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Model of mucociliary clearance in cystic fibrosis lungs

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ABSTRACT

Mucus clearance is a primary innate defense mechanism in the human airways. Cystic fibrosis (CF) is a genetic disease caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. CF is characterized by dehydration of airway surface liquid and impaired mucociliary clearance. As a result, microorganisms are not efficiently removed from the airways, and patients experience chronic pulmonary infections and inflammation. We propose a new physiologically based mathematical model of muco-ciliary transport consisting of the two major components of the mucociliary clearance system: (i) periciliary liquid layer (PCL) and (ii) mucus layer. We study mucus clearance under normal conditions and in CF patients. Restoring impaired clearance of airway secretions in one of the major goals of therapy in patients with CF. We consider the action of the aerosolized and inhaled medication dornase alfa, which reduces the viscosity of cystic fibrosis mucus, by selectively cleaving the long DNA strands it contains. The results of the model simulations stress the potential relevance of the location of the drug deposition in the central or peripheral airways. Mucus clearance was increased in case the drug was primarily deposited peripherally, i.e. in the small airways.
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1. Introduction

Mucus clearance is a primary innate defense mechanism in the human airways (Knowles and Boucher, 2002). It protects the lungs by trapping and transporting inhaled microorganisms and particles from the lower airways to the mouth. We consider the mucociliary clearance system to have two major components: (i) the periciliary layer (PCL), with cilia on the apical surface of the airway epithelial cells and (ii) the mucus layer residing on top of the PCL. The cilia are embedded in the PCL with only their tips penetrating the mucus layer (Puchelle et al., 1998; Sanderson and Sleigh, 1981).

The PCL is a watery layer, occupied by a grafted brush of membrane-spanning mucins and mucopolysaccharides. This brush prevents penetration of the mucus into the periciliary space and causes mucus to form a distinct layer (Button et al., 2012). Inhaled material is trapped on the viscoelastic mucus, whereas the PCL allows the cilia to move freely, propelling the mucus layer towards the mouth. The mucus layer mainly consists of two gel-forming glycoproteins (mucins) secreted by the goblet cells (mucin MUC5AC) and the submucosal glands (mucin MUC5B) (Thornton et al., 2008; Hovenberg et al., 1996).

Moving down to the more peripheral airways, the mucosal epithelium becomes thinner and it changes in nature. Fewer cilia and no mucus-producing cells are present in the terminal bronchioles (Mercer et al., 1994). In the alveoli any deposited particles can only be removed by phagocytosis by alveolar macrophages. Effective clearance of mucus requires both adequate ciliary activity and an appropriate balance between PCL and mucus layer. Under normal conditions, the cilia beat in a coordinated fashion in the PCL propelling the mucus above towards the mouth. When mucociliary clearance fails, cough (high expiratory airflow) becomes the most important mechanism for clearance of mucus.

CF is a genetic disease caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This protein is situated in the apical cell membrane in epithelial cells of many organs, including the lung, liver,

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pancreas, digestive tract and skin. It mainly serves as a chloride anion channel, which in the airways allows for chloride secretion from the cell into the bronchial lumen. CFTR and the sodium channel ENaC are co-regulated. In CF airways chloride secretion is decreased, while up-regulated ENaC facilitate increased sodium absorption (Berdiev et al., 2009). Both mechanisms contribute to a decreased efflux of water into the bronchial lumen. Osmotic equilibrium between PCL and mucus layer is needed for a correct water balance between the layers (Button et al., 2012). If it is not respected, the PCL becomes thinner and effective clearance of the mucus layer by the airway cilia is hampered. Many factors can increase mucus production, but little is known about factors that decrease its production. Due to relatively little autofeedback between the removal of mucus from the airway surface and the secretion of mucins by goblet cells and submucosal glands, mucus production continues even if it locally accumulates (Evans and Koo, 2009).

Failure of this primary defense mechanism to directly remove microorganism from the airways leads to chronic bacterial infections and inflammation. Ongoing inflammation leads to the decay of many white blood cells, releasing their genetic material as long DNA strands in the mucus (Shak et al., 1990; Ratjen et al., 2005). This results in a further increase of mucus viscosity. Moreover mucus can change from a highly viscous solution to show predominant characteristics of an elastic gel (Hill et al., 2014). The resultant thick and tenacious mucus cannot be cleared effectively from the lung. It becomes a vicious cycle with more inflammation, increased viscosity and ineffective mucociliary clearance, eventually leading to irreversible damage of the airways (O'Sullivan and Freedman, 2009). Despite multiple treatment options, progressive lung damage still remains the most important cause of the significantly reduced life expectancy in patients with CF (Anon, 2006).

