



OPEN Mechanochemical active ratchet

Artem Ryabov^{1,2,3} & Mykola Tasinkevych^{2,3,4,5}✉

Self-propelled nanoparticles moving through liquids offer the possibility of creating advanced applications where such nanoswimmers can operate as artificial molecular-sized motors. Achieving control over the motion of nanoswimmers is a crucial aspect for their reliable functioning. While the directionality of micron-sized swimmers can be controlled with great precision, steering nano-sized active particles poses a real challenge. One of the reasons is the existence of large fluctuations of active velocity at the nanoscale. Here, we describe a mechanism that, in the presence of a ratchet potential, transforms these fluctuations into a net current of active nanoparticles. We demonstrate the effect using a generic model of self-propulsion powered by chemical reactions. The net motion along the easy direction of the ratchet potential arises from the coupling of chemical and mechanical processes and is triggered by a constant, transverse to the ratchet, force. The current magnitude sensitively depends on the amplitude and the periodicity of the ratchet potential and the strength of the transverse force. Our results highlight the importance of thermodynamically consistent modeling of chemical reactions in active matter at the nanoscale and suggest new ways of controlling dynamics in such systems.

Chemistry and physics of micron- and nano-sized self-propelled particles are rapidly growing fields exploring optimal designs and fundamental concepts of self-propulsion mechanisms. A current intense discussion focuses on a possible self-propulsion of individual catalytic macromolecules that could serve as basic components for artificial nanomachines^{1–9}.

The self-propelled (active) motion of micron-sized particles is driven by a large number of chemical reactions and/or hydrodynamic flows in an ambient fluid. Relatively large dimensions of these objects lead to negligible fluctuations in the magnitude of their active velocities. This renders the particle dynamics accurately controllable by employing laser fields^{10,11}, concentration gradients^{12–16}, local heating^{17,18}, using external magnetic fields in combination with suitably prepared magnetic particles^{19–21}, or by a specific chemical patterning of surfaces^{22–25}. The precise guidance is essential for several applications including targeted drug delivery^{16,26,27}, biosensing²⁸, transport of microcargoes in lab-on-chip devices²⁹, or assembly of microstructures^{30–33}.

In contrast, strong fluctuations are unavoidable at the nanoscale, where dimensions of active particles are on par with those of intracellular molecular motors like kinesins, myosins, and ribosomes^{34–36}, and artificial molecular machines and pumps^{37–39}. Active motion at these scales can be caused by a comparably small number of reactions and is strongly influenced by thermal noise. Large fluctuations of the magnitude and the direction of self-propulsion velocity hinder the development of methods to efficiently control the dynamics of nanoswimmers.

Here, we use a minimal thermodynamically consistent model of particle's self-propulsion^{40–43} to demonstrate a novel physical mechanism for rectifying and guiding trajectories of chemical nanoswimmers. The mechanism benefits from the presence of strong fluctuations in the direction of self-propulsion velocity and it arises as a direct consequence of the main premise that the chemical reactions driving the active motion comply with the principle of microscopic reversibility (MR)^{44–47}. The resulting rectification effect can be used to guide and sort active nanoparticles based on their propulsion mechanisms, because a corresponding reference model without the MR, as well as passive Brownian particles, does not exhibit this type of rectified motion.

Results and discussion

Stochastic Markovian models become thermodynamically consistent if rates of elementary transitions obey the local detailed balance⁴⁸. For an overdamped Brownian motion subjected to an external force $F(r)$ and to thermal fluctuations represented by the zero-mean Gaussian white noise $\xi(t)$, the local detailed balance condition is included in the Langevin equation for the particle velocity, $\dot{r} = \mu F(r) + \sqrt{2D} \xi(t)$, by requiring that the

¹Department of Macromolecular Physics, Faculty of Mathematics and Physics, Charles University, V Holešovičkách 2, 18000 Praha 8, Czech Republic. ²Departamento de Física, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal. ³Centro de Física Teórica e Computacional, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal. ⁴SOFT Group, School of Science and Technology, Nottingham Trent University, Clifton Lane, Nottingham NG11 8NS, UK. ⁵International Institute for Sustainability with Knotted Chiral Meta Matter, Hiroshima University, Higashihiroshima 739-8511, Japan. ✉email: mykola.tasinkevych@ntu.ac.uk

translational diffusion constant D is related to the mobility μ via the fluctuation-dissipation relation $D = \mu k_B T$, T being the temperature of ambient fluid.

