Low frequency limit for thermally activated escape with periodic driving

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Abstract

The period-average rate in the low frequency limit for thermally activated escape with periodic driving is derived in a closed analytical form. We define the low frequency limit as the one where there is no essential dependence on frequency so that the formal limit $\Omega \to 0$ in the appropriate equations can be taken. We develop a perturbation theory of the action in the modulation amplitude and obtain a cumbersome but closed and tractable formula for arbitrary values of the modulation amplitude to noise intensity ratio $A/D$ except a narrow region near the bifurcation point and a simple analytical formula for the limiting case of moderately strong modulation. The present theory yields analytical description for the retardation of the exponential growth of the escape rate enhancement (i.e., transition from a log-linear regime to more moderate growth and even reverse behavior). The theory is developed for an arbitrary potential with an activation barrier but is exemplified by the cases of cubic (metastable) and quartic (bistable) potentials.

Keywords: Kramers’ theory, thermally activated escape, periodic driving.

1 Introduction

Thermally activated escape over a potential barrier is ubiquitous in physics, chemistry and biology (see [1], [2], [3], [4], [5] and refs. therein). This phenomenon is important for both quantum [1], [2], [6], [7], [8], [9] and classical [1], [2], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23] systems. It can proceed in strong friction (overdamped), weak friction (underdamped) and needless to say intermediate regimes (see refs. above). The case of thermally activated escape unperturbed by additional external influences pioneered by Kramers is exhaustively investigated and by now is a well understood phenomenon.

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However in most physical realizations the thermally activated escape is modulated by some external driving. In this case the stationary limit that may be a rather good approximation in the absence of external driving is already inapplicable. In the presence of the latter the system becomes intrinsically non-equilibrium and the problem in known to be notoriously difficult for analytical treatment [2]. The particular case of periodically driven escape [2], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23] is relevant among others for chemical physics [26], [24], [25] (where a chemical reaction can be influenced by, e.g., laser electric field) and enzymology [27] (where an enzymatic reaction can be influenced by an oscillating electric field produced by the dynamics of protein structure [28]). According to [17] the periodic driving force “heats up” the system by changing its effective temperature thus giving rise to lowering of the activation energy of escape which can be much bigger than the real temperature even for comparatively weak fields”.

Revealing the physical aspects of enzyme action may well become one of the most important grounds for application of the periodically modulated thermally activated escape theory. In support of this point of view it is worthy to note that understanding the role of driving at activated escape in biological systems is considered by the authors of [17] as "a fundamentally important and most challenging open scientific problem”. The reasons for the above statement are as follows. The problem of enzyme catalysis is the main unsolved interdisciplinary enigma of molecular biophysics, biochemistry and needless to say enzymology. Up to now there is no definite and commonly accepted understanding of "how does an enzyme work?" (see, e.g., heat controversy at a recent conference in the subject issue of Phil. Trans. R. Soc. B (2006) 361). The idea that dynamical effects may play a crucial role at enzyme action is very popular at present and the concept of the so-called rate promoting vibration is a central one in modern enzymology. However the practitioners engaged in chemical enzymology traditionally discuss the phenomenon of enzyme catalysis in terms and notions of the transition state theory (as can be seen from the materials of the above mentioned conference). The latter is essentially equilibrium one that is embedded into its cornerstone postulate and is poorly suited for taking into account dynamical effects in a reaction rate. The main tool to study such effects is the Kramers’ theory [1], [2], [5], [29]. Regrettfully at present this theory is much less known and necessitated for applications in enzymology than its transition state theory counterpart.

The thermally activated escape problem at periodic driving in the overdamped classical regime was conceptually solved in the papers [11], [12], [13], [14], [15], [16], [18], [19], [20], [21], [22], [23]. Two mutually complementary theories [11], [12], [13] and [14], [15], [20], [21], [22], [23] provide deep insights on the behavior of many physical values of interest. They are based on a physical idea of the optimal path and are able to provide an imaginable picture of the process. The papers [2], [14], [17] provide description of the escape rate
enhancement at weak modulation (the so-called log-linear regime) where the change of the activation energy is linear in the modulation amplitude. Most important of all, the escape rate enhancement exhibits the replacement of the log-linear regime by more moderate growth with the increase of modulation amplitude to noise intensity ratio. Such behavior for the intermediate regime of moderately strong and moderately fast driving is well described by the \cite{11}, \cite{12} theory that is corroborated by high-precision numerical results. The scaling behavior of the prefactor near the bifurcation point is investigated in details \cite{20}, \cite{21}, \cite{22}, \cite{23}. In particular the so called adiabatic regime is most thoroughly investigated \cite{2}, \cite{18}, \cite{22}, \cite{23}. This regime is defined by the authors of \cite{14}, \cite{15}, \cite{17}, \cite{20}, \cite{21}, \cite{22}, \cite{23} as the limit of slow modulation $\Omega << 1$ where ”the driving frequency is small compared to the relaxation rate in the absence of fluctuations and the system remains in quasi-equilibrium” and by the authors of the \cite{11}, \cite{12}, \cite{13} theory as the one that ”goes up to driving frequencies of the order of the inverse instanton time which is related to the curvatures of the potential”. In the adiabatic regime the scaling behavior of the prefactor for the cubic potential is given by a simple analytical formula \cite{22}, \cite{23}.

However the existing literature leaves room for parallel activity for the following reasons. To attract attention of chemists and biochemists to the modulated thermally activated escape theory within the Kramers’ approach it is necessary to present its final results in as simple and understandable form as is done, e.g., in the transition state theory. On the contrary the results of both \cite{11}, \cite{12}, \cite{13} and \cite{14}, \cite{15}, \cite{20}, \cite{21}, \cite{22}, \cite{23} theories are presented via involved notions and values characterizing the optimal action corresponding to the minimizing path. Correct making use of these results requires profound comprehension of their physical content and mastering in depth the methods involved in their deriving. As a matter of fact people engaged in applications (whom the author of the present manuscript belongs to) as a rule are concerned with much more modest objective: how at a given combination from the parameter space (noise intensity $D$, modulation amplitude $A$, modulation frequency $\Omega$ and characteristics of the static potential $U(x)$) to evaluate the escape rate enhancement in the presence of driving at least for a simple analytically smooth (i.e., not piecewise) metastable or bistable potential? That is why it is desirable to have the period-average escape rate in a closed analytical form and explicitly expressed only via the parameters $D$, $A$, $\Omega$ and characteristics of the static potential $U(x)$ including no other physical values. In other words a theory convinient for applications should restrict the physical content of the resulting formula only by the notions used at initial setting the problem. Besides both \cite{11}, \cite{12}, \cite{13} and \cite{14}, \cite{15}, \cite{20}, \cite{21}, \cite{22}, \cite{23} theories invoke to rather sophisticated methods such as, e.g., path integrals technique. The initial mathematical formulation of the problem is a partial differential equation and it seems interesting to see what results can be obtained among others by means of usual mathematics. These reasons motivate
the appearance of the present manuscript. Our aim is to derive by means of elementary methods a closed analytical form of the formula for the escape rate enhancement in the low frequency limit for arbitrary values of the modulation amplitude to noise intensity ratio $A/D$ except a narrow region near the bifurcation point. Our approach is not based on a physical idea a priory inserted into the theory but rather is a direct purely mathematical treatment of the problem. We define the low frequency limit as the one where there is no essential dependence on frequency so that the formal limit $\Omega \to 0$ in the appropriate equations can be taken. At the same time we observe the requirement $\Gamma_K << \Omega$ (where $\Gamma_K$ is the stationary Kramers’ rate) that is necessary for the efficient averaging over the period to be possible. The latter means that all interesting phenomena related to the so called stochastic resonance (taking place at $\Omega = \pi \Gamma_K$) are beyond the scope of the present theory. As the value $\Gamma_K \propto \exp[-(U_{\text{max}} - U_{\text{min}})/D]$ is usually vanishingly small there certainly should be a range (perhaps $\Gamma_K << \Omega << D$) where the contradictory requirements $\Gamma_K << \Omega$ and $\Omega \to 0$ can be reconciled. As this range turns out to be more restricted than that of slow modulation $\Omega << 1$ we use the term low frequency limit instead of adiabatic regime to avoid confusion.

