Modelling the Effects of Cystic Fibrosis on the Velocity Profile of Mucus in Human Bronchioles

1. Abstract

In this paper, a mathematical model created to determine the velocity profile of mucociliary clearance in the bronchioles of healthy lungs and lungs affected by cystic fibrosis. This model, which depicts a flow above an oscillating plate, uses the Navier-Stokes equation to simulate the movement of the mucus. Three heatmaps were generated to demonstrate the velocity profile of the mucus in the bronchioles under different conditions. In the end, the trends observed in the heatmaps agreed with those from literature.

2. Introduction and Motivation

Cystic fibrosis (CF) is a fatal genetic disease affecting more than 70,000 people worldwide [1] and remains one of the most common genetic diseases. CF is caused by one of the 1700 different genetic mutations in the cystic fibrosis transmembrane regulator (CFTR) gene[2]. These mutations cause the CFTR protein to become dysfunctional, which leads to severe damage in various organs such as the lungs, pancreas, liver and intestines [3].

The investigation undertaken in this paper will focus primarily on the effects of CF in the bronchioles of the lungs. In a healthy respiratory tract, a thin layer of mucus coats the airways of the lungs to capture dirt, bacteria and other debris. Then, small hair-like projections called cilia help to sweep the mucus out of the lungs. In individuals who suffer from CF, the mucus is much thicker and stickier, inhibiting the cilia's ability to displace the mucus. This causes the mucus to clog the lungs which can lead to chronic airway infections, difficulty breathing and increased production of phlegm.

This paper serves to mathematically model the bronchioles in healthy lungs and the lungs of patients with CF. By understanding the differences in air velocity in the two models, we may be able to develop better tailored therapies for patients living with CF. Currently, no conclusive or accurate model of respiratory airways exists, either for healthy lungs or lungs with CF. This is due to a lack of physiological data and a proper characterization of fluid mechanics in the airways. This field begs to be rigorously explored, so this paper serves as an rudimentary investigation to that end.

3. Mathematical Model of Bronchioles

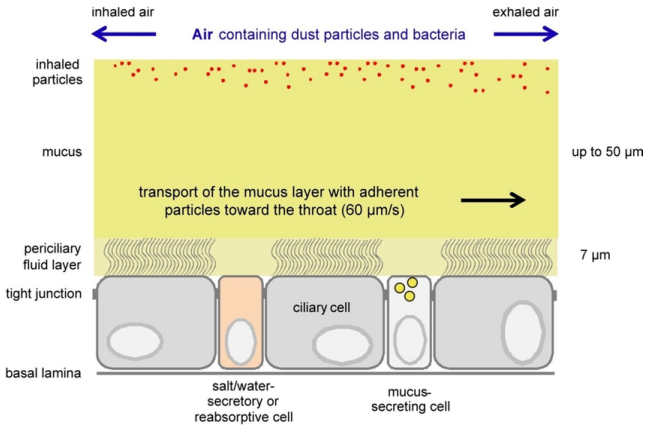

Figure 1. Mucus Clearance Model [4]

The system to be modelled is the mucus clearance by cilia in human bronchioles. More specifically, this paper will investigate the velocity profile of mucus clearance in healthy human

bronchioles, bronchioles affected by CF (with minimal airflow) and clogged bronchioles affected by CF (ie. no air passing through) affected by CF. Figure 1 shows a sketch of the proposed model and in the following sections is a description of each component and how they were modelled.

3.1 Cilia Model

In the bronchioles, cilia are slender, microscopic, hair-like structures that extend from the surface of epithelial cells. They beat back and forth in an oscillatory fashion to clear the bronchioles of mucus. The exact mechanism by which cilia beat is still unclear, however, one of the most rigorous models created by L. Gheber and Z. Priel [5], depicts two phases in a cilia motion: the power stroke and the recovery stroke.

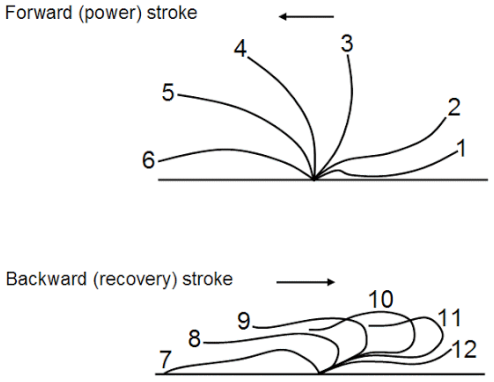

Figure 2. Power and Recovery strokes of a cilium [6]

