T)$, where $\ker(a^T)$ denotes the kernel of a^T.

We are interested in the dynamics under a small perturbation δu of the control u, Specifically, we assume that v in (6) is of the form

$$v_t = c(X_t)\delta u(t) \tag{13}$$

so that equation (7) that determines the change of measure in terms of the auxiliary control variable ξ (and thus the linear response) reads

$$\sqrt{2\beta^{-1}}\gamma^{1/2}\xi_t = D(X_t)\,\delta u(t)\,.$$

Hence the equation for ξ_t is solvable if and only if $\mathrm{range}(D(\cdot)) \perp \ker(\gamma^{1/2})$, which, since γ has full rank, means no restriction on $D(\cdot)$.

To be more specific, the equation we are considering has the form

$$dX_t = (J-R)\nabla H(X_t)dt + c(X_t)(u(t) + \varepsilon\delta u(t))dt + a\, dB_t\,. \tag{14}$$

In this case the linear response formula (10) becomes

$$\lim_{\varepsilon\to 0}\frac{\mathbf{E}_{P_x^\varepsilon}[\varphi] - \mathbf{E}_{P_x^0}[\varphi]}{\varepsilon} = \mathbf{E}_{P_x^0}\left[\varphi\int_0^T (\sigma^{-1}D(x_s)\,\delta u(s))\cdot dB_s\right] \tag{15}$$

with the shorthands $\sigma = \sqrt{2\beta^{-1}}R^{1/2}$ and

$$\varphi = \int_0^T f(x_s)ds + g(x_T)\,.$$

In other words:

$$\mathbf{E}_{P_x^\varepsilon}[\varphi] \approx \mathbf{E}_{P_x^0}[\varphi] + \varepsilon \mathbf{E}_{P_x^0}\left[\varphi \int_0^T (\sigma^{-1} D(x_s)\, \delta u(s)) \cdot dB_s\right] . \tag{16}$$

Here, as before, the expectation on the right hand side of the linear response formula is over all realizations of (14) for $\varepsilon = 0$ starting at x; see also the remark below on the choice of initial conditions.

Numerical realization

As one can easily get lost in the various transformations, involving path measures P, Q, P_x^ε, P_x^0 or phase space densities ρ^ε, ρ^0, ρ_∞, it may be helpful to understand how the linear response formulas (10) or (15) can be realized algorithmically. To this end, let $(x_0, x_1, x_2, x_3, \ldots)$ with x_k be the numerical realization of (6a). Let us further suppose that the initial value $x_0 = x$ is fixed. The simplest possible numerical discretization would be the Euler scheme

$$x_{n+1} = x_n + \Delta t\, b(x_n, t_n) + \sqrt{\Delta t}\, a(x_n)\eta_{n+1}\,, \quad x_0 = x\,,$$

with time step $\Delta t = t_{k+1} - t_k$ and η_k i.i.d. Gaussian random variables with mean 0 and unit covariance. (For a Langevin equation such as (14) the Euler scheme is not recommended, but the basic idea stays the same.) Now a simple unbiased estimator of the linear response—i.e. the right hand side in (10)—would be

$$\hat{R} = \frac{1}{M} \sum_{i=1}^{M} \left\{ \varphi(\{x_k(\omega_i)\}_{0\le k\le N}) \sum_{j=0}^{N-1} \hat{\xi}_i(\omega_i) \cdot \eta_{j+1}(\omega_i) \right\} \tag{17}$$

with $N = \lfloor T/\Delta t \rfloor$ and $x_k(\omega_i)$ denoting the i-th realization of x_k, that is generated by the i-th realization $(\eta_1(\omega_i), \ldots, \eta_k(\omega_i))$ of the Gaussian noise sequence $(\eta_k)_{k\in\mathbf{N}}$. The time-discrete control variable is given by

$$a(x_k)\hat{\xi}_k = v_{t_k}$$

for any given perturbation $v\colon [0,T] \to \mathbf{R}^m$.

Remarks. Some comments on the above result are in order:

(i) The rightmost term in (16) is the linear response to the reference nonequilibrium process (driven by u_t with $\varepsilon = 0$). From (11) we can also get the second order response term. The latter is bounded if the controls have bounded second moment, which is a typical requirement in optimal control applications. Higher order moments need not exist.

