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Toward the modeling of mucus draining from the human lung: role of the geometry of the airway tree

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Abstract

Mucociliary clearance and cough are the two main natural mucus draining methods in the bronchial tree. If they are affected by a pathology, they can become insufficient or even ineffective, then therapeutic draining of mucus plays a critical role to keep mucus levels in the lungs acceptable. The manipulations of physical therapists are known to be very efficient clinically but they are mostly empirical since the biophysical mechanisms involved in these manipulations have never been studied. We develop in this work a model of mucus clearance in idealized rigid human bronchial trees and focus our study on the interaction between (1) tree geometry, (2) mucus physical properties and (3) amplitude of flow rate in the tree. The mucus is considered as a Bingham fluid (gel-like) which is moved upward in the tree thanks to its viscous interaction with air flow. Our studies point out the important roles played both by the geometry and by the physical properties of mucus (yield stress and viscosity). More particularly, the yield stress has to be overcome to make mucus flow. Air flow rate and yield stress determine the maximal possible mucus thickness in each branch of the tree at equilibrium. This forms a specific distribution of mucus in the tree whose characteristics are strongly related to the multi-scaled structure of the tree. The behavior of any mucus distribution is then dependent on this distribution. Finally, our results indicate that increasing air flow rates ought to be more efficient to drain mucus out of the bronchial tree while minimizing patient discomfort.

Introduction

The wall of the conductive part of the respiratory tract is lined up with an epithelium which plays a protective role in absorbing, filtering or excreting different types of molecules. The airway surface liquid layered on the epithelium consists in a thin sol layer (periciliary liquid layer) and a mucus layer. As part of the epithelium, the goblet cells secrete the layer of mucus that is the first barrier of protection against external aggressions since it captures the aero-contaminers [1, 2]. Mucus is a heterogeneous fluid that consists mainly of water and biopolymer [2]. It is moved upward toward the oropharyngeal bifurcation thanks to the motion of the cilia. This phenomenon is called the mucociliary clearance [4–6] and has already been the subject of micro-scale models in the past [2, 7, 8]. Cilia stand on the ciliated cells which are the most frequent cells in the bronchia epithelium [3]. Mucus is not excreted homogeneously along the bronchial tree, because the

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density of goblet cells decreases from the proximal parts to the distal parts. In particular, they are not present in the terminal bronchioles (from the 16th generation) and consequently in the alveoli [9, 10].

Under pathological conditions, mucus characteristics and mucociliary clearance efficiency can be altered. For example ciliary movement can become ineffective, for instance with a modification of mucus viscosity or with cilia degradation; this induces mucus stasis that often leads to infections [3]. Cough has also a role to play in mucus clearing [11–13] and protects from hypersecretion by preserving normal air flow rates, but its effects are efficient only for relatively healthy adults. Actually, cough has a low efficiency for aged adults or adults with strong chronic respiratory failures. Cough is immature for small children, the proportion of children able to spontaneously evacuate mucus increases with age but is smaller than 10% at the age of six and does not reach 12% at twelve [14]. Actually, the proportion of goblet cells in children is proportionally larger than for adults but bronchi diameters are smaller and the muscular command remains weak. Cough is less efficient than for adults, and bronchial obstructions often happens and induce serious respiratory failures.

In normal condition, the regime of ventilation plays an important role on mucus characteristics and clearance [15]. Airflow stresses can produce transepithelial fluid flow and improve mucus hydration, thus changing its viscosity and yield stress. Airflow stresses can also alter mucociliary clearance, for example clearance efficiency is decreased during sleep and increased during exercise. Hence, ventilation rate plays an important role on mucus evacuation. This observation has greatly influenced the therapeutic strategies of physical therapists since it is the base of their technique of expiratory flow modulation that ought to favor expectoration [16]. Although the efficiency of these techniques has been validated clinically for years, as of today they lack a true scientific insight from a biophysical point of view. Indeed interesting studies have been made in tube-like geometries [17–19] or with a few generations [20]. But these studies did not take into account the multi-scaled structure of the lungs which plays an important role in the inner fluid dynamics [21] and must largely interfere with mucus distribution and clearance. Moreover, to our knowledge, no study has ever tried to model the consequences of the manipulation of physical therapists.

Hence, the model we build in this work is a first step toward a global model of mucus draining in the lungs. We take into account some of the most important features of the system: the geometry, the mucus properties and the amplitudes of air flux rate. In the following, we will first describe the geometry of our model and the air and mucus dynamics modeling. Next, we describe the analytical and numerical methods used to solve the physical equations. Then we will study mucus distribution in the tree when it is at equilibrium with air flow and when it is moved up the generations during the transitory regime.

Modeling

Geometry

Lung has about twenty-four generations of bronchi that can be divided into two distinctive parts: a conductive region (eighteen first generations), where pulmonary air circulates with a quasi unaffected gas composition, and an exchange region called the acinus that corresponds to the last six generations and where exchanges with blood take place. Most of the alveoli are located in the subacinus that corresponds to the last four generations [22]. Moreover, while diameters are decreasing regularly in the conductive region, they stay almost constant in the acinus [22]. The alveoli contribute about 90% of the total lung volume, and most of the change of lung volume during ventilation is due to the change of volume of the alveoli [22]. Thus, we can consider that air circulation is induced by the change of volume of the 300 millions of alveoli in the last generations.

Very little mucus is present in the deepest bronchi [9, 10] that consist mostly in an assemblage of alveoli. This indicates that mucus draining occurs only from generation zero to generation seventeen. Consequently, the contribution of the deepest part of the lungs to the model was limited to their role on the flow in the tree.

The models of the lungs used in this work assume that the lung is a cascade of cylinders associated in a dichotomous tree of N generations (typically $N = 18$, numbered from 0 to 17). It also assumes that branches bifurcate symmetrically. Because all branches of a given generation are identical, it is sufficient by symmetry to consider only one branch at each generation with an adequate flow rate. We call $r_{b,i}$ the radius of a bronchi in the ith generation and $l_{b,i}$ its length. We will neglect inertial effects in both air flow and liquid flow because they are mostly present only in the largest bronchi [23], consequently the symmetric branching induces that air flow is divided by two at each bifurcation.

At some point, a more precise description of the tree geometry is needed to reach further predictions. In this case, we assume that the tree geometry obeys a scaling law, which is a typical assumption for lung modeling [21]. Each time a branch is bifurcating, the radius and length of its daughter branches are reduced by a constant homothetic ratio $h < 1$. Consequently, the diameters and length of the branches only depend on their generation index and on the sizes of the first generation branch. Thus, if the branch of the first generation (trachea) has a radius $r_{b,0}$ and a length $l_{b,0}$, then the radius of a branch of the ith generation is $r_{b,i} = r_{b,0}\ h^i$ and its length is $l_{b,i} = l_{b,0}\ h^i$. Such a tree is known to be a good first approximation model for the lungs [21, 24–26].