The manuscript is organized as follows. In Sec.2 the problem is formulated and its solution is argued to be sought by perturbation technique for the action in powers of the modulation amplitude. Sec.3 and Sec.4 are devoted to the first and second order contributions into action respectively. In Sec.5 the results are combined in a closed form for the escape rate enhancement in the low frequency limit. In Sec.6 the formula is used to obtain plots. In Sec.7 a simple analytical formula for the limiting case of moderately strong modulation $D << A << \sqrt{D}$ is obtained. In Sec.8 the results are discussed and the conclusions are summarized. In the Appendix some technical details are presented.

2 Formulation of the problem

2.1 Setting the stage

In this preliminary Sec. we pose the problem and remind some facts on the Kramers’ theory to introduce designations and notions used further. In the Kramers’ model a chemical reaction is considered as the escape of a Brownian particle from the well of a potential $U(x)$ along the reaction coordinate $x$ with $x_a$ being the point of the bottom of the well and $x_b$ being the point of its top. The problem of interest is to take into account the presence of periodic driving with modulation amplitude $A$ and frequency $\Omega$. For the driving we
adopt without any serious loss of generality the commonly used form

\[ f(t) = A \sin(\Omega t) \]  

(1)

The results obtained for this simplest case can be directly generalized to any arbitrary periodic driving because the latter can be expanded into a Fourier series. In the overdamped limit (strong friction case) the Fokker-Planck equation (FPE) for the probability distribution function \( P(x, t) \) is

\[ \dot{P}(x, t) = -F'(x)P(x, t) - \left[ F(x) + f(t) \right] P'(x, t) + DP''(x, t) \]  

(2)

where the dot denotes a derivative in time, the prime denotes a derivative in coordinate, \( F(x) = -U'(x) \) is the time independent force field and \( D \) is the so called noise intensity that is actually the ratio of temperature in energetic units to the barrier height. In the absence of periodic driving \( (f(t) = 0) \) the stationary limit of (2) is

\[ 0 = \dot{P}(x, t) = -\left[ F(x)P(x, t) - DP'(x, t) \right] ' \]  

(3)

which can be integrated to yield for the stationary (Kramers’) probability distribution function \( P_K(x) \) the equation

\[ J = -DP'_K(x) + F(x)P_K(x) \]  

(4)

where \( J \) is the stationary flux. If we adopt the boundary condition as the absorption \( P_K(x_c) = 0 \) at some point \( x_c \) (with \( x_c > x_b \) where \( x_b \) is the barrier top) then we have

\[ P_K(x) = \frac{J}{D} \exp\left(-U(x)/D\right) \int_x^{x_c} dy \exp\left(U(y)/D\right) \]  

(5)

For the Kramers’ rate (taking into account that \( N = \int_{-\infty}^{x_b} dx \ P_K(x) \approx 1 \) ) we have

\[ \Gamma_K = \frac{J}{N} \approx J \approx \frac{\omega_a\omega_b}{2\pi} \exp\left[-\frac{U(x_b) - U(x_a)}{D}\right] \]  

(6)

where \( \omega_a = \sqrt{U''(x_a)} \) and \( \omega_b = \sqrt{|U''(x_b)|} \).
In the presence of driving the position of the barrier top becomes time dependent \( (q_b(t) \approx x_b - f(t)) \) and the population of the well is

\[
N(t) = \int_{-\infty}^{q_b(t)} dx \ P(x, t) \tag{7}
\]

A convenient operational definition of the reaction rate constant (adopted, e.g., in \[11\], \[12\] and \[13\]) is

\[
\Gamma(t) = -\frac{\dot{N}(t)}{N(t)} \tag{8}
\]

It should be stressed that the behavior of this value is sensitive to the actual choice of the absorption boundary \( x_c(t) \) where we set \( P(x_c(t), t) = 0 \). The requirement we adopt further is that the absorption point should be sufficiently far from the barrier top

\[
x_c(t) - x_b(t) \gg A \tag{9}
\]

This requirement is in accordance with that to measure the current well behind the boundary argued in \[23\].

Let us consider, e.g., the the simplest cubic (metastable) potential \( U(x) = x^2/2 - x^3/3 \) (CP). In this case \( x_a = 0, x_b = 1, \omega_b = 1, \omega_a = 1 \) and \( q_b(t) \approx 1 - A \sin(\Omega t), q_a(t) \approx A \sin(\Omega t) \). By analogy we adopt for the general case

\[
q_b(t) \approx x_b - A \sin(\Omega t); \quad \dot{q}_b(t) = -\dot{f}(t); \quad q_a(t) \approx x_a + A \sin(\Omega t) \tag{10}
\]

For the quartic (bistable) potential \( U(x) = -x^2/2 + x^4/4 \) (QP) we also have \( \omega_b = 1 \) while \( x_a = -1, x_b = 0 \) and \( \omega_a = \sqrt{2} \).

