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MUCUS TRANSPORT IN THE HUMAN LUNGS: A MATHEMATICAL ANALYSIS

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Abstract: In this paper, a planar two layer fluid model is proposed to study mucus transport in the human lungs under steady state condition due to cilia beating and air-motion by considering mucus as a visco-elastic fluid. The effect of air-motion is considered by prescribing air-velocity at the mucus air interface. It is shown that mucus transport increases as the pressure drop, air velocity due to air-motion and the velocity generated by cilia tips increase. It is also noted that the effect of gravity is similar to that of the pressure drop. It is also observed that mucus transport decreases as the viscosity of serous layer fluid or that of mucus increases, but any increase in mucus viscosity at its larger values does not seem to affect the mucus transport. It is also found that for given total depth of serous layer and mucus layer, there exists a serous fluid layer thickness for which mucus transport is maximum. It is also shown that mucus transport decreases as its elastic modulus increases.

Keywords: Mucus transport, visco-elastic mucus, air velocity, cilia beating.

1. Introduction

The muco-ciliary system is one of the most important primary defense mechanisms of the human lung airways for cleaning the inspired air of contaminants and for removing entrapped particles such as bacteria, viruses, cellular debris, carcinogens in tobacco smoke, etc. from the lungs through mucus transport. It consists of three layers namely: a mucus layer, a serous layer and the cilia which are small hair-like projections lining with the epithelium of the bronchial respiratory tracts. The serous layer fluid is considered as a Newtonian fluid while mucus as a visco-elastic fluid. It has been pointed out that, in general, mucus transport depends upon the structure of cilia, the functions imparted by cilia tips in the serous sub-layer fluid, the thicknesses and the viscosities of the serous fluid and mucus and the interaction of mucus with the serous layer fluid. Mucus transport is also dependent on the pressure drop in the airways generated by the processes such as inspiration, expiration, coughing, etc. It also depends on gravity. Mucus transport also depends on air-motion and when mucus is assumed as visco-elastic fluid, the mucus transport depends on the relaxation time. (Blake [3] and Sleigh et al.[8]). In recent decades, the mucus transport in the human lungs has been studied by several researchers. In particular, an analytical model has been presented by Barton and Raynor [2] by considering the cilium as an oscillating cylinder with a greater height during the effective stroke and a smaller height during the recovery stroke. Agarwal and Verma [1] and Verma [10,11] have studied the mucus transport by analyzing the effect of porosity due to the formation of porous matrix bed by immotile cilia. Ross and Corrsin [7] modelled muco-ciliary pumping by representing the beating of cilia by a travelling surface wave (envelop) and predicted that mucus behaves like an elastic slab and its transport decreases as the fractional depth of serous layer fluid decreases. King et al. [4] have given a planar two-layer fluid model by considering mucus as a visco-elastic fluid. They have taken the effect of cilia beating and air-motion due to forced expiration and other processes by prescribing shear stress at the mucus-air interface. Tanner [9] has shown that the load capacity of a given film of lubricant is lowered and the coefficient of friction is increased by viscoelastic effects.

In view of the above, we are interested to study the mucus transport in the human lungs by taking the following aspects into account:

(i) The serous layer fluid is considered as incompressible Newtonian fluid while mucus layer is considered as a visco-elastic fluid.

(ii) The serous layer fluid is divided into two sub-layers, one in contact with the epithelium and other in contact with the mucus. It is assumed that cilia during beating impart a velocity at the mean level of their tips, causing the serous sub–layer in contact with mucus to undergo motion. No net flow is assumed in the serous sub layer in contact with the epithelium.

(iii) The effect of air – motion is considered by prescribing air-velocity at the mucus-air interface as a boundary condition.

(iv) The effects of pressure gradients and gravity are also incorporated in the model.

2. Mathematical Formulation

The physical situation of the transport of serous fluid and mucus in the human lung airways may be represented by a planar two-layer fluid model as shown in Fig.1.

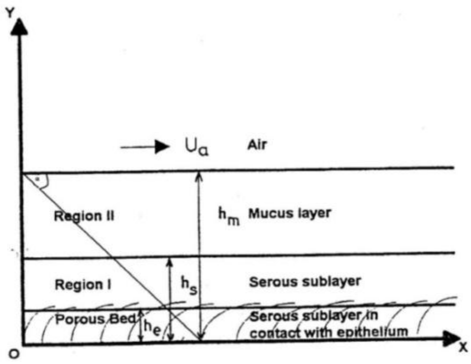

Fig.1. Mucus transport in the Human Lungs.