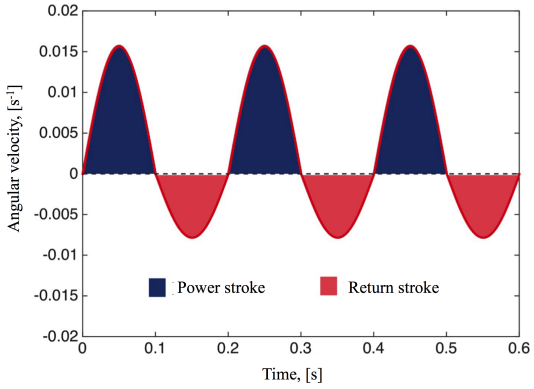

Figure 3. Plot of the power and return strokes cilia [7]

The power stroke consists of a fast effective stroke in the plane perpendicular to the epithelial cell surface in which the cilia follow an arc-like path as seen in Figure 2 (top). This stroke pushes the mucus forwards. The recovery stroke, seen in Figure 2 (bottom) is slower than the power stroke. In this stroke, the cilia move in a plane inclined to the epithelial cell surface, returning to their initial positions. The cilia have much less contact with the layer of mucus during the recovery stroke, so although they do pull the mucus backwards, the force is not significant enough to change the direction of mucus flow. In this way, the layer of cilia can be modelled as a simple 1D oscillating plate whose amplitude of angular velocity differs from the power stroke to the recovery stroke as seen in Figure 3.

Furthermore, the equation for the angular velocity, derived by P. Vasquez et. al [7], is given by the sinusoidal piecewise function:

$$f(t) = P_0 \cos(\frac{\pi}{2} - \omega_p t) \; for \; 0 < t < \frac{\pi}{\omega_p}$$

$$f(t) = R_0 \cos(\frac{\pi}{2} - \omega_r t) \; for \; \frac{\pi}{\omega_p} < t < \frac{\pi}{\omega_p} + \frac{\pi}{\omega_r}$$

where P_0 and R_0 are the angular velocity amplitudes during the power and recovery strokes, respectively, and ω_p and ω_r are the frequencies of the power and return strokes, respectively [7]. The values for each variable can be found further below in Table 1. Additionally, the layer of cilia will act as a boundary equation in the model.

3.2 Mucus Model

As mentioned before, there is a thin layer of mucus coating all the airways in the lungs which helps to trap dirt, bacteria and other debris. The particle-containing mucus eventually ends up in the stomach, where stomach acid renders the particles harmless[8]. Furthermore, mucus is a non-Newtonian

fluid and is incompressible, which allows us to model its behaviour as a flow above an oscillating plate. The governing equation is a simplified version of the Navier-Stokes Force Balance Equation:

$$\rho\left(\frac{\delta v_x}{\delta t}\right) = \mu\frac{\delta^2 v_x}{\delta y^2}$$

where ρ and μ are the density and viscosity of the mucus, respectively. See Table 1 for their values.

3.3 Air Model

Right above the layer of mucus, a layer of air moves in and out of the bronchioles as humans breathe. In this model, we simulate air velocity, V_0, as the speed of an average human exhaling (see Table 1 for value), as it fits into the 0.2s timeframe of the simulated model. The layer of air will act as one of the boundary conditions for the system.

3.4 Boundary Conditions

Below are the two no-slip boundary conditions for the model:

1. Mucus-air interface: $v_x(y=H,t) = V_0$ where H is the height of the mucus (see Table 1 for values)
2. Cilia-mucus interface: $v_x(y=0,t) = f(t)$ where y=0 is the surface of the cilia layer

Table 1. Parameters and values for model

	Value		**Value**
P_0	4.71×10^4 micrometers*Rad/s	μ	Healthy Lungs: 10^{-6}g/(μm*s)
R_0	2.37×10^4 micrometers*Rad/s		CF Lungs: 1.958×10^7g/(μm*s)
ω_p	10π Rad/s	V_0	Healthy Lungs: 2.5×10^6 μm/s
ω_r	10π Rad/s		CF Lungs: (unclogged) 1.25×10^6 μm/s; (clogged) 0
ρ	10^{-12} g/μm	H	Healthy Lungs: 50 μm
			CF Lungs:(unclogged)200μm; (clogged) 500μm

3.6 Assumptions and Simplifications

Below are assumptions made either due to lack of data or in an effort to simplify the problem.

