To go with the flow: Molecular motors are a drag
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Chapter 4

Cell Transport Enhanced By Hydrodynamic Interactions

In the following 3 chapters, the effect of the solvent on the transport of bound and suspended molecular motors with cargoes will be analysed. The simulation models described in this chapter, and those in chapter 6, were developed in close collaboration with Ignacio Pagonabarraga (Departament de Física Fonamental, Universitat de Barcelona, Spain). The experimental work was performed by Agnieszka Esseling-Ozdoba in the group of Anne-Mie Emons (Wageningen University, Laboratory of Plant Cell Biology, the Netherlands). In this chapter results are presented that were obtained via simulation studies using a lattice model. Most of these results have been published [149]. Experimental work done in the group of Prof. Emons is discussed in chapter 5 and in [150]. In chapter 6, results obtained using a subsequently developed continuum model, are presented.

This chapter is an extended version of the original publication: D. Houtman et al., "Hydrodynamic flow caused by active transport along cytoskeletal elements" EPL, 2007, 78 [149] and has been reproduced with kind permission from EPL (Europhysics Letters) - IOPscience. In addition, it features a section where the effect of the choice of the mobility tensor is discussed. Moreover, the simulations are repeated for a system with two filaments of opposite polarities. Finally, the motor-cargo transport is studied for the situation where there are gaps in the cytoskeleton.

Introduction

In chapter 2 it was shown by means of the Stokes number (eq.2.27) that small suspended organelles and other suspended cytoplasmic objects are sensitive to momentum transport via each other’s flow field. Thus, the motion of these organelles will be affected through hydrodynamic interactions. However, this effect alone will not necessarily give rise to enhanced transport inside the cell. In most situations it has a negligible effect as
the cell’s cytosol is a crowded environment consisting of a multitude of cytoskeletal elements with small mesh size [151]. Moreover, organelles are dragged towards both the plus and minus ends of the individual bio-filaments (see chapter 1) mostly cancelling out the hydrodynamic effects. Therefore, for the momentum transfer via the fluid to have a positive effect on the transport, a number of conditions need to be met. Firstly, many cargoes have to be actively transported simultaneously along the same or along different bio-filaments. This is a key requirement as the hydrodynamic drag is additive. Secondly, the bulk of this transport has to take place in unidirectional fashion as motion in opposite direction will counteract the effect. Thirdly, to maximise the effect, the cytoskeletal elements have to be oriented more or less parallel to each other. Finally, the fluid friction force acting upon an organelle is larger in a viscous fluid, such as cytosol, than in water. Thus, the effect of the additional positive force on the organelle via hydrodynamic interactions is desirable in a viscous fluid. See Fig.1.3 in chapter 1, where it is shown that adding molecular motors (i.e. a positive force) to an organelle has only a small effect on its velocity in water. However, it yields a substantial velocity increase in the cell. Different systems exist that abide to the above. We will limit ourselves to two situations, cytoplasmic streaming in plant cells [30] and axoplasmic streaming in neurons [152]. In cytoplasmic streaming the bound and suspended organelles follow a given trajectory through the entire cell (e.g. see Fig.4.1 for cytoplasmic streaming in *Tradescantia virginiana*). In neurons organelles can be transported from one extreme of the neuron to another*. In both systems, the transport takes place on very long length scales with respect to the size of the cargoes (≈500 nm\(^1\)). It is this transport that will be analysed using computer simulations. For the remainder of the chapter, motor-cargo complexes will be referred to as motors, unless specified otherwise.

### Expanding The Exclusion Process With a Solution

As discussed in chapter 3, Lipowsky et al. [129, 130] were the first to present an exclusion process that captures the dynamics of molecular motors (with or without cargoes) along a bio-filament as well as the diffusion of the motors in solution. Both the driven motion along the bio-filament and the diffusion in solution are mapped on a lattice. Furthermore, the motor positions are confined to the lattice nodes with spacing, \(l\). The mesh size is proportional to the motor diameter. In addition, excluded volume is taken into account by treating the motors as hard spheres. Thus, allowing for only one motor on a lattice site at a given moment in time.

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\(^*\)The length of the *recurring laryngeal nerve* of a Giraffe can be up to 5 meter and the nerve cells in a Blue Whale are estimated to be 30 m long [153].

\(^1\)See table 1.1.
During one simulation time step, a motor is allowed to move to an adjacent lattice node in $x$, $y$ and $z$-direction or dwell in its position. This yields a maximum displacement, $x$, per time step of $x = s \sqrt{t}$ where, $s$, is the number of dimensions in the system. The bio-filament(s) are modelled as a linear array of lattice nodes with properties different from those in solution (see Fig.3.5) accounting for the dynamics of bound and suspended motors. We define the motor concentration in the solution, $\phi_s$, and on the bio-filament, $\phi_{\mu}$, as the fraction of lattice nodes occupied by motors. This model will be expanded and adapted in the next sections to analyse the importance of hydrodynamic interactions in intra-cellular transport. A more detailed description of the dynamics of the bound motors and the detaching from and attaching to the bio-filament can be found in appendix A.

**Moving Along The Lattice**

The dynamics of the ASEP-type bio-filaments and the solution are adapted to model the influence of the fluid on the motor transport. Rather than performing costly simulations where the motors, bio-filaments and the very large number of cytosol molecules are modelled individually, an approximate method is used [69]. This method involves omitting the cytosol molecules and introducing the influence of the solution on the solutes as a combination of random forces and frictional terms. For this purpose the equation of motion for suspended objects, the Langevin equation, will be mapped on the lattice. This equation depends upon the physical parameters of the motors and takes the friction of the cytosol into account. More importantly, via this equation the moment-
tum transfer giving rise to hydrodynamic interactions between the different motors can be studied (see chapter 2). The Langevin equation that describes the motion of an organelle $i$ in a solution of organelles $j$ is given by:

$$\frac{dr_i}{dt} = V_i = \mu_{ii} \cdot F_i + \sum_{j,j\neq i} \mu_{ij} \cdot F_j + g_i(t) = V_{i,0} + \dot{V}_{i,d} + V_{i,r}. \quad (4.1)$$

