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A Free Energy Based Mathematical Study for Molecular Motors[1]

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Abstract—We present a Parrondo's paradox for free energy in a classical flashing ratchet model and use it as an alternative way to interpret the working mechanism of molecular motors. We also study the efficiency of molecular motors measured by their free energies. Our example demonstrates that a molecular motor can gain up to 20% in its free energy during the process. In addition, we report a noise induced free energy increasing phenomenon, which is similar to the stochastic resonance, in flashing ratchet models.

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Dedicated to Professor Henk Broer for his 60th Birthday

1. INTRODUCTION

In this paper, we consider some properties of Parrondo's paradox, flashing ratchet models, molecular motors and their associated free energy functionals. Parrando's paradox is a well known concept in the game theory. Roughly speaking, this paradox says that it is *possible* to construct a winning strategy by playing two losing strategies alternately or randomly. The paradox has been considered by many authors in different disciplines, although its original example is based on a coin toss game. Readers are referred to [4, 6, 7] and references therein for more information.

Molecular motors we consider in this paper are related to proteins that conduct movements in living organisms. There are different kinds of molecular motors, such as Myosin, Kinesin, Dynein, Actin, Microtubule, Dynamin, ATP synthase and RNA polymerase. These tiny biological machines perform most forms of movements in the living world. Although different kinds of molecular motors are for different biological tasks, they share a similar basic working principle, which is to convert chemical energy into mechanical motions. There exist many different models which provide explanation to the working mechanism of molecular motors[1, 9, 23]. However, despite the differences among different models, most authors use Brownian motions to handle the uncertainties in molecular motors. One reason that one needs to consider uncertainties is that molecular motors have extreme small sizes, and they are very sensitive to thermal fluctuations.

Among different mathematical models for molecular motors, a flashing ratchet model, which is related to Parando's paradox, has been used in recent years. The main idea behind the flashing ratchet model is that it describes molecular motors as Brownian particles moving in an asymmetric potential field that is turned on and off periodically or randomly. The oscillatory pattern in time

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of the potential field causes directional motions of the Brownian particles, just as flashing ratchets allowing movements in designed directions. More precisely, the flashing ratchet model describes the motion of a molecular motor $X \in \mathbb{R}^d$ by a stochastic differential equation,

$$\mathrm{d}X = -\nabla\Psi(X,t)\mathrm{d}t + \sqrt{2\tau}\mathrm{d}W_t, \tag{1.1}$$

where $\Psi(x,t)$ is a time dependent asymmetric potential function taking non-negative values for different time intervals, W_t is the standard Brownian motion in $\mathbb{R}^d$, and τ is proportional to the temperature of the system. The flashing ratchet has been studied by many authors (see, for example [1, 8, 11, 13–15, 19, 20, 24]). Inspired by the work reported in [8], we present in this paper an explanation of the flashing ratchet models which is based on the time evolution of free energy as in the case of Parrondo's paradox.

The free energy is a commonly used concept in many scientific areas. Roughly speaking, it refers to the maximal amount of work that can be extracted from a system. The definition of free energy for molecular motors can be given in the following manner. By (1.1), the motion of a molecular motor is a random function. We denote its probability density function by P. Then the free energy can be expressed as a functional of P:

$$F(P) = U(P) - \tau S(P), \tag{1.2}$$

where $U(P)$ is the potential energy, $S(P)$ is the entropy, and τ is a constant that is proportional to temperature. More precisely, we have:

$$U(P)(t) := \int_{\mathbb{R}^d} \Psi(x,t)P(x,t)dx.$$

$$S(P)(t) := -\int_{\mathbb{R}^d} P(x,t)\log P(x,t)dx,$$

We note that $S(P)$ is often called the Gibbs–Boltzmann entropy functional and is known as Shannon entropy if the ambient space $\mathbb{R}^d$ is replaced a finite set. In fact, the entropy functional has been used to measure the efficiency of molecular motors [9, 15–17].

Many of the existing studies are based on the steady state probability distribution, called Gibbs' distribution, for computing the entropy functional. However, this is not a suitable choice for the flashing ratchet model because of the oscillatory time dependency of the potential function $\Psi(X,t)$. In fact, we need to know the time dependent probability density function P in order to understand how the free energy changes as time increases.

The probability density function P can be computed from its Fokker–Planck equation, which is a linear parabolic equation that describes the time evolution of the probability density function of a stochastic process. For the flashing ratchet motions defined by (1.1), the corresponding Fokker–Planck equation is

$$\frac{\partial P(x,t)}{\partial t} = \nabla\cdot(\nabla\Psi(x,t)P(x,t)) + \tau\Delta P(x,t). \tag{1.3}$$

see [8] for more details.

