Propulsion of a molecular machine by asymmetric distribution of reaction–products

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A simple model for the reaction-driven propulsion of a small device is proposed as a model for (part of) a molecular machine in aqueous media. Motion of the device is driven by an asymmetric distribution of reaction products. The propulsive velocity of the device is calculated as well as the scale of the velocity fluctuations. The effects of hydrodynamic flow as well as a number of different scenarios for the kinetics of the reaction are addressed.

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Molecular motors are machines that convert chemical energy to mechanical work [1, 2]. Examples are the cytoplasmic motors that move along biological (protein) tracks in the cell by converting the energy released upon ATP hydrolysis into mechanical work [3, 4]. These complex machines act as the inspiration for the design of macromolecular devices [5] with the ability to sort, sense and transport material in chip-sized laboratories [6]. Consequently a major area of current chemical research is the construction of much simpler molecular machines for nanotechnological applications [7].

In this spirit, we study in this Letter a simple model of a self-propelling device driven by chemical reactions on its surface. It is simple enough that not only is the construction using chemical techniques feasible, but it should also be possible to change parameters in order to optimize particular features or functions.

We consider a spherical particle (colloid or vesicle) of radius $R$ that has a single enzymatic site located on its surface at a fixed position, as sketched in Fig. 1. In the presence of a reactive substrate in a non-equilibrium state, the enzyme promotes the reaction rate in its vicinity and produces a dynamic and asymmetric distribution of product particles of (hydrodynamic) diameter $a \ll R$ which exert osmotic or interfacial forces (depending the boundary properties) and hence propel the sphere in a fixed direction. We consider both uniform and periodic reactions and calculate the propulsive velocity of the sphere. We find that the velocity of propulsion is set by the size of the product particles, the properties on the boundary, and the reaction rate. Upon considering the variations in the rate particle release (and taking account of density fluctuations), we find that the ratio of the mean-square velocity fluctuations to the mean velocity depends on the ratio of the time for a product particle to diffuse a distance $R$ to the typical time between the production of successive product particles.

The reaction site on the sphere, located at $r_s = -\hat{z}R$ (see Fig. 1), is an enzyme catalyzing the break up of an available substrate into two product particles. If one of the product particles is similar in size to the original substrate (see below), we can assume that the reaction site effectively acts as a source of excess particles that are being released at the reaction site at a rate $\frac{dN_p(t)}{dt}$, and the diffusion equation for the density of the excess product particles can be written as

$$\partial_t \rho(r, t) - D \nabla^2 \rho(r, t) = \frac{dN_p(t)}{dt} \delta^3(r - r_s),$$  \hspace{1cm} (1)

where $D$ is the diffusion constant of these particles. The density profile can be obtained from Eq. (1) subject to the boundary condition of vanishing normal current on the surface of the sphere, $\hat{r} \cdot \nabla \rho|_{\text{sphere}} = 0$.

The resulting distribution of product particles around the sphere is asymmetric, with a non-zero first moment of $\rho_1(t) = \int_0^\pi \sin \theta d\theta \cos \theta \rho(r = R, \theta, t)$, leading to phoretic motion of the sphere. It is well known that colloidal particles in externally imposed solute gradients will be set in motion by a variety of phoretic mechanisms [8]. Here in contrast, the gradient (of products) is self-generated [9] by the device itself. We thus obtain a general expression for the velocity of propulsion in the $z$-direction $v = -\frac{k_B T}{\eta} \frac{\lambda^2}{\bar{\lambda}} \rho_1$, where $\eta$ is the viscosity of the solvent and the length-scale $\lambda$ depends on the particular phoretic mechanism [8, 10]. The other components of the velocity vanish due to symmetry. Two
mechanisms valid for non-ionic product particles are the “diffusiophoresis” of a totally impermeable sphere \([11]\), because the depletion of the product particles near its surface causes a lateral slip velocity that results in net motion of the sphere, and the “osmiophoresis” of a spherical shell which is permeable to solvent but impermeable to product particles which develops a non-zero velocity due to osmotic forces that cause radial flows of solvent across the membrane \([12]\).