In this equation, $V_{i,0} = \mu_{ii} \cdot F_i = (V_{0,0}, 0, 0)$, is the ballistic self-velocity of the organelle that depends on the organelle’s mobility and the molecular motor force acting upon it. The hydrodynamic interactions of organelles $j$ on organelle $i$ are given by: $\dot{V}_{i,d} = \sum_{j,j\neq i} \mu_{ij} \cdot F_j$. This additive effect depends upon the force on each organelle as well as the position dependent inter-organelle mobilities $\mu_{ij}$. Note that the forces depend upon the motor’s position in the system. The force generated by bound molecular motors through hydrolysing ATP is non-zero $F_i = (F_{0,0}, 0, 0)$. However, motors suspended in solution are not attached to a bio-filament and therefore cannot propel themselves, hence the driving force is zero for these organelles $F_i = (0, 0, 0)$. Finally, the random velocities from thermal fluctuations are accounted for via, $V_{i,r}(t)$, which have the following properties [63]:

$$\langle V_{i,r}(t) \rangle = 0$$

$$\langle V_{i,r}(t) V_{j,r}(t') \rangle = 2D_{ij}\delta(t-t'). \quad (4.2)$$

As mentioned in chapter 2, these random velocities are not statistically independent as they rely on the motor positions, via $D_{ij}$, in the system. In order to calculate the time evolution of the system, the tensor $D_{ij}$ needs to be calculated at the beginning of each time step. Where, $D_{ij}$, a set of $3 \times 3$ matrices for each pair of motors, represents the diffusive and frictional effects in a dilute system [69]. The generation of correlated random numbers is described in the section on the Ermak and McCammon Algorithm below.

### Ermak and McCammon Algorithm

Ermak and McCammon [72] presented an algorithm that uses normal random deviates*, $\zeta$, to generate the correlated random numbers needed for simulating the Langevin equation. The algorithm consists of four steps: Firstly, at the beginning of a simulation time step, a matrix is generated consisting of elements $C_{ij} = 2D_{ij}$. Here, the indices, $ij$, refer either to one motor (for $i = j$) or to a pair of motors ($i \neq j$). Secondly, since $C$ is a square, symmetrical and positive definite matrix [154, 155] a Cholesky Decomposition ($C = LL^T$) [155] can be used where, $L$, is a lower triangular matrix and, $L^T$, its

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*{$\zeta_i; \langle \zeta \rangle = 0; \langle \zeta_i \zeta_j \rangle = 2\delta_{ij}\Delta t \ [72]$.
transpose. The elements of the matrix, $L_{ij}$, are constructed using the following recursive algorithm:

$$
L_{ii} = \left[ C_{ii} - \sum_{k=1}^{i-1} L_{ik}^2 \right]^{0.5}
$$

$$
L_{ij} = \frac{C_{ij} - \sum_{k=1}^{j-1} L_{ik}L_{jk}}{L_{jj}}
$$

(4.3)

Thirdly, a set of uncorrelated random numbers, $\zeta_j$, is generated for each motor in each dimension. Finally, the values $L_{ij}$ are used as weighing factors to yield the correlated random velocities, $g_i(t)$, using:

$$
g_i(t) = V_{i,r} = \sum_{j=1}^{i} L_{ij} \zeta_j.
$$

(4.4)

In other words this means that motor 1 diffuses freely (not statistically correlated) through the solution. The diffusion of motor 2 however cannot be chosen at random as motor 1 has generated a flow field in solution via momentum transfer. Therefore, its random velocity needs to be correlated to correct for the hydrodynamic interactions via the flow field of motor 1. Subsequently, the diffusive motion of the third motor needs to be correlated to correct for the flow fields set up by the first two motors, etc.

**Allowing For Larger Displacements**

The Lipowsky model is further extended by allowing for moves of magnitudes $\pm 2l$ additionally to the original $\pm l$ and dwell steps in $x$, $y$, and $z$-directions. This increases the maximum displacement per time step to $x = 2\sqrt{5}l$. The calculated velocities are translated into displacements per simulation time step using the following recipe: for small displacements, $\leq 0.25l$, the motors are forced to dwell in their current position; intermediate displacements, $0.25l < |\Delta x| < 1.5l$, causes the motor to displace one lattice node. Displacements larger then $1.5l$ are restricted to a move of two lattice nodes. Note that excluded volume always has to be accounted for and thus moves of $\pm 2l$ are only permitted if the whole path is free. If the second node is occupied the motor will only displace one node. The displacement recipe is shown in Fig. 4.2 below. Note that this description gives rise to spurious lattice effects. The latter is discussed in appendix B.
Figure 4.2: Mapping of calculated motor displacements on the lattice. Small displacements, \(-0.25l < \Delta x < 0.25l\) will cause the motor to dwell in its current position. Intermediate displacements, \(0.25l \leq |\Delta x| \leq 1.5l\), will be mapped on the adjacent lattice node. Large steps, \(|\Delta x| \geq 1.5l\) will be mapped on the second neighbour node.

**Langmuir-type Kinetics**

Next, the motor processivity is accounted for by allowing the motors to detach from the bio-filament with a given probability \(\gamma_d\). Motors in solution close to the filament, in turn, can attach to the bio-filament with probability \(\gamma_a\). Motor interchange between the bio-filament and the solution determines the ratio between the solution and filament volume fractions, \(\phi_s\) and \(\phi_\mu\) respectively. Assuming uniform concentrations along the microtubule and in the solution, the mass flux balance that predicts the steady state relationship between solution concentration and bio-filament occupation is given by:

\[
\begin{align*}
\text{Particle flux out} &= \text{Particle flux in} \\
\phi_\mu (1 - \phi_s) \gamma_d &= p_1 \phi_s (1 - \phi_\mu) \gamma_a + p_2 \phi_s (1 - \phi_s) (1 - \phi_\mu) \gamma_a \\
\phi_\mu &= \frac{1}{1 + \frac{\gamma_d (1 - \phi_s)}{\gamma_a \phi_s [p_1 + p_2 (1 - \phi_s)]}}.
\end{align*}
\]  

(4.5)

Here, \(p_1\), is the probability the motors diffuse towards the bio-filament from a lattice node adjacent to the bio-filament. Moreover, \(p_2\), is the probability to attach from the second neighbouring row of nodes. These probabilities are a direct consequence of the magnitude of the diffusion coefficient. For the simulations in the result sections, we have chosen values of \(\gamma_d\) to ensure the required filament and solution concentrations. We have found that using \(\gamma_a = \sqrt{2D_0}\), \(p_1=0.4\) and \(p_2=0.2\) for desired values \(\phi_s\) and \(\phi_\mu\) yields the following estimate for \(\gamma_d\):

