Membranes with Rotating Motors

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We study collections of rotatory motors confined to two-dimensional manifolds. These systems show a nontrivial collective behavior since the rotational motion leads to a repulsive hydrodynamic interaction between motors. While for high rotation speed motors might exhibit crystalline order, they form at low speed a disordered phase where diffusion is enhanced by velocity fluctuations. These effects should be experimentally observable for motors driven by external fields and for dipolar biological motors embedded into lipid membranes in a viscoelastic solvent.

Membranes are an essential part of a cell. They define its external boundaries and partition it into various compartments. However, the function of biological membranes is much more complex than merely being a passive barrier. They participate in a number of essential cell functions, such as transport, cell locomotion, and intercompartmental transport. These functions are mediated by specific proteins, which consume and convert energy. Thus, from a statistical physics point of view, biological membranes are strongly out of equilibrium.

Realistic models of biological membranes have to account for these nonequilibrium properties. Whereas the shapes and fluctuations of model fluid membranes at thermal equilibrium are by now well understood [1], the investigation of active membranes (i.e., membranes containing active components) has just started. Recently, a theoretical nonequilibrium statistical physics approach has been developed to describe the shapes and fluctuations of membranes containing active pumps [2]. Experiments have been carried out which have confirmed the theoretical predictions that under appropriate conditions nonequilibrium noise enhances the shape fluctuations of the membrane [3].

So far, the theoretical analysis of active membranes has concentrated on pumps and channels. However, there is a class of biologically relevant macromolecules which exhibit rotational motion. Most important are the motor adenosine triphosphate synthase (ATPsynthase) [4] and certain cilia [5].

ATPsynthase is a large multisubunit protein, consisting of an enzymatic protruding portion F_1 attached to a membrane-embedded, proton-conducting portion F_0 [4]. It is thought that the protons passing through the transmembrane carrier cause the stalk to spin rapidly within the head, inducing the synthesis of ATP in F_1. The motor is reversible and an excess of ATP provokes a rotation in the opposite direction and a reverse flux of protons. Cilia are hairlike structures that extend from the surface of many kinds of eucaryotic cells. They are formed from specialized groupings of microtubules called "basal bodies." Their primary function is to move fluid over the surface of a cell or to propel single cells through a fluid. However, as observed in Ref. [5] nodal cilia can also exhibit rotational motion.

Other rotatory motors have been experimentally realized in a completely different nonbiological context. Whitesides *et al.* have studied pattern formation of rotating magnetic disks confined to a two-dimensional interface [6,7]. Similar effects should also occur for rotors stirred by laser tweezers [8]. While these motors are rotational monopoles driven by an external field, the biological macromolecules are driven by internally generated forces and correspond to rotational dipoles.

Here, we study both rotational monopoles confined to a two-dimensional manifold (which could be a membrane or any other surface) and dipolar motors embedded into membranes (which could be biological motors in a lipid membrane). We show that these systems exhibit, in contrast to membranes containing pumps and channels, a nontrivial collective behavior since the rotational motion may induce repulsive hydrodynamic interactions between motors. Consequently, at high rotation speed, the motors might form a crystalline phase. Upon decreasing speed (by, e.g., changing the ATP concentration), the lattice melts to form a disordered phase. For this ("high-temperature") phase we predict an enhancement of diffusion, and we comment on the existence of stable limit cycles for the movement of the motors.

We assume the motors to be embedded in a flat manifold at $z = 0$ with a shear surface viscosity η_m. The manifold is surrounded by an incompressible solvent of density ρ_l which is either Newtonian or viscoelastic. The manifold contains N motors at position $\boldsymbol{r}_i$, where $\boldsymbol{r} \equiv (\boldsymbol{x}, z)$ denotes the position in three-dimensional space and $\boldsymbol{x} \equiv (x_1, x_2)$ the position on the surface.

