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Non-cyclic geometric phase in stochastic processes: corrections to Michaelis-Menten kinetics and application to a cell growth model.

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We generalize the concept of the geometric phase in stochastic kinetics to a noncyclic evolution. Its application is demonstrated on kinetics of the Michaelis-Menten reaction. It is shown that the noncyclic geometric phase is responsible for the correction to the Michaelis-Menten law when parameters, such as a substrate concentration, are changing with time. We also discuss a model, where this correction qualitatively changes the outcome of reaction kinetics.

I. INTRODUCTION

After the Berry's discovery of geometric phases in periodically driven quantum mechanical systems[1], a number of its generalizations were proposed e.g. to nonabelian and nonadiabatic regimes. Similar geometric phases were also found in other fields, for example, in dissipative dynamics[2–5].

Recently, new geometric phases where found in the domain of purely classical stochastic kinetics[6–8]. They were shown to be responsible for the stochastic pump and other ratchet-like effects, and thus they are of certain importance for the theory of molecular motors, operating in strongly stochastic environment[9,10]. This finding raises the question of existence and meaning of possible generalizations of such a geometric phase. For example, recently its nonadiabatic counterpart was introduced in Ref. 11, and was shown to be responsible for a non-adiabatic current contribution, that has no analog under stationary conditions.

In this Letter, another generalization of the geometric phase in stochastic kinetics, namely to a noncyclic evolution in the parameter space, is considered. Its quantum and optical versions were explored in a series of studies[12–20]. However, the role of noncyclic geometric phase in quantum physics still remains mainly unclear, although identities have been found that relate it to a system susceptibility[13]. In this work, we show that the gauge invariant noncyclic geometric phase in stochastic kinetics can be unambiguously defined, and that it can be naturally interpreted as being responsible for the leading nonadiabatic correction in the expression for stochastic fluxes, which can qualitatively change kinetics of a chemical reaction.

II. GENERATING FUNCTION FOR THE MICHAELIS-MENTEN REACTION

The Michaelis-Menten (MM) reaction[21] is the most fundamental and simplest type of biochemical processes. It describes a conversion of one type of molecules, called the substrate, into another type, called the product, via an intermediate reaction with one more type of molecules called enzymes. Schematically the MM reaction can be represented as follows,

$$S + E \underset{k_{-1}}{\overset{k_1 n_s}{\rightleftharpoons}} SE \underset{k_{-2} n_p}{\overset{k_2}{\rightleftharpoons}} E + P, \tag{1}$$

where S and P denote substrate and product respectively, and E represents enzyme molecules. S and P interact via creating a complex SE which is unstable and dissociates either back into E and S or forward into E and P. Enzymes are not modified after this reaction. Their role is to speed up the substrate-product conversion. We assumed that the rates to create the SE-complex are proportional either to substrate or to product concentrations n_s and n_p, while the complex dissociation rates are independent of those concentrations.

Originally, Michaelis and Menten considered a strongly nonequilibrium situation when the process with the coefficient k_{-2} can be neglected due to smallness of the number of product molecules. However, we will keep it for generality because all kinetic rates can be of the same order, at least near the thermodynamic equilibrium. If the number of S and P molecules is much larger than that of enzymes, the latter have to pass through many cycles of the reaction (1) in order to change S and P concentrations noticeably. This fact was employed by Michaelis and Menten to simplify the enzyme-mediated dynamics by assuming that enzymes quickly equilibrate at current substrate and product concentrations.

Stochastic kinetics of the conversion of S into P is suitably described by the moments generating function $Z(\chi,t)$ (mgf) and the cumulants generating function $S(\chi,t)$ defined as[6,22,23]

$$Z(\chi,t)=e^{S(\chi,t)}=\sum_{n=-\infty}^{\infty}P_n e^{in\chi}, \tag{2}$$

where P_n is the probability to find totally n product molecules generated during the observation time t. For a small number of enzymes, their reaction events can be considered statistically independent, so the cumulants generating function is simply their number times the generating function of molecules produced via a single enzyme. Thus we will restrict our study only to the case of a single enzyme in the system. It is convenient also to introduce generating functions $U_E=\sum_{n=-\infty}^{\infty}P_{nE}e^{in\chi}$ and $U_{SE}=\sum_{n=-\infty}^{\infty}P_{nSE}e^{in\chi}$, where P_{nE} is the probability that at a given time the number of generated product molecules is n and the enzyme is in the unbound state. Respectively, P_{nSE} is the probability that enzyme is bound into the SE-complex while the number of product molecules generated is again equal to n. The master equation in such a case reads