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\[ \gamma_d = \sqrt{2D_0 \phi_s \left( \frac{0.4}{1 - \phi_s} + 0.2 \right) \left( \frac{1}{\phi_t} - 1 \right)} . \] (4.6)

Conversion Of Units

We will use the experimental data from the reference system presented in chapter 2 (table 2.2) for the motor-organelle complexes in the simulations. However, these values are very small (e.g. \( F_0 = 4.15 \times 10^{-12} \) N) and could cause inaccurate results, via round-up errors, due to the computer’s finite numerical accuracy. Therefore, similar to the method of reduced units [69,156], the relevant simulation parameters need to be of order one. To translate the experimental data to the simulations it is necessary to fix three simulation parameters from which all other values can be calculated. Using the experimental data for the radius, force and velocity and by fixing these values in the simulation model we obtain the following conversion factors for length \( L \), time \( T \) and mass \( M \). The conversion between lattice units and the experimental data is given in table 4.1.

<table>
<thead>
<tr>
<th>Property</th>
<th>Unit</th>
<th>Experiments</th>
<th>Model</th>
<th>Factor</th>
<th>Calculated</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a )</td>
<td>m</td>
<td>2.5 \times 10^{-7}</td>
<td>0.1</td>
<td>L</td>
<td>2.5 \times 10^{-7}</td>
</tr>
<tr>
<td>( V_0 )</td>
<td>m/s</td>
<td>8.0 \times 10^{-7}</td>
<td>0.4</td>
<td>L/T</td>
<td>8.0 \times 10^{-7}</td>
</tr>
<tr>
<td>( F_0 )</td>
<td>N</td>
<td>4.15 \times 10^{-12}</td>
<td>1.061</td>
<td>ML/T^2</td>
<td>4.15 \times 10^{-12}</td>
</tr>
<tr>
<td>( \mu_0 )</td>
<td>m/Ns</td>
<td>1.93 \times 10^5</td>
<td>0.3769</td>
<td>T/M</td>
<td>1.93 \times 10^5</td>
</tr>
<tr>
<td>( \eta )</td>
<td>Pas</td>
<td>1.1</td>
<td>1.407</td>
<td>M/LT</td>
<td>1.1</td>
</tr>
<tr>
<td>( \rho )</td>
<td>kg/m^3</td>
<td>1200</td>
<td>7.67 \times 10^{-9}</td>
<td>M/L^3</td>
<td>1200</td>
</tr>
<tr>
<td>( D_0 )</td>
<td>m^2/s</td>
<td>8.26 \times 10^{-16}</td>
<td>0.3769</td>
<td>L^2/T</td>
<td>1.89 \times 10^{-12}</td>
</tr>
<tr>
<td>( k_0T )</td>
<td>J</td>
<td>4.28 \times 10^{-21}</td>
<td>1</td>
<td>ML^2/T^2</td>
<td>9.78 \times 10^{-18}</td>
</tr>
<tr>
<td>( m )</td>
<td>kg</td>
<td>7.85 \times 10^{-17}</td>
<td>3.21 \times 10^{-11}</td>
<td>M</td>
<td>7.85 \times 10^{-17}</td>
</tr>
<tr>
<td>( \tau )</td>
<td>s</td>
<td>1.52 \times 10^{-11}</td>
<td>1.21 \times 10^{-11}</td>
<td>T</td>
<td>1.51 \times 10^{-11}</td>
</tr>
</tbody>
</table>

Table 4.1: Conversion table between lattice units and experimental data (See table 2.2 in chapter 2). The conversion factors are: \( L = 2.5 \times 10^{-6} \), \( T = 1.25 \), \( M = 2.4446 \times 10^{-6} \) and were determined by fixing the radius \( (a) \), velocity \( (V_0) \) and force \( (F_0) \) in the simulation model*. The column ‘calculated’ is obtained by multiplication of the columns ‘model’ and ‘factor’ and it reflects how well the simulation parameters represent the experimental data.

The table shows that the found conversion factors can be used to retrieve the experimental values from the simulation settings. However, the moves of the motor-organelle complexes in the simulations are mapped on a lattice using the method described in

*For \( a = 0.2 \) the conversion factors become: \( L = 1.25 \times 10^{-6} \), \( T = 0.625 \), \( M = 1.2223 \times 10^{-6} \).
Fig. 4.2. To recover the bound motor velocities in the system, the motor diffusion has to be large enough to span the range of moves described in the mapping algorithm. To ensure this the thermal energy \((k_b T)\) had to be increased in the system, thus effectively performing the simulations at a higher temperature. The consequences are a larger diffusion coefficient as can be seen in the column labelled calculated of table 4.1. In this thesis we are interested in studying the quantitative effect of hydrodynamic interactions on intra-cellular motor transport. As these interactions depend upon the motor’s position, mobility and forces, the larger diffusion coefficient will not modify this behaviour.

**Flow Sheet Of Simulation**

The simulations are performed according to the flow sheet shown in Fig.4.3. The flow sheet consists of a number of consecutive steps where one step needs to be completed before going to the next. Computer experiments are not that different from real experiments. As Frenkel and Smit [156] point out in their book the basic steps are the same. Firstly, a sample needs to be prepared. This happens in the initialisation step. Here, motors are distributed randomly along the bio-filament and in solution until the desired occupation fractions are reached. Secondly, the system is allowed to reach a steady-state* situation during a predetermined number of simulation steps. At the start of each simulation time step, the inter-organelle forces, mobilities, and velocities are calculated after which the motors are displaced along the lattice. The size of the moves is determined via calculation of the different motor velocity components (eq.4.1). The resulting velocity is subsequently mapped on the lattice using the procedure shown in Fig.4.2. Next, the motors are moved one-by-one to their destinations followed by either rejection or acceptance of the new position by taking excluded volume into account. In the case of organelle collisions, the motors will not be moved. The driving force on these motors is subsequently set to zero to ensure proper calculation of the flow field in the next time step. As the drag velocity on a motor is calculated via, \(V_{i,t} = \sum_{j,j\neq i} \mu_{ij} \cdot F_j\), at the beginning of each time step this is necessary. After the steady-state is reached, the velocities, occupation fractions and fluxes will be sampled until the end of the simulations is reached.

