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Discrete multi-physics simulations of diffusive and convective mass transfer in boundary layers containing motile cilia in lungs

Mostapha Ariane [a,*], Stavros Kassinos [b], Sitaram Velaga [c], Alessio Alexiadis [a]

[a] School of Chemical Engineering, University of Birmingham, Edgbaston, Birmingham, B15 2TT, United Kingdom
[b] Department of Mechanical and Manufacturing Engineering, University of Cyprus, 1678, Nicosia, Cyprus
[c] Pharmaceutical Research Group, Division of Medical Science, Department of Health Science, Luleå University of Technology, 971 87, Luleå, Sweden

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ABSTRACT

In this paper, the mass transfer coefficient (permeability) of boundary layers containing motile cilia is investigated by means of discrete multi-physics. The idea is to understand the main mechanisms of mass transport occurring in a ciliated-layer; one specific application being inhaled drugs in the respiratory epithelium. The effect of drug diffusivity, cilia beat frequency and cilia flexibility is studied. Our results show the existence of three mass transfer regimes. A low frequency regime, which we called shielding regime, where the presence of the cilia hinders mass transport; an intermediate frequency regime, which we have called diffusive regime, where diffusion is the controlling mechanism; and a high frequency regime, which we have called convective regime, where the degree of bending of the cilia seems to be the most important factor controlling mass transfer in the ciliated-layer. Since the flexibility of the cilia and the frequency of the beat changes with age and health conditions, the knowledge of these three regimes allows prediction of how mass transfer varies with these factors.

1. Introduction

Motile cilia are hair-like structures present on the surface of a variety of cells. They are found in large numbers in the human body and beat in coordinated waves to perform a number of different functions. For instance, in the conducting and central airways of the lungs, cilia are surrounded by mucus that traps particulate materials and pathogens. The coordinated motion of the cilia propels these materials towards the pharynx where they are swallowed or expelled via coughing, a phenomenon known as mucociliary clearance or mucociliary escalator [1]. Mathematical modelling of this phenomenon has attracted the interest of various researchers in material, biological and pharmaceutical sciences. The main motivation is to understand the factors controlling the effectiveness of mucociliary clearance since this is important in the context of environmental exposure (see Ref. [2] for a detailed review). Ref. [3] introduced an analytical model of a mucus layer with cilia motion. Their findings suggested that the mucus flow in contact with the airway is governed by a viscosity gradient in the mucus layer, but in this work, the cilia were only considered as rigid rods. Later, Ref. [4] implemented a more realistic cilia motion model including effective and recovery stroke in a two layers system. The outcomes highlighted the role of the cilia penetration (in the mucus layer) on the mucus transport effectiveness. At the beginning of the new century, Ref. [5] focused their researches on the mucus draining in an idealised rigid bronchial tree with an air flow effect. Their model showed the viscosity-dependence of the mucus transport as well as the important role of the geometry. The emergence of the Immersed Boundary Method (IBM) has allowed a significant enhancement in mucociliary clearance modelling. Ref. [6] studied the effects of the velocity, the viscosity, the beat cilia frequency, the number of cilia and the depth of the periciliary layer. The main results showed that (i) the velocity of the periciliary fluid is linearly proportional to the cilia beat frequency, (ii) the mucus viscosity plays a little role on the mucus flow rate contrary to the number of cilium which increases the mucus transport, and (iii) a minimum depth of periciliary layer is needed to generate a mucociliary transport. Ref. [7] extended the two-dimensional [6] model to a three-dimensional representation and thus were able to capture the cilia motion in the normal direction; they confirmed the previous results. Additionally, the same authors in another publication [8], focused on cilia dysfunction and malformation. They emphasized the negative effects of too elastic and too rigid cilia beat patterns on the mucus transport. Then, a method coupling IBM with a lattice Boltzmann method was used by Ref. [9] to implement an Oldroyd-B model and to simulate a viscoelastic fluid. They found that an increase of the mucus viscosity accelerates the movement of mucus layer. Ref. [10] with a

* Corresponding author.
E-mail address: mxa437@bham.ac.uk (M. Ariane).

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penalty technique, also concentrated their researches on genetic cilia diseases and defective mucus clearance using a non-Newtonian model. They correlated, in the case of cystic fibrosis, mucus velocity and rheology with a mucus maturation model and highlighted that shear-thinning mucus can accentuate agglomeration phenomena in regions with ineffective clearance. Most of the previous studies have focused on the altered effectiveness of mucociliary clearance under disease states, for example in primary or acquired ciliary dyskinesia. Here, we also take a look how impairments to the ciliary function can modify the speed with which pollutants, irritants and toxic agents can reach the airway epithelium.

While mucociliary escalator is one of the major defence mechanisms protecting the lungs, it has important implications in pulmonary drug delivery. In the case of inhaled aerosolized medicines, mucociliary clearance competes with the particle dissolution and absorption that eventually determines the lung bioavailability of the inhaled drugs [11]. Smaller particles trapped in the mucus layer progressively dissolve and diffuse towards the epithelium and the drug gets absorbed (Fig. 1a). On the other hand, larger or slowly dissolving particles are partly cleared by the ciliary action, thus reducing the amount of drug absorbed (Fig. 1b). Mucociliary clearance concerns the mass transfer of particles trapped in the mucus layer to the pharynx for clearance, whilst the drug absorption depends on the diffusion of particles towards the epithelium through the mucus and the ciliated-layer. The role that the cilia beat pattern plays as part of the mucociliary clearance mechanism has been studied in the past. While the cilia beat is also likely to affect mass transfer, to the best of our knowledge, it has received no attention in the literature from this perspective.