In the serous sub layer $0 \leq y \leq h_e$, i.e. in the serous sub-layer in contact with the epithelium, no net flow of the fluid is assumed. However, in the serous sub layer $h_e \leq y \leq h_s$ (region I) and in the mucus layer $h_s \leq y \leq h_m$ (region II), the flow of respective fluids is governed by interactions of cilia beating, air- motion in contact with the mucus, pressure gradients present in the fluid and gravity. The equations governing the motion of the serous layer fluid and the mucus under steady state and low Reynold's number flow approximations, by taking the effect of gravity into account in the direction of flow, can be written as follows:

Region I $h_e \leq y \leq h_s$ (Serous layer):

$$\mu_s \frac{\partial^2 u_s}{\partial y^2} = \frac{\partial p}{\partial x} - \rho_s \, g \cos\alpha \qquad ...(1)$$

Region II $h_s \leq y \leq h_m$ (Mucus layer):

$$\frac{\partial \tau_m}{\partial y} = \frac{\partial p}{\partial x} - \rho_m g \cos\alpha \qquad ...(2)$$

$$\mu_m \frac{\partial u_m}{\partial y} = \tau_m \left[1 + \lambda^2 \left(\frac{\partial u_m}{\partial y}\right)^2\right] \qquad ...(3)$$

where p is the pressure that is constant across the layers; u_s and u_m are the velocity components of serous sub-layer fluid and mucus in x- direction respectively; ρ_s, μ_s, ρ_m and μ_m are their respective densities and viscosities; g is the acceleration due to gravity and α is the angle by which the airway in the lung is inclined with the vertical. Here, h_e is the mean thickness measured from the surface of the epithelium to the tips of cilia during beating i.e. the interface between the two serous sub-layers; h_s is the thickness measured from the surface of the epithelium to the interface between serous sub-layer and mucus and h_m is the thickness measured from the surface of the epithelium to the mucus air-interface, λ ($=\frac{\mu_m}{G}$) is the relaxation time, G is the shear modulus of elasticity and τ_m is the shear stress in the mucus layer. Equation (3) gives the relationships between the shear stress and the velocity gradient for visco-elastic fluid i.e. for mucus in the case of one dimensional flow (King et al. [4]).

The following boundary and matching conditions are taken for the system of equations (1) - (3)**:**

Boundary Conditions

$$u_s = U_0 \,, \qquad y = h_e \qquad ...(4)$$

$$u_m = U_a \,, \qquad y = h_m \qquad ...(5)$$

where condition (4) incorporates the mean velocity U_0 imparted by cilia tips during beating in the serous sub – layer at the level y = h_e. The condition (5) incorporates the air velocity U_a due to air-motion similar to the analysis of Blake [3] and King et al. [4].

Matching Conditions

$$u_s = u_m = U_1 , \qquad y = h_s \qquad \text{...(6)}$$

$$\mu_s \frac{\partial u_s}{\partial y} = \tau_m , \qquad y = h_s \qquad \text{...(7)}$$

where U_1 is the mucus-serous sub layer interface velocity to be determined by using equation(7). The conditions (6) and (7) imply that the velocities and the shear stresses are continuous at mucus-serous layer interface.

3. Analytical Solution

Solving (1)-(3) and using boundary and matching conditions (4)-(7), we get (Tanner [9]):

$$u_s = \frac{\phi_s}{2\mu_s}(y - h_s)(y - h_e) - \frac{(y - h_s)}{(h_s - h_e)} U_0 + \frac{(y - h_e)}{(h_s - h_e)} U_1 \qquad \text{...(8)}$$

$$u_m = \frac{\phi_m}{2\mu_m}(y - h_m)(y - h_s) + \frac{\lambda^2 \phi_m^3}{64\mu_m^3}[\{(y - h_m) + (y - h_s)\}^4 - (h_m - h_s)^4] + U_a \qquad \text{... (9)}$$

where

$$U_1 = U_0 - \frac{\phi_s}{2\mu_s}(h_s - h_e)^2 - \frac{\phi_m}{2\mu_s}(h_m - h_s)(h_s - h_e) \qquad \text{...(10)}$$

and $\phi_s = \frac{\partial p}{\partial x} - \rho_s g \cos\alpha, \phi_m = \frac{\partial p}{\partial x} - \rho_m g \cos\alpha$ ...(11)

The volumetric flow rates i.e. fluxes in the two layers are respectively defined as follows:

$$Q_s = \int_{h_e}^{h_s} u_s dy \quad \text{and} \quad Q_m = \int_{h_s}^{h_m} u_m dy$$

which after using (8) and (9) are found as:

$$Q_s = -\frac{\phi_s}{3\mu_s}(h_s - h_e)^3 - \frac{\phi_m}{4\mu_s}(h_m - h_s)(h_s - h_e)^2 + U_0(h_s - h_e) \qquad \text{...(12)}$$

$$Q_m = -\frac{\phi_m^3}{80\mu_m G^2}(h_m - h_s)^5 - \frac{\phi_m}{12\mu_m}(h_m - h_s)^3 - \frac{\phi_m}{4\mu_s}(h_s - h_e)(h_m - h_s)^2 - \frac{\phi_s}{4\mu_s}(h_s - h_e)^2(h_m - h_s) + \frac{1}{2}(U_a + U_0)(h_m - h_s) \qquad \text{...(13)}$$