**Hydrodynamic Interactions in Cytoplasmic Streaming**

To quantify the momentum transfer between motors via the fluid, a liquid is embedded between two slabs. These slabs are covered by bio-filaments that have a given polarity. Both the solution and the cytoskeletal elements are mapped on a 3d lattice. We now

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*In steady-state the bio-filament and solution concentrations are, on average, constant in time.*
Figure 4.3: Flow sheet of model. At the initialisation motors are placed in the system. Next, the system is brought in steady-state situation after which velocities, concentrations and fluxes are sampled until the end of the simulation is reached.

take a 2d cut from our system in the direction perpendicular to the slabs. The resulting 2d system is shown in Fig.4.4.

As a test case we studied cytoplasmic streaming in plant cells (see Fig.4.1). In these cells, cytoplasmic strands are found. These are long, channel-like, structures with a length ranging up to tens of micrometers. In the strands bio-filaments are found that span its entire length or a part of it. The model captures a section of a cytoplasmic
strand in which many motors are present along the bio-filament and in solution. To study the dynamics of a large strand periodic boundary conditions (PBC) [69,156] are used in axial direction i.e. in the direction of transport. Using PBC is a computational trick to model an infinitely large system with a minimum of computational expense and was originally developed to minimise boundary effects when modelling bulk-phases. Consequently, the model in Fig.4.4 is treated as a primitive cell in an infinite periodic lattice of identical cells. In each cell the number density of motor-cargo complexes is kept constant. If a particle leaves the system, its periodic image will enter. It is unclear what the effect of PBC is on the long-range hydrodynamic interactions as these interactions fall off with \(1/r\), which is typically longer than half the box size [69]. We will limit the hydrodynamic interactions to the nearest images.

\[ V = V_{\text{bias}} + V_{\text{drag}} + V_{\text{diffusion}} \]

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*In the section on different hydrodynamic interaction tensors we correct for this effect by presenting data for a truncated and shifted tensor.*
Effect Of Hydrodynamic Interactions On Transport

We have considered the simplest geometry in which motors move in the two dimensional plane confined between two bio-filaments, although the hydrodynamic interactions correspond to those of a 3d fluid (we presume that the structure of the motors in the transverse direction can be neglected). Such a case can be regarded as a suspension of motors between substrates covered by a parallel set of bio-filaments. Such an idealised example contains the basic dynamic couplings and facilitates the analysis. In order to analyse the interplay between activity, excluded volume and hydrodynamic forces, we fix the solution concentration to a small value, $\phi_s = 0.05$ and analyse the collective behaviour of the suspension+bio-filament complex at different degrees of bio-filament’s occupation. In units of the lattice spacing, $l$, and simulation time step, $\Delta t$, for motors of unit mass we vary the force exerted by the filament between 1/2 and 2 to control the single motor velocity, which should take values of the order (but smaller than) a lattice spacing. Simulations are run for systems size $L$, containing around 1000 motors and for a few thousand time steps after thermalisation. Within the Oseen description (eq.2.25) it is known that values of $A$ close to the motor radius may lead to numerical instabilities in configurations where motors are close to each other. To avoid such problems, and making use of the linearity of the system, we keep $A/l$ smaller than $1/5$. For these parameters the motor Péclet number (eq.2.34) is of order one. Nevertheless, the results we will discuss should not be severely affected by this fact, since we focus on mean collective motor velocities.

In Fig.4.5A we show the velocity at which motors move along a filament divided by the measured single motor velocity, $\langle V_0 \rangle$, as a function of the filament occupation, $\phi_\mu$. In the absence of hydrodynamic interactions (HI) the velocity decreases linearly with increasing occupation fraction due to excluded volume interactions. Note that, due to spurious lattice effects, the measured single motor velocity, $\langle V_0 \rangle$, deviates from the nominal single motor velocity that was given by: $V_0 = \mu_0 F_0$. For example, for $F_0 = 1.061$ and $\mu_0 = 0.3769$ the nominal velocity is $V_0 = 0.4$ while the measured value is $\langle V_0 \rangle = 0.43$. See appendix B for an explanation of this effect. Therefore, all normalisations in this chapter are performed using the measured single motor velocities.

When HI are considered, the drag first increases the overall bound motor velocity. At higher concentrations a second regime is achieved, where hindering due to excluded volume effects causes this velocity to decrease. Nevertheless, for all occupations the motor’s velocity is larger than the corresponding one in the absence of HI. A second,

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Kirby [59] mentions in his book that the isolated sphere relation is accurate as long as particle-particle separations exceed $x = 10A$. For a hydrodynamic radius $A = 0.1l$, the minimum particle separation $x_{\text{min}} = l - 2A = 0.8l = 8A$ which suggests that the simulation results are less accurate at high $\phi_\mu$.

For organelles of typical size $l \sim 1 \mu m$ that move along a bio-filament with a velocity $u \sim 1 \mu m/s$ and assuming a diffusion coefficient of $10^{-12} m^2/s$ we find a Péclet number of order $Pe \sim 1$. 

---

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Figure 4.5: A) The normalised velocity for different degrees of bio-filament occupation, $\phi_\mu$. B) Effective force (in pN) acting on motors for different filament occupations. The open triangles represent the hydrodynamic force acting on the motors. The open circles refer to the bio-filament, the open squares to the solution, the filled squares show data without hydrodynamic interactions. The simulation settings were: $F_0=1.061$, $\mu_0=0.3769$, $\langle V_0 \rangle=0.43$, $N_{\text{part}} \approx 1000$, $T_{\text{max}}=7000$ (HI) and 10000 (no HI).

Qualitative, effect of the cooperativity induced by the solvent is displayed in the same figure where we show the average velocity of motors in solution. In the absence of HI motors can only display a net displacement along the bio-filament. However, in the case with HI, there clearly exists a well defined solution velocity which increases with $\phi_\mu$ until it reaches a maximum after which it decreases. Note that with increasing bio-filament concentration the average distance between suspended and bound motors decreases. This results in a larger hydrodynamic coupling i.e. the velocity difference between bound and suspended motors becomes smaller. The position of the maximum depends on the specific parameters considered. There seems to be an optimum bio-filament occupation which is different for both the bio-filament ($\phi_\mu \approx 0.2$) and the solution ($\phi_\mu \approx 0.5$). The position of these maxima seems to be insensitive for all simulation parameters explored (data not shown).