(ii) In the above derivation, we have tacitly assumed that the reference and the perturbed nonequilibrium processes start from the same initial value or have the same initial distribution. For fixed initial values (i.e. points) this assumption cannot be relaxed (because otherwise dP/dQ and dQ/dP do not exist). For distributed initial values, however, there is no problem for the unperturbed and perturbed dynamics to have different initial distribution as long as both distributions are strictly positive almost everywhere. In this case one can apply a similar reweighing approach between the initial distribution as we used it for the trajectory ensemble.

(iii) If one wants to calculate the same expectation value for a family of nonequilibrium perturbations δu then one does not need to repeat the calculations of (16) for every member of the family. If it is possible to express different δu in the same basis, then the responses must only be calculated for the single basis functions. Then with a linear combination of the responses on basis functions, one can derive the responses for the whole family. This feature will be used below when discussing optimal control as an application of the linear response formula.

3. Application of the nonequilibrium response formula: optimal control

The nonequilibrium linear response formula can be used for solving certain optimal control problems. To this end, let us remain in the setting of equations (14)–(16) and assume that we are interested in choosing the nonequilibrium forcing u, such that the expected value $I = \mathbf{E}[\psi]$ of some utility function

$$\psi(u) = \int_0^T \left\{ f(x_s) - \frac{1}{2}|u(s)|^2 \right\} dt + g(x_T)$$

is maximized where x_t is the solution to the controlled Langevin equation (14) for $\varepsilon = 0$; the functions f and g are the running cost and the terminal cost, which are assumed to be continuous and bounded from above; without loss of generality, f and g are assumed to depend only on the positions $q := x_1$ and not on the momenta $p := x_2$. The quadratic term is a penalization that makes sure that the optimal control remains bounded [16, 17]. Let us moreover assume that the controls are open-loop (i.e. without feedback) and can be represented by

$$u(t) = \sum_{k=1}^{K} a_k \Phi_k(t)\,, \quad a_k \in \mathbf{R}\,,$$

with suitably chosen time dependent, bounded and Lipschitz continuous vector fields $\Phi_k \colon [0,T] \to \mathbf{R}^n$, $k = 1, \ldots, K$. Specifically, we want to solve the optimal control problem of the following standard form:

$$\begin{aligned} &\max_{u \in \mathcal{U}} I(u) \quad \text{s.t.} \\ &\quad dq_t = \nabla_p H(q_t, p_t) dt \\ &\quad dp_t = -\nabla_q H(q_t, p_t) dt - \gamma \nabla_p H(q_t, p_t) dt + D(q_t) u(t) dt + \sigma dB_t\,, \end{aligned} \tag{18}$$

with (q_0, p_0) being subject to a given initial distribution μ, and

$$I(u) = \mathbf{E}\left[\int_0^T \left\{ f(q_s) - \frac{1}{2}|u(s)|^2 \right\} dt + g(q_T) \right], \tag{19}$$

with the expectation being over all realizations of the controlled Langevin dynamics in (18) with the prescribed initial distribution. Here, the space of admissible controls $\mathcal{U}$ consists of all bounded controls of the form

$$u(t) = \sum_{k=1}^{K} a_k \Phi_k(t)\,, \quad a_k \in \mathbf{R}\,, \tag{20}$$

Gradient method from linear response

In principle, optimal control problems such as (18)–(19) can be solved by dynamic programming, i.e. by solving the corresponding Hamilton-Jacobi-Bellman PDE [18]. Except for very simple, essentially one-dimensional systems, solving Hamilton-Jacobi-Bellman equations is not an easy task, so we pursue a different strategy here. The idea is to use that we have restricted our space of admissible controls to functions of the form (20) with given basis vector fields and that we can do a gradient search in the unknown coefficients a_k, using the iteration

$$u^{(n+1)} = u^{(n)} + \tau_n \nabla I(u^{(n)}) \,,$$

with $\tau_n > 0$ being an adjustable parameter that determines the length of each gradient step. The gradient of I can be easily evaluated using the linear response formula. To see this recall the notion of functional (Gâteaux) derivatives as directional derivatives along a function v (from a suitable function space):

$$\frac{\delta I}{\delta u} = \left.\frac{d}{d\varepsilon}\right|_{\varepsilon=0} I(u+\varepsilon v) = \langle \nabla I(u), v \rangle \,.$$