It can be seen by using equation of fluid continuity that Q_s and Q_m are constants, therefore, from equations (12) and (13), we note that $-\frac{\partial p}{\partial x}$ is also constant. Hence, replacing it by the pressure drop over the length L of the cilia beating zone, the expressions for the fluxes in the two regions may be written as:

$$Q_s = \frac{\phi_{s0}}{3\mu_s}(h_s - h_e)^3 + \frac{\phi_{m0}}{4\mu_s}(h_m - h_s)(h_s - h_e)^2 + U_0(h_s - h_e) \qquad \text{...(14)}$$

$$Q_m = \frac{\phi_{m0}^3}{80\mu_m G^2}(h_m - h_s)^5 + \frac{\phi_{m0}}{12\mu_m}(h_m - h_s)^3 + \frac{\phi_{m0}}{4\mu_s}(h_s - h_e)(h_m - h_s)^2$$

$$+\frac{\phi_{s0}}{4\mu_s}(h_s-h_e)^2(h_m-h_s)+\frac{1}{2}(U_a+U_0)(h_m-h_s) \quad ...(15)$$

$$\phi_{s_0}=(\frac{\Delta p}{\Delta L}+\rho_s g\cos\alpha) \quad \text{and} \quad \phi_{m_0}=(\frac{\Delta p}{\Delta L}+\rho_m g\cos\alpha) \quad ...(16)$$

where $\Delta p = p_0 - p_L$, $p=p_0$ at $x=x_0$, $p=p_L$ at $x=L$. It is noted that the effect of acceleration due to gravity is similar to that of the pressure drop.

Now, when $\phi_{m_0}=0$, $\phi_{s_0}=0$, then the expressions for the fluxes in the two regions become:

$$Q_s=U_0(h_s-h_e) \quad ...(17)$$

$$Q_m=\frac{1}{2}(U_a+U_0)(h_m-h_s) \quad ...(18)$$

$$Q_s=\frac{\phi_{s0}}{3\mu_s}(h_s-h_e)^3+\frac{\phi_{m0}}{4\mu_s}(h_m-h_s)(h_s-h_e)^2+U_0(h_s-h_e) \quad ...(19)$$

$$Q_m=\frac{\phi_{m0}^3}{80\mu_m G^2}(h_m-h_s)^5+\frac{\phi_{m0}}{12\mu_m}(h_m-h_s)^3+\frac{\phi_{m0}}{4\mu_s}(h_s-h_e)(h_m-h_s)^2$$
$$+\frac{\phi_{s0}}{4\mu_s}(h_s-h_e)^2(h_m-h_s)+\frac{1}{2}U_0(h_m-h_s) \quad ...(20)$$

Remarks: The following remarks can be made by close observation of equations (14)-(15) and (17)-(20) regarding flow rates Q_s and Q_m:

(i) From equations (15), (18) and (20), we note that the effect of G on mucus transport is dependent on U_a, ϕ_{m0} and ϕ_{s0}. When these quantities are zero, Q_m does not depend on either G or μ_m. In fact, in such a case, $\frac{Q_m}{(h_m-h_s)}$, the mucus mean linear velocity is independent of mucus depth and depends only on velocity due to cilia beating. This result is in line with the analytical results of King et al. [4].

(ii) When $\phi_{s0}=0$ and $\phi_{m0}=0$ and if there is no pressure drop in the fluid layers and no effect of gravity, then from equations (17) and (18), we observe that both Q_s and Q_m increase as the velocity of cilia tips during its beating phase increases. Q_m Increases further as the air-velocity at the mucus-air interface caused by air-motion increases. Again, Q_s increases as the serous layer thickness increases and Q_m increases as the mucus thickness increases. The mucus transport remains relatively independent of mucus viscosity, implying that mucus moves as an elastic slab which is in the line with the findings of Ross and Corrsin [7].

Further, when $h_s \to h_e$ i.e. for negligible thickness of serous layer and $U_0=0$, from equation (17), we get $Q_s=0$ and from equation (18) it is noted that Q_m increases as the mucus thickness increases or air-velocity increases. These results are similar to those obtained by King et al. [5, 6] in their experiments.

(iii) When $U_a = 0$, i.e. in the absence of air motion, from equations (19)-(20), we clearly note that Q_s and Q_m increase as the pressure drop, gravity and velocity of the cilia tips increase mucus transport Q_m also increases as its elastic modulus G decreases. Further, in this case, Q_s and Q_m decreases as the viscosities of mucus and serous layers increase.