$$\begin{aligned}\tfrac{d}{dt}P_{nE}&=-(k_1n_s+k_{-2}n_p)P_{nE}+k_{-1}P_{nSE}+k_2P_{(n-1)SE},\\ \tfrac{d}{dt}P_{nSE}&=-(k_{-1}+k_2)P_{nSE}+k_1n_sP_{nE}+k_{-2}n_pP_{(n+1)E}.\end{aligned} \tag{3}$$

Multiplying (3) by $e^{i\chi n}$ and summing over n we find the equation for generating functions,

$$\frac{d}{dt}\begin{pmatrix}U_E\\U_{SE}\end{pmatrix}=-\hat{H}(\chi,t)\begin{pmatrix}U_E\\U_{SE}\end{pmatrix}, \tag{4}$$

where

$$\hat{H}(\chi,t)=\begin{pmatrix}k_1n_s+k_{-2}n_p & -k_{-1}-k_2e^{i\chi}\\ -k_1n_s-k_{-2}n_pe^{-i\chi} & k_{-1}+k_2\end{pmatrix}. \tag{5}$$

If we set $n=0$ at initial moment $t=0$, then the initial conditions for (4) are $U_E(t=0)=p_E(0)$, and $U_{SE}(t=0)=p_{SE}(0)$, where $p_E(0)$ and $p_{SE}(0)$ are probabilities that the enzyme is respectively free or in the substrate-enzyme complex. Also, note that $Z(\chi,t)=U_E(\chi,t)+U_{SE}(\chi,t)$. The formal solution for the mgf (2) thus can be expressed as the following average of the evolution operator

$$Z(\chi,t)=\langle 1|\hat{T}\left(e^{-\int_0^t\hat{H}(\chi,t)dt}\right)|p(0)\rangle, \tag{6}$$

where $\langle 1|=(1,1)$, and $|p(0)\rangle=(p_E(0),p_{SE}(0))$ is the vector of initial probabilities of enzyme states, and $\hat{T}$ is the time-ordering operator.

Before we proceed with the case where parameters are time dependent, it is instructive to look first at the stationary regime. To simplify (6) one can find normalized left and right eigenvectors $\langle u_{0/1}|$, $|u_{0/1}\rangle$ and corresponding eigenvalues $\epsilon_{0/1}$ of the "Hamiltonian" $\hat{H}(\chi)$, where indeces 0 and 1 correspond to two eigenvalues with respectively lower and larger real parts. There is one left and one right eigenvectors for each eigenvalue.

Every vector, such as $|p(0)\rangle$ can be expressed as a sum of eigenvectors of $\hat{H}(\chi)$, for example,

$$|p(0)\rangle=\langle u_0|p(0)\rangle|u_0\rangle+\langle u_1|p(0)\rangle|u_1\rangle, \tag{7}$$

where we define $\langle\alpha|\beta\rangle=\alpha_1\beta_1+\alpha_2\beta_2$ to be a standard scalar product of two vectors. Substituting (7) into (6), for the time-independent Hamiltonian we find the steady state mgf,

$$Z_{st}(\chi,t)=e^{-\epsilon_0(\chi)t+\ln(\langle 1|u_0\rangle\langle u_0|p(0)\rangle)}+e^{-\epsilon_1(\chi)t+\ln(\langle 1|u_1\rangle\langle u_1|p(0)\rangle)}, \tag{8}$$

At time scales $t\gg 1/k_{-1},1/k_2,1/(k_1n_s),1/(k_{-2}n_p)$, the second term in (8) is exponentially suppressed in comparison to the first exponent, because we assumed that $Re(\epsilon_1)>Re(\epsilon_0)$, and the expression for the mgf simplifies,

$$Z_{st}(\chi,t)\approx e^{-\epsilon_0(\chi)t+\ln(\langle 1|u_0\rangle\langle u_0|p(0)\rangle)}. \tag{9}$$

