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Nanotransport controlled by means of the ratchet effect

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Contents

Abstract. The directional motion of micro- and nanoparticles can be induced not only directly due to the effect of forces with a nonzero average value, which set the direction of the motion, but also, in the absence of such forces in systems with broken mirror symmetry, under the effect of nonequilibrium fluctuations of various natures (the motor or ratchet effect). Unlike other reviews on nanoparticle transport, we focus on the principles of nanotransport control by means of the ratchet effect, which has numerous practical applications and, in particular, is a promising mechanism for targeted delivery of drugs in living organisms. We explain in detail various techniques to arrange directional motion in asymmetric media by means of rectification of the nonequilibrium fluctuations that supply energy to the system and feature a zero average value of applied forces, whether actual or generalized. We consider in depth the properties and characteristics of ratchet systems, their dependences on temperature, load forces, and features of the periodic potential profile in which nanoparticles move, such as the frequency of fluctuations of this profile and its spatial and time asymmetry. A systematic description of factors that determine the direction of motion of ratchet systems is presented.

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1. Introduction

The directional motion of micro- and nanoscale particles — molecular and ionic clusters, associates, ensembles — is an amazing and at the same time ubiquitous phenomenon: it is an integral part of the processes occurring in inanimate and living nature, as well as various areas of human activity [1–5]. For example, almost all biological processes *in vitro* and *in vivo* include the transport of micro- and nanoparticles in liquid media [6–8]. We consider among an immense number of examples two phenomena related to the transportation and segregation of medical preparations and biological materials: electro- and dielectrophoresis. These two processes are best known among the so-called electrostatic classifiers — techniques to affect the spatial arrangement of particles in accordance with their electrical properties [9].

Despite the variety of types of electrostatic classifiers, they operate based on one common property of charges of the opposite sign, i.e., their ability to attract each other. Electrostatic classification, in which a charge is imparted to particles, is called electrophoresis [10]. Medical electrophoresis is widely known. It is the process in which medical preparations are transported by an electric field to a lesion site due to electrolytic dissociation caused by the current, i.e., drugs disintegrate into ions with opposite charges and advance to the opposite-polarity electrodes through the organs and tissues of the human body. In approaching the opposite-charge electrode, ions undergo electrolysis, i.e., lose a charge from their shell to become atoms that feature high physical and chemical activity. Thus, medical electrophoresis is a highly effective physiotherapeutic procedure in which a medicine is administered noninvasively (without injection) and instantly affects the target area; in addition, the activity of drugs is enhanced by galvanic current. The disadvantages of this method are that its application is limited (not all drugs can be administered using the electrophoretic technique), a high concentration of the drug cannot be attained, and the degree of its accumulation at the target site cannot be determined.

The separation of materials by means of electrophoresis is based on the difference in electrical conductivity or the

triboelectric properties of their particles. In industry, electrophoresis (electrodeposition) makes it possible to deposit small particles onto a surface, providing deep penetration into the indents and pores, and to create uniform and dense coatings of objects having a very complex shape. However, a disadvantage of the method is that the thickness of electrophoretic coating applied is 20–25 μm, and it cannot be increased further, since the already deposited layer, being an insulator, prevents the passage of current [11].

If a particle as a whole remains neutral but is polarized, i.e., acquires a dipole moment, then it begins to move, if the electric field is nonuniform. This phenomenon is referred to as dielectrophoresis [12–14]. Taking into account the effect of a nonuniform field on opposite ends of the particle and on the medium in which it is located, it can be shown that particles whose polarizability is higher than that of the medium are drawn into the region of higher electric field strength (positive dielectrophoresis), while those with a lower polarizability are pushed into the region of a weaker field (negative dielectrophoresis). The strength of the effect is determined by the gradient of the time-averaged field squared and does not depend on the direction of the field. The separation of particles is in this case based on the difference between their polarizabilities and, consequently, on the difference between the dipole moments they acquire, which depend on the dielectric properties and structure of the material, as well as on the size and shape of the particles.

Typically, this separation is carried out in a liquid. Since the field direction does not affect the motion of particles, the field may be created using alternating current with frequencies of 10 MHz and higher. The effect of the interaction between the particles and the field, which is proportional to their volume, is exhibited much more strongly in separating relatively large particles (more than 2 μm in size). Dielectrophoresis as a classification method requires a strongly nonuniform electrostatic field with a relatively high strength (much higher than that used in electrophoresis). In media with a low dielectric constant ($\varepsilon \sim 2-7$), it is usually 10^4 V m^{-1}, but if permittivity is high (for example, 80, as that of water), the field strength may be decreased to 500 V m^{-1}. Furthermore, for dielectrophoresis to be used, the difference between the dielectric constant of the particles and the medium in which the separation occurs should be significant ($\Delta\varepsilon \sim 2-100$). It has also been noticed that the dielectrophoretic effect is more pronounced in liquids with low viscosity.

H Pohl [14, 15], who laid the foundations of the theory of dielectrophoresis, was the first to apply this mechanism to microbiological objects [16]. Having applied a high-frequency electric field (2.55 MHz) and a moderate voltage (tens of volts) and using a medium with a low ion content (deeply desalinated water) and electrodes whose shapes were significantly different (to create field nonuniformity), Pohl observed that living yeast cells separated from dead ones. He also availed himself of the significant difference between the polarizabilities of water and microorganism cells that was found by H Schwan [17]. The dielectric constant of water and very dilute aqueous solutions is 80, while that of living cells is 10^2-10^4; specific electrical conductivity varies accordingly in a range of $3\times10^{-6}-2\ \Omega^{-1}$ cm^{-1} for water and 10^{-2}–$10\ \Omega^{-1}$ cm^{-1} for microorganisms.

The segregation of biomaterial is ensured in this case by the following main factors: (1) a high-frequency (HF) alternating field is used, (2) the process is carried out in a medium with very low electrical conductivity, (3) a nonuniform electric field is applied, and (4) there is a significant difference between the dielectric constants of microorganisms and that of the environment. Owing to significant differences among the dielectric properties of biological objects, dielectrophoresis has been actively used for several decades in medicine and biological research to transport and sort various types of cells, for example, to separate cancer cells from healthy cells or extract certain types of blood cells from the blood [18–22]. On the other hand, this method can also be used to characterize particles, in particular, to determine their dielectric characteristics and geometric parameters, as has been done, for example, in [23].

Although dielectrophoresis is widely employed to transport and segregate large (micrometer-sized) particles and cells, the use of electric fields to affect individual nanomolecules and nanoparticles remains completely undeveloped [12]. For small particles, to obtain forces that dominate over the Brownian effect, large, not yet realized field gradients are needed. Therefore, in operating facilities that use electric and optical fields (in devices such as laser tweezers), particles smaller than 100 nm still cannot be retained or separated. Experimentalists are now quite successfully handling micrometer-sized particles. However, according to estimates [12], there is a conceptual possibility that a nanotube tip with a radius of curvature of about 1 nm subjected to a voltage of 50 mV may create at a distance of 100 nm around a 1-nm-sized particle dielectrophoresis forces that exceed the thermal effect; should this be case, it would enable nanoparticles to be retained and sorted. The same estimates show that the dielectrophoresis forces in the vicinity of a nanotip can prove to be so large that they will be able not only to affect individual molecules and stretch them, but even to exceed the strength of the chemical bonds in molecules and lead to their breaking, thereby opening a way to new chemical transformations.

Thus, for the selective dielectrophoretic effect on individual nanoparticles (nanomolecules) to be realized, high field gradients are needed, i.e., very thin (nanometer in diameter) electrodes with nanometer distances between adjacent protrusions are required. However, the lithography methods tested so far, as well as the use of nanofibers to create electrodes, have failed to overcome the aforementioned difficulties and to produce working setups for nanodielectrophoresis [12, 24].

Conceptually new methods of directional particle transport have emerged in recent decades and are now actively being developed. They not only are competitors with standard techniques but in some cases may be combined with them. Particular attention is now being focused on theoretical studies and the practical application of so-called molecular, or Brownian, motors (ratchets), which play a crucial role in the directional motion of nanoparticles. These nanomachines, first discovered in living nature, are devices that, under the effect of nonequilibrium fluctuations of various nature, transform chaotic Brownian motion into directional translational, reciprocal, or rotational motion. Brownian protein motors provide contractile activity of tissues (muscle function), cell mobility (motion of bacteria flagella), and intracellular and intercellular transport of organelles and relatively large particles of matter (cell nutrition and disposal of waste emerging from cell activity). These processes feature surprisingly high efficiency, approaching 100%. These systems operate based on the ratchet effect: the Brownian motion is rectified due to nonequilibrium fluctuations that supply energy to the system

and are characterized by a zero average value of applied actual or generalized forces.

The control of nanotransport using the ratchet effect is based on external processes of various nature [25–29]. These processes in human-made ratchets usually have a deterministic character, are cyclically repeated in time, and are described by periodic functions [26, 27, 29–33]. On the other hand, in ratchets of natural origin (operating in living and nonliving objects), stochastic processes usually occur [25, 29, 34–39]. It is of importance that the average value of the forces that affect a particle during such processes is zero (the case of unbiased fluctuations); however, the asymmetry of the system and the nonlinearity of the potential-energy fluctuations generated by these processes result in the emergence of directional motion. One of the first examples of this kind is the emergence of a direct electric current under the effect of a high-frequency electromagnetic field in media without a center of symmetry (photovoltaic effect) [40].

Ratchets that operate due to deterministic fluctuations can be most simply designed if the fluctuations are harmonic in time [41, 42]. The deterministic dichotomous process, which can be represented as a model with two alternating states with constant characteristics [43–46], is also often used to implement the ratchet effect. At the same time, there exist ratchets with a relaxation retarded response to the deterministic dichotomous process. Periodic laser pulses are used, for example, as such a process: they cause a periodic delayed response of the electron subsystem in a nanoparticle [47]. This case is described by a theory that considers arbitrary periodic processes [44, 47, 48].

The emergence of stochastic fluctuations in a Brownian ratchet usually implies that there is a set of discrete states, for example, conformational states of proteins, between which transitions occur with certain rate constants [25]. Since the interaction of protein with the environment depends on the conformational state, the potential energy of the particle is a function of the state, and its dynamics are described by kinetic equations that contain the rate constants of transitions between the states. If the states are well defined and the times of transitions between them are significantly shorter than their lifetimes, it may be assumed that the transition rate constants are independent of the history of the process, i.e., the process is classified as a Markov process. For convenience of description, only a small number of states [49–51] are considered, most often two [43, 44, 51–61]; the process is referred to in this case as stochastic dichotomous. Along with the Markov processes that control the ratchet effect, models of anomalous molecular motors are considered for a number of systems that are characterized by non-Markov diffusion [28, 62–70]. In most studies of the ratchet effect, the particle mass is not taken into account, since the Brownian motion is considered in the overdamped regime, when friction prevails over inertia. This approximation is well substantiated for many biological applications [25, 71].