In addition to the force- and thermally-driven movements, the velocity of a self-propelled nanoparticle is influenced by its chemically-powered active dynamics. The particle center of mass position $\mathbf{r}(t) = (x(t), y(t))$ then obeys the Langevin equation

$$\frac{d\mathbf{r}}{dt} = v_a(\mathbf{r}, t)\mathbf{n}(t) + \mu\mathbf{F}(\mathbf{r}) + \sqrt{2D}\boldsymbol{\xi}(t), \quad (1)$$

where the first term on the right-hand side represents the active velocity of magnitude $v_a(\mathbf{r}, t)$ oriented in the direction of $\mathbf{n}(t)$, see Fig. 1a.

The vector $\mathbf{n}(t) = (\cos\phi(t), \sin\phi(t))$, giving the orientation of the nanoparticle, performs rotational diffusion⁴⁹, i.e., the angle $\phi(t)$ undergoes the Brownian motion

$$\dot{\phi}(t) = \sqrt{2D_r}\xi_r(t), \quad (2)$$

with D_r being the rotational diffusion constant and $\xi_r(t)$ a zero-mean Gaussian white noise.

The speed $v_a(\mathbf{r}, t)$ corresponds to the chemically-driven particle motion in the direction of $\mathbf{n}(t)$. If the kinetics of the underlying reactions comply with the principle of MR, then, on the mesoscopic timescale, where an infinitesimal time interval dt covers many chemically-driven particle jumps, we may approximate the speed by⁴²

$$v_a(\mathbf{r}, t) \approx u + \mu_c \mathbf{n}(t) \cdot \mathbf{F}(\mathbf{r}) + \sqrt{2D_c}\xi_c(t). \quad (3)$$

Here, u is the constant mean active speed in the zero-force case ($\mathbf{F} = 0$), the dot \cdot denotes the scalar product, and $\xi_c(t)$ is a Gaussian white noise stemming from fluctuations of the number of chemical reactions per unit time. Positive constants D_c and μ_c are related by $D_c = \mu_c k_B T$. The white noises $\xi_\alpha(t)$ in Eqs. (1)–(3) satisfy $\langle \xi_\alpha(t) \rangle = 0$, and $\langle \xi_\alpha(t)\xi_\beta(t') \rangle = \delta_{\alpha\beta}\delta(t-t')$, $\alpha, \beta \in \{x, y, r, c\}$. A derivation of Eq. (3) starting from the mesoscopic jump-diffusion model can be found in Ref. ⁴². The central assumption of this derivation is that the rates of motion-powering chemical reactions satisfy the local detailed balance condition. This is equivalent to assuming MR of the kinetics of these reactions, which means that their underlying microscopic dynamics are symmetric with respect to the time-reversal⁴⁸. A general aim of the current work is to demonstrate the impact of individual terms in (3) on the dynamics of an active nanoparticle diffusing in external force fields.

According to Eq. (3), the active speed depends on the component $\mathbf{n}(t) \cdot \mathbf{F}(\mathbf{r})$ of the external force along $\mathbf{n}(t)$. This term describes the mechanochemical coupling⁵⁰ and allows to sculpt a free energy landscape of the macromolecule by the action of external forces. The coupling is utilized in various single-molecule force spectroscopies^{11,51,52}, biosensing⁵³ and underlies the ability of molecular motors to exert forces and torques^{38,54–58}.