Also, when $h_s \to h_e$ i.e. for negligible thickness of serous layer from equation (19), we get $Q_s = 0$ from equation (20), we noted that Q_m increases as the mucus thickness. Also, for $\phi_{m0} = 0$, Q_m does not depend on mucus viscosity. However, for $\phi_{m0} > 0$, Q_m decreases as mucus viscosity increases. This particular case corresponds with experimental studies of King et al. [5, 6]. The predictions of the mathematical model are in general agreement with those obtained experimentally, i.e. positive dependence mucus thickness and pressure drop and negative dependence on viscosity in the absence of serous layer.

(iv) To see the effect of mucus thickness on mucus transport in the general case, we find the rate of change of Q_m for a fixed total thickness of mucus and serous layers from equation (15) as follows:

$$\frac{\partial Q_m}{\partial h_s} = \frac{\phi_{s0}}{4\mu_s}\{2(h_m - h_s) - (h_s - h_e)\}(h_s - h_e)$$

$$+\frac{\phi_{m0}}{4\mu_s}\{(h_m - h_s) - 2(h_s - h_e)\}(h_m - h_s)$$

$$-\frac{\phi_{m0}}{4\mu_m}\left[1 + \left\{\frac{\phi_{m0}}{2G}(h_m - h_s)\right\}^2\right](h_m - h_s)^2 - \frac{1}{2}(U_a + U_0) \quad ...(21)$$

From equation (21), we note that $\frac{\partial Q_m}{\partial h_s}$ can be negative, zero or positive depending on the values of h_s and other parameters. This implies that there may exist a critical value h_0 of h_s for which Q_m may be maximum. Thus, for fixed total thickness of mucus and serous layers and for some values of $h_s > h_0$, mucus transport may increase with decreasing serous layer thickness (i.e., with increasing mucus thickness), while for the other values of $h_s < h_0$, mucus transport may decrease with decreasing thickness of the serous layer. The former result is in line with the experimental observations of King et al. [5] as pointed out earlier, while the latter result is similar to that obtained by Ross and Corrsin [7].

(v) In general case, from equation (15), we notice that the coefficient of $\frac{1}{G^2}$ is always positive; hence, the mucus transport Q_m increases as elastic modulus G decreases for given values of various parameters. This implies that mucus transport increases as its elastic modulus decreases in the general case also. The result is in line with the experimental observations of King et al. [5, 6] for mucus gel simulants. Similar results have also been obtained by Verma and Tripathee [12].

4. Results and Discussion

To study the effect of various parameters on mucus transport rate quantitatively, the expression for Q_m given by (15) can be written in non-dimensional form as:

$$\bar{Q}_m = \frac{\bar{\phi}_{m0}{}^3\bar{\lambda}_0{}^2}{80\bar{\mu}_m{}^3}\left(1-\bar{h}_s\right)^5 + \frac{\bar{\phi}_{m0}}{12\bar{\mu}_m}\left(1-\bar{h}_s\right)^3 + \frac{\bar{\phi}_{m0}}{4\bar{\mu}_s}\left(\bar{h}_s-\bar{h}_e\right)\left(1-\bar{h}_s\right)^2$$
$$+\frac{\bar{\phi}_{s0}}{4\bar{\mu}_s}\left(\bar{h}_s-\bar{h}_e\right)^2\left(1-\bar{h}_s\right)+\frac{1}{2}\left(1+\bar{U}_a\right)\left(1-\bar{h}_s\right) \qquad ...(22)$$

by using the following non-dimensional parameters:

$$\bar{h}_e = \frac{h_e}{h_m}, \bar{h}_s = \frac{h_s}{h_m}, \bar{\mu}_s = \frac{\mu_s}{\mu_0}, \bar{\mu}_m = \frac{\mu_m}{\mu_0}, \bar{\phi}_{s0} = \frac{\phi_{s0}h_m^2}{\mu_0 U_0}, \bar{\phi}_{m0} = \frac{\phi_{m0}h_m^2}{\mu_0 U_0},$$
$$\bar{U}_a = \frac{U_a}{U_0}, \bar{G} = \frac{Gh_m}{\mu_0 U_0}, \bar{\lambda}_0 = \frac{1}{\bar{G}}, \bar{Q}_m = \frac{Q_m}{h_m U_0}. \qquad ...(23)$$

where μ_0 is the viscosity of the serous sub layer fluid in contact with epithelium. Expression for $\bar{Q}_m$ given by equation (22) is plotted in Fig. 2 to 6 using the following set of parameters which have been calculated by using typical values of various characteristics related to airways:

$$\bar{h}_e = 0.10, \bar{h}_s = 0.10-0.50, \bar{\mu}_s = 1-10, \bar{\mu}_m = 10-100, \bar{\phi}_{s0} = 1,$$
$$\bar{\phi}_{m0} = 5-20, \bar{U}_a = 0.020-0.040, \bar{\lambda}_0 = 0-0.10. \qquad ...(24)$$

