EXACT DYNAMICAL COARSE-GRAINING
WITHOUT TIME-SCALE SEPARATION

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ABSTRACT. A family of collective variables is proposed to perform exact dynamical coarse-graining even in systems without time scale separation. More precisely, it is shown that these variables are not slow in general but they satisfy an overdamped Langevin equation that statistically preserves the sequence in which any regions in collective variable space are visited and permits to calculate exactly the mean first passage times from any such region to another. The role of the free energy and diffusion coefficient in this overdamped Langevin equation is discussed, along with the way they transform under any change of variable in collective variable space. These results apply both for systems with and without inertia, and they can be generalized to using several collective variables simultaneously. The view they offer on what makes collective variables and reaction coordinates optimal breaks from the standard notion that good collective variable must be slow variable, and it suggests new ways to interpret data from molecular dynamic simulations and experiments.

It is often desirable to eliminate degrees of freedom in large and complex multi-dimensional systems, and represent their dynamics via a reduced set of coordinates, known as coarse-grained or collective variables. From a computational perspective such a reduction is necessary to reach the biologically relevant length and time scales inaccessible by all-atom molecular simulations [1, 2], while in terms of modeling it permits to explain the inner working of the system by focusing on the most salient features of its evolution [3]. To give just one example, the folding of proteins has been described by various models of decreasing complexity, from all-atom [4], to beads and Go models, to elastic networks [5, 6], all the way down to a one-dimensional overdamped diffusion on the free energy landscape associated with the fraction of native contacts being formed [7, 9]. Taken together, these models not only facilitate the simulation of proteins but they also offer simple organization principles of protein design and function [10, 12]. As these examples show, coarse-graining typically involves a drastic reduction in dimension and a natural question is when and why does it work. The predominant view, shaped by the Mori-Zwanzig (MZ) projection formalism [13, 14], has been that adequate collective variables must be sufficiently slow, so that the rest of the degrees of freedom remain at equilibrium (adiabatically slaved) with respect to them – in this case the evolution of the collective variables can indeed be described by a standard Langevin equation that can e.g. be derived from the Markovian approximation to MZ [15, 16] or by standard averaging theorems [17]. From this perspective coarse-graining is unfortunately quite restricted: slow collective variables simply do not
exist in most cases of interest, and the evolution of complicated dynamical systems typically span the totality of their wide range of time scales, from their fastest to their slowest, without any clear separation in between. For example, the fraction of native contacts in a protein is not a slow variable in the standard sense of the term since it is not adiabatically separated from the rest of the degrees of freedom in the system.

An alternative view that departs from the notion that good collective variables must be slow variables has recently emerged in the context of activated processes and reactive events \([18–20]\). The description of these events offers similar challenges: they are infrequent because they require many failed attempts before occurring, but when they finally happen they typically do so quite fast. This means that there is no slow coordinate to describe the advancement of the reaction in general. In spite of this, the committor function, also known as the commitment probability or p-fold, is a good reaction coordinate \([21–23]\) that permits to explain the mechanism of the reaction and give exact expressions for its rate \([24–26]\). Even though it is not a slow variable, the special properties of the committor suggest that it may be useful in the context of dynamical coarse-graining as well. This idea was exploited in the context of Elber’s milestoneing procedure \([27]\), in which the original dynamics is reduced to independent transitions between hypersurfaces (the milestones): in \([28, 29]\), it was shown that mean first passage times between these milestones can be calculated exactly from Markovian milestoneing as long as we use isocommittor surfaces for them. More recently Berezhkovskii and Szabo \([30]\) (see also \([31]\)) wrote a closed, one-dimensional Fokker-Planck (diffusion) equation whose probability flux through the isocommittor surfaces is conserved and always equal to the exact reaction rate.

The aim of the present communication is to elaborate on the statements made in \([30]\), and introduce a class of collective variables, related to the committor, to perform dynamic coarse-graining. These variables are not slow in general, and they depart from the standard committor in that there are not directly connected to a reaction – in fact, as we will see, there are no reactant nor product states \(\textit{per se}\) in our construction, and infinitely many different collective variables of the type we consider can be introduced in any given system. Yet, as we will show, for any collective variable in this class we can write down a closed overdamped Langevin equation that permits to calculate exactly the mean first passage times between any two regions in which this collective variable takes constant values. This overdamped Langevin equation can, via specific transformations that preserve the iso-surfaces of the collective variable but relabel their values, be written either as a driftless overdamped equation, whose associated Fokker-Planck equation has the same form as that derived by Berezhkovskii and Szabo \([30]\), or as a standard overdamped equation whose coefficients involve the gradient of the free energy and a specific diffusion coefficient. As we will see, these results apply both to systems with and without inertia, and they can be generalized to vector-valued (i.e. multidimensional) collective variables. These results offer a new view on dynamical coarse-graining that gives a criterion for optimality of reaction coordinates and collective variables complementary to those proposed in \([9, 30–32]\). They also shed
light on the dynamical meaning of the pair free energy/diffusion coefficient that do not rely on the Markovian approximation to MZ.