Air and mucus mechanics in a bronchus

We assume that air and mucus velocities are axi-symmetric in all the bronchi. Each bronchi is framed with cylindrical coordinates (r,θ,z) where (z) axis is the axis of the cylinder and (r,θ) parameterize the circular section of the bronchi. Although it is known that air Reynolds number can be up to 1000 at rest in the trachea [21, 23], air and mucus inertia is

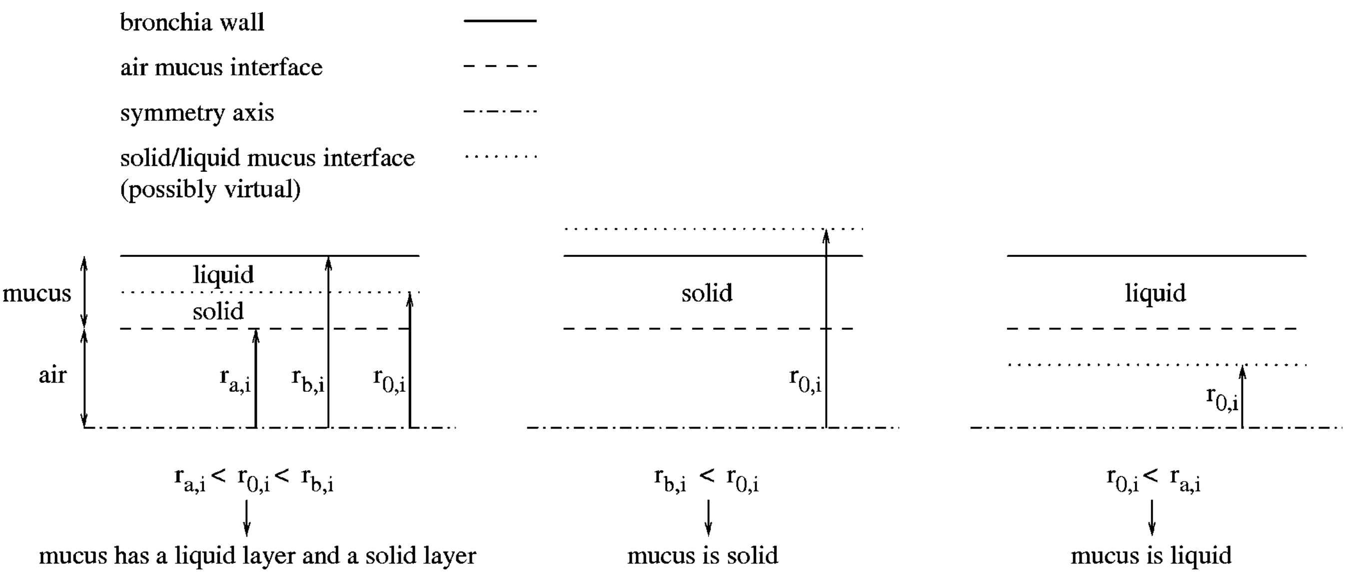

Figure 1. Bronchi i is assumed axi-symmetric and a layer of mucus stands on its wall. Mucus can either be divided into two layers (one liquid and one solid) or be fully solid or be fully liquid. Its state depends on the relative localization of the bronchi radius $r_{b,i}$, the air/mucus interface radius $r_{a,i}$ and the radius of solid/liquid interface of mucus (which can be virtual if all the mucus is solid or liquid). In the case of the existence of a solid and a liquid layer of mucus, the liquid part is always in the region with higher shear rates, i.e. closer to the bronchia wall.

neglected in our model for the sake of simplicity. Because of axi-symmetry and fully developed flow hypotheses, the fluids velocities have only a z component and depend only on the radial r coordinate.

In each bronchus, the thickness of the layer of mucus is assumed constant (independent of z and θ). The geometry and the different radii involved are depicted in figure 1. We recall that $r_{b,i}$ is the radius of a bronchi of the ith generation and $l_{b,i}$ is its length. The radius $r_{a,i}$ is the radius of the air lumen area of the bronchi or of the position of the air/mucus interface (the thickness of mucus is $r_{b,i}$–$r_{a,i}$). The virtual tree whose branches diameter are $r_{a,i}$ is called the *effective tree*, it is the tree that contains air. The radius $r_{0,i}$ is the radius that separates the liquid phase of mucus and the solid phase of mucus (see below), $r_{0,i}$ can be virtual if it is not in the range $[r_{a,i}, r_{b,i}]$.

In a bronchus, the general equations of mechanics of an incompressible fluid in permanent regime and zero Reynolds number (no inertia) are

$$\mathrm{div}(\Sigma) = 0 \quad \text{and} \quad \mathrm{div}(V) = 0, \tag{1}$$

where Σ is the tensor of the inner stress of the fluid and V its velocity. The inner stresses consist in the sum of the pressure stress (tensor $-pI$) and of the viscous stress. Since we assume that the velocity depends only on r and has only a component v along z, the sole non-zero viscous stress component is $\Sigma_{zr} = \Sigma_{rz}$ and corresponds to a shear stress. Under these hypotheses, equation (1) shows that pressure depends only on the z coordinate and in a linear way, consequently $C_i = \partial p/\partial z$ is a constant in each bronchus of generation i. Finally, equation (1) can be reduced to

$$-\frac{1}{r}\frac{\partial}{\partial r}(r\Sigma_{zr}) + \frac{\partial p}{\partial z} = 0.$$

By integration of this last equation between 0 and r, it becomes (denoting $C_i = \partial p/\partial z$ in a bronchus of generation i)

$$\Sigma_{zr} = \frac{C_i r}{2}. \tag{2}$$

Now it is necessary to determine the tensor of the viscous stress Σ_{zr} depending on the fluid considered. Air is a Newtonian fluid with viscosity μ_a; its viscous shear stress Σ_{zr} is

$$\Sigma_{zr} = \mu_a \partial v/\partial r \qquad (\text{air, for radii } r \text{ such that } 0 \leqslant r \leqslant r_{a,i}). \tag{3}$$

We will assume that mucus is a non-Newtonian Bingham fluid. This hypothesis is a well-known approximation of the physical behavior of mucus which behaves like a gel for low range of shear stress [7, 27, 28]. Such a fluid behaves like a solid if shear stress is smaller than a threshold value σ_0 (yield stress) and becomes a fluid with viscosity μ_m if the shear stress is larger than this threshold (see figure 2). Thus, Bingham fluid is liquid when $\Sigma_{zr} > \sigma_0$, and its viscous shear stress Σ_{zr} as a fluid is

$$\Sigma_{zr} = \sigma_0 + \mu_m \partial v/\partial r$$
$$(\text{liquid mucus, for radii } r \text{ such that } r_{0,i} \leqslant r \leqslant r_{b,i}). \tag{4a}$$

Bingham fluid is solid when $\Sigma_{zr} \leqslant \sigma_0$ and being solid implies that all its points are moving at the same velocity, i.e.

$$\partial v/\partial r = 0$$
$$(\text{solid mucus, for radii } r \text{ such that } r_{a,i} \leqslant r \leqslant r_{0,i}). \tag{4b}$$

The yield stress σ_0 represents a fundamental parameter from a physiological point of view: if the viscous forces per unit of area σ are below this value, no more mucus flow can be induced. Equation (2) shows that a radius threshold can be associated with the shear stress threshold, this radius is referred

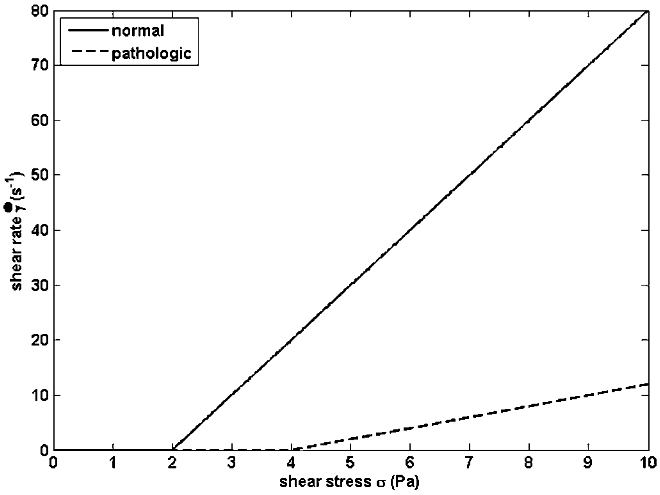

Figure 2. Example of a Bingham fluid model. When the shear stress σ is too small, Bingham fluid behaves like a solid and remains motionless (shear rate or velocity gradient $\dot{\gamma} = \partial v/\partial r = 0$), but when shear stress reaches the yield stress σ_0 (here 2 Pa for normal case and 4 Pa for pathologic case), Bingham fluid starts to flow and its shear rate $\dot{\gamma}$ depends linearly of the shear stress. In this example, the pathological case viscosity is five times larger than the normal case viscosity (0.1 Pa s). Thus, the pathological case needs more shear stress than the normal case to reach the same value of shear rate.

to by $r_{0,i}$ in the bronchus i; it is equal to $|2\sigma_0/C_i|$. When $r_{0,i}$ is larger than $r_{b,i}$, the whole mucus layer remains solid and mucus is not flowing; in contrast, when $r_{0,i}$ is smaller than $r_{a,i}$, the whole mucus layer is liquid and is flowing. When $r_{0,i}$ is larger than $r_{a,i}$ but smaller than $r_{b,i}$, the mucus layer is divided in two sub-layers: the first sub-layer, closest to the branch wall, is liquid and is flowing; the second sub-layer is solid and is gliding on the first sub-layer. The different situations are depicted in figure 1.

