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On the effect of mucus rheology on the muco-ciliary transport

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ABSTRACT

A two dimensional numerical model is used to study the muco-ciliary transport process in human respiratory tract. Here, hybrid finite difference-lattice Boltzmann method is used to model the flow physics of the transport of mucus and periciliary liquid (PCL) layer in the airway surface liquid. The immersed boundary method is also used to implement the propulsive effect of the cilia and also the effects of the interface between the mucus and PCL layers. The main contribution of this study is on elucidating the role of the viscoelastic behavior of mucus on the muco-ciliary transport and for this purpose an Oldroyd-B model is used as the constitutive equation of mucus for the first time. Results show that the viscosity and viscosity ratio of mucus have an enormous effect on the muco-ciliary transport process. It is also seen that the mucus velocity is affected by mucus relaxation time when its value is less than 0.002 s. Results also indicate that the variation of these properties on the mucus velocity at lower values of viscosity ratio is more significant.

1. Introduction

The ventilation of human lung typically ranges between 1000 and 21,000 l a day depending on body size and physical activities [1]. Air which passes into the lungs from the surrounding environment is often polluted with varieties of particles such as fungi and bacteria which could be harmful for the lungs. As such, the airway surface liquid (ASL), which is a fluid layer coating the interior epithelial surfaces of the bronchi and bronchioles, plays an important defensive role against foreign particles and chemicals entering the lungs [2]. Indeed, the ASL exhibits a two-layer structure. The upper layer consists of highly viscous and non-Newtonian mucus which is a nonhomogeneous, viscoelastic fluid containing water, salt and glycosylated mucin proteins [3]. Lai et al. [4] in a valuable research reviewed the biochemistry that governs mucus rheology, the macro- and microrheology of human and laboratory animal mucus. They [4] clearly reveal the physical properties of mucus to advancing the field of drug and gene delivery. The lower layer of ASL is a watery lubricating fluid, or 'periciliary liquid' (PCL) layer. The origin of the PCL is not known, but is hypothesized to originate from osmosis across the epithelium [5]. The cilia, which are hair-like structures, are embedded in PCL with only the tips of the cilia contacting mucus layer. The bending of the cilium is produced by an internal arrangement of microtubules [6]. Each cilium have two quite distinct stages to their beat cycle, the effective stroke when the cilium is extended out of the cell surface, and the recovery stroke when it creeps back to the start of its effective stroke. The effective stroke occupies a shorter period of the beat than the recovery stroke [7]. Hence, the work done during the effective stroke is several times the amount of work done performed during the recovery stroke [8]. It is hypothesized that the PCL serves both as a lubricant to allow movement of the viscous mucus layer and as a lower viscosity medium more favorable to the movement of cilia [9].

Considerable researches have been published in the field of modeling muco-ciliary transport. A quick review of the literature shows the Newtonian behavior of mucus has become the center of attention in the literature. The earliest analytical reference on the investigation concerning muco-ciliary flow was performed by Barton and Raynor [10]. They assumed cilium as a rigid rod, which automatically shortens during the recovery stroke. Use of this assumption would limit the accuracy of cilia motion. Lee et al. [11] used hybrid immersed boundary- finite difference method to simulate muco-ciliary transport process. In their study [11] the velocity of the PCL-mucus interface and the force exerted on the fluids by cilia are computed via the Immersed Boundary Method (IBM), which was originally introduced by Peskin [12] for studying blood flow patterns around heart valves [13] and since then has been used by many researches for simulating simple geometries [14–19] and also for biological problems [[11,20–28]. Lee et al. [11] basically studied the dependency of mean mucus velocity on the mucus viscosity, the cilia beat frequency, the numbers of cilia, the thickness of PCL, and the surface tension at the interface between the mucus and PCL. Their results show that the cilia beat frequency, the number of cilia, and the depth of PCL are the

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critical factors affecting the muco-ciliary transport. Jayathilake et al. [27] also used the IBM to develop a three-dimensional numerical model to simulate human pulmonary cilia motion in the PCL layer. Their results indicate the effects of the phase difference between cilia, the cilia beating frequency, the viscosity of PCL, the PCL height, and the ciliary length on the PCL motion. They concluded that the maximum PCL velocity in the stream-wise direction occurs if cilia have phase differences in both stream-wise and spanwise directions. Jayathilake et al. [28] in another numerical investigation studied various abnormalities of the cilia (e.g. cilia beat pattern, ciliary length, immotile cilia, beating amplitude and uncoordinated beating of cilia) on muco-ciliary transport of human respiratory tract. Their results show that the mucus velocity decreases by reducing the beat amplitude. They also represent that the windscreen wiper motion and rigid planar motion of cilia would decrease or almost stop the mucus transport. Chatelin and Poncet [29] modeled muco-ciliary clearance by using a hybrid scheme combining an Eulerian scheme for the Stokes equations and a particle method for transport equations. They [29] considered non-Newtonian aspects of viscosity in their method and study different mechanisms of mucus propelling and found dominant factors in muco-ciliary clearance, particularly in the context of cystic fibrosis and aerosol therapy. Similar investigations were performed to study mucus flow using similar methods [30–33]. Mauroy et al. [34] by considering mucus as a Bingham fluid (gel-like), studied the effects of geometry, mucus physical properties and amplitude of flow rate on the muco-ciliary clearance. Their results showed that both geometry and physical properties of mucus (yield stress and viscosity) play a vital role in mucus flow.