In this paper, we describe in detail how we use the free energy to construct a Parrondo's paradox for a flashing ratchet model that explains the working mechanism of molecular motors. We also present a new method to estimate the efficiency of molecular motors. Furthermore, we show an interesting behavior that the efficiency of molecular motors would reach its maximum at a certain level of environmental noise. This phenomenon is similar to stochastic resonance.

We remark that we assume the movements of particles are relatively slow due to their small sizes and short time scales. Therefore, we do not consider the kinetic energy of the molecular motors in this paper.

2. PARRONDO'S PARADOX IN FLASHING RATCHET: OLD AND NEW

The flashing ratchet model is based on a randomly perturbed dynamical equation (1.1), which describes the motion of a molecular motor. Meanwhile, flashing ratchet model is also a classical example of Parrondo's paradox [8, 11]. In this section, we review the classical Parrondo's paradox of flashing ratchet model, and then demonstrate another explanation of Parrondo's paradox from the time evolution of the free energy.

In both cases, the key component in the model is that the asymmetric potential field $\Psi(x,t)$ is time dependent and can be turned on and off periodically or randomly, i.e. we can assume that the potential function $\Psi(x,t)$ is a given asymmetric function $G(x)$ when it is turned on and 0 when turned off:

$$\Psi(x,t) = \begin{cases} G(x) & \text{if} \quad n \le t < n+1/2 \\ 0 & \text{if} \quad n+1/2 \le t < n+1. \end{cases}$$

We remark that the integer time intervals $[n, n+1/2)$ and $[n+1/2, n+1)$ are taken for convenience. And they can be other time intervals with non-integer lengths.

For models of molecular motors, it is necessary to select an asymmetric potential function $G(x)$, for example, a seesawed function as in Figure 2.

$$G(x) = \begin{cases} -1.5x - 1.2 & \text{if} \quad x \le -1 \\ 5x + 5.3 & \text{if} \quad -1 < x \le -0.5 \\ -1.5x + 2.05 & \text{if} \quad -0.5 < x \le 1 \\ 3x - 2.45 & \text{if} \quad x \ge 1. \end{cases}$$

The asymmetry of $G(x)$ is reflected around each minimal point, at which the slope from the left is different from the slope from the right. When molecular particles are subjected to alternating forces from the asymmetric potential field and Brownian motions, one may observe a directed motion.

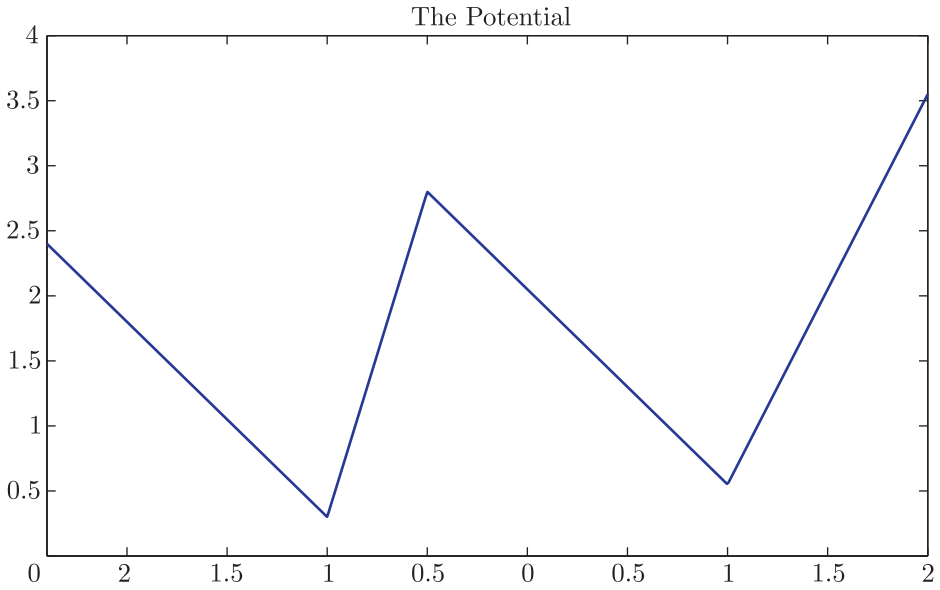

Fig. 1. The asymmetric potential function.

The classical Fokker–Planck equation gives the time evolution of the probability density function which could provide an explanation of this directed motion. Thus the mechanism in flashing ratchet is not difficult to understand. When the potential is "turned off", the molecular particles move randomly and isotropically in all directions, just like Brownian motions. They can easily get out of the potential wells that attracted them in the previous stage when the potential was switched on. In this example, it is obvious that more particles move cross the maximal potential location

(potential is switched off at this stage though) from left hand side to its right hand side than the reverse direction because the distance from the maximal location to the left minimum is closer than it to the right minimum. When the potential is "turned on", the particles will be driven to the vicinity of the local minima. Due to the asymmetry in the potential function, more particles from the left side than from the right side move to a local minimum. Repeating of the process leads to more particles moving from left to the right, as a directed motion.