Mathematical modelling of mucociliary transport has been attracting attention since the end of the 1960s. One of the first models was proposed by Barton and Raynor (1967) where they idealized cilia beat cycle. The average shear stress at the PCL and mucus interface was assumed to be the driving force of mucus motion. Later Ross (1971) developed a model of mucociliary transport using an envelope approach in which the mucus–cilia interface was presented as an impermeable wavy sheet. The authors made a first attempt to model mucus as a viscoelastic fluid without modeling the periciliary fluid movement. However, the envelope approach is not well adapted to represent the ciliary beat, which displays antiplectic metachronism (Sleigh et al., 1977). In an effort to construct the models in a more realistic way Blake (1973) and Liron and Mochon (1976) used a discrete cilia-sublayer approach, in which force singularities are distributed along cilia centre-lines. Another way to model mucociliary transport was developed by Keller (1975), applied to ciliated microorganisms. In their "traction layer" model the cilia are modeled by a continuous volume force distribution. Later Blake and Winet (1980) used this approach to model mucociliary transport in the lung. They distinguished the PCL layer, modeled as a porous medium, and the mucus layer. Mucus was considered as a Newtonian fluid. More recently, a more sophisticated traction layer model was proposed by Smith et al. (2007), in which the PCL layer was modeled as an "active porous medium". Viscoelastic properties of the mucus were now taken into account. The propulsive force of the cilia acting in the traction layer is based on ciliary activity (Sanderson and Sleigh, 1981).

In this paper we propose a new model of mucociliary transport, partially based on the model of Smith et al. (2007). The authors describe the transport of mucus and PCL in the airways taking into account the movement of individual cilia. Each cell of the ciliated epithelium contains 200–500 cilia each performing 20–30 beating cycles per second. In our simulations, in order to approach the physiological process of mucociliary clearance, we consider movement of ciliated epithelium up to the 16th generation of the bronchial tree and take into account the physiological properties, length, diameter and the number of tubes in each generation. In order to make it feasible to model the mucociliary clearance process, which takes several hours, we consider a macroscopic model replacing the force of all individual cilia by a force acting on the mucus averaged over time and space.

We will model mucus as a viscous Newtonian fluid. Importantly, mucus also has elastic properties, which may be essential for the description of high-frequency oscillations of individual cilia. However, the elastic relaxation time of mucus is of the order 10^{-5}–10^{-4} s (Smith et al., 2007), which is much less than the characteristic time of mucus motion in the process of mucociliary clearance. Therefore, in this model with averaged forces of the cilia we did not include the elastic properties of mucus. Periciliary liquid also has a complex structure (Button et al., 2012) and its rheological properties are not exactly known. Following Smith et al. (2007, 2008) we suppose that this can also be approximately modeled as a Newtonian fluid.

We take into account mucus production by goblet cells and submucosal glands as well as mucus transport from previous, more peripheral, sections. Moreover, age is introduced in the model by means of scaling the trachea and bronchus sizes in all patients, depending on their body height (Phalen et al., 1985). We also introduce the possibility of different viscosities of mucus in each generation, which is important due to the heterogeneity of medication deposition in the bronchial tree (Gerrity et al., 1979). Section 2 contains a detailed presentation of the mucociliary clearance model in normal and CF lungs.

In Section 3 we study the effect of the aerosolized inhaled medication dornase alfa, an evidence based treatment in CF, which reduces the viscosity of CF mucus by selectively cleaving the long DNA strands (Fuchs et al., 1994). We calculate mucus velocity and the decrease in mucus quantity in the bronchial tree due to dornase alfa action. The results show how mucociliary clearance increases with a higher percentage of drug deposition in the lower airway generations.

2. Model

Let us consider the model of mucociliary transport. The airway surface liquid consists of the periciliary and the mucus layer. Hereafter, the mucus layer is modeled with two sublayers (Smith et al. (2007) as described below. We consider the bronchial tree up to its 16th generation and the trachea is defined as generation 0. The total length of the modeled part of the bronchial tree is L. Each generation (s, $s=0\ldots15$) consists of a given number of tubes n (Yeh and Schum, 1980). Mucus height is much less than the diameter of one given tube. Although possible, we currently do not study the case in which a tube is completely obstructed by mucus. We consider the simplified situation in which mucus flow is the same in all tubes belonging to the same generation. The total width of the flow Φ_s is equal to $n\pi d_s$, where d_s is the diameter of the tube (Fig. 1).

Let us now consider the cross-section of mucus flow, consisting of three layers following Smith et al. (2007) (Fig. 2). The lower layer $0<y<h^P$, representing the PCL, is modelled as a viscous fluid with viscosity μ^P. The traction layer region, $h^P<y<h^F$, represents the region of the mucus in which the tips of the cilia penetrate. The upper layer, $h^F<y<H$, represents the mucus above this penetration region. Viscosity in the traction layer and the mucus layer is denoted by μ^M.

