The Berry phase and the pump flux in stochastic chemical kinetics

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Abstract – We study a classical two-state stochastic system in a sea of substrates and products (absorbing states), which can be interpreted as a single Michaelis-Menten catalyzing enzyme or as a channel on a cell surface. We introduce a novel general method and use it to derive the expression for the full counting statistics of transitions among the absorbing states. For the evolution of the system under a periodic perturbation of the kinetic rates, the latter contains a term with a purely geometrical (the Berry phase) interpretation. This term gives rise to a pump current between the absorbing states, which is due entirely to the stochastic nature of the system. We calculate the first two cumulants of this current, and we argue that it is observable experimentally.

Abstract – We study a classical two-state stochastic system in a sea of substrates and products (absorbing states), which can be interpreted as a single Michaelis-Menten catalyzing enzyme or as a channel on a cell surface. We introduce a novel general method and use it to derive the expression for the full counting statistics of transitions among the absorbing states. For the evolution of the system under a periodic perturbation of the kinetic rates, the latter contains a term with a purely geometrical (the Berry phase) interpretation. This term gives rise to a pump current between the absorbing states, which is due entirely to the stochastic nature of the system. We calculate the first two cumulants of this current, and we argue that it is observable experimentally.

Single-molecule experiments [1] have led to a resurgence of work on the stochastic version of the classical Michaelis-Menten (MM) enzymatic mechanism that describes the enzyme-driven catalytic conversion of a substrate into a product [2]. A lot of progress (analytical and numerical) has been made under various assumptions and for various internal enzyme structures [3–7]. Still, many questions linger. Specifically, linear signal transduction properties of biochemical networks, such as frequency-dependent gains, are of a high interest [8–10]. These are studied by probing responses to periodic perturbations in the input signals (in our case, kinetic rates) due to fluctuations in chemical concentrations, in temperature, or due to other signals. However, such approaches usually disregard a phenomenon known from the theory of stochastic ratchets [11], especially in the context of biological transport [12–15]. Namely, a system’s symmetry may break, and, under an influence of a periodic or random zero-mean perturbation, the system may respond with a finite flux in a preferred direction. This, indeed, happens for the MM reaction [16], and we study the phenomenon in detail in this work.

The ratchet or pump effect manifests itself during periodic driving of simple classical systems, such as a channel in a cell membrane, which is formally equivalent to the MM enzyme [16–26]. The prevalence of the transport terminology over the chemical one in the literature is grounded in experiments, where driving is achieved by application of periodic electric field or nonequilibrium noise that modulate barrier heights for different channel conformations. The resulting cross-membrane flux has contributions that have no analog in stationary conditions.

In a related system, a quantum pump [27–29], pump fluxes admit a purely geometrical Berry phase interpretation [30]. A similar interpretation has been introduced for some special classical cases [31,32]. However, the Berry phase has not yet been derived for classical stochastic Markov chains that model chemical kinetics, even though recent developments strongly hint at the possibility [16,33–37]. For example, such systems admit introduction of a vector potential for the fluxes to characterize circular motion [34], allow reformulation of the Langevin dynamics in the form that strongly resembles wave packet equations in quantum mechanics with a nontrivial Berry curvature of Bloch bands [36–38], and result in pump currents that depend on contour integrals over the the evolution of the system’s parameters [16]. Although currents in most analyzed models were produced by the lack of the detailed balance rather than by external time-dependent perturbations, a dual description in terms of an external noise induced ratchet effect is usually possible. Conversely, time-dependent perturbations can break the detailed balance and induce the catalytic cycle [18].

In the present work we demonstrate that a theory based on the Berry phase can be constructed for a purely classical adiabatically slowly driven stochastic dynamics. The theory leads to an elegant interpretation of prior
and we assume the adiabatic approximation, i.e., the rates $k_m$ oscillate with the frequency $\omega \ll \min_m k_m$. Since $P_e = 1 - P_f$, (2) is equivalent to a formally solvable first-order linear differential equation. However, expressing the solution in a simple form requires approximations (e.g., small fluctuations) even for a harmonic dynamics of the parameters [16]. Additionally, the solution provides little information about the fluxes beyond their mean values, and it is not easy to generalize to the case of more complicated, multi-state stochastic systems. Thus here we pursue a different analysis technique.