Thus taking into account that \( N(t) \approx 1 \) and \( (2) \) we obtain from \( (8) \)

\[
\Gamma(t) \approx -DP'(q_b(t), t) + [F(q_b(t)) + f(t) + \dot{f}(t)]P(q_b(t), t) \tag{11}
\]

The rate constant averaged over the period of oscillations \( T = 2\pi/\Omega \) is

\[
\Gamma = \frac{1}{T} \int_{t}^{t+T} ds \ \Gamma(s) \tag{12}
\]
Our final aim is to calculate the escape rate enhancement

\[ \Delta \equiv \frac{\Gamma}{\Gamma_K} \approx \frac{1}{TJ} \int_t^{t+T} ds \left[ F(q_b(s)) + f(s) + f'(s) \right] P(q_b(s), s) - \]

\[ \frac{D}{TJ} \int_t^{t+T} ds P'(q_b(s), s) \]  

To attain this goal we will also need the probability distribution function near the bottom of the well that is known to be \([30], [23]\)

\[ P(x, t) \approx \frac{1}{\sqrt{2\pi D\sigma_a^2(t)}} \exp \left\{ \frac{-[x - q_a(t)]^2}{2D\sigma_a^2(t)} \right\} \]  

Here \(\sigma_a(t)\) is the dispersion that can be identified with the inverse frequency of the well \(\sigma_a(t) = 1/\omega_a(t)\). The latter can be evaluated, e.g., for the CP \(\omega_a(t) \approx 1 - f(t)\). By analogy we adopt for the general case

\[ \omega_a(t) \approx \omega_a - f(t) \]  

Substituting \([11]\) and \([15]\) into \([14]\) we obtain

\[ P(x_a, t) \approx \frac{\omega_a - Asin(\Omega t)}{\sqrt{2\pi D}} \exp \left\{ \frac{-\left[Asin(\Omega t)(\omega_a - Asin(\Omega t))\right]^2}{2D} \right\} \]  

2.2 Form of the action

We seek the solution of \([2]\) in the form

\[ P(x, t) = P_K(x)u(x, t) \]  

The form \([17]\) means that

\[ P(x_c, t) = 0 \]  

because \(P_K(x_c) = 0\), i.e., adopting this form we have to neglect the possible dependence of the absorption point \(x_c(t)\) on time in the presence of driving and assume \(x_c(t) = x_c\) where \(x_c\) is that in the absence of driving. The latter may be justified by the requirement \([9]\). In the present approach we adopt
this approximation without further discussing its validity. Substitution of (17) into (13) with taking into account (5) yields for the value of interest

$$\Delta = \frac{1}{T} \int_t^{t+T} ds \ u(q_b(s), s) + \frac{1}{TD} \int_t^{t+T} ds \ \exp\left(-U(q_b(s))/D\right) \times$$

$$\int_{q_b(s)}^{x_c} dy \ \exp\left(U(y)/D\right) \left[ \left[ f(s) + \dot{f}(s) \right] u(q_b(s), s) - Du'(q_b(s), s) \right]$$

(19)

We denote

$$\Psi(x) = \frac{P_K'(x)}{P_K(x)}$$

(20)

For the function $u(x, t)$ we obtain the equation

$$\dot{u}(x, t) = Du''(x, t) -$$

$$\left[ F(x) + f(t) - 2D\Psi(x) \right] u'(x, t) - f(t)\Psi(x)u(x, t)$$

(21)

At $A = 0$ we must have $u(x, t) \equiv 1$ for asymptotically large time that suggests to seek the solution of (21) in the form

$$u(x, t) = \exp[A\alpha(x, t)]$$

(22)

This form can not be exact because in the limit $A \rightarrow 0$ we obtain $P(x, t) = P_K(x)$ that can be valid only asymptotically at $t \rightarrow \infty$. We denote

$$\Phi(x) = 2D\Psi(x) - F(x)$$

(23)

For the function $\alpha(x, t)$ we obtain the equation

$$\dot{\alpha}(x, t) = D\alpha''(x, t) + DA[\alpha'(x, t)]^2 +$$

$$\left[ \Phi(x) - A\sin(\Omega t) \right] \alpha'(x, t) - \Psi(x)\sin(\Omega t)$$

(24)

In the present manuscript we argue the point of view that in the low frequency limit the function $\alpha(x, t)$ can be sought as a perturbation series in the modulation amplitude $A$

$$\alpha(x, t) = \varphi(x, t) + A\chi(x, t) + A^2\mu(x, t) + O(A^3)$$

(25)
The function $\alpha(x, t)$ by its final result in (13) plays the same role as the action from the theories [14], [20], [22], [23] and [11], [12], [13]. That is why we will also use this name.

The results of the present manuscript testify that at least in the low frequency limit $\alpha' \propto 1/D$ so that $u'(x, t) \sim A/D u(x, t)$. Thus taking into account that $f(t) \propto A$ and $\int_{q_b(s)}^{x_c} dy \exp\left(U(y)/D\right) \sim \sqrt{D} \exp\left(-U(x_b)/D\right)$ (see below) we generally have for the escape rate enhancement

$$\Delta \approx \frac{1}{T} \int_t^{t+T} ds \ u(q_b(s), s) \left[1 + O\left(\frac{A}{\sqrt{D}}\right)\right]$$

(26)

Though at large ratios $A/D$ the term $O\left(\frac{A}{\sqrt{D}}\right) \sim 1$ we will not take it into account in the present paper despite of the fact that the method of calculation developed below enables us to treat it. This term seems to give minor correction and its role will be considered elsewhere.

Substituting (25) in (22), (21) and collecting the terms at powers of $A$ we obtain the following system of equations

$$\dot{\varphi}(x, t) = D\varphi''(x, t) + \Phi(x)\varphi'(x, t) - \Psi(x)\sin(\Omega t)$$

(27)

$$\dot{\chi}(x, t) = D\chi''(x, t) + \Phi(x)\chi'(x, t) + D\left[\varphi'(x, t)\right]^2 - \sin(\Omega t)\varphi'(x, t)$$

(28)

$$\dot{\mu}(x, t) = D\mu''(x, t) + \Phi(x)\mu'(x, t) + \left[2D\varphi'(x, t) - \sin(\Omega t)\right]\chi'(x, t)$$

(29)

etc. From (2), (18) and (21) we obtain the boundary conditions

$$\varphi'(x, t) = \frac{1}{2D}\sin(\Omega t); \quad \chi'(x, t) = 0; \quad \ldots$$

(30)

From (16) we obtain

$$\varphi(x, t) = -\frac{1}{\omega_a}\sin(\Omega t); \quad \chi(x, t) = -\frac{\omega_a^2}{2D}\sin^2(\Omega t); \quad \ldots$$

(31)
3 First order contribution into action

3.1 Equations for the first order contribution into action

We start from (27). Its solution for asymptotically large time can be sought in the form

$$\varphi(x, t) = g(x)\sin(\Omega t) + h(x)\cos(\Omega t)$$  \hspace{1cm} (32)$$

From (30) and (31) we obtain the boundary conditions

$$g'(x_c) = \frac{1}{2D}; \quad h'(x_c) = 0$$ \hspace{1cm} (33)$$
$$g(x_a) = -\frac{1}{\omega_a}; \quad h(x_a) = 0$$ \hspace{1cm} (34)$$

