SIMULATING MUCOCILIARY TRANSPORT
USING
THE METHOD OF REGULARIZED STOKESLETS

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Abstract

Mucociliary clearance is a process whereby cilia lining the airways propel mucus and entrapped particles away from the lungs. Understanding this process is critical to treating ciliary defects, as well as to developing effective inhaled drug treatments. In this paper, we formulate a fluid model to simulate mucociliary transport of a single particle. The method of regularized Stokeslets, in combination with the method of images, is used to compute the velocity field in the mucus layer due to ciliary beating. The advective and diffusive motion of the particle is then modeled using the forward Euler method. Finally, our simulation is used to gain insight into the effect on mucociliary transport of various biological parameters, including ciliary spacing, ciliary phase differences, particle diffusivity, and particle starting location.

Key Words: mucociliary transport, regularized Stokeslets

1 Introduction

The airways consist of several fluid layers. Extending from the epithelial surface, the cilia are immersed in a periciliary liquid (PCL), above which is a layer of mucus. Particles that have been inhaled (e.g. bacteria, dust, smoke) are often trapped by this mucus. To prevent these particles from reaching the lungs, the cilia engage in periodic motion known as the ciliary beat cycle. During the first part of this cycle, the so-called effective stroke, the cilia extend themselves and rotate away from the lungs, penetrating the mucus layer as they do so. The cilia then bend closer to the epithelium and rotate back to their original position at a slower speed, a process which is called the recovery stroke. The work performed during the effective stroke is much greater than that performed during the recovery stroke; thus the net effect of the ciliary beat cycle is to transport mucus and particles *away* from the lungs [4].

The viscosity coefficient of mucus is several orders of magnitude higher than that of periciliary liquid [1], and thus we will use a viscous fluid in our model. In particular, we consider the low Reynolds number limit, in which fluid dynamics can be described as the creeping flow approximation to the Navier-Stokes equations. The resulting *Stokes flow equations* are linear, a property which allows us to formulate their solution as a superposition of fundamental solutions called *Stokeslets*. We numerically approximate this solution using the *method of regularized Stokeslets*, which computes the velocity field due to a collection of forces applied over small regions [2], [3]. These forces are expressed as regularized delta functions. In contrast to other techniques, such as the immersed boundary method, the method of regularized Stokeslets is mesh-free.

2 Methods

2.1 The method of regularized Stokeslets

We begin by formulating a model of the velocity field induced in the fluid by the ciliary beat. The fluid under consideration is characterized by having a low Reynolds number, which is a dimensionless number expressing the ratio of the inertial forces to the viscous forces in a fluid:

$$Re = \frac{\rho UL}{\mu},$$

where ρ is the fluid density, U and L are characteristic velocity and length scales, respectively, and μ is the dynamic viscosity. Motion of low Reynolds number fluids is described by the Stokes flow equations

$$\mu \Delta \mathbf{u} = \nabla p - \mathbf{F} \tag{1}$$

$$\nabla \cdot \mathbf{u} = 0, \tag{2}$$

where $\mathbf{u}$ is the fluid velocity, p is the pressure, and $\mathbf{F}$ is an external force. (Note that the Stokes flow equations are the Navier-Stokes equations in the zero Reynolds number limit). In the context of mucociliary clearance, $\mathbf{u}$ is the velocity of the fluid and $\mathbf{F}$ is the force exerted by a cilium as it beats in the fluid.

Since equation (1) is linear in $\mathbf{u}$, we may solve for the velocity of the fluid by taking a superposition of fundamental solutions, called *Stokeslets*; that is, we discretize the surfaces of the cilia so that each cilium consists of a number of points, each of which exerts a force on the surrounding fluid. The Stokeslet, $\mathbf{u}_s$, due to the point force at $\mathbf{x}_0$ satisfies the equation

$$\mu \Delta \mathbf{u}_s = \nabla p - \mathbf{f}_0 \delta(\mathbf{x} - \mathbf{x}_0),$$

where $\mathbf{f}_0$ is the given point force. The solution is given by

$$\mathbf{u}_s = \frac{\mathbf{f}_0}{8\pi\mu r} + \frac{(\mathbf{f}_0 \cdot (\mathbf{x} - \mathbf{x}_0))(\mathbf{x} - \mathbf{x}_0)}{8\pi\mu r^3},$$