Experimental estimates for the diffusiophoretic, \(\lambda_D\) and the osmiophoretic, \(\lambda_0\) lengthscales are available from the literature. Measurements on latex particles in gradients of Dextran by Staffeld and Quinn \([13]\) obtained values of \(\lambda_D \approx 38\ \text{nm}\). Studies of micron sized lipid vesicles of radius \(R\) in gradients of sucrose by Nardi et al \([14]\) have obtained an osmiophoretic lengthscale \(\lambda_0 \sim 0.3R\). Theoretical treatments of phoretic propulsion implement local momentum conservation by solving the Stokes’ equation for the solvent (\(\text{Re} \ll 1\)) taking account of the product particles and force balance on the sphere \([8]\). For diffusiophoresis, Anderson and Prieve \([15]\) have calculated \(\lambda_D^2 = \int_0^\infty dl \left[ 1 - e^{-\lambda_0 R/l} \right] \), where \(\lambda_0\) is the interaction energy between the solute particles and the rigid wall of the sphere at a normal separation \(l\). This is consistent with the experiments above \([13]\) for an interaction range given by the hydrodynamic radius of Dextran. For osmiophoresis, Anderson \([12]\) has obtained, \(\lambda_0^2 = R^2 \left[ \frac{\eta L_p/R}{2\pi + \eta L_p/R} \right] \), where \(L_p\) is the filtration coefficient of the membrane. For a \(R = 2\ \mu\text{m}\) lipid vesicle, using \(\eta = 10^{-3}\ \text{Pa.s}\) and \(L_p = 10^{-7}\ (\text{m/s})/\text{atm} \([16]\), one obtains \(\lambda_0^2 \sim 0.01\) significantly lower than the experiments above \([14]\). This discrepancy between theory and experiment remains an open problem \([10]\).

Solving Eq. \([1]\) subject to the appropriate boundary condition mentioned above, we find \(p_1\), which together with the above expression for the velocity of propulsion yields

\[
v(t) = \ell \int \frac{d\omega}{2\pi} e^{-i\omega t} f(\omega) \left[ 1 - i \left( \frac{\ell \omega R^2}{D} \right) \right] \left[ 1 - i \left( \frac{\ell \omega R^2}{D} \right) \right],
\]

where \(\ell = \frac{k_BT}{\pi \eta D}\) and \(f(\omega)\) is the Fourier transform of \(\frac{dN_j(t)}{dt}\). Using Einstein’s formula for the diffusion coefficient \(D = k_BT/(3\pi \eta a)\), we find

\[
\ell = a \left( \frac{3 \lambda_0^2}{4 R^2} \right).
\]

The time dependence of the velocity will depend on the particle release rate. Two important cases of uniform and periodic particle release are considered.

**Uniform Particle Release.** Consider the case where a particle source with a uniform rate is switched on at

\[
t = 0; \quad \text{i.e.} \quad \frac{dN_j(t)}{dt} = \frac{1}{\tau_i} \vartheta(t),
\]

where \(\tau_i\) is the average inverse reaction rate or “firing” time of the product particles, and \(\vartheta(t)\) is the Heaviside step function. Using Eq. \([2]\), we find the average velocity of the sphere as

\[
v(t) = v_0 \vartheta(t) G \left( \frac{R^2}{\ell \tau_i} \right),
\]

where the stationary velocity is given by

\[
v_0 = \frac{\ell}{\tau_i}.
\]

and \(G(s) = 1 - \cos 2s - \sin 2s + 4 \sqrt{s} F_1\left(1; \frac{3}{2}, \frac{5}{2}; -s^2\right)\), where \(F_1(1, \frac{3}{2}, \frac{5}{2}; -s^2)\) is a generalized hypergeometric function \([17]\). The time response of the force is plotted in Fig. \(2\). The function starts at \(t = 0\) with an infinite slope and asymptotes to its final value around \(t = R^2/D\).

