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ESTIMATION OF MUCUS CLEARANCE IN PULMONARY AIRWAYS BY MEANS OF A REGRESSION MODEL

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Abstract- In this study, a multivariate regression analysis was performed on a dataset obtained from experimental tracheal model for mucus clearance in pulmonary airways. Several simulations have been done to verify the validity of the generated regression model. In general, the clearance of mucus in the airways is achieved by the beating action of cilia inside the serous layer which is the primary means of removing inhaled particulates and airway debris from airways in healthy people. In this study, two types of mucus simulants are used in the experimental setup. Clearance distances of a teardrop shape simulant are measured for different velocities, slope angles and surfaces properties. On the obtained data by applying several genuine transformations we developed a multiple regression model that is able to predict clearance up to 86% accuracy. Simulations revealed several important data like direct relation between velocity and clearance and indirect relation between angle and clearance.

Key Words- Mucus Simulant, Tracheal Model, Multivariate Regression Analysis, Linear Model, Simulation.

1. INTRODUCTION

Coughing is necessary for removing inhaled particulates and airway debris from pulmonary airways. There are several studies in the literature for coughing experiments. In some studies, to simulate pulmonary airway, a tygon tube [7], a rigid channel [8], or an endotracheal tube [3-9] were used. Airflow limitation is due to excess mucus and the effectiveness of the mucociliary clearance depends on rheology and the quantity of mucus as well as activity of the cilia indicated by King [11]. Mucus simulants were prepared by cross-linking locust bean gum with sodium tetra borate, 12% to simulate more gel-like mucus with a low V/E (viscosity/elasticity) ratio [1-5]. Aliquots of 3% simulant resemble to normal lung mucus and the stimulant obtained by mixing a higher amount of sodium tetra-borax correlate with diseases such as cystic fibrosis, chronic bronchitis, and asthma [12]. Mucus clearance was investigated mechanically and experimentally (in vitro) for different air velocities, coughing angles and surfaces using different simulants in references before [3-9]. Other references will be explained in the text as appropriate.

In this study, we have performed a multivariate regression analysis on the data set obtained from the tracheal model [4-10] where air flow was controlled by a 3-way solenoid valve between a constant pressure source and the test section, and the duration of flow was 0.2-0.3 seconds. Two different mixtures were used as mucus simulant (MS). During multivariate regression analysis five variables have been used.

2. STATISTICAL TOOLS

In the world of statistics, regression is often used to predict or estimate the future of a given data set. Either linear or logistic regression formula is often used to describe a given data set and thus it helps to predict further values. The formula is selected according to the dataset behavior; scatter diagrams provide a visual technique to display data which show the functional relationship between variables and behavior [13]. In our case the dataset shows linear behavior, as shown in Figure 1 (i.e., for 15 angle, slippery surface and 12% mucus simulant) where clearance increases when velocity increases and data are distributed linearly.

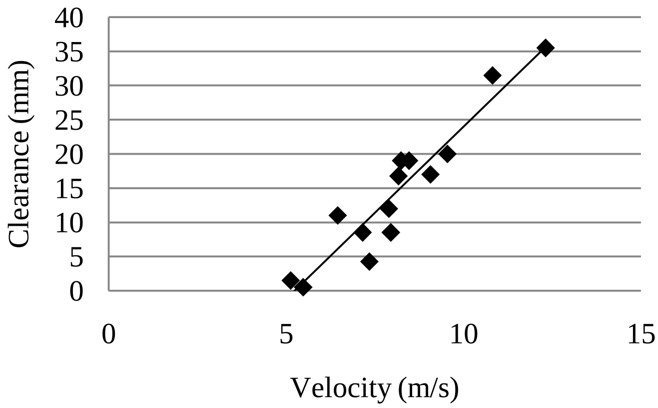

Figure 1. Scatter diagram between variables

Multivariate regression analysis includes techniques for modeling and analyzing several variables and focuses on the relationship between dependent and one or more independent variables. The general formula for linear regression model is given in equation (1). The proper constant coefficients are obtained when model's squared error is minimal [13]. The x_i are independent variables where they can represent several characteristics of a model for our case see Table 1 and Y is a dependent variable which depends on values of x_i variables, β_i coefficients and c_j constant, thus changes accordingly.

$$Y_i = \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_p x_{ip} + c_i = \sum_{i=1}^{k} \beta_i X_{ij} + c_j \quad (1)$$

The format of the paper is as follows; the materials and methods are explained in Section 3, simulation results and discussions are given in Section 4 and the lastly we address the conclusions of the work.

3. MATERIALS AND METHODS

In this section, in-vitro experimental procedure for mucus clearance and multivariate regression analysis procedure configurations for the tracheal model are discussed.