The force-dependence of $v_a(\mathbf{r}, t)$ is a direct consequence of MR of the self-propulsion mechanism and it has prominent impacts on particle dynamics^{42,43}. We shall use this dependence to design a new method of nanoparticle guiding, which is inaccessible in systems lacking the mechanochemical coupling, like in the case of micron-sized particles with constant active speed, see Eq. (10) below. In particular, we report on a ratchet effect that occurs if the particle is subjected to the external force

$$\mathbf{F}(\mathbf{r}) = (f_{\parallel} - V'(x), f_{\perp}), \quad (4)$$

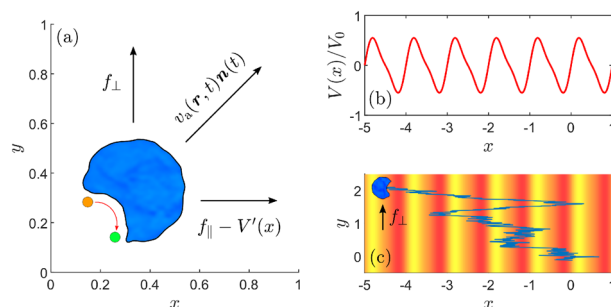


Figure 1. Illustration of the model. (a) An active nanoparticle (blue) whose self-propelled motion with speed $v_a(\mathbf{r}, t)$ occurs in the direction of orientation $\mathbf{n}(t)$ (diagonal arrow) and is powered by chemical reactions (red arrow). Assuming the microscopic reversibility of the self-propulsion mechanism gives rise to the mechanochemical coupling term $[\mu_c \mathbf{n}(t) \cdot \mathbf{F}(\mathbf{r})]$ in Eq. (3) for $v_a(\mathbf{r}, t)$. The x - and y -component of the external force $\mathbf{F}(\mathbf{r})$, Eq. (4), are represented by the horizontal and vertical arrows. (b) The periodic asymmetric potential $V(x)$ given in Eq. (5) normalized by its barrier height V_0 for $\lambda = 1$. (c) Sketch of a trajectory of the nanoparticle diffusing in the potential $V(x)$ (dark red marks the potential minima, light orange the maxima) and subjected to a constant force with the amplitude $f_{\perp} > 0$ acting in the y -direction and with no constant force component in the x -direction ($f_{\parallel} = 0$). The nonzero perpendicular bias f_{\perp} can induce a net particle motion along the x -axis. This special consequence of the mechanochemical coupling term in $v_a(\mathbf{r}, t)$ is illustrated in Fig. 2. If $f_{\parallel} > 0$, the direction of the motion can be reversed by changing f_{\perp} as shown in Fig. 3.

determined by the constant components f_{\parallel} and f_{\perp} , and by the derivative of the asymmetric λ -periodic potential

$$V(x) = \frac{V_0}{2} \left[\sin\left(\frac{2\pi x}{\lambda}\right) + \frac{1}{4} \sin\left(\frac{4\pi x}{\lambda}\right) \right], \quad (5)$$

shown in Fig. 1b. A trajectory of the particle moving in $V(x)$ and being acted upon by $f_{\perp} > 0$ is sketched in Fig. 1c.

The asymmetric sawtooth-like potential $V(x)$ is qualitatively similar to potentials used in various theoretical and experimental studies of ratchets^{59–71}. A distinctive feature of the ratchet mechanism discussed below is that the emergent current of particles in the x -direction is induced by the transverse force f_{\perp} applied perpendicular to it in the y -direction. Although here we focus on the two-dimensional case, in an actual experiment, the force f_{\perp} can point in any direction in the yz -plane.

Assuming that the force in Eq. (4) can be accurately adjusted in an experiment, we discuss the dependence of the ratchet effect on f_{\parallel} , f_{\perp} , and V_0 . The phenomenological model parameters D , D_r , D_c , and u will be kept fixed. All results reported below are obtained assuming $\lambda = 100$ nm. To get the results, we have integrated Eqs. (1) and (2) numerically, see Supplementary Note 1 and 2 for technical details.

The values of the diffusion constants D and D_r were chosen having catalytically active enzymes in mind^{72–74}. Thus, D was approximated by the Stokes-Einstein equation $D = k_B T / 6\pi\eta R_h$, and $D_r = k_B T / 8\pi\eta R_h^3$ valid for a sphere of radius R_h , η is the fluid dynamic viscosity. With $R_h = 15$ nm, $T = 300$ K, and $\eta = 8.53 \times 10^{-4}$ Ns/m², which corresponds to the dynamic viscosity of water at this temperature, we find