The probability distribution of molecular motors are governed by Fokker–Planck equation (1.3). In the example, the environmental noise level is set as $\tau = 0.2$. We take the initial distribution given by the solid curve as shown in Figure 2, we also show the distribution of molecular motors at $t = 60$ by the dashed curve in the same figure. Clearly, the mass of the distribution function is shifted from the left to the right, which implies that more particles move from the left to the right. However, we note that the given potential function $G(x)$ has lower values on the left end and higher values on the right. The molecules move from lower potential places to higher ones, which is certainly against the normal intuition. This fits well to the classical Parrondo's paradox — two losing game strategies can form a winning strategy. This has been studied in [8, 11] and a rigorous analysis is given in [14].

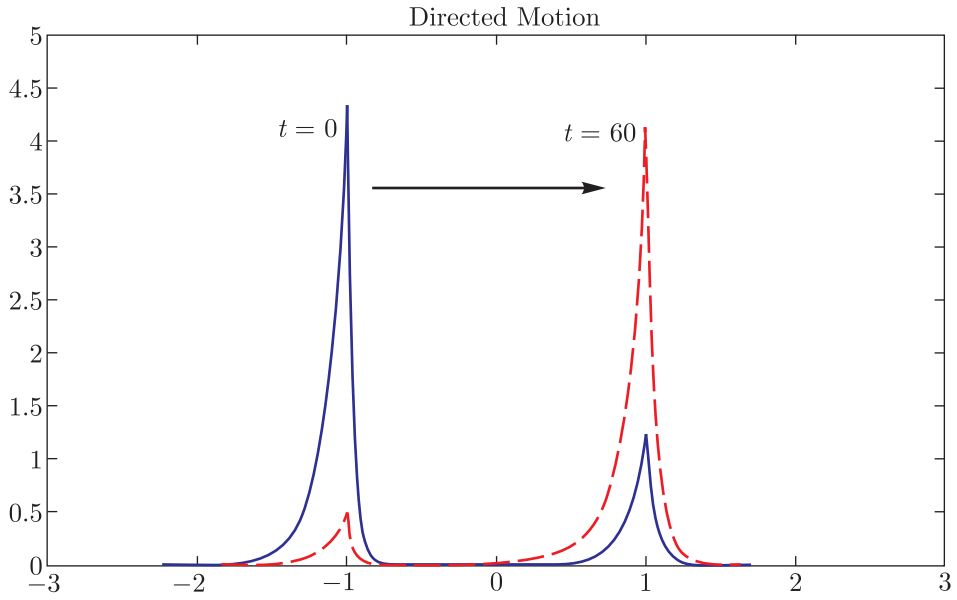

Fig. 2. The solid curve is the probability density function at $t = 0$; the dotted curve is the probability density function at $t = 60$.

With the definition given in (1.2), it is natural that we extend this explanation of Parrondo's paradox to free energy. It is well known that if the potential function does not depend on time, the free energy decreases along the solution of Fokker–Planck equation as shown in [10, 12, 21]. However, this is no longer true for the flashing ratchet model, due to the temporal oscillatory pattern of $\Psi(x,t)$. In fact, we have two different processes depending on whether the potential function is 0 or $G(x)$. For convenience, we call the stochastic process with $\Psi(x,t) = G(x)$ "Process A" and the pure diffusion process with $\Psi(x,t) = 0$ "Process B".

The time evolution of the probability density function in Process A is governed by

$$\frac{\partial P(x,t)}{\partial t} = \nabla \cdot (\nabla G(x) P(x,t)) + \tau \Delta P(x,t), \tag{2.1}$$

while the time evolution of the probability density function in Process B is given by

$$\frac{\partial P(x,t)}{\partial t} = \tau \Delta P(x,t). \tag{2.2}$$

Clearly both processes are energy dissipative, i.e. the free energy decreases with both processes (losing strategies). However, when applying Process A and Process B alternatively, the free energy increases with time (winning strategy). This is an analogue of Parrondo's paradox .