We will consider first a system whose evolution is governed by the overdamped Langevin equation (the generalization to systems with inertia is considered below):\(^1\)

\[
\dot{x}(t) = -\beta D(x(t)) \nabla V(x(t)) + \nabla \cdot D(x(t)) \eta(t),
\]

where \(x(t) = (x_1(t), \ldots, x_N(t))^T \in \mathbb{R}^N\) denotes the instantaneous position of the system, \(V(x)\) the potential, \(D(x)\) the diffusion tensor, \(\beta = 1/(k_B T)\) the inverse temperature, and \(\eta(t) = (\eta_1(t), \ldots, \eta_N(t))^T\) is a \(N\)-dimensional white-noise process satisfying \(\langle \eta_i(t) \rangle = 0, \langle \eta_i(t) \eta_j(s) \rangle = \delta_{i,j} \delta(t-s)\). Associated with (1) is the Fokker-Planck (diffusion) equation for the probability density function \(\rho(x, t)\) of \(x(t)\), which reads

\[
\frac{\partial}{\partial t} \rho(x, t) = \nabla \cdot \left( e^{-\beta V(x)} D(x) \nabla \left( e^{\beta V(x)} \rho(x, t) \right) \right). \tag{2}
\]

The stationary solution to this equation is the Boltzmann-Gibbs (canonical) density, which is also the equilibrium probability density function of (1):

\[
\rho_e(x) = Z^{-1} e^{-\beta V(x)}, \tag{3}
\]

where \(Z = \int_{\mathbb{R}^N} e^{-\beta V(x)} dx\) is a normalization factor. If we now introduce a (dimensionless) scalar-valued collective variable, \(\theta : \mathbb{R}^N \to \mathbb{R}\), a simple application of Ito’s lemma\(^3\) indicates that \(\Theta(t) \equiv \theta(x(t))\) satisfies

\[
\dot{\Theta}(t) = (L\theta)(x(t)) + \sqrt{2} \nabla \theta(x(t)) \cdot D^{1/2}(x(t)) \eta(t), \tag{4}
\]

where the generator \(L\) is the adjoint of the operator at the right hand side of (2) and its action on \(\theta(x)\) reads

\[
(L\theta)(x) \equiv e^{\beta V(x)} \nabla \cdot \left( e^{-\beta V(x)} D(x) \nabla \theta(x) \right). \tag{5}
\]

Since the right hand side of (4) depends on \(x(t)\) rather than \(\Theta(t)\) alone, this equation is not closed – this is the issue of dynamical coarse-graining made explicit\(^2\).

To proceed further, let us introduce a specific class of collective variables \(\theta(x)\) via the solution to

\[
\nabla \cdot (\rho_e(x) D(x) \nabla \theta(x)) = \tau \left( \delta(x-a) - \delta(x-b) \right), \tag{6}
\]

\(^1\)Mathematically, (1) and (4) should be interpreted as the Ito stochastic differential equations (SDE)

\[
dx(t) = -\beta D(x(t)) \nabla V(x(t)) dt + \nabla \cdot D(x(t)) dt + \sqrt{2} D^{1/2}(x(t)) dW(t),
\]

\[
d\Theta(t) = (L\theta)(x(t)) dt + \sqrt{2} \nabla \theta(x(t)) \cdot D^{1/2}(x(t)) dW(t),
\]

where \(W(t)\) is a \(N\)-dimensional Wiener process.

\(^2\)Note that (4) can be closed for any \(\theta(x)\) using time-dependent averaging conditional on \(\Theta(t) = \theta(x(t))\) (rather than the standard equilibrium conditional averaging using \(\rho_e(x)\)). The result, however, is a non-equilibrium evolution equation with time-dependent coefficients. For details see [34].
where \( \tau \) is an arbitrary time scale introduced for dimensional consistency, and \( \mathbf{a} \in \mathbb{R}^N \) and \( \mathbf{b} \in \mathbb{R}^N \) are two arbitrary points in configuration space. By varying the location of these points, different \( \theta(x) \) can be defined that each can be thought of as the potential associated with the pair of opposite point charges at \( \mathbf{a} \) and \( \mathbf{b} \), with \( \rho_e(x) D(x) \) playing the role of dielectric
\footnote{Under additional assumptions, we could introduce the potential associated with a single point charge, rather than the pair at \( \mathbf{a} \) and \( \mathbf{b} \), or with different distribution of charges. We chose to work with  for simplicity: notice in particular that the Fredholm’s alternative guarantees that this equation has a unique solution since \( \int \left( \delta(x - \mathbf{a}) - \delta(x - \mathbf{b}) \right) dx = 0. \)}. Note that the solution to (6) maps \( \mathbb{R}^N \setminus \{ \mathbf{a}, \mathbf{b} \} \) onto \( (-\infty, \infty) \) and has no extrema in its domain, which makes \( \theta(x) \) suitable as a collective variable – see Fig. 1 for an illustration on a two-dimensional example. Note also that (6) can be rewritten using the generator \( L \) as
\[
(L\theta)(x) = \tau \rho_e^{-1}(x) \left( \delta(x - \mathbf{a}) - \delta(x - \mathbf{b}) \right),
\]
which implies that \( L\theta = 0 \) at every point except \( \mathbf{a} \) and \( \mathbf{b} \). This property will be key in the developments below. The potential \( \theta(x) \) is related to the committor. To see why, let \( A \) and \( B \) be the two one-parameter family of sets defined as
\[
A = \{ x \mid \theta(x) \leq \theta_A \}, \quad B = \{ x \mid \theta(x) \geq \theta_B \},
\]
where $\theta_A < \theta_B$ can take arbitrary values, and define the function $q_{AB}(x)$ as