The role of the term $-\epsilon_0(\chi)t$ in (9) has been studied previously[6,23]. The second part is new. It does not grow with time. This is the boundary term, that depends on the initial conditions and the averaging over the final states of the enzyme. One can safely disregard it in comparison to the first contribution after a long measurement time, however,

we note that its relative effect decays as $1/t$, i.e. not exponentially. We will keep the boundary term in the following discussion because it will play an important role to restore the gauge invariance of the noncyclic geometric phase. At first look, it leads to a contradictory result after setting $t \to 0$, i.e at the initial moment of the evolution. In this limit, the boundary term does not disappear, namely

$$S_{bound}^{t=0} = \ln\left(\langle 1|u_0(0)\rangle\langle u_0(0)|p(0)\rangle\right) \neq 0. \tag{10}$$

One can expect $S_{bound}^{t=0}$ to be zero, because at the initial moment the number of new product molecules is zero, so the mgf should be identically equal to unity. The resolution of this problem can be found if we notice that (14) was derived after a coarse graining process, so it should be valid only at time scales much larger than the time-scale of a single elementary chemical reaction event. Hence the boundary term is responsible for the initial fast relaxation to the stationary regime. For more insight, one can calculate the contribution of the boundary term to the average number of product molecules. Using the normalization condition $p_{SE}(0) = 1 - p_E(0)$ one can find

$$\delta N_p^b = -i\left(\frac{\partial S_{bound}^{t=0}}{\partial \chi}\right)_{\chi=0} = \frac{(k_2 + k_{-2}n_p)(k_2 + k_{-1} - Kp_E(0))}{K^2}, \tag{11}$$

where $K = k_{-1} + k_2 + k_1 n_s + k_{-2} n_p$. If one assumes that the initial probability $p_E(0)$ for the enzyme to be free is at the equilibrium value, i.e. $p_E(0) = (k_2 + k_{-1})/K$, then Eq. (11) returns $\delta N_p^b = 0$, as expected. One can also derive (11) by a standard master equation approach. Calculating the average number of new product molecules $\delta N_p(t)$, one would find that after sufficiently long time

$$\delta N_p(t) = \delta N_p^b + \frac{k_1 k_2 n_s - k_{-1} k_{-2} n_p}{K} t \tag{12}$$

The second term in Eq. (12) is the average number of product molecules produced during time t at a steady state. It is the standard prediction of the MM-theory, and the first term is a correction, which is nonzero when the initial state of enzymes is not the same as in a steady state.

III. NONCYCLIC GEOMETRIC PHASE IN STOCHASTIC KINETICS.

Assume now that there are several slowly time-dependent parameters in the model. We will group them in a vector λ. In case of MM-reaction, one can consider that such time-dependent parameters are concentrations of substrate and product ($\lambda = (n_s, n_p)$). However, the discussion in this section is completely general.

Following Ref. 6 we split the time interval into pieces at which kinetic rates can be considered almost constant, and insert the resolution of the identity operator ($\hat{1} = |u_0(t)\rangle\langle u_0(t)| + |u_1(t)\rangle\langle u_1(t)|$) in (6) after every such an interval. One can find then that the boundary term becomes $S_{bound} = \ln\left(\langle 1|u_0(t)\rangle\langle u_0(0)|p(0)\rangle\right)$. Importantly, it is no longer gauge invariant, i.e. it is sensitive to the redefinition of eigenstates of the Hamiltonian (5) such as $|u_0\rangle \to e^{\phi(\lambda)}|u_0\rangle$ and $\langle u_0| \to \langle u_0|e^{-\phi(\lambda)}$. Therefore alone it has no direct physical meaning. It will be convenient to rewrite it as a sum of a gauge invariant part and a term that is an integral from a pure derivative, i.e.

