To go with the flow: Molecular motors are a drag
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Chapter 7

Outlook

Introduction

This chapter serves to provide the reader with a potential extension of the work presented in previous chapters. In this thesis a plausible explanation was given for the biological phenomena cytoplasmic and axoplasmic streaming. The results presented in chapters 4, 5 and 6 suggest that the actively transported organelles set up a non-negligible flow in the surrounding medium capable of displacing suspended objects in an otherwise quiescent fluid. So far only translational hydrodynamic interactions in planar geometries have been studied. It can be expected that the same mechanism yields alternative types of flow in different geometries. Indeed, in chapter 3 experiments [96, 98] and simulations [97] were discussed of particles moving on a Brownian ratchet in a toroidal trap. These studies showed that hydrodynamic interactions between the particles make these particles move faster along their rotational trajectory thus setting up a rotational flow field. Moreover, Goldstein et al. [209] showed that a complex flow field appears in cytoplasmic streaming of algal species such as Chara and Nitella. Here motors carry cargoes along actin filaments that are attached to the cylindrical cell wall. The filaments are arranged in two spiralling bands of opposite polarity, thereby allowing for simultaneous transport in opposite directions. The arising flow field consists of two components: Firstly, a component parallel to the spiral, and secondly, flow perpendicular to the spiral in radial direction. The combination of both gives rise to rotational flow and allows for fluid mixing.

In the review of Shimmen on cytoplasmic streaming [6] reference was made to experiments by Kuroda and Shimmen. These authors prepared a cytoplasmic drop in which chloroplasts were rotating in absence of external forces. Shimmen mentions that the rotational motion is thought to be driven by the same mechanism as cytoplasmic

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1See section ‘Brownian Ratchets Featuring Hydrodynamic Interactions’.

2Similar to the red and white bands of a barber pole.
streaming. Without knowledge of the details of the biological system or the physics that drive the chloroplasts, I would like to suggest answering a related question: is it possible for molecular motors, that are carrying cargoes while walking along the surface of a spherical object, to transfer enough momentum through the fluid for this object to start rotating? To study this effect the theory of translational hydrodynamic interactions that was discussed in chapter 2 has to be expanded with rotational interactions.

In the sections below the theory on hydrodynamic interactions is expanded by introducing rotational hydrodynamic interactions. Moreover, a model is proposed that could be used for testing the hypothesis that molecular motors can make an object rotate via hydrodynamic interactions. This work is accessible to both simulations and experiments. Finally, possible applications for microfluidic devices are discussed.

Rotational Hydrodynamic Interactions

In chapter 2 the Langevin Equation was introduced for interacting organelles (eq.2.43). This equation includes the hydrodynamic interactions between the organelles. The latter is included to account for the momentum that is transferred into the cytosol by the actively transported organelles. It is possible, by means of a hydrodynamic interaction tensor, to solve the flow field that arises from this transport. For example, assuming that the active organelles are treated as point particles, the arising flow field (eq.2.23) can be solved using the Oseen tensor (eq.2.25), that only includes long-range interactions. In addition, a description for the flow field that includes the size of the organelles, short and long range interactions is found using the Rotne-Prager tensor (eq.4.10). In the theory in chapter 2 only translational motion has been considered and rotational motion has been neglected. However, if an organelle is under influence of an external torque, \( \mathbf{T} \), it will rotate with constant angular velocity, \( \mathbf{\omega} \), and subsequently, via molecular momentum transfer, set up a flow field. The magnitude of this rotational flow field, \( \mathbf{V}_r \), is given by [66, 155]:

\[
\mathbf{V}_r = \left( \frac{a}{r} \right)^3 \mathbf{\omega} \times \mathbf{r}.
\] (7.1)

The required torque for an organelle \( i \) to overcome the fluid friction and maintain rotation is given by the equation below [57]:

\[
\mathbf{T}_i = 8\pi \eta a^3 \mathbf{\omega}_i = \frac{1}{\mu_0} \mathbf{\omega}_i.
\] (7.2)

In this equation, the constant of proportionality is the rotational self-mobility \( \mu_0^r \). The solution of the flow fields governed by momentum transport in both translational (superscript \( t \)) and rotational (superscript \( r \)) directions can be expressed as a combination of forces, torques and a mobility tensor. Ignoring thermal fluctuations, the following...
equations for the translational and rotational velocities, can be written for the interactions between an organelle \( i \) and all other organelles \( j \) [154,155]:

\[
V_i = \mu_{tt}^{ii} \cdot F_i + \sum_{j \neq i} \mu_{tt}^{ij} \cdot F_j + \sum_{j \neq i} \mu_{tr}^{ij} \cdot T_j
\]

and

\[
\omega_i = \mu_{tt}^{ii} \cdot F_i + \sum_{j \neq i} \mu_{tt}^{ij} \cdot F_j + \sum_{j \neq i} \mu_{rr}^{ij} \cdot T_j.
\]