$$q_{AB}(x) = \frac{\theta(x) - \theta_A}{\theta_B - \theta_A} \quad \text{if} \ x \notin A \cup B$$

and $q_{AB}(x) = 0$ if $x \in A$ and $q(x) = 1$ if $x \in B$. It is easy to verify from (6) that $q_{AB}(x)$ is the solution to

$$(Lq_{AB})(x) = 0, \quad \text{if} \ x \notin A \cup B,$$  

(10)

with boundary condition $q_{AB}(x) = 0$ if $x \in \partial A$ and $q_{AB}(x) = 1$ if $x \in \partial B$. Hence, $q_{AB}(x)$ is just the committor function for the transition between the ‘reactant’ set $A$ and the ‘product’ set $B$, that is, $q_{AB}(x)$ gives the probability that a trajectory starting at point $x$ will reach $B$ rather than $A$ next [24]. Note however that the family of reactant and product states defined above do not need to be associated with an actual reactive process – in particular, they do not need to be metastable. Also, $\theta(x)$ is an actual collective variable that can be used everywhere, unlike $q_{AB}(x)$ that is constant inside $A$ and $B$.

Next, let us consider the evolution of $\Theta(t) = \theta(x(t))$ when $\theta(x)$ solves (6). Since $L \theta = 0$ as long as the dynamics stays away from the points $a$ and $b$ (which happens with probability 1 if the space dimension is $N > 1$), (4) reduces to the driftless equation

$$\dot{\Theta}(t) = \sqrt{2} \nabla \theta(x(t)) \cdot D^{1/2}(x(t)) \eta(t).$$

(11)

The absence of drift term in this equation has an important consequence. If we introduce the (random and dimensionless) rescaled time

$$s(t) = \int_0^t |\nabla \theta(x(t'))| \cdot D(x(t')) |\nabla \theta(x(t'))| dt',$$

(12)

then the right hand side of (11) has the same statistical properties (i.e. the same law or distribution) as $\dot{s}(t) \eta(s(t))$, where $\eta(s)$ is a one-dimensional white-noise. In other words, in terms of $s$, (11) simply reads

$$\frac{d \Theta}{ds} = \sqrt{2} \eta(s),$$

(13)

which, unlike (11), is closed. Of course, the simplicity of (13) is deceptive, since the rescaled time defined in (12) depends on $x(t)$ and is not known explicitly. In other words, in (13) we have lost the physical time information about the process. Still, (13) is a useful starting point for further developments. Indeed, the fact that

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Note that $q_{AB}(x)$ is independent of $\tau$, the arbitrary time scale introduced in the definition of $\theta(x)$.

Mathematically (11) should be interpreted as the Ito SDE

$$d \Theta(t) = \sqrt{2} \nabla \theta(x(t)) \cdot D^{1/2}(x(t)) dW(t),$$

and we are using the following identity in law (meaning that both sides of the equality have the same distribution)

$$\int_0^t \nabla \theta(x(t')) \cdot D^{1/2}(x(t')) dW(t') \overset{\text{d}}{=} W(s(t)), $$

where $W(s)$ is a one-dimensional Wiener process. As a result the SDE for $\theta(t)$ can be written in terms of $s(t)$ as $d \Theta(s) = \sqrt{2} dW(s)$, which is (13).
we can put (11) in the form of (13) by rescaling time (something that cannot be done with (4) with a general \( \theta(x) \) due to presence of the drift term \((L\theta)(x(t))\) in this equation), means that (13) captures exactly, if not the times, at least the order of the sequence in which the trajectory \( x(t) \) visits different regions defined via \( \theta(x(t)) \) – for example, any sets of hypersurfaces defined as \( \theta(x) = \theta_j, j = 1, \ldots, M \) for any \( M \in \mathbb{N} \) and any values of the constants \( \theta_j \). This property was already used in the context of milestoning to introduce a set of optimal milestones between which the sequence of transitions is Markov [28]. It also suggests that we might be able to recover some kinetic information about the process by reintroducing the time, at least in some average sense, as was also done in optimal milestoning [28]. A natural procedure to do this is to canonically average (11) conditionally on \( \theta(x(t)) = \Theta(t) \).