The mucus motion in the model occurs due to two forces. The first one is the volume propulsive force f from the cilia, the second

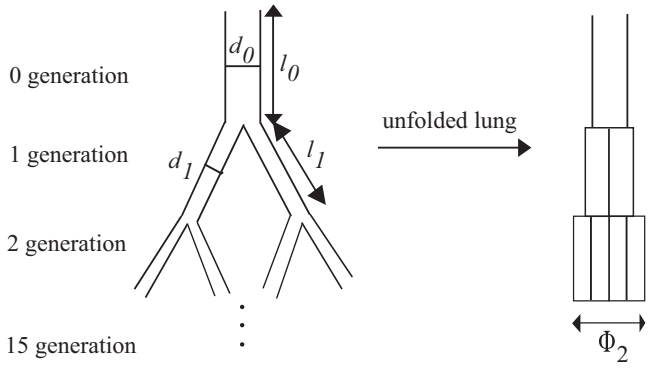

Fig. 1. Schematic representation of the lung.

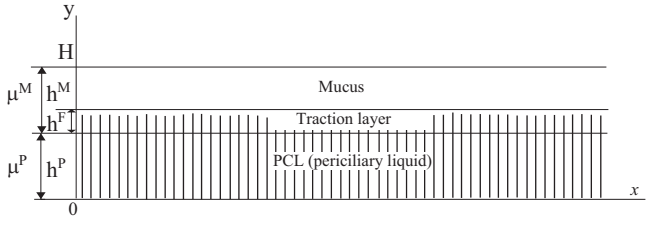

Fig. 2. Schematic representation of the three-layer model. Vertical line segments in the periciliary liquid and in the traction layer represent cilia.

one is the surface force f^P appearing due to viscous friction between the PCL surface and the mucus. We neglect airflow and air drag at the surface of mucus as well as gravity force. The propulsive force is considered similar to Smith et al. (2007). Let us shortly recall its action on the mucus. The mat of cilia resists the flow of mucus in the PCL, somewhat like a porous medium. Therefore, the resistive force is proportional to the mucus velocity u, that is $f_{\text{res}} = -\gamma u$, where γ is the resistance coefficient. Relative motion of mucus and the mat of cilia at each point in space is considered, so that the resistance force is given by the relation $f_{\text{res}} = \gamma(u_{\text{cilia}} - u)$. The propulsive force by the cilia acting on the mucus is described as follows:

$$f = F(\alpha x + \sigma t)\gamma(u_{\text{cilia}} - u), \quad 0 < y < h^F, \tag{1}$$

where $u_{\text{cilia}} = y\sigma\nu C(\alpha x + \sigma t)$ is the cilia velocity, t is the time, α, σ are parameters described below. The resistance coefficient γ is negligible in the PCL layer. The function C takes into account that the effective stroke is five times faster than the recovery stroke (Smith et al., 2007, 2009). The function F represents positive propulsion for one-fifth of the beat-cycle – based on the data of Sanderson and Sleigh (1981) – rising to maximum value and then falling back to zero. The parameter α is the wavenumber $2\pi/\lambda$, where λ is the wavelength, σ is the cilia beat frequency, and ν is the duration of the cilia beat as a fraction of the duration of the effective stroke. The coefficient of resistance is considered as follows: $\gamma = \gamma^M \mu^M$, where

$$\gamma^M = \frac{4\pi}{(\log(d/r_0) - 0.5(d^4 - r_0^4)/(d^4 + r_0^4))d^2},$$

d is the spacing of the cilia, r_0 is the radius of a cilium (Happel, 1959; Smith et al., 2007).

The size of the modeled lung length L is varied between 15 and 25 cm. These values correspond to the lung size in children and adults. The entire mucus clearance process from lower airways to mouth takes several hours. In order to take into account the dependence of mucus clearance on the length L, we introduce the macroscopic model with averaged force and cilia velocity. Instead of cilia velocity u_{cilia} and force f we consider averaged velocity of cilia and force, denoted by $\overline{u}_{\text{cilia}}$ and $\overline{f}$, respectively

$$\overline{u}_{\text{cilia}} = h^P \sigma \nu a, \tag{2}$$

$$\overline{f} = 0.5 a \gamma^M \mu^M (\overline{u}_{\text{cilia}} - u), \tag{3}$$

where a is the averaged parameter (Table 3).