The interaction between air and mucus occurs at their interface, where shear stress and velocity are continuous between air and mucus. Finally, we can estimate boundary conditions for mucus velocity on bronchus wall, at the interface between mucus and the cilia layer. Boundary cilia layer velocities have been reported in the literature to be about 10 μm s^{-1} [8]; however, cilia excitation is known to depend on the position in the bronchial tree and on the regime of ventilation [5, 6]. Practically, this velocity remains very small comparatively to the velocities implied by air flow and can thus be set to zero in our model.

In order to solve these equations in a bronchus of generation i, we have to determine $C_i = \partial p/\partial z$ and the thickness of mucus in the bronchus. These quantities are determined in the next section thanks to flow conservation of air and mucus in the full tree.

Flows conservation of mucus and air in the tree structure

In the preceding section, we have written the equations for air and mucus that define their velocity fields in a bronchus as soon as the pressure drop per unit length and the thickness of mucus in the bronchus are known. To go on, pressure drops per unit length and mucus thicknesses have to be calculated in each bronchus. Both are determined by air and mucus flow conservation in the tree bifurcations.

Pressure drops per unit length. Pressure drops are not easily measured in the lungs and cannot be used directly in our model. We choose to work with total air flow in the tree instead. Total air flow Φ_A corresponds to the amount of air that gets out of the mouth each second. This quantity is used on a daily basis for diagnostics by practitioners and thus is easily accessible.

In a bifurcation of our model, air flow in a daughter branch is half the air flow in the mother branch because of the branching symmetry and air flow conservation. So the knowledge of total air flow Φ_A (at mouth level) is sufficient to determine the air flow $\Phi_{A,i}$ in each bronchus of generation i in the tree:

$$\Phi_{A,i} = \frac{\Phi_A}{2^{i-1}}. \tag{5a}$$

The fluid equations (2)–(4a) and (4b) show that we have a one to one correspondence between pressure drop per unit length and air flow in a bronchus; thus, the knowledge of air flow in a bronchus is sufficient to determine the pressure drop per unit length C_i in that bronchus, as soon as we know mucus thickness in that bronchus:

$$C_i = F(\Phi_{A,i}, r_{a,i}). \tag{5b}$$

The function F has an analytical expression (see appendix).

Mucus thicknesses. The thickness of mucus in a bronchus of generation i is determined by the radius of air lumen area $r_{a,i}$ since mucus thickness is equal to $r_{b,i}$–$r_{a,i}$ (see figure 1). The air lumen area radii in the tree $(r_{a,i})_{i\,=\,1,\ldots,N}$ have to be determined from mucus flow conservation in the tree. Under the influence of airflow, mucus is motioned in bronchi and its thicknesses evolve with time following a transitory dynamics we will study. Each $r_{a,i}$ is thus a function of time. The volume of the mucus in a bronchus of generation i is equal to

$$V_m^{(i)}(r_{a,i}) = \pi\left(r_{b,i}^2 - r_{a,i}^2\right) l_{b,i}. \tag{6a}$$

The variation of the volume of mucus per unit time in a bronchus of generation i is equal to the balance of the flow of mucus that gets in and out of the bronchus. The mucus that gets in is the mucus that gets out of its two daughter branches (whose generation is $i + 1$). We call $Q_{\mathrm{out}}^{(k)}(r_{a,k})$ the flow of mucus that gets out of a bronchus of generation k, this flow is a function of the radius of the air lumen area in that generation $r_{a,k}$. Then

$$\begin{aligned}\frac{\mathrm{d}V_m^{(i)}(r_{a,i})}{\mathrm{d}t} &= -2\pi\, l_{b,i}\, r_{a,i} \frac{\mathrm{d}r_{a,i}}{\mathrm{d}t} \\ &= -Q_{\mathrm{out}}^{(i)}(r_{a,i}) + 2.Q_{\mathrm{out}}^{(i+1)}(r_{a,i+1}).\end{aligned} \tag{6b}$$

The flow of mucus in a bronchus of the ith generation is calculated by integration of the z-component of its velocity

$v_i(r)$ between the radii $r_{a,i}$ and $r_{b,i}$ (where mucus stands, see figure 1), i.e.

$$Q_{\text{out}}^{(i)}(r_{a,i}) = 2\pi \int_{r_{a,i}}^{r_{b,i}} v_i(r) r \, \mathrm{d}r. \tag{6c}$$

The velocity v_i is calculated from the fluid equations (2)–(4*a*) and (4*b*). Although v_i is a function of $r_{a,i}$, this is not shown in the equation to ease reading. The flow of mucus that gets out of the tree is represented by $Q_{\text{out}}^{(0)}$. No mucus comes out of the acini, thus $Q_{\text{out}}^{(18)} = 0$.

Finally, equations (6*a*)–(6*c*) lead to a set of N equations (one for each generation) which determines all $r_{a,i}$ and consequently all mucus thicknesses in the tree:

$$\begin{cases} \dfrac{\mathrm{d}r_{a,i}}{\mathrm{d}t} = \dfrac{Q_{\text{out}}^{(i)}(r_{a,i}) - 2 \cdot Q_{\text{out}}^{(i+1)}(r_{a,i})}{2\pi \, l_{b,i} \, r_{a,i}} & (7a) \\ Q_{\text{out}}^{(i)}(r_{a,i}) = 2\pi \displaystyle\int_{r_{a,i}}^{r_{b,i}} v_i(r) r \, \mathrm{d}r. & (7b) \end{cases}$$

Equation solutions

For each bronchus, we need to solve the system of equations (2), (3), (4*a*) and (4*b*), (5*a*) and (5*b*) and (7*a*) and (7*b*) to find the air lumen area radii $r_{a,i}$ that gives mucus distributions in the tree. These equations stand for generation i and are all coupled together. Moreover, generations are also coupled two by two in equation (7*a*): the mucus that gets out of generation $i + 1$ enters generation i.

Mucus dynamics behavior. We study how an initial distribution of mucus thicknesses in the tree evolves with time when it is submitted to a given airflow at mouth level. The system of equations (2), (3), (4*a*) and (4*b*), (5*a*) and (5*b*) and (7*a*) and (7*b*) is a system of differential equations in which the unknown is the time dependent function $r_{a,i}(t)$. An initial condition at $t = 0$ is needed to solve the time-dependant equations; we assume that bronchi are initially almost completely filled with mucus: $r_{a,i}(t = 0) = 0.1 \; r_{b,i}$. A given total air flow rate has also to be provided and can be time-dependent. To solve the system, we built a numeric function that evaluates the right-hand side of equation (7*a*) for any $r_{a,i}$ given, then we integrated the system of differential equations with a Runge Kutta 45 method (Matlab function *ode45*).