To better illustrate Parrondo's paradox of free energy, we use the following numerical example. The asymmetric potential field $G(x)$ is given in Figure 3,

$$G(x) = \begin{cases} -4(x+7)+1 & \text{if} \quad x < -7 \\ -(x+4)/3 & \text{if} \quad -7 \le x < -4 \\ 3(x+4) & \text{if} \quad -4 \le x < -3.5 \\ -(x+0.5)/3 + 0.5 & \text{if} \quad -3.5 \le x < -0.5 \\ 3(x+0.5)+0.5 & \text{if} \quad -0.5 \le x < 0 \\ -(x-3)/3+1 & \text{if} \quad 0 \le x < 3 \\ 3(x-3)+1 & \text{if} \quad 3 \le x < 3.5 \\ -(x-6.5)/3+1.5 & \text{if} \quad 3.5 \le x < 6.5 \\ 4(x-6.5)+1.5 & \text{if} \quad x \ge 6.5 \end{cases}$$

There are four local minima and their heights increase from left to right. We pick the initial distribution as the Gibbs distribution, denoted by $\Phi(x)$, the global minimum of free energy functional, given by

$$\Phi(x) = \frac{1}{K} e^{-\Psi(x)/\tau}$$

where $K = \int_{\mathbb{R}^N} e^{-\Psi(x)/\tau} dx$ is the normalizer. The Gibbs distribution as $\tau = 0.1$ concentrates at the left local minimum, as shown in Figure 4. At this initial state, the system has the free energy value 0.1091.

We use the following finite difference scheme to carry out numerical simulations to demonstrates this directed motion,

$$\begin{aligned} P_i^{n+1} = P_i^n + \frac{\delta t}{\delta x^2} \Big(& \sum_{j \in N(i), \bar{\Psi}_j > \bar{\Psi}_i} ((\Psi_j + \tau \log P_j) - (\Psi_i + \tau \log P_i)) P_j \\ & + \sum_{j \in N(i), \bar{\Psi}_j < \bar{\Psi}_i} ((\Psi_j + \tau \log P_j) - (\Psi_i + \tau \log P_i)) P_i \Big), \end{aligned} \tag{2.3}$$

where $N(i) = \{i-1, i+1\}$, $\bar{\Psi}_i^n = \Psi_i^n + \tau \log P_i$, and δt and δ_x are temporal and spatial mesh sizes respectively. This is a special upwind scheme for Fokker–Planck equation, and its properties have been reported in [2]. It is worth to point out that this scheme converges to the Gibbs' distribution independent of the spatial mesh size, which is different from other commonly used schemes such as the central difference scheme.

After turning on and off the potential function periodically with period $T = 1$ for 1200 times, we observe the directed motion from the left end to the right. And the probability distribution is concentrated at the right local minimum, which has higher potential energy and lower entropy. The overall free energy, which is increased to 1.5009, is higher at the final state.

Figure 5 shows the free energy values at each time when the potential function is turned off. Clearly, the free energy is increased. Comparing the values at $t = 0$ with that at $t = 500$, the free energy increases from 0.1091 to 1.5009.

To see the detail of the free energy changes, we plot the free energy values in the first 10 periods in alternating Process A and B in another example. The time interval is still $T = 1$, while the noise level is set as $\tau = 0.4$. The upper branches correspond to Process A when the potential is turned on. The lower branches are for Process B when the potential field is turned off. Clearly, both processes cause decrease in the free energy (so they are all "losing game"), while jumps occurs when the potential is turned on and off. Overall, the free energy is increased as in Figure 6 — two losing games form a winning strategy. The free energy at five points A, B, C, D, E are $-0.2085, -1.9681, -2.1806, -0.1184, -0.2009$ respectively. In the end of the simulation, the free energy is increased from -0.2085 to -0.2009.

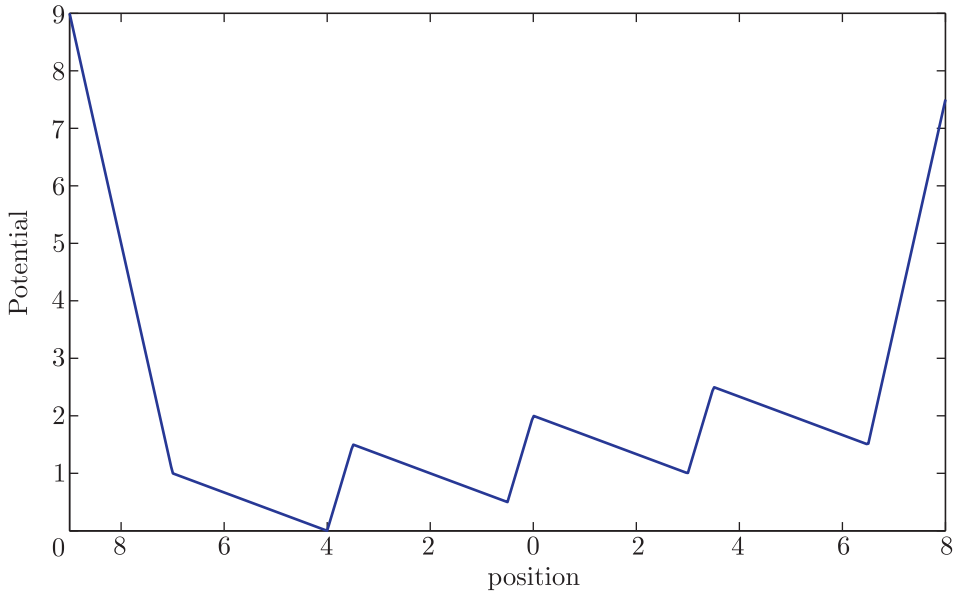

Fig. 3. A seesawed potential function.