We can estimate the steady state propulsive velocity for a spherical device of radius \(R = 2\ \mu\text{m}\) with the enzyme on its’ surface catalyzing a fast reaction such as that of acetylcholinesterase, which hydrolyzes acetylcholine in the synaptic cleft into components acetate and choline at the rate of \(1/\tau_i \approx 25000\ \text{s}^{-1}\) \([18]\). The corresponding product particle will be acetate with a hydrated diameter of \(a = 0.8\ \text{nm}\). Using the estimates above \([13, 15]\) for \(\lambda_D\) we find a steady-state propulsive velocity from diffusiophoresis of a hard sphere as \(v_D \sim 1\ \text{nm/s}\). This rather small value could be improved by “engineering” the strength and range of the interaction of products with the surface. The high experimental value of \(\lambda_D\) measured \([14]\) for closed vesicles imply a much higher velocity of propulsion \(v_0 \sim 1\ \mu\text{m/s}\) for a semipermeable shell. Theoretical estimates \([12]\) however predict a much smaller velocity \(v_0 \sim 1\ \text{nm/s}\).

**Periodic Particle Release.** If the reactions occur at well defined time intervals of \(\tau_i\), then

\[
f(\omega) = \sum_{m=-\infty}^{\infty} e^{i\omega m \tau_i} = \frac{2\pi}{\tau_i} \sum_{m=-\infty}^{\infty} \delta(\omega - 2\pi m/\tau_i)
\]

in Eq. \([2]\) and the velocity reads

\[
v(t) = v_0 \sum_{m=-\infty}^{\infty} e^{-i2\pi mt/\tau_i} A_m \left( \frac{R}{\sqrt{D\tau_i}} \right),
\]

where \(A_m(x) = \frac{1 + (1 - i)\sqrt{m^2 x}}{1 + (1 - i)\sqrt{m^2 x} - i2\pi mx}\). The above expression can be simplified in two limiting cases. For \(\frac{R}{\sqrt{D\tau_i}} \ll 1\), the expression in the brackets can be approximated as \(1\) and the
series can be summed up to \( v(t) \approx v_0 \sum _{n=-\infty }^{+\infty } \delta (t/t_1 - n) \). This corresponds to the case where the diffusion time around the sphere is much less than the firing time. In this case we expect the initial inhomogeneous profile of the product particles to lead to instantaneous impulses that are immediately screened due to fast homogenization. In the opposite limit of \( \frac{R}{\sqrt{D \tau _1}} \gg 1 \), however, the rapid release of the product particles maintains a stabilized inhomogeneous profile and the velocity is approximately constant: \( v(t) \approx v_0 \). The time evolution of the velocity is plotted in Fig. 3 for an intermediate case of \( \frac{R}{\sqrt{D \tau _1}} = 1 \). We note that the relative magnitude of the velocity fluctuations and the average velocity is set by the ratio between the firing time and the diffusion time.

Velocity Fluctuations. The velocity calculated in Eq. 2 should be considered as the average of a fluctuating quantity. There are two sources of fluctuations that need to be taken into consideration for a quantitative assessment of the velocity fluctuations, namely, product particle density fluctuations and randomness in the reaction that leads to the particle release.