Equilibrium states of mucus layers. Time-independent mucus distributions are temporal equilibriums of mucus layers thicknesses. These distributions correspond to limit-distributions reached with the dynamic case when mucus is submitted to a constant airflow for a relative long time. When mucus has reached this state, it cannot be moved anymore except by an increasing of the amount of airflow. To compute these equilibriums, we used the same equations (2), (3), (4*a*) and (4*b*), (5*a*) and (5*b*) and (7*a*) and (7*b*) but with $r_{a,i}$ independent of time, i.e. with $\mathrm{d}r_{a,i}/\mathrm{d}t = 0$. In this case, equation (7*a*) states that the flow of mucus that enters the bronchus and the flow of mucus that gets out the bronchus are equal:

$$- Q_{\text{out}}^{(i)}(r_{a,i}) + 2.Q_{\text{out}}^{(i+1)}(r_{a,i}) = 0.$$

No mucus is coming from the most distal (deeper) branches ($Q_{\text{out}}^{(18)} = 0$), so the previous equation is equivalent to

$$Q_{\text{out}}^{(i)}(r_{a,i}) = 0. \tag{8}$$

This means either that there is no mucus layer at all in the bronchi or that the entire mucus layer remains solid. The first situation corresponds to the air lumen area filling all the bronchus section ($r_{a,i} = r_{b,i}$). In the second situation, shear stress in the mucus layer is always smaller than the shear stress threshold σ_0, and the (virtual) interface between solid and liquid mucus is outside the bronchus, i.e. $r_{0,i} \geqslant r_{b,i}$. In both case, the bronchi mucus thicknesses are not any more coupled in the equations.

If the air flow rate in a bronchus is given, there is not a unique mucus layer at equilibrium in that bronchus. If we consider a mucus layer which is at equilibrium with an air flow in a bronchus, then any smaller thickness of mucus corresponds to a wider air lumen, i.e. to lower shear stresses in the bronchus. Since the shear stress has to overcome the shear stress threshold σ_0 to make mucus flow, any layer with smaller thickness is also at equilibrium. If the air flow rate in a bronchus is given, the thickness of its mucus layer cannot however increase indefinitely without breaking the equilibrium with air flow rate. This reasoning defines a (unique) maximal thickness for the mucus layer in a bronchus given an air flow rate inside that bronchus. The *saturated equilibrium* in the tree corresponds to the situation where all the tree branches have a mucus layer whose thickness is maximal relatively to the air flow rate inside them. Because air flow rates divide in two at each bifurcation and because bronchi sizes change from one generation to the next, the distribution of the maximal mucus thicknesses in the tree is strongly correlated to the multi-scale structure of the tree as it will be emphasized by the analytical study in the next section (see equation (11)).

To find the saturated equilibrium of mucus in the tree, we solved the set of equations (2), (3), (4*a*) and (4*b*), (5*a*) and (5*b*) and (8) relatively to $r_{a,i}$ (one equation per bronchus i). We studied the equilibrium case with analytical tools whenever it was possible. When it was not, we used a numerical method based on Newton method (Matlab function *fsolve*). We were careful that the mucus thicknesses found numerically were truly maximal. To do that verification, we increased slightly the mucus layer thicknesses found numerically for saturated equilibrium and checked that the new distribution was not at equilibrium with airflow.

Results

The parameters needed by our model were chosen in the range given by the physiology. Most particularly, our model of mucus is controlled (i) by the yield stress and (ii) by the viscosity of the mucus when yield stress has been reached. In our simulations, we chose numeric values for viscosity and yield stress which can be roughly considered as healthy physiological values [29, 30], although a lot of variation is observed amongst non-pathological individuals. Data for healthy and cystic fibrosis patient in [29] give a yield stress ranging from 2 Pa for healthy individuals up to 20 Pa for non-healthy individuals. Hence, we used a yield stress of 2 Pa. Similarly, data for viscosity found in the literature range from 0.01 to 2 Pa s, and for healthy individuals the value $\mu_m = 0.1$ Pa s shows up as a reasonable estimation [29, 30]. Higher viscosities can be encountered, up to 100 Pa s but such high values induce a stagnation of the mucus for physiological air flows; thus, they will not be used [7, 30].

In order to understand better mucus behavior in a tree structure, we started first with the study of the saturated equilibrium of mucus, i.e. when the mucus layers are at equilibrium with air flows in the whole tree. That situation helps to characterize and understand the dynamics of the mucus, studied in a second step.

Saturated equilibrium of mucus

General results. In this section, we work with a dichotomous tree with $N + 1$ generations without no hypotheses on the size of its branches. A total air flow rate $\Phi_{A,0}$ is given at tree root (mouth level). Our goal is to study the saturated equilibrium of mucus in the tree. The saturated equilibrium of mucus in the tree is reached when mucus and air flow rates are at equilibrium in all the branches of the tree and when the thickness of the mucus layers is maximal (i.e. a slight increase of mucus quantity breaks the equilibrium).

Distributions of mucus that are at equilibrium with air flows in the tree correspond to situations where mucus flows are zero in each branch (equations (8)). At branch level, this happens either when there is no mucus inside the branch ($r_{a,i} = r_{b,i}$, see figure 1) or when all the mucus in the branch remains solid (shear stress in the mucus layer is everywhere smaller than σ_0, i.e. $r_{0,i} \geqslant r_{b,i}$, see figure 1). Actually, each branch i is able to sustain a maximum unmoving quantity of mucus for a given air flow rate $\Phi_{A,i}$. At equilibrium there is no mucus flow and when the thickness of the mucus layer increases while air flow remains constant, the shear stresses increase. Shear stresses can increase and keep mucus at equilibrium as long as $\sigma \leqslant \sigma_0$ in the mucus layer. The maximum quantity of mucus in a branch is thus determined when the maximum shear stress in mucus layer, reached on the bronchi wall (for $r = r_{b,i}$), is equal to σ_0: equation (2) gives then the equality $|C_i| = 2\sigma_0/r_{b,i}$. Air flow in such a branch is then $\Phi_{A,i} = -\frac{\pi C_i}{8\mu_A} {r_{a,i}}^4$ and we can calculate the value of the corresponding radius of air lumen area by combining and integrating equations (2) and (3): $r_{a,i} = \left|\frac{4\mu_A}{\pi\sigma_0}\Phi_{A,i} r_{b,i}\right|^{\frac{1}{4}}$. Since the branch i belongs to the ith generation of a dichotomical tree, flow conservation implies that $\Phi_{A,i} = \Phi_{A,0}/2^i$. Consequently, the radius $r_{a,i}$ of the lumen area of a bronchi of the ith generation filled with a maximal thickness of mucus is

$$r_{a,i} = \left(\frac{1}{2}\right)^{\frac{i}{4}} \left|\frac{4\mu_A \Phi_{A,0}}{\pi\sigma_0} r_{b,i}\right|^{\frac{1}{4}}. \qquad (9)$$

This result is very general because the tree is only assumed dichotomous.

The radii $r_{a,i}$, which reflects here the maximal thickness of the mucus layers for a given air flow, define an *effective tree* in which air circulates. The equivalent hydrodynamic resistance [21] of the effective tree is $R_a = \sum_{i=0}^{N} \frac{1}{2^i} \frac{8\mu_A l_{b,i}}{\pi r_{a,i}^4}$ which measures the efforts needed to make air circulate in the tree accounting for mucus layers. Mixing $r_{a,i}$ expression (equation (9)) with R_a expression shows that, in a tree where the mucus is present on the wall of every branch ($r_{a,i} \leqslant r_{b,i}$) at maximal quantity (saturated), the hydrodynamic resistance of the effective tree is proportional to the shear stress threshold σ_0 and inversely proportional to the air flow $\Phi_{A,0}$ at tree root:

$$R_a = \frac{2\sigma_0}{\Phi_{A,0}} \sum_{i=0}^{N} \frac{l_{b,i}}{r_{b,i}}. \qquad (10)$$

Thus, a tree at saturated equilibrium with mucus (maximal mucus thickness in every branch) has a hydrodynamic resistance which depends very differently on the geometry parameters than a 'naked' tree whose resistance is $R_b = (8\mu_a/\pi) \sum_{i=0}^{N} l_{b,i}/\left(2^i r_{b,i}^4\right)$. At saturated equilibrium with mucus, the hydrodynamic resistance depends on the tree geometry only by the ratios of lengths over diameters of its branches. The mean of these ratios in the human lungs has been found to be about 3 [25].