The formal solution of (2) is

$$p(t) = \hat{T} \left( e^{-\int_0^t \hat{H}(\tau) d\tau} \right) p(0),$$

where $\hat{T}$ stands for the time-ordering operator, $p(t) \equiv [P_e(t), P_f(t)]^T$, and

$$\hat{H} = \begin{bmatrix} k_1 + k_{-2} & -k_{-1} - k_2 \\ -k_1 - k_{-2} & k_{-1} + k_2 \end{bmatrix}.$$  

It is useful to separate the parts of $\hat{H}$ that are directly responsible for the transition into or out of the $R$-state, namely $\hat{H} = \hat{H}_0 - \hat{V}_+ - \hat{V}_-$, where

$$\hat{H}_0 = \begin{bmatrix} k_1 + k_{-2} & -k_{-1} \\ -k_1 & k_{-1} + k_2 \end{bmatrix},$$

$$\hat{V}_+ = \begin{bmatrix} 0 & k_2 \\ 0 & 0 \end{bmatrix}, \quad \hat{V}_- = \begin{bmatrix} 0 & 0 \\ k_{-2} & 0 \end{bmatrix}.$$  

With this, we can write a formal expression for the probability $P_n$ to have $n$ net transitions from the bin into $R$ during time $t$. This is similar to [6], but we also allow $k_{-2} \neq 0$, counting transitions from $R$ into the bin with the negative sign. For example,

$$P_{n+1} = 1^+ \left[ \int_{t_0}^t dt_1 U_0(t,t_1) \hat{V}_+(t_1) U_0(t_1,t_0) \\ + \int_{t_0}^t dt_2 U_0(t,t_2) \hat{V}_-(t_2) \int_{t_2}^t dt_3 U_0(t_3,t_2) \hat{V}_+(t_3) \int_{t_3}^t dt_4 U_0(t_4,t_3) \hat{V}_-(t_4) \cdots \right] p(t_0).$$

Here $1^+$ is the vector with all unit entries and

$$U_0(t,t') = \hat{T} \left( e^{-\int_{t'}^t \hat{H}_0(\tau) d\tau} \right).$$

We introduce the probability generating function (pgf) for the number of transitions from the bin into $R$,

$$Z(\chi) = e^{S(\chi)} = \sum_{n=0}^{\infty} P_{n} \chi^n.$$  

$\chi$ is called the counting field, $S(\chi)$ is the full counting statistics, and its derivatives give cumulants (or connected
correlation functions) of \( P_n \), e.g. \( \langle n \rangle = -i\partial S(\chi)/\partial \chi|_{\chi=0}, \langle \delta^2 n \rangle = \langle n \rangle^2 - \langle n \rangle^2 = (-i)^2 \partial^2 S(\chi)/\partial \chi^2|_{\chi=0}, \text{etc.} \)

We derive the full counting statistics similarly to [6,39], but we extend the method by allowing for an explicit time-dependence of \( H \). First notice that (9) with the expansion of probabilities as in (7) is equivalent to an expansion of an evolution operator with a \( \chi \)-dependent Hamiltonian:

\[
Z = \mathbf{1}^+ \hat{T} \left( e^{-\int_0^t \hat{H}(\chi,t) dt} \right) \mathbf{p}(t_0),
\]

where

\[
\hat{H}(\chi,t) = \hat{H}_0(t) - \hat{V}_1(t)e^{i\chi} - \hat{V}_2(t)e^{-i\chi} = \begin{bmatrix} k_1 + k_2 & -k_{-1} - k_2 e^{i\chi} \\ -k_{-1} - k_2 e^{-i\chi} & k_1 + k_2 \end{bmatrix}.
\]

We define the two instantaneous eigenstates of \( \hat{H}(\chi,t) \) as \( |u_0 \rangle \) and \( |u_1 \rangle \). There are also the left eigenstates \( |u_0 \rangle \) and \( |u_1 \rangle \) with the same eigenvalues; we normalize them so that \( \langle u_0 | u_0 \rangle = \delta_{nm} \).

Let us introduce an intermediate time scale \( \delta t, 1/\omega \gg \delta t \gg \text{max}(1/k_m) \). During this time, typically, many transitions happen but \( k_m 's \) are approximately constant. Consider time-points \( t_j = t_0 + j\delta t, j = 1 \ldots N \), and \( t_N \equiv t \).

