Towards a General Theory of Molecular-Scale Energy Transfer

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A general theory of molecular-scale energy transfer promises to yield insights into the mechanisms of molecular machines and to unify a diverse range of experiments and phenomenological models. We progress towards a general theory by deriving analytic solutions to Brownian motion on a multi-dimensional tilted periodic free-energy potential. Analogous to the tight-binding model of quantum mechanics, we consider the limit of deep potential wells and show that the continuous theory transforms to a discrete master equation describing hopping between localized (meta-)stable states. For non-separable potentials the master equation describes energy transfer between degrees of freedom and we derive expressions for the efficiency and rate of energy transfer valid beyond the near-equilibrium limit. Our predictions are consistent with non-equilibrium fluctuation theorems and the Onsager relations and provide an opportunity to experimentally test the theory.

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Biological cells use specialized proteins to convert and utilize chemical energy while operating far from equilibrium, with minimal inertia, and in the presence of significant thermal fluctuations [1–3]. Insights into the mechanisms of these molecular machines are being provided by single-molecule experiments [1, 2] and the artificial synthesis of molecules that mimic motor proteins [4–8]. Building on one-dimensional theoretical studies of stochastic non-equilibrium transport [2], Brownian motion on a multi-dimensional free-energy landscape has been proposed as a mechanism for molecular-scale energy transfer [12, 13]. In this paper we begin with the continuous stochastic theory for overdamped Brownian motion on a multi-dimensional tilted periodic potential and derive a discrete master equation valid in the limit of deep potential wells. This master equation describes hopping between localized (meta-)stable states and can be solved analytically. We demonstrate that this approach has the key elements required for a general theory of molecular-scale energy transfer: (i) it is based on a physically compelling microscopic theory, (ii) it is consistent with well-established non-equilibrium thermodynamic results such as non-equilibrium fluctuation theorems [14, 15] and the Onsager relations [16, 17], and (iii) it provides specific testable predictions.

We consider overdamped Brownian motion on a multi-dimensional tilted periodic potential described by the Smoluchowski equation [18]

\[ \frac{\partial P(r,t)}{\partial t} = \mathcal{L}_f P(r,t) = -\nabla \cdot J(r,t), \]  

(1)

where \( P(r,t) \) is the probability density of finding the system at position \( r \) at time \( t \) and \( \mathcal{J}(r,t) \) is the probability current density. Each degree of freedom is a generalized coordinate capturing the main conformal motions of the molecules and representing displacements in real space or along reaction coordinates [19]. In Eq. (1), the evolution operator is defined by \( \gamma L_f = k_B T \nabla^2 + \nabla \cdot \nabla V_f(r) \), where \( T \) is the temperature, \( k_B \) is Boltmann’s constant, and \( \gamma \) is the damping constant. For notational simplicity we choose uniform damping although the generalization to coordinate variations is straightforward [20].

The free-energy potential \( V_f(r) \) has both entropic and mechanical contributions [13]. We assume a potential in the form of a rapidly varying periodic part and a slowly varying linear tilt [13], i.e., \( V_f(r) = V_0(r) - f \cdot r \), where \( V_0(r+An) = V_0(r) \), \( A_{jj'} = a_j \delta_{jj'} \) and \( n = \sum_j n_j r_j \) with \( n_j \) integer. The minima of the periodic potential (centered at \( r = An \)) define microscopic (meta-)stable states and the potential barriers between minima determine the probability of hopping transitions. The linear potential represents a constant macroscopic thermodynamic force due to an external mechanical force or an entropic force such as a concentration gradient across a membrane or an out-of-equilibrium chemical concentration.

In the \( f = 0 \) case, the steady state has the form \( J_{ss}(r) \propto \exp[-V_0(r)/k_BT] \) and the probability current density vanishes everywhere, i.e., \( J_{ss}(r) = 0 \). In contrast, for \( f \neq 0 \) the force induces a finite current and drives the system out of thermal equilibrium [2]. Energy transfer occurs when the force in one coordinate gives rise to current in another. This is only possible when the potential \( V_f(r) \) contains a non-separable term [12].