Idealized tree. To go further, we will now consider an idealized tree (see geometry section above). It is defined with four parameters: the radius $r_{b,0}$ and length l_0 of its first generation branch, its homothety factor h and its total number of generations $N + 1$ (numbered from *0* to *N*). The branches radii verify $r_{b,i} = r_{b,0}\ h^i$ and the branches length verify $l_i = l_0\ h^i$. In the case of an idealized tree, equation (9) becomes

$$r_{a,i} = \left(\frac{h}{2}\right)^{\frac{i}{4}} \left|\frac{4\mu_A \Phi_{A,0} r_{b,0}}{\pi\sigma_0}\right|^{\frac{1}{4}} = \left(\frac{h}{2}\right)^{\frac{i}{4}} r_{a,0}. \qquad (11)$$

Equation (11) shows that the minimum radius of air lumen area at saturated equilibrium with mucus follows a scaling law that depends on the scaling law driving the diameters of the bronchi radii. The effective tree has a diameter reduction factor $h_{\text{diam}} = (h/2)^{1/4}$. The effective tree has the same length reduction factor than the bronchi length: $h_{\text{length}} = h$. The dependence of h_{diam} relatively to h is shown in figure 3. In particular, if h is smaller than $h_c = (1/2)^{1/3}$ then h_{diam} is larger than h, and vice versa.

The maximum mucus thickness in a branch could however be zero. If the bronchi radius is sufficiently small, then shear stresses can be high enough to drain all the mucus out, i.e. inducing $r_{a,i} = r_{b,i}$. Using equation (9) in this last equality, a minimum bronchus radius $r_{s,i}$ for generation i can be computed. If the bronchus of generation i has a radius $r_{b,i}$ smaller than this minimum radius $r_{s,i}$, then no mucus layer can remain in the bronchus at saturated equilibrium:

$$r_{b,i} \leqslant \left|\frac{4\mu_A \Phi_{A,0}}{\pi\sigma_0}\right|^{\frac{1}{3}} h_c^i = r_{s,i} = r_{s,0} h_c^i$$

and consequently $\quad r_{b,i} = r_{b,0} h^i \leqslant r_{s,0} h_c^i$

where $r_{s,0} = |4\mu_A \Phi_{A,0}/\pi\sigma_0|^{1/3}$ is the minimum radius of the first generation (case $i = 0$).

Table 1. Radius of the first generation of the tree $r_{b,0}$ and its homothety ratio h affect the existence and structure of the mucus layers along the generations of the tree. n_c is defined as the integer part of $\ln(r_s/r_{b,0})/\ln(h/h_c)$.

	$r_{b,0} \leqslant r_{s,0}$	$r_{b,0} > r_{s,0}$
$h < h_c$	No mucus layer in the tree	Mucus layer from generation 0 to $n_c - 1$; no mucus from generation n_c to the last
$h = h_c$	No mucus layer in the tree	Mucus layer from generation 0 to $n_c - 1$; no mucus from generation n_c to the last
$h > h_c$	No mucus layer from generation 0 to n_c, mucus later from generation $n_c + 1$ to the last	Mucus layer everywhere

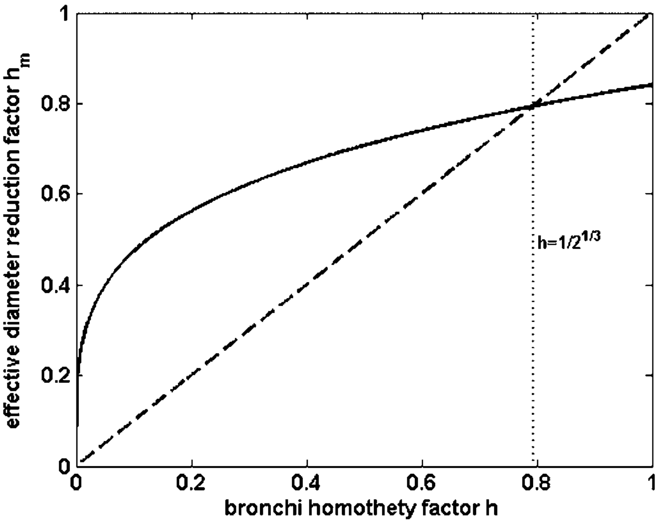

Figure 3. The continuous curve represents the diameter reduction factor h_{diam} of the effective tree (tree with mucus layers) versus the homothetic factor h of the original tree (without mucus). The dashed curve represents the homothety factor h of the original tree. $h_c = (1/2)^{1/3}$ separates two behaviors: if h is smaller than h_c, then the effective tree has a diameter reduction factor larger than h; if h is larger than h_c, then the effective tree has a diameter reduction factor smaller than h. The vertical dotted line corresponds to $h = (1/2)^{1/3}$.

Mucus distribution at saturated equilibrium can then be classified in different cases that depend on the relative position of $r_{b,0}$ with $r_{s,0}$ and on the relative position of h with h_c. A critical generation n_c can be introduced; it separates the region with and without mucus and is defined by the integer part of $\ln(r_{s,0}/r_{b,0})/\ln(h/h_c)$, see table 1.

The mean homothety factor has been estimated for the lungs [25]; it is slightly larger than $h_c = (1/2)^{1/3} \approx 0.79$ and the radius of the first generation $r_{b,0}$ is around 1 cm. With $\sigma_0 = 2$ Pa (non-pathologic), we can estimate that $r_{s,0}$ is ranging from 1 (rest regime) to 7–8 mm (cough), which is smaller than $r_{b,0}$. Hence, the results shown in table 1 indicate that a mucus layer should be present in the whole tree, at least at first approximation.

Transitory mucus distribution

The previous studies correspond to equilibriums with maximum mucus thicknesses 'authorized' by a given air flow. These situations would probably correspond to pathologies involving high mucus secretion. The saturated equilibrium of mucus in a tree depends on air flow level at tree root ($\Phi_{A,0}$), mucus shear stress threshold (σ_0) and tree geometry. As soon as the mucus layer is thinner than the characterized maximum thickness then the distribution also remains unaffected by the air flow.

Physical therapy focuses on removing the larger quantity of mucus from the tree thanks to manipulations of the thorax while seeking a minimal discomfort for the patient. The air flow rate that exits the mouth during the manipulations determines partly the efficiency of the draining (the higher the air flow rate, the larger the shear stresses in the bronchi). However, the time during which the therapist sustains this

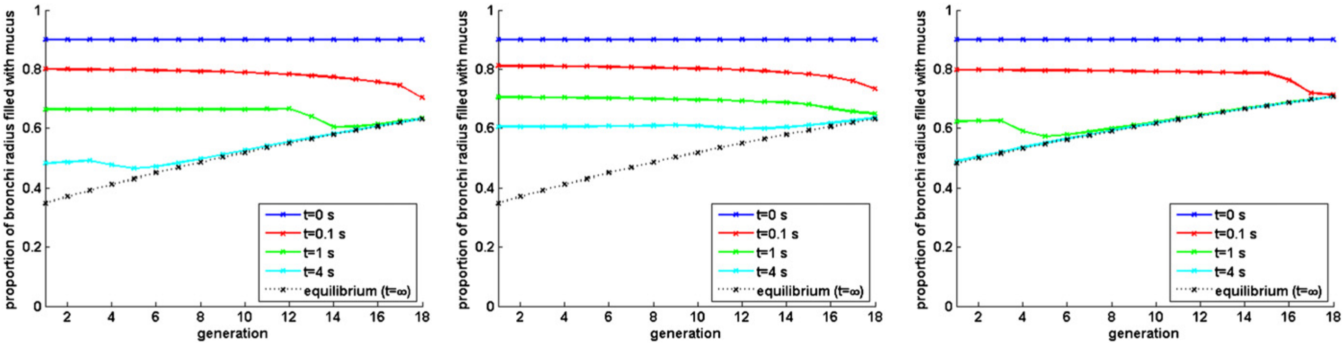

Figure 4. Evolution of the mucus layers in the tree for a mean velocity at mouth level of 50 m s^{-1}. Airflow is the most effective during the initial seconds. The deepest bronchi empty quicker than the others because they have less daughter branches and thus they receive less mucus from the bottom of the tree. The left plot corresponds to $\mu_m = 0.1$ Pa s and $\sigma_0 = 2$ Pa; the middle plot corresponds to $\mu_m = 1$ Pa s and $\sigma_0 = 2$ Pa; the right plot corresponds to $\mu_m = 0.1$ Pa s and $\sigma_0 = 5$ Pa.