This gives

\[ \dot{\Theta}(t) = \sqrt{2} \sigma(\Theta(t)) \eta(t), \]  

where we defined \( \sigma \) as the square root of the conditional expectation

\[
\sigma^2(\Theta) = \left\langle \nabla \theta(x) \cdot D(x) \nabla \theta(x) \mid \theta(x) = \Theta(t) \right\rangle = \frac{\int_{\mathbb{R}^N} \nabla \theta(x) \cdot D(x) \nabla \theta(x) \rho_e(x) \delta(\Theta(t) - \theta) dx}{\int_{\mathbb{R}^N} \rho_e(x) \delta(\Theta(t) - \theta) dx}.
\]  

(15)

(14) is not equivalent to (11) (i.e. it is not exact), but it permits to calculate exactly the mean first passage times taken by trajectory of the original process \( x(t) \) to travel between any two regions defined via \( \theta(x) = \Theta(t) \) – for example, between any two hypersurfaces defined as \( \theta(x) = \Theta(t) \) and \( \Theta(t) = \Theta(t) \). A similar statement was also made by Berezhkovskii and Szabo [30] – here we will prove it by using the connection between the potential \( \theta(x) \) and the committor function, and using results from transition path theory (TPT) [24–26]. Before doing so, however, let us rewrite (14) in a way that makes apparent the connection with the results in [30].

To this end note that \( \sigma^2(\Theta) \) can also be written as

\[ \sigma^2(\Theta) = \nu e^{\beta G(\Theta)}, \]  

where \( G(\Theta) \) is the free energy associated with \( \theta(x) \),

\[
G(\Theta) = -\beta^{-1} \ln \langle \delta(\Theta(x) - \theta) \rangle \\
\equiv -\beta^{-1} \ln \int_{\mathbb{R}^N} \rho_e(x) \delta(\Theta(x) - \theta) dx,
\]  

(17)

and we defined

\[ \nu = \int_{\mathbb{R}^N} \nabla \theta(x) \cdot D(x) \nabla \theta(x) \rho_e(x) \delta(\Theta(x) - \theta) dx. \]  

(18)

Footnote 6: It is natural to average (11) to get mean first passage times because such first passage times are the sum of passage times between isosurfaces of \( \theta(x) \), and the average of a sum is the sum of the averages. Note however that this also explains why higher order moments of the first passage times cannot, in general, be calculated exactly from (14).
This factor is a constant (independent of $\theta$) as can be seen by taking its derivative of $\nu$ with respect to $\theta$:

\[
\int_{\mathbb{R}^N} \nabla \theta(x) \cdot D(x)\nabla \theta(x) \rho_e(x) \delta' (\theta(x) - \theta) \, dx
\]

\[
= - \int_{\mathbb{R}^N} \rho_e(x) \nabla \theta(x) \cdot D(x) \nabla \delta (\theta(x) - \theta) \, dx
\]

\[
= \int_{\mathbb{R}^N} \nabla \cdot (\rho_e(x) D(x) \nabla \theta(x)) \delta (\theta(x) - \theta) \, dx = 0,
\]

where we used the chain rule to get the first equality, integration by parts to get the second, and (6) to get the third. Using (16) in (14), we see that the Fokker-Planck equation for the probability density of $\Theta(t)$ solution to (14) is

\[
\frac{\partial}{\partial t} \bar{\rho}(\theta, t) = \nu \frac{\partial^2}{\partial \theta^2} \left( e^{\beta G(\theta)} \bar{\rho}(\theta, t) \right), \tag{19}
\]

which is essentially a rewriting of Eq. (3.6) in [30], the only difference being that we wrote (19) (and (14)) using the potential $\theta(x)$ rather than the committor function – this is because we want (14) (and (19)) to be defined everywhere, which is the case if we use $\theta(x)$, but not the committor (since this function is constant inside the reactant and product states). In particular, Eq. (3.6) in [30] needs boundary conditions at the reactant and product states, whereas (19) does not. Note also that the stationary solution to (19) is $\bar{\rho}_e(\theta) = e^{-\beta G(\theta)}$ as it should be.