Substitution of (32) into (27) yields a system of coupled equations

$$D g''(x) + \Phi g'(x) + \Omega h(x) = \Psi(x)$$ \hspace{1cm} (35)$$
$$D h''(x) + \Phi h'(x) - \Omega g(x) = 0$$ \hspace{1cm} (36)$$

This system is rather difficult for analytical treatment. However in the present manuscript we restrict ourselves by the low frequency limit $\Omega \to 0$. In this case the equations (35), (36) are decoupled

$$g''(x) + \frac{\Phi}{D} g'(x) = \frac{\Psi(x)}{D}$$ \hspace{1cm} (37)$$
$$h''(x) + \frac{\Phi}{D} h'(x) = 0$$ \hspace{1cm} (38)$$

Taking into account that

$$\exp \left[ \frac{1}{D} \int_z^s dr \Phi(r) \right] = \frac{P_K^2(s)}{P_K^2(z)} \exp \left[ \frac{U(s) - U(z)}{D} \right]$$ \hspace{1cm} (39)$$

we obtain the solution of (37), (38) satisfying (33), (34) as

$$g(x) = -\frac{1}{\omega_a} - \frac{1}{D} \int_{x_a}^x dy \frac{\exp \left( \frac{-U(y)}{D} \right)}{P_K^2(y)} \int_{x}^{x_c} dy' P_K^2(y') \exp \left( \frac{U(y)}{D} \right) \Psi(z)$$ \hspace{1cm} (40)$$
\[ h(x) \equiv 0; \quad h'(x) \equiv 0 \quad (41) \]

We substitute \( P_K(x) \) from (3) into (40) and notice that

\[
dy \frac{\exp \left( \frac{U(y)}{D} \right)}{\int_y^x ds \exp \left( \frac{U(s)}{D} \right)} = d \frac{1}{\int_y^x ds \exp \left( \frac{U(s)}{D} \right)} \quad (42) \]

Making use of integration by part and denoting

\[
\Gamma_0(x) = \int_x^{x_c} ds \exp \left( \frac{U(s)}{D} \right) \quad (43) \]

\[
E_1(x) = \int_x^{x_c} dz \Psi(z) \exp \left( -\frac{U(z)}{D} \right) \left[ \int_z^{x_c} ds \exp \left( \frac{U(s)}{D} \right) \right]^2 \quad (44) \]

\[
E_2(x) = \int_x^{x_a} dz \Psi(z) \exp \left( -\frac{U(z)}{D} \right) \int_x^{x_c} ds \exp \left( \frac{U(s)}{D} \right) \quad (45) \]

we obtain

\[
g(x) = -\frac{1}{\omega_a} - \frac{1}{D} \left\{ \frac{1}{\Gamma_0(x)} E_1(x) - \frac{1}{\Gamma_0(x_a)} E_1(x_a) + E_2(x) \right\} \quad (46) \]

Making use of (20) and (5) we obtain

\[
E_1(x) = -\exp \left( -\frac{U(x)}{D} \right) \Gamma_0^2(x) + \int_x^{x_c} ds \exp \left( \frac{U(s)}{D} \right) (s - x) \quad (47) \]

\[
E_2(x) = \exp \left( -\frac{U(x)}{D} \right) \Gamma_0(x) - \exp \left( -\frac{U(x_a)}{D} \right) \Gamma_0(x_a) \quad (48) \]

We recall (11) and denote

\[
S(q_b(t)) = \frac{1}{\Gamma_0(q_b(t))} \int_{q_b(t)}^{x_c} ds \exp \left( \frac{U(s)}{D} \right) (s - q_b(t)) - \frac{1}{\Gamma_0(x_a)} \int_{x_a}^{x_c} ds \exp \left( \frac{U(s)}{D} \right) (s - x_a) \quad (49) \]
\[ \lambda = \frac{\omega_b^2}{2D} \]  

(50)

\[ Q_n(x) = \int_x^{x_c} ds \exp \left[ -\lambda(s - x_b)^2 \right] (s - x)^n \]  

(51)

Making use of N2.3.15.1 from [31] we obtain

\[ Q_n(q_b(t)) \approx n!(2\lambda)^{-\frac{n+1}{2}} \times \]

\[ \exp \left[ -\frac{\lambda A^2 \sin^2(\Omega t)}{2} \right] D_{-(n+1)} \left[ -\sqrt{2\lambda} Asin(\Omega t) \right] \]  

(52)

where \( D_n(x) \) is a parabolic cylinder function. Making use of its known properties we have

\[ Q_0(q_b(t)) = \frac{\sqrt{\pi}}{2\sqrt{\lambda}} \text{erfc} \left[ -\sqrt{\lambda} Asin(\Omega t) \right] \]  

(53)

\[ \Gamma_0 \left( q_b(t) \right) \approx \frac{\sqrt{\pi D}}{\sqrt{2\omega_b}} \exp \left( \frac{U(x_b)}{D} \right) \text{erfc} \left( \frac{-\omega_b Asin(\Omega t)}{\sqrt{2D}} \right) \]  

(54)

\[ Q_1(q_b(t)) = \frac{\sqrt{\pi}}{2\sqrt{\lambda}} Asin(\Omega t) \text{erfc} \left[ -\sqrt{\lambda} Asin(\Omega t) \right] + \]

\[ \frac{1}{2\lambda} \exp \left( -\lambda A^2 \sin^2(\Omega t) \right) \]  

(55)

where \( \text{erfc}(x) \) is an additional error function. Making use of (53) and (55) we obtain (see Appendix for details)

\[ S(q_b(t)) \approx -(q_b(t) - x_a) + O(\sqrt{D}) \]  

(56)

and

\[ g(q_b(t)) \approx \frac{q_b(t) - x_a}{D} - \frac{1}{\omega_a} \]  

(57)

The value \( \frac{1}{\omega_a} \) is negligibly small compared with \( \frac{x_b - x_a}{D} \) and can be omitted. Thus finally we obtain the first order contribution into action as

\[ \varphi(q_b(t), t) \approx \left[ \frac{x_b - Asin(\Omega t) - x_a}{D} \right] \sin(\Omega t) \]  

(58)
4 Second order contribution into action

4.1 Equations for the second order contribution into action

From (28) and the results for the first order contribution into action we obtain

\[
\dot{\chi}(x, t) = D\chi''(x, t) + \Phi(x)\chi'(x, t) + L(x)[1 - \cos(2\Omega t)]
\] (59)

where we denote

\[
L(x) = \frac{g'(x)[Dg'(x) - 1]}{2}
\] (60)

We seek the solution of (59) in the form

\[
\chi(x, t) = v(x) + \phi(x, t)
\] (61)

where the new functions obey the equations

\[
Dv''(x) + \Phi(x)v'(x) = -L(x)
\] (62)

\[
\dot{\phi}(x, t) = D\phi''(x, t) + \Phi(x)\phi'(x, t) - L(x)\cos(2\Omega t)
\] (63)