Since the motion of Brownian (molecular) ratchets can be controlled — and if energy is supplied to them, they can perform some work — the use of such machines as nanorobots seems very promising. The practical potential of molecular motors has won the highest international recognition: the 2016 Nobel Prize in Chemistry was awarded to J-P Sauvage, J F Stoddart, and B L Feringa "for their design and production of molecular machines" [72, 73]. The most straightforward ways to use them in biology and medicine are targeted drug delivery and segregation of biological products (in living and nonliving objects).

It is expected that Brownian ratchets will be able in the near future to enhance, supplement, and in some cases replace standard methods of transportation and segregation of medical preparations and biological materials, such as the electro-and dielectrophoresis techniques considered above.

Ratchets with a fluctuating force [25] can operate inside the body when there is a spatially periodic static potential (electrostatic or entropic in its nature [74]), and the electrophoretic effect in an alternating field is the force that drives charged particles. From the theoretical viewpoint, there are no restrictions for attaining with the help of such ratchets any, and in addition accurately measurable, concentration of medicinal substances on the target site. This would expand the scope of medical electrophoresis.

The use of Brownian ratchets under dielectrophoretic conditions could provide selectivity for the motion of nanoobjects and thereby create an alternative or supplement to the dielectrophoretic effect. The list of advantages of 'dielectrophoretic ratchets' includes a larger number of parameters to control motion, including temperature, frequency, and pulse shape of the applied field, viscosity of the medium, etc. An experiment of this kind, however, with micrometer-sized particles (latex beads) was carried out by L Gorre-Talini et al. [75].

The effect of a spatially asymmetric potential on particles combined with their diffusion resulted in the emergence of directional motion of the particles. The required potentials were generated in a dielectrophoretic cell, i.e., electrodes of a special shape were immersed in a suspension of particles to create nonuniform alternating electric fields. Two modes of the ratchet effect were used: with and without a diffusion stage. In the first case, two states alternated, in one of which the Brownian particle was at the minimum of the sawtooth potential, while in the second it freely diffused. In the regime without a diffusion stage, two potentials with similar characteristics, shifted with respect to each other by a fraction of the period, were alternately used, and the Brownian particle, consequently, moved between the minima of these potentials. In both modes, good agreement was observed with theoretical estimates of the characteristics of particle motion. In particular, particles of different sizes moved with different macroscopic velocities, providing a conceptual opportunity to develop an effective separation technique and the selective transport of particles in a given direction.

Unlike the existing reviews and monographs on Brownian motors [25–29, 76], the goal of this review is to present the principles of nanotransport control by means of the ratchet effect that could be used in various practical areas, including drug delivery in animals and humans. The presentation is organized as follows. Section 2 contains the most common classification of Brownian motors to date and a discussion of the basic principles of their functioning. Conditions for the emergence of the ratchet effect and its parameters and characteristics are presented in Section 3. The issue of most interest and importance for practice, which arises when discussing the ratchet effect, is to elucidate the factors that determine the direction in which a Brownian particle drifts. Section 4 contains an overview of such factors based on the results of recent publications; it outlines the advantages of the ratchet effect in controlling the motion of nanoobjects over simple methods, which are reduced to the effect of gradients of concentration or forces with nonzero average values. These advantages are discussed in more detail in the final section of the review.

2. Classification and principles of operation of Brownian motors

The directional movement of nanoparticles that is induced by the ratchet effect may be due to various factors and, accordingly, described by various models. The classification of these models that has been developed to date reflects the various principles under which Brownian motors operate. This classification is based on belonging to a particular mathematical model; it is determined by the specific equations that are used to find the average velocity of the directional motion and the way of introducing nonequilibrium fluctuations that bring energy into the system. Therefore, this section presents to the reader the information needed to classify the phenomena under consideration. Examples of actual experimental setups that illustrate the principles of ratchets operation are also given. For clarity, we primarily consider one-dimensional systems in which friction prevails over inertia, i.e., the so-called overdamped regime is implemented. At the same time, the most impressive examples of going beyond the limits of the one-dimensional description in the overdamped regime that take into account inertial, entropic, collective, and quantum effects are also given.

The basic equation of the theory of Brownian motors is the Smoluchowski equation for the distribution function $\rho(x, t)$ [77]:

$$\frac{\partial \rho(x, t)}{\partial t} = D \frac{\partial^2 \rho(x, t)}{\partial x^2} + \frac{1}{\zeta} \frac{\partial}{\partial x} U'(x, t)\, \rho(x, t)\,, \qquad (1)$$

where $D = k_B T/\zeta$ is the diffusion coefficient (k_B is the Boltzmann constant, T is the absolute temperature, and ζ is the friction coefficient), and the applied force $-U'(x, t)$ is spatially periodic, $U'(x + L, t) = U'(x, t)$, where L is the period. This equation describes the inertialess motion of a nanoparticle with a time-dependent potential energy $U(x, t)$, when friction prevails over inertia (the overdamped regime). A description based on the Smoluchowski equation corresponds to a situation where the time for the establishment of the equilibrium Maxwell distribution in the phase space of velocities $\tau_v = m/\zeta$ (m is the mass of the particle, ζ is the friction coefficient) is the smallest characteristic time of the system.

Given the spatial periodicity of the applied force, to simplify the calculations of the characteristics of Brownian motors, it is reasonable to assume that each spatial period L contains on average one particle. It is convenient then to introduce the reduced distribution function $\tilde{\rho}(x, t) = \sum_{n=-\infty}^{\infty} \rho(x + nL, t)$ normalized to unity, $\int_0^L \tilde{\rho}(x, t)\, \mathrm{d}x = 1$, that satisfies the Smoluchowski equation (1), and the flow [25]

$$\tilde{J}(x, t) = \sum_{n=-\infty}^{\infty} J(x + nL, t) = -D \exp\big(-\beta U(x)\big) \times \frac{\partial}{\partial x}\big[\exp\big(\beta U(x)\big)\, \tilde{\rho}(x, t)\big], \quad \beta = (k_B T)^{-1} \qquad (2)$$

(for notational brevity, the tilde sign above these symbols will be omitted below). An advantage of using the reduced quantities $\rho(x, t)$ and $J(x, t)$ is that it is now possible to supplement the Smoluchowski equation with periodic boundary conditions and simplify (in the case of steady-state processes) the calculation of the main characteristic of a Brownian motor, viz., the average velocity of directional motion. A rigorous definition of this quantity, applicable to both stochastic and deterministic fluctuations of potential energy, is given by the following formula:

$$\langle v \rangle \equiv \lim_{T \to \infty} \frac{1}{T} \int_0^T \mathrm{d}t \int_0^L \mathrm{d}x\, J(x, t)\,. \qquad (3)$$

An indicator that the motor effect emerges is a nonzero value of the velocity $\langle v \rangle$. Definition (3) may be simplified for steady-state deterministic processes that are periodic both in space and in time (with a period τ) when the functions $\rho(x, t)$ and $J(x, t)$ also become periodic in time:

$$\langle v \rangle = \frac{1}{\tau} \int_0^\tau \mathrm{d}t \int_0^L \mathrm{d}x\, J(x, t)\,. \qquad (4)$$

Various approaches to the classification of Brownian motors have been developed. One of the most general classification criteria is the source of nonequilibrium (the type of fluctuations) in the Smoluchowski equation. Consequently, ratchets with a fluctuating temperature, a fluctuating coefficient of friction, and a fluctuating potential energy are distinguished. The nature of fluctuations, in turn, enables smaller subclasses to be distinguished [25].

The first important class of theoretical models includes Brownian motors in which nonequilibrium is introduced through the coordinate and/or time dependence of the temperature that enters the expression for the intensity $2\zeta k_B T(x, t)$ of Gaussian white noise $\xi(t)$ (normalized by the condition $\langle \xi(t)\xi(t') \rangle = 2\zeta k_B T \delta(t - t')$). This class of motors is referred to as thermal (temperature) ratchets, thermal motors, or Seebeck motors. If the friction coefficient $\zeta(x, t)$ that varies with the coordinate and/or over time and also determines the intensity of Gaussian white noise is used, a second class of Brownian motors, referred to as friction ratchets, may be introduced. It should be noted that, strictly speaking, the noise $\xi(t)$ in these two classes of motors is no longer equilibrium, since it is a product of truly equilibrium white noise and a factor that introduces nonequilibrium into the system (due to its dependence on x and t).

The third class of Brownian motors includes systems with fluctuating potential energy (T and ζ are assumed to be constant). Subclasses are distinguished within this class that differ in how space and time asymmetries of potential energy are manifested in the characteristics of the directional motion of motors. For convenience of discussion, we present the total potential energy of the particle $U(x, t)$ as a sum of the spatially periodic contribution $V[x, f(t)] = V[x + L, f(t)]$ and the contribution of a uniform fluctuating external (deflecting) force $F(t)$ (the so-called tilting force):

$$U(x, t) = V[x, f(t)] - F(t)\, x\,. \qquad (5)$$

The first subclass of ratchets with potential energy of the form (5) consists of models in which $f(t) = 0$, and directional motion is induced by time fluctuations of the external force $F(t)$ with a zero average value in the presence of a stationary spatially periodic potential $V(x)$. Such ratchets are referred to as tilting. Fluctuating force ratchets, for which $F(t)$ changes stochastically, and rocking ratchets with periodic driving force $F(t)$ are distinguished in this subclass. It is the rocking ratchets that are the most significant for controlling in practice the potential energy of the system. The 'rocking ratchet' term in many studies implies both stochastic and deterministic fluctuations of the external force, i.e., it

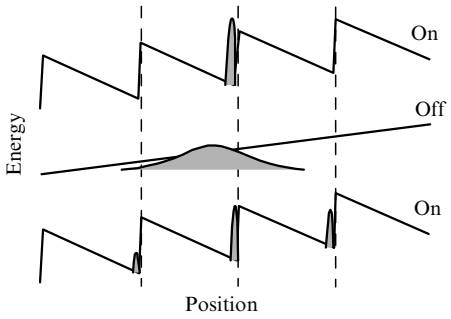

Figure 1. Three states of an on-off ratchet that explain how directional motion of nanoparticles emerges. The shaded bell-shaped contours display the distribution functions (probability densities) for a nanoparticle in each state before switching the potentials.

combines both types of ratchets and is used as a synonym for the 'tilted ratchet' term. Ratchets with stochastic changes in the external force $F(t)$ are often referred to as correlation ratchets [25, 78, 79].