In the adiabatic limit, one can approximately rewrite the expression for the time ordered exponent in (10) as a product of evolution operators over time intervals of the size \( \delta t \) with parameters set to constants at times \( t_j \), i.e.,

\[
Z \approx 1^+ e^{-\hat{H}(\chi,t_N) \delta t} e^{-\hat{H}(\chi,t_{N-1}) \delta t} \ldots e^{-\hat{H}(\chi,t_0) \delta t} \mathbf{p}(t_0).
\]

Now we insert the resolution of the identity

\[
\mathbf{1} = |u_0(t_j)\rangle \langle u_0(t_j)| + |u_1(t_j)\rangle \langle u_1(t_j)|
\]

after every exponent at \( t_j \). We define \( |u_0(t_j)\rangle \) as the eigenstate of the eigenvalue \( \lambda_0 \) with the smallest real part. Since \( \delta t \gg 1/k_i, \exp[-\lambda_0(\chi,t_i)\delta t] \gg \exp[-\lambda_1(\chi,t_i)\delta t], \)

and terms containing \( |u_1(t)\rangle \) can be neglected. Moreover, after long evolution, any information about the initial and the final states is lost. Thus we rewrite the pgf as

\[
Z \approx e^{-\lambda_{\text{min}}(\chi,t) \delta t} \prod_{i=1}^N e^{-\lambda_0(\chi,t_i) \delta t} \langle u_0(t_0)|u_0(t_{i-1})\rangle,
\]

Finally, we approximate \( \langle u_0(t_j)|u_0(t_{i-1})\rangle \approx \exp[-\delta t \langle u_0(t_j)|\partial_t|u_0(t_{i-1})\rangle] \), which allows us to write

\[
S(\chi) \approx S_{\text{geom}} + S_{\text{cl}} = -\frac{T}{T_0} \int_0^{T_0} dt \langle u_0|\partial_t|u_0\rangle + \lambda_0(\chi,t),
\]

where \( T_0 = 2\pi/\omega \) is the period of the rate oscillations and \( T \gg T_0 \) is the total measurement time. The last term in (15) would be the same even for a time-independent problem, and it has been discussed before [39]. Diagonalizing \( \hat{H} \), and denoting \( c_{\pm \chi} = e^{\pm i\chi} - 1 \), we get for this term

\[
S_{\text{cl}} = \frac{T}{2T_0} \int_0^{T_0} dt \left[ K - \sqrt{K^2 + 4(\kappa_+ c_{+\chi} + \kappa_- c_{-\chi})} \right].
\]

The first term in (15) is more interesting. Since it depends only on the choice of the contour in the \( k \) space, but not on the rate of motion along the contour (at least in the adiabatic approximation), it has a geometric interpretation. We write

\[
S_{\text{geom}} = -\frac{T}{T_0} \oint_{C} A \cdot \mathbf{dk}, \quad A_m = \langle u_0(k)|\partial_{h_m}|u_0(k)\rangle,
\]

where the integral is over the contour in the 4-dimensional parameter space (the \( k \)-space) drawn during one cycle.

To estimate the error in our results, we note that (10) is exact, and then assumptions followed. First, we neglected the initial nonequilibrium relaxation on a time scale of \( \sim k_m^{-1} \). Since the \( S(\chi) \sim T \), this introduces an error in \( S \) of \( \sim 1/(k_m T) \), which vanishes for long observation times. Second, we projected the evolution only to the subspace of states with the smallest real part of the eigenvalue. The resulting error is exponentially suppressed in the adiabatic limit by \( \exp(-\langle \chi, -\lambda_0 \rangle/\omega) \). Third, there is the coarse graining in (12). To the lowest order, it introduces errors in \( S \) in the form of commutators, such as \( [H(t_i), H(t_j)] \), \( |t_j - t_i| < \delta t \). Since \( \langle u_0(t + \delta t)|[H(t_i), H(t_j)]|u_0(t)\rangle \sim O(\omega^\delta t^2) \) for \( t < t_j, t_j < t + \delta t \), this error is less significant than the \( O(\omega) \) contribution from the geometric term in \( S \). Finally, the error due to the approximation of \( \langle u_0(t_i)|u_0(t_{i-1})\rangle \) in (14, 15) is of the same order.