For the systems mentioned above flow occurs at low Reynolds number Re since for ATPase the angular velocity $\omega \simeq 100$–1000 s^{-1} and its typical size $R \simeq 10$ nm [9,10], whereas for cilia $\omega \simeq 10$–100 s^{-1} and $R \simeq 5$ μm [5]. Therefore Re $\simeq 10^{-7}$ and Re $\simeq 10^{-3}$, respectively. For

rotors driven by an external field $\omega \simeq 10$–100 s^{-1} and $R \simeq 100$ μm should be realizable. Then, Re $\simeq 10^{-1} - 1$.

We first consider the simplest monopolar motor given by a spinning sphere of radius R embedded into a surface with negligible surface viscosity ($\eta_m = 0$) surrounded by a Newtonian fluid with viscosity η. The velocity field $\boldsymbol{v}$ induced by a rotation with angular velocity vector $\boldsymbol{\omega} = \omega \boldsymbol{e}_z$ is in the direction of $\boldsymbol{e}_\varphi \equiv \boldsymbol{e}_z \times \boldsymbol{r}/r$ in spherical coordinates. In the limit of small Reynolds number, $\boldsymbol{v}$ is a solution of the Stokes equation and is given by [11]

$$\boldsymbol{v} = \frac{R^3}{r^3}\boldsymbol{\omega} \times \boldsymbol{r}. \tag{1}$$

In the simplest description, rotational dipoles on such a surface can be thought of as being built up by two spheres separated by a distance d with angular velocity vectors $-\boldsymbol{\omega}$ and $\boldsymbol{\omega}$. If the two spheres are located at $\boldsymbol{r}_1 = (0, z = 0)$ and $\boldsymbol{r}_2 = (0, z = d)$, then the velocity field at $\boldsymbol{r}$ (for $r \gg d$) is at first order in d given by

$$\boldsymbol{v}(\boldsymbol{r}) = v_\varphi \boldsymbol{e}_\varphi = \frac{3R^3 zd}{r^5}\boldsymbol{\omega} \times \boldsymbol{r}. \tag{2}$$

Because of rotational symmetry the flow field (1) is independent of η. However, η sets the scale for the relevant forces. The viscous torque exerted by the fluid on the rotating sphere is given by $\tau = -8\pi\eta R^3 \omega$, with $\boldsymbol{\tau} = \tau \boldsymbol{e}_z$.

For a more realistic description of the biological (dipolar) motors one must take into account the membrane viscosity $\eta_m \neq 0$ so that the viscosities seen by the two rotating portions of the motor are different. For simplicity, we assume that the motor consists of two circular disks with radii R at $z = d$ and $z = 0$. We restrict the analysis to the limit $d/z \ll 1$ and describe the flow field of one motor as being created by a set of localized forces in the fluid. Since a motor that is not subject to an external field cannot inject momentum into the fluid, the total torque associated with the force distribution vanishes. By introducing a discrete distribution of force centers at the edge of the disks the velocity field can be calculated. The coupled Stokes equation in the external fluid and in the membrane in the presence of this force field gives the velocity field in polar coordinates

$$\boldsymbol{v}(\boldsymbol{r}) = -\boldsymbol{e}_\varphi \frac{\tau}{8\pi\eta}\int_0^\infty dq\, q^2 h G(q,l) e^{-q|z|} J_1(qx), \tag{3}$$

where $h = d$ [12]. The velocity is as above parallel to the plane of the membrane and in the orthoradial direction. Here, J_ν denotes the Bessel functions of the first kind [13] and the propagator is given by $G(q,l) \equiv (1 + ql)^{-1} - \alpha 2\theta(z)$, where $\theta(x)$ is the Heaviside function, $l \equiv \frac{\eta_m}{2\eta}$ and $\alpha = 1$. In principle, the scale of l is set by the membrane thickness, but experimentally it is found to be at least 100 times larger [14].