Let us now justify the claim that (14) permits to calculate mean first passage times exactly. We recall from TPT that the statistical properties of the reactive trajectories (that is, the pieces of trajectories during which they transition from $A$ to $B$ without any return to $A$ along the way) can be expressed in terms of $\rho_e(x)$ and $q_{AB}(x)$. In particular, the reaction rate from $A$ to $B$ (that is, the average number

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Mathematically, the way to prove that $\nu$ is constant is to use the co-area formula to express it as the surface integral

\[
\nu = \int_{S_\theta} \hat{n}_{S_\theta}(x) \cdot D(x) \nabla \theta(x) \rho_e(x) \, d\sigma(x)
\]

where $S_\theta = \{ x \mid \theta(x) = \theta \}$, $\hat{n}_{S_\theta}$ is the unit normal pointing in direction of increasing $\theta(x)$ and $d\sigma(x)$ is the Hausdorff measure on $S_\theta$. By the divergence formula, for any $\theta_A < \theta_B$, we then have

\[
\int_{S_{\theta_A}} \hat{n}_{S_{\theta_A}}(x) \cdot D(x) \nabla \theta(x) \rho_e(x) \, d\sigma(x)
\]

\[
- \int_{S_{\theta_B}} \hat{n}_{S_{\theta_B}}(x) \cdot D(x) \nabla \theta(x) \rho_e(x) \, d\sigma(x)
\]

\[
= \int_{\Omega_{AB}} \nabla \cdot (\rho_e(x) D(x) \nabla \theta(x)) \, dx = 0.
\]

where $\Omega_{AB} = \{ x \mid \theta_A < \theta(x) < \theta_B \}$. 
of reactive trajectories observed per unit of time) can be calculated as

$$\nu_{AB} = \int_{(A\cup B)^c} \nabla q_{AB}(x) \cdot D(x) \nabla q_{AB}(x) \rho_e(x) \, dx$$

$$= \int_{(A\cup B)^c} \frac{\nabla \theta(x) \cdot D(x) \nabla \theta(x)}{(\theta_B - \theta_A)^2} \rho_e(x) \, dx$$

$$= \frac{1}{(\theta_B - \theta_A)^2} \int_{\theta_A}^{\theta_B} \int_{\mathbb{R}^N} \nabla \theta(x) \cdot D(x) \nabla \theta(x)$$

$$\times \rho_e(x) \delta(\theta(x) - \theta) \, dx \, d\theta$$

$$= \frac{\nu}{\theta_B - \theta_A},$$

where we started from the result from TPT, then used (9), (18), and the constancy of $\nu$. Similarly the mean first passage time from $A$ to $B$ (that is, the average time it takes to return to $B$ after hitting $A$ the first time after leaving $B$) is given by

$$\tau_{AB} = \nu_{AB}^{-1} \int_{\mathbb{R}^N} \rho_e(x)(1 - q_{AB}(x)) \, dx$$

$$= \nu^{-1} \int_{(A\cup B)^c} \rho_e(x)(\theta_B - \theta(x)) \, dx$$

$$+ \nu^{-1}(\theta_B - \theta_A) \int_{A} \rho_e(x) \, dx$$

$$= \nu^{-1} \int_{\theta_A}^{\theta_B} (\theta_B - \theta)e^{-\beta G(\theta)} \, d\theta$$

$$+ \nu^{-1}(\theta_B - \theta_A) \int_{-\infty}^{\theta_A} e^{-\beta G(\theta)} \, d\theta.$$  \hspace{1cm} (21)

This last formula justifies our claim: indeed the mean first passage time $\tau_B(\theta)$ from any $\theta < \theta_B$ to $\theta_B$ of the solution to (13) solves

$$\nu e^{\beta G(\theta)} \frac{d^2 \tau_B}{d\theta^2} = -1, \quad \tau_B(\theta_B) = 0, \quad \lim_{\theta \to -\infty} \frac{d\tau_B}{d\theta} = 0.$$  \hspace{1cm} (22)

It is easy to see that the solution to this equation evaluated at $\theta = \theta_A$ coincide with (21). $\tau_B(\theta_A) \equiv \tau_{AB}$. Since $\theta_A$ and $\theta_B > \theta_A$ are arbitrary in this argument, and we can easily generalize it to the case with $\theta_B < \theta_A$, we can indeed calculate exactly mean first passage times of the original process $x(t)$ from any surface $\theta(x) = \theta_A$ to any any surface $\theta(x) = \theta_B$ using (14).

One thing still remain to be done, namely show that (14) can be recast into a (or rather infinitely many, all equivalent) standard overdamped Langevin equation(s). Clearly, we can change the form of (14) without affecting the physics behind this equation by any change of variable, i.e. by introducing $\Theta(t) = h(\Theta(t))$ for any monotonic (one-to-one) function $h$ mapping $\mathbb{R}$ onto $\mathbb{R}$. This corresponds to using
\[ \tilde{\theta}(x) = h(\theta(x)) \]

as new collective variable, and it turns (14) into

\[ \dot{\tilde{\Theta}}(t) = -\beta m(\tilde{\Theta}(t)) \tilde{G}'(\tilde{\Theta}(t)) + m'(\tilde{\Theta}(t)) \]
\[ + \sqrt{2m^{1/2}(\tilde{\Theta}(t))} \eta(t), \tag{23} \]

where \( \tilde{G}(\theta) \) is the free energy associated with \( \tilde{\theta}(x) \),

\[ \tilde{G}'(\theta) = -\beta^{-1} \ln(\delta(\tilde{\theta}(x) - \tilde{\theta})), \tag{24} \]

and the diffusion coefficient \( m(\tilde{\theta}) \) is given by \[ m(\tilde{\theta}) = \langle \nabla \tilde{\theta}(x) \cdot D(x) \nabla \tilde{\theta}(x) \mid \tilde{\theta}(x) = \tilde{\theta} \rangle. \tag{25} \]