where $r = |\mathbf{x} - \mathbf{x}_0|$ is the distance between the evaluation point and the point source. Notice that the expression for the Stokeslet has a singularity at $r = 0$, which may lead to the computation of nearly-singular integrals if we attempt to evaluate the velocity close to the cilia. To eliminate this problem, we make use

of the method of regularized Stokeslets, which instead of a point force considers the velocity due to a force spread over a small region [2], [3]. In this case, $\mathbf{u}_{rs}$ satisfies

$$\mu \Delta \mathbf{u}_{rs} = \nabla p - \mathbf{f}_0 \phi_\epsilon(\mathbf{x} - \mathbf{x}_0),$$

where the function $\phi_\epsilon(\mathbf{x})$ (called a *blob*) has the typical properties of a Gaussian curve; that is, ϕ is radially symmetric and integrates to 1. The parameter ϵ controls the spread of the blob.

To aid in solving for the regularized Stokeslet, we make the following definitions. Let $G_\epsilon(\mathbf{x})$ and $B_\epsilon(\mathbf{x})$ satisfy

$$\Delta G_\epsilon(\mathbf{x}) = \phi_\epsilon(\mathbf{x}) \quad \text{and} \quad \Delta B_\epsilon(\mathbf{x}) = G_\epsilon(\mathbf{x}).$$

Note that G_ϵ and B_ϵ depend on our choice of blob. Taking the divergence of (1) and using (2), we determine that

$$\Delta p = \nabla \cdot \mathbf{F},$$

which, in the case of $\mathbf{F} = \mathbf{f}_0 \phi_\epsilon(\mathbf{x} - \mathbf{x}_0)$, yields

$$p = \mathbf{f}_0 \cdot \nabla G_\epsilon.$$

We use this expression for pressure to rewrite (1) as

$$\mu \Delta \mathbf{u}(\mathbf{x}) = (\mathbf{f}_0 \cdot \nabla) \nabla G_\epsilon - \mathbf{f}_0 \phi_\epsilon,$$

from which we conclude that the regularized Stokeslet is given by

$$\mu \mathbf{u}_{rs}(\mathbf{x}) = (\mathbf{f}_0 \cdot \nabla) \nabla B_\epsilon(\mathbf{x} - \mathbf{x}_0) - \mathbf{f}_0 G_\epsilon(\mathbf{x} - \mathbf{x}_0).$$

Suppose that there are N forces, $\mathbf{f}_k$, centered at the points $\mathbf{x}_k$. Then, as alluded to earlier, the final expression for the velocity at evaluation point $\mathbf{x}$ is given by the sum of the regularized Stokeslets:

$$\mathbf{u}(\mathbf{x}) = \frac{1}{\mu} \sum_{k=1}^N [(\mathbf{f}_k \cdot \nabla) \nabla B_\epsilon(\mathbf{x} - \mathbf{x}_k) - \mathbf{f}_k G_\epsilon(\mathbf{x} - \mathbf{x}_k)]. \quad (3)$$

Since ϕ_ϵ is radially symmetric, so are the functions G_ϵ and B_ϵ . Using the formula $r = |\mathbf{x}|$, we find that

$$\nabla B_\epsilon = B'_\epsilon(r) \frac{\mathbf{x}}{r} \quad \text{and} \quad (\mathbf{f} \cdot \nabla) \nabla B_\epsilon = \mathbf{f} \frac{B'_\epsilon(r)}{r} + (\mathbf{f} \cdot \mathbf{x}) \mathbf{x} \left[\frac{r B''_\epsilon(r) - B'_\epsilon(r)}{r^3} \right].$$

Thus equation (3) becomes

$$\mathbf{u}(\mathbf{x}) = \frac{1}{\mu} \sum_{k=1}^N \left\{ \mathbf{f}_k \left[B'_\epsilon(r_k) \frac{\mathbf{x}}{r_k} - G_\epsilon(r_k) \right] + [\mathbf{f}_k \cdot (\mathbf{x} - \mathbf{x}_k)] (\mathbf{x} - \mathbf{x}_k) \left[\frac{r_k B''_\epsilon(r_k) - B'_\epsilon(r_k)}{r_k^3} \right] \right\}. \quad (4)$$