From (30) and (31) we obtain the boundary conditions

\[
v(x_a) = -\frac{\omega_a^2}{4D}; \quad v'(x_c) = 0
\] (64)

\[
\phi(x_a, t) = \frac{\omega_a^2}{4D}\cos(2\Omega t); \quad \phi'(x_c, t) = 0
\] (65)

4.2 $v(x)$ function

The solution for the function $v(x)$ is

\[
v(x) = -\frac{\omega_a^2}{4D} + \frac{1}{D} \int_{x_a}^{x} dy \frac{\exp(-U(y)/D)}{P_{K}(y)} \int_{y}^{x_c} dz \ L(z) P_{K}^{2}(z) \exp(U(z)/D)
\] (66)

We denote

\[
I(x) = -\int_{x}^{x_c} dz \ L(z) \exp\left(-\frac{U(z)}{D}\right) \int_{x}^{x_c} ds \ \exp\left(-\frac{U(s)}{D}\right) \int_{s}^{z} dy \ \exp\left(-\frac{U(y)}{D}\right)
\] (67)
After straightforward calculations we obtain
\[
v(q_b(t)) = -\frac{\omega_a^2}{4D} + \frac{1}{D} \left\{ \frac{I(q_b(t))}{\Gamma_0(q_b(t))} - \frac{I(x_a)}{\Gamma_0(x_a)} \right\}
\] (68)

The inner integrals for both \(I(q_b(t))\) and \(I(x_a)\) mave maximum at \(z \approx x_b\). That is why we adopt the following approximations
\[
I(q_b(t)) \approx -L(q_b(t)) \Theta
\] (69)
\[
I(x_a) \approx -L(x_b) \Lambda
\] (70)

where
\[
\Theta = \int_{q_b(t)}^{x_c} dz \exp \left( -\frac{U(z)}{D} \right) \int_{q_b(t)}^{x_c} ds \exp \left( \frac{U(s)}{D} \right) \int_{x_c}^{z} dy \exp \left( \frac{U(y)}{D} \right)
\] (71)
\[
\Lambda = \int_{x_a}^{x} dz \exp \left( -\frac{U(z)}{D} \right) \int_{x_a}^{x} ds \exp \left( \frac{U(s)}{D} \right) \int_{x_a}^{z} dy \exp \left( \frac{U(y)}{D} \right)
\] (72)

Denoting
\[
H = \frac{\omega_a^2}{4} - \frac{\Lambda}{\Gamma_0(x_a)} L(x_b) + \frac{\Theta}{\Gamma_0(q_b(t))} L(q_b(t))
\] (73)
we obtain
\[
v(q_b(t)) = -\frac{H}{D}
\] (74)

4.3 \(\phi(x, t)\) function

We seek the solution of (63) in the form
\[
\phi(x, t) = r(x)\sin(2\Omega t) + s(x)\cos(2\Omega t)
\] (75)

For the new functions we obtain the equations
\[
Dr''(x) + \Phi r'(x) + 2\Omega s(x) = 0
\] (76)
\[
Ds''(x) + \Phi s'(x) - 2\Omega r(x) = L(x)
\] (77)
Recalling that we are in the low frequency limit we decouple the equations (the limit $\Omega \to 0$ in (76), (77))

\[ r''(x) + \frac{\Phi}{D} r'(x) = 0 \tag{78} \]
\[ s''(x) + \frac{\Phi}{D} s'(x) = \frac{L(x)}{D} \tag{79} \]

From (64), (65) we obtain the boundary conditions for these equations

\[ r(x_a) = 0; \quad r'(x_c) = 0 \tag{80} \]
\[ s(x_a) = \frac{\omega_a^2}{4D}; \quad s'(x_c) = 0 \tag{81} \]

The solutions satisfying these boundary conditions are

\[ s(x) \equiv -v(x) \tag{82} \]
\[ r(x) \equiv 0; \quad r'(x) \equiv 0 \tag{83} \]

Thus we obtain

\[ s(q_b(t)) = \frac{H}{D} \tag{84} \]

4.4 $\chi(x, t)$ function

Combining the results we obtain the second order contribution into action

\[ \chi(q_b(t), t) \approx -\frac{H}{D} (1 - \cos(2\Omega t)) \tag{85} \]

To calculate $H$ from (73) we need $L(x_b)$ and $L(q_b(t))$. Taking into account (60) the latter means that we need $g'(x_b)$ and $g'(q_b(t))$. From (40) we have

\[ g'(x) = -\frac{E_1(x)}{DG_0(x)} \exp \left( \frac{U(x)}{D} \right) \tag{86} \]

From (17) and (55) we obtain

\[ E_1(x_b) = -G_0(x_b) \exp \left( -\frac{U(x_b)}{D} \right) + \frac{1}{2\lambda} \exp \left( \frac{U(x_b)}{D} \right) \tag{87} \]
where
\[ \Gamma_0(x_b) \approx \frac{\sqrt{2\pi D}}{2\omega_b} e^{\exp \left( \frac{U(x_b)}{D} \right)} \] (88)

As a result we have
\[ g'(x_b) = \frac{\pi - 2}{\pi D} \] (89)

Thus
\[ L(x_b) = -\frac{\pi - 2}{\pi^2 D} \] (90)

From (54) and (55) we obtain
\[
g'(q_b(t)) = \frac{1}{D}\left\{ 1 - \frac{2\omega_b^2}{\pi} e^{\exp \left( \frac{U(q_b(t)) - U(x_b)}{D} \right) } \text{erf} \left( \frac{-\omega_b A\sin(\Omega t)}{\sqrt{2D}} \right) \right\} \times \left[ \frac{\sqrt{2\pi A\sin(\Omega t)}}{2\omega_b \sqrt{D}} \text{erf} \left( \frac{-\omega_b A\sin(\Omega t)}{\sqrt{2D}} \right) + \frac{1}{\omega_b^2} e^{\exp \left( -\frac{\omega_b^2 A^2 \sin^2(\Omega t)}{2D} \right) \right] \right\} \] (91)

Substitution of (91) into (60) yields \( L(q_b(t)) \) that is not written out explicitly to save room.