In fact, it is easy to see that (14) itself is in the form of (23), with \( m(\theta) \equiv \sigma^2(\theta) = \nu e^{\beta G(\theta)} \), which implies that \( -\beta m(\theta) \tilde{G}'(\theta) + m'(\theta) = 0 \). Since (23) contains the same physics as (14) it can again be used to calculate exactly first passage times from any surface where \( \tilde{\theta}(x) = \tilde{\theta}_A \) to any from any surface where \( \tilde{\theta}(x) = \tilde{\theta}_B \). To derive (23), notice first that Ito’s lemma implies that \( \dot{\tilde{\Theta}}(t) = h(\tilde{\Theta}(t)) \)

\[ \dot{\tilde{\Theta}}(t) = \sigma^2(\Theta(t))h''(\Theta(t)) + \sqrt{2h'(\Theta(t))}\sigma(\Theta(t))\eta(t). \tag{26} \]

To cast this equation in the form (23), by looking at the noise term we see that we must take

\[ m(h(\theta)) = |h'(\theta)|^2 \sigma^2(\theta), \tag{27} \]

On the other hand the free energies \( G(\tilde{\theta}) \) and \( G(\theta) \) are related as

\[ G(h(\theta)) = -\beta^{-1} \ln \int \rho_c(x) \delta(h(\theta(x)) - h(\theta)) dx \]
\[ = -\beta^{-1} \ln \int \rho_c(x) \delta(h(\theta(x))) - h(\theta)) dx \]
\[ = -\beta^{-1} \ln \int \rho_c(x) |h'(\theta)|^{-1} \delta(\theta(x) - \theta) dx \]
\[ = -\beta^{-1} \ln(|h'(\theta)|^{-1} e^{-\beta G(\theta)}) \]
\[ = G(\theta) + \beta \ln |h'(\theta)|. \]

Together with (16), this relationship implies that

\[ \sigma^2(\theta) \equiv \nu e^{\beta G(\theta)} = \frac{\nu e^{\tilde{G}(h(\theta))}}{h'(\theta)}, \]

Notice that (23) holds for any choice of \( h(\theta) \): however, for the specific choice \( h'(\theta) = \exp(-\frac{1}{\beta}G(\theta)) \), we have \( m(\tilde{\theta}) = \nu \), and so (23) reduces to

\[ \dot{\tilde{\Theta}}(t) = -\beta \nu \tilde{G}'(\tilde{\Theta}(t)) + \sqrt{2\nu} \eta(t), \]

which is an overdamped equation with a constant diffusion coefficient \( \nu \). While simpler than (23) with a \( \theta \)-dependent \( m(\tilde{\theta}) \), this equation is not better – it is completely equivalent to (23). Note also that, in the vector-valued case, no change of variable permits to turn (19) into an equation in which the diffusion tensor is constant.

Note that \( m(\tilde{\theta}) \), like \( \nu \), has the dimension of the inverse of a time since \( \theta(x) \) is dimensionless.
which we can combine with (27) to get
\[ m(h(\theta)) = \nu e^{\beta \tilde{G}(h(\theta))} h'(\theta). \]  
(28)

Solving this equation in \( h'(\theta) \), then differentiating over \( \theta \) and multiplying by \( \sigma^2(\theta) = \nu e^{-\beta \tilde{G}(h(\theta))/h'(\theta)} \) gives
\[ \sigma^2(\theta) h''(\theta) = m'(h(\theta)) - \beta m(h(\theta)) G'(h(\theta)). \]  
(29)

This shows that the drift term in (26) is also equal to that in (23). Finally, to show that \( m(\theta) \) is given by (25), use the definition (18) of \( \nu \) in (28) to get
\[
\begin{align*}
  m(h(\theta)) &= e^{\beta \tilde{G}(h(\theta))} h'(\theta) \int_{\mathbb{R}^N} \nabla \theta(x) \cdot D(x) \nabla \theta(x) \\
  &\quad \times \rho_e(x) \delta(\theta(x) - \theta) dx \\
  &= e^{\beta \tilde{G}(h(\theta))} \int_{\mathbb{R}^N} \nabla h(\theta(x)) \cdot D(x) \nabla h(\theta(x)) \\
  &\quad \times \rho_e(x) \delta(h(\theta(x)) - h(\theta)) dx.
\end{align*}
\]

Note that even if \( \Theta(t) \) solves (14), in order for (23) to preserves the right physics for any \( \tilde{\Theta}(t) = h(\Theta(t)) \) both the free energy \( G(\theta) \) and the diffusion coefficient \( m(\theta) \) must be changed consistently: in other words, the pair \( \tilde{G}(\tilde{\theta}), m(\tilde{\theta}) \) rather than the free energy alone carries dynamical meaning [23, 35–37]. Our results generalizes this observation to situations without time-scale separation, as long as a potential \( \theta(x) \) solution of (6) is used as collective variables.