(This figure is in colour only in the electronic version)

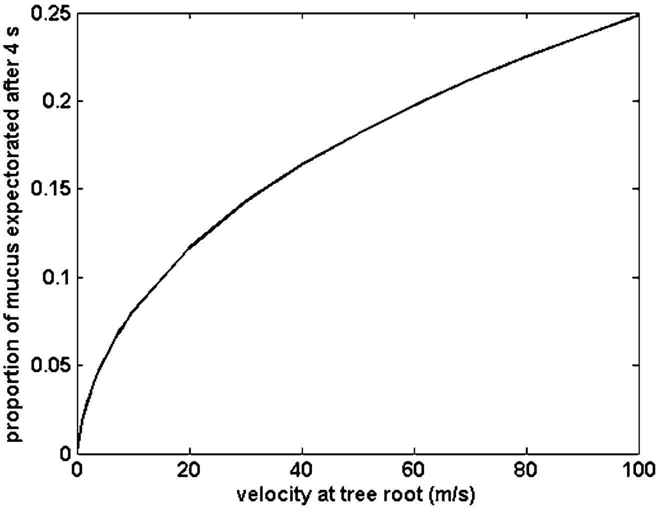

Figure 5. Proportion of the mucus volume initially in the tree that has been expectorated after 4 s for the corresponding velocity at mouth level.

flow in order to reach a distribution at quasi-equilibrium is extremely important, because it is directly connected to patient discomfort. This indicates that information on the time needed to reach a distribution at equilibrium could help to optimize the manipulations; this motivates our study of the transitory behavior of mucus. The draining efficiency can be measured by the hydrodynamic resistance of the effective tree since it is directly related to the ease of breathing of the patient. The hydrodynamic resistance of the effective tree can be decreased either by draining the mucus out of the tree or by a redistribution of the mucus in the bronchi.

In the simulations, we used an idealized tree with $N = 17$, $r_{b,0} = 1$ cm and $h = 0.83$. To study the transitory phenomena appearing when airflow and mucus interact, we chose as initial distribution a state where bronchi are almost completely filled with mucus at $t = 0$ s, i.e. $r_{a,i}(t = 0) = 0.1\ r_{b,i}$. Figure 4 shows mucus distributions in the tree for five different times for a mean velocity in tree root (trachea) of 50 m s^{-1}. Each figure corresponds to a set of mucus parameters—left figure: $\mu_m = 0.1$ Pa s and $\sigma_0 = 2$ Pa (non-pathologic); middle figure: $\mu_m = 1$ Pa s and $\sigma_0 = 2$ Pa; right figure: $\mu_m = 0.1$ Pa s and $\sigma_0 = 5$ Pa. The curves represent the proportion of the bronchi radii filled with mucus. In each figure, the black dotted line represents the saturated equilibrium of mucus in the tree; it is the lowest possible thickness for mucus at this flow rate. Whatever the parameters, mucus motion is the most effective during the first instants. A higher viscosity slows down mucus and longer manipulation times are needed to reach the same distribution than for a lowest viscosity (middle plot in figure 4). Mucus thicknesses at saturated equilibrium in the tree are higher when yield stress is higher (right plot in figure 4). Figure 5 shows the proportion of mucus that gets out of the tree after 4 s of manipulation at constant airflow rate.

The saturated equilibrium of mucus in the tree is the best possible distribution achievable with constant airflow manipulations. However, these distributions are achieved only for long time lengths. Thus, we estimated the time length needed to reach a configuration that would be 'relatively close' to that ideal distribution. To do so, we used the hydrodynamic resistance of the effective trees (trees whose branch radii are $r_{a,i}$). We calculated the hydrodynamic resistance $R_{a,s}$ of the effective tree at saturated equilibrium. Then, we estimated the hydrodynamic resistance $R_a(t)$ of the effective tree during a manipulation at constant airflow rate. The manipulation is stopped when the hydrodynamic resistance $R_a(t)$ is 50 percent larger than the hydrodynamic resistance of the tree at saturated equilibrium $R_{a,s}$ (i.e. we stop when $R_a(t) = 1.5\ R_{a,s}$). The initial mucus distribution fills almost the whole tree ($r_{a,i}(t = 0) = 0.1\ r_{b,i}$) and has been chosen in order to bring the air lumen area radius $r_{a,i}(t = 0)$ to be smaller than the threshold radius $r_{0,i}$ in the bronchi i for all the air flows tested. We tested air flows ranging from rest regime (1 m s^{-1}) to cough regime (100 m s^{-1}). The stop time is represented in figure 6; it increases with air flow in the trachea.

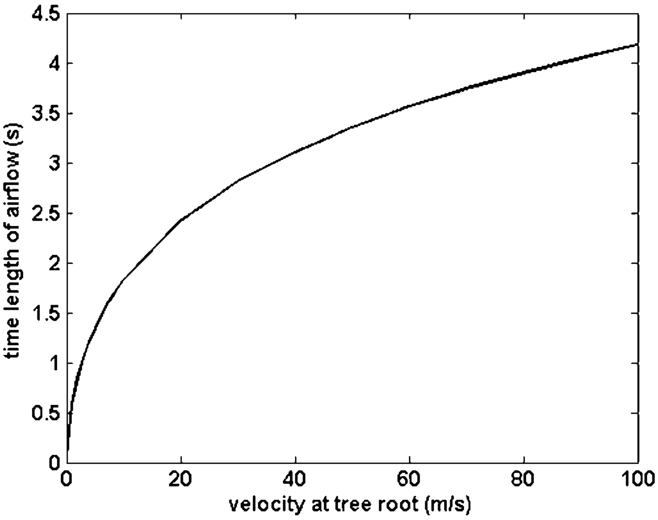

Figure 6. Duration of manipulations at constant airflow versus mean air velocity in the trachea. The manipulation is stopped when the hydrodynamic resistance of the effective tree is 50% larger than the hydrodynamic resistance of the effective tree at saturated equilibrium (see text). Mucus is redistributed in the tree either by being drained out of the tree or by being pushed up the generations.

Discussion

We have shown that the distribution of a mucus-like fluid in a rigid tree is the result of complex interactions between fluid rheology (threshold effect), tree geometry and air flow rates. The study of these selected phenomena and their interactions are one of the most important steps in understanding the structure of mucus distribution in the lungs and to understand how it can be moved forward efficiently toward the trachea. Our model is able to give qualitative predictions of chest physiotherapy techniques that used air flow to drain secretions out of the bronchial tree (cough assistance, assisted 'huffing', expiratory flow modulation, etc). These techniques have been validated empirically and are known to be efficient clinically. Our work is their first biophysical justifications. With some improvements, this model should be able to give predictions for a wider range of techniques (such as postural draining or percussion techniques) and bring interesting information on their efficiency.

On mucus distribution

An airway tree with a Bingham fluid layer on its branches wall has a 'saturated' configuration when the Bingham layer is at equilibrium with the air flow in the tree. Each branch is able to sustain a maximal quantity of Bingham fluid on its wall for a given air flow rate. This maximal configuration can be predicted analytically from the topology of the tree and the total air flow rate in the root of the tree. The geometry and hydrodynamic property of this configuration is altered by simple changes of the air flow rate entering the tree. The interactions between air flow and Bingham fluid layers structure the Bingham fluid layers in the tree, and the resulting effective tree (tree whose branches radius is that of the air lumen area) has interesting properties. For example, the hydrodynamic resistance of the effective tree can be inversely proportional to the air flow entering the tree. The hydrodynamic resistance of the effective tree is correlated to the geometry of the original tree through the branches ratios of length over diameter. When the diameters of the original tree follow a scaling law, the effective tree does the same, at least on a known number of successive generations, and both laws are directly related. Such predictions can be used to solve inverse problems on the geometry of the original tree or on the Bingham fluid (estimation of the hydrodynamic resistance, of the diameters). These properties could potentially be developed into medical measurement tools and potentially become diagnostic criterions.