In this work, we use a modelling technique called discrete multi-physics [12–17] to investigate how the motion of the cilia affects mass transfer conditions in the ciliated-layer. By means of discrete multi-physics, the following research questions are addressed. Does the presence of the cilia enhance or hinder the mass transfer in the ciliated layer? For example, it is known that smoking, age, and health conditions affect the frequency of the cilia beat [18]. Thus, it is of interest to understand how drug absorption is sensitive to the frequency of the beat. Finally, does the flexibility of the cilia, which also depends on age and health conditions [19], play a role too?

Answering these questions can provide insights not only to the development of inhalation medicines, or to the dynamics of harmful chemicals during environmental exposure, but also the design of artificial cilia needed for lab-on-a-chip or organ-on-a-chip applications [20].

2. Preliminary considerations and background

2.1. Cilia beat

In the past, several studies [21–27] have investigated the cilia motion in the respiratory epithelium. The results are not always fully consistent with each other (e.g. Fig. 2), but in general, the cilia motion is divided into two phases: an ‘effective stroke’, in which the cilia move forward and propel the mucus layer in the same direction; and a ‘recovery stroke’, in which the cilia return to their initial position.

Moreover, the movement of each cilium (Fig. 2) is coordinated with that of the others producing a wave-like overall motion known as metachronal wave. A variety of cilia beat frequencies in the range between 3 and 20 Hz have been observed in the respiratory epithelium, with the frequency being a function of temperature, age and health conditions [25–27]. Artificial cilia used in lab-on-a-chip applications, on the other hand, can reach higher frequencies in the order of 50 Hz [28].

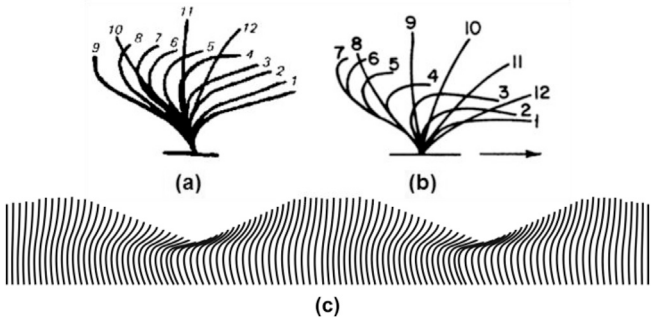

Fig. 2. Cilium's motion according to (a) Sandersonand Sleigh [22] and (b) Aielloand Sleigh [21] and (c) metachronal wave.

2.2. Membrane permeability and mass transfer

In general, the rate of absorption of a certain drug into the body depends on the permeability P_{me} [m s^{-1}] of the cellular membrane to that specific drug. In experiments, the drug's flux through the membrane J [kg m^{-2} s^{-1}] is measured and the permeability calculated from

$$J = P_{me}(c_1 - c_2), \tag{1}$$

where $c_2 - c_1$ [kg m^{-3}] is the difference of drug's concentration across the membrane (Fig. 3a).

If before permeating the membrane, the drug diffuses through an additional mass transfer resistance (e.g. the layer of mucus), the total permeability P_{TOT} of the mucus + the membrane layer is given by

$$\frac{1}{P_{TOT}} = \frac{1}{P_{me}} + \frac{1}{P_{mu}}, \tag{2}$$

where P_{mu} is the drug's permeability of the mucus layer.

In the respiratory epithelium, between the mucus layer and the membrane, there is a third layer, the periciliary layer (PCL), where a low-viscosity fluid is agitated by motile cilia. The overall permeability of the mucus + ciliated + membrane layer is, therefore,

$$\frac{1}{P_{TOT}} = \frac{1}{P_{me}} + \frac{1}{P_{mu}} + \frac{1}{P_{pcl}}, \tag{3}$$

where P_{pcl} is the permeability of the ciliated−layer.

Permeability is the term mostly used in biology and medicine; in physics and engineering, it is often replaced by the molecular diffusivity D [m^2 s^{-1}], which is linked to permeability by the relation

$$P = \frac{D}{\delta}, \tag{4}$$

where δ [m] is the thickness of the layer where the drug diffuses. There is, however, a fundamental difference between mass transfer in the

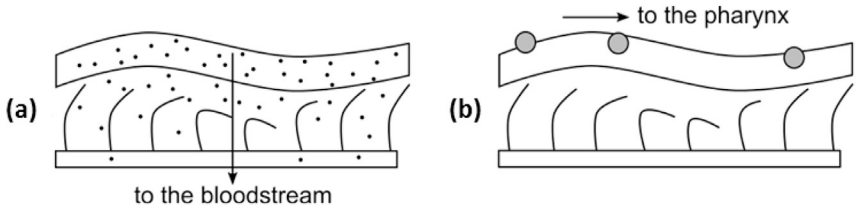

Fig. 1. Drug absorption (a) versus mucociliary clearance (b).