Using table 4.1 the simulation data can be converted into real units. The resulting forces are shown in Fig.4.5B. The largest effective force acting on a bound motor was measured at $\phi_\mu=0.2$ and equals 5.2 pN, 25% larger than the single motor force needed to move the model organelle through the fluid. This force lies within the stall force of the kinesin motor (5.4±1.0 pN [15]) and shows that the added hydrodynamic force compensates for the drag force acting upon the motors. Moreover, experiments have shown that a positive force exerted upon a bound molecular motor increase its velocity (Kinesin [11]; Myosin-V [55]). The hydrodynamic coupling gives rise to such a force. Interestingly, the maximum hydrodynamic force on bound motors is found to be 1.9 pN at $\phi_\mu=0.4$. For suspended motors this value can be as large as 2.7 pN (at $\phi_\mu=0.5$).
At large bio-filament occupations, the average particle separations are small and the Oseen approximation become less accurate. This in combination with using periodic boundary conditions and spurious lattice effects yields unrealistically large forces.

In Fig. 4.6A, we show the increase of the motors’ velocity with respect to their biased velocity. Due to the linearity of the hydrodynamic coupling, in the regime where excluded volume interactions are negligible, the profiles are linear in \( \phi \). Hence, different systems collapse in a single curve as a function of filament occupation. We can then use eq.4.1 to estimate the initial increase in motors’ velocity. By inserting eq.2.25 and by using, \( \langle V \rangle = \mu \cdot F \), the equation can be rewritten as:

\[
\frac{(\langle V \rangle - \langle V_0 \rangle)}{\langle V_0 \rangle} = \frac{3}{4} \sum \frac{I + \hat{r}_{ij}}{r_{ij}}, \quad i \neq j.
\]  

Next, the right hand side can be approximated assuming a continuous and uniform distribution of motors

\[
\frac{(\langle V \rangle - \langle V_0 \rangle)}{\langle V_0 \rangle} = \frac{3}{2} \frac{I \phi \mu}{2a} \ln \frac{L}{r_{ij}},
\]

which agrees quantitatively with the simulation results. For total filament occupation, \( \phi = 1 \), motors cannot move along the filament, \( \langle V \rangle = 0 \).

*See the section ‘Different Hydrodynamic Interaction Tensors’ below.
In Fig.4.6B we display the mean velocity of unbound motors; these two plots show how the hydrodynamic coupling can be tuned by controlling the motors’ size and biased velocity. When using a more realistic choice for the mobility tensor for motors at small separations (Brenner [157], Rotne-Prager [158,159]) this data does not change (see the section on different tensors), indicating that the mechanism described is generic and comes from the algebraic correlations induced by the embedding solvent.

Fig.4.7A shows the concentration of unbound motors across the width, \( D \), of the system. It shows that the interactions between the attached and suspended motors induce a uniform distribution of suspended motors, independently of bio-filament occupation. The hydrodynamic interactions have no effect on the concentration profile between the bio-filaments as the increased concentration near the bio-filament is caused by the Langmuir-type dynamics alone (compare with the black triangles). Also the velocity profile, as displayed in Fig.4.7B, shows that the velocity in solution is modified only in the bio-filaments’ neighbourhood, which is more pronounced at higher occupation fractions.

**Figure 4.7:** A) Concentration profiles for unbound motors. \( D \) is the distance between bio-filaments, and \( X \) the distance to the lower bio-filament. Error bars are shown for \( \phi_s=0.2 \). Closed triangles are for \( \phi_s=0.4 \) in the absence of hydrodynamic interactions. B) Normalised velocity over the distance, \( D \), between the bio-filaments for a distance, \( X \), from the lower bio-filament for different bio-filament occupation, \( \phi_s \). Error bars are shown for \( \phi_s=0.4 \). For both figures: Open squares \( \phi_s=0.2 \); open triangles \( \phi_s=0.4 \); open circles \( \phi_s=0.6 \). Simulation parameters: \( F_0=1.061, \mu_0=0.3769, N_{\text{part}}=1000, T_{\text{max}}=7000, V_0=0.4 \) and \( \langle V_0 \rangle =0.43 \).

**Increased Motor Concentration In Solution**

The simulations are repeated for a higher motor concentration in solution \( (\phi_s=0.1) \) for two different values for the biased velocity \( (\langle V_0 \rangle =0.43 \) and \( \langle V_0 \rangle =0.63 \)). The normalised velocity for bound motors and suspended motors are presented in Fig.4.8A. The data
confirms the robustness of the earlier results both in shape as well as the position of the maxima. However, the velocities are slightly smaller. The latter is a direct result from the increased motor concentration in solution. The larger number of motors increases the probability for detaching motors to collide with motors in solution and thus effectively increasing the motors processivity. This effect is compensated for by choosing the proper detachment probability, $\gamma_d$, in the simulations (via eq.4.5) and therefore does not lead to large changes in bio-filament concentration.

Figure 4.8: A) The normalised velocity for different degrees of bio-filament occupation, $\phi_\mu$. Closed triangles: $\phi_b=0.05, V_0=0.4$ and $\langle V_0 \rangle=0.43$. The open symbols represent data for $\phi_b=0.1$ (open squares $V_0=0.4, \langle V_0 \rangle=0.43, F_0=1.061$; open triangles $V_0=0.6, \langle V_0 \rangle=0.63, F_0=1.592$). B) Concentration profiles for unbound motors. $D$ is the distance between bio-filaments, and $X$ the distance to the lower bio-filament for $\phi_b=0.1, V_0=0.4$ and $\langle V_0 \rangle=0.43$. C) Normalised velocity over the distance $D$ for $V_0=0.4$ and $\langle V_0 \rangle=0.43$. D) Normalised velocity over the distance $D$ for $V_0=0.6$ and $\langle V_0 \rangle=0.63$. For all figures: $\mu_0=0.3769$; $N_{\text{part}} \approx 1000 (\phi_b=0.05)$ and $\approx 1200 (\phi_b=0.1); T_{\text{max}}=7000$

The motor concentration profile between the bio-filaments is shown in Fig.4.8B (see Fig.4.7A for comparison with $\phi_b=0.05$). The profile shows that the profile is shifted to the new value of $\phi_b=0.1$ and $\langle V_0 \rangle=0.43$, retaining its overall uniform shape with increased values near the bio-filament due to the interaction of bound and suspended motors.
The solution concentration is not sensitive to the filament occupation. Moreover, the data is robust to the choice of $V_0$ (data not shown).