For existence of the functional derivative with respect to general Itô stochastic processes, we refer to [19]. Now the idea is to use that we have restricted our space of admissible controls to functions of the form (20) with given basis vector fields and do a gradient search in the unknown coefficients a_k. This requires to compute the gradient with respect to the coefficients. Let the vector

$$\delta u = \sum_{k=1}^{K} \delta a_k \Phi_k(t)$$

denote the direction along which we want to differentiate where $\delta a_1, \ldots, \delta a_K$ are the coefficients of the vector δu in the basis of the Φ_k, and note that

$$\begin{aligned}
\frac{\delta I}{\delta u} &= \left.\frac{d}{d\varepsilon}\right|_{\varepsilon=0} I(u+\varepsilon\delta u) \\
&= \left(\lim_{\varepsilon\to 0} \frac{I(u+\varepsilon\delta u) - I(u)}{\varepsilon} \right) \cdot \delta u \\
&= \left(\lim_{\varepsilon\to 0} \frac{\mathbf{E}_{P^\varepsilon}[\psi(u+\varepsilon\delta u)] - \mathbf{E}_{P^0}[\psi(u)]}{\varepsilon} \right) \cdot \delta u
\end{aligned}$$

provided that the limit exists. The above iteration therefore is equivalent to

$$a_k^{(n+1)} = a_k^{(n)} + \tau_n \left.\frac{\partial I}{\partial a_k}\right|_{a_k = a_k^{(n)}} \,, \tag{21}$$

with

$$\frac{\partial I}{\partial a_k} = \mathbf{E}_{P^0}\left[\psi \int_0^T (\sigma^{-1} D(q_s)\Phi_k(s)) \cdot dB_s + \int_0^T u(s) \cdot \Phi_k(s)\, ds \right] \,, \tag{22}$$

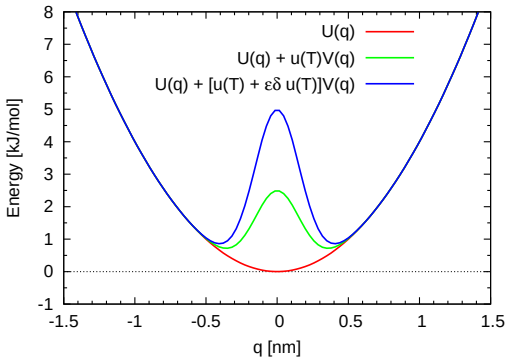

Figure 1. The single-well potential with splitting driving force. Time $T = 20$ ps. Since the driving force is of gradient form, $D(q) = -\nabla_q V(q)$, we plot the nonequilibrium driving energy of the system. The red, green and blue lines are the potential energy without nonequilibrium driving, with nonequilibrium driving and the nonequilibrium driving perturbed by $\varepsilon\delta u(t)$, respectively.

and $\mathbf{E}_{P^0}[\cdot]$ being the expectation over all realizations of (14) with $\varepsilon = 0$ and $u = u^{(n)}$ being the current iterate and arbitrary initial conditions $x = (q, p)$, e.g.,

$$\mathbf{E}_{P^0}[\psi] = \int_{\mathbf{R}^{2n}} \mathbf{E}_{P_x^0}[\psi]\, d\mu(x)\,,$$

with P_x^0 denoting the corresponding path measure with deterministic initial condition, and μ is the prescribed initial distribution. A related result on computing the parameter sensitivity can be found in Ref. [20]. Note that we can compute all partial derivatives $\partial I/\partial a_k$, $k = 1, \ldots, K$ from just one ensemble of nonequilibrium paths of (q_t, p_t). Further note that, in general, the updated coefficient $a^{(n+1)}$ and hence the updated control $u^{(n+1)}$ will depend on the distribution of the initial conditions at the n-th iteration stage; in particular, if the controls are computed on-the-fly, the controls will actually be feedback controls depending on the current state and the time elapsed since $t = 0$.

4. Numerical Experiments

4.1. *Splitting a single-well potential*

We use the idea of nonequilibrium linear response to investigate the nonequilibrium phase space probability density, denoted by $\rho^\varepsilon(q, p, t)$, of a one-dimensional model system: one particle in a splitting single-well potential as shown in Fig. 1. For convenience, we let the mass of the particle to be 1 amu, and the friction coefficient to be 1 ps^{-1}. The temperature is the room temperature 300 K, $k_B T = 2.48$ kJ/mol. The unperturbed Hamiltonian of the system is given by:

$$H(p, q) = \frac{1}{2}p^2 + U(q) \tag{23}$$

with potential

$$U(q) = \frac{1}{2}\, k\, q^2 \tag{24}$$

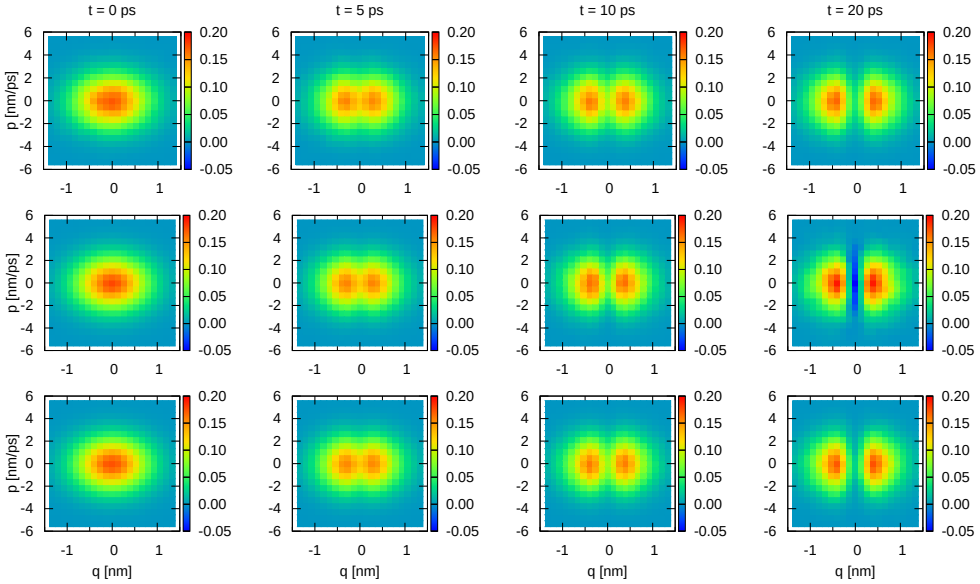

Figure 2. The plot of $\rho^{\varepsilon}(q,p,t)$ in phase space under the perturbed nonequilibrium driving described in the text. From left to right the columns present results at times $t = 0$, 5, 10 and 20 ps. First row: Results of a brute force nonequilibrium simulation. Second row: Results of classical equilibrium linear response theory, see the text for details. Third row: Results using the nonequilibrium linear response result.

Here $k = 8$ kJ/(mol nm^2). See the red line in Fig. 1 for the potential U. The nonequilibrium driving D is given by a force of gradient form:

$$D(q) = -\nabla_q V(q), \tag{25}$$

where the driving potential $V(q)$ has a Gaussian profile:

$$V(q) = \frac{1}{\sqrt{2\pi\Sigma^2}} \exp\Big\{ -\frac{q^2}{2\Sigma^2} \Big\} \tag{26}$$

we use $\Sigma = 0.16$ nm. The strength of nonequilibrium driving $u(t)$ is set to be linearly growing, i.e. $u(t) = k_e \cdot t/T$, where k_e is a unitless constant. We consider the perturbation to the system given by $\varepsilon\delta u(t) = \varepsilon k_e \cdot t/T$. We use the following parameters: end time $T = 20$ ps, $k_e = 1$ and $\varepsilon = 1$, see Fig. 1 for the nonequilibrium driving potential and perturbed potential at time $t = T$. The initial distribution $\rho^0(q,p,0)$ is set to be equilibrium distribution of the unperturbed system. We use Euler scheme with time step of 10^{-4} to discretize the Langevin equation. The initial configurations for nonequilibrium simulation are generated by taking configurations from an equilibrium simulation of 10^6 ps at an 1 ps time interval. Then starting with these initial configurations according to $\rho_\infty \propto \exp(-\beta H)$, the nonequilibrium Langevin equation is integrated until 20 ps with the same numerical scheme and time step.

Fig. 2 presents the numerical results for the phase space probability distribution for the splitting single-well potential. From left to right the four columns present the distribution of the system at time $t = 0$, 5, 10 and 20 ps. The first row presents the result of a brute force nonequilibrium simulation. It is clear that at the beginning the distribution has only one peak around $q = 0$ and $p = 0$. As time evolves, an energy barrier develops in the center of the simulation region and, therefore, the single peak splits into two equally sized peaks. In the end, the two peaks are entirely separated. The brute force nonequilibrium simulation serves as the precise result to which the response theory should be compared. The second row shows