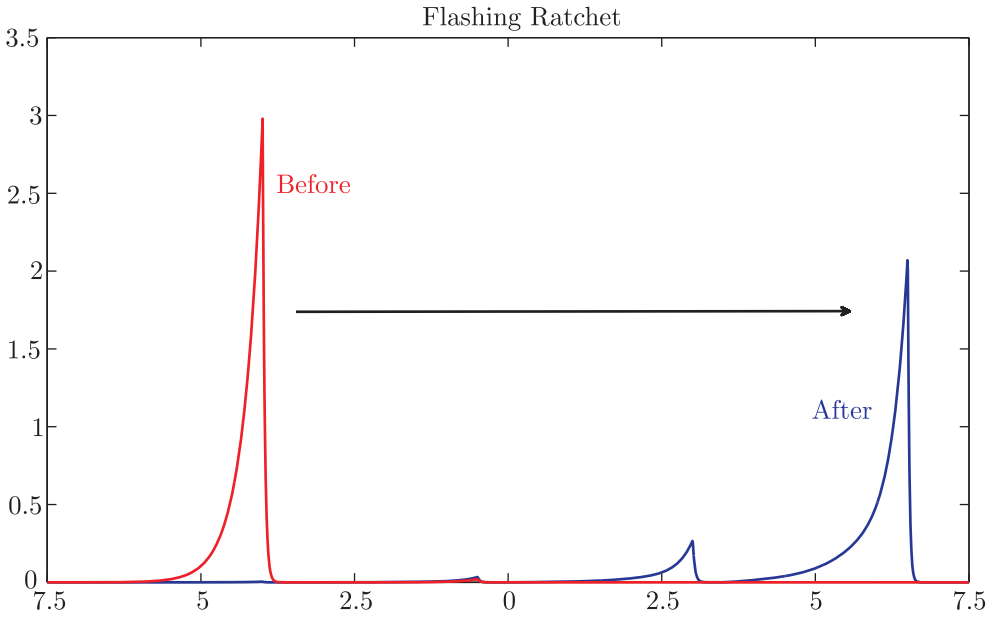

Fig. 4. Probability density function shows a directed motion by molecular motors.

3. APPLICATION IN MOLECULAR MOTOR

From the previous section, we see that alternating two energy dissipative processes actually causes the increase in the free energy, which we call it Parrondo's paradox of free energy. Actually, Parrondo's paradox is more than a mathematical game, it can give a new viewpoint of molecular motors.

To discuss this new viewpoint of molecular, one should answer a natural question: where the energy comes from? Furthermore, we can ask whether it is possible to use the free energy to compute the efficiency of molecular motors. Actually, the efficiency of molecular motors is discussed in existing articles such as by using different methods or models. One classical method is computing the average kinetic energy of particles as the output of motors [3, 9, 13, 15–17, 22, 24]. Others also count the entropy production into the dissipation of energy [15], while the basic viewpoint is still based on the kinetic energy. The classical method works well when the kinetic energy could be

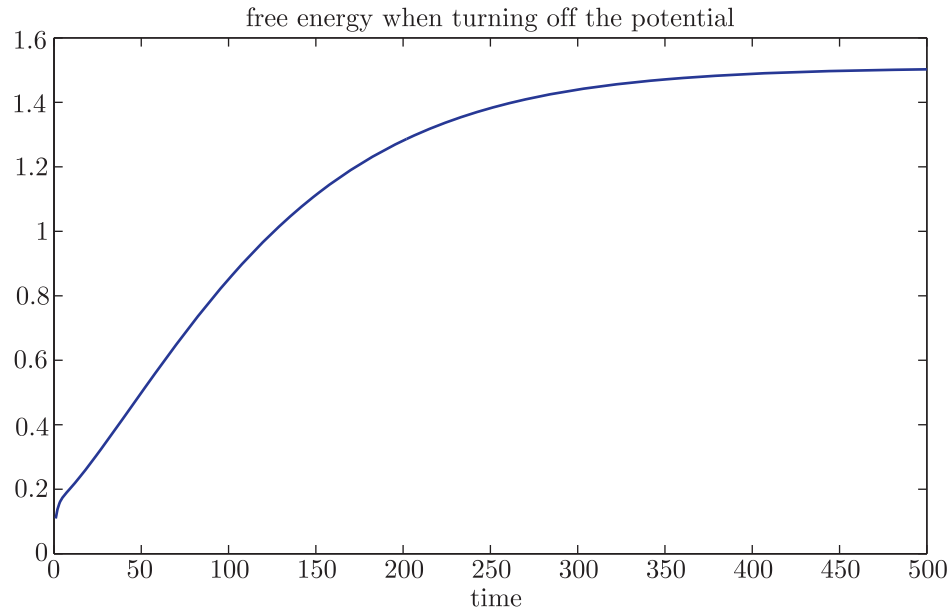

Fig. 5. The free energy at each time when the potential is turned off.