The velocity profile for $(V_0)=0.43$ and 0.63 in Fig.4.8C and D respectively. The solution velocities are presented for different bio-filament occupation fractions. The shape of the profile is not modified with increasing suspended motor concentration (compare with Fig.4.7B). Consistently with Fig. 4.8A, the velocity in solution lies below the velocity measured for $s_0=0.05$. Here the error bars are smaller as the statistics are improved with the larger number of suspended motors. These simulations again confirm that hydrodynamic interactions give rise to a non-negligible flow in solution.

Note that the simulations for both values of $(V_0)$ are performed in identical systems for the same number of time steps. However, the error bars for $(V_0)=0.63$ are smaller. This is understood from the calculation of the standard deviation, $\sigma_{(V)/(V_0)}$, given by [160]:

$$\sigma_{(V)/(V_0)} = \left( \frac{\langle V \rangle}{\langle V_0 \rangle} \right)^2 + \left( \frac{\sigma_{(V_0)}}{\langle V_0 \rangle} \right)^2.$$ (4.9)

In the above equation, $\sigma_{(V)}$ is the measured standard deviation for the suspended motors which is $\sim0.1$ for both $\langle V_0 \rangle$ and $\sigma_{(V_0)}$ is the standard deviation for $\langle V_0 \rangle$. The latter is found to be 0.002 (not shown). Insertion of a larger value for $\sigma_{(V_0)}$ in eq.4.9 thus improves the statistics.

**Different Hydrodynamic Interaction Tensors**

In the above sections hydrodynamic interactions were introduced using the Oseen tensor (see eq.2.25), a hydrodynamic interaction tensor that gives a possible solution for the flow field around spherical objects. This tensor has its limitations. Studying the effect of this choice is the topic of this section. Firstly, there is a short discussion on the different tensors, followed by a comparison of the simulation results. Note that for all hydrodynamic interaction tensors holds that $\mu_{ii} = \mu_{0}\hat{I}$, thus only the inter-organelle components $\mu_{ij}$ will be discussed.

$$\mu_{ij} = \frac{3}{4} \mu_{0} \frac{a}{r_{ij}} [\hat{I} + \hat{r}_{ij} \otimes \hat{r}_{ij}]. \quad i \neq j$$ (2.25)

As explained in chapter 2, the Oseen tensor only takes the long-range interactions between suspended objects into account and ignores the short-range interactions. As long as the organelle separation exceeds $x=10.4$, the values are accurate [59] since long-range-interactions dominate at this length scale. At shorter separations a tensor taking
short-range interactions into account, such as the Rotne-Prager tensor (see eq. 4.10 [158, 159]) given below, would be more accurate.

\[
\mu_{ij} = \frac{3}{4} \mu_0 \frac{a}{r_{ij}} \left( \hat{I} + \hat{r}_{ij} \otimes \hat{r}_{ij} \right) + \frac{1}{2} \mu_0 \left( \frac{a}{r_{ij}} \right)^3 \left( \hat{I} - 3 \hat{r}_{ij} \otimes \hat{r}_{ij} \right), \quad i \neq j. \tag{4.10}
\]

One known issue of the Oseen tensor is that it has a singularity at \( r_{ij} = 0 \) i.e. when motors overlap. This could result in unrealistically large velocities induced by one motor on the other. In simulations this can yield spurious effects on on velocity fluctuations [157]. To remove this singularity Brenner [157] introduced the following equation for the particle separation, \( \tilde{r}_{ij} \), which can be used in any hydrodynamic interaction tensor:

\[
\tilde{r}_{ij} = \sqrt{x_{ij}^2 + y_{ij}^2 + z_{ij}^2 + 1}. \tag{4.11}
\]

Finally, Allen and Tildesley [69], mention in their chapter on Brownian Dynamics that because of the long-range character of the hydrodynamic interaction tensors it is not clear if they can be used in combination with periodic boundary conditions. This includes solutions with and without Ewald summations. We will introduce a both truncated and shifted version of the Oseen tensor in which we ignore interactions beyond half the simulation box size, \( r_{box}/2 \). The new tensor, \( \mu_{ij}^{TS}(r_{ij}) \) is given by:

\[
\mu_{ij}^{TS}(r_{ij}) = \begin{cases} 
\mu_{ij}(r) - \mu_{ij}(r_{box}/2) & r_{ij} \leq r_{box}/2, \\
0 & r_{ij} > r_{box}/2.
\end{cases} \tag{4.12}
\]

Fig.4.9A, shows the normalised velocity data for both bound and suspended motors for different hydrodynamic interaction tensors. The data for the Oseen tensor, with or without Brenner extension, and the Rotne-Prager all collapses. This suggests that the hydrodynamic motor radius \( a \) was chosen small enough for the data presented in this chapter till now. Moreover, this justifies the choice for the computationally cheapest Oseen tensor as the data does not change by choosing a more advanced version of the tensor. The truncated and shifted potential data deviates from the other tensors as both the bound and suspended motors move at slower velocity. However, even for this tensor, hydrodynamic interactions give rise to a non-negligible flow of motors in solution, again showing the robustness of the phenomenon. The shape of the concentrations profile is independent of the hydrodynamic interactions (Fig.4.9B), thus purely an effect of the Langmuir-type interactions. Fig.4.9C, confirms that the choice of the tensor does not affect the shape of the velocity profile between the bio-filaments. In line with Fig.4.9A, the velocity of suspended motors of the truncated and shifted tensor lies below the other tensors, but still shows a non-negligible effect increase in velocity. Fig.4.9D shows the effective forces acting on bound and suspended motors. Interestingly, using the
Figure 4.9: A) The normalised velocity for different degrees of bio-filament occupation, $\phi_\mu$. Upper series (starting at value one) refers to bound motor velocities, lower series (starting at value zero) to average velocity of suspended motors. B) Concentration profiles for unbound motors. $D$ is the bio-filament separation, and $X$ the distance to the lower bio-filament ($\phi_\mu=0.4$). C) Normalised velocity over the distance $D$ ($\phi_\mu=0.4$). For figures A-C: Filled squares - Oseen tensor (eq.2.25); Open squares - Oseen tensor with Brenner modification (eq.4.11); open triangles - Rotne-Prager tensor (eq.4.10); Open diamonds - Truncated and shifted Oseen tensor (eq.4.12). D) Effective force (in pN) acting on motors for different filament occupations. The filled data points - Oseen tensor (see Fig.4.5B), open points - truncated and shifted Oseen tensor. The squares refer to forces acting on the bound motors, the circles show the force from hydrodynamic interactions and the triangles show the data in solution. Simulation settings: $F_0=1.061$, $\mu_0=0.3769$, $V_0=0.4$, $\langle V_0 \rangle=0.43$, $N_{\text{part}}=1000$, $\phi_s=0.05$ and, $T_{\text{max}}=7000$.