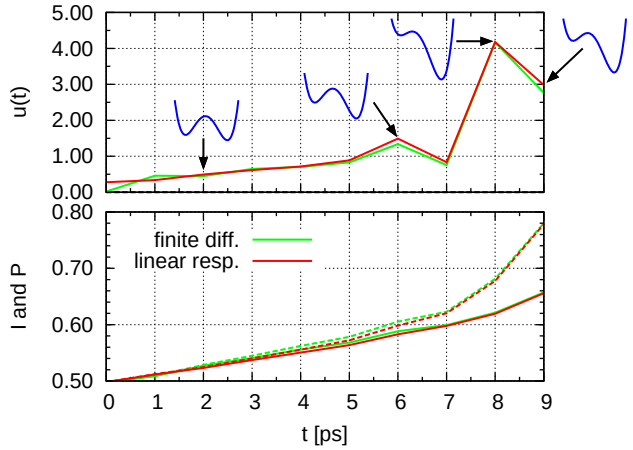

Figure 3. Illustration of the optimal control for tilting the potential. In this plot, $T = 9$ ps. Top panel: Optimal control o_t as calculated based on a family of piecewise linear ansatz functions with time interval 1 ps; the blue insertions show the shape of the nonequilibrium driving potential $U + o_t V$ at the times indicated by the black arrows. Bottom panel: Optimal gain $I = F(o_t)$ (solid lines) and the probability P of being in the right well associated with o_t (dashed lines) as functions of time along the optimal control. Red lines: computation using the nonequilibrium linear response theory. Green lines: brute force computation as described in the text.

the result of the traditional equilibrium linear response theory. In this case, the reference simulation is in equilibrium and we have set the perturbation to

$$\varepsilon v_t = D(q_t)(u(t) + \varepsilon\delta u(t)) = 2\varepsilon D(q_t)k_e \cdot t/T =: 2\varepsilon D(q_t)\delta u(t),$$

so that the effective perturbation is of strength $2\varepsilon = 2$. At $t \leq 10$ ps, the accuracy of the equilibrium linear response is perfect. At $t = 20$ ps, magnitude of the peaks are relatively too strong, and in the gap between them the distribution is actually negative. Since the probability distribution is always positive, the numerical solution of the equilibrium linear response is qualitatively wrong. The poor accuracy is due to the fact that the strength of perturbation is no longer small so that the preliminary assumption of the classical response theory ("small perturbation") is not satisfied.

The third row of Fig. 2 presents the results computed using the novel nonequilibrium linear response formula: we first start from the equilibrium distribution, apply $u(t)$, arrive at a nonequilibrium distribution and then, in a second step, compute the effect of the nonequilibrium driving $\delta u(t)$. The numerical results are satisfactorily consistent with the brute force nonequilibrium simulation, because the perturbation is still small enough and the novel linear response theory achieves good accuracy.

4.2. *Optimal tilting of a double-well potential*

In this section, we consider the following double well potential:

$$U(q) = \frac{1}{2}k(q^2 - a^2)^2 \tag{27}$$

Here $k = 8$ kJ/(mol nm^4), and $a = 1$ nm. See the leftmost blue insertion of Fig. 3 for the shape of the potential. The perturbation is given by a gradient form tilting of $U(q)$ by means of

$$D(q) = -\nabla_q V(q) = 1, \tag{28}$$

with $V(q) = -q$. Starting from a fully equilibriated system, we want to optimally design the tilting such that the probability of being in the right well is as high as possible at the end time of the process under a constraint on the energy used for the control in the sense of the following optimal forcing problem:

$$I = \max_{u \in \mathcal{U}_L} I(u)\,, \quad I(u) = \mathbf{E}\left[-\int_0^T \frac{1}{2}|u(s)|^2\, dt + g(q_T) \right],$$

with $g(q_T) = \chi_{[a-\delta,a+\delta]}(q_T)/\eta$ representing the probability of the end point of the trajectory, q_T, being in the right well (χ_I denotes the indicator function of the interval I) with η being a weighting constant, $\mathcal{U}_L$ denoting the space of function that are piecewise linear on $[0, T]$ in uniform intervals of length 1 ps. Then

$$\mathbf{P}[q_T \in [a-\delta, a+\delta]] = \eta \mathbf{E}[g(q_T)]$$

is the probability of being in the right well at time T. It is therefore convenient to scale the cost functional according to $I \mapsto \eta I$ and redefine I as follows:

$$I(u) = \mathbf{P}[q_T \in [a-\delta, a+\delta]] - \frac{\eta}{2} \int_0^T |u(s)|^2\, ds\,.$$

It is clear that for an unbiased double-well, the probability to be in the right well at any time T is 0.5 if we choose ρ_∞ to be the initial distribution. The remaining integral term in I denotes the "cost" of the control and η indicates the relative magnitude of this cost.