The above formalism provides a from-first-principles mathematical framework that encompasses all molecular-scale energy transfer, including energy conversion in cytoskeletal motors, rotary motors such as ATP synthase, and ion pumps [4]. This theory also provides a compelling physical picture of a molecular-scale system undergoing Brownian motion on a potential landscape that directs the average behavior of the system thereby enabling energy coupling between degrees of freedom. Even in the two-dimensional case, the Smoluchowski equation [4] is not analytically tractable in general and is difficult to connect with experiments, phenomenological models, and other general results from non-equilibrium thermo-
In dynamics. In the experimentally relevant regime of deep potential wells, we transform Eq. \(1\) to a master equation that can be solved analytically.

Analogous to the tight-binding model of a quantum particle in a periodic potential \([21]\), we consider that the periodic potential \(V_0(r)\) creates deep potential wells. The microscopic (meta-)stable states centered at each potential minima are strongly localized and the evolution operator \(L_f\) induces infrequent hopping transitions. Formally, \(\nabla V_f(r)\) is periodic so we invoke Bloch’s theorem \([21]\). In the \(f = 0\) case, the eigenvalue problem for Eq. \(1\) has the form \(\mathcal{L}_0 \phi_{\lambda_0,k}(r) = -\lambda_0 \phi_{\lambda_0,k}(r)\), where \(\phi_{\lambda_0,k}(r) = e^{i\mathbf{k} \cdot \mathbf{r}} \phi_0(\mathbf{r})\) and \(\phi_0(\mathbf{r})\) has the periodicity of the periodic potential. As for a quantum particle in a periodic potential, the eigenvalues \(\lambda_{\alpha,k}\) are real and separate into bands denoted by the band index \(\alpha\) and \(k\) is confined within the first Brillouin zone \([21]\). Periodic boundary conditions are used with period \(Na\) where \(N\) is a diagonal matrix of integers. We choose an infinite spatial extent \((N_{jj} \rightarrow \infty)\) which means \(k\) is continuous. Similar results can be obtained for rotary motors by taking \(N_{jj}\) finite and \(k\) quantized. The eigenstates \(\phi_{\alpha,k}(r)\) form a complete orthonormal set \([20]\): \[\text{exp}[V_0(r)/\hbar B] \int \mathcal{B} dk \phi_{\alpha,k}(r') \phi_{\alpha,k}(r') = \delta(r - r') \text{ and } \int d\mathbf{r} \text{exp}[V_0(r)/\hbar B] \phi_{\alpha,k}(r) \phi_{\alpha,k}(r') = \delta_{\alpha\alpha} \delta(k - k'),\]
where the \(\mathcal{B}\) subscript on the \(k\) integral denotes a single Brillouin zone. Unlike for a quantum particle, \(\lambda_{\alpha,k} \geq 0\) is to be interpreted as a decay rate rather than a frequency/energy and the ground state is \(\phi_{000}(\mathbf{r}) \propto \exp[-V_0(\mathbf{r})/\hbar B] \text{ with } \lambda_{000} = 0\).

In the tight-binding regime it is convenient to define the localized Wannier states \(w_{\alpha,n}(r) = D \int \mathcal{B} dk \phi_{\alpha,k}(r) \exp(-i\mathbf{k} \cdot \mathbf{A} n),\) where \(D = \prod_j (a_j/2\pi)\). These Wannier states also form a complete orthonormal set and we expand the probability density as \(P(r,t) = (1/D) \sum_{\alpha,n} P_{\alpha,n}(t) w_{\alpha,n}(r)\). Using this expansion, Eq. \(1\) can be transformed to a discrete form. In general this discrete master equation can be interpreted in terms of hopping between Wannier states within a band and coupling between bands induced by the tilting potential. Assuming that the tilt is sufficiently weak that inter-band coupling is small compared to gaps in the band structure, inter-band coupling can be neglected. In this case the band structure of eigenvalues enables a separation of timescales between the rapidly decaying higher bands and the slowly evolving lowest band governing the long-time behavior of the system. Retaining only the lowest band and dropping the band subscript for the remainder of this paper, we write the resulting master equation \([20]\)

\[
\frac{dp_n(t)}{dt} = \sum_{n'} \left[ \kappa_f^{f-n} p_{n'}(t) - \kappa_f^{n-n'} p_n(t) \right],
\]
where

\[
\kappa_f^{f-n} = \frac{1}{D} \int d\mathbf{r} e^{V_0(\mathbf{r})/\hbar B} w_{n'}(\mathbf{r}) L_f w_0(\mathbf{r}).
\]