- The phase of the wave is consistent across the entire layer of cilia, whereas in reality, the phase changes asymmetrically (many papers assume the same to simplify the model).
- The swirling flow caused by the true movement of cilia will be neglected. Hence, only the oscillatory motion in the x-direction will be considered.
- The effects of the mucus-air interface (ex. surface tension) will be neglected for simplicity
- We will assume that the cilia form a continuous layer across bronchiole walls. In reality, the cilia layer is interrupted by various secretory cells, but these cells take up much less surface area compared to the layer of cilia, so the assumption is not terrible.
- We will neglect any pressure gradient effects other than those already captured by the velocity of the air to simplify the problem.
- The effects of gravity will be neglected for simplicity
- ρ for CF mucus could not be found, so it is assumed to be the same as that of regular mucus

4. Results & Discussions

The governing equation was solved with the provided boundary conditions using a derivation similar to that of Dr. Daniel Coombs [14]. The final answer was equation for velocity was:

$$v_x = C_1 e^{ay} cos(ay + \omega t - \frac{\pi}{2}) + C_2 e^{-ay} cos(ay - \omega t - \frac{\pi}{2})$$

$$a = \frac{1}{\sqrt{2}} \sqrt{\frac{\omega \rho}{\mu}}$$

$$C_1 = \frac{V_0 - C_2 (e^{-aH} cos(aH - \omega t + \frac{\pi}{2}))}{cos(aH + \omega t - \frac{\pi}{2}) e^{aH}}$$

$$C_2 = \frac{U cos(aH + \omega t - \frac{\pi}{2}) e^{aH} - V_o}{cos(aH + \omega t - \frac{\pi}{2}) e^{aH} - cos(aH - \omega t + \frac{\pi}{2}) e^{-aH}}$$

$$U = P_0 \, and \, \omega = \omega_P \, for \, 0 < t < \frac{\pi}{\omega_p}$$

$$U = R_0 \, and \, \omega = \omega_R \, for \, \frac{\pi}{\omega_p} < t < \frac{\pi}{\omega_p} + \frac{\pi}{\omega_R}$$