To take account of the density fluctuations, we can go back to the Langevin dynamics of the particles described as \( \delta \dot{r}_i(t) = u_i(t) \) for the \( i \)-th particle, where \( u_i(t) \) is a random noise with a distribution \( P[u] = \exp \left[ -\frac{1}{2D} \sum _i \int dt \, u_i(t)^2 \right] \). We can construct a stochastic density as \( \dot{\rho}(r,t) = \sum _i \delta ^3(r - r_i(t)) \) and show that it satisfies Eq. 1, with an additional noise term \( \dot{Q}(r,t) \) added to its right hand side, whose moments can be calculated using the above distribution as \( \langle \dot{Q}(r,t) \rangle = 0 \) and \( \langle \dot{Q}(r,t) \dot{Q}(r',t') \rangle = 2D (-\nabla ^2) \delta ^3(r - r') \delta (t - t') \rho (r,t) \), where \( \rho (r,t) = \langle \dot{\rho}(r,t) \rangle \). To incorporate the randomness of the reaction, we write the particle release rate as \( \frac{dN_n(t)}{dt} = \sum _i \delta (t - \sum _{j<n} \tau _j) \), where we have defined a time interval \( \tau _n \) between the release of the \( n+1 \)-th and the \( n \)-th particles. We further assume that the reaction leading to the product release is a Poisson process, in which case the probability distribution of the time intervals between two consecutive particle release events is given by \( P(\tau) = \frac{1}{\tau _n} e^{-\tau /\tau _n} \).

Using the formulation outlined above (details of which will be presented elsewhere [10]), we can calculate the fluctuations of the velocity about its mean value. We find the long-time behavior of the velocity correlations as \( \langle \Delta v(t) \Delta v(0) \rangle \sim \frac{t^2}{\tau _1} \), where the over-line denotes averaging with respect to the time-interval distribution. This result implies diffusive behavior, and we obtain an effective diffusion coefficient \( D_{zz} \sim \frac{t^2}{\tau _1} \), for the sphere in the propulsion direction. Similar results are obtained for the effective diffusion coefficients \( D_{yy} \) and \( D_{yy} \) in the lateral directions. We can also estimate the relative importance of the velocity fluctuations as compared to the average velocity by calculating \( \langle \Delta v \rangle = \sqrt{\frac{\langle v_v - v_0 \rangle^2}{v_0^2} \sum _i \sum _{n<i} \tau _n} \). In the long-time limit, we find \( \langle \Delta v \rangle \sim \frac{\tau _1}{R^2}, \) for \( R \gg a \). The velocity fluctuations are thus controlled by the ratio between the firing time and the time it takes for the product particles to diffuse across the sphere and homogenize their profile. For robust propulsion, the firing time must be considerably less than the diffusion time.

Effect of Hydrodynamic Flow. To make the calculations self-consistent we should also take account of the fact that the diffusion of the product particles will be affected by the hydrodynamic flow around the sphere. The velocity profile of the solvent around the sphere can be shown to have a \( 1/r^3 \) dependence, which is characteristic of phoretic flows [12]. A corresponding convective term should then be added to Eq. 1, which suggests a systematic solution of the equations as a perturbative series in the Péclet number \( Pe = vR/D \). Previous work has shown that the first correction term is of the order of \( Pe^2 \) for osmiophoresis [12], and \( Pe (\lambda _D/R) \) for diffusiophoresis [13]. These corrections are negligible for the cases considered here (see below).

Reaction Kinetics. It is illuminating to examine more closely the conditions under which the above simplified picture holds, taking into account the reaction kinetics. We have a solution of substrate \( S \) at a relatively high concentration \( CS \) that has a natural slow tendency to dissociate, \( S \rightarrow S' + P \) where \( S' \) and \( P \) represent the product particles that are assumed to exist in vanishingly small concentrations in the bulk. This means that the entire bulk of the system is in a non-equilibrium condition that will not relax to equilibrium in laboratory time scale. The presence of an enzyme \( E \) catalyzes this reaction, so that it takes place considerably faster in the vicinity of the enzyme, which leads to an increased production of \( S' \) and \( P \) with corresponding concentrations, \( CS' \), and \( CP \) respectively. There will also be a depletion of \( S \) in the neighborhood of the enzyme. The products will slow down the reaction by moving it towards equilibrium using the backward path \( S' + P \rightarrow S \) that is inevitably present, but one can show that it is only a small perturbation to the reaction condition, because all the concentrations have to match smoothly with those of the bulk that are maintained out of equilibrium. The net propulsion of the sphere depends on all three concentra-
tions. If the diffusion constants (i.e. the hydrodynamic radii) and other properties of the $S$ and the $S'$ particles are not that different, the sum of the two concentrations $C_S + C_{S'}$ remains constant and their contributions to the phoretic propulsion cancel [19]. This leads to the simplified picture presented above of a diffusive process with a localized source where $\rho = C_P$ in Eq. (1).