In the tight-binding limit where the system is stongly localized at the minima of the potential wells, the summation in Eq. \(2\) need only be extended over nearest neighbors. The coefficients \(p_n(t)\) are real and can be interpreted as the probability that the system is localized in the \(nth\) potential well. The hopping rates \(\kappa_f^{f-n}\) are also real and satisfy \(\sum_n \kappa_f^{f-n} = 0\). If the potential \(V_0(\mathbf{r})\) is separable, the hopping rate \(\kappa_f^{f}\) has the form

\[
\kappa_f^{f} = \sum_j \kappa_f^{f,j} \prod_j \delta_{n_j,0},
\]
and hopping transitions occur independently along each coordinate. Energy transfer can not occur in this case.

The hopping rate \(\kappa_f^{f}\) is in general a complicated function of \(f\). However, in the case of tight binding and weak tilt a simple functional dependence can be derived. The Smoluchowski operator can be written in the form \(\mathcal{L}_f = \text{exp}[V_0(\mathbf{r})/\hbar B] \mathcal{H}_f \text{exp}[V_0(\mathbf{r})/\hbar B],\) where \(\gamma \mathcal{H}_f = \hbar B \nabla^2 - U_f(\mathbf{r})\) is a self-adjoint operator with the potential \(U_f(\mathbf{r}) = [\nabla V_0(\mathbf{r}) - f]/\hbar B - \nabla^2 V_0(\mathbf{r})/2\) \([18]\). In the tight-binding approximation when the tilt is a small perturbation near the potential minima, the Wannier functions decay fast compared to the slowly varying linear potential and we write \(w_{\alpha,n}(\mathbf{r}) \approx w_{\alpha,0}(\mathbf{r}) \exp(f \cdot \mathbf{r}/\hbar B)\) \(\approx w_{\alpha,0}(\mathbf{r}) \exp(f \cdot \mathbf{A} n/\hbar B)\). Furthermore, the main contributions to the integral \(3\) come from regions around the minima of \(U_f(\mathbf{r})\) where the localized Wannier states are non-vanishing. Assuming the tilt is sufficiently small that it does not significantly alter the position of the \(f = 0\) potential minima, we take \(U_f(\mathbf{r}) \approx U_0(\mathbf{r})\). Combining these results yields \([20]\)

\[
\kappa_f^{f} \approx \frac{1}{D} \int d\mathbf{r} e^{V_0(\mathbf{r})/\hbar B} w_{\alpha,0}(\mathbf{r}) e^{f \cdot \mathbf{A} n/\hbar B} \times e^{-V_0(\mathbf{r})/\hbar B} \mathcal{H}_f e^{V_0(\mathbf{r})/\hbar B} w_0(\mathbf{r})
\approx \kappa_0 e^{f \cdot \mathbf{A} n/\hbar B}.
\]

We estimate the validity regime for Eqs. \(2\) and \(3\) by approximating the potential in the vicinity of its minima by a harmonic potential. In this limit the Wannier states are the harmonic oscillator states of the potential minima and the separation between the lowest and first eigenvalue bands is of order \(\Omega\), the smallest eigenvalue of the matrix \(M_{jj'} = \partial^2 V_0(\mathbf{r})/\partial r_j \partial r_{j'}\big|_{r = \mathbf{A} n}/\gamma\). Therefore, all bands except the lowest can be neglected for \(t \gg 1/\Omega\). To derive Eq. \(3\), we have also assumed that \(f^2/2\hbar B \ll \gamma \Omega\). Under this condition the tilt is small enough that transitions to higher eigenvalue bands of the \(f = 0\) potential are negligible. When a single maximum of \(V_0(\mathbf{r})\) separates the potential minima, the hopping rates \(\kappa_f^{f}\) can be approximated by Kramer’s relation \([20, 22, 23]\). In fact, the physical justification for Eq. \(3\)
closely parallels the physical argument in the derivation of Kramer’s relation [22, 24]: rapid relaxation within potential wells accompanied by slow transitions between wells. The hopping rates $\kappa_n^f$ in general can be calculated directly from the free-energy potential of the system and the potential can be determined by single-molecule experiments [25] or molecular dynamics simulations (e.g., [26]).