4.5 \( \Lambda \) value

Let us evaluate the integral \( \Lambda \) given by (72). The maximum of the inner integrals takes place at \( z \approx x_b \). In this case both inner integrals \( \propto e^{\exp \left( \frac{U(x_b)}{D} \right) } \), otherwise only one of them is such and the whole integral should be smaller. Thus we approximate at \( z \approx x_b \)
\[
\int_{x_a}^{x_c} ds \ e^{\exp \left( \frac{U(s)}{D} \right)} \approx \frac{\sqrt{2\pi D}}{2\omega_b} e^{\exp \left( \frac{U(z)}{D} \right) } \] (92)
\[
\int_{x_a}^{z} dy \ e^{\exp \left( \frac{U(y)}{D} \right)} \approx \frac{\sqrt{2\pi D}}{2\omega_b} e^{\exp \left( \frac{U(z)}{D} \right) } \] (93)

As a result we obtain
\[ \Lambda \approx \frac{(2\pi D)^{3/2}}{4\omega_b^3} e^{\exp \left( \frac{U(x_b)}{D} \right) } \] (94)
Taking into account that
\[ \Gamma_0(x_a) \approx \frac{\sqrt{2\pi D}}{\omega_b} \exp \left( \frac{U(x_b)}{D} \right) \] (95)
we obtain
\[ \frac{\Lambda}{\Gamma_0(x_a)} \approx \frac{\pi D}{2\omega_b^3} \] (96)

4.6 \( \Theta \) value

Now we start rather tedious evaluation of the function \( \Theta \) given by (71). Let us first calculate the auxiliary value \( \Theta_0 \)
\[
\Theta_0 = \int_{x_b}^{x_c} dz \exp \left( \frac{-U(z)}{D} \right) \int_{x_b}^{x_c} ds \exp \left( \frac{U(s)}{D} \right) \int_{x_b}^{z} dy \exp \left( \frac{U(y)}{D} \right) \] (97)

The inner integrals have maximum at \( z \approx x_b \). In this case we expand the last integral into a Taylor series
\[
\int_{x_b}^{z} dy \exp \left( \frac{U(y)}{D} \right) \approx (z - x_b)\exp \left( \frac{U(x_b)}{D} \right) \approx (z - x_b)\exp \left( \frac{U(z)}{D} \right) \] (98)

Then
\[ \Theta_0 \approx \frac{\sqrt{2\pi D}}{2\omega_b} Q_1(x_b) \] (99)

Making use of (55) we obtain
\[ \Theta_0 \approx \frac{(2\pi D)^{3/2}}{4\pi \omega_b^3} \exp \left( \frac{U(x_b)}{D} \right) \] (100)

To calculate \( \Theta \) we decompose it as follows
\[ \Theta = \Theta_0 + W_1 + W_2 + W_3 \] (101)
where we denote

\[
W_1 = \left[ \int_{q_b(t)}^{x_b} dy \exp \left( \frac{U(y)}{D} \right) \right] \int_{q_b(t)}^{x_c} dz \exp \left( -\frac{U(z)}{D} \right) \int_{q_b(t)}^{z} ds \exp \left( \frac{U(s)}{D} \right) \quad (102)
\]

\[
W_2 = \int_{q_b(t)}^{x_b} dz \exp \left( -\frac{U(z)}{D} \right) \int_{q_b(t)}^{x_c} ds \exp \left( \frac{U(s)}{D} \right) \int_{q_b(t)}^{z} dy \exp \left( \frac{U(y)}{D} \right) \quad (103)
\]

\[
W_3 = \left[ \int_{q_b(t)}^{x_b} dy \exp \left( \frac{U(y)}{D} \right) \right] \int_{q_b(t)}^{x_b} dz \exp \left( -\frac{U(z)}{D} \right) \int_{q_b(t)}^{z} ds \exp \left( \frac{U(s)}{D} \right) \quad (104)
\]

We begin with the integral in the square brackets from \(W_1\) and \(W_3\). It can be evaluated as follows

\[
\exp \left( -\frac{U(x_b)}{D} \right) \int_{q_b(t)}^{x_b} dy \exp \left( \frac{U(y)}{D} \right) \approx \int_{q_b(t)}^{x_b} dy \exp \left( -\lambda(y-x_b)^2 \right) =
\]

\[
\int_{-\lambda A \sin(\Omega t)}^{0} ds \exp \left( -\lambda s^2 \right) = \frac{\sqrt{\pi}}{2\sqrt{\lambda}} \text{erf} \left( \sqrt{\lambda} \lambda A \sin(\Omega t) \right) \quad (105)
\]

Then \(W_1\) can be approximated as

\[
W_1 \approx \frac{\sqrt{\pi}}{2\sqrt{\lambda}} \text{erf} \left( \sqrt{\lambda} \lambda A \sin(\Omega t) \right) \int_{x_b}^{x_c} dz \int_{x_b}^{z} ds \exp \left( \frac{U(s)}{D} \right) \quad (106)
\]

Altering the order of integration in the double integral we obtain

\[
\int_{x_b}^{x_c} dz \int_{x_b}^{z} ds \exp \left( \frac{U(s)}{D} \right) =
\]

\[
\int_{x_b}^{x_c} ds \exp \left( \frac{U(s)}{D} \right) (s-x_b) \approx \exp \left( \frac{U(x_b)}{D} \right) Q_1(x_b) \quad (107)
\]

Making use of (55) we obtain

\[
W_1 \approx \Theta_0 \text{erf} \left( \frac{\omega_b A \sin(\Omega t)}{\sqrt{2D}} \right) \quad (108)
\]
At evaluation of the inner integrals in $W_2$ we apply the same arguments as those used for deriving (98). Then we have

$$W_2 \approx \frac{\sqrt{2\pi D}}{2\omega_b} \int_{q_b(t)}^{x_b} dz \exp \left( \frac{U(z)}{D} \right) (z - x_b)$$  \hspace{1cm} (109)$$

After evaluation of the integral we obtain

$$W_2 \approx \Theta_0 \left[ \exp \left( -\frac{\omega_b^2 A^2 \sin^2(\Omega t)}{2D} \right) - 1 \right]$$  \hspace{1cm} (110)$$

For $W_3$ after taking into account (106) we have the approximation

$$W_3 \approx \frac{\sqrt{\pi}}{2\sqrt{\lambda}} \text{erf} \left( \sqrt{\lambda} A \sin(\Omega t) \right) \int_{q_b(t)}^{x_b} dz \int_z^{x_c} ds \exp \left( \frac{U(s)}{D} \right)$$  \hspace{1cm} (111)$$

For the double integral we have

$$\int_{q_b(t)}^{x_b} dz \int_z^{x_c} ds \exp \left( \frac{U(s)}{D} \right) \approx \sqrt{\pi} \exp \left( \frac{U(x_b)}{D} \right) \int_{-\text{Asin}(\Omega t)}^{0} dv \text{erf} c(\sqrt{\lambda} v)$$ \hspace{1cm} (112)$$

Making use of N1.5.1.9 from [32] we obtain

$$W_3 \approx \frac{\pi D}{2\omega_b^2} \exp \left( \frac{U(x_b)}{D} \right) \text{erf} \left( \frac{\omega_b A \sin(\Omega t)}{\sqrt{2D}} \right) \left\{ A \sin(\Omega t) \times \right.$$  
$$\left. \text{erf} c \left( -\frac{\omega_b A \sin(\Omega t)}{\sqrt{2D}} \right) + \frac{\sqrt{2\pi D}}{\pi \omega_b} \left[ \exp \left( -\frac{\omega_b^2 A^2 \sin^2(\Omega t)}{2D} \right) - 1 \right] \right\}$$ \hspace{1cm} (113)$$