We now have a formula for the velocity at a given point in the fluid due to N point forces, $\{\mathbf{f}_k\}$, centered distances $\{r_k\}$ from the evaluation point. This system of equations can be written as

$$\mathbf{u}(\mathbf{x}_i) = \frac{1}{\mu} \sum_{k=1}^N M_{ik}(\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_N) \mathbf{f}_k,$$

or, more compactly, as

$$\mathbf{U} = \frac{1}{\mu} M \mathbf{F}, \quad (5)$$

where $\mathbf{U}$ is a $3N \times 1$ vector of the velocities at the evaluation points, $\mathbf{F}$ is a $3N \times 1$ vector of the point forces (located along the cilia), and M is a $3N \times 3N$ matrix whose elements depend on the evaluation points, the regularization paramter ϵ , and the surface discretization of the cilia. This matrix equation can be used to solve for the velocities in the fluid given the external forces, and vice versa.

2.2 The method of images

The epithelial surface from which the cilia project can be modeled as a no-slip wall; that is, one along which the fluid has zero velocity. There are several methods of enforcing this boundary condition, one of which is to discretize the epithelial barrier and set the velocity equal to zero at each discretization point. However, this method would require increasing the size of the vector $\mathbf{U}$ in equation (5), which effectively increases the size of the matrix M and results in a more computationally expensive problem. Instead we use the method of images, which allows us to satisfy the given boundary condition without constructing the wall out of point forces [1].

Suppose the fluid domain consists of points $\mathbf{x} = (x, y, z)$ with $x > w$, where $x = w$ defines a plane at which the fluid velocity vanishes (see Figure (1)). Let $\mathbf{x}_e$ and $\mathbf{x}_0 = (w + h, y, z)$ denote an evaluation point and a point force, respectively. Note that both are located within the fluid domain. The method of images applies various solutions of Stokes flow equations to the mirror point force, denoted $\mathbf{x}_{0,im} = (w - h, y, z)$, which is located outside the fluid domain. By taking the correct linear combination of these solutions, we can cancel the fluid velocity at points along the wall, as desired.

Figure 1: In the method of images, the wall is located at $x = w$, while the Stokeslet is located at $\mathbf{x}_0$ (within the fluid domain) and the image point is located at $\mathbf{x}_{0,im}$ (outside the domain) [1].

Before proceeding, we introduce the following definitions.

1. The Stokeslet

The Stokeslet is as defined in equation (4). Using the notation

$$H_1(r) = \frac{B'_\epsilon}{r} - G_\epsilon \quad \text{and} \quad H_2(r) = \frac{rB''_\epsilon - B'_\epsilon}{r^3},$$

we can write the Stokeslet velocity due to a force $\mathbf{f}$ located at the point $\mathbf{x}_0$ as

$$S_\epsilon[\mathbf{f}] = \mathbf{f}H_1(r) + (\mathbf{f} \cdot (\mathbf{x} - \mathbf{x}_0))(\mathbf{x} - \mathbf{x}_0)H_2(r).$$

2. The Stokeslet doublet

The Stokeslet doublet is the directional derivative of a Stokeslet in the direction of a constant vector $\mathbf{b}$. For a Stokeslet of strength $\mathbf{g}$, we define

$$\begin{aligned} SD_\epsilon[\mathbf{g}, \mathbf{b}] &= (\mathbf{b} \cdot \nabla) S_\epsilon[\mathbf{g}] \\ &= (\mathbf{g} \cdot \mathbf{b})(\mathbf{x} - \mathbf{x}_0)H_2(r) + (\mathbf{g} \cdot (\mathbf{x} - \mathbf{x}_0))\mathbf{b}H_2(r) + (\mathbf{b} \cdot (\mathbf{x} - \mathbf{x}_0))\mathbf{g}\frac{H'_1(r)}{r} \\ &\quad + (\mathbf{g} \cdot (\mathbf{x} - \mathbf{x}_0))(\mathbf{b} \cdot (\mathbf{x} - \mathbf{x}_0))(\mathbf{x} - \mathbf{x}_0)\frac{H'_2(r)}{r}. \end{aligned}$$