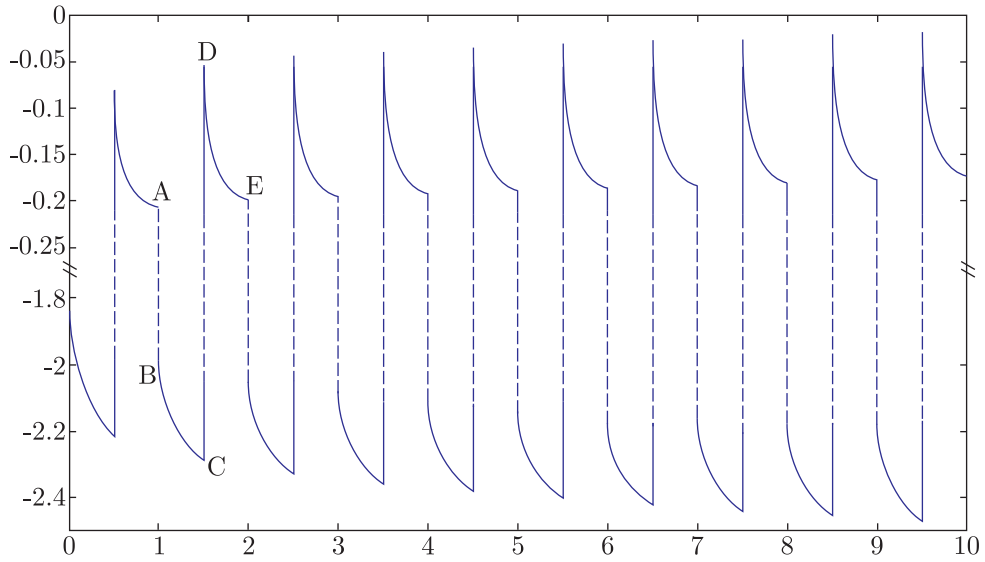

Fig. 6. The free energy in the first 10 periods. The y-axis on the upper half is the free energy with potential turned on, on the lower half is the free energy with potential turned off.

significant, for example in an open system with external forcing. However, in an isothermal system with high viscosity, the change of free energy may overcome the very small kinetic energy in case of no external force given. This may suggest that if we omit the change of free energy, we may miscalculate the efficiency of the motors.

Regarding the energy source in the processes, the free energy actually comes from the change of potential energy when the potential is switched off. When the potential is turned off, the particles are only subject to the Brownian diffusion. After a period of Brownian motion, when the potential is turned on again, the potential energy has increased. In Figure 6, when the potential is turned on again at D, we could see the increase of free energy clearly. So in another word, the switching of the potential field is not free, generally one must spend some extra energy to "turn on" the potential field again. The following paragraphs give an example about how could the potential be switched, and how could the system obtain energy during this procedure.

To understand this mechanism better, we may recall the illustration of the working mechanism of a molecular motor given in [1]. Here we use the same symbols as used in [1] to represent the proteins and particles involved in the system. We consider a negatively charged protein E which is moving in an asymmetric potential field formed by the protein molecules with electrical polarity as shown in Figure 7. Moreover, we assume E is an enzyme that catalyzes a chemical reaction (Picture 1 and 2 in Figure 8), i.e.

$$SH \Longleftrightarrow S^- + H^+.$$

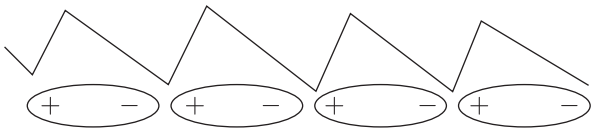

Fig. 7. An asymmetric electric field.

The compound EHS is negatively charged initially. When S^- dissociates from EHS, EH becomes neutrally charged. So the protein E does not sense the existence of the potential field, and moves as a Brownian particle (Picture 3 in Figure 8). This is corresponding to Process B, in which the potential function is turned off. When H^+ dissociates from the protein, E becomes negatively charged again. Then the protein moves with the influence of the potential field (Picture 4 in Figure 8). This is Process A. Both processes are repeated periodically and the protein E moves from low potential area to high potential region with increased free energy.