The second subclass includes ratchets for which $F(t) = 0$, and directional motion is induced by time fluctuations of the spatially periodic potential energy $V[x, f(t)]$. In Reimann's terminology [25], such ratchets are referred to as pulsating. This subclass includes fluctuating potential ratchets, whose potential energy $V[x, f(t)]$ may be represented in a multiplicative form $V[x, f(t)] = V(x)[1+f(t)]$, i.e., temporary (periodic or stochastic) changes in potential energy occur due to changes in its amplitude. It is often assumed that the function $f(t)$ takes only two values (dichotomous process). Then the motor effect is possible only for the asymmetric function $V(x)$ and in the presence of thermal noise. A special case of this type of ratchets with a fluctuating periodic profile of potential energy is so-called on-off ratchets, or flashing ratchets, that are now under intense theoretical end experimental exploration. For these ratchets, $f(t) = \pm 1$ (a value of $+1$ corresponds to the 'on' state, while a value of -1 corresponds to the 'off' state). Flashing ratchets mean in a number of studies the entire second subclass of models with $F(t) = 0$ in Eqn (5).

Let the nanoparticle be in a periodic piecewise linear (sawtooth) asymmetric potential (Fig. 1) that cyclically switches from the 'on' state to the 'off' state. If the potential is turned on, the coordinate of the maximum probability density of the particle coincides with the minimum of the potential well. If the potential is switched off, the particle diffuses with equal probability to the left and to the right (the probability density distribution broadens), and, if an additional load force is present, it also simultaneously moves in the direction set by that force (in graphical terms, the introduction of this force is equivalent to tilting the potential contour by a certain angle). Since the potential is asymmetric, and each minimum is shifted to the right with respect to the middle of the distance between two neighboring maxima, the next time the potential is switched on, the particle is more likely to be in the right well than in the left one, relative to its initial position. Thus, periodic alternations of the on- and off-potential combined with the diffusion process result in the motion of the nanoparticle to the right, including the motion in the direction opposite to the load force in effect [80]. The presence of thermal noise is in this case of crucial importance: it enables diffusion in the off state of the motor process. Energy is supplied to the system by switching between potentials, and part of it is converted into the useful work performed by the particle against the load force. If the asymmetry of the potential is reversed (the sign of the 'saw' tooth tilt changed to the opposite), the direction of the induced motion of the particle also changes to the opposite one.

It should be noted that the considered ratchet effect with a deterministic on-off potential has many practical applications. For example, it underlies the diffusion separation of particles, in particular, the separation of particles by size that occurs in dielectrophoretic ratchets [81]. At the same time, the ratchet effect with random (stochastic) switching of the potential provides directional motion of KIF1A single-headed kinesins [82]. The fluorescent labeling method was used to show that the characteristic values of the effective diffusion coefficient and average directional velocity are of the order of 10,000 $\mathrm{nm^2\ s^{-1}}$ and 300 $\mathrm{nm\ s^{-1}}$, respectively.

The two subclasses of ratchets considered above exhibit different analytical dependences of the average velocity on the coefficients of spatial (κ) and time (ε) asymmetries, which are defined in such a way that the spatial symmetry is characterized by the value $\kappa = 0$ and time symmetry by the value $\varepsilon = 0$. Consequently, $\langle v\rangle = \kappa\Phi_{r\kappa} + \varepsilon\Phi_{r\varepsilon}$ for rocking ratchets and $\langle v\rangle = \kappa(\Phi_{f\kappa} + \varepsilon\Phi_{f\varepsilon})$ for fluctuating-potential ratchets, where Φ are certain functions of the motor parameters [83]. In addition, the average velocity in the adiabatic limit $\tau \to \infty$ is nonzero for the first subclass and tends to zero for the second subclass.

Figure 2 shows functional diagrams of Brownian motors in these two subclasses. The potential energy has the form $U(x, t) = V(x) - Fxs(t)$ for ratchets with a fluctuating uniform force (Fig. 2a) and $U(x, t) = V(x)[u + w\sigma(t)]$ for ratchets with a fluctuating periodic potential energy (Fig. 2b), where $\sigma(t) = \varepsilon + s(t) = \pm 1$ with $\langle s(t)\rangle = 0$, and w and u are dimensionless parameters. The $s(t)$ function takes two values with the durations τ_+ and τ_- whose sum is equal to the period of the cyclic process τ. The asymmetry κ of the $V(x)$ function determines the shift of the minima of this function relative to the middle of the distance between the nearest maxima. Due to symmetric force fluctuations ($\tau_+ = \tau_- = \tau/2$, $\varepsilon = 0$), the periodic potential relief is tilted to the right and to the left by equal angles. In this case, as a result of spatial asymmetry of this relief ($\kappa \neq 0$), when moving to the right, the particle has to overcome higher potential barriers than when moving to the left (the left side of Fig. 2a). Due to asymmetric force fluctuations ($\varepsilon \neq 0$), the periodic potential relief is tilted at different angles, which gives rise to motion in the direction of the larger tilt (the right side of Fig. 2a). Thus, the direction of motion, which is determined by the relief asymmetry, may be reversed by introducing a nonzero coefficient of time asymmetry.

The mechanism of operation of Brownian motors with fluctuating periodic potential energy is completely different. In the case of symmetric time fluctuations ($\varepsilon = 0$), directional motion emerges due to the fact that in a state with a smaller amplitude of the asymmetric potential relief, transitions of the particle are facilitated for the potential barrier which is closer to the minimum of the potential well (the left side of Fig. 2b). On the contrary, if time fluctuations are asymmetric ($\varepsilon \neq 0$) and the sign of the potential energy fluctuates ($u = 0$), directional motion emerges exclusively due to the different lifetimes of the states of the dichotomous process, i.e., the time asymmetry. Particle localization near the minimum of the potential well is thermodynamically justified in the state with the longer lifetime, while the kinetic effect of a rapid

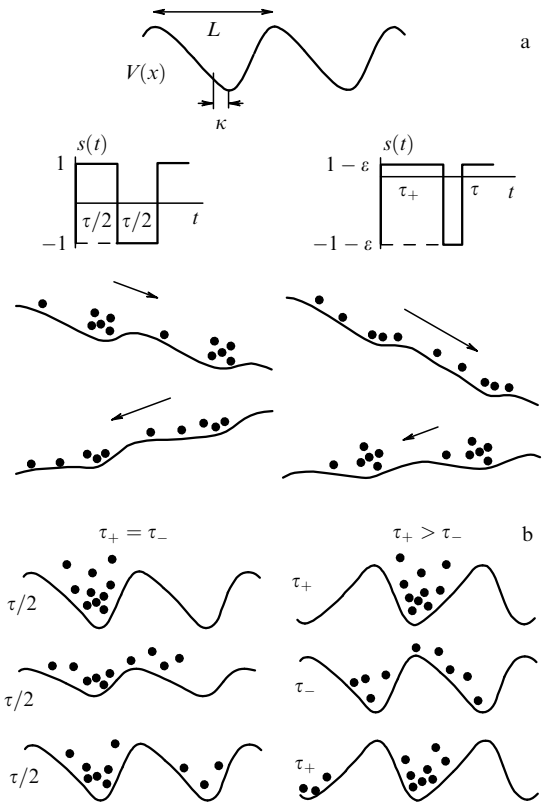

Figure 2. Functional diagrams of two subclasses of Brownian motors: (a) with a fluctuating uniform force, (b) with a fluctuating periodic potential energy.

descent of a particle on a steep section of the potential profile prevails in the state with a shorter lifetime (the right side of Fig. 2b). The direction of motion in this case is opposite to that realized in the case $\varepsilon = 0$ and $u \neq 0$.

For pulsating ratchets of a general kind, in which not only the amplitude but also the shape of the potential profile changes, the presence of thermal noise and the asymmetry of fluctuating potential profiles are no longer the necessary conditions for the existence of the motor effect. Pulsating ratchets also include so called traveling potential ratchets with the potential of the form $V[x, f(t)] = V[x - f(t)]$. It is assumed in the simplest case that $f(t) \equiv ut$, where u is the constant drift velocity of the potential relief itself. Such 'genuine traveling potential ratchets' describe the Stokes shift of particles placed in a drifting periodic potential. As a second example, we present ratchets that operate due to the dichotomous process of cyclic switching between the potentials shifted by half a period; in this case, the periodic function $f(t)$ defined on the interval $0 < t < \tau$ has the form $f(t) = (L/2)\,\theta(\tau_a - t)$, where τ_a and $\tau_b = \tau - \tau_a$ are the lifetimes of the states a and b ($\theta(t) = 1$ if $t > 0$ and $\theta(t) = -1$ if $t < 0$). Both of these ratchet models are characterized by high efficiency under certain conditions.

A prototype of such models is presented by two-headed kinesins, whose motion along a microtubule consists of periodically repeating cycles. The energy needed by these motor proteins to move against viscous friction forces is supplied by the reaction of binding and hydrolytic decomposition of ATP (adenosine triphosphate) into ADP (adenosine diphosphate) and inorganic phosphate P_i ($ATP + H_2O \rightarrow ADP + P_i + 20k_BT$, where $T \approx 300$ K), so that each cycle provides an energy output of $20k_BT$ [84, 85]. Kinesin heads are alternately in states when one of them is in contact with the microtubule tubulin, while the second, bound to the ADP molecule, is remote from the microtubule and does not contact it. In one step of the motor protein along the microtubule, each head moves a distance of 2 tubulin dimers (8 nm) and can reach a velocity of about 800 nm s^{-1}, performing work against a load force of up to 5 pN [86, 87].

There are other types of ratchets that are combinations and generalizations of the two subclasses discussed above. An example is a model based on synchronous fluctuations of a symmetric potential and applied uniform force. The principle of operation of such ratchets is very simple. If the functions $f(t)$ and $F(t)$ in Eqn (5) synchronously fluctuate between two sets of values, it is possible to create the so-called gating mechanism, i.e., to make the potential profile be turned off at positive values of $F(t)$ and slow down the reverse movement at negative values of $F(t)$. As a result, if $\langle F(t) \rangle = 0$, the particle will move towards positive values of $F(t)$ even in the spatially symmetric potential $V[x, f(t)]$. Such a mechanism can be implemented in a 2D near-surface motor that moves simultaneously in longitudinal and transverse directions relative to the polar substrate plane due to fluctuations of an external force tilted with respect to the surface [83, 88, 89].

Going beyond a one-dimensional description provides new options for implementing the ratchet effect. Directional motion can occur in a medium with periodically placed asymmetric scatterers under the effect of an oscillating force with a zero average value (the ratchet effect in a 2D system with a fluctuating uniform force) [90].