$$S_{bound} = S_{bound}^{t=0} + \int_{\mathbf{c}} \mathbf{P} \cdot d\lambda, \quad \mathbf{P} = \partial_\lambda \ln\langle 1|u_0\rangle, \tag{13}$$

where $\mathbf{c}$ is the contour in the variable parameter space. By analogy with Ref. 6, and including the boundary contribution (13), the moments generating function in the adiabatic limit can be written as the exponent of the sum of two terms

$$Z(\chi) = e^{S_{geom}(\chi) + S_{qst}(\chi)}, \tag{14}$$

where

$$S_{qst}(\chi) = -\int_0^t \epsilon_0(\chi, t')dt' + S_{bound}^{t=0} \tag{15}$$

is the quasistationary part of the generating function averaged over time. This is the part that transfers into the steady state result (9) for fixed values of all parameters. Another term in (14) is

$$S_{geom} = \int_{\mathbf{c}} [\mathbf{P}(\lambda) - \mathbf{A}(\lambda)] \cdot d\lambda, \quad \mathbf{A}(\lambda) = \langle u_0|\partial_\lambda u_0\rangle. \tag{16}$$

It is the geometric phase contribution responsible for additional reaction events. It has no analog in a strict steady state regime. Here, unlike Ref. 6 we do not assume a cyclic evolution of parameters, and therefore the term in the integral of the Berry connection $\mathbf{A}$ over the path in the parameter space ($-\int_c \mathbf{A}(\lambda)\cdot d\lambda$) should not be gauge invariant. However, one can easily check that the non-gauge-invariant contribution due to the boundary term exactly cancels the non-gauge-invariant part of the contour integral from $\mathbf{A}$.

Here we would like to mention that the definition (16) is similar but differs from the most often encountered definitions of the non-cyclic geometric phase in quantum mechanics. For example, Pati *et al.*[12,13] suggested that the noncyclic geometric phase is given by $\gamma_{gp} = \int_c [\mathbf{A}(\lambda) - \mathbf{P}(\lambda)] \cdot d\lambda$, where $\mathbf{P} = -\Im\left(\frac{\langle u(\lambda(0))|\partial_\lambda u(\lambda)\rangle}{\langle u(\lambda(0))|u(\lambda)\rangle}\right)$. In the present context the meaning of this definition is unclear, while the geometric phase defined in (16) is derived directly from the exact representation of the generating function.

Since $\mathbf{P}$ is a pure gauge, it is important only when looking at an evolution along an open path in the parameter space. If the parameter vector λ returns to its initial value at the end of the evolution, the expression (16) becomes equivalent to the cyclic geometric phase defined in Ref. 6.

IV. CORRECTIONS TO MICHAELIS-MENTEN LAW

Consider now the average current in the Michaelis-Menten system under the condition of slow parameter evolution. The average number of new product molecules is $\langle \delta N_p(t)\rangle = -i\,(\partial Z(\chi,t)/\partial\chi)_{\chi=0}$. Like the cumulants generating function, the average rate of P-molecule production $\langle J_p\rangle = d\langle \delta N_p(t)\rangle/dt$ can be written as a sum of quasistationary J_{qst} and the geometric phase J_{geom} contributions

$$\langle J_p\rangle = J_{geom} + J_{qst} = \frac{d}{dt}\left(\frac{\partial S_{geom}}{\partial\chi}\right)_{\chi=0} + \left(\frac{\partial \epsilon_0(\chi,t)}{\partial\chi}\right)_{\chi=0}. \tag{17}$$

The geoemtric phase is time-dependent only via the time-dependence of the parameter vector λ. In the case of MM-reaction with time-dependent concentrations n_s and n_p, the time derivative of the first term in (17) can be expressed as $d/dt \to (dn_s/dt)\partial/\partial n_s + (dn_s/dt)\partial/\partial n_p$. Substituting the eigenvectors and eigenvalues of $\hat{H}(\chi,\lambda)$ into (17) we then find

$$J_{qst} = \frac{(k_1 n_s(t))k_2 - (k_{-2}n_p(t))k_{-1}}{K}, \tag{18}$$

$$J_{geom} = -(k_2+k_{-1})\frac{(k_2+k_{-2}n_p(t))(k_1\dot{n}_s(t) + k_{-2}\dot{n}_p(t))}{K^3}. \tag{19}$$