For $l = 0$ Eq. (3) reduces to Eq. (2) and we recover the case of free spheres. For cilia which are immobile in the membrane one can set $l = \infty$ and one has $\boldsymbol{v}(\boldsymbol{r}) = 2v_\varphi \boldsymbol{e}_\varphi \theta(z)$, where v_φ is given by Eq. (2). In the case of a solidlike membrane the flow field does not penetrate through the membrane.

The case of monopolar motors embedded into a membrane with $\eta_m \neq 0$ can be treated in a similar way. Here, $\boldsymbol{v}(\boldsymbol{r})$ is also given by Eq. (3) provided one sets $h = 1/q$ and $\alpha = 0$ [in the definition of $G(q,l)$]. This equation reduces to Eq. (1) for $l = 0$. For large l one finds $\boldsymbol{v}(\boldsymbol{r}) = \boldsymbol{e}_\varphi x R^3 \omega/[lr(z + r)]$.

We now consider an ensemble of N motors confined to a flat surface and discuss the effect of the hydrodynamic interactions between them.

(I) Monopolar motors.—Since Stoke's equation is linear, the flow field for an assembly of N motors at positions $\boldsymbol{x}_i$ reads (for $\eta_m = 0$)

$$\boldsymbol{v}_t(\boldsymbol{r}) = R^3 \int d^2 x' \rho(\boldsymbol{x}')\boldsymbol{\omega} \times \frac{\boldsymbol{r} - \boldsymbol{r}'}{|\boldsymbol{r} - \boldsymbol{r}'|^3}, \tag{4}$$

where $\rho(\boldsymbol{x}) = \sum_{i=1}^N \delta(\boldsymbol{x} - \boldsymbol{x}_i)$ is the two-dimensional density of motors. This expression is formally equivalent to the Biot and Savart law of classical electrodynamics (see, e.g., [15]). Here, $\boldsymbol{v}$ plays the role of the magnetic field $\boldsymbol{B}$ which is induced by a current $\boldsymbol{j}(\boldsymbol{x}, z) = \rho(\boldsymbol{x})\boldsymbol{\omega}\delta(z)$. Furthermore, vortex lines in rotating superfluid helium create the same velocity field [16]. Thus, nondipolar motors can be interpreted as vortex points in two dimensions of strength $\kappa = \oint d\boldsymbol{l} \cdot \boldsymbol{v} = 2\pi\omega R^2$.

We assume that each motor follows the local flow. Thus, a motor at position $\boldsymbol{r}_0$ has velocity $\boldsymbol{v}_t(\boldsymbol{r}_0)$. For a discrete set of motors in an external field one finds

$$\frac{d\boldsymbol{x}_i}{dt} = R^3 \sum_{\substack{j \\ j \neq i}} \frac{\boldsymbol{\omega} \times (\boldsymbol{x}_i - \boldsymbol{x}_j)}{|\boldsymbol{x}_i - \boldsymbol{x}_j|^3} + \mathcal{O}\left(\frac{R^6 \omega}{|\boldsymbol{x}_i - \boldsymbol{x}_j|^5}\right). \tag{5}$$

The neglected terms arise from the fact that the flow field $\boldsymbol{v}(\boldsymbol{x}_j)$ of motor j alters the no-slip boundary condition for motor i at position $\boldsymbol{x}_i$. However, these corrections are small for low densities, i.e., for $|\boldsymbol{x}_i - \boldsymbol{x}_j| \gg R$.