3. The potential dipole

The potential dipole is the result of applying the negative Laplacian to the Stokeslet. For a Stokeslet of strength $\mathbf{q}$, we obtain

$$PD_\epsilon[\mathbf{q}] = -\Delta S_\epsilon[\mathbf{q}] = \mathbf{q}D_1(r) + (\mathbf{q} \cdot (\mathbf{x} - \mathbf{x}_0))(\mathbf{x} - \mathbf{x}_0)D_2(r),$$

where

$$D_1(r) = \frac{G'_\epsilon}{r} - \phi_\epsilon \quad \text{and} \quad D_2(r) = \frac{rG''_\epsilon - G'_\epsilon}{r^3}.$$

4. The rotlet

A rotlet of strength $\mathbf{L}$ is the antisymmetric part of the Stokeslet doublet and is given by

$$R_\epsilon[\mathbf{L}] = \mathbf{L} \times \nabla G_\epsilon(|\mathbf{x} - \mathbf{x}_0|).$$

Ainley, et al. show that the image system for a Stokeslet of strength $\mathbf{f}$, regularized using a blob ϕ_ϵ , is given by

$$-S_\epsilon[\mathbf{f}] - h^2 P D_\epsilon[\mathbf{g}] + 2h S D_\epsilon[\mathbf{e}_1, \mathbf{g}] + 2h R_\epsilon^\phi[\mathbf{L}] - 2h R_\epsilon^\psi[\mathbf{L}], \quad (6)$$

where $\mathbf{g} = 2(\mathbf{f} \cdot \mathbf{e}_1)\mathbf{e}_1 - \mathbf{f}$ and $\mathbf{L} = \mathbf{f} \times \mathbf{e}_1$. Notice that the rotlets must be derived from two different blobs, which in this case we have taken to be

$$\phi_\epsilon(r) = \frac{15\epsilon^4}{8\pi(r^2 + \epsilon^2)^{7/2}} \quad \text{and} \quad \psi_\epsilon(r) = \frac{3\epsilon^2}{4\pi(r^2 + \epsilon^2)^{5/2}}.$$

Thus given N regularized Stokeslets located at the points $\{\mathbf{x}_{i,0} = (w + h_i, y_i, z_i)\}$, let $\{\mathbf{x}_{i,im} = (w - h_i, y_i, z_i)\}$ be the set of corresponding image points and let $\mathbf{x}_e$ be a point in the fluid domain at which we want to evaluate the velocity. Let $\mathbf{x}_i^* = \mathbf{x}_e - \mathbf{x}_{i,0}$ and $\mathbf{x}_i = \mathbf{x}_e - \mathbf{x}_{i,im}$. Then the fluid velocity at $\mathbf{x}_e$ is given by

$$\begin{aligned} \mathbf{u}(\mathbf{x}_e) = & \frac{1}{\mu} \sum_{i=1}^N [\mathbf{f}_i H_1(|\mathbf{x}_i^*|) + (\mathbf{f}_i \cdot \mathbf{x}_i^*) \mathbf{x}_i^* H_2(|\mathbf{x}_i^*|)] - [\mathbf{f}_i H_1(|\mathbf{x}_i|) + (\mathbf{f}_i \cdot \mathbf{x}_i) \mathbf{x}_i H_2(|\mathbf{x}_i|)] \\ & - h_i^2 [\mathbf{g}_i D_1(|\mathbf{x}_i|) + (\mathbf{g}_i \cdot \mathbf{x}_i) \mathbf{x}_i D_2(|\mathbf{x}_i|)] - 2h_i \left[\frac{H'_1(|\mathbf{x}_i|)}{|\mathbf{x}_i|} + H_2(|\mathbf{x}_i|) \right] (\mathbf{L}_i \times \mathbf{x}_i) \\ & + 2h_i [(\mathbf{g}_i \cdot \mathbf{e}_1) \mathbf{x}_i H_2(|\mathbf{x}_i|) + (\mathbf{x}_i \cdot \mathbf{e}_1) \mathbf{g}_i H_2(|\mathbf{x}_i|) + (\mathbf{g}_i \cdot \mathbf{x}_i) \mathbf{e}_1 \frac{H'_1(|\mathbf{x}_i|)}{|\mathbf{x}_i|} \\ & + (\mathbf{x}_i \cdot \mathbf{e}_1) (\mathbf{g} \cdot \mathbf{x}_i) \mathbf{x}_i \frac{H'_2(|\mathbf{x}_i|)}{|\mathbf{x}_i|}], \end{aligned} \quad (7)$$