Our model predicts the existence of a mucus layer in the lungs in all the generations; this is particularly interesting because the presence of mucus layers tends to move the diameter reduction factor closer to $h_c = (1/2)^{1/3}$ (see figure 3). The number h_c is important since it reflects many theoretical optimization processes related to the lungs and more generally to dichotomical tree structures, see for example [21]. The diameter reduction factor h in the lungs has been estimated in the literature [25] and found to be not far from h_c. Our results indicate that regions of the bronchial tree with mucus layers should have lumen areas diameter reduction factor closer to the value h_c.

From a physiological point of view, mucus production is the most important in the medium generations of the lungs (from 5 to 12) but remains small in the other. Thus, before mucus can be expectorated, it has to progress toward the upper generations. As stated before, we show that this transport occurs only if the thickness of mucus is sufficient. The minimal thickness depends on the generation and on the properties of mucus (yield stress σ_0). Because the first generations of the lungs contain less mucus; mucus has first to fill them before it can go out of the tree. This re-organization is however very important, since it modifies the hydrodynamic resistance of the tree. Even though theoretically, mucus progression in the tree could lead to an increase of resistance, we did not observe this behavior, probably because it is often less costly in term of hydrodynamic resistance to have the narrowest bronchi less filled at the expense of the widest bronchi (the hydrodynamic resistance of a bronchi is proportional to the inverse of its radius at the power 4). Consequently, mucus re-organization can ease respiratory difficulties of a patient even if mucus is not drained out, because of a decrease of the hydrodynamic resistance of her/his lungs.

It is necessary to perform successive manipulations to reach a distribution at equilibrium with air flow (minimum hydrodynamic resistance) because the quantity of air available in the lungs is limited. The maximum quantity of air in the lungs for adults is about 3 liters, which is expired in 1 s if trachea velocity is 10 m s^{-1} (exercise) and 0.1 s if trachea velocity is 100 m s^{-1} (cough). Thus, to perform successive manipulations, it is necessary to refill the lungs with air using inspirations. During inspiration, it is critical not to bring mucus back down the generations. This needs an inspiration slow enough (rest regime) because the air flow should not affect the mucus layers. Consequently, the control of inspirations is likely to be important to maximize the efficiency of the manipulations during physical therapy. Our model is also able to simulate inspiratory flow, thus it can be used to predict the effect of inspirations when they are not easily controlled.

In our model, the only way to mobilize more mucus is to increase the air flow; a higher air flow will reduce the mucus minimal thickness. The larger the air flow, the better we are able to make mucus progress toward the mouth. More importantly we showed that high flows are the most efficient because they are able to mobilize the largest quantity of mucus. However, in physical therapy, another important criterion has to be taken into account: patient discomfort. This discomfort increases with air flow: pressure variation in the lungs tissue is roughly proportional to the air flow and the physical therapist has to overcome this pressure variation. Hence, to reach high flows, she/he has to apply strong forces and thus increase the patient discomfort. This indicates that even if low air flows (but not too low since yield stress has to be overcome) make mucus progress only slightly toward the mouth, their use is not worthless since this progression has been gained with low discomfort. Our model has the potential to predict an optimal duration for each flow rate (for example from results on hydrodynamic resistance such as those plotted in figure 6). These predictions can be used to minimize the time spent at high flow rates and thus to reduce the discomfort of the patient.

Finally, the existence of a maximal mucus layer on bronchi walls predicts that the deepest part of the mucus layer could potentially not be motioned with physiologically acceptable airflows. This situation may arise when mucus yield stress is high. If mucociliary clearance is ineffective, this could potentially lead to mucus stasis. In such situations, the solution is either to be able to reduce mucus yield stress or to use alternative expectoration techniques.

Role of physical parameters

The role of mucus physical parameters is intimately linked to the geometry of the tree. Mucus yield stress determines whether mucus will move easily or not under the action of air flow. If yield stress is too high, then mucus cannot move in the tree under reasonable values of air flow rates. In contrast, if yield stress is small, then mucus can be easily put to motion (however, if yield stress is too small, then the fluid is almost Newtonian and gravity becomes non-negligible). A shear stress that overcomes the yield stress in the mucus layer is thus the trigger of mucus displacement. In our model, the amount of shear stress in a bronchia is driven by two parameters, one from the fluid and one from the geometry: (1) the amplitude of the flow rate—larger flow rates induce comparatively larger shear stresses and (2) the size of the air lumen area in the bronchia—smaller air lumen area induce comparatively higher shear rates. A small air lumen area can be found in bronchi whose radius is small, in bronchi that bear a large quantity of mucus, or finally in bronchia that combines these two properties. When mucus is pushed forward in a bronchus, the lumen area increased. If the flow rate remains the same, the radius of the lumen area can become too large to keep a shear stress high enough to overcome the yield stress and to keep the mucus moving. In contrast, when a bronchus is highly obstructed, its mucus moves easily and fills the upper bronchus that is potentially less obstructed. The air flow in that upper bronchus is initially too small to overcome the yield stress, but since mucus keeps coming in, the lumen area decreases and the shear stresses inside the bronchus increase. Eventually, shear stress becomes sufficiently large to overcome yield stress and mucus starts moving forward. These phenomena describe how mucus progress in the tree and can fill the less obstructed bronchi with mucus coming from the more obstructed ones. At the end, this phenomenon makes the mucus spread along the generations of the tree. Mucus reached a stationary distribution characterized with mucus thicknesses reflecting equilibrium between the mucus yield stress and the shear stresses in the bronchi.

Mucus viscosity determines at which velocity the mucus will flow when shear stress is larger than yield stress. Thus, the quantity of mucus that gets out of the tree or the reduction of the hydrodynamic resistance of the effective tree achieved with a timed manipulation is directly related to mucus viscosity: low mucus viscosity means that mucus will progress quickly in the tree, get out of the tree and reorganize in the tree rapidly; high mucus viscosity means the contrary. Thus, to achieve the same result, more timed manipulations are needed for high mucus viscosities than for low mucus viscosities.

Model improvements

In this work, we give indications on the possible effects a rigid geometry would have on mucus distribution and draining in the lungs. We showed that the system restricted to interactions between air flow, mucus layers and rigid geometry is still very complex, even with simplified hypotheses for fluids behavior (low flow regime, Bingham fluid). Thus, it was important to restrict the number of phenomena to be able to fully understand the fundamental behaviors anchored in this system. However, to reach realistic and quantitative predictions on mucus draining in the lungs, it is necessary to include some other important phenomena that are discussed below.

The physics of the fluids should be improved. Hence, Bingham fluid captures only the most basic behaviors of mucus. Mucus is known to have viscoelastic and thixotropic behaviors that may induce more complex time dependent results [31]: shear stresses applied for a relatively long time on mucus may induce a decrease of the yield stress and of the fluid viscosity.

Inertial effects and turbulence are known to exist and to induce complex behaviors for both air and mucus (mucus splitting at bifurcations, mucus waves and plugs, mucus detachment, etc) [4]. Moreover, air and mucus profiles around the bifurcations are not axi-symmetric. Consequently, axi-symmetry hypothesis is a strong approximation. A model that integrates all these phenomena cannot be axi-symmetric.