As we described above, two opposite forces act on the mucus layer. The first force is created by the cilia $\overline{f}$ (3), the second force is from the PCL surface layer

$$f^P = \mu^P \frac{\partial u}{\partial y} \approx \mu^P \frac{u}{h^P}. \tag{4}$$

Equating these two forces $f^P = h^F \overline{f}$, we obtain the formula to calculate mucus velocity

$$u = h^P \sigma \nu a \frac{1}{\left(\frac{2\mu^P}{a h^F h^P \gamma^M \mu^M} + 1\right)}. \tag{5}$$

This formula is valid for healthy subjects. However, in subjects with CF the viscosity of mucus increases and the width of the PLC decreases (Button et al., 2012). The traction layer also becomes narrower if mucus viscosity increases, because it is more difficult for cilia to penetrate. Therefore the force exerted by cilia on the mucus decreases and as a resultant mucus velocity decreases (Gerrity et al., 1979). This effect of increased mucus viscosity is approximated, in agreement with experimental data, by linear dependence. Hence we replace (5) by the formula

$$u = h^P \sigma \nu a \frac{1}{\left(\frac{2\mu^P}{a h^F h^P \gamma^M \mu^M} + 1\right)} \frac{\mu_2 - \mu^M}{\mu_2 - \mu_1}, \tag{6}$$

where $\mu_1 < \mu^M < \mu_2$ is the range of mucus viscosity for CF patients. Thus, mucus velocity depends on its viscosity in two ways. For normal values of viscosity, $\mu^M < \mu_1$, mucus velocity increases with viscosity. For the values of viscosity corresponding to CF patients, $\mu_1 < \mu^M < \mu_2$, it decreases. We set $\mu_1 = 80$ cP, $\mu_2 = 1000$ cP (Dawson et al., 2003; Hill et al., 2014; Nielsen et al., 2004).

Let us now consider mucus dynamics in different generations of the lungs. We will describe it in a thin-layer approximation. For simulations we will use a finite-difference method. Let us introduce space discretization along the axis x, $x_i = i\Delta x$, $i = 1 \ldots N$, $\Delta x = L/(N-1)$, where N is the number of nodes. Each node i is characterized by the total width of generation Φ_i, by the quantity of produced mucus J_i by gland cells, by the velocity of mucus u_i and by mucus height H_i. Let us consider equation of mass conservation for the ith element of mesh, $x_i < x < x_{i+1}$, during time $t^n < t < t^{n+1}$

$$\rho H_i^{n+1} \Delta x \Phi_i - \rho H_i^n \Delta x \Phi_i = \rho J_i \Delta t \Delta x \Phi_i + \rho u_{i+1} \Delta t H_{i+1}^{n+1} \Phi_{i+1} - \rho u_i \Delta t H_i^{n+1} \Phi_i, \tag{7}$$

where ρ is the density of mucus which is assumed to be constant, Δt is a time step , $t^n = n\Delta t$, n is the number of time step. The first term in the right-hand side of Eq. (7) represents the mass of mucus produced in the ith element, the second term represents the mass of mucus coming through the right boundary of ith element, the third term corresponds to the mass of mucus going out through the left boundary of this element. The total variation of mass of mucus during one time step is presented in the left-hand side of the equation. In the limit ($\Delta x \to 0$, $\Delta t \to 0$) we obtain the conventional thin-layer equation

$$\Phi \frac{\partial H}{\partial t} = \Phi J + \frac{\partial (uH\Phi)}{\partial x}. \tag{8}$$

Similarly to the previous Eq. (8), we obtain the equation of mucus viscosity changing along the axis. In every part of the lung, there is a mixture of mucus produced in the goblet cells and mucus coming from the previous generations. Therefore, the

mucus viscosity can be described as follows:

$$\Phi\frac{\partial\mu^M H}{\partial t}=\Phi J\mu_0^M+\frac{\partial(u\mu^M H\Phi)}{\partial x}. \quad (9)$$

We note that the first term in the right-hand side of this equation represents the volume of mucus produced by goblet cells with the given viscosity μ_0^M. The value of parameter J in Eqs. (8) and (9) representing the quantity of mucus produced by goblet cells and submucosal cells is not the same in the different lung generations. In humans such cells are not homogeneously distributed and their number decreases from central down to peripheral generations (Cerkez et al., 1986). We take this effect into account by a linear decrease in their number. Therefore J also decreases from the 0th to the 15th generations. The value of J is adjusted to obtain the total mucus production 100–150 ml per day (Waldron, 2007).

In the following section, when simulating CF patients, we suppose that mucus produced by goblet cells and submucosal glands has initially increased viscosity which corresponds to the severity of CF. To our knowledge, there is no data showing whether the mucus produced initially has normal or increased viscosity. Recent studies show that relative lack of bicarbonate secretion by CFTR channel in CF leads to improper unfolding of secreted mucins, leading to dense and impermeable mucus (Gustafsson et al., 2012).

Table 1
Simulated TMV in CF subjects of different severities.

Viscosity (cP)	TMV (mm/min)
92	5.24
108	4.8
167	3.6
198	3
257	2.4
369	1.63
494	1.01

Table 2
Comparison of simulated TMV in CF subjects with observed data in humans.