A separate type of Brownian motor, so-called geometric or entropic ratchets, is associated with Brownian motion in tubes and channels, whose cross section periodically changes. The entropy of a diffusing particle is determined under such conditions by the space region accessible to it, i.e., depends on its coordinate along the channel axis. The entropy of the particle multiplied by its thermal energy can be considered then as the entropy potential [91] that performs as a conventional energy potential in the one-dimensional diffusion problem. Based on this analogy, it may be expected that periodic or random unbiased effects on a particle in asymmetric tubes and channels may result in the emergence of the ratchet effect. Entropic ratchets, similar to standard energy ratchets, operate due to fluctuations in force [92] and periodic potential [74, 93] (entropic rocking and flashing ratchets). It is noteworthy that, with the same channel shape, the space regions available for diffusion of spherical particles depends on their radius: if the radius is small, these regions almost coincide with the inner space of the channel, while for a large radius they can be much smaller. Therefore, not only the diffusion coefficient but also the entropy potential depend on the particle radius. Owing to this, an effective mechanism may be proposed for separating nanoparticles by size under the effect of a fluctuating force [94]. Furthermore, if the particle size can be changed using some external process, the entropic ratchet will operate due to fluctuations of both the diffusion coefficient and the entropy potential [74, 93]. Such an external process may be represented by pulsed ultraviolet (UV) irradiation that creates or destroys cross links between photochromic groups [95] or by alternating UV and visible-range irradiation that causes a reversible change in the size of particles in a photosensitive microgel [96].

It is of interest that the collective ratchet effect in tubes and channels with a periodically varying cross section can also be achieved under the effect of a fluctuating force in the presence of repulsion between diffusing particles. Indeed, such repulsive interactions cause particles to be pressed to the channel walls, and their distribution is subject to spatial modulation. It is asymmetric for asymmetric channels and as a result of this, a directional motion initiated by unbiased fluctuations of the force emerges [26]. Study [97] was the first to simulate this phenomenon by the molecular dynamics method using as an example the transport of fluxons in superconducting devices.

Taking into account quantum-mechanical laws in models of human-made Brownian motors results in basically new phenomena that are not possible in the classical description. The quantum nature of fluctuations and the quantum evolution laws governed by quantum statistical mechanics enabled the discovery of unexpected transport mechanisms that emerge due to sub-barrier tunneling and over-barrier reflection of a particle, as well as due to explicit consideration of its inertia [26]. The particle transport mechanism is determined in this case by the particle mass, medium temperature, height and shape of the barrier to be overcome, and fluctuations in the reaction system and molecular environment [98–101]. The temperature dependence of the tunneling transport rate constant is affected by the reorganization of the medium [102], changes in the shape and height of the potential barrier in intermolecular vibrations [99,100], and energy dissipation due to various fluctuations (see reviews [26, 101] and references therein).

The first theoretical description of a quantum ratchet was provided in the pioneering work of Reimann, Griffoni, and Hänggi [103], who discovered a number of impressive implications of quantum effects. First, the average velocity of the directional motion of quantum particles was much higher than that of the same particles in the classical description. This difference was especially pronounced in the low-temperature region, where the particle velocity vanished in the classical description but remained nonzero in the quantum description due to sub-barrier tunneling. However, the most surprising implication of taking quantum effects into account was that the direction of motion reversed with decreasing temperature, a theoretical result that was soon confirmed in experiments [104]. At present, the ratchet effect is also studied in systems that in no way can be described without a quantum-mechanical theory. These systems include, for instance, electronic ratchets and cold atoms in optical lattices [105]. Unusual manifestations of the ratchet effect in purely quantum systems (coupled Josephson junctions, quantum dots, molecular wires, etc.) are discussed in detail in review [26].

3. Ratchet effect, its parameters and characteristics

In studying the ratchet effect, the interest is focused on measuring or calculating its certain characteristics, which depend on the parameters of the environment, the spatio-temporal behavior of the potential energy, and nonequilibrium fluctuations that supply energy to the system. Depending on the values of these parameters, various approximations are chosen that are used in the theoretical description of the ratchet effect.

The ratchet effect occurs when a number of conditions are met [25, 106, 107]. The first is the presence of nonequilibrium fluctuations that provide energy to the system from various external sources. The fluctuations may originate from radiation, thermal processes, fast chemical reactions, or rapidly changing electric fields that cause, e.g., jump-like changes in the rate constants of chemical reactions associated with directional transport of nanoparticles. The second important condition for directional motion to emerge is the presence of a preferred direction in the system that arises from the asymmetry of the potential energy of the nanoparticle in the medium under consideration. The examples of the implemented ratchet effect presented in Section 2 clearly show that these conditions must be fulfilled.

The ratchet effect parameters depend on the type of nonequilibrium fluctuations and the form of potential energy that describes the interaction between the nanoparticle and the medium. The temperature of the medium and the coefficient of friction, which determine the diffusion coefficient of the particle in the medium, are also the ratchet effect parameters. For example, in considering deterministic fluctuations described by a periodic function of time, the most important parameter is its period τ. An analog of the period for a stochastic dichotomous process is the inverse sum $(\gamma_+^{-1} + \gamma_-^{-1})^{-1}$ of the inverse frequencies (γ_+ and γ_-) of transitions between the two states of this process. Another parameter, the sum of the transition frequencies, determines the inverse correlation time $\Gamma = \gamma_+ + \gamma_-$. All these time parameters that characterize fluctuations may compete with the time parameters that describe properties of the space-periodic potential profile. The latter parameters include, first of all, the characteristic diffusion time τ_D on the period L of the potential profile, $\tau_D = L^2/D$, where D is the diffusion coefficient. If the potential profile contains narrow segments whose length is $l \ll L$, where it rapidly changes, another characteristic diffusion time, $\tilde{\tau}_D = l^2/D$, emerges for these segments, which is much shorter than τ_D. Therefore, as the fluctuation period τ (or frequency Γ) changes, a special behavior of the ratchet characteristics may be expected if τ proves to be of the order of τ_D and $\tilde{\tau}_D$ [44, 47, 48, 61, 76, 108].

Figure 3 shows the frequency dependences of the average velocity in dimensionless units calculated using relations from [61] for two main subclasses of ratchets that operate due to the asymmetry of the sawtooth potential ($V(x) = V_0 x/l$ for $x \in [0, l]$ and $V(x) = V_0(L-x)/(L-l)$ for $x \in [l, L]$), viz., ratchets with a fluctuating force (the upper part of the figure)

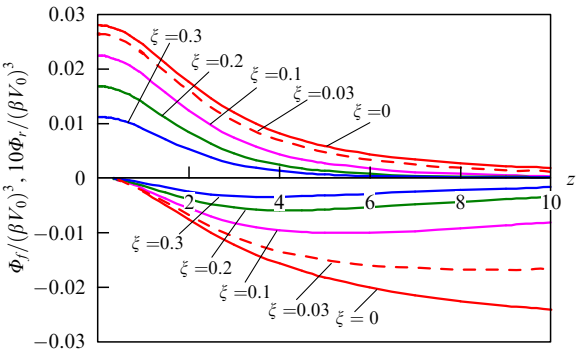

Figure 3. Families of the frequency dependences of the average velocity (in dimensionless units) for a ratchet with a fluctuating force (the upper part of the figure) and a pulsating on-off ratchet (the lower part of the figure) calculated using Eqns (7) for the same sawtooth potential with various ratios of the linear segment length l to the period L, $\xi = l/L$.

and pulsating on-off ratchets (the lower part of the figure) (similar frequency dependences were discussed in [53, 76]). Given the same asymmetry of the potential profile $V(x)$, the directions of motion for these two subclasses of ratchets are opposite. The low-frequency (LF) limit of the average velocity of a pulsating ratchet is zero, whereas for a ratchet with a fluctuating force, it is nonzero. The τ_D parameter identifies the LF region ($\Gamma < \tau_D^{-1}$), in which the velocity barely depends on frequency for the ratchet with a fluctuating force and decreases linearly with Γ for the pulsating ratchet. Due to the presence of segments $l \ll L$ and small characteristic times $\tilde{\tau}_D \ll \tau_D$ for pulsating on-off ratchets, in the region of high frequencies (HF) τ^{-1} that correspond to times τ of the order of $\tilde{\tau}_D$, the average velocity decreases very slowly with increasing frequency and tends to a nonzero value in the case of an extremely asymmetric sawtooth potential with $l \to 0$ [60, 61, 109]. As for ratchets with a fluctuating force, the HF region is characterized by a decrease in the velocity proportional to τ^{-3} for arbitrary smooth potentials, $\tau^{-5/2}$ for a sawtooth potential with cusps, but without jumps ($l \neq 0$), and τ^{-1} in the presence of jumps ($l = 0$) [61, 110]. Thus, the HF region proves to be very sensitive to the shape of the potential profile.

In the LF region, an adiabatic mode of motion is realized, for which the dependences of the average velocity (and energy characteristics) on the shape of the potential profile may be represented in an analytical form [76, 106, 111]. For example, the average velocity for a ratchet with a sawtooth potential that switches between the states a and b is given by the relations [112, 113]

$$\langle v\rangle = \frac{L}{2\tau}\kappa f(a,b)\,,$$
$$f(a,b) = \frac{a}{\sinh^2 a} + \frac{b}{\sinh^2 b} - \frac{a+b}{a-b}\,\frac{\sinh(a-b)}{\sinh a \sinh b}\,, \qquad (6)$$

where $a = \beta V_a/2$, $b = \beta V_b/2$, V_a and V_b are the heights of potential barriers in the states a and b, $\kappa = 1 - 2l/L$ is the asymmetry parameter, and the function $f(a,b)$ is displayed in Fig. 4.

Another approximation, which is widely used in the ratchet theory to obtain analytical relations, corresponds to the small ratios of the potential barrier heights to the thermal energy $k_B T$; it is referred to as the high-temperature [44] (or low-energy [83]) approximation. An example is the representation [61]

$$\langle v\rangle_f = \frac{L}{\tau}\Phi_f\,,\quad \langle v\rangle_r = -\beta L\zeta^{-1}F^2\Phi_r\,,\quad \Phi_r = 2\Phi_f + \Delta\Phi_r\,,$$
$$\Phi_f = \frac{(\xi'-\xi)(\beta V_0)^3}{128(\xi'\xi z^2)^2}\left[6f_1(z,\xi) - 3f_2(z,\xi) + f_1(z,\xi)f_2(z,\xi)\right],$$
$$\Delta\Phi_r = -\frac{(\xi'-\xi)(\beta V_0)^3}{16(\xi'\xi z^2)^2}\left[2f_1(z,\xi) - f_2(z,\xi)\right], \qquad (7)$$
$$f_1(z,\xi) = 1 - \frac{\sinh(z\xi)\sinh(z\xi)'}{\xi\xi' z\sinh z}\,,\quad f_2(z,\xi) = 1 - \frac{\sinh[z(\xi-\xi')]}{(\xi-\xi')\sinh z}\,,$$
$$z = \frac{L}{\sqrt{D\tau}} = \sqrt{\frac{\tau_D}{\tau}}\,,\quad \xi = \frac{l}{L}\,,\quad \xi' = 1-\xi\,,$$

which is valid for stochastic switching between states with identical frequencies $\gamma_+ = \gamma_- = 2/\tau = \Gamma/2$ for an on-off ratchet pulsating between sawtooth and zero potentials (indices f) and a ratchet with fluctuating force (indices r), in which the sawtooth potential undergoes fluctuations $\pm Fx$. The dependences plotted in Fig. 3 represent Eqns (7).