where $\{\mathbf{g}_i = 2(\mathbf{f}_i \cdot \mathbf{e}_1)\mathbf{e}_1 - \mathbf{f}_i\}$ are the potential dipole strengths, $\{\mathbf{L}_i = \mathbf{f}_i \times \mathbf{e}_1\}$ are the rotlet strengths, and

$$\begin{aligned} H_1(r) &= \frac{1}{8\pi(r^2 + \delta^2)^{\frac{1}{2}}} + \frac{\delta^2}{8\pi(r^2 + \delta^2)^{\frac{3}{2}}}, \\ H_2(r) &= \frac{1}{8\pi(r^2 + \delta^2)^{\frac{3}{2}}}, \\ D_1(r) &= \frac{1}{4\pi(r^2 + \delta^2)^{\frac{3}{2}}} - \frac{3\delta^2}{4\pi(r^2 + \delta^2)^{\frac{5}{2}}}, \\ D_2(r) &= -\frac{3}{4\pi(r^2 + \delta^2)^{\frac{3}{2}}}. \end{aligned}$$

The terms in equation (7) comprise the elements of the revised matrix M . Comparing equation (7) with equation (4), we see that the new elements are more complicated than the original ones; however, we have succeeded in maintaining the same computational cost for our problem by maintaining the original size of the matrix M .

2.3 Model formulation

We have a matrix system, $\mathbf{U} = \frac{1}{\mu} M \mathbf{F}$, that expresses the relationship between the forces exerted on a fluid and the resultant velocities within a domain bounded on one side by a no-slip wall. We can now compute

the velocity and force at each of the discretization points along the cilia. To do so, we use the truncated Fourier series developed by Blake [4]:

$$\xi(s, t) = \frac{1}{2}\mathbf{a}_0(s) + \sum_{n=1}^6 \mathbf{a}_n(s) \cos(n\sigma t) + \mathbf{b}_n(s) \sin(n\sigma t),$$

where s is the dimensionless arc length of the cilium, σ is its angular beat frequency, $\mathbf{a}_i$ for $i = 0, \dots, 6$ are vector constants, and ξ is the position of the point in the plane. By differentiating this equation, we can compute the velocity at each point along the cilium at a given time t . In our model, we use $N = 80$ discretization points. These points are taken to be equi-spaced along the cilium when it is completely upright, at which time the cilium is approximately $6 \mu m$ in length.

Substituting these prescribed velocities into equation (5), we solve for the force that must have been exerted by each point in order to achieve the given velocities. Using these forces, we can then evaluate the velocity at any point, $\mathbf{x}_e$, in the surrounding fluid, using a quadrature formula. Consider an arbitrary cilium in our domain. Suppose the bottom point on the cilium is located at $\mathbf{x}_{1,0} = (w + h_1, y_1, z_1)$ and the top point at $\mathbf{x}_{80,0} = (w + h_{80}, y_{80}, z_{80})$. Let p_i be the i^{th} term in the sum given in equation (7) and let $\tilde{h}$ denote the distance between adjacent points on the cilium. Then the velocity at the evaluation point due to the force exerted by this cilium is

$$\mathbf{u}(\mathbf{x}_e) = \sum_{i=1}^N \tilde{h} \left[\frac{1}{2}p_1 + \sum_{i=2}^{79} p_i + \frac{1}{2}p_{80} \right]. \quad (8)$$

In Figure 2, we see that the nearby mucus has a net velocity in the positive y -direction when the cilium is engaged in the effective stroke, and a net velocity in the negative y -direction when the cilium is in the recovery stroke.

Figure 2: Velocity field due to ciliary beating at one time during the effective stroke (left) and during the recovery stroke (right)

We are interested in determining the velocity, $\mathbf{u}$, at the point where the particle is located. Obtaining this velocity allows us to track the particle's motion over time using the stochastic differential equation

$$d\mathbf{p}_t = \mathbf{u}_t dt + \omega \mathbf{W}_t, \quad (9)$$

where $\mathbf{p}_t$ is the position of the particle at time t , ω is a measure of the particle's diffusive capacity, and $\mathbf{W}_t$ represents the Wiener process (often called Brownian motion). We solve this equation in discrete form:

$$\mathbf{p}_t = \mathbf{p}_{t-h} + h\mathbf{u}(\mathbf{p}_{t-h}) + \omega(\mathbf{W}_{t+h} - \mathbf{W}_t), \quad (10)$$

where h is the time step. Notice that in equation (10) the particle's location is updated via two mechanisms: advection, represented by the term $h\mathbf{u}(\mathbf{p}_{t-h})$, and diffusion, represented by the term $\omega(\mathbf{W}_{t+h} - \mathbf{W}_t)$. The Wiener process is characterized by the property $\mathbf{W}_{t+h} - \mathbf{W}_t \sim \mathcal{N}(0, 1)$; thus the coefficient in the diffusion term, ω , controls the degree to which the particle moves randomly.