Note that the mobility tensor consists of translational (superscript \( tt \)), rotational (\( rr \)), and combined components (\( tr \) and \( rt \)). It is possible to write these equations more concisely via introduction of a velocity, \( v = [V_1, \ldots, V_N; \omega_1, \ldots, \omega_N] \), and a force vector \( f = [F_1, \ldots, F_N, T_1, \ldots, T_N] \). This yields [155]:

\[
v = M \cdot f.
\]

In this equation, the generalised mobility matrix, \( M \), is introduced that consists of sets of 3x3 Cartesian mobility tensors. It is defined as [155]:

\[
M = \begin{bmatrix}
\mu_{tt} & \mu_{rt} \\
\mu_{tr} & \mu_{rr}
\end{bmatrix}
\]

This matrix is square, symmetrical and positive definite* [154,155], thus \( M = M^T \). Moreover, the generalised Einstein relation holds, in which, \( D \), is the diffusivity matrix:

\[
D = k_b T M.
\]

Analogous to eq.2.41, the diffusivity matrix is a 3-dimensional position dependent tensor. The elements of the generalised mobility matrix (eq.7.6) can be solved using the Rotne-Prager approximation\(^1\). The latter yields a solution for the different mobility tensors that is accurate up to \( (a/r_{ij})^3 \) and the components of this matrix are given as [155]\(^1\):

\[
A \text{ positive definite matrix requires that the following inequalities hold: } \mu_{tt} > 0, \mu_{rr} > 0 \text{ and } \det M = \mu_{tt} \mu_{rr} - (\mu_{rt})^2 > 0 \text{ [154].}
\]

\(^1\)This approximation includes the Rotne-Prager tensor given by eq.4.10.

\(^1\)An alternative method for calculating the elements can be found in [210,211].
\[
\mu_{ij}^{\text{tt}} = \begin{cases} 
\hat{1} \mu_0 & 
i \neq j \\
3/2 \mu_0 \frac{a}{r_{ij}^3} \left( \hat{1} + \hat{r}_{ij} \hat{r}_{ij} \right) + \frac{1}{2} \mu_0 \left( \frac{a}{r_{ij}} \right)^3 \left( \hat{1} - 3 \hat{r}_{ij} \hat{r}_{ij} \right) & 
i \neq j 
\end{cases}
\]

\[
\mu_{ij}^{\text{tr}} = \begin{cases} 
\hat{1} \mu_0 & 
i \neq j \\
-1/2 \mu_0 \left( \frac{a}{r_{ij}} \right)^3 \left( \hat{1} - 3 \hat{r}_{ij} \hat{r}_{ij} \right) & 
i \neq j 
\end{cases}
\]

\[
\mu_{ij}^{\text{rt}} = \mu_{ij}^{\text{tr}} = \begin{cases} 
0 & 
i \neq j \\
\mu_0 a \left( \frac{a}{r_{ij}} \right)^2 \hat{r}_{ij} \times & 
i \neq j 
\end{cases}
\] (7.8)

Adding thermal noise to eq.7.5, yields the following Langevin equation for the system [146,212](compare with eq.2.42):

\[ v = \frac{dX}{dt} = M \cdot f + k_b T (\nabla \cdot M) + g(t). \] (7.9)

In this Equation, \( X \), refers to the position of the organelle. As the elements of the mobility matrix, \( M \), are position dependent, thermal fluctuations can result in additional drift terms. This is compensated for by including the drift term \( k_b T (\nabla \cdot M) \) [146,212]. The mean and variance of the thermal fluctuations acting upon the organelles are given by [145,146]:

\[ \langle g(t) \rangle = 0 \]
\[ \langle g(t) g(t') \rangle = 2 k_b T M \delta(t - t'). \] (7.10)

The thermal forces exhibit a correlated diffusion as the generalised mobility matrix depends upon the organelle positions in the system. The Ermak and McCammon algorithm [72], (see chapter 4), can be used to generate the correlated thermal fluctuations. Next, the Langevin equation is integrated from time \( t \) to \( t + \Delta t \) and discretized with respect to time to yield the following equation that can be solved using computer simulations [146]:

\[ \Delta X_t = (M \cdot f) \Delta t + k_b T (\nabla \cdot M) \Delta t + g(\Delta t). \] (7.11)