$$D \approx 1.7 \times 10^{-11} \text{ m}^2/\text{s}, \quad (6)$$

$$D_r \approx 5.7 \times 10^4 \text{ s}^{-1}. \quad (7)$$

Contrary to D and D_r , the behavior of the phenomenological parameter D_c remains poorly understood. To approximate its value, we have used $D_c \approx (\delta r)^2(k_+ + k_-)/2t$, where k_+ is the rate of the reaction causing the nanoparticle displacement $\delta r \mathbf{n}$ (at $\mathbf{F} = 0$), and neglected the rate k_- of the reversed reaction, which causes the displacement by $-\delta r \mathbf{n}$. For $k_+ = 10^5 \text{ s}^{-1}$ and $\delta r = 5$ nm,

$$D_c \approx 1.3 \times 10^{-12} \text{ m}^2/\text{s}. \quad (8)$$

We note that the very existence of the reported ratchet effect follows from the condition $D_c > 0$ and does not depend on the actual value of D_c . Equation (11) derived below will demonstrate that the ratios $D_c f_{\perp} / k_B T$ and $\mu V_0 / \lambda$ are the two key parameters that control the occurrence and the strength of the ratchet effect. Their values can be changed in an experiment by adjusting the force f_{\perp} , the barrier height V_0 , and the period λ .

For the constant part of the speed (3), we have used $u = 10$ nm/s. The reported results, however, are insensitive to the actual value of u , as we have checked several alternative values of u between 0 and 10^3 nm/s. The negligible effect of u on the translational dynamics results from the large D_r , Eq. (7), characteristic for small particles ($D_r \sim 1/R_h^3$) as compared to the slower translational motion whose speed is determined by D in (6) ($D \sim 1/R_h$), u and by D_c (8). This is in sharp contrast to the motion of micron-sized active particles that move ballistically for significant periods of time due to relatively large u and small D_r ^{1,75–80}.

We quantify the ratchet effect in terms of the mean velocity $\langle v_x \rangle$ of the particle motion in the x -direction. It is defined as the average

$$\langle v_x \rangle = \frac{1}{N_{\text{tr}}} \sum_{i=1}^{N_{\text{tr}}} \frac{x_i(t_{\text{max}})}{t_{\text{max}}} \quad (9)$$

over N_{tr} simulated trajectories, where $x_i(t_{\text{max}})$ is the final x -coordinate of the i th trajectory. We have used $D_r t_{\text{max}} = 10^3$, $N_{\text{tr}} = 10^4$, and checked that increasing t_{max} and N_{tr} does not affect the displayed results.

Figure 2 shows $\langle v_x \rangle$ for $f_{\parallel} = 0$, i.e., when there is no net force in the x -direction. Symbols mark $\langle v_x \rangle$ of the active nanoparticle with the microscopically reversible self-propulsion mechanism (MR ANP) described by the active speed $v_a(\mathbf{r}, t)$ in (3). Dashed lines represent $\langle v_x \rangle$ of the so-called active Brownian particle (ABP) model^{76,78,79,81–93} which is a paradigmatic model for micron-sized active colloidal particles^{1,75–79} and is characterized by the constant active speed

$$v_a^{(\text{ABP})} = u. \quad (10)$$

The ABP model is formally obtained from the MR ANP model after neglecting the mechanochemical coupling and the noise in Eq. (3), i.e., by setting $\mu_c = D_c / k_B T = 0$.

The simulated mean velocities $\langle v_x \rangle$ for these two models are plotted in Fig. 2 as the functions of the perpendicular force f_{\perp} for three representative values of the barrier height V_0 :

(i) $V_0 = 1 k_B T$, light-blue symbols, where the barrier height is equal to the energy of thermal fluctuations. Thus, the asymmetric potential $V(x)$ has only a minor influence on the dynamics and $\langle v_x \rangle$ of MR ANP is vanishingly small.

(ii) $V_0 = 6 k_B T$, yellow symbols. Here, thermal fluctuations can induce hopping-like transitions of particles over the barriers of $V(x)$. As a result of the ratchet effect, MR ANP exhibits a nonzero mean velocity in the negative direction of the x -axis ($\langle v_x \rangle \leq 0$). There exists an optimal value of f_{\perp} leading to a maximal negative velocity of MR ANP. In the limits of small ($f_{\perp} \rightarrow 0$) and large ($f_{\perp} \rightarrow \infty$) perpendicular forces, $\langle v_x \rangle$ vanishes.