The effect of the nature of fluctuations on the frequency dependence of the average velocity of motion was studied in [108] using the high-temperature approximation and sinusoidal spatial dependence $w(x)$ of the fluctuation part of the potential energy that has an additive-multiplicative form $U(x, t) = u(x) + \sigma(t)w(x)$. It turned out that for an arbitrary asymmetric form of the stationary part $u(x)$ of the potential profile, the frequency dependence of the average velocity is proportional to the functional $\Psi\{\sigma(t)\}$ of the function $\sigma(t)$ that describes the time dependence of deterministic or stochastic fluctuations. Figure 5 displays how this functional depends on the inverse fluctuation period (the inverse average period in the stochastic case) for fluctuations of various types. Figure 5 shows that deterministic fluctuations are characterized by narrower frequency distributions than are stochastic ones, and, in the case of deterministic fluctuations, the stepwise dichotomous change in the function $\sigma(t)$ yields a larger effect than the sinusoidal change. On the other hand, the LF asymptotics of the average velocity show the same

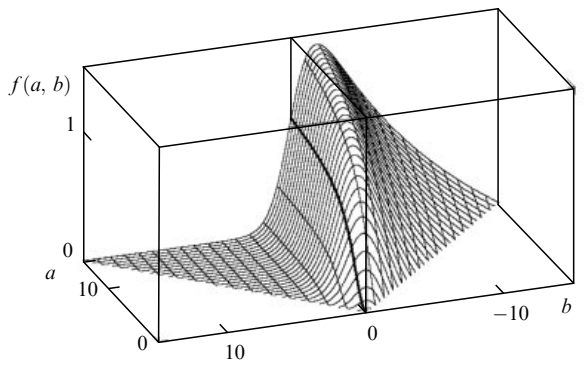

Figure 4. Average velocity of motion (in dimensionless units) for an adiabatic ratchet operating in the dichotomous mode $a \rightleftarrows b$ (Eqn (6)) as a function of the amplitudes $V_a/2$ and $V_b/2$ of the spatial variation of potential energies scaled to thermal energy $k_B T$.

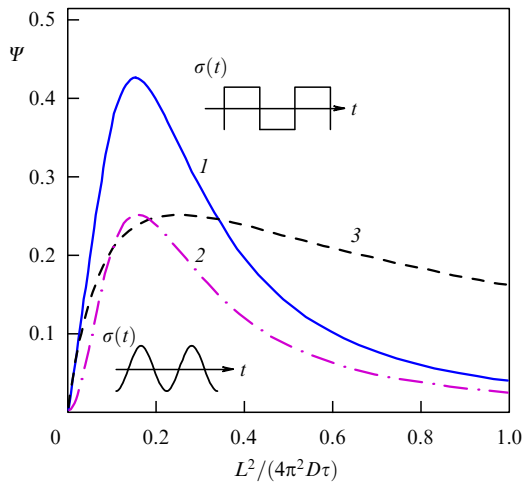

Figure 5. Frequency dependence of the average velocity of motion for various types of deterministic or stochastic fluctuations, namely, for deterministic stepwise and sinusoidal time dependences $\sigma(t)$ (solid (*1*) and dashed-dotted (*2*) curves) and the stochastic dichotomous process with the same average period (dashed curve (*3*)).

linear behavior for deterministic and stochastic dichotomous fluctuations and quadratic behavior for sinusoidal fluctuations.

A more efficient but at the same time more complex approximation, which requires employment of the Green's function technique, is the small-fluctuation approximation. It assumes an arbitrary amplitude of variation of the space-periodic function $u(x)$ in the formula $U(x, t) = u(x) + \sigma(t)w(x)$, the $\sigma(t)$ function of order of one, and a small ratio of the amplitude of variation of the $w(x)$ function to the thermal energy $k_B T$. The average ratchet velocity may be represented in this approximation using a unified formula [114]:

$$\begin{aligned} \langle v\rangle &= L\beta^2 D^2 \int_0^L \mathrm{d}x\, \rho_+(x)\, w'(x) \int_0^L \mathrm{d}x'\, S(x, x') \\ &\quad \times \frac{\partial}{\partial x'}\, w'(x')\, \rho_-(x') + O(w^3)\,, \\ S(x, x') &= \int_0^\infty \mathrm{d}t\, g(x, x', t)\, K(t)\,, \\ \rho_\pm(x) &= \frac{\exp(\pm\beta u(x))}{\int_0^L \mathrm{d}x \exp(\pm\beta u(x))}\,, \end{aligned} \tag{8}$$

where $g(x, x', t)$ is the retarded Green's function ($g(x, x', t) = 0$ if $t < 0$) for diffusion in the stationary potential $u(x)$, and $K(t) \equiv \langle \sigma(t_0 + t)\sigma(t_0)\rangle$ is the correlation function. Equation (8) is valid for both deterministic and stochastic time dependences $\sigma(t)$. Moreover, this equation provides all known analytical formulas for $\langle v\rangle$ obtained in various approximations and additionally expanded in the small parameter $w(x)$ [76]. If $w(x)$ is a periodic function ($w(x + L) = w(x)$), the obtained results relate to pulsating ratchets, while the substitution $w(x) = Fx$ ($F = \mathrm{const}$, $\langle \sigma(t)\rangle = 0$) corresponds to ratchets with a fluctuating force. For example, in the case of an on-off ratchet with smooth $u(x)$ and $w(x)$ functions and with stochastic switching between the states, the average velocity in the HF region is inversely proportional to frequency Γ and is determined by the formula [112, 115] (see also [25, 76])

$$\langle v\rangle_f = \frac{LD^2\beta^3}{\Gamma}\, \frac{\int_0^L \mathrm{d}x\, u'(x)[w'(x)]^2}{\int_0^L \mathrm{d}x \exp(\beta u(x)) \int_0^L \mathrm{d}x \exp(-\beta u(x))}\,. \tag{9}$$

In addition to the basic kinematic characteristic of a Brownian motor, viz., the average directional velocity $\langle v\rangle$ (see definitions (3) and (4)), there are also important energy characteristics, namely, the input energy E_{in} and the useful work (output energy) E_{out} that the motor performs against additionally introduced load force F_{l} [56, 111]. For cyclic processes, the values relate to the period of the process τ. The corresponding power values, power input P_{in} and power output P_{out}, are defined as E_{in}/τ and E_{out}/τ. As a result of an additional force F_{l} being introduced, the potential energy considered earlier (5) is replaced by the total potential energy $U(x, t) = V[x, f(t)] - F(t)x + F_{\mathrm{l}}x$. Here, the positive sign of $F_{\mathrm{l}}x$ corresponds to the load force vector oriented against the direction of motion of the motor, and the magnitude of F_{l} itself is introduced as a magnitude of this vector. The useful work per unit time is defined as the product of the load force and the velocity of the motor:

$$P_{\mathrm{out}} \equiv F_{\mathrm{l}}\langle v\rangle\,. \tag{10}$$

The supplied power is defined in the theory of Brownian motors as the average energy transmitted to a particle per unit time by means of a change in its potential energy:

$$P_{\mathrm{in}} \equiv \tau^{-1} \int_0^\tau \mathrm{d}t \int_0^L \mathrm{d}x\, \frac{\partial U(x, t)}{\partial t}\, \rho(x, t)\,. \tag{11}$$

The dissipative function Π (also referred to as the entropy production that characterizes the rate of conversion of the supplied energy to heat) and the efficiency η of converting the supplied energy into useful work are easily calculated using Eqns (10) and (11) [57, 116]:

$$\Pi \equiv P_{\mathrm{in}} - P_{\mathrm{out}}\,, \qquad \eta \equiv \frac{P_{\mathrm{out}}}{P_{\mathrm{in}}}\,. \tag{12}$$

It should be noted that an accurate definition of the output power P_{out} as a scalar product of the force vector and the velocity vector implies that it is negative for motors, since the direction of the load force vector is opposite to that of the average velocity of the motor. Since F_{l} is defined as the magnitude of the load force vector, and P_{out} in Eqn (10) as a positive value, the dissipative function in (12) is represented as the difference between P_{in} and P_{out}. Therefore, the requirement $\Pi \geqslant 0$ that follows from the second law of thermodynamics yields the conditions $P_{\mathrm{out}} \leqslant P_{\mathrm{in}}$ and $\eta \leqslant 1$.

The average velocity of directional motion $\langle v\rangle$ is a monotonically decreasing function of the load force F_{l} (Fig. 6) [117]. It assumes the greatest value at $F_{\mathrm{l}} = 0$ and vanishes at a certain value $F_{\mathrm{l}} = F_{\mathrm{s}}$ that corresponds to the motor stopping point. The value of F_{s} is an important characteristic of the motor, because it shows the ability of the motor to resist the load. Equations (10) and (11) show that the efficiency of the Brownian motor is proportional to the product $F_{\mathrm{l}}\langle v\rangle$; therefore, it vanishes both for $F_{\mathrm{l}} = 0$, and for $F_{\mathrm{l}} = F_{\mathrm{s}}$. This implies that the efficiency is a nonmonotonic function of the load force, which takes the maximum value $\eta_{\max}$ for a certain value of F_{l} (see Fig. 6). Based on an analysis of various models of pulsating ratchets [25, 43, 48, 51, 56, 57, 109, 111, 117], which ensure the directional motion of a nanoparticle in a time-dependent periodic potential, the necessary and sufficient conditions for their highly efficient operation ($\eta_{\max} \to 11$) have been formulated [48, 51, 57, 106]: (1) the adiabatic (slow or fast) process of changing the

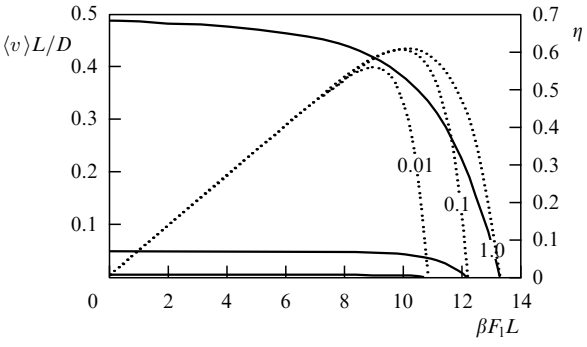

Figure 6. The average velocity $\langle v\rangle$ (solid lines, left axis) and the efficiency η (dashed lines, right axis) as functions of the load force F_{l} for an extremely asymmetric sawtooth potential with $\beta V_0 = 15$ that fluctuates by half a period with the dimensionless frequencies $\Gamma L^2/2D$ ($\gamma_+ = \gamma_- = \Gamma/2$), the values of which label the curves.

potential relief in time, (2) the shift (continuous or jump-like) of the potential extrema, (3) the presence of an effective mechanism to rectify nonequilibrium fluctuations at large amplitudes of the potential profile (exceeding thermal energy), and, in addition, a certain asymmetric shape of this profile in the case of an adiabatically fast mode.