To gain further insight on what controls the effective particle release rate, we consider the following general multi-stage reaction pathway

$$ S + E \xrightarrow{k_1} SE \xrightarrow{k_2} P_2E + P_1 \xrightarrow{k_3} P_1 + P_2 + E, \quad (5) $$

where the two products $P_1$ (1st) and $P_2$ (2nd) represent $S'$ and $P$, the order depending on which of them ($S'$ or $P$) is released first. The backward reaction paths in Eq. (5) have been eliminated for simplicity, and they can be shown to have negligible effect provided the nonequilibrium working condition described above is maintained [11]. Under steady-state reaction conditions, the diffusion-reaction equations take on the form of Eq. (1), with the same rate (as a sink for the substrate and source for the products) appearing on the right hand side of these equations. The mean rate constant is given by the Michaelis–Menten rule [20]

$$ \frac{1}{\tau_1} = \left( \frac{k_2 k_3}{k_2 + k_3} \right) \frac{C_S(E)}{K_M + C_S(E)}, \quad (6) $$

where $K_M \equiv \frac{1}{k_1} \left( \frac{k_2 k_3}{k_2 + k_3} \right)$, is the Michaelis constant and $C_S(E)$ is the substrate concentration at the position of the enzyme.

The concentration of the substrate at the position of the enzyme, which we expect to be depleted in comparison to the bulk concentration $C_0$, can be found by solving the corresponding reaction-diffusion equation with the appropriate boundary condition. We find

$$ C_S(E) = \frac{1}{3} \sqrt{\left[ C_0 - \left( 1 + \frac{3k_1 \eta a_S}{k_B T a_S} \right) K_M \right]^2 + 4K_M C_0} + \frac{1}{2} \left[ C_0 - \left( 1 + \frac{3k_1 \eta a_S}{k_B T a_S} \right) K_M \right], \quad (7) $$

where $a_S$ is the hydrodynamic radius of the substrate and $a_E$ is a typical size of the enzyme.

**Discussion.** The molecular locomotive device will be useful if it can perform directed motion over a distance that is large compared to its own size. A very important limiting factor for directional motion is rotational diffusion, whose time scale for a spherical colloid is $\tau_R = 8\pi \eta R^3/(k_BT)$, which implies that we can achieve more directed motion by increasing the size of the sphere. The rotational diffusion time turns out to be of the order of 50 s, for $R = 2 \mu m$, which means that given an optimal propulsive velocity of $v_0 \sim 0.5 \mu m/s$, a locomotive of that size can travel of the order of ten times its own size before it loses sense of its original orientation. The effective diffusion constants derived from the velocity fluctuations above contributes negligibly to the orientational memory loss, giving a rotational diffusion time of the order of $\tau_R \sim (R/l)^2 \tau_1 \sim 1000 \text{s}$. We also note that the typical time that the system spends in a transient regime after a change is given by $\tau_0 = R^2/D$ (see Fig. 2), which is of the order of 5 ms. The effect of the hydrodynamic flow can be seen to be unimportant, because $Pe \sim 10^{-2}$.

In conclusion, we have proposed a model design for a molecular machine that can propel a vessel in aqueous media with a mechanism that involves asymmetric release of reaction products. The motor may be thought of as a diffusive equivalent of the jet engine: it releases asymmetrically the reaction products in a viscous medium, lets them diffuse and takes advantage of their thermodynamic forces, instead of gaining inertial thrust by ejecting the exhaust.

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