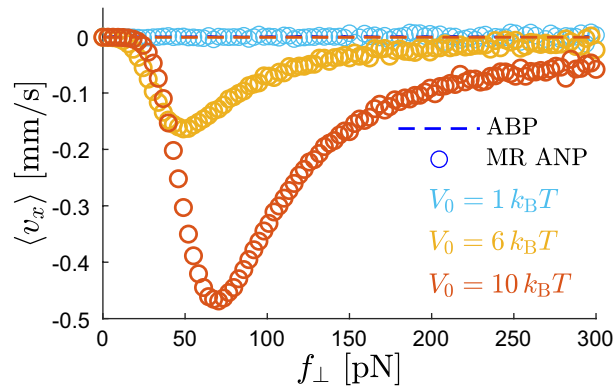


Figure 2. Rectified particle motion. Net particle translation is induced by the mechanochemical coupling term in the active speed (3). The mean particle velocity $\langle v_x \rangle$ in the x -direction is plotted as the function of the perpendicular force f_{\perp} acting in the y -direction for three values of the barrier height V_0 (colors) and $f_{\parallel} = 0$. Parameters D, D_r, D_c are given in Eqs. (6)–(8), $\lambda = 100$ nm, and $u = 10$ nm/s. Symbols represent simulated $\langle v_x \rangle$ of the active nanoparticle with the microscopically reversible self-propulsion mechanism (MR ANP) illustrated in Fig. 1. Dashed lines show corresponding results for the active Brownian particle (ABP) model with constant active speed (10). The three dashed lines overlap.

(iii) $V_0 = 10 k_B T$, red symbols. In this case, the barriers of $V(x)$ are large compared to the energy of thermal fluctuations. The cross-well transitions of MR ANP are driven dominantly by the active velocity. The ratchet effect becomes the most pronounced out of the three cases.

In Fig. 2, the three dashed lines marking $\langle v_x \rangle$ for the ABP model overlap and follow closely the line $\langle v_x \rangle = 0$ for all f_{\perp} .

These observations suggest that the ratchet effect should be caused by the force-dependence of the active speed (Eq. 3). Can we understand this effect qualitatively, e.g., by relating it to some of the well-understood ratchet mechanisms? It turns out that this is not only possible but is indeed an insightful step as it will lead to yet another way of control over the motion of the nanoparticle.

For the considered values of parameters, the Langevin equation for the x -coordinate of MR ANP (and for $f_{\parallel} = 0$) approximately reduces to

$$\frac{dx}{dt} \approx \frac{\mu_c f_{\perp}}{2} \sin[2\phi(t)] - \tilde{\mu} \frac{dV}{dx} + \sqrt{2\tilde{D}} \xi_x(t), \quad (11)$$

where the effective enhanced mobility $\tilde{\mu} = \mu + \mu_c/2$, and the enhanced diffusivity $\tilde{D} = D + D_c/2$ (compared to μ and D), satisfy the fluctuation–dissipation relation $\tilde{D} = \tilde{\mu} k_B T$. Indeed, due to the fast rotational diffusion, we can neglect u in Eq. (3) as discussed above, yielding $v_a(\mathbf{r}, t) \cos \phi \approx \mu_c f_{\perp} \sin(2\phi)/2 - \mu_c V'(x) \cos^2 \phi + \cos \phi \sqrt{2D_c} \xi_c$ for the x -component of the active velocity. Since ϕ is a fast process and $\mu \gg \mu_c$, $\cos^2 \phi$ can be replaced by its mean value, $\cos^2 \phi \approx 1/2$. The noise term is then simplified accordingly: $\cos \phi \sqrt{2D_c} \xi_c = \sqrt{2D_c \cos^2 \phi} \xi_c \approx \sqrt{D_c} \xi_c$, and is added to the thermal noise $\sqrt{2D} \xi_x$, which eventually leads to (11); see Supplementary Note 3 for more technical details and tests of validity of this approximation.