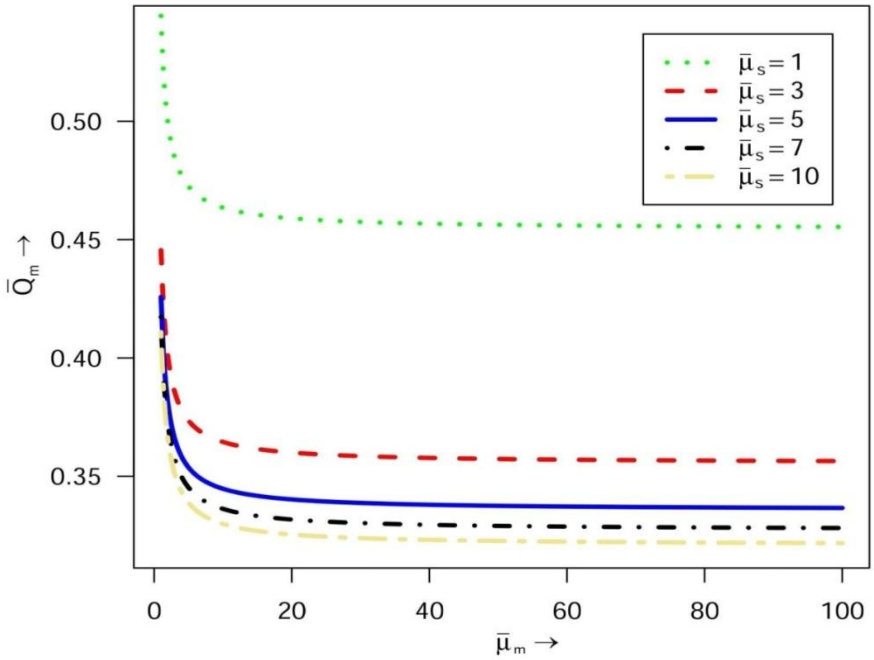

Fig.2: Variation of $\bar{Q}_m$ with $\bar{\mu}_m$ for different values of $\bar{\mu}_s$.

Fig.2 illustrates that for the fixed values of $\bar{h}_e = 0.10$, $\bar{h}_s = 0.20$, $\bar{\phi}_{s0} = 1$, $\bar{\phi}_{m0} = 5$, $\bar{U}_a = 0.020$, and $\bar{\lambda}_0 = 0.20$, mucus transport decreases as the viscosity of the serous layer fluid or that of the mucus increases. However, increase in mucus viscosity at larger values do not have any significant effect on its transport. This corresponds to the result that mucus moves as an elastic slab (Ross and Corrsin [7]).The result is also in line with the analytical results of King et al. [4] and experimental findings of King et al. [5, 6].