To investigate the hydrodynamic interactions between the motors, it is useful to introduce the pseudoenergy

$$E_{\text{kin}} = \pi\rho_l R^6 \omega^2 \sum_{j \neq i} \frac{1}{|\boldsymbol{x}_i - \boldsymbol{x}_j|}. \tag{6}$$

A direct calculation shows that $E_{\text{kin}} = \frac{1}{2}\rho_l \int d^3 r\, \boldsymbol{v}_t^2(\boldsymbol{r})$ is the total kinetic energy of the fluid. The equation of motion (5) of a motor can then be rewritten as

$$2\pi\rho_l R^3 \frac{d\boldsymbol{x}_i}{dt} \times \boldsymbol{\omega} = -\frac{\delta E_{\text{kin}}}{\delta \boldsymbol{x}_i}. \tag{7}$$

The assembly of motors therefore reaches a steady state if the effective energy E_{kin} is extremal. Note, in Eq. (6) ρ_l has been introduced artificially, and there are no inertial effects in this force balance. The effective hydrodynamic interactions between motors are thus long range and repulsive and decay as $1/x$ [17]. In the absence of thermal fluctuations we thus predict that in a steady state, the

motors should form a Wignerlike "crystal" and order on a triangular lattice [18].

Thus, even though we are considering a viscous system the kinetic energy provides the relevant functional for the equations of motion. This is in agreement with the equivalent electrodynamical problem, where the energy density $\mathcal{E}_{em} = B^2/(16\pi c)$. Since B corresponds to $v_t(r)$, $\mathcal{E}_{em}$ corresponds to the kinetic energy E_{kin} of the system.

To discuss the stability of the lattice of motors, we consider a slightly disturbed lattice where motor i has been displaced from its equilibrium position $R_i = R_i^{(0)} + \delta R(t)$. By analyzing the equation of motion for $\delta R(t)$ it is easy to see that the displaced motor performs a rotation around its initial position with constant frequency $\tilde{\omega} \simeq 36\omega \frac{R^3}{a^3}$, where a is the lattice constant.

Thus, at the level of linear hydrodynamics, the triangular lattice of motors is only marginally stable. A full stability analysis requires nonlinear hydrodynamics. This goes beyond the scope of this work, and we give only a qualitative argument. It is shown in Refs. [6,7] that the first order inertial correction to the Stokes equation generates a force acting on the displaced motor. This force is the Magnus force $F_M = -2\pi\rho_l R^4 \tilde{\omega} e_\varphi \times \omega$. The Magnus force on the displaced motor points towards the equilibrium position and thus stabilizes the lattice.

In order to estimate the relaxation towards the equilibrium position, we assume that the motor is at position $\delta R(t) = r(t)(\cos\tilde{\omega}t, -\sin\tilde{\omega}t)$ and we calculate $r(t)$ by balancing F_M with a viscous drag force with a Stokes friction of order $6\pi\eta R$. Then, $r(t)$ decays exponentially with a relaxation time $1/t_R \sim \rho_l \omega \tilde{\omega} R^2/(3\eta)$. The critical frequency ω_c at which the crystal melts can be obtained by comparing the relaxation time t_R with a characteristic time of thermal fluctuations given by the diffusion time over a lattice constant $t_D = a^2/D = 6\pi\eta R a^2/kT$. Melting occurs for $t_R \simeq t_D$ or at frequencies $\omega < \omega_c$ with

$$\omega_c^2 \simeq \frac{akT}{72\pi t_v R^4 \eta}, \qquad (8)$$

where $t_v = \rho_l R^2/\eta$ is the time scale of diffusion of vorticity. Equation (8) is equivalent to the Lindeman criterion, where $kT = a^2 \partial^2 U(\omega = \omega_c)/\partial x^2$ with $\partial U/\partial x = F_M$.

If inertial effects are negligible, crystallization does not occur in ideal Newtonian fluids where no viscous analog of the Magnus force exists [19]: a viscous Magnus force F_M^v would have to break time-reversal symmetry, and in the absence of additional time scales any combination of $v \times \omega$ is symmetric under time reversal. In real (viscoelastic) fluids such an additional time scale is present given by the viscoelastic relaxation time t_m. Then, $F_M^v = 6\pi\eta R t_m v \times \omega$ [20]. For the biological materials considered here, viscoelastic effects dominate over inertia and one can replace t_v by t_m in Eq. (8). For a crystal of rotating objects with the size of a few nanometers one has $\omega_c \simeq t_m^{-1}$ (at room temperature).