Our results can be generalized to systems with inertia, e.g. when (1) is replaced by the Langevin equation
\[ m \ddot{x} + \gamma(x) \dot{x} = -\nabla V(x) + \sqrt{2\beta^{-1}} \gamma^{1/2}(x) \eta(t), \]
(30)
where \( m \) is the mass matrix and \( \gamma(x) \) is the friction tensor, related to the diffusion tensor \( D(x) \) in (1) via Einstein’s relation: \( \gamma(x) = \beta^{-1} D^{-1}(x) \). Then, the potential \( \theta(x) \) becomes a function \( \vartheta(x, p) \) of both positions \( x \) and momenta \( p = m^{-1} \dot{x} \) and satisfies (compare (6))
\[
\begin{align*}
  &\beta^{-1}(\partial_x \partial_p) \cdot \left( \varrho_e(x, p) \begin{pmatrix} 0 & \text{Id} \\
  -\text{Id} & \gamma(x) \end{pmatrix} \right) \vartheta(x, p) \\
  &= \tau \left( \delta(x - x_a) \delta(p - p_a) - \delta(x - x_b) \delta(p - p_b) \right).
\end{align*}
\]
(31)

Here \( (x_a, p_a) \) and \( (x_b, p_b) \) are two arbitrary points in phase-space, and \( \varrho_e(x, p) \) is the equilibrium (canonical) probability density of (30):
\[ \varrho_e(x, p) = Z^{-1} e^{-\beta H(x, p)} \]
(32)

where \( H(x, p) = \frac{1}{2} p \cdot m^{-1} p + V(x) \) and \( Z \) is the partition function. If we use \( \vartheta(x, p) \) as collective variable, the results obtained in the overdamped case can be straightforwardly generalized to the present situation. In particular if we set
\[ \Theta(t) = \vartheta(x(t), p(t)) \] and use the rescaled time (compare (12))

\[ s(t) = \beta^{-1} \int_0^t \left| \partial_p \vartheta(x(t'), p(t')) \right| dt' \]

(33)

then \( \Theta(s) \) satisfies the closed equation (13). Similarly, we can calculate exactly mean first passage times between any two regions where \( \vartheta(x, p) \) is constant by using (14) with \( \zeta(\theta) \) replaced by \( \varsigma(\theta) = \sqrt{\tau} \exp \left( \frac{1}{2} \beta \mathcal{G}(\theta) \right) \), where \( \mathcal{G}(\theta) \) is the free energy associated with \( \vartheta(x, p) \),

\[ \mathcal{G}(\theta) = -\beta^{-1} \ln \langle \delta(\vartheta(x, p) - \theta) \rangle \]

\[ \equiv -\beta^{-1} \ln \int_{\mathbb{R}^N} \rho_c(x, p) \delta(\vartheta(x, p) - \theta) dx dp, \]

(34)

and \( v \) is given by

\[ v = \beta^{-1} \int_{\mathbb{R}^N} \partial_p \vartheta(x, p) \cdot \gamma(x) \partial_p \vartheta(x, p) \rho_c(x, p) \]

\[ \times \delta(\vartheta(x, p) - \theta) dx dp. \]

(35)

Like \( \nu \), this factor is constant (independent of \( \theta \)). Finally, by using the gauge transformation \( \vartheta(x, p) = h(\vartheta(x, p)) \), it is easy to see that \( \Theta(t) = h(\Theta(t)) \) satisfies (23) with \( G \) replaced by \( \mathcal{G} \) and \( m \) replaced by

\[ \mu(\bar{\theta}) = \beta^{-1} \langle \partial_p \vartheta(x, p) \cdot \gamma(x) \partial_p \vartheta(x, p) \rangle \mid \vartheta(x, p) = \bar{\theta}. \]

(36)

Another generalization involves introducing vector-valued collective variables. In the overdamped case, this can be done by picking \( M + 1 \) points \( a_i, i = 0, \ldots, M \) and defining \( M \) potentials via

\[ \nabla \cdot (\rho_c(x) D(x) \nabla \theta_i(x)) = \tau (\delta(x - a_i) - \delta(x - a_0)) \]

(37)

for \( i = 1, \ldots, M \). The components of \( \Theta_i(t) = \Theta(x(t)) = (\theta_1(x(t)), \theta_2(x(t)), \ldots, \theta_M(x(t))) \) then satisfy the equivalent of (21),

\[ \dot{\Theta}_i(t) = \sqrt{2} \nabla \theta_i(x(t)) \cdot D^{1/2}(x(t)) \eta(t), \]

(38)