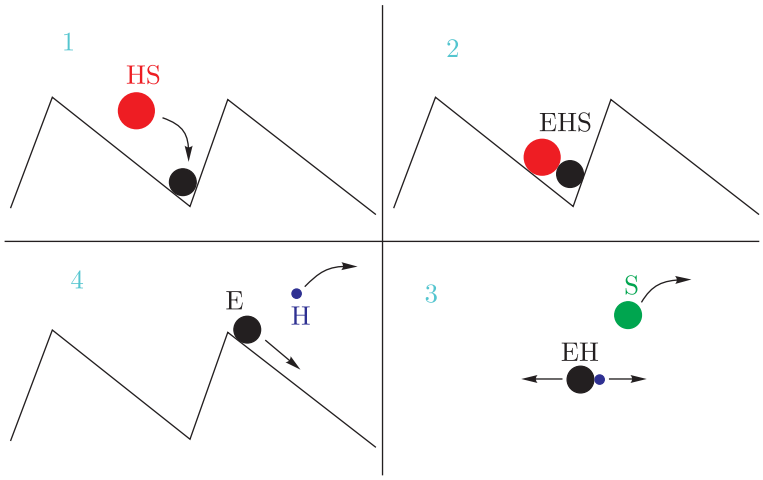

Fig. 8. A the mechanism of a molecular motor.

When the potential field is "turned off", it does not really vanish. In fact, it is only neutralized by H^+. Therefore the potential energy of EH does not change before the dissociation of H^+. However, the potential energy of H^+ decreases. As a consequence, the potential energy of E must increase to maintain the overall potential energy by EH. Hence, when the potential field is "turned on" again, the free energy of E increases. In summary, the increased free energy comes from the decreased potential energy of H^+ when it dissociates from E. On the other hand, not all of the lost potential energy of H^+ can be converted into the free energy of E due to the environmental noise.

Moreover, we can compute the efficiency of the molecular motor. Again, we take figure 6 as an example. We consider the free energy at five points A, B, C, D and E, and the free energy at A, D, E are F_A, F_D, F_E respectively; the free energy with vanished potential (or the negative entropy) at B and C are S_B and S_C respectively.

At time $t = A = B$, the potential function is turned off. The free energy at this time is

$$F_A = U_A + S_A = U_A + S_B$$

where U is the potential energy.

At time $t = C = D$, the potential function is turned on again. At this time, the free energy with vanished potential is S_C, the free energy with regular potential is F_D. Then we have

$$F_D = U_D + S_D = U_C + S_C$$

So the total energy that comes from external environment is

$$U_C - U_B = F_D - F_A + S_B - S_C$$

And the gains of the free energy is $F_E - F_A$. So the efficiency of the molecular motor is

$$\gamma = \frac{F_E - F_A}{F_D - F_A + S_B - S_C}$$

From stochastic process (1.1), it is clear that the noise level $\epsilon = \sqrt{2\tau}$ and time interval T of switching the potential field on and off are two major factors to determine the free energy gain by molecular motors. We plot their relationships in the following example in Figure 9. We vary the noise level ϵ from 0 to 5, and the time interval T from 0 to 0.5. From the plot, we see higher efficiency with faster switching. But please note that the rate of free energy gain does not increase with faster switching, so this is a trade-off — faster switching gives higher efficiency as well as less power. On the other hand, the efficiency are smaller for too low and too high level of noise. In fact, as shown in Figure 10, there exists a value for τ that the efficiency reaches it maximal. This corresponds to the maximal efficiency for molecular motors. In other words, the molecular motors attains its maximal efficiently if the noise level is set at the right place. Like in the classical bistable model of stochastic resonance, the noise does not disturb the model, but enhance the performance of the model. We call this a stochastic resonance like behavior. In fact, the mechanism of this phenomenon is different from that of the classical bistable model as well as that of the stochastic resonance in the quantum Brownian motors [18, 19].