One can recognize J_{qst} as the average current that would be in the steady state of the system at fixed values of parameters. In fact, (18) is what is known as the Michaelis-Menten law. Our results, however, show that this law is not exact when concentrations of substrate and product have their own time-dependent evolution. The geometric contribution is the first correction to the Michaelis-Menten kinetics that becomes nonzero when substrate/product concentrations change with time. In the most frequently found case when $n_p \approx 0$, the average rate of the coarse grained MM-reaction per one enzyme becomes

$$\langle J_p\rangle \approx \frac{k_2 n_s}{n_s + \frac{k_2+k_{-1}}{k_1}} - (k_2+k_{-1})\frac{k_2 k_1 \dot{n}_s(t)}{(k_1 n_s + k_2 + k_{-1})^3}, \tag{20}$$

i.e. even in this case, the time-dependence of the substrate concentration introduces corrections to the reaction rate.

It is possible to understand the result (19) with a simpler approach, however, which is hard to generalize to describe higher current cumulants and demonstrate geometric nature of the effect. The probability P_e of the enzyme to be unbound evolves according to the master equation

$$\frac{d}{dt}p_E = -[k_1 n_s(t) + k_{-2}n_p(t)]p_E + (k_2+k_{-1})(1-p_E), \tag{21}$$

with a solution

$$p_E(t) = (k_2+k_{-1})\int_0^t e^{-\int_{t_1}^t [k_1 n_s(\tau) + k_{-2}n_p(\tau) + k_2 + k_{-1}]d\tau} dt_1. \tag{22}$$

The lower limit in this integral is not important because we work in the adiabatic approximation, which means that the information about the initial state is quickly erased. Then the exponent of the integral over τ in (22) can be approximated by

$$e^{-\int_{t_1}^{t}[k_1 n_s(\tau)+k_{-2}n_p(\tau)+k_2+k_{-1}]d\tau} \approx e^{-[k_1 n_s(t)+k_{-2}n_p(t)+k_2+k_{-1}](t-t_1)}\left(1+\frac{k_1\dot{n}_s(t)+k_{-2}\dot{n}_p(t)}{2}(t-t_1)^2\right). \quad (23)$$

Performing the remaining integration we find the expression for the probability of the enzyme to be unbound.

$$p_E \approx \frac{k_2+k_{-1}}{K}+\frac{(k_2+k_{-1})(k_1\dot{n}_s(t)+k_{-2}\dot{n}_p(t))}{K^3}. \quad (24)$$

From (24), one can calculate the average reaction rate and check that indeed, it is the sum of the quasi-stationary and geometric components determined in (18) and (19),

$$J(t)=(1-p_E(t))k_2-p_E(t)k_{-2}n_p(t)=J_{qst}+J_{geom}. \quad (25)$$

V. MODEL OF CELL GROWTH.

Generally, the geometric correction (19) should be much smaller than the main contribution (18) when the enzyme concentration is much smaller than that of substrates and products. However, this correction has very different properties, and thus can change a system behavior under special conditions. Similar situations are common in the solid state physics, where the Berry phase was found to be responsible for a number of important phenomena such as anomalous and spin Hall effects[24,25]. Hall currents in these systems are weak, however, they originate from a geometric phase that creates the force that breaks symmetries respected by other current sources. So ignoring such geometric phases would miss a number of effects, that play quite an important role in the modern solid state physics despite their relative weakness.

In biochemistry, the quasi-steady state contribution to the kinetic rate can also be vanishing due to a symmetry relation, such as the detailed balance condition, which guaranties that all chemical fluxes at the thermodynamic equilibrium state are zero on average. Thus, if a system is slowly driven externally so that it always remains close to the thermodynamic equilibrium, the quasi-steady state approximation does not predict appearance of extra product molecules on average. Contrary to this, the geometric contribution does not have to remain zero. The following model of a reaction induced by a cell growth is a biochemical example of such a situation.

Consider the MM-reaction with concentrations of substrate and product n_s and n_p, that we will treat deterministically. Lets initially the system is at an equilibrium,

$$k_1k_2n_s(0)=k_{-1}k_{-2}n_p(0). \quad (26)$$

Next we assume that due to a cell growth, concentrations decrease with time by the same factor $v(0)/v(t)$,

$$n_s(t)=n_s(0)\frac{v(0)}{v(t)}, \quad n_p(t)=n_p(0)\frac{v(0)}{v(t)}, \quad (27)$$

where $v(t)$ is the cell volume. Since the ratio $n_s(t)/n_p(t)$ is not affected by this time dependent dilution, the quasi-steady state reaction rate remains zero.