Like (11), each of these equations is driftless. However, unlike (11), they cannot all be put in a form equivalent to (13) by a single rescaling of time: that is because such a rescaling can only act on one equation in the system at a time, and cannot be made globally for the all system. We can, however, do such a rescaling on the equation for any linear combination of the \( \Theta_i(t) \), i.e. on the equation for \( \sum_{i=1}^N c_i \Theta_i(t) \) where \( c_i, i = 1, \ldots, M \) are arbitrary constants. As a result, we can calculate exactly the mean first passage time between any two regions where \( \sum_{i=1}^N c_i \Theta_i(x) \) is

\[ A \text{ similar construction holds in the Langevin case and is omitted for the sake of brevity.} \]

\[ B \text{ Note that } a_0 \text{ is used as a reference point here, but it is not special in any way: if we relabel the points } a_i, i = 0, \ldots, M, \text{ the new set of potentials can be related to the ones in the original labeling by a simple linear transformation.} \]
constant (again for an arbitrary set of $c_i$’s) by using the closed system of equations obtained by averaging (38) (compare (14)):

$$\dot{\Theta}_i(t) = \sqrt{2} \sum_{j=1}^{M} \sigma_{ij}(\Theta(t))\eta_j(t), \quad i = 1, \ldots, M$$ (39)

Here $\eta_j(t)$ for $j = 1, \ldots, M$ are independent white-noise processes, and the entries $\sigma_{ij}(\theta)$ are defined via

$$\sum_{k=1}^{M} \sigma_{ik}(\theta)\sigma_{kj}(\theta) = \nu_{ij}e^{G(\theta)},$$ (40)

where $G(\theta)$ is the free energy associated with $\theta$:

$$G(\theta) = -\beta^{-1} \ln\langle \delta(\theta(x) - \theta) \rangle$$

$$\equiv -\beta^{-1} \ln \int_{\mathbb{R}^N} \rho_e(x)\delta(\theta(x) - \theta)dx,$$ (41)

and $\nu_{ij}$ are the constants given by

$$\nu_{ij} = \int_{\mathbb{R}^N} \nabla \theta_i(x) \cdot D(x)\nabla \theta_j(x)\rho_e(x)\delta(\theta(x) - \theta)dx.$$ (42)

If we let $\tilde{\Theta} = h(\Theta)$, where $h : \mathbb{R}^M \rightarrow \mathbb{R}^M$ is a one-to-one map, (39) becomes (compare (23))

$$\dot{\tilde{\Theta}}_i(t) = -\beta \sum_{j=1}^{M} m_{ij}(\tilde{\Theta}(t))\partial_{\theta_j} \tilde{G}(\tilde{\Theta}(t))$$

$$+ \sum_{j=1}^{M} \partial_{\theta_j} m_{ij}(\tilde{\Theta}(t)) + \sqrt{2} \sum_{j=1}^{M} g_{ij}(\tilde{\Theta}(t))\eta_j(t)$$ (43)

where $\tilde{G}(\tilde{\theta})$ is the free energy associated with $\tilde{\theta}(x) = h(\theta(x))$, the entries $m_{ij}(\tilde{\theta})$ are defined as (compare (25))

$$m_{ij}(\tilde{\theta}) = \langle \nabla \tilde{\theta}_i(x) \cdot D(x)\nabla \tilde{\theta}_j(x) | \tilde{\theta}(x) = \tilde{\theta} \rangle.$$ (44)

and $g_{ij}(\tilde{\theta})$ satisfies $\sum_{k=1}^{M} g_{ik}(\tilde{\theta})g_{kj}(\tilde{\theta}) = m_{ij}(\tilde{\theta})$. The result above is not a complete generalization to vector-valued collective variables since such a generalization should permit to compute exactly mean first passage times between any regions where each $\theta_i(x)$ takes independent constant values rather than those where $\sum_{i=1}^{N} c_i \theta_i(x) = \text{cst}$. Yet, the ability to pick the $c_i$’s arbitrarily in this expression (and the $a_i$’s in (37)) still offers a lot of flexibility in the range of regions between which mean first passage times can be calculated exactly.

Let us end this communication with a few comments about the practical implications of our results. While it is conceptually pleasing that we can perform exact dynamical coarse-graining with collective variables that are not slow (and thereby break free from the limitations of the standard approach based on Markovian approximation to MZ), the calculation of these variables involves solving (6) or (31), which is by no means straightforward. Techniques such as transition path
sampling \cite{19,38} or the string method \cite{35,39,40} could be used for this purpose. Alternatively, our results could be used to test the quality of putative collective variables. For example, the method proposed in \cite{41}, which test whether a collective variable is Markovian in physical time (which, in general, requires that it be a slow variable), could be generalized to test for Markovianity after time rescaling, like in \cite{14} (which requires that the collective variable approximates a potential $\theta(x)$ or $\theta(x,p)$ but not that it be slow). In some sense, this approach is already at the core of optimal milestoning \cite{28,29}, but it certainly could be developed further, and also used to analyze simulation or experimental data in ways alternative to those proposed e.g. in \cite{42-44}.

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