(II) Dipolar motors.—To describe the motion of dipolar motors in a Newtonian solvent, we introduce the bulk friction $\zeta \sim 6\pi\eta R$ for the fluid part of the motor and the membrane friction for the membrane-embedded part $\zeta_m \sim 6\pi\eta l$. The actual velocity v of the motor is given by the balance of the friction forces on the motor, i.e., $\zeta(v - v_t(d)) + \zeta_m(v - v_t(0)) = 0$, where the velocities above the membrane $v_t(d)$ and in the membrane $v_t(0)$ for one motor are given by Eq. (3) in the limits where $z \to 0^+$ and $z \to 0^-$, respectively. Summing over the velocity fields created by all motors, we find

$$v_t(x) = \frac{\tau d}{4\eta\omega} \int d^2 x' G(x - x') \omega \times \nabla\rho(x'). \qquad (9)$$

The kernel G is obtained by inverse Fourier transformation of $G(q)$ of Eq. (3) (for $z < 0$)

$$G(x) = \frac{1}{2\pi l x} \left[1 - \frac{\pi x}{2l} [H_0(x/l) - N_0(x/l)] \right], \qquad (10)$$

where H_0 is the Struve function and N_0 the Neumann function [13]. If $x \ll l$, $G(x) = 1/(2\pi l x)$, and if $x \gg l$, $G(x) = l/(2\pi x^3)$. The velocity of a motor vanishes both for $l = 0$ because of symmetry and for $l \to \infty$ since then no motion is possible.

The interactions between the motors are studied in a similar way as for nondipolar motors. We introduce the pseudoenergy $E = 2\pi^2 \rho_l R^6 \omega^2 d \int d^2 x \int d^2 x' \rho(x)\rho(x') \times G(x - x')$ and the equation of motion of a motor is given by Eq. (7) with E replacing E_{kin}. A steady state distribution of the motors therefore corresponds to an extremum of E. The energy E corresponds to the kinetic energy of the fluid only for $G(x) = 1/x$. The hydrodynamic interactions between motors are again long range and repulsive, and the dipolar motors tend to arrange on a triangular lattice. Since for motors in a membrane the viscous friction is in general dominated by the membrane friction $\zeta_m \sim \eta_m \sim \eta l$, the critical frequency is $\omega_c \sim [a^3 kT/(t_v R^4 \eta l d)]^{1/2}$ at low densities ($a \gg l$) and $\omega_c \sim [alkT/(t_v R^4 \eta d)]^{1/2}$ at high densities ($a \ll l$). Again, for viscoelastic fluids ω_c can be obtained by replacing t_v by t_m in these formulas. All these results can be easily generalized to monopoles in membranes (by using the correspondence $d = 1/q$ and $\alpha = 0$).

Inserting typical values for the lattice constant $a \sim 10R$, we find an extremely high ω_c for nanometer scale motors in a Newtonian solvent. However, for viscoelastic solvents the hydrodynamic interactions are much stronger and melting occurs at experimentally achievable frequencies. The discussed effects might even be large enough to be relevant for real biological systems (such as, e.g., ATPsynthase in mitochondria). Ordering phenomena can probably be observed by attaching actin filaments to the F_1 portion [10] or by using motors of the size of cilia. For monopolar macroscopic motors, ordered structures have been observed [6,7].