Truncated and shifted tensor improves the force calculation at large bio-filament occupations. Using this tensor raises the maximum physically plausible hydrodynamic force on suspended motors from an occupation of 75% to 85%. This shows that using hydrodynamic interaction tensors with periodic boundary conditions gives rise to an enhanced hydrodynamic coupling, this effect is largest at large bio-filament occupation fractions.
Opposing Filaments

The bio-filaments in cells are not always aligned with matching polarities. In the case of rotational streaming (e.g. Chara or Nitella [6, 161]), the bio-filaments can be found having opposite polarities at the different cell boundaries. For these cells sigmoidal velocity profiles between the bio-filaments have been reported [6, 161]. To study this type of situation, our model will now be adapted by reversing the polarity of the upper bio-filament as shown in Fig.4.10.

Figure 4.10: Schematic view of the model system, i.e. a cytoplasmic strand in a plant cell. A solution is embedded between two bio-filaments and mapped on a lattice. Moreover, both bio-filaments have opposite polarities, thus the walking distance of bound motors depends on the bio-filament. Motors on the bottom bio-filament walk to the right and motors at the upper bio-filament move in the opposite direction. All possible moves of the motor-cargo complexes are shown. Excluded volume and the processivity of the motors are accounted for. To mimic the dynamics of a infinite system, periodic boundary conditions are used in axial direction.

The results in Fig.4.11A show that the absolute values of the normalised velocities on both bio-filaments are equal as expected. Moreover, the opposing microtubules influence each others bound motor velocities via hydrodynamic momentum transfer. This results in motors on one bio-filament slowing down the motors on the opposite one and vice versa. Contrary to the parallel bio-filaments with equal polarity, the bound velocity does not surpass the single motor velocity at any value of $\phi_\mu$. However, comparison with the theoretical ASEP velocity (line in figure, see eq.A.2 in appendix A) shows that there still is a non-negligible increased motor velocity caused via hydrodynamic interactions. The maximum velocity difference, $\Delta V=0.06$, between the measured and ASEP velocity is found at $\phi_\mu=0.4$ and corresponds to a hydrodynamic force of 0.6 pN.
Figure 4.11: A) The (absolute) normalised velocity for different degrees of bio-filament occupation, $\phi_\mu$. The closed squares represent the reference system with parallel bio-filaments with equal polarities. The open squares and triangles refer to a system with opposing polarities ($V_{0,1}=0.43$ and $V_{0,2}=-0.43$). The line shows the theoretical velocity (ASEP) in the absence of hydrodynamic interactions. B) Concentration profiles for unbound motors. $D$ is the bio-filament separation, and $X$ the distance to the lower bio-filament. C) Normalised velocity profile over the distance $D$. Figures B-D: Open squares - $\phi_\mu=0.2$; Open triangles - $\phi_\mu=0.4$; Open circles - $\phi_\mu=0.6$; Open diamonds - $\phi_\mu=0.8$. D) Effective force (in pN) acting on motors for different filament occupations. The open and closed symbols represent data for opposing and parallel bio-filaments respectively. Squares - bound motor-forces; circles - hydrodynamic force on bound motors; triangles - suspended motors. The simulation settings for all figures were: $\mu_0=0.3769$, $F_{0,1}=1.061$, $F_{0,2}=-1.061$, $V_{0,1}=0.4$, $V_{0,2}=-0.4$, $N_{\text{part}}\approx1000$, $\phi_s=0.05$, and, $T_{\text{max}}=7000$.

Consistently with earlier findings, the hydrodynamic interactions have no effect on the shape nor the magnitude of the concentration profile between the bio-filaments (Fig.4.11B). The velocity profile shown in Fig.4.11C, presents a new situation. The suspended motors move in the direction corresponding to the polarity of the nearest bio-filament. The closer to the bio-filament the faster the motors. The motor velocity drops with the distance away from the bio-filament until a velocity of zero is reached at the
centre of the system. Here the hydrodynamic drag forces are balanced. Further away, the velocity reverses direction creating an inverted mirror image. The shape of the full profile differs from the sigmoidal velocity profiles presented in literature [6, 161]. The aforementioned profiles show a small drop in velocity near the bio-filament followed by a large drop near the centre of the system followed by inversion of the velocity. There are two differences between both measurements. Unlike the data from literature, we present the suspended motor velocity and not the fluid velocity. Moreover, we assumed the cytosol to be a Newtonian fluid which is an approximation. Fig.4.11D shows that the hydrodynamic interactions acting upon bound motors gives rise to a small but relevant hydrodynamic forces.

Crossing Gaps In The Cytoskeletal Tracks

In the introduction of this chapter axoplasmic streaming was mentioned. This is directed transport of organelles and molecules along nerve cell axons [2] and can take place over long distances (e.g. up to several meters in the Giraffe [153]) with respect to the cargo size. For axoplasmic streaming these neurons rely on active motor transport which is more efficient than passive diffusion*, for transport of organelles. The molecular motors walk along the axonal cytoskeleton that lines the inside of the axon in axial direction. For the stability of the axon as well as for enabling active transport it is important for the cytoskeleton to span the whole length of the axon. However, what happens to the axonal streaming if, due to decease or trauma, the cytoskeletal tracks are interrupted? To study this situation, the following simulation model, shown in Fig.4.12, is used.

In the model, there is a gap in both of the parallel bio-filaments where the motor’s cytoskeleton track is missing. Walking motors that reach the end of the track will leave the cytoskeleton with unit probability and diffuse away from the filament. Similar to the original model (see Fig.4.4), the motors can hydrolyse ATP only when attached to the cytoskeleton. Thus, in the gap, there is no net force generated by the motors. Suspended motors along the cell wall or in the bulk can attach to the cytoskeleton with unit probability taking excluded volume into account. The gap is chosen to be large in comparison to the organelle size (20l or 60l wide, where l is the lattice spacing) but short with respect to the length, L, of the system (L=750l). The width of the system is 12l.