TMV mean (SD) mm/min	Ref/comment
3.45 (1.74)	Simulations
2.60 (3.30)	Wood (1975) from Elkins et al. (2005)
3.42 (3.58)	Yeates (1976) from Elkins et al. (2005)
0.37 (3.16)	Wong (1977) from Elkins et al. (2005)

3. Results

We use the model described above to study treatment of CF with the aerosolized medication, dornase alfa. We calculate mucus velocity and decrease of mucus quantity in the lung as a result of dornase alfa action. In order to validate the model we compare simulated tracheal mucous velocity (TMV) with results observed in humans (Elkins et al., 2005). Simulated TMV for healthy subjects with viscosity of μ_{min} is 6.6 mm/min. This result is in a good agreement with the mean TMV in previous studies (Elkins et al., 2005), where TMV ranged between from 3.6 and 8.9 mm/min. Viscosity value for healthy subjects is taken from the work by Feather and Russell (1970). The results obtained with the model described above show that TMV is lower in subjects with CF than in healthy subjects (Elkins et al., 2005). We simulated different severities of CF disease by varying mucus viscosity. Results are presented in Table 1. They are in a good agreement with data observed in CF subjects in clinic (Table 2). All parameter values used in the simulations are presented in Table 3.

The drug dornase alfa breaks down the long DNA strands that accumulate in stagnant mucus, thus decreasing its viscosity. In Shak et al. (1990) the authors observe an exponential relation between DNA viscosity and dornase alfa dose. However, the exact quantitative effect of dornase alfa on the viscosity of CF mucus in patients is not known. We introduce in the model the effect of dornase alfa on the viscosity of CF mucus with the function $\mu_0^M e^{-kx}$, where μ_0^M is the initial mucus viscosity before application of the drug, x is the drug mass per unit of mucus volume in the airway generations where the drug is deposited. Parameter k characterizes the rate of viscosity decrease as a function of drug concentration. Because the exact value for k is not known, we will study the influence of treatment for different values. We assume that the drug penetrates the entire mucus layer where it is deposited.

Another aspect of treatment that should be considered in the model is the deposition pattern of particles of inhaled drug in the lung. Numerous conditions influence this deposition, among them particle size plays an important role. It is known that large particles (larger than about 2 μm) have significant momentum and are more often deposited by impaction in the larger airways. Particles with sizes between 1 μm and 2 μm are mostly deposited by sedimentation in smaller conductive airways. Finally, particles

Table 3
Basic parameter values.

Parameter		Value	Unit	Ref/comment
	PCL			Smith et al. (2007)
h^P	Depth of the PCL	5.5e−006	m	
μ^P	Viscosity	1	cP	
	Traction layer			Smith et al. (2007)
h^F	Depth of the traction layer	5e−007	m	
	Mucus layer			Dawson et al. (2003), Hill et al. (2014), and Nielsen et al. (2004)
μ_1	Viscosity	80	cP	
μ_2	Viscosity	1000	cP	
	Cilia			Smith et al. (2007)
a	Average constant value of cilia force	0.22		
σ	Cilia beat frequency	60	rad s^{-1}	
ν	Sublayer velocity scaling	0.83		
	Drug			
	Total applied drug dose of dornase alfa	2.5	mg	

with diameters between 0.1 and 1 μm are deposited by sedimentation and/or diffusion in peripheral airways (Gerrity et al., 1979; Lippmann, 2011). Particle deposition can be patient specific, depending also on airway obstruction. In this work we model different severities of the disease with different mucus viscosities, but we suppose that there is no complete obstruction of lung airways and as a consequence aerosol particles will reach all considered generations.

Hereafter we present the process of mucus clearance as a result of the drug action (Fig. 3). When there is no drug applied, mucus height reaches its steady state in each patient with a given viscosity of mucus. There is no evolution of the disease due to the short timeframe considered in this model. This steady state in one simulated patient is represented by the black curve, which resembles a step function (Fig. 3a). Each step corresponds to one lung generation starting from the trachea on the left. As previously mentioned we assume a linear decrease of mucus production J by goblet cells and submucosal glands from trachea to the peripheral generations and we thereby distinguish 16 different values of J, depending on the generation. Therefore we observe a step-wise decrease of mucus height from one generation to another. The length of all generations is normalized by dividing it by the total length of the airways. After drug action, the mucus viscosity decreases and the velocity of mucus clearance increases. Evolution of mucus height, measured at different time points, is presented in Fig. 3a. We can observe that mucus height increases about 5–7 times compared to the steady state before being expulsed from trachea (gray point-dashed curve) due to conservation of matter. This increase of mucus height is observed in all simulations. In this study we do not consider the case with complete obstruction of the airway. We consider the simplified situation in which mucus flow is the same in all tubes belonging to the same generation. Therefore, an obstruction of one generation would mean total occlusion of the lung. After mucus is cleared we observe about a 10-fold decrease of mucus height in the trachea (gray solid curve). At the end of drug action, the system returns to its steady state condition due to continuous production of viscous mucus by goblet cells and submucosal glands.