3 Results

Having formulated a model that tracks the position of the particle over time, we now investigate how various biological parameters affect this motion. From the many factors involved in mucociliary clearance, we have chosen to consider the effect of phase differences in the ciliary beat, the initial location of the particle, ciliary spacing, and particle diffusivity. In each case we take the following parameters to be constant:

- Number of discretization points along each cilium: 80
- Frequency of ciliary beat: 15 Hz, as suggested in [4]
- Fluid viscosity: $0.482 \frac{kg}{m \cdot s}$, as suggested in [5].

The epithelium from which the cilia extend is represented as the plane $P = \{(x, y, z) : x = 0, y \in [0, 10], z \in [0, 10]\}$, and the number of cilia in the y - and z -directions is fixed at $\frac{10}{\eta_y}$ and $\frac{10}{\eta_z}$, where η_y and η_z denote the ciliary spacing in the y - and z -directions, respectively.

3.1 Base case

Figure 3: A typical particle trajectory. We have set ciliary spacing to $2 \mu m$, diffusivity to $10^{-2} \frac{\mu m^2}{s}$, and phase differences to $\Phi = \frac{\pi}{10}$.

To understand how a particle typically moves in a mucociliary environment, we set the cilia to be spaced $2 \mu m$ apart in the y - and z - directions, with particle diffusivity on the order of $10^{-2} \frac{\mu m^2}{s}$. Initially the tips of the cilia are located at a height of $4.593 \mu m$ above the epithelium. Therefore we start the particle at position $(x, y, z) = (4.7, 5, 0)$; in other words, just above the carpet of cilia. We also introduce uniform phase differences of $\Phi = \frac{\pi}{10}$ between adjacent cilia. Note that these phase differences are only applied in the z -direction, since the cilia beat in the yz plane. Thus the beating cilia form a wave that propagates in the z -direction. From Figure 3, we see that the particle (depicted in red) initially moves in the positive z -direction, i.e. in the direction of the effective stroke. However, when the cilia beneath the particle begin to engage in the recovery stroke, the particle is propelled backward in the direction from whence it came. When it meets an effective stroke, it will once again move in the positive z -direction, so that the net motion of the particle is in the direction of the effective stroke. Motion in the xy plane (i.e. perpendicular to the wavefront) is due to diffusion.

3.2 Effect of phase differences

The first parameter that we investigate is that of phase differences in the ciliary beat cycle. (Note that these phase shifts are applied in the z -direction only). In the base case, the phase difference was $\Phi = \frac{\pi}{10}$; here, we set Φ equal to $\frac{\pi}{25}$, $\frac{7\pi}{50}$, and $\frac{\pi}{5}$. All other parameter values are as they were.

When the phase difference is small, for instance $\Phi = \frac{\pi}{25}$, we see that the particle travels swiftly in the direction of the effective stroke, arriving at the opposite end of the cilia patch in approximately 0.006 seconds (see Figure 4). However, when the phase difference is larger, as in the base case, we see that within the same time frame the particle moves forward and backward in the yz plane. When Φ is increased to $\frac{7\pi}{50}$, this

behavior is even more pronounced. The particle changes direction in the yz plane a total of four times before it reaches the opposite end of the domain. As a result of this oscillatory motion, it takes the particle 0.12533 seconds to travel across the patch, 20 times as long as it does when $\Phi = \frac{\pi}{25}$ (see Figure 5). Similarly, when $\Phi = \frac{\pi}{5}$, the particle travel time is 0.118 seconds.

Figure 4: Particle trajectory for phase difference of $\Phi = \frac{2}{100}$.

Figure 5: Particle trajectory at various times for phase difference of $\Phi = \frac{7}{100}$.