In a chemical system, the rates \( k_m \) can be changed by many means, e.g., by varying the system’s temperature. However, the simplest scenario is to couple the substrate and the product to particle baths and to vary the corresponding chemical potentials for both species. Since the rates \( k_1 \) and \( k_{-2} \) are proportional to the particle numbers, they will oscillate as well. Thus in what follows we assume that \( k_1 \) and \( k_{-2} \) are time dependent, while \( k_2 \) and \( k_{-1} \) are constants. Then, using Stokes theorem, we write

\[
\oint_{S_c} A \cdot \mathbf{dk} = \iint_{S_c} dk_2 \mathbf{dk}_1 F_{k_1,k_{-2}},
\]

where the integration is over the surface \( S_c \) enclosed by the contour \( c \), and

\[
F_{k_1,k_{-2}} = \frac{\partial A_{-2}}{\partial k_1} - \frac{\partial A_{1}}{\partial k_{-2}}.
\]

We will call \( F_{k_1,k_{-2}} \) the Berry curvature by analogy with similar definitions in quantum mechanics. The advantage of working with \( F \) rather than with the potentials \( A_m \) is that the Berry curvature is gauge invariant, i.e., it does not depend on an arbitrary \( k \)-dependent normalization of \( |u_0(k)\rangle \). It is a truly measurable quantity. In our case,

\[
F_{k_1,k_{-2}} = \frac{e^{-\chi}(e^{+\chi} k_2 + k_{-1})}{[4k_+ e^{+\chi} + 4k_- e^{-\chi} + K^2]^{3/2}}.
\]

Note that, with \( \chi = 0 \), the Berry curvature is zero, so it is the counting field \( \chi \) that introduces a nontrivial topology in the phase space of the eigenstates of \( \hat{H}(\chi,t) \). More
generally, a normal Markovian evolution corresponds to \( \chi = 0 \), where the normalization of \( P \) ensures that \( F|_{\chi=0} = 0 \). This may be the reason why nobody discussed the Berry phases in the context of Markov chains.

Knowing the full counting statistics, one can study both the particle flux and its fluctuations. Importantly, from (15, 17), all cumulants will have the geometric and the classical terms. In particular, for the mean \( L \to R \) flux per unit time, we get

\[
J = J_{\text{pump}} + J_{cl} = \int d^{2}k \frac{k_{2} + k_{-1}}{T_{0}K^{3}} + \int_{0}^{T_{0}} dt \frac{j_{3}(t)}{T_{0}},
\]

(21)

where \( j_{3} \) is the classical current defined in (1). Generally, the ratio of geometric and classical terms is \( \sim \omega/k_{m} \ll 1 \).

For the large observation time \( T \), the total expected \( L \to R \) particle flux is \( \langle n(T) \rangle = J T \). Similarly, its fluctuations are given by (6) \( \langle n(T) \rangle = J^{(2)} T \), where

\[
J^{(2)} = -\frac{1}{T} \frac{\partial^{2} (S_{\text{geom}} + S_{cl})}{\partial \chi^{2}}|_{\chi=0} = J^{(2)}_{\text{pump}} + J^{(2)}_{cl},
\]

(22)

\[
J_{\text{pump}}^{(2)} = \int d^{2}k \left[ \frac{k_{2} - k_{-1}}{T_{0}K^{3}} - \frac{12(k_{2} + k_{-1})(\kappa_{+} - \kappa_{-})}{T_{0}K^{5}} \right],
\]

(23)

\[
J_{cl}^{(2)} = \frac{1}{T_{0}} \int_{0}^{T_{0}} dt \left[ \frac{\kappa_{+} + \kappa_{-}}{K} - \frac{(\kappa_{+} - \kappa_{-})^{2}}{K^{3}} \right].
\]

(24)

The ratio of the pump and the classical noises is again \( \sim \omega/k_{m} \). Importantly, we see that, in general, expectations of the total, the classical, and the pump currents are not equal to their variances. Thus none of the currents in the MM problem is Poissonian. This is a general property of complex, multi-step reactions, which is often neglected in computational studies of biochemical reaction networks.

Also note that \( J_{\text{pump}}^{(2)} \) in (23) is not necessarily positive and can, in fact, decrease the total noise. However, the total noise variance \( J^{(2)} \) is strictly positive.

While the pump current in this system has been analyzed, cf. [16], to our knowledge, an expression for \( J \) parameterized by the rates, rather than by internal enzyme parameters has not been available. Even more importantly, expressions for the noise (either classical or pump) for variable kinetic rates have not existed either.

The smallness of the pump effect compared to the classical current complicates its observation. However, several opportunities exist. One is the dependence of \( J_{\text{pump}} \) on the frequency of the perturbation, while \( J_{cl} \neq J_{cl}(\omega) \). The second possibility is to vary the rates along a contour with \( J_{cl} = 0 \). However, even in this case the noise may still be dominated by the classical contribution.