Due to the living cell growth and divisions, the volume increases from $v(0)$ to the formally infinite value. If concentrations always satisfy the condition (26), then the average number of new product molecules, produced by a single enzyme is completely determined by a geometric part of the kinetic rate (19),

$$\delta N_p=\int_{v(0)}^{\infty}dv\left[-(k_2+k_{-1})\frac{(k_2+k_{-2}n_pv(0)/v)(k_1\partial_v(n_s(0)v(0)/v)+k_{-2}\partial_v(n_p(0)v(0)/v)}{K^3(v)}\right]= \quad (28)$$

$$\frac{k_1k_2n_s(0)}{(k_2+k_{-1})(k_{-1}+k_1n_s(0))}.$$

On one hand, this effect is very small. The results of (28) is that the average number of new product molecules per one enzyme is a fraction of unity, while we considered that there is a large number of already existing substrate and product molecules. On another hand, for this model, the geometric contribution qualitatively changes the result, predicting on average nonzero amount of new product molecules, which is not expected from the standard Michaelis-Menten kinetics.

The result (28) would be valid only if we can treat concentrations as parameters, changing only due to the volume growth. In a closed system chemical fluxes eventually should be compensated by the reverse fluxes due to the violation of the steady state condition (26). Thus the geometric flux should be possible to detect by measuring the deviation of the ratio n_s/n_p from the one for a nongrowing volume.

Considering intermediate stages of the cell expansion, the number of newly produced molecules depends only on the initial and final volumes, i.e. the average number of produced proteins depends on the stage of the evolution but not on its rate, which could be utilized by living organisms in order to control some processes depending on the stage of cell's life cycle. Unfortunately effect is very small to say that it can definitely be used by living cells. However, it should be interesting to explore its detectability *in vivo* and employ it in an artificial biochemical circuit design.

VI. DISCUSSION.

We generalized the notion of the geometric phase in evolution of the moments generating function to the non-cyclic processes. For this, the contour integral from the Berry connection should be supplemented by an extra term, which restores the gauge invariance of the geometric contribution to the cumulants generating function. This term originates from the boundary contribution responsible for proper description of the initial and final moments of the measurement.

In a case of nonequilibrium initial conditions the boundary terms are responsible for the initial fast relaxation to the steady state, i.e. although our approach is adiabatic, it also rigorously captures initial fast relaxation effects. Our non-cyclic geometric phase is different from the ones often encountered in quantum mechanical applications. Its uniqueness follows from the existence of a special gauge that should be imposed in order to describe stochastic kinetics correctly.

We showed that our phase is responsible for nonadiabatic corrections to the standard Michaelis-Menten approximation. Such corrections are usually small in comparison to the quasi-steady state prediction, however, they explicitly break time-reversal symmetries, and therefore can produce a qualitatively different result when a chemical system is driven closely to a thermodynamic equilibrium, as in the model of a cell growth that we studied in this work.

It is by now unclear whether this effect can be utilized by living cells, considering its smallness. However, we note that we studied only the simplest its realization. The introduced noncyclic geometric phase is completely general and should appear practically in any interacting chemical system, driven by external fields. Other interesting realizations can follow, for example, from the theory of molecular motors, where geometric effects play an important role[10].

It would also be very interesting to find out whether the noncyclic geometric phase is related to the existence of fluctuation theorems[26]. Indeed, instead of chemical fluxes, it is possible to use the same formalism to count work or dissipated energy in a driven stochastic system. The absence of anholonomies, such as cyclic geometric phases may indicate the existence of fluctuation relations, because then the counting statistics depends only on initial and final values of external parameters, at least in the adiabatic limit. Generalizations of our approach to a nonadiabatic evolution should also be possible, since similar generalizations simultaneously to a noncyclic and nonadiabatic evolution in quantum mechanics have been developed previously[27].

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