3.3 Effect of particle starting location

Letting $\Phi = \frac{\pi}{10}$ and setting the spacing between cilia to be $2 \mu m$, we now examine the effect of the initial location of the particle. Comparing Figure 3 with Figure 6, in which the particle is started at $x = 6$ and then at $x = 8$, we see that the further above the cilia the particle is located, the less it moves back and forth in the yz plane. This is most likely due to the fact that the cilia induce a high velocity in the fluid close to the patch and a weaker velocity in the fluid further away.

(We note that when the particle's initial location is at $x < 4.7$, the particle begins to travel in the direction of the effective stroke, then reverses direction, and is eventually cleared from the fluid domain at $z = 0$).

3.4 Effect of ciliary spacing

Next we examine ciliary spacing; that is, the distance between adjacent cilia. (To simplify matters, we set the separation in the y - and z - directions to be identical). Using the same particle diffusivity, phase differences, and starting location as in the base case, we now allow the spacing to assume values of 0.5, 1, 2, 3 and $4 \mu m$. We find that as the ciliary spacing increases, the time it takes for the particle to cross the fluid domain increases as well (see Figure 7). This is to be expected: when the cilia are spaced close together, their forces combine to induce a high velocity in the nearby fluid, whereas when the cilia are spaced further apart, they do not have the opportunity to interact as much. Interestingly, when the cilia are spaced $0.5 \mu m$ apart, the particle exhibits a significant amount of motion in the x -direction; it begins just above the tips of the cilia, but ends far higher. When the ciliary spacing is increased to $1 \mu m$, we see similar behavior, albeit to a lesser degree.

Figure 6: Particle trajectory for an initial location of (a) $(x, y, z) = (6, 5, 0)$ and (b) $(x, y, z) = (8, 5, 0)$.

From the base case, we know that ciliary spacing of $2 \mu m$ leads to the particle being pushed back and forth in the yz plane. When the spacing is 3 or $4 \mu m$, the particle takes longer to cross the patch because of this backward motion. The main difference between the values of 2, 3, and $4 \mu m$ is the degree of motion in the xy plane. When the cilia are spaced $2 \mu m$ apart, the particle moves left and right in the xy plane as it is propelled backward and forward. However, the further apart the cilia are spaced, the less of this motion we see. Instead, the particle almost retraces its steps, moving nearly along a line in this plane (see Figure 8).

Figure 7: Particle trajectory for ciliary spacing of (a) $0.5 \mu m$, (b) $1 \mu m$, and (c) $3 \mu m$.

Figure 8: Particle trajectory for ciliary spacing of $4 \mu m$.

3.5 Diffusivity

Lastly we alter the diffusivity of the particle, denoted ζ , allowing it to assume the values 10^{-4} , 10^{-3} , 10^{-2} , 10^{-1} and $1 \frac{\mu m^2}{s}$. The diffusivity does not appear to have a significant impact on the particle's motion when it is sufficiently small ($\zeta < 10^{-2} \frac{\mu m^2}{s}$); the time required to cross the domain is the same in each case. Thus, at biologically relevant diffusivity, particle motion is driven mostly by advection. When the diffusivity is

$O(10^{-1}) \frac{\mu m^2}{s}$, it takes the particle slightly longer to cross the patch of cilia, and when the diffusivity is $O(1)$, the particle's motion appears entirely random, as expected.

4 Conclusion

We have formulated a model describing the motion of a general particle in the mucociliary environment of the human air passages. Our model uses the method of images for regularized Stokeslets to compute the velocity field in a viscous fluid due to two-dimensional (planar) ciliary beating with a no-slip epithelial wall. The advective and diffusive motion of the particle through the fluid is then modeled using the forward Euler method. The numerical results show that our model successfully illustrates mucociliary transport, and therefore can be used to gain insight into which biological factors impact clearance. We have found that when small phase differences exist between adjacent cilia, when the inter-ciliary spacing is small, and when the particle begins close to the patch of cilia, the time required for the particle to cross the domain decreases; that is, mucociliary clearance is most effective under these conditions. Diffusivity appears to have a negligible effect on the particle's motion. Ultimately we would like to model *mucus* transport driven by ciliary motion. The mucus layer can be described as a viscoelastic fluid that lies on top of the periciliary liquid layer, described as Stokes flow. The mucus-periciliary liquid interface can be simulated using linear springs, as in Lukens et al. [6]. The resulting two-fluid system should provide many interesting challenges for analysis and numerical techniques.

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