To test our predictions, we choose one particular such contour with \( J_{cl} = 0 \). \( J_{\text{pump}} \neq 0 \) for a numerical analysis:

\[
k_{1} = A + R \cos(\omega t), \quad k_{-2} = A + R \sin(\omega t), \quad k_{-1} = k_{2} = 1.
\]

(25)

To estimate \( J^{(2)} \) numerically, we implemented a Gillespie-like scheme [40] that admits an explicit time dependence of the rates. However, since \( J_{\text{pump}} \ll \sqrt{J_{cl}^{(2)}} \), such Monte Carlo estimation of \( J \) would take too long. Instead, we numerically solved the master equation \( J \) with a time discretization \( dt \ll \min_{m}(1/k_{m}) \). This gave a better precision than an analytical result of [16], which assumes \( R \to 0 \). Knowing \( P_{f} \), \( j(t) = k_{2}P_{f} - k_{-2}(1 - P_{f}) \). Figure 2 shows an excellent agreement of our theory with the numerical results for both \( J \) and \( J^{(2)} \).
Intuitively, the flux cannot keep increasing linearly as $\omega$ grows and the adiabatic approximation fails. To understand the behavior at large frequencies, we consider the case of $\max k_m \ll \omega$. We look for the probabilities in the form $P_{\epsilon/f} = P_{\epsilon/f} + \delta P_{\epsilon/f}$, where $P_{\epsilon/f}$ are calculated for the time-averaged parameter values, namely, $P_{\epsilon} = \langle (k_2) + (k_{-1}) \rangle / K$, $P_f = 1 - P_{\epsilon}$, and $\delta P_{\epsilon/f}$ are small and oscillate fast. The latter can be found from (2). For example, when $k_1 = (k_1) + \delta k_1 \cos(\omega t)$, $k_{-2} = (k_{-2}) + \delta k_{-2} \sin(\omega t)$, and $k_2, k_{-1}$ are constants, we find $\delta P_{\epsilon} = -(\delta k_1 P_{\epsilon}/\omega) \sin(\omega t) + (\delta k_{-2} P_f/\omega) \cos(\omega t)$.

Then the current averaged over the oscillation period is $J = J_{cl}\{\langle k_m \rangle \} + J_{pump}$, where $J_{pump} = \delta k_1 \delta k_{-2} \bar{P}_f/(2\omega)$ is the correction due to the fast rate oscillations. For the parameters as in (25), we again get $J_{cl} = 0$, but $J_{pump} \neq 0$. However, the dependency of $J_{pump}$ on $\omega$ has changed from $\sim \omega$ in the adiabatic case to $\sim 1/\omega$ for fast oscillations. This agrees with [16], which used a different approximation and showed that there is a single maximum in the pump current at $\omega \sim k_m$. 

The phenomenon of $J_{pump} \neq 0$ can be explained in simple terms. Since a particle spends a finite time bound to the enzyme, the values of $k_1$ and $k_{-2}$ cannot influence the system during the mean unbinding time following a binding event. If, during an oscillation, the left binding rate is higher than the right one during the upramp of the cycle, then $k_1$ "shields" growing values of $k_{-2}$ from having an effect, while $k_{-2}$ shields decreasing values of $k_1$ during the downramp. This leads to a phase-dependent asymmetry that is the source of the pump flux. Larger frequencies lead to more shielding, hence the linear $\omega$ dependence. However, for $\omega \to \infty$, the information about the phase of the oscillations is lost while a particle is bound, decreasing the asymmetry and the flux.

Is the pump flux observable experimentally in biochemical (rather than channel transport) experiments? Exact zeroing of $J_{cl}$, as in the numerical example above, which would make $J_{pump}$ the leading effect, may be difficult to achieve. However, the classical current is also small near the classical steady state, $(k_1)k_2 = k_{-1}(k_{-2})$. In this case, if $k_{1,-2} = (k_{1,-2}) + \delta k_{1,-2} \cos(\omega t - \phi_1 - \phi_2)$, and if the oscillations are small, $\delta k_{1,-2}/k_{1,-2} \ll 1$, then we can disregard variation of the Berry curvature inside the contour, and

$$J_{pump} \approx \omega k_{2} + k_{-2} \delta k_1 \delta k_{-2} \sin \phi, \quad (26)$$

$$J_{pump}^{(2)} \approx \omega k_{2} + k_{-2} \delta k_1 \delta k_{-2} \sin \phi, \quad (27)$$