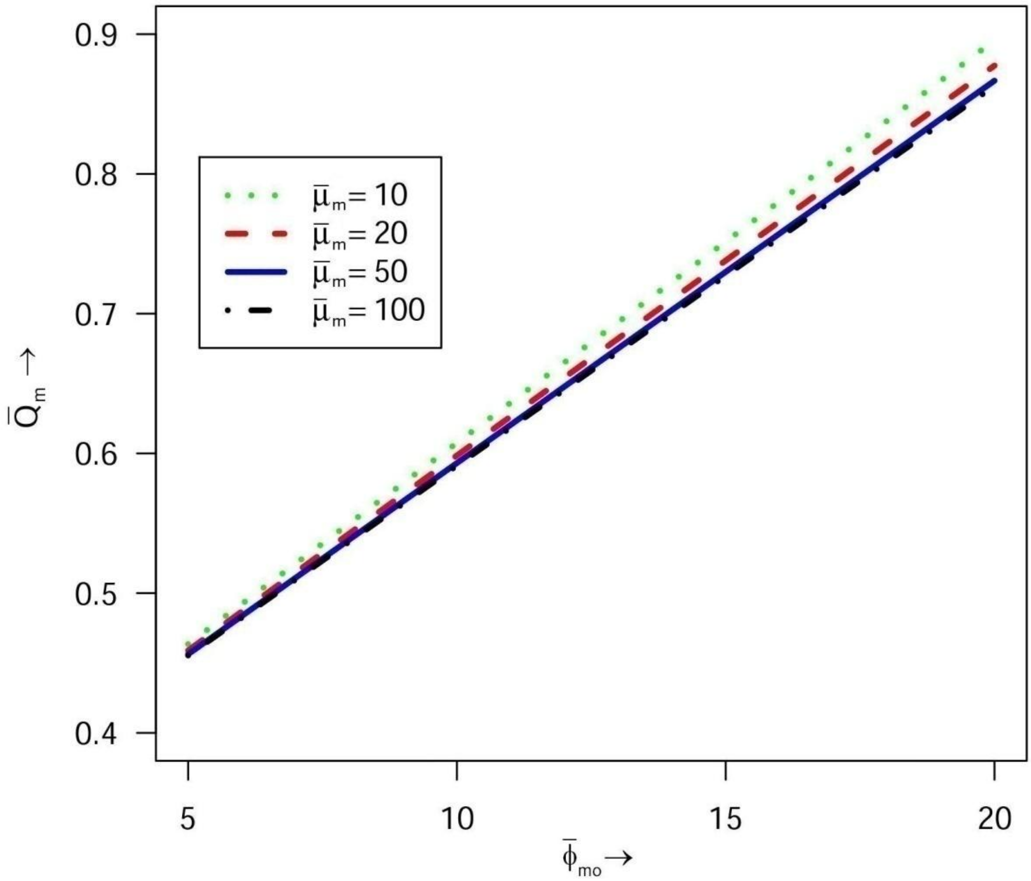

Fig. 3: Variation of $\bar{Q}_m$ **with** $\bar{\phi}_{m0}$ **for different values of** $\bar{\mu}_m$.

Fig.3 illustrates that for the fixed values of $\bar{h}_e = 0.10$, $\bar{h}_s = 0.20$, $\bar{\phi}_{s0} = 1$, $\bar{\phi}_{m0} = 5$, $\bar{U}_a = 0.020$, and $\bar{\lambda}_0 = 0.20$, mucus transport increases as the pressure drop in mucus layer or gravity increases, but it decreases with increase in its viscosity, the relative decrease being larger at larger values of pressure drop or gravity. This result is in line with the analytical results of Agarwal and Verma [1], Verma [10, 11], King et al. [4] and the experimental findings of King et al. [6].

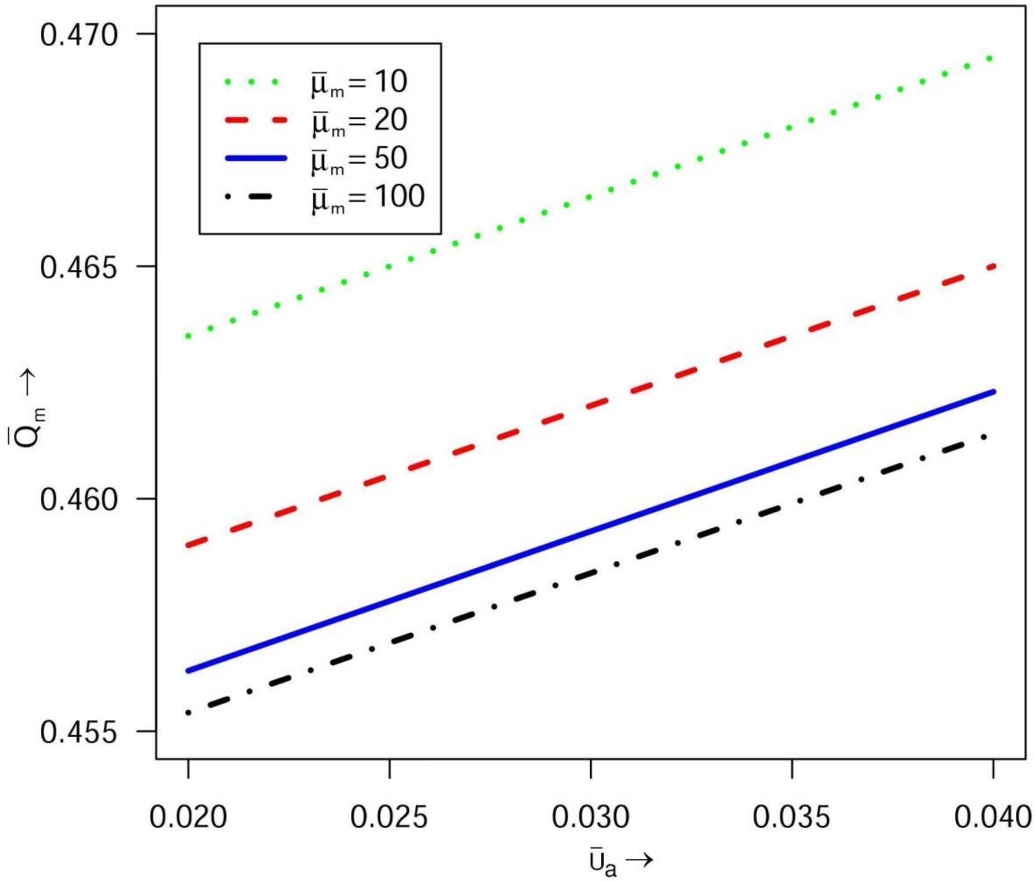

Fig. 4: Variation of $\overline{Q}_m$ **with** $\overline{U}_a$ **for different values of** $\overline{\mu}_m$.