It is readily acknowledged that mucus exhibit a variety of rheological complexities which cannot be described even qualitatively using the Newtonian fluid behavior and well-known Navier–Stokes equations. Experiments show that, rheological measurements including viscosity (resistance to flow) and elasticity (stiffness) are often used together to describe the consistency of mucus [4]. A review of the above mentioned researches clearly reveals that simulation of muco-ciliary transport has been investigated extensively considering the Newtonian behavior of mucus. In contrast, much less is known about the viscoelastic behavior of the mucus. Ross [35] in an analytical investigation considered mucus as a nonlinear Maxwell fluid. This study [35] has a few shortcomings that limit its general application. First, the PCL was not modeled in this study and mucus is modeled as a single layer. Secondly, the mucus–cilia interface was modeled as an impermeable wavy wall. Blake [36] stated that the latter assumption i.e. considering the tips of the cilia with a no-slip boundary is not appropriate because the tips of the cilia may penetrate the mucus layer during the effective stroke. As such, he [36] suggested a new approach in which the cilia could be modeled by distributing force singularities along their centerlines. This approach was also modified by some other researches later [37–39]. King et al. [40] used a simple analytical model to study the effect of mucus viscoelasticity on the muco-ciliary transport system. They concluded that mucus transport would intensify when the shear modulus of elasticity is reduced. They assumed that in their model there was no net transport of PCL in the cilia sublayer. However, the experiments of Matsui et al. [41] on human tracheobronchial epithelial culture showed that the transport of PCL approximately equals to the transport of mucus layer. King et al. [40] also assumed that there was a layer of PCL between the top of the cilia sublayer and the mucous layer although micrographs taken by Puchelle et al. [42] shows cilia penetrating into the mucus layer. Smith et al. [43] in an analytical investigation studied transport of mucus and periciliary liquid in the airways by considering mucus as a linearly viscoelastic fluid. In this work [43] the penetration of cilia into the mucus layer was modeled by considering the ASL as three fluid layers separated by flat interfaces. The lower PCL layer was modeled as a Newtonian fluid while the middle layer (traction layer), which represents the region of cilia penetration into the mucus, was modeled by a Maxwell viscoelastic fluid with viscosity μ_{M1} and relaxation time λ_1. The upper mucus layer was modeled by a Maxwell fluid of viscosity μ_{M2} (which is greater than μ_{M1}) and the same relaxation time λ_1. In addition, the mat of cilia was modeled as an active porous medium. The propulsive effect of the cilia was modeled by time-dependent force acting in a shear-thinned traction layer between the mucus and the PCL. They studied various parameters on the motion of the mucus layer. Their results show that the dependency of mucus transport on the choice of physical parameters would be nonlinear. It was concluded that transport was only significantly disrupted by a reduction in cilia frequency. Their study [43] has two important shortcomings. First, they [43] considered the mucus layer as a linear viscoelastic fluid, while such a time-dependent problem in which the non-Newtonian viscosity plays a dominant role and hence the elastic effects must be also considered in the simulation. However, the elastic effects cannot be studied by linear viscoelastic models properly [44]. The other shortcoming of the model [43] is that they considered the mucus-PCL interface as completely flat.

It is true that linear viscoelastic models have the advantage of being simple and convenient to implement in many computer modeling packages. However, although most biological materials are expected to behave linearly for small deformations ($<$ 2–3%), biological materials typically exhibit nonlinear behavior at greater strains [45] and hence it would be important to include non-linear behaviors when modeling those biological systems. As the equations of linear viscoelasticity is not valid for large deformations since they do not satisfy the principle of frame invariance, Oldroyd and others developed a set of frame-invariant differential constitutive equations by defining time derivatives in frames that deform with the material elements. To extend the linear Maxwell model to the nonlinear regime, several time derivatives (e.g. upper convected, lower convected and corotational) are proposed to replace the ordinary time derivative in the original model. The idea of these derivatives is to express the constitutive equation in real space coordinates rather than local coordinates and hence fulfilling the Oldroyd's admissibility criteria for constitutive equations. The Oldroyd-B model is a simplification of the more elaborate and rarely used Oldroyd 8-constant model which also contains the upper convected, the lower convected, and the corotational Maxwell equations as special cases. Oldroyd-B model is apparently the most popular in viscoelastic flow modeling and simulations [46].

In the current study, a computational model is used to simulate muco-ciliary transport process where mucus is considered as a viscoelastic fluid. The major thrust of this study is to make the role of rheological properties of mucus clearer in the muco-ciliary transport system by using an Oldroyd-B model as the constitutive equation of mucus. The Oldroyd-B model is discussed in term of the convected components of the stress tensor and the metric coefficients of the convected coordinate system. Material constants appeared in this constitutive equation and also temperature history could be included if it is desired to account for nonisothermal effects [44]. To the best our knowledge, this is the first attempt to introduce a proper model of the effects of the rheology properties of mucus in much greater details. The study of the selected properties is one of the most important steps in understanding the structure of mucus distribution in the lungs and to understand how mucus can be moved forward efficiently toward the trachea. In addition, it is believed that prescribing a drug for changing the rheological properties of mucus would be easier than changing the other properties like cilia frequency or length of cilia.

We begin with by presenting the governing and constitutive equations describing this class of flows which is shown in Fig. 1 with appropriate boundary conditions in Sections 2 and 3. Section 4 describes the numerical calculation procedure for the muco-ciliary transport model in details. This is followed by a detailed description of the influence of rheological characteristic of mucus on the muco-ciliary transport problem in Section 5.