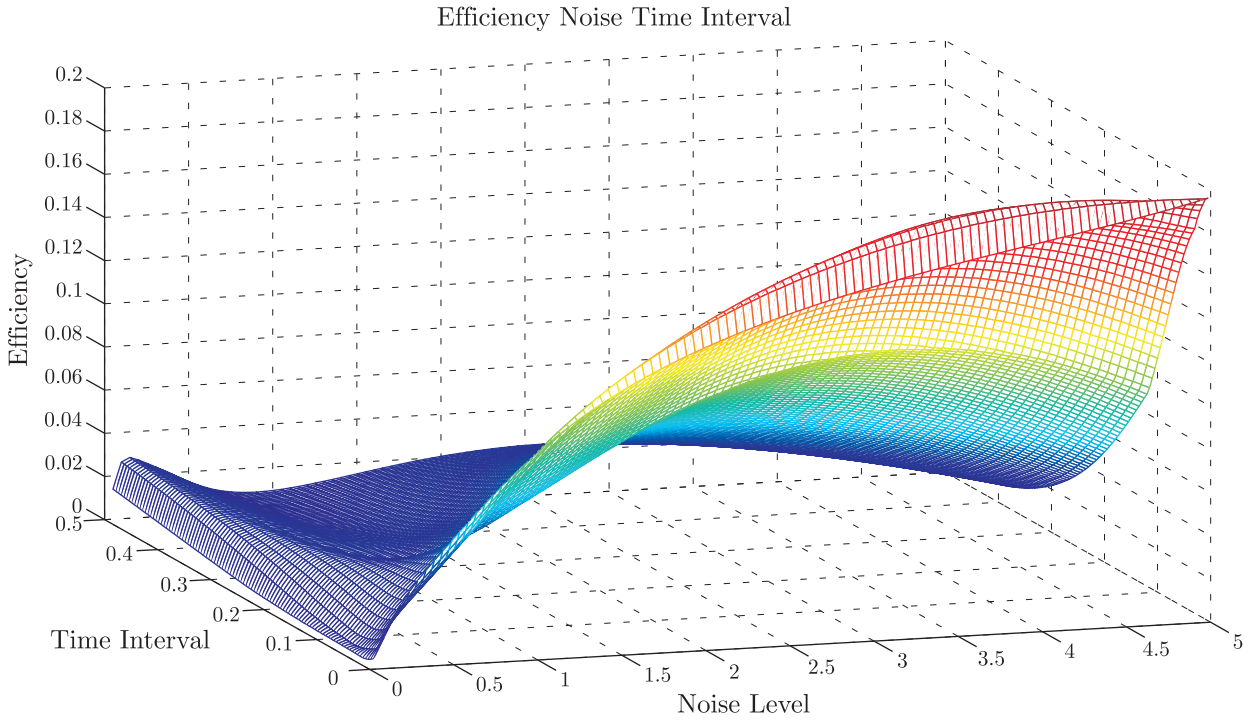

Fig. 9. Free energy gain v.s. noise level and time interval of switching potential field.

We remark that evaluating the performance of molecular motors from the free energy point of view is different from the existing studies, such as the method used in [13], in which the output energy is calculated by the power of the stopping force. The efficiency of molecular motors measured in the free energy can reach near 20 %. For example, with the potential function in our example,

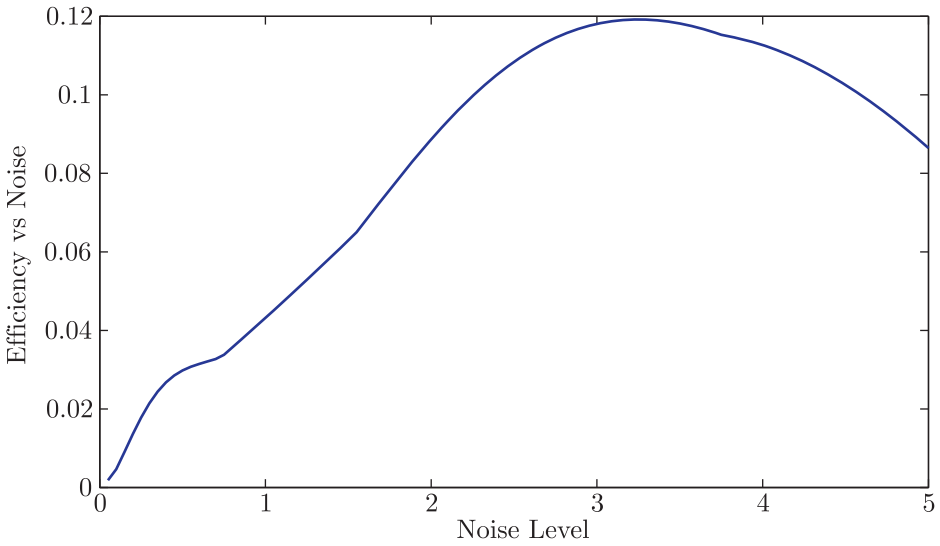

Fig. 10. Stochastic resonance — noise vs. efficiency.

when the time interval is $T = 0.001$, and the noise level is $\epsilon = 3.5$, the maximal efficiency is as high as $\gamma = 18.74\,\%$. This is different from the observations reported in [13], which indicates a low efficiency (around $5\,\%$) of molecular motors. (In some open systems with external force, the efficiency could be higher [15], which is different form our case)

Finally, if the state space is not a Euclidean space but a finite set of points, then our new Parrondo's paradox of free energy and our viewpoint of molecular motor based on the free energy (and also applied by using Fokker–Planck equation(s)) are also true. For details in the discrete case, please see [2].

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