In the above equation \( g(\Delta t) \) has identical statistical properties to \( g(t) \) (see eq.7.10) [146]. The spurious drift term, \( k_b T (\nabla \cdot M) \), vanishes since at Rotne-Prager level only two-body interactions are taken into account i.e. \( (\nabla \cdot M) = 0 \) [155]. This simplifies the equation to:

\[ \Delta X_t = (M \cdot f) \Delta t + g(\Delta t). \] (7.12)
This Langevin equation can be used to calculate the trajectories of interacting organelles taking both translational and rotational hydrodynamic interactions into account.

The Model

The stochastic Langevin equation (eq.7.12) can subsequently be used to solve the model shown in Fig.7.1. In this system a hollow or solid bead is suspended in an otherwise quiescent fluid with a viscosity similar to cytosol (~1 Pas). The latter is important to maximise the hydrodynamic coupling between the organelles and between the organelles and the bead. The organelles and the bead are subject to thermal fluctuations but other external forces such as gravity can be neglected (see chapter 2). The molecular motors with cargoes walk along the cytoskeleton in unidirectional direction. On each organelle acts a net driving force, but it is assumed that the organelles do not rotate i.e. the external torque on each organelle is zero. Thus, the velocity of any organelle, $i$, in the Langevin equation (eq.7.12) depends on the force acting upon it, the hydrodynamic coupling via the forces acting upon all other organelles, $j$, plus momentum transfer from the torque on the bead. The bead has no net external force or torque acting upon it, its rotation is purely driven by the momentum transferred via the fluid. However, as mentioned above, when it rotates it will influence the velocities of the organelles.

Using computer simulations the following questions can be answered:

- Is this a plausible mechanism to make the bead rotate?
- What minimum motor density (required energy) is necessary to make the bead rotate?
- Is there a relation to be found between the organelle size, mass, and the motor density?

Experiments

The predictions from the computer simulations can subsequently be tested in an experimental set-up. For this purpose a bead of a convenient material for experiments can be etched with parallel tracks that span all the way around the sphere. Next, these tracks can be lined with cytoskeletal elements using one of the techniques described in literature for microfluidic devices [213–216]. The motor-cargo complexes can be added to the system in the form of bead assays i.e. as micrometer scale beads coated with molecular motors [3]. Previous chapters showed that the hydrodynamic coupling is strongest
in viscous fluids such as cytosol. One possible fluid with a viscosity of 1 Pas\(^*\) is Xanthan [45]. It has been shown that using this water-soluble bacterial exopolysaccharide increases the cargo velocity in gliding assays [45]. The experiments could confirm the validity of the hypothesis and give a possible explanation for cytoplasm rotation.

**Applications For Microfluidic Devices**

Recently, many papers have been dedicated to research of microfluidic devices (see reviews [213–216]), which are nanoscale systems that are inspired by cell biology. In these synthetic structures molecular motors are used as a power source to create a mechanical force for either autonomous transport of cargoes and/or for actuation of other processes\(^\dagger\). Possible applications are sorting, separation, purification and assembly of materials [216]. In most systems the molecular motors are used in the configuration of a gliding or bead assay. It is possible to guide the motor-cargo complexes directly using the surface of the chip by mechanical confinement in designed channels, selective pat-

\(^*\)At a concentration of 2 mg/ml, \(M_w = 1 \times 10^6 - 7 \times 10^6\).

\(^\dagger\)Similarly, artificial cilia are studied to create pumping and/or mixing in microfluidic devices [217].
terning of the surface with motors or filaments or by a combination of both [214]. Additionally it is possible to steer via external stimuli [213,216] such as electrical fields [218], magnetic fields [219] and flow fields [220]. The latter is important for this thesis as the flow fields considered were driven by an external force or a gradient. We propose the via hydrodynamic interactions it is possible to generate a flow field locally by using hydrodynamic interactions between the cargoes. This novel idea might well give rise to a whole new range of applications.

The results presented in this thesis could directly be applied to work presented by Bull et al. [221]. The authors performed simulations of a microfluidic pump. The pump consisted of an annular channel of which the surface was coated with molecular motors. The molecular motors were aligned in unidirectional fashion. Through the channel a single bead was actively transported (gliding assay). The simulations showed that the microfluidic pump produces a flow in the range of $10^{-18} - 10^{-12}$ l/s. The fluid used in the system was water. This result could be improved by increasing the number of beads in the system although this effect would be larger in a more viscous environment.