The transformation from a continuous stochastic multi-dimensional formalism to a discrete master equation represents a significant simplification of the system dynamics and has been attempted elsewhere [13, 27–29]. The benefit of our approach is that we make this transformation explicit providing analytic expressions for the hopping rates. Furthermore, in the tight-binding limit, Eq. (6) gives the functional dependence of the hopping rates on the macroscopic thermodynamic force. Solving the master equation (2) to determine physical properties of the system provides an opportunity to test the theory against established non-equilibrium thermodynamics results and experiment.

General non-equilibrium thermodynamics results are not imposed as constraints on our theory but instead can be determined analytically. In particular, the hopping rates (5) can be used to determine the ratio of forward to backward hopping, i.e.,

$$\frac{\kappa_n^f}{\kappa_n^b} = e^{f \cdot A_n / k_BT}. \quad (7)$$

Equation (4) is consistent with general non-equilibrium fluctuation theorems [12, 13].

The spatial drift $v = d \langle n \rangle / dt = \sum_n n dp_n(t) / dt$ represents the average rate of hopping and can be determined from the master equation to be

$$v = \sum_n n \kappa_n^0 e^{f \cdot A_n / 2k_BT}. \quad (8)$$

Equation (8) shows the functional dependence of the drift on the macroscopic thermodynamic force, and vanishes for $f = 0$. Interpreting $X_j = f_j a_j / T$ as the generalized thermodynamic forces and $v_j$ as the conjugate fluxes, Eq. (8) represents a generalized force-flux relation. Near equilibrium, $|X_j| / k_B \ll 1$ and Eq. (8) reduces to $v = \sum_n n \kappa_n^0 \sum_j X_j n_j / k_BT$. Therefore, $v_j = \sum_j L_{jj'} X_{j'}$ with $L_{jj'} = \sum_n n_j n_j' \kappa_n^0 / k_BT = L_{jj'}$, which satisfies the Onsager relations [16, 17].

Force and velocity are directly measurable in single molecule experiments [7, 13, 30]. To explore these properties in detail, consider the conceptually simpler two-dimensional case. The force-flux relation (8) becomes

$$v_x = (\kappa_{1,0}^f - \kappa_{1,-1}^f) + (\kappa_{1,1}^f - \kappa_{1,-1}^f)$$

$$= 2\kappa_{0,1}^0 \sinh(X_x / 2k_BT) + 2\kappa_{0,1}^0 \sinh(X_y / 2k_BT + X_y / 2k_BT)$$

$$v_y = (\kappa_{1,0}^f - \kappa_{1,1}^f - \kappa_{1,0}^f) + (\kappa_{1,1}^f - \kappa_{1,-1}^f)$$

$$= 2\kappa_{0,1}^0 \sinh(X_y / 2k_BT) + 2\kappa_{0,1}^0 \sinh(X_x / 2k_BT + X_y / 2k_BT)$$

where in the nearest-neighbor sum we have assumed that $|\kappa_{1,-1}^0| \ll |\kappa_{1,0}^0|, |\kappa_{0,1}^0|, |\kappa_{1,1}^0|$. The hopping rates $\kappa_{1,0}^0$ and $\kappa_{0,1}^0$ represent transitions occurring independently along each coordinate while the hopping rates $\kappa_{1,1}^0$ represent coupling transitions that transfer energy between the two degrees of freedom.

In the case that the linear potential is downhill in direction $x$ ($X_x > 0$) and uphill in direction $y$ ($X_y < 0$), energy transfer from $x$ to $y$ is thermodynamically viable when the coupling transitions are downhill ($X_x + X_y > 0$). The efficiency of energy transfer can be determined by the ratio of the power output $P_{out} = -v_y X_y T$ to input $P_{in} = v_x X_x T$, i.e.,

$$\eta = \frac{P_{out}}{P_{in}} = -\frac{v_y X_y}{v_x X_x}. \quad (10)$$

Equation (10) can be written explicitly in terms of $X_i$ by inserting Eqs. (9). The efficiency satisfies $0 \leq \eta \leq 1$, and $\eta \rightarrow 1$ when the independent hopping transitions are negligible, $|\kappa_{1,0}^0|, |\kappa_{0,1}^0| \ll |\kappa_{1,1}^0|$, and when $X_x \rightarrow X_y$. The latter condition can be recognized as the approach to thermal equilibrium along the coupled coordinate. Equation (10) can be interpreted as a trade-off between the power output $P_{out}$ and the efficiency $\eta$ [31]. This trade-off may have important biological consequences [31, 32] and its characteristics beyond the near-equilibrium regime will be explored in future work.