4. Factors that determine the direction of motion

As was noted above, the main factor that sets the direction of motion of a Brownian motor is the asymmetry of the potential profile. If this profile changes its shape over time, it is very difficult, and often impossible, to determine in advance, without specific calculations, the direction of motion induced by the ratchet effect. The multiplicative form of potential energy, $V[x, f(t)] = V(x)[1 + f(t)]$, contains only one time-independent coordinate function $V(x)$. If an additive-multiplicative form, $U(x, t) = u(x) + \sigma(t)w(x)$, is used, two coordinate functions, $u(x)$ and $w(x)$, must be considered. At the same time, the direction of motion can also be affected by the form of the time dependence of the potential energy set by the functions $f(t)$ and $\sigma(t)$. Inertial and quantum effects introduce additional factors that can reverse the direction of motion. This section is devoted to a consideration of these features.

First, we return to considering the simplest potential profile with one maximum and one minimum on the spatial period L (see Fig. 1). It can be easily seen that the on-off ratchet moves in the direction that corresponds to a shorter distance from some minimum to the nearest maximum (see details in Section 2). We now consider the more complex potential profile shown in Fig. 7a. The potential profile period contains two minima, the right minimum at x_r and the left minimum at x_l. The right minimum is closer to the largest maximum located at the point $x = L$, while the left minimum is closer to the same maximum at the point $x = 0$. However, the right minimum is deeper than the left one by an energy ΔV. In the case of low temperatures, if $k_B T \ll \Delta V$ ($\beta \Delta V \gg 1$), the probability of a particle being in the left minimum tends to zero, so the problem reduces to that of the single-well potential profile considered above, and the particle will move to the right due to the ratchet effect.

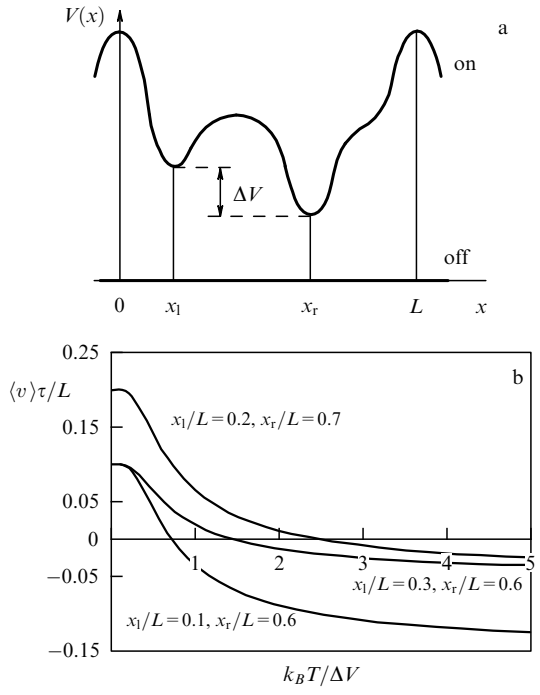

Figure 7. (a) Schematic presentation of a double-well potential profile in the on-off ratchet model that allows for reversal of the direction of motion of the Brownian particle as temperature changes. (b) The family of temperature dependences of the average ratchet velocity for various pairs of values of x_l and x_r.

We now assume that the distance between the left local minimum and the left barrier is smaller than that between the right absolute minimum and the right barrier, i.e., $x_l < L - x_r$. As temperature increases, the probability of a particle being localized near the left minimum also increases, and conditions emerge for the particle to move to the left. The described example of how the direction of motion is reversed with an increase in temperature may be described in quantitative terms [118] using the adiabatic approximation and kinetic approach:

$$\langle v \rangle = \frac{1}{\tau}\left[\frac{x_r + x_l \exp(-\beta \Delta V)}{1 + \exp(-\beta \Delta V)} - \frac{L}{2}\right]. \qquad (13)$$

A family of temperature dependences of the average velocity for various pairs of values of x_l and x_r is displayed in Fig. 7b. It can easily be shown that the stopping point of the Brownian motor corresponds to the temperature

$$T_s = \frac{k_B^{-1} \Delta V}{\ln[(L/2 - x_l)/(x_r - L/2)]}, \quad x_l + x_r < L. \qquad (14)$$

Thus, if $T < T_s$, the Brownian particle moves to the right, while if $T > T_s$, it moves to the left, and the direction of motion may be controlled by changing temperature.

When considering switching between complex potential reliefs with several minima and maxima per period, determination of the direction of motion induced by the ratchet effect is a challenging problem. On the other hand, if processes are explored in which diffusion is not a dominant factor and the directional motion occurs even at zero temperature, the sign of the average velocity may be determined quite simply. Similar processes were considered in modeling muscle contraction: the myosin protein molecule was shifted relative to the actin fiber directly due to ATP hydrolysis (tight mechanochemical coupling) [119]. The power stroke of such a protein motor is not related to the diffusion (or thermally activated) particle motion [120]; therefore, it was long believed that this type of motor (power stroke motors) cannot be described in terms of the theory of Brownian motors (ratchets). It was found later that the concept of the Brownian motor is equally well applicable to processes with a weak and strong mechanochemical coupling that generates directional motion [51]. It is sufficient to consider fluctuations of potential energy with constant (in the former case) or changing (in the latter case) positions of extrema [106]. Variation of extremum positions is also one of the necessary conditions for the high efficiency of a Brownian motor.

We now consider the motion of a Brownian particle whose potential energy fluctuates between two periodic (with the same period L) potential reliefs $U_\sigma(x)$ ($\sigma = \pm 1$) with lifetimes so long that thermodynamic equilibrium can be established in each of them (the adiabatic approximation). The difference between the stochastic and deterministic switching between potential reliefs is blurred in the adiabatic approximation [44],

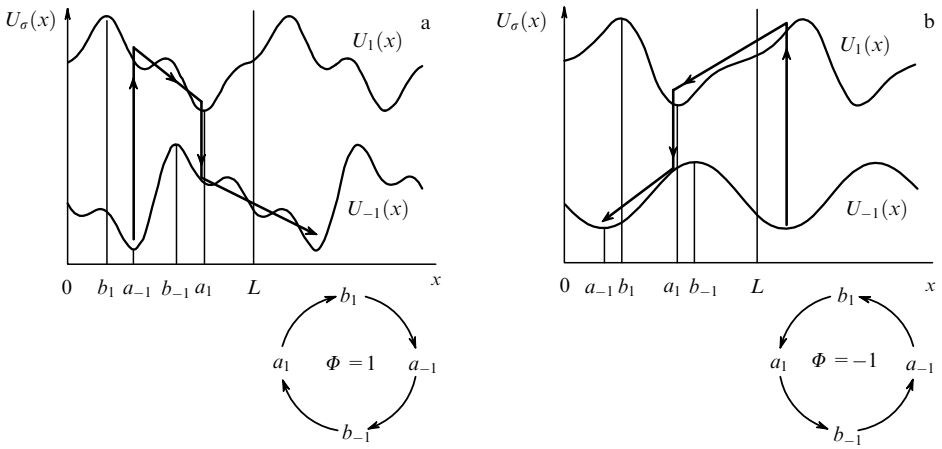

Figure 8. Mechanism of the emergence of directional motion to the right (a) and to the left (b) under switching of potentials. Motion at low temperatures becomes possible if the positions of the maxima and minima of the switching potentials alternate.

owing to which the fluctuation process can be considered cyclic with a period $\tau = \tau_1 + \tau_{-1}$. Let a_σ and b_σ ($a_\sigma, b_\sigma \in (0, L)$), respectively, denote the coordinates of the smallest minimum and the largest maximum of the potential relief $U_\sigma(x)$ (Fig. 8). It can be shown [121] that, in the adiabatic approximation and at low temperatures (however, sufficient to overcome small barriers between neighboring local minima), the average velocity and its sign can be determined rather straightforwardly by calculating the function Φ:

$$\langle v \rangle = \frac{L}{\tau}\Phi\,, \quad \Phi = \sum_{\sigma=\pm1} \left[\theta(b_\sigma - a_\sigma) - \theta(b_\sigma - a_{-\sigma})\right], \qquad (15)$$

where $\theta(x)$ is the theta function equal to 1 if $x > 0$, 1/2 if $x = 0$, and -1 if $x < 0$. The presence or absence of motion in the low-temperature limit, as well as the direction of this motion, are determined by the relative location of the four extrema a_σ and b_σ ($\sigma = \pm 1$). For potentials whose amplitude fluctuates, the positions of the extrema of the two potentials coincide, namely, $a_1 = a_{-1}$, and $b_1 = b_{-1}$, if the positions of the minima and maxima are identical in both potentials, and $a_1 = b_{-1}$, and $b_1 = a_{-1}$ if the minimum of one potential becomes the maximum of the other and vice versa. It is easy to check that in these cases $\Phi = 0$. The average velocity of motion is nonzero only if the positions of the minima and maxima of fluctuating potentials alternate (circular diagram in Fig. 8). The positive and negative directions of motion (Fig. 8a, b) correspond to a circling of extrema clockwise and counterclockwise. An analysis of the motion paths (arrows along and across the profiles of potential energy) shows that the resulting direction of motion is determined by the direction from the maximum to the minimum of some potential, provided that the maximum of the other potential is located between them. With this arrangement of extrema, the particle moves in each potential relief to a minimum point, escaping the barriers of the other potential due to switching between the two potentials. It is easy to check that, in the case of symmetric potentials, when $|a_\sigma - b_\sigma| = L/2$, the positions of the minima and maxima of fluctuating potentials do not alternate, so that the average velocity is zero, as it should be.