In our numerical tests for the optimal control problem, the Langevin dynamics Eq. (18) is discretized by the Euler scheme with a time step of 10^{-3} ps. The initial distribution is set to be the equilibrium distribution $\rho_\infty \propto \exp(-\beta H)$ of the unperturbed system. Therefore, an equilibrium simulation of 10^6 ps is firstly performed (with the same numerical scheme and time step), and configurations are saved every 10 ps (in total 10^5 configurations) along the trajectory. Then by using these configurations as initial configurations, 10^5 nonequilibrium trajectories are integrated until 9 ps, while at the same time the nonequilibrium responses are calculated and then averaged to estimate the ensemble average on the r.h.s of Eq. (22). The statistical uncertainty of this estimate varies by each step of iteration, but is roughly 7×10^{-4}. The statistical uncertainty for the optimization target I is roughly 1×10^{-3}.

Fig. 3 presents the numerical results for $\eta = 0.01$. Starting from an initial guess of a linearly interpolated control between $u_0 = 0$ and $u_T = 1$, the gradient search (21) uses a constant $\tau_n = 30$ and converges at the 22nd step, when the maximum increment of the control coefficient $\max_k |\delta a_k^{(n)}|$ is smaller than 0.02, the termination threshold. The magnitude of the optimal control

$$o(\cdot) = \operatorname*{argmax}_{u \in \mathcal{U}_L} I(u)$$

is presented in the upper panel of Fig. 3, with blue insertions showing the shape of the time-dependent optimal control potential $U(q) + o(t)V(q)$ (optimally tilted double-well potential). The maximum I and the corresponding optimal probability to end up in the right well are given as functions of time in the lower plot by the solid and dashed lines, respectively. The red lines in the figure are produced by the nonequilibrium linear response theory developed in this work, i.e., using (22), and

the green lines represent the brute force reference simulations that has been performed as follows: The optimal control from $\mathcal{U}_L$ is calculated by a gradient descent based optimization method in which the gradient of the functional with respect to the control is computed by numerical differentiation (central finite differences) at each step. The good agreement between the red and green lines demonstrates that the linear response theory computes the gradient correctly. Note that in order to calculate the gradient by the finite difference scheme, one needs to do $2K$ nonequilibrium simulations (where K is the dimension of $\mathcal{U}_L$; here $K = 10$). In contrast, the nonequilibrium response theory only needs one nonequilibrium simulation.

When $t < 8$ ps, the magnitude of the control is still small. Near the end time T, the magnitude of the control firstly quickly goes up, and then falls down a little bit. This implies some interesting information. If the system were able to immediately relax to its equilibrium state (sometimes called quasi-equilibrium), the population in the right well (dashed lines in Fig. 3) would immediately go down, as the control decreases. The fact that this does not happen, indicates that the speed of changing the control is relatively fast compared to the time scale of quasi-equilibration of the system, so the system does not have enough time to fully relax. Therefore, the observed phenomenon is truly nonequilibrium, and our nonequilibrium linear response theory is a tool that facilitates the investigation of this optimal forcing problem in the nonequilibrium setting. The fact that the optimal control is decreasing at the end of the interval is understandable since the population in the right well needs time to be build and increasing the control until $t = T$ would be a waste of control without leading to a significant population gain.

5. Conclusions and Remarks

We derived the first and second order response formulas for nonequilibrium molecular dynamics (driven Langevin dynamics), which is a generalization of the standard finite-time equilibrium linear response theory. The novel nonequilibrium response theory does not rely on any reversibility or stationarity assumption on the dynamics. We validated the formula in numerical experiments in comparison to brute-force nonequilibrium simulations. There, we demonstrated that the nonequilibrium linear response formula allows to extend the algorithmic use of linear response theory to significantly stronger perturbations of the system since it permits intermediate drivings, with which the effective perturbations still lie in the linear range.

By means of this theory we outlined how to use linear response theory for the computation of optimal controls in molecular dynamics where one desires to find the optimal perturbation/control that maximizes a target functional, that is, a certain expectation value (like the population of a certain region of state space) under a constraint on the energy used in the perturbation. Application of our nonequilibrium theory allows to compute the gradient of the target functional by computing expectation values *only* for the dynamics at hand which permits efficient application of standard optimization techniques. We illustrated this technique in application to a simple test case and validated it in comparison to brute force optimization.

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