The eigenvalue band structure plays a key role in determining the system properties. The master equation (2) can be transformed to the diagonal form $d c_k(t) / dt = -\lambda_k^f c_k(t)$, where the eigenstates are $c_k(t) = \sum_n p_n(t) e^{i k A_n}$ and the eigenvalues are

$$\lambda_k^f = 4\kappa_{1,0}^0 \sin (k_x a_x / 2) \sin (k_x a_x / 2 + i X_x / 2k_BT)$$

$$+ 4\kappa_{0,1}^0 \sin (k_y a_y / 2) \sin (k_y a_y / 2 + i X_y / 2k_BT)$$

$$+ 4\kappa_{1,1}^0 \sin (k_x a_x / 2 + k_y a_y / 2) \sin (k_x a_x / 2 + k_y a_y / 2 + i X_x / 2k_BT + i X_y / 2k_BT). \quad (11)$$

Equation (11) defines the lowest Bloch band in the tight-binding limit. The gradient of the imaginary part of the eigenvalue at the origin is proportional to the drift, i.e., $\nabla_B \text{Im}(\lambda_k^f)|_{k=0}$, and the curvature of the real part at the origin is proportional to the time derivative of the covariance matrix [33], i.e., $d ((n_i n_j) - \langle n_i \rangle \langle n_j \rangle) / dt \propto \partial^2 \text{Re}(\lambda_k^f) / \partial k_i \partial k_j |_{k=0}$. Figure 1 shows contour plots of the real and imaginary parts of the eigenvalues throughout the first Brillouin zone for (a) weak coupling near equilibrium, (b) strong coupling near equilibrium, and (c) strong coupling far from equilibrium. From (a) to (b), the drift goes from $v_y < 0$ to $v_y > 0$ despite the fact the $X_y < 0$. Only quantitative differences are observed far from equilibrium.
three elementary reactions

\[ A \rightleftharpoons B, \quad C \rightleftharpoons D, \quad A + C \rightleftharpoons B + D, \]  

numbered 1 to 3 from left to right. The Gibbs free energies \( \Delta G_j \) are the thermodynamic forces driving the system and thermodynamic consistency requires \( \Delta G_1 + \Delta G_2 = \Delta G_3 \). The net rate for each chemical reaction is

\[ \dot{r}_j = R_j^f - R_j^b = R_j^f (1 - e^{\Delta G_j / k_B T}), \]  

where \( R_j^f \) and \( R_j^b \) are the forward and backward reaction rates, respectively, given by the usual mass-action expressions in terms of species activities and reaction rate constants. In our formalism, the generalized thermodynamic forces are \( X_j = -\Delta G_j / T \) and the generalized fluxes are \( v_x = r_1 + r_3 \) and \( v_y = r_2 + r_3 \). If reaction 1 is spontaneous (\( \Delta G_1 < 0 \)), and reaction 2 is non-spontaneous (\( \Delta G_2 > 0 \)), reaction 3 enables energy transfer between reactions 1 and 2 and this occurs spontaneously when \( \Delta G_3 < 0 \). Reactions 1 and 2 represent dissipative leak reactions that by-pass the coupling mechanism of reaction 3 [34].

The benefit of a general theory of molecular-scale energy transfer is the opportunity to gain deeper theoretical insights into the mechanisms and characteristics of molecular machines and to unify a diverse range of experimental results and phenomenological models. Brownian motion on a multi-dimensional tilted periodic potential provides a compelling candidate for such a general theory. On that basis, we have derived a discrete master equation in the limit of deep potential wells. This master equation is consistent with non-equilibrium fluctuation theorems and the Onsager relations and provides specific predictions that are experimentally accessible. Possible extensions to this work include: (i) detailed comparisons with experiments and phenomenological models; (ii) energy transfer between a tightly bound degree of freedom and a weakly bound one [2, 13]; (iii) multiple-step systems [13]; (iv) large tilts where inter-band coupling is important; and (v) the inclusion of inertial forces [18].