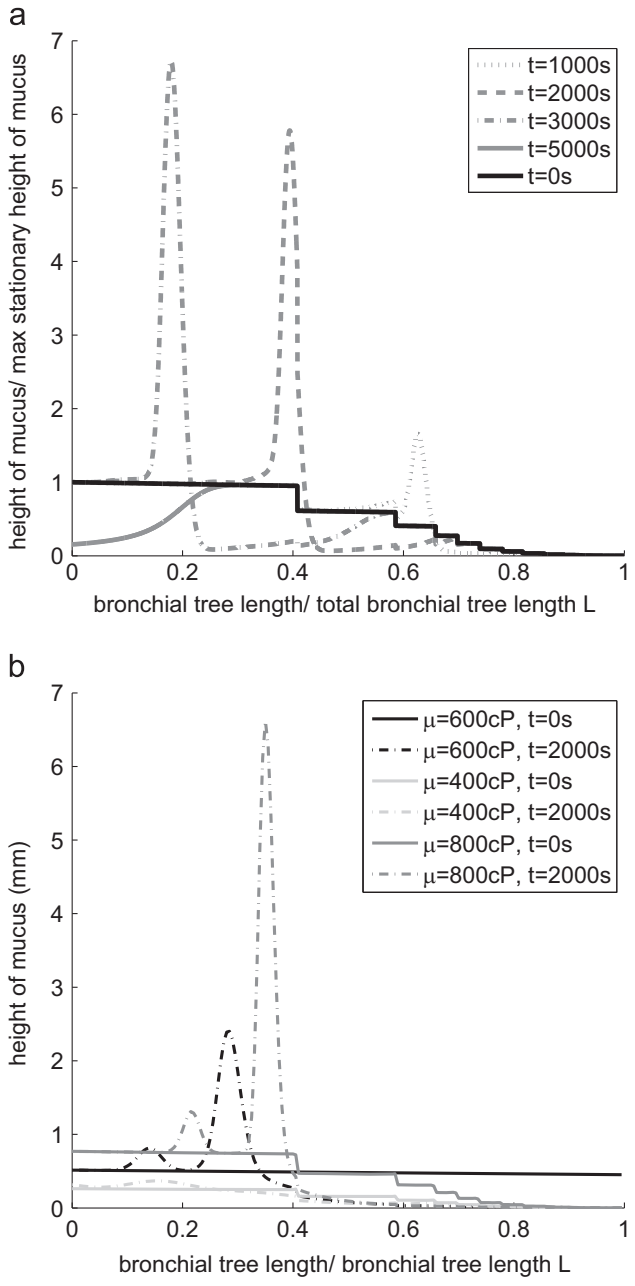

Fig. 3. (a) Evolution of mucus height after drug action in one patient. Initial mucus viscosity is 126 cP. Without drug action ($t=0$) mucus height reaches a steady state (black line). After drug action, mucus viscosity decreases and velocity of mucus clearance increases. Evolution of mucus height, measured at different time points, is presented. The length of all generations is normalized by dividing it by the total length of the airways L (x-axis). In the y-axis we present the height of mucus divided by its maximum height in the stationary case. (b) Comparison of mucus height in simulated patients with different mucus viscosities measured at the same time points after drug administration. Solid and dashed curves represent mucus height in these patients before and after action of the drug, respectively.

Next, we compare mucus height in simulated patients with different mucus viscosities measured at the same time points after drug application (Fig. 3b). Solid curves represent mucus height in these patients before the action of the drug. Mucus is higher in patients with more severe CF lung disease. We also notice that in more severely affected subjects mucus is transported slower (pointed curve) than in less severely affected subjects (dash-pointed curve).

Further, we consider two different modes of inhaled particle deposition in the lung. In the first mode we suppose that the largest mass of the drug is deposed in the proximal generation 0 and that the mass of deposited drug linearly decreases towards the peripheral generations. It becomes 0 in the 15th generation. Let us call it mode I. On the contrary, in the second mode we consider a linear increase from proximal to the peripheral lung airways. We will call it mode II.

Numerical simulations of drug action can be characterized by the maximal decrease of the total mucus quantity (MD) and by the duration of drug action (DDA). The DDA corresponds to the time which is needed to evacuate the mucus from the 16th generation to the mouth. Therefore when all other parameters remain fixed, each simulation corresponds to one point on the MD-DDA plane. If we vary the relative lung length L and the initial mucus viscosity μ_0^M, then we obtain two families of curves on this plane. Fig. 4 shows these sets of simulations for the mode I (proximal drug deposition) for two different values of k. Each curve in Figs. 4 and 5 corresponds to a set of simulations where one parameter is varied while other parameters are fixed. The upper curves with filled triangular points correspond to the fixed relative lung length, $L=1.2L_0$ ($L_0=25$ cm) and for different values of the viscosity μ_0^M which vary from 80 to 1000 cP. Relative viscosity equal to zero corresponds to 80 cP and equal to 1 corresponds to 1000 cP. The lower curves with unfilled triangular points correspond to the relative lung length 0.7. In the family of perpendicular curves, the initial mucus viscosity is fixed and the relative lung length is varied.