Now, considering the bronchial tree properties, the choice of a tree model with symmetrical bifurcations is obviously an approximation [24, 25, 32]. The rigid hypothesis is very strong; it is well known that bronchi walls have complex mechanics and that they are made of generation-dependant proportions of various deformable biomaterials (cartilaginous structure, muscles, etc). The fact that they are deformable is important because changes in lungs volume alter the calibers of the bronchi. Physical therapists use these constrictions to move secretions upward in the lungs; however, bronchi occlusions should be avoided. The constriction of the bronchi depends on the volume of the lungs; thus, the lungs response to manipulations changes over the course of the maneuver. Because of bronchial constriction, increasing the applied pressure does not systematically bring an increase of the air flow, in particular at low lungs volume.

Mucus distribution in the lungs is very complex and not spread homogeneously. It can depend on the pulmonary lobe where the bronchus is located. Moreover, mucus is secreted continuously by the bronchi cells and its volume regulated by ion transport mechanism. So an improvement of the model would be to take into account the physiological volume regulation of mucus.

Consequently, the hypotheses made in this work have to be kept in mind to interpret correctly the predictions of our model. However, in order to well understand the effects of each characteristics of the system, it is essential to work with a limited number of hypotheses. This is the reason why we chose, as a first step, to limit our work to the sole influence of the tree geometry with a simplified fluid frame.

Conclusion

To our knowledge, this work is the first to introduce a model of the effects of air flow on mucus distribution in a tree with the goal to help the physical therapist to optimize her/his manipulations. This model is an initial step toward a justification of the suitability of the expiratory flow in physical therapy and this work brings up the notion of minimal flow as a possible criterion of mucus draining efficiency.

We investigated the role of the airway tree geometry, air flow and mucus physical parameters on mucus distribution at equilibrium states and at transitory regimes. Our results showed the fundamental importance of these three aspects and of their interactions. Our model gives predictions in terms of mucus distribution in the tree. For a given geometry, air flow and mucus yield stress, a maximal stationary distribution of thicknesses of the mucus layers exist in the bronchi. It has its own structure that follows a scaling law if the geometry of the tree follows a scaling law. This distribution cannot be changed without changing the amplitude of the air flow. Our model also gives qualitative predictions on how mucus progresses in the tree. We have been able to determine the time needed to reach a distribution of mucus close to the stationary distribution. This duration is strongly related to mucus viscosity: the lower the viscosity, the quicker mucus moves in the tree.

We are also able to propose, in the limitations of our model, some of the following qualitative optimizations for the manipulations of the physical therapists.

- To make mucus flow upward, mucus yield stress has to be overcome: if air flow rates are too small, mucus cannot move. So for each configuration, there exists a minimal flow that is able to move mucus.
- When mucus moves, some of it can get out of the tree but mainly it fills the upward generations and eventually reach a stationary distribution. This new stationary distribution is less resistive than the initial one and can ease the breathing of the patient. Once this new configuration is reached, the only way to mobilize more mucus is to increase the air flow rate.
- Thus, the minimal air flow rate able to move mucus increased progressively when manipulations are performed. An air flow rate can be efficient at the beginning of a set of physical therapists manipulations but could become inefficient after a few manipulations.
- Patient discomfort is higher for higher air flow rates, so to minimize patient discomfort, the physical therapist should always be slightly over the minimal air flow rate that is able to make mucus flow. Consequently, air flow rate used in manipulations should be increasing in time, keeping up with mucus redistribution in the lungs. This is an important conclusion of this study, and one that could lead to a testable hypothesis for experimental physiotherapy.
- Inspirations are needed to refill the lungs with air between each manipulation; they should be made at low air flow rate to keep mucus from going back down the tree.

This model remains yet a first approximation and thus can only catch some qualitative aspects of the complex behaviors involved in human mucus draining, mostly concerning the role of the geometry and the parameters of a basic description of mucus. Consequently, we plan to improve this model in order to increase its predictive power and in order to bring more quantitative information to the practitioner, in particular concerning the adaptation of the manipulation to the patient specificity (number of manipulations needed, amplitudes of successive air flow rates, patient dependent definition of discomfort, etc).

Appendix. Determination of the pressure drop per unit length knowing r_a, r_b and Φ_a.

In this appendix, we describe the calculations of pressure drops per unit length for the different cases of mucus states. All calculations take place in a branch of the tree whose radius is r_b and air lumen area radius is r_a. The yield stress of mucus is σ_0. We call $C = \partial p/\partial z$ the pressure drop per unit length in the branch. The air flow in the branch is known and is equal to Φ_a. Finally, we call s the sign of $C = \partial p/\partial z$ ($s = 1$ if $C \geqslant 0$ and $s = -1$ if $C < 0$).

Air flow is equal to

$$\Phi_a = 2\pi \int_0^{r_a} v(r) r \, \mathrm{d}r.$$

Integrating by parts and using equations (2) and (3) lead to

$$\Phi_a = 2\pi \left(v(r_a) \frac{r_a^2}{2} - \frac{C}{4\mu_a} \frac{r_a^4}{4} \right),$$

where $v(r_a)$ is the velocity on the air/mucus interface. Its expression depends on the following states of mucus.

(1) First state: mucus is liquid between the branch wall located at $r = r_b$ and the radius $r = r_0$ (associated with the yield stress $r_0 = |2\sigma_0/C|$) and solid elsewhere (case $r_a < r_0 < r_b$).

In this case $v(r_a) = v(r_0)$ since mucus is solid between r_0 and r_a. Integrating equations (2) and (4*a*) leads to

$$v(r_a) = v(r_0) = -\frac{C}{4\mu_m}(r_b - r_0)^2.$$

Replacing $v(r_a)$ with the previous relation in the expression of Φ_a and using the fact that $r_0 = |2\sigma_0/C|$, then C is the solution of a second degree polynomial. The solutions are

$$C_1 = \frac{1}{2} \times \frac{8\pi r_a^2 \mu_a r_b s\sigma_0 - 8\Phi_a \mu_a \mu_m + 4\sqrt{-8\pi r_a^2 \mu_a^2 r_b s\sigma_0 \Phi_a \mu_m + 4\Phi_a^2 \mu_a^2 \mu_m^2 - 2\pi^2 r_a^6 \mu_a \sigma_0^2 \mu_m}}{\pi r_a^4 \mu_m + 2\pi r_a^2 \mu_a r_b^2}$$

$$C_2 = \frac{1}{2} \times \frac{8\pi r_a^2 \mu_a r_b s\sigma_0 - 8\Phi_a \mu_a \mu_m - 4\sqrt{-8\pi r_a^2 \mu_a^2 r_b s\sigma_0 \Phi_a \mu_m + 4\Phi_a^2 \mu_a^2 \mu_m^2 - 2\pi^2 r_a^6 \mu_a \sigma_0^2 \mu_m}}{\pi r_a^4 \mu_m + 2\pi r_a^2 \mu_a r_b^2}.$$

We have two possible pressure drops per unit length which gives two possible values for $r_0 = |2\sigma_0/C|$; however, they are easily discriminated since only one at a time can verify $r_b < r_0 < r_a$.

(2) Second state: mucus is liquid everywhere, i.e. $r_0 < r_a$. The integration of equations (2) and (4*a*) leads to

$$v(r_a) = \frac{C}{4\mu_m}(r_a - r_b)(r_a + r_b - 2r_0).$$

Mixing with the expression of Φ_a, we have

$$C = -\frac{8\mu_a}{\pi r_a^2} \frac{\Phi_a \mu_m - \pi r_a^3 s\sigma_0 + \pi r_a^2 r_b s\sigma_0}{r_a^2 \mu_m + 2r_a^2 \mu_a - 2\mu_a r_b^2}.$$

(3) Third case: mucus is completely solid ($r_0 > r_a$).
In that case $v(r_a) = 0$ and

$$C = -\frac{16\mu_a \Phi_a}{2\pi r_a^4}.$$

The function $C_i = F(\Phi_{a,i}, r_{a,i})$ (equation (5*b*)) is built with these expressions of C. To discriminate between the different possibilities and know the mucus state, we compute for each case the value of C and we calculate its associated radius $r_0 = |2\sigma_0/C|$. The case is correct only if the position of the radius r_0 relatively to r_a and r_b is compatible with the case hypotheses.

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