Combining the results we finally obtain

$$\frac{\Theta}{\Gamma_0(q_b(t))} \approx \frac{D}{\omega_b^2} \left\{ \exp \left( -\frac{\omega_b^2 A^2 \sin^2(\Omega t)}{2D} \right) + \frac{\pi \omega_b A \sin(\Omega t)}{\sqrt{2\pi D}} \text{erf} \left( \frac{\omega_b A \sin(\Omega t)}{\sqrt{2D}} \right) \right\}$$ \hspace{1cm} (114)$$
5 Result for the escape rate enhancement

Combining the results and taking into account that $T = \frac{2\pi}{\Omega}$ we finally obtain the escape rate enhancement in the low frequency limit

$$\Delta \approx \frac{1}{2\pi} \int_0^{2\pi} d\phi \exp\left\{ \frac{A}{D} [x_b - \text{Asin}(\phi) - x_a] \sin(\phi) - \right.$$ 

$$\frac{2A^2\sin^2(\phi)}{D} \left[ \frac{\omega_a^2}{4} + \frac{\pi - 2}{2\pi \omega_b^2} - \frac{1}{\pi} \exp\left( -\frac{\omega_b^2 A^2 \sin^2(\phi)}{2D} \right) \right] exp\left( \frac{U(x_b - \text{Asin}(\phi)) - U(x_b)}{D} \right) \times$$

$$\left[ 1 - \frac{2\omega_b^2}{\pi} \exp\left( \frac{U(x_b - \text{Asin}(\phi)) - U(x_b)}{D} \right) / \text{erfc}\left( \frac{-\omega_b \text{Asin}(\phi)}{\sqrt{2D}} \right) \right] \times$$

$$\left\{ \frac{\sqrt{2\pi} \text{Asin}(\phi)}{2\omega_b \sqrt{D}} \text{erfc}\left( \frac{-\omega_b \text{Asin}(\phi)}{\sqrt{2D}} \right) + \frac{1}{\omega_b^2} \exp\left( -\frac{\omega_b^2 A^2 \sin^2(\phi)}{2D} \right) \right\} \right\}$$

$$\times$$

$$\left\{ \frac{\sqrt{2\pi} \text{Asin}(\phi)}{2\omega_b \sqrt{D}} \text{erfc}\left( \frac{-\omega_b \text{Asin}(\phi)}{\sqrt{2D}} \right) \right\} \times$$

$$\left\{ \frac{1}{\omega_b^2} \exp\left( -\frac{\omega_b^2 A^2 \sin^2(\phi)}{2D} \right) \right\} / \text{erfc}\left( \frac{-\omega_b \text{Asin}(\phi)}{\sqrt{2D}} \right) \right\}$$

$$\right\}$$

This formula is the first result of the present manuscript.

5.1 Plots

The formula (115) notwithstanding it looks very cumbersom can be easily treated by, e.g., Mathematica. Prior doing it we recall that we want to stay within the so called subthreshold driving regime. The latter provides that the potential surface always has a minimum and a maximum, i.e., the oscillating field is small enough not to distort the physical picture of the chemical reaction as the Brownian particle escape from the metastable state. This regime is defined by the requirement $A \leq A_c$ where $A_c = 0.25$ for the case of the cubic (metastable) potential $U(x) = x^2/2 - x^3/3$ (CP) and $A_c = 2/(3\sqrt{3}) \approx 0.4$ (see, e.g., [18]) for the case of the quartic (bistable) potential $U(x) = -x^2/2 + x^4/4$ (QP). In Fig.1 and Fig.2 the results for the CP and QP respectively at relatively large values of the noise intensity are depicted. At the value $D = 5 \cdot 10^{-2}$ we have $A_c/D \approx 5$ and $A_c/D \approx 8$ for the case of the CP and QP
respectively. In Fig.3 and Fig.4 the results for the CP and QP respectively at relatively small values of the noise intensity are depicted. At the value $D = 3 \cdot 10^{-3}$ we have $A_c/D \approx 83$ and $A_c/D \approx 130$ for the cases of the CP and QP respectively. These values limit the horizontal coordinate in the plots.

5.2 Limit $1 << \frac{A}{D} << \frac{1}{\sqrt{D}}$

Let us consider the limiting case of moderately strong modulation $D << A << \sqrt{D}$. We denote

$$p = 1 + \frac{2}{\omega_b^2} \left[ \frac{\omega_a^2}{4} + \frac{\pi - 2}{\pi} \left( \frac{1}{2\omega_b} - \frac{1}{\pi} \right) \right]$$  \hspace{1cm} (116)$$

Taking into account the requirement $A/\sqrt{D} << 1$ and discarding in (115) the terms $O(\frac{A}{\sqrt{D}})$ we obtain

$$\Delta \approx \frac{1}{2\pi} \int_0^{2\pi} d\phi \exp \left\{ \frac{A}{D} \left[ (x_b - x_a) \sin(\phi) - A_p \sin^2(\phi) \right] \right\}$$  \hspace{1cm} (117)$$

Taking into account $A/D >> 1$ we can evaluate the integral by the steepest descent method and obtain a simple formula

$$\Delta \approx \frac{\sqrt{D}}{2\pi A \left[ (x_b - x_a)/2 - A_p \right]} \exp \left\{ \frac{A}{D} \left[ x_b - x_a - A_p \right] \right\}$$  \hspace{1cm} (118)$$

where $p$ is the constant given by (116). For the case of CP we have $p \approx 1.632$ while for the QP we have $p \approx 2.132$. For both of them we have $x_b - x_a = 1$. In the considered range $D << A << \sqrt{D}$ the expression under the square root in the denominator can not be zero at physically reasonable values of the noise intensity $D \leq 10^{-1}$. The formulas (116) and (118) are the second result of the present manuscript.

6 Conclusions

The results obtained testify that the perturbation expansion for the action $\alpha$ in the modulation amplitude $A$ yields a reasonable and convergent expression at least in the low frequency limit. In this case we restrict ourselves by the second order term $O(A/D)$. In our opinion the corrections from the third and
higher order contributions (which are $O(A^2/D)$) will not distort the results appreciably except in a narrow region near the bifurcation point $A_c$. In this region our results diverge with the scaling laws obtained in [20], [21], [22], [23]. For the regime of weak modulation our results precisely coincide with those known from the literature. The formula (118) in the low limit of its validity range $D << A << \sqrt{D}$ (A small enough for the terms $O(A^2)$ to be neglected) with taking into account that $x_b - x_a = 1$ for both the CP and QP yields the formula (6.34) from [2] obtained for the case of the QP in the limit of small driving frequencies. The value $x_b - x_a$ is a coefficient before the linear in $A/D$ term in the exponent of the escape rate enhancement and is actually the so-called logarithmic susceptibility from the [14], [15], [20], [21], [22], [23] theory. The value 1 is in agreement with $\chi(0) = \lim_{\Omega \to 0} \left[ \pi \Omega / sh(\pi \Omega) \right] = 1$ obtained in [14] for the case of the CP.