As the system makes use of periodic boundary conditions in axial direction, the dynamics of an infinitely large system, with a gap every given number of lattice nodes, is studied. The system was initialised from a uniformly distributed configuration† for a period of 100,000 simulation steps in the absence of hydrodynamic interactions. From

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*See table 2.3 in chapter 2.
†The final configuration from an earlier simulation with ϕs=0.05 and ϕμ=0.4 (no gap).
Figure 4.12: Schematic view of the model system, i.e. an axon of a neuron. A solution is embedded between two bio-filaments and mapped on a lattice. The bio-filaments have a given polarity which determines the walking direction of the motor-cargo complexes. There is a gap in both bio-filaments where the motor-cargo complexes diffuse freely along the cell wall without directional preference. All possible moves of the motor-cargo complexes are shown. Excluded volume and the processivity of the motors are accounted for. To mimic the dynamics of an infinite system, periodic boundary conditions are used in axial direction.

In this starting configuration, simulations were performed for 25,000 time steps, a period long enough for the system to reach a steady-state, with or without hydrodynamic interactions. In the previous sections, the axial velocity and radial concentration profiles did not change in axial direction i.e. in the direction of the active transport. As now there is a gap in the filaments, these values will vary depending on the axial position in the system. To show the local concentrations and velocities, the system has been divided into sections (bins). In each bin, the motor concentration and velocities are measured for each row of lattice nodes i.e. on a bio-filament or in any row parallel to it and subsequently the average values are taken. Since the system is mirrored in the radial direction the statistics are improved by taking the average value (concentration or velocity) over a row of nodes and its mirror image. For example, the average values were taken for the row of lattice nodes directly below the upper filament and the row directly above the lower filament. The bins are chosen such that the spatial resolution can qualitatively show the local dynamics. For this purpose the system has been divided into 10 bins, 8 of equal length to describe the filaments (+solution) and 2 describing the gap.

In Fig.4.13A is shown that, in the absence of hydrodynamic interactions, the gap causes a traffic jam along the filament. This is as expected since motors are actively
transported towards the gap and can leave only by diffusion, a much slower process*. In addition, the motor concentration in solution strongly increases, before and at the begin of, the gap after which the concentration decreases again. At a sufficient distance from the gap (before or after) the system reaches a constant filament and solution concentration as observed in the absence of the gap (See e.g. Fig.4.7A). The latter steady-state is reached by the Langmuir Kinetics in the system (see eq.4.5 and 4.6). In-

*Similarly, the combination of active transport towards a wall and diffusion away from it causes a traffic jam and motor accumulation in solution (Fig.3.5C).
creasing the size of the gap further increases the accumulation of organelles at the gap (Fig.4.13C) and thereby further depletes the motor concentration in the rest of the system. When hydrodynamic interactions are included (Fig.4.13B) a small concentration increase is observed in the gap, albeit much smaller than without hydrodynamic interactions. The momentum transfer, via the fluid, helps the motors to cross the gap, thus preventing a large local organelle accumulation. In addition, the traffic jam around the gap is much smaller. Most importantly, the organelle transport is not impared, as the average motor concentration over the whole system is close to that observed in a reference system without a gap (see Fig.4.7A, $\phi_a=0.05$ and $\phi_b=0.4$). Increasing the gap size (Fig.4.13D) enhances the organelle accumulation around the gap but does not impair organelle transport.

The normalised velocity profile in the absence of hydrodynamic interactions (see Fig.4.14A) clearly shows the effect of the traffic jam before the gap. Here the velocity decreases when the bound organelle concentration near the gap increases. In solution, the average velocity is zero as there are no external forces acting upon the organelles. However, in the gap, there is a small positive motor velocity. This is a result from the net motor flux that compensates for the concentration gradient. When the gap is increased (Fig.4.14C), the average bound organelle velocity increases. This can be understood from the larger accumulation of organelles at the gap, that effectively yields a smaller bound organelle concentration (Fig.4.13C). When hydrodynamic effects are included, the bound motor-organelle velocity is larger than for a single motor. Moreover, in solution the organelles move at a non-negligible velocity. The found velocities are in line with the reference system without gap (Fig.4.5). In the gap the velocity of all organelles decreases but stays significant. The velocity of the motors at the cell wall drops down to a velocity slightly above the one measured in the bulk. Increasing the size of the gap (Fig.4.14D) shows a slightly higher velocity at the filament and a smaller value in solution.

Discussion

We have shown that long range collective hydrodynamic interactions lead to a substantial increase in the effective velocity of motors attached to a filament. Moreover, their motion leads also to a net transport of the nearby unbound particles. This mechanism is not captured by models that consider only the activity and steric interactions of motors attached to bio-filaments. Such an additional transport mechanism may be numerically as relevant as the mass transport obtained by direct motion of attached motors.

The additive hydrodynamic force, as induced by the processivity of the filament, might not be large compared with the driving force which generates the motion of the attached motors but the cumulative effect can give rise to a net significant mass trans-
Figure 4.14: A) and B) The normalised velocity per row of lattice nodes. \( L \) is the length of the system, \( W \) the width, and \( X \) the horizontal coordinate. The system is divided into bins for which the average velocities are shown. The gap size is 20 lattice nodes. Filled symbols with hydrodynamic interactions (HI), Open symbols no HI; Squares - Filament; Circles - 1st row of lattice nodes neighbouring the bio-filament; Triangles - 2nd row; Inverted triangles - 3rd; Diamonds - 4th; Pentagon - 5th i.e. centre row. The vertical lines represent the beginning and end of the gap respectively. C) and D) Idem for a gap of 60 lattice nodes. The simulation settings: \( L=750l, W=12l, \mu_0=0.3769, F_0=1.061, V_0=0.4, N_{\text{part}} \approx 1000, \) and, \( T_{\text{max}}=25,000. \)

In this sense, such a mechanism can be envisioned to be more important in situations as found in neurons or in cytoplasmic strands in plant cells. The outcome of our simulations suggests that this mechanism is indeed a plausible explanation for how cytoplasmic and axoplasmic streaming really takes place.