Equation (11) describes the dynamics of a basic model of a Brownian motor, the so-called overdamped tilting ratchet^{59,64,66,94,95}. Discussion of the dynamics governed by Eq. (11) can provide a further physical understanding of the mechanism leading to the reported ratchet effect. Below, we focus on qualitative arguments and intuitive interpretation of the effect. For a thorough mathematical analysis of various classes of tilting ratchet models, we refer to Sect. 5 of the review article⁵⁹.

In particular, Eq. (11) describes the dynamics of an overdamped Brownian particle diffusing in the potential $V(x)$ subject to the time-dependent stochastic force $(f_{\perp}/2) \sin[2\phi(t)]$. If the magnitude of the force becomes large enough, the particle may start surmounting potential barriers of $V(x)$ located in the direction of the force. Because $V(x)$ is asymmetric, shapes of the left (moderate slope) and right (steeper slope) barrier surrounding a given well differ and the barrier-crossing is easier in one of the two directions: in $(-x)$ -direction in the present case. After surpassing multiple barriers in both directions, the asymmetry of $V(x)$ translates into the nonzero mean motion in the easy $(-x)$ -direction giving a nonzero mean velocity $\langle v_x \rangle$ observed in Fig. 2.

The velocity $\langle v_x \rangle$ attains its maximum for moderate values of f_{\perp} . If $f_{\perp} \rightarrow 0$, $\langle v_x \rangle$ vanishes because a weak force does not affect the rate of the barrier-crossings. At large f_{\perp} , $\langle v_x \rangle$ vanishes too: When the force is extremely strong, the potential barriers of $V(x)$ have only a minor influence on the particle motion and the effect of their asymmetry becomes negligible. Such a release of nanoparticles from deep potential wells that is induced by a strong perpendicular force f_{\perp} can be utilized for controlling the direction of $\langle v_x \rangle$. This is demonstrated in Fig. 3 showing a reversal of the direction of $\langle v_x \rangle$ for particles subjected to a weak force $f_{\parallel} > 0$ acting in the x -direction.

For small and moderate f_{\perp} , the results shown in Fig. 3 resemble those in Fig. 2: MR ANP experiences the ratchet effect and moves on average with $\langle v_x \rangle < 0$. However, at larger f_{\perp} , as the barriers of $V(x)$ become less significant for the MR ANP dynamics, the direction of the net particle motion is reversed, and $\langle v_x \rangle > 0$. Eventually, as $f_{\perp} \rightarrow \infty$, $\langle v_x \rangle$ converges towards the solid line given by

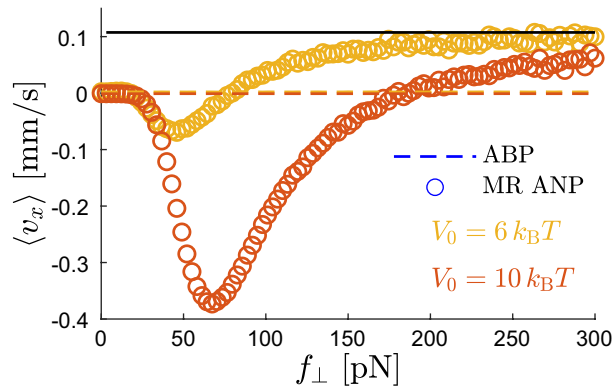


Figure 3. The ratchet effect and the velocity reversal. The mean nanoparticle velocity $\langle v_x \rangle$ in the x -direction (symbols), for the case when the nanoparticle is subjected to the nonzero parallel force $f_{\parallel} = 0.025$ pN. Other parameters are the same as in Fig. 2. The black solid line represents the velocity (12) of a Brownian particle moving in a flat potential with the enhanced mobility $(\mu + \mu_c/2)$. The two dashed lines marking corresponding results for the ABP model overlap.

$$\langle v_x^{(0)} \rangle = \left(\mu + \frac{\mu_c}{2} \right) f_{\parallel}, \quad (12)$$

which equals to the mean velocity of an overdamped Brownian particle diffusing in a flat potential [$V(x) = 0$] with the enhanced mobility $\tilde{\mu} = \mu + \mu_c/2$, cf. the mobility in Eq. (11).