Fig. 4 illustrates that for the fixed values of $\bar{h}_e = 0.10$, $\bar{h}_s = 0.20$, $\bar{\mu}_s = 1$, $\bar{\phi}_{s0} = 1$, $\bar{\phi}_{m0} = 5$ and $\overline{\lambda_0} = 0.20$, mucus transport increases as the air-velocity (due to air-motion) at the mucus air-interface increases, but it decreases as its viscosity increases. This is in line with the analytical results of Verma [10].

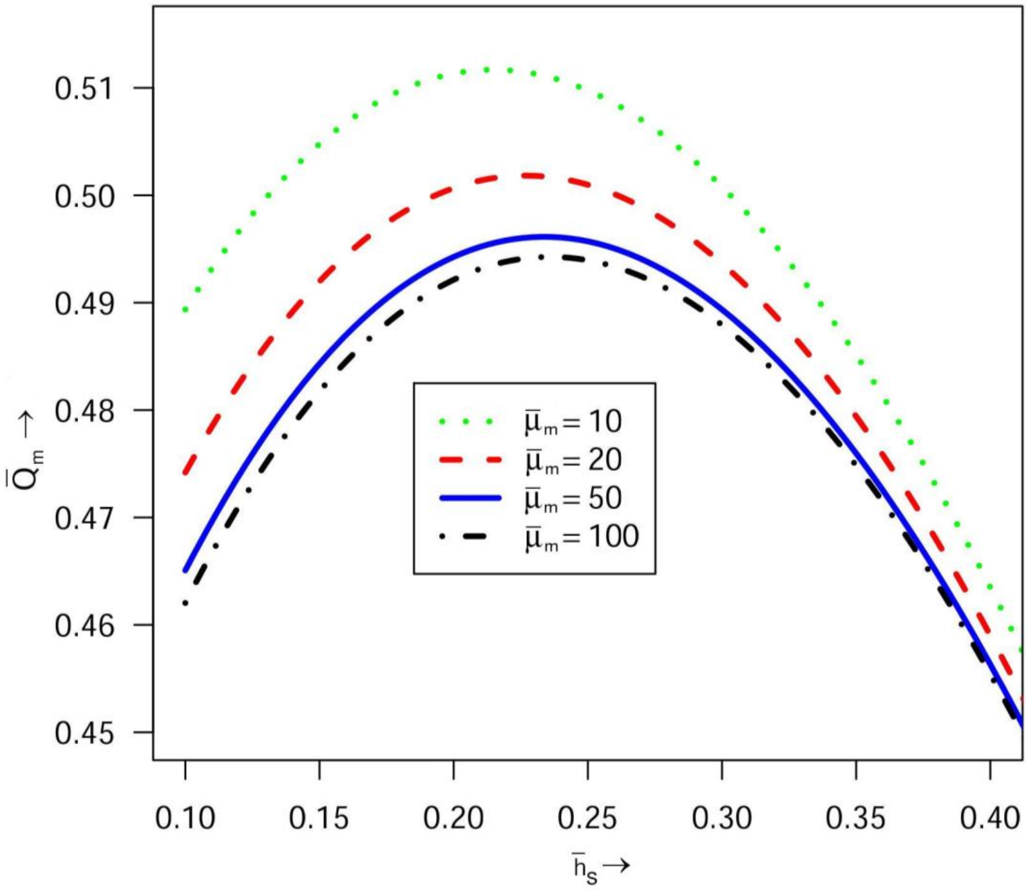

Fig. 5: Variation of $\bar{\boldsymbol{Q}}_{\boldsymbol{m}}$ **with** $\bar{\boldsymbol{h}}_{\boldsymbol{s}}$ **for different values of** $\bar{\boldsymbol{\mu}}_{\boldsymbol{m}}$.

Fig.5 illustrates that for the fixed values of $\bar{h}_e = 0.10$, $\bar{\mu}_s = 1$, $\bar{\phi}_{s0} = 1$, $\bar{\phi}_{m0} = 5$, $\bar{U}_a = 0.020$ and $\bar{\lambda}_0 = 0.20$, mucus transport increases as $\bar{h}_s$ increases upto a critical values of $\bar{h}_s$(approximately equal to 0.22) after which it start decreasing with increasing $\bar{h}_s$. Since $\bar{Q}_m$ approaches to unity, this implies that for a fixed total thickness of mucus and serous layer, there exists an optimum value of $\bar{Q}_m$ for some values of serous layer thickness. The conclusion corresponding to decrease in mucus transport with decrease in serous layer thickness is in line with the analysis of Ross and Corrsin [7], Agarwal and Verma [1] and Verma [11].