The direction of motion can be easily reversed in those cases when the shape of the stationary part of the potential relief $u(x)$ differs from that of its fluctuating part $w(x)$ in the additive-multiplicative representation of the potential energy $U(x, t) = u(x) + \sigma(t)w(x)$. For example, if $u(x)$ is a sawtooth potential, the asymmetry of which is characterized by the ratio $\lambda = l/L$, and $w(x)$ is described by the harmonic $w(x) = w\cos[2\pi(x/(L - \lambda_0))]$ with a phase shift λ_0 (Fig. 9a), the direction of motion depends on the values of the parameters λ and λ_0. This dependence may be represented in the high-temperature approximation using a diagram in the phase space of the parameters λ and λ_0 (Fig. 9b) [108].

Apart from the asymmetry and specific features of the potential relief, the phenomenon of the emergence of directional motion due to nonequilibrium fluctuations is also significantly affected by dynamic effects. The most spectacular example of such an effect is given in [60]. We consider the stochastic switching between two symmetric potentials $U_+(x) = U_+\cos(2\pi x/L)$ and $U_-(x) = U_-\sin(4\pi x/L)$ with frequencies γ_+ and γ_- (see the inset in Fig. 10). It should be stressed that each of these potentials is symmetrical; therefore, the asymmetry of the system arises exclusively due to the dynamic effect of switching. The high-temperature approximation and the simplest forms of potential profiles restricted to the first and second spatial harmonics can be used to derive a simple formula for the average velocity of motion:

$$\langle v \rangle = -\frac{\pi}{4}v^*(1-\varepsilon^2)\,Z\,\frac{1-2(1-3\varepsilon)\,Z}{(1+4Z)^2(1+Z)}\,,$$
$$Z = \frac{(\gamma_+ + \gamma_-)\,L^2}{(4\pi)^2 D}\,, \quad v^* \equiv \frac{U_+^2 U_-}{(k_{\mathrm{B}}T)^3}\,\frac{D}{L}\,, \quad \varepsilon = \frac{\gamma_- - \gamma_+}{\gamma_- + \gamma_+}\,. \qquad (16)$$

The ratio $\langle v \rangle / v^*$ as a function of the dimensionless frequency parameter Z for various values of the time asymmetry parameter ε is displayed in Fig. 10. It is noteworthy that the ratchet effect also occurs if there is no time asymmetry ($\varepsilon = 0$). This result agrees well with popular concepts, according to which space symmetry may be broken by dynamic effects (for example, the mixing of harmonics [122] or a dynamic selection of the direction of motion by the ensemble of interacting particles [123]). In our case, the symmetry is broken due to the shift of the minima of the switching potential reliefs.

The stopping points, where the direction of motion is reversed, also emerge in a broad range of variation of the time

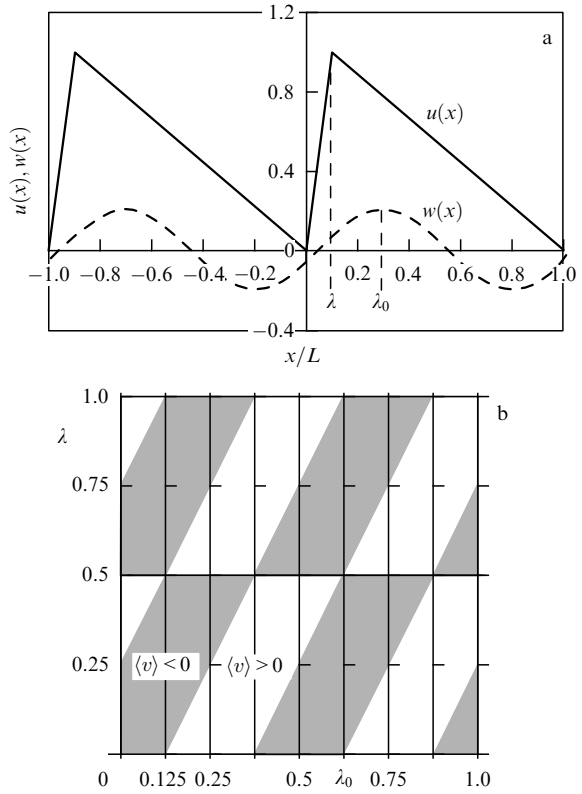

Figure 9. (a) Sawtooth stationary relief $u(x)$ and harmonic fluctuation component $w(x)$ of the potential energy of a Brownian motor. (b) Phase diagram of the parameters λ and λ_0 that sets the range of values corresponding to the motion to the right or to the left (light and shaded areas, respectively).

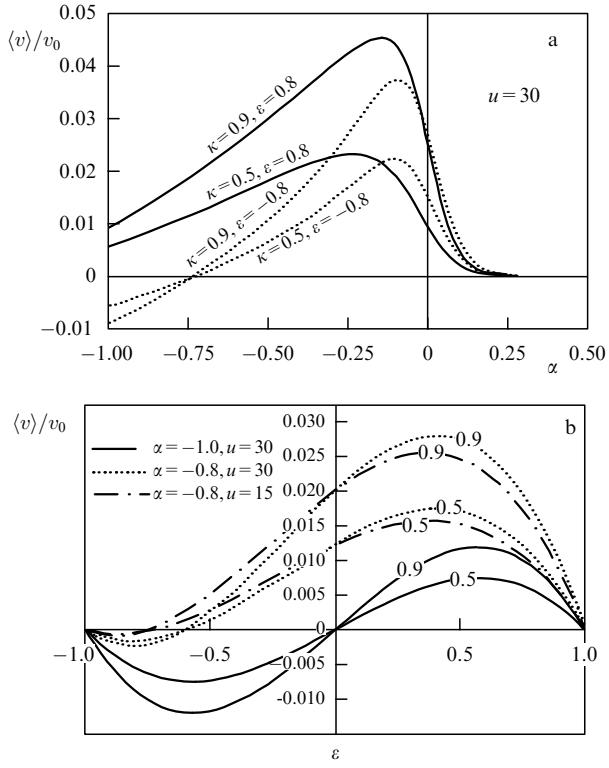

Figure 11. Average velocity (in units of $v_0 = V_0/\zeta L$, where V_0 is the sawtooth potential barrier) as a function of the ratio of the potential amplitudes α (a) and the time asymmetry parameter ε (b) for various values of the space asymmetry parameter $\kappa = 1 - 2l/L$ and other parameters (indicated on the corresponding curves and in the plot corners). The fluctuation frequencies satisfy the relation $(\gamma_+ + \gamma_-)\zeta L^2/V_0 = 1$.

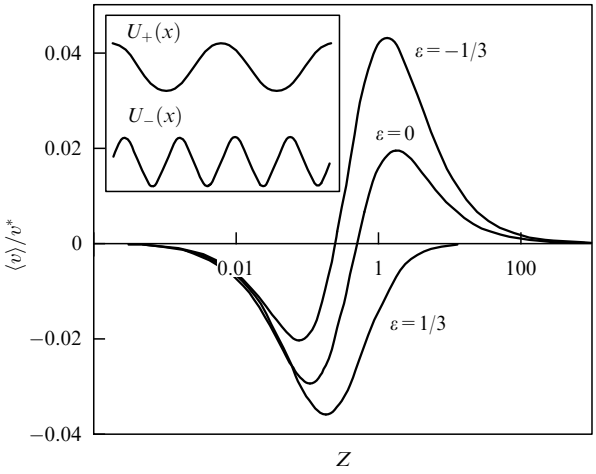

Figure 10. Average velocity (in units of the parameter v^* defined in Eqn (16)) as a function of the dimensionless frequency parameter Z for various values of the time asymmetry parameter ε. Symmetric potential reliefs $U_\pm(x)$ are shown in the inset.

asymmetry parameter $\varepsilon \in (-1, 1/3)$ that includes the point $\varepsilon = 0$. Also, since the parameter Z depends not only on the sum of the frequencies γ_+ and γ_- of the potential switching but also on temperature (via the diffusion coefficient D), the direction of motion may be controlled by means of temperature. It should be noted that the parameter v^*, proportional to $U_+^2 U_-$, vanishes for on-off ratchets (when either U_+ or U_- tends to zero). This observation corresponds to expectations, since the on-off ratchet cannot operate with a symmetric potential profile.

We present another, more general example that shows how dynamic effects affect the reversal of motion if the multiplicative potential energy $V[x, f(t)] = V(x)[1 + f(t)]$ is subject to dichotomous changes: $U_+(x) = V(x)$, $U_-(x) = \alpha V(x)$, where $\alpha \in (-1, 1)$ and $V(x)$ is a sawtooth potential with the barrier V_0 (Fig. 11). If $\alpha = 1$, there are no fluctuations in the potential, and hence the ratchet effect is absent. The case $\alpha = 0$ corresponds to an on-off ratchet that provides the directional motion due to spatial asymmetry ($\kappa \neq 0$). If $\alpha = -1$, when the sign of the potential energy fluctuates, the ratchet effect may only occur due to time asymmetry ($\varepsilon \neq 0$). The stopping points and reversal of motion are possible in the range of negative α values, provided $\kappa > 0$ and $\varepsilon < 0$, since only then does time asymmetry compete with this type of spatial asymmetry.

Additional options for controlling nanotransport emerge in the case of sufficiently massive nanoparticles, for which inertial effects should be taken into account. Under certain conditions, a setup is possible where a particle of small mass m moves in one direction due to the ratchet effect, while a particle loaded with an additional mass M moves in the opposite direction. This model of motion, referred to as the molecular shuttle model [124], may be used to move loads between two given points. To illustrate this mechanism, we give the expression for the average velocity of an adiabatic high-temperature ratchet with the additive-multiplicative potential energy $U(x, t) = u(x) + \sigma(t)w(x)$ taking into

account a small inertial correction [113]:

$$\langle v\rangle = -\frac{4L}{\pi\tau}\beta^3\,\mathrm{Im}\,(u_1w_1w_2^* + 2u_2^*w_1^2) \times\left[1+\frac{1}{3}\Lambda+\frac{12\pi^2 m}{\beta\zeta^2L^2}\left(1+\frac{7}{9}\Lambda\right)\right], \quad (17)$$

$$\Lambda = \frac{\mathrm{Im}\,(u_1w_2w_3^* + 4u_2w_1w_3^* + 9u_3^*w_1w_2)}{\mathrm{Im}\,(u_1w_1w_2^* + 2u_2^*w_1^2)}\,.$$

In this formula, u_q and w_q are the Fourier components of the terms $u(x)$ and $w(x)$, which are taken into account up to the first harmonics ($q = \pm1, \pm2, \pm3$), and $\sigma(t) = \pm1$ describes a dichotomous process with a large period τ. The smallness of the inertial correction entails the smallness of the dimensionless quantity $mV/(\zeta^2L^2)$, while the use of the high-temperature approximation results in the smallness of the quantity βV, where V is the characteristic value of the amplitudes of the potentials $u(x)$ and $w(x)$. Therefore, in the high-temperature region, the contribution of the inertial correction $12\pi^2m/(\beta\zeta^2L^2)$ may be comparable to the main contribution of the order of $(\beta V)^3$.