At sufficiently low ω, hydrodynamic interactions are small and the motors form a disordered gas on the membrane. Local density fluctuations induce then local fluctuations of the velocity field. The convection by these velocity fluctuations creates an active diffusion of the motors. The active contribution to the diffusion constant is given by $\delta D = \frac{1}{2}\int_0^\infty dt \langle \boldsymbol{v}(\boldsymbol{x}, t)\boldsymbol{v}(\boldsymbol{x}, 0)\rangle$. By using Eq. (9) and by describing the motors as an ideal gas with $\langle \rho(\boldsymbol{q}, t)\rho(\boldsymbol{q}', 0)\rangle = 4\pi^2\delta(\boldsymbol{q} - \boldsymbol{q}')\rho \exp(-D_m q^2 t)$, where ρ is the average density in the membrane and $D_m \sim (6\pi\eta l)^{-1}$ the two-dimensional diffusion constant of the motors in the membrane, one obtains

$$\frac{\delta D}{D_m} = \frac{9\pi\rho d^2}{16}\left(\frac{\tau}{kT}\right)^2 \log(1 + q_{max}l) + \mathcal{O}\left(\frac{\delta D^2}{D_m^2}\right). \quad (11)$$

The active contribution to the diffusion constant is small for bare ATPase (where $\tau \simeq 0.01$ kT) but it can become important for actin-labeled ATPase ($\tau \simeq 10$ kT) and larger objects of the size of cilia.

So far, we have considered only flat membranes and ignored the coupling between the undulation fluctuations of the membrane and the rotating motors. Shape fluctuations influence the flow field on the membrane and thus alter the distribution of motors and the active contribution to the in-plane diffusion constant $D_m + \delta D$. Furthermore, the flow created by the motors can perturb the membrane fluctuations [3]. However, here the flow remains parallel to the average plane of the membrane even in the presence of shape undulations and the fluctuation spectrum is not modified [21].

In the high temperature phase motors might form aggregates which are stationary in shape. A possible configuration is a circle of radius r_0 consisting of N uniformly distributed motors. The far field of such a distribution is identical to that created by a single motor localized at the center of the circle rotating at a frequency $N\omega$, i.e., $v(x) = R^3 N\omega/x^2 + \mathcal{O}(r_0^2/x^2)$. Inside the circle, one has $v(x) = R^3 N\omega x/r_0^3 + \mathcal{O}(x^2/r_0^2)$. Thus, the circular arrangement rotates as a whole, with an x-dependent frequency, which vanishes as $r_0/R \to \infty$. However, this circular configuration is stable only in the limit where thermal fluctuations are negligible: if a motor diffuses away from the boundary of the aggregate, it starts to rotate around it, and the Magnus force caused by this motion then drives the motor even further away.

Nonhomogeneous motor distributions might also be related to the pathology situs inversus. Its origin has been tracked down to the absence of flow in the node region of mouse embryos, which is normally generated by rotating cilia [5]. It is assumed that the randomization of the left-right placement of organs associated with situs inversus is due to defective ciliary movement in the embryonal phase. For a collection of motors (which all rotate in the same direction) restricted to a nonsymmetric triangular geometry (which seems to be the shape of the node in mouse embryos) left-right symmetry is broken.

For a homogeneous arrangement of motors the associated transport is weak since for finite lattices only the motors close to the boundaries contribute. However, homogeneous arrangements restricted to a *finite* geometry are unstable. To demonstrate this we have numerically integrated Eq. (5) for N mobile motors restricted to a triangular geometry. Upon introducing adsorbing boundary conditions on the sides of the triangle, we found that density gradients build up which lead to an enhancement of the symmetry-breaking transport [12].

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[17] It should be emphasized that our analysis is valid only for $N > 2$. For $N = 2$ the motors simply rotate around their center of mass and their interaction has no radial component. However, the presence of additional motors gives rise to a radial interaction which, in general, is repulsive.

[18] We refer to this ordered state as a crystal even though it is not evident that it indeed exhibits quasi-long-ranged translational order since dislocation pairs are free to separate to arbitrary (but finite) distances.

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[21] However, ATPsynthase is not only a rotating motor that exerts a torque dipole but it is also a proton pump which exerts a local force quadrupole. In the linear theory considered here, the two contributions decouple and only the proton pump has an effect on the membrane fluctuations.