If we fix the relative lung length and increase the initial mucus viscosity, then both characteristics of treatment, MD and DDA,

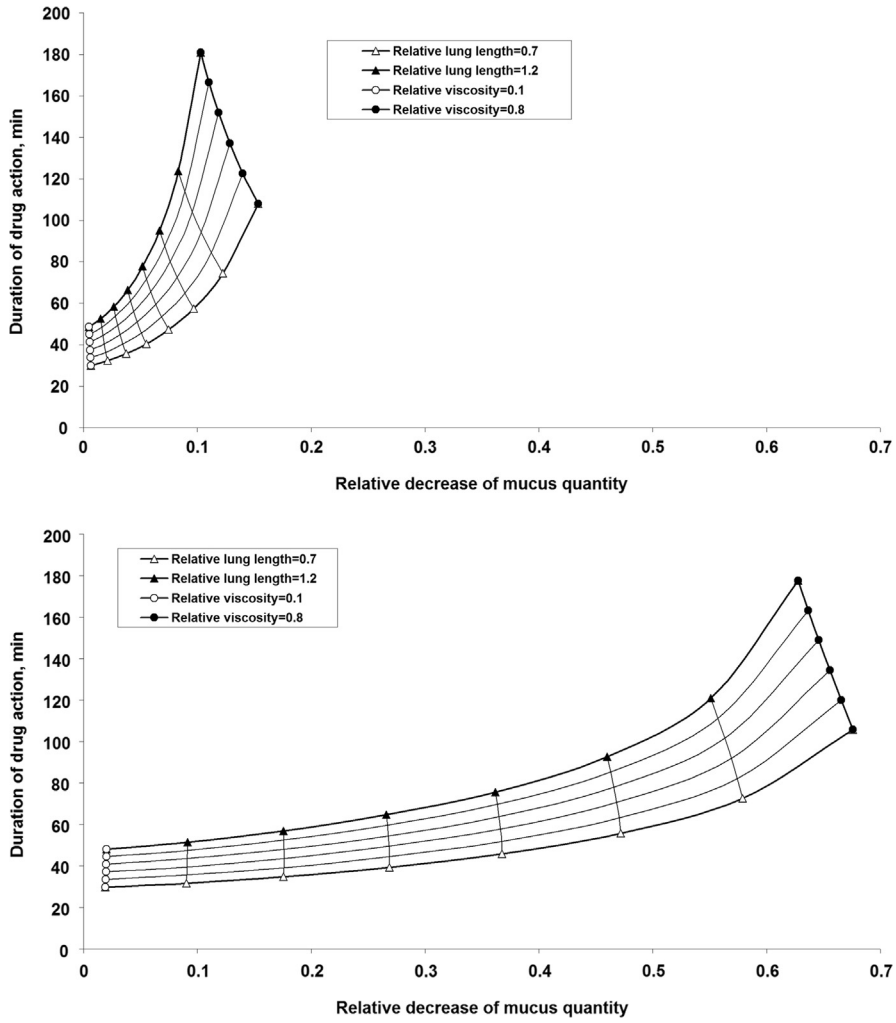

Fig. 4. Simulations of drug action are characterized by the maximal decrease of the total mucus quantity (MD) and by the duration of drug action (DDA). Each point on the MD-DDA plane corresponds to one simulation. When we vary the relative lung length and the initial mucus viscosity, we obtain two families of curves for $k=0.05$ (upper figure) and for $k=2$ (lower figure). In both cases, proximal drug deposition is considered. More explanations are given in the text.