We further note that $\bar{Q}_m$ decreases as $\bar{\mu}_m$ increases, the relative decrease in $\bar{Q}_m$ with $\bar{\mu}_m$ is smaller for values of $\bar{h}_s$ greater than its optimal values.

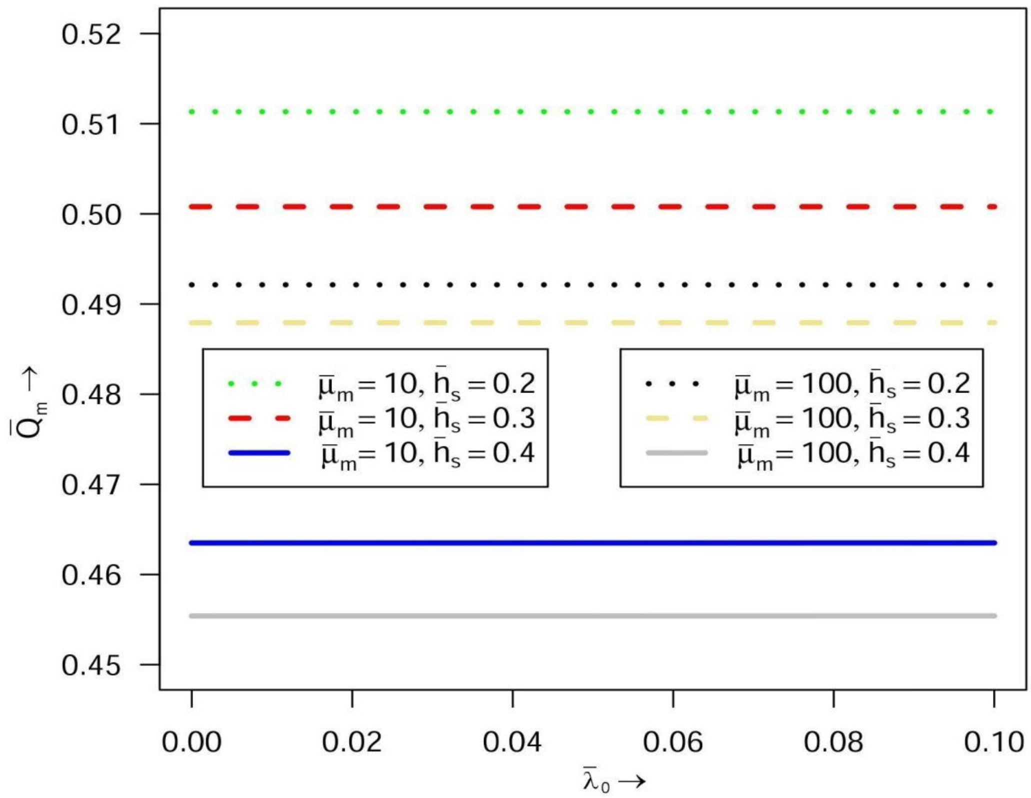

Fig. 6: Variation of $\bar{Q}_m$ **with** $\overline{\lambda_0}$ **for different values of** $\bar{\mu}_m$ **and** $\bar{h}_s$**.**

Fig.6 illustrates that for the fixed values of $\bar{h}_e = 0.10$, $\bar{\mu}_s = 1$, $\bar{\phi}_{s0} = 1$, $\bar{\phi}_{m0} = 5$ and $\bar{U}_a = 0.020$, mucus transport deceases as $\bar{h}_s$ increases or as the mucus viscosity increases. This figure also illustrates that the mucus transport becomes independent with $\overline{\lambda_0}$ for a fixed value of mucus viscosity. This concludes that the mucus transport decreases as its elastic modulus increases. Again, this is in line with the analytical results of King et al. [4].

5. Conclusion

In this paper, we have presented a planar two-layer mathematical model to study mucus transport in the human lungs under steady state condition due to cilia beating and air-motion by considering mucus as a visco-elastic fluid. The effect of air-motion is considered by prescribing air-velocity at the mucus air interface.

The governing equations of motion are solved analytically and the effect of various parameters on the mucus transport rate have been discussed. Furthermore, the effect of values of various parameters on mucus transport rate have been computed numerically and have been explained graphically.

It is shown that mucus transport increases as the pressure drop, air velocity due to air-motion and cilia tip velocity generated by cilia tips increase. It is also noted that the effect of gravity is similar to that of the pressure drop. It is also observed that mucus transport decreases as the viscosity of serous layer fluid or that of mucus increases, but any increase in mucus viscosity at its higher values does not seem to affect the mucus transport. It is also found that for given total depth of serous layer and mucus layer, there exists a serous fluid layer thickness for which mucus transport is maximum. It is also seen that mucus transport decreases as its elastic modulus increases.

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