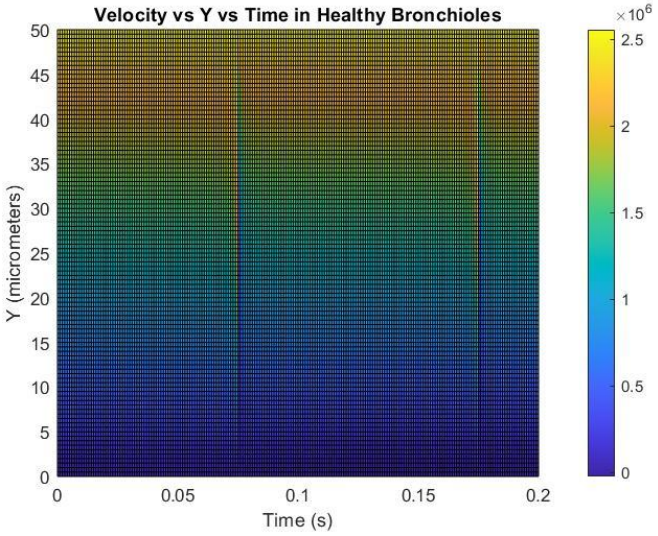

Figure 4. Velocity profile of mucus clearance through healthy human bronchioles

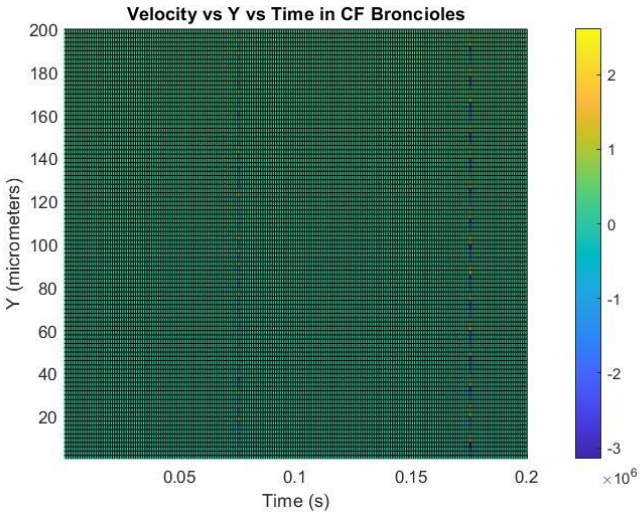

Figure 5. Velocity profile of mucus clearance through human bronchioles with CF

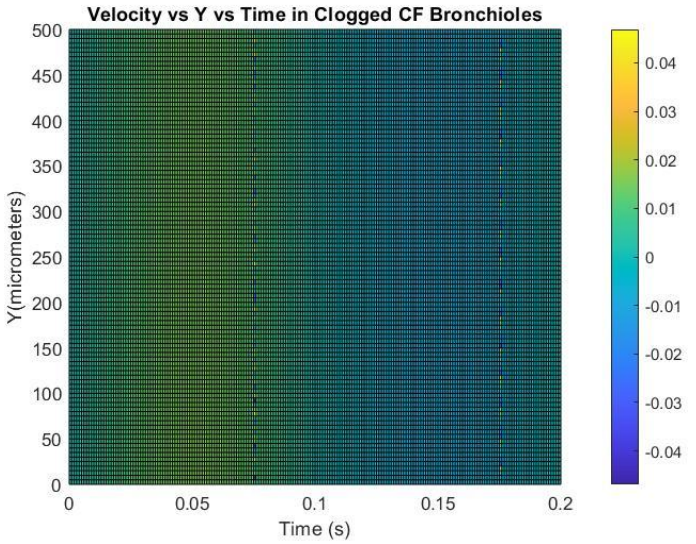

Figure 5. Velocity profile of mucus clearance through clogged human bronchioles with CF

Three heatmaps were produced to visually represent the velocity profile of mucus under different conditions (to see the implementation of the code used to create the heatmaps, please visit [15]). The heatmap in Figure 4 depicts the velocity profile of mucus being cleared by cilia in healthy human bronchioles. The velocity of the mucus changes as a function of y, with the highest velocity at the top of the mucus layer. This makes sense because when y=50 μm, we have reached the mucus-air interface where the velocity of air moves at about 2.5 x 10^6 μm/s. This is 2 orders of magnitude faster than the mucus velocity at the cilia-mucus interface (y=0). The velocity between y=0 to y = 20μm is relatively constant, then from y=20μm to y=50μm, the velocity increases, likely due to the fact that the air above it has a greater effect on its velocity. These results agree with findings from literature [16], in which a steady increase in mucus velocity was observed as y increased. At the air-mucus interface, the mucus velocity plateaued over time, matching the velocity of the air. In Figure 4, there are also two distinctive vertical lines at t ≈ 0.075s and t≈0.17s where the velocity drops drastically, then resumes its original profile. I believe that these vertical lines should be at t = 0.1s and t=0.2s, representing the velocities at the moments when the cilia change their stroke direction. The times are likely skewed due to the assumptions and approximations made during modelling.

The heatmap in Figure 5 depicts the velocity profile of mucus being cleared by cilia in human bronchioles with CF. In this model, the mucus layer has thickened from y=50μm to y=200μm compared to the model in Figure 4 and the viscosity of the mucus has also increased by 1 order of magnitude. We can see that these changes are reflected in the velocity profile of the mucus, as the velocity hovers just above 0μm/s during the entire time frame of the model. These results agree with conclusions drawn from models of CF in different airways (ex. bronchioles, trachea etc.) of the lungs; the mucus velocity is reduced by 50-80% compared to the velocity in healthy human airways[13]. Similar to the plot in Figure 4, the plot in Figure 5 has two distinctive vertical lines at t ≈ 0.075s and t≈0.17s, likely for the same reasons described above.

The heatmap in Figure 6 depicts the velocity profile of mucus being cleared by cilia in human bronchioles with CF where the mucus completely clogs the airway. As expected, the velocity profile is almost constant for all values of y. As shown by the colorbar, the velocity values are between 0.04μm/s and -0.04 μm/s which is practically just 0μm/s. Although there was very little information on models for

these conditions, the results from Figure 4 make logical sense. Since the bronchioles are clogged with thick mucus that the cilia are unable to sweep, the velocity of the mucus should be zero. Furthermore, the trend of the two vertical lines is the same as in Figures 4 and 5.

Conclusion

The model created in this investigation follows the general trends found in literature, as observed in the *Results and Discussions* section. However, there is much room for improvement as the model is extremely rudimentary and oversimplified. At best, it could serve to offer a high-level overview of the fluid transport occurring in the complex system. The bulk of the inaccuracies in this model stem from the assumptions that gravity, shear stress and the pressure gradient at the mucus-air interface could be neglected. Furthermore, models that are more correct than that presented in this paper take into account the true movement of cilia, in which the cilia swirls around itself in the recovery stroke. This swirling changes the velocity at the mucus-cilia interface, likely causing sinusoidal velocities of differing phase and amplitude. Therefore, $v_x(y)$ has a much more dynamic velocity profile than those plotted in Figure 3-5. Overall, however, the model presented in this paper succeeds in capturing the important features of mucociliary transport, which offers a nice introduction to the fluid transport in the bronchioles of the lungs.

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