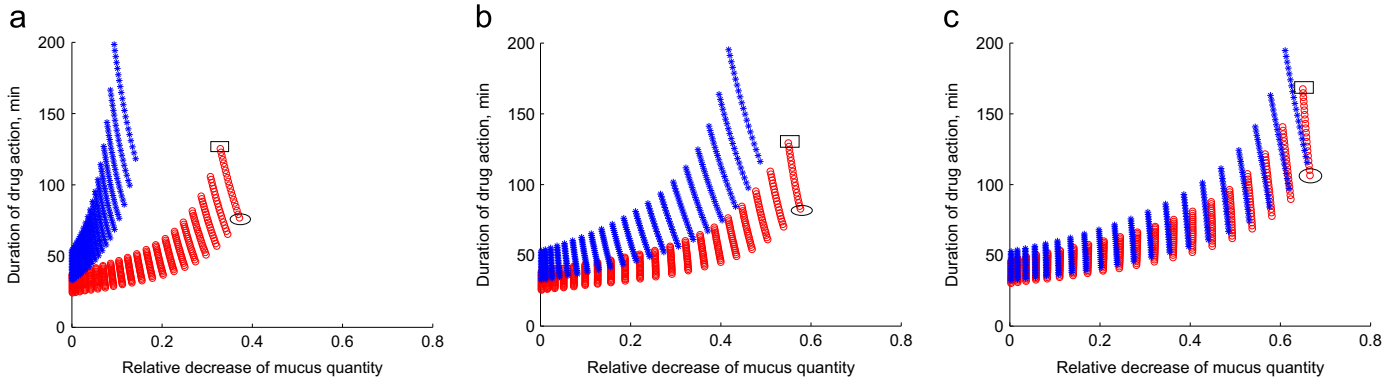

Fig. 5. The same presentation of the simulations as in Fig. 4. Each vertical curve represents a set of simulations where the relative lung length is varied and all other parameters are fixed. Different curves correspond to different values of mucus viscosity. Blue asterisks correspond to aerosol particle deposition mostly in proximal parts of lungs (mode I), red circles correspond to aerosol particle deposition mostly in peripheral parts (mode II). Black rectangles represent the tallest patients, black ellipses represent the shortest patients. (a), (b), and (c) show the relationship between drug deposition mode, time of drug action and relative decrease of mucus quantity, respectively. Parameter k represents different relations of mucus viscosity with dornase alpha concentration. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

increase. This result has a clear biophysical meaning. In case mucus is highly viscous, there will be a stronger decrease in viscosity due to the drug effect; therefore the relative decrease of the mucus quantity is also greater. On the other hand, more viscous mucus moves slower, and time needed to evacuate it increases. Therefore the duration of drug action also increases.

Let us now fix the initial mucus viscosity and increase the relative lung length from 0.7 to 1.2. Then the duration of drug

action increases while the maximal decrease of the total mucus quantity decreases.

Next, we compare two different values of the parameter k, which characterizes how mucus viscosity depends on drug concentration. The main difference between $k=0.05$ (upper image in Fig. 4) and $k=2$ (lower image) is that the relative mucus quantity decrease is much larger for the latter. It is an expected result since the mucus viscosity has a stronger decrease for greater values of k.

We will now compare two modes of drug deposition. We will use the same characterization of simulations. We measure the relative decrease of total mucus quantity in the lungs after drug action corresponding to one inhalation session of dornase alfa. Decrease of total mucus quantity signifies an increase in mucus clearance. With relatively small values of parameter k the model shows that inhaled particles deposited in the peripheral parts of the lung strongly increase the mucus clearance compared to particles deposited mostly in trachea and proximal regions (Fig. 5a). However, with augmentation of parameter k the difference between two deposition modes of aerosol particles becomes less pronounced (Fig. 5b) and finally almost disappears (Fig. 5c). This can be explained by the fact that with increasing values of parameter k mucus viscosity decreases greatly as a result of the drug effect, and a plateau of the effect is reached even for small quantities of the drug. In this situation, small quantities of drug deposited in the peripheral airways with mode I have almost the same efficacy as with mode II. This is further illustrated by the fact that the relative decrease of total mucus quantity (x axes of Fig. 5) becomes higher for both deposition modes when the value of parameter k increases. Results show that using mode II deposition, the mucus from the 16th generations is evacuated more rapidly compared with mode I. It is also noticeable that in the tallest subjects the relative decrease of total mucus quantity in the lungs after drug action is less than in the shortest subjects (Fig. 5a). It can be explained by the constant quantity of the administrated medication in all patients, despite differences in age and height. We conclude that the model confirms that administered medication dose should be age specific.

4. Conclusions

We have developed a new model of mucociliary clearance in patients with CF. This model takes into account mucus influx from previous generations and its production by submucosal glands and goblet cells. Characteristic size of the modeled lung (up to the sixteenth generation) is 25 cm and characteristic time of mucus clearance process is several hours.

In order to decrease the simulation time we introduced a global model with averaged force and cilia velocity. PCL and mucus layer are both considered as a Newtonian fluid. We do not take into account gravity force and air drag on the surface of mucus. However, increased airflow as well as muscular contraction of the lungs should be considered during coughing, which was not included in this study. These questions will be studied in the subsequent works.

The model output of tracheal mucus velocity showed good correlation with previous clinical data. We modeled the effects of inhaled dornase alfa on mucus viscosity and mucus clearance. This approach can be used to model the effects of drugs in virtual clinical trials, in order to efficiently optimize multiple aspects of a trial (e.g. protocol of drug administration, medication dose, dosing interval, trail design, trial duration, sample size), before performing a clinical trial in real patients.

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