The parameter Λ is equal to zero for the widely used two-harmonic potentials ($u_3 = w_3 = 0$), and the inertial correction $12\pi^2m/(\beta\zeta^2L^2)$ can only enhance the ratchet effect. If the shape of the potential relief becomes more complicated (contains more extrema in the spatial period), then $u_3 \neq 0$, $w_3 \neq 0$, and $\Lambda \neq 0$, and the velocity sign may be changed. It follows from Eqn (17) that such a possibility arises if the values of the parameter Λ fall in the range $-3 < \Lambda < -9/7$. If this condition is fulfilled, the direction of motion is reversed at a temperature $T = -(2\pi)^{-2}(\zeta^2L^2/mk_B)(3+\Lambda)/(9+7\Lambda)$.

Figure 12a shows the average velocity for the on-off ratchet as a function of inverse temperature for the potential energy of the form

$$u(x) = w(x) = \frac{V}{2}\left[\sin\left(\frac{2\pi x}{L}\right)+\frac{1}{4}\sin\left(\frac{4\pi x}{L}\right) -\frac{1}{2}\sin\left(\frac{6\pi x}{L}\right)\right] \quad (18)$$

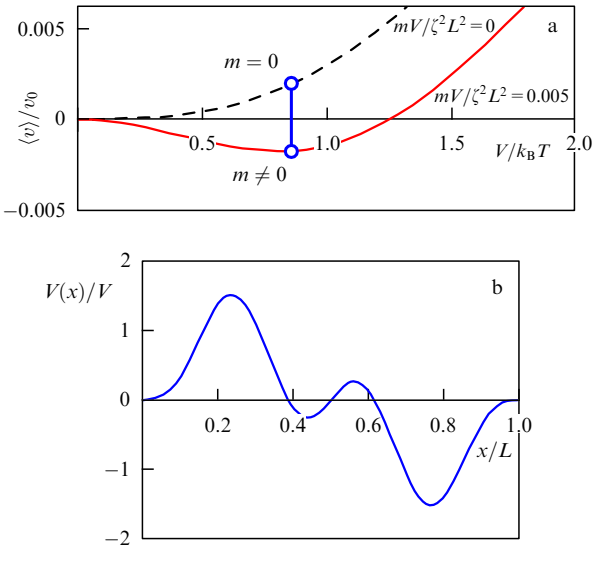

Figure 12. (a) Average velocity of the inertial on-off ratchet as a function of inverse temperature, (b) the potential relief defined by Eqn (18) that was used in calculating the average velocity.

(the corresponding potential relief is shown in Fig. 12b). If there is no inertia ($m \to 0$), the velocity is positive, and the nanoparticle moves to the right. It can move in this mode from point A to point B. If it is loaded at point B with mass $m \neq 0$, then, at sufficiently low temperatures (below the temperature at which it stops), the velocity is negative, and the nanoparticle moving to the left returns to point A. It can be unloaded there and repeat the trip. This implies that it can operate in a molecular shuttle mode.

Quantum effects open up new ways to control the direction of motion of a particle capable of sub-barrier tunneling. A situation was described in [103], where, at sufficiently high temperatures, the ratchet effect made the particle move in one direction (the same as in the classical description), whereas at low temperatures, when tunneling motion was only possible, the particle moved in the opposite direction. It should be noted that the described reversal of the direction of motion can be facilitated by the features of the temperature dependence of the tunneling transport rate constant [99, 125, 126].

5. Conclusion

Unlike conventional methods of controlling nanotransport, e.g., by applying forces or by creating a concentration gradient, the ratchet effect depends on many factors related to the temperature and viscosity of the medium, parameters of the asymmetric potential relief, and its fluctuations, and therefore provides alternative options to control its characteristics. This advantage becomes especially obvious if compared with standard methods of directional transportation of materials. Indeed, nanoobjects usually move under the effect of a magnetic or electric field. To realize directional motion, for example, in a magnetic field, a drug is applied to a ferromagnetic nanoparticle or a particle that contains a ferromagnetic layer. Then it can be moved using a permanent magnet or when placing the patient in a capsule with a strongly nonuniform magnetic field. It should be noted that the procedures for preparing magnetic nanoobjects and removing magnetic components after delivery of drugs are rather complex.

If an electric field is used to transport a drug, its particles must either be charged or have a significant dipole moment. In the first case, it is necessary to use a certain technology for the separation of charges, and this separation must be maintained throughout the entire delivery procedure. In addition, since the initial field is greatly attenuated in blood having a large dielectric constant, a sufficiently strong, i.e., unsafe, field has to be applied to the patient's body; otherwise, its particle-transporting capability will be quite low. If dipole particles of drugs must be transported, the external electric field should be significantly nonuniform; moreover, notable nonuniformity should exist on the dipole scale, at distances less than the particle size. Creating a field with such a structure is very difficult.

The situation with the transport of drugs using ratchets is completely different. The ratchet effect emerges due to rectification of nonequilibrium fluctuations of various nature, leading to time dependences of the potential energy of interaction between the particle and the environment. This effect can also emerge as a result of specially arranged external processes in which the average forces acting on the particle are equal to zero (see Sections 2 and 3). In the course of ratchet operation, particle flows occur without the action of macroscopic forces: all acting forces are local

being effective at distances of the order of one potential period. The directional motion (ratchet effect) is maintained in this case throughout the entire duration of fluctuations and can make the particle move over distances that significantly exceed the spatial period of potential energy or effective fields. It should be noted that the standard mechanisms of transport and separation of materials used in medicine (electrophoresis, chromatography, etc.) employ macroscopic gradients.

If the directional movement of nanoobjects is due to the ratchet effect and is described by diffusion dynamics laws, the term Brownian motors is used, and if the ratchet effect is caused by irradiation of nanoparticles, then we speak about Brownian photomotors. Radiation (in particular, as emitted by lasers) causes electronic transitions in the particle and, consequently, changes its characteristics, including dipole, quadrupole, and higher moments, polarizability, geometric parameters, etc. For example, in the case of the photomotors considered in [47], the driving force of the ratchet effect only emerges if the nanoobject acquires a dipole moment, and this phenomenon occurs when a photon is absorbed. It is of importance that the duration, duty cycle, wavelength, and intensity of the exciting laser radiation can be adjusted using in this way many control degrees of freedom. Of great importance is the interaction of the particle with the environment, and the fact that the nonuniformity scale of the fields affecting the particle actually corresponds in this case to the size of the dipole. In other words, the theory developed in [47] enables tuning of radiation parameters to achieve the maximum (optimal) velocity of the photomotor in a given direction. It is also possible to control the size of a nanoobject using light and induce its directional motion due to the entropic ratchet effect [74, 93].

It should be noted that the average rate of drug transport due to the dielectrophoretic exposure of a 1-μm particle to an electric field of the order of 10 kV m^{-1} with a nonuniformity scale of 1 mm may be as high as 1 μm s^{-1} [13]. The velocity of the same particle due to the ratchet effect, which is caused by fluctuations in the electric field of the order of 1000 kV m^{-1} created by a mesh of electrodes with a period of 10 μm, may be as high as 0.1 μm s^{-1} for fluctuation periods of the order of 10 s [75]. Thus, though the ratchet effect, generally speaking, results in small velocities of directional motion compared with direct methods, these velocities may be significantly enhanced due to large gradients of fluctuating electric fields. On the other hand, the ratchet effect is advantageous, since the magnitude and sign of the velocity of motion may be controlled by changing the temperature and viscosity of the medium, as well as the frequency and time asymmetry of fluctuations (see examples in Figs 6, 8–10).

Deterministic fluctuations in the potential energy of a nanoparticle yield a relatively narrow frequency distribution of the average velocity, which has a bell-shaped curve (see Fig. 5). The highest maximum is obtained in this case for a dichotomous (stepwise) time dependence of the fluctuation part of the potential energy. Since the dimensionless frequency parameter $\Gamma L^2/D$ contains, apart from the fluctuation frequency Γ, the diffusion coefficient $D = k_B T/\zeta$, which, in turn, is determined by the temperature T, the viscosity of the medium η, and the particle size R ($\zeta \sim 10R\eta$), this type of fluctuations is of practical interest in those cases when only particles of a certain size or at a certain temperature of the medium must come into motion. If, on the contrary, the goal is to transport particles of various sizes and at various temperatures, it is advisable to use stochastic fluctuations, which yield a rather wide frequency distribution. Due to the extended HF wing of this distribution, relatively high velocities of motion of large nanoparticles and at sufficiently low temperatures may be attained.

The ratchet effect can perform useful work against load forces, both actual (gravity or a stationary electric field acting on a charged particle) and generalized (concentration gradients). Brownian motors with the highest values of the load forces at which the motion is reversed or with maximum energy efficiency are naturally the most promising (see Fig. 6). An analysis of various models of pulsating ratchets showed that their high efficiency is achieved with a large asymmetry of the potential profile and adiabatic fluctuations in the positions of extrema [48, 51, 57, 106].

Given the various factors that affect the direction of motion (Section 4), the easiest way to achieve the desired effect is to arrange competition between spatial and time asymmetry. Indeed, the creation of two competing potential wells on the period of the potential profile (Fig. 7a) is a rather laborious task compared to changing the duty cycle of radiation pulses, which also affects the direction of motion of a photomotor (see Figs 10 and 11). An additional option to control the direction of motion arises from changing the phase shift of the spatial harmonic of the fluctuation contribution to the potential energy of the particle (see Fig. 9). This effect can be implemented experimentally using the interference of laser beams that propagate in opposite directions and form a spatially periodic potential (as occurs in ratchets in optical lattices [127–129]). However, it is necessary to take into account in this case that manifestations of the ratchet effect may be forbidden for reasons of symmetry [107, 130, 131].

The most impressive example of reversing the direction of motion is the molecular shuttle, whose velocity sign depends on the total mass of the nanoparticle (the mass of the nanoparticle itself and of the load it can transport) [124]. Such a shuttle can apparently be used for multiple transport of a drug from the point of introduction into the body to the target area where this drug has a therapeutic effect.

We described in this review the mechanisms of directional motion that use the ratchet effect, presented its main parameters and characteristics, and listed the factors that set the direction of motion. A detailed description of specific implementations of the ratchet effect, which requires a more detailed analysis of the properties of real systems, is beyond the scope of this review, the main goal of which was to present the basic aspects of ratchets operation.

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