Contrary to this complex behavior, $\langle v_x \rangle$ in the ABP model does not depend on f_{\perp} and is vanishingly small because the ABP spends most of the time being trapped near the minima of $V(x)$ regardless of the value of f_{\perp} .

Finally, let us note that the magnitude of $\langle v_x \rangle$ and the range of f_{\perp} values, where the transverse ratchet effect occurs, depend on the value of the phenomenological parameter $\mu_c = D_c/k_B T$ characterising the strength of the mechanochemical coupling. This dependence is demonstrated in Fig. 4, where blue circles correspond to μ_c used in all other figures and obtained from the estimate (8) and red triangles (yellow squares) represent simulation results for μ_c being 5 times (10 times) larger. Hence, for stronger mechanochemical coupling, the ratchet effect becomes more pronounced and occurs at lower values of the transverse force f_{\perp} .

Summary and perspectives

The principle of microscopic reversibility is fundamental for nonequilibrium statistical mechanics and thermodynamics. Here, we have discussed the physical origins and fundamental properties of a novel ratchet mechanism resulting from the MR of the chemically-driven self-propulsion mechanism of an active nanoparticle. The mechanism enables efficient control of the velocity of a nanoswimmer propelled by chemical reactions. It is based on an interplay of the particle translational diffusion in an asymmetric periodic potential $V(x)$ and the modification of its self-propulsion speed because of the mechanochemical coupling. The resulting ratchet effect manifests itself most strikingly by the emergent net particle motion in the easy direction of the ratchet potential, when a constant force f_{\perp} is applied to the particle in a perpendicular direction. The mean velocity $\langle v_x \rangle$ of this motion can be controlled by adjusting the barrier heights V_0 of the periodic potential and the magnitude of f_{\perp} . For a

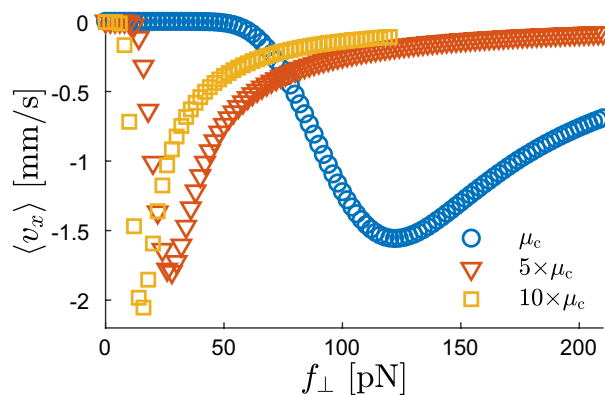


Figure 4. Impact of μ_c on the ratchet effect. The mean velocity $\langle v_x \rangle$ of MR ANP in the x -direction for $f_{\parallel} = 0$, $V_0 = 20 k_B T$, and three values of μ_c . Circles represent results for μ_c obtained from (8), triangles (squares) for five (ten) times larger μ_c . Other parameters are the same as in Figs. 2 and 3.

given V_0 , there exists an optimal value of f_{\perp} , for which the mean speed $|\langle v_x \rangle|$ attains a maximum. Furthermore, if a constant force f_{\parallel} is applied in the x -direction, the mean velocity can be reversed by changing f_{\perp} .

In addition to numerical results, we have shown that for the model parameters roughly corresponding to catalytic enzymes, the dynamics of the nanoparticle in the x -direction is equivalent to that of a Brownian tilting ratchet. This mapping provides an intuitive physical interpretation of the reported ratchet effect and demonstrates that it cannot occur in active dynamics lacking the mechanochemical coupling. In the present model, this coupling arises as a consequence of the microscopic reversibility of the fluctuating chemical kinetics powering nanoparticle self-propulsion. Further exploration of such coupled thermodynamic processes at the nanoscale can inspire novel designs for micromanipulation techniques, where macromolecules are acted upon by externally applied electromagnetic or/and mechanical forces. Additionally, testing such effects in experiments may contribute toward a resolution of the long-standing question of whether active enzymes self-propel or not.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability

The computer codes used to produce the results presented in the article are available from the corresponding author upon reasonable request.

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Author contributions

A.R. and M.T. conceived the idea. A.R. developed the model, A.R. and M.T. performed the numerical calculations and wrote the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to M.T.

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