where $\phi = \phi_2 - \phi_1$. This should be compared to the classical contributions in the same limit

$$J_{cl} \approx k_{2} \delta k_1^2 + k_{-2} \delta k_{-2}^2 + (k_{-2} - k_{-1}) \delta k_1 \delta k_{-2} \cos \phi \quad \frac{\sin(\phi)}{2(K)^2}, \quad (28)$$

$$J_{cl}^{(2)} \approx \frac{2k_1 k_2}{\langle K \rangle}. \quad (29)$$

We see that, while $J_{pump}/J_{cl} \sim \omega/(K)$, the ratio of the variances is further suppressed, $J_{pump}^{(2)}/J_{cl}^{(2)} \sim (\omega/K)\delta k_1 \delta k_{-2}/(k_{1,2})$. Thus overcoming the classical variance is the biggest concern for a successful experiment.

Our model has a single substrate and a single product. Thus the enzyme we are discussing is an EC 5 enzyme. Properties of such enzymes vary dramatically depending on a reaction, a biological species, and mutations in protein sequences [41]. A typical range of $k_2$ in vitro is $10^{-2} \cdots 10^3$ s$^{-1}$. Similarly, the Michaelis constant, $K_M = (k_{-1} + k_2)/k_1$ in our notation, varies between 0.01 and 10 mM (here $[S]$ is the substrate concentration). For our analysis, we take $k_2 \sim 10$ s$^{-1}$, and $K_M = 1$ mM. While little is known about $k_{-1}$ and $k_2$ separately, it is reasonable to assume $k_{-1} \sim k_2$. Similarly, we take $k_{-2} \sim k_1 [P]/[S]$ since both rates are often dominated by the mean particle-enzyme collision time [3] (for example, for triose phosphate isomerase reaction, $k_{-2}/k_1 \approx 2[P]/[S]$ [42]). Many enzymes with similar parameters have been characterized in the BRENDA database [41]. Then, with $[S] \sim [P] \sim 1$ mM and with $\delta k_{1,2}/k_{1,2} \sim 10\%$, we get $J_{pump}\sim J_{pump}^{(2)} \sim 10^{-2}/T_0, J_{cl} \sim 10^{-1}$, and $J_{cl}^{(2)} \sim 10$ particles per second. Oscillation periods of $\sim 1$ s are attainable (and still satisfy $\omega \ll k_m$), which puts the flux ratio at $\sim 10^{-1}$. Different dependence on $\phi$ can further improve detectability of $J_{pump}$ compared to $J_{cl}$. At these parameters, the pump flux becomes equal to the total flux standard deviation for an experiment lasting a few days. Alternatively, working with, say, $\sim 10^6$ enzymes, $J_{pump}$ and $J_{pump}^{(2)}$ become observable in less than a minute. While real experiments will certainly have additional complications, it is clear that our predictions should be experimentally testable, at least in principle.

In conclusion, we constructed the Berry phase theory of a purely classical adiabatic stochastic pump in a simple Michaelis-Menten enzymatic mechanism. Our approach allowed calculation of the particle flux and its variance, including the classical and the pump effect contributions. We believe that these predictions can be checked experimentally, and it should be interesting to consider their importance in the context of enzymatic signal processing.

While we analyzed only one specific model system, the Berry phase approach is general and can be employed for many processes that can be reduced to slowly driven Markov dynamics. Examples range from charge transport in quantum dots at strong decoherence, to particle transport through cell membrane channels, and to various biochemical reaction systems. For these problems, our method has several advantages compared to already known techniques. First, it provides a formal recipe for an analysis of an arbitrary Markov chain: one should construct a Hamiltonian with counting fields, find its eigenvalue with the lowest real part and the Berry curvature from the corresponding eigenstate, and then the counting statistics is given by eqs. (15), (17). Second, the method provides a solution not only for average fluxes,
but also for the full counting statistics and thus for all flux cumulants. This is important in the context of elimin- 
ation of fast degrees of freedom for construction of coarse-
grained biochemical reaction models (e.g., MM or Hill 
phenomenological laws), where a correct treatment of 
noise in the remaining degrees of freedom has always 
been a point of contention. Third, the method allows to 
transfer many results of the well-developed Berry phase 
theory for dissipative quantum dynamics [43–45] to the 
field of chemical kinetics. In particular, techniques exist to extend 
our work and to calculate flux cumulants to all orders in 
\( \omega/k_{\text{min}} \) [46].

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