From Fig.1, Fig.2, Fig.3 and Fig.4 we see that the present theory yields analytical description for the retardation of the exponential growth of the escape rate enhancement (i.e., transition from a log-linear regime to more moderate growth). Moreover Fig.2 exhibits the examples of the reverse behavior when the escape rate enhancement attains a maximum at some value of $A/D$ and then becomes to decrease with the further increase of $A/D$. It is worthy to note that this phenomenon vividly manifests itself for the QP and is not noticed for the CP. Regretfully the [11], [12], [13] and [14], [15], [20], [21], [22], [23] theories were not exemplified by the case of the QP and our prediction cannot be directly compared with the results of those theories.

From the comparison of Fig.1, Fig.2 and Fig.3, Fig.4 respectively we see that at a given $A/D$ the periodic driving produces stronger escape rate enhancement for the case of CP than that of QP. The latter certainly can not be explained by the fact that the barrier height for the CP ($1/6$) is smaller than that for the QP ($1/4$) because the barrier height does not enter the formulas (115) and (118). This phenomenon can be attributed to the only difference between these potentials manifested in the value of the frequency near the bottom of the well $\omega_a$. For the QP this value ($\sqrt{2}$) is higher than that for the CP (1). The latter means that the QP goes steeper from the bottom of the well that hinders the escape rate enhancement by periodic driving. Thus the precise shape of the potential is of utmost importance for the phenomenon of interest.

We obtain two forms of the resulting formula valid for arbitrary potentials with an activation barrier. The formula (115) encompasses the case of arbitrary $A/D$ except a narrow region near the bifurcation point. Its drawback is that it is very cumbersome. Nevertheless it can be easily tackled by a computer with the help of, e.g., Mathematica. Its main merit is that it contains only the notions used at initial setting the problem and can be used by people engaged in applications of the theory without reading the rest parts of the present manuscript. The formula (118) is valid for the case of moderately
strong modulation $D \ll A \ll \sqrt{D}$. Its merit is that it has closed and quite simple analytical form to be used by practitioners in chemistry and biochemistry for quick by hand estimates. The exponent in this formula explicitly and vividly demonstrates how the linear term $O(A/D)$ dominating at weak modulation (comparatively small $A/D$) and responsible for the log-linear regime is replaced by that subtracted by the term $O(A^2/D)$ at further increase of $A/D$ providing the retardation of the exponential growth of the escape rate enhancement. Regretfully we can not directly compare our results with those of the [11], [12], [13] theory because the latter is inapplicable for the case of slow modulation.

The formula (118) is valid in a rather narrow range of the parameters. However this range turns out to be relevant for applications in enzymology. The typical value of noise intensity at enzymatic reactions is $D \approx 3 \cdot 10^{-3}$ [27]. In this case we have the range of validity for (118) as $1 << A/D << 18$. The typical values of $A/D$ for a particular model suggested in [27] were estimated as $A/D \approx 10$ and find themselves at some stretch within this range. The stringent results for this case are given by the formula (115) and can be seen in Fig.3 and Fig.4.

We conclude that for the particular case of the low frequency limit the aim to obtain tractable and convenient formulas describing the escape rate enhancement by periodic driving seems to be attained. The mathematical tools used at their deriving are within the scope of elementary methods.

7 Appendix

We denote

$$R = \frac{1}{\Gamma_0(q_b(t))} \int_{q_b(t)}^{x_c} ds \exp \left( \frac{U(s)}{D} \right) s - \frac{1}{\Gamma_0(x_a)} \int_{x_a}^{x_c} ds \exp \left( \frac{U(s)}{D} \right) s$$

(119)

then

$$S(q_b(t)) \approx -(q_b(t) - x_a) + R$$

(120)

Our aim here to show that the term $R$ is $O(\sqrt{D})$ then (56) will be proven. Let us write

$$R = \frac{1}{2\lambda} \frac{\partial}{\partial x_b} \ln \left\{ \int_{q_b(t)}^{x_c} ds \exp \left[ -\lambda(s - x_b)^2 \right] / \int_{x_a}^{x_c} ds \exp \left[ -\lambda(s - x_b)^2 \right] \right\}$$

(121)
Making use of the substitution $r/\sqrt{\lambda} = s - x_b$ we obtain

$$R \approx \frac{1}{2\lambda} \frac{\partial}{\partial x_b} \ln \left\{ \int_{\sqrt{\lambda}(q_b(t)-x_b)}^{\infty} dr \exp \left( -r^2 \right) \right\}$$

As a result of straightforward calculations we have

$$R \approx \frac{D}{\omega_b^2 Q_0 (q_b(t))} \exp \left( -\frac{\omega_b^2 A^2 \sin^2(\phi)}{2D} \right)$$

Taking into account (53) we obtain the required result

$$R \sim \sqrt{D}$$

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Fig. 1. The dependence of the escape rate enhancement on the driving amplitude to noise intensity ratio for the case of cubic (metastable) potential $U(x) = x^2/2 - x^3/3$. The values of the noise intensity $D$ from the down line to the upper one respectively are: $5 \cdot 10^{-2}$; $4 \cdot 10^{-2}$; $3 \cdot 10^{-2}$; $2 \cdot 10^{-2}$; $1 \cdot 10^{-2}$. 
Fig. 2. The dependence of the escape rate enhancement on the driving amplitude to noise intensity ratio for the case of quartic (bistable) potential $U(x) = -x^2/2 + x^4/4$. The values of the noise intensity $D$ from the down line to the upper one respectively are: $5 \cdot 10^{-2}$; $4 \cdot 10^{-2}$; $3 \cdot 10^{-2}$; $2 \cdot 10^{-2}$; $1 \cdot 10^{-2}$.
Fig. 3. The dependence of the escape rate enhancement on the driving amplitude to noise intensity ratio for the case of cubic (metastable) potential \( U(x) = x^2/2 - x^3/3 \). The values of the noise intensity \( D \) from the down line to the upper one respectively are: \( 3 \cdot 10^{-3}, 2 \cdot 10^{-3}, 1 \cdot 10^{-3} \).
Fig. 4. The dependence of the escape rate enhancement on the driving amplitude to noise intensity ratio for the case of quartic (bistable) potential $U(x) = -x^2/2 + x^4/4$. The values of the noise intensity $D$ from the down line to the upper one respectively are: $3 \cdot 10^{-3}$; $2 \cdot 10^{-3}$; $1 \cdot 10^{-3}$. 