3.1. Experimental Procedure For In Vitro Mucus Clearance

The experimental tracheal model is shown in Figure 2 [6]. The controlled air flow was supplied with constant pressure towards mucus stimulant resting on a removable flat wall inside a half cylindrical pipe. The angle between the tracheal model and the horizontal was changed during the experiment. Mucus clearance was observed for different angles and air velocities. The setup was composed of the following parts: tracheal model, laminar flow element to prevent turbulent flow, computer, and software which controls air flow, solenoid valve, a close-up high rate imaging system, light source, and a ruler. The stimulant lost its property during long waiting period due to heating of high power light source. That's why the experiments should have been performed rapidly. 1 mm^3 simulant was placed on the tracheal model removable flat wall using a small syringe and allowed settling before sliding it into test section. The air flow was supplied for 0.3 seconds which is approximate coughing duration and the clearance was measured by observing the ruler on the video images and/or also was read directly using the ruler. The experiments were performed for different angles, different surface properties (dry, adhesive, slippery) and different simulants. The angles are 0, 15, 30, 45, 60 and 75 degrees.

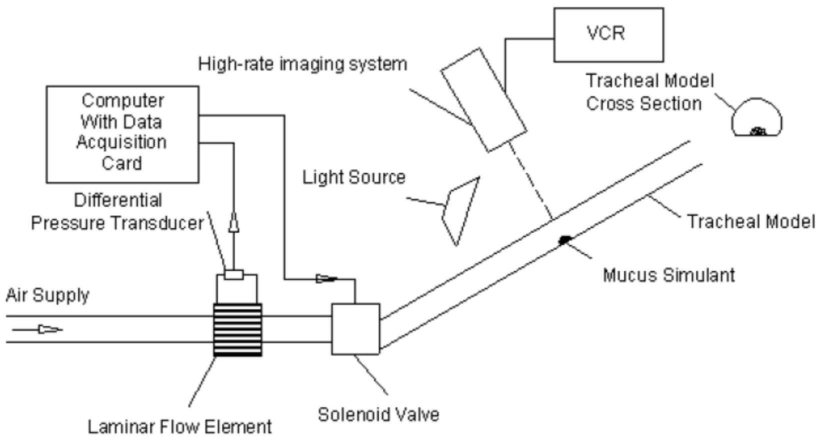

Figure 2. Experimental Tracheal Model [4-6]

3.2. Multivariate Regression Analysis Procedure Configurations

While developing the regression model, we have identified one dependent (i.e., clearance) and four independent variables (i.e., mucus simulant – MS, surface – S, velocity – V and CV – transformed variable see Section 3.2.1). Selections were performed according to correlations between dependent and independent variables. Outliers' detection operation which removes the inconsistent data obtained under the same conditions has been performed by checking the residues. For the identification of values for surface and mucus simulants Non-linear Solver Algorithm (i.e., types of algorithms which tend to improve the results in each run, in our case to decrease the squared error [13]) have been used. For our data-set the Non-linear Solver Algorithm showed the best results and fitted our data-set better as compare to other prediction algorithms. The parameters are given in the experimental values part in Table I for details see Section 3. The coefficient values obtained using non-linear solver algorithm is as follows: mucus simulants are 0.6 and 0.2 for 3% and 12% respectively; surfaces are 0.3, 0.6 and 0.9 for slippery, dry and adhesive respectively. To test validity of the regression model several simulations have been performed by using prediction ranges.

Table 1. Variables parameters

	Experimental Values	Prediction Ranges
S	[0.3, 0.6, 0.9]	[0,1]
MS	[0.6, 0.2]	[0,1]
V	[9, 25]	[0, 30]
CV	[9,25]	[0, 30]

3.2.1. Transformations on Variables

We have found that when we perform a transformation on variables as stated in the formula "cos(slope in degrees)*Velocity (mm/s)" the correlation increases and gives a positive impact on a linear model due to the physical notation of increasing the effect of force. When slope increases the component of weight of mucus droplet in the direction of motion increases, thus the clearance decreases. Rubin et al. [14] indicated an inverse correlation of cough clearing with the contact angle and adhesiveness of mucus.

4. RESULTS AND DISCUSSION

4.1. Linear regression model

During multivariate regression analysis, we checked the correlations between dependent and independent variables by observing scatter diagrams and performing detection and omission of outliers. As a result after performing residue analysis on 650 observations the output data set decreased to 480. The equation of a linear model is given in equation [8], for parameters given in Table 1.

$$Clearance = 19{,}51 * S - 4{,}00 * MS - 0{,}36 * V + 0{,}74 * \cos(\theta) * V \quad (2)$$

During the tracheal model experiments some of the measurements did not result as expected. At the initial stages the regression analysis showed very low R and R^2. After performing the residual analysis and applying the non-linear solver algorithm, the prediction rate increased substantially as given in Table 2. Simulations showed that clearance decreases with increasing angle. Similarly clearance became larger at higher air velocities (Section 4.2).

Table 2. Statistical parameters

R	0.86
R^2	0.73

4.2. Model simulations

In this part of our work we explain the results of simulation in order to understand the experimental model and test the regression model. We have observed several important details that are explained in sections below. As stated above mucus shows a very rapid decrease in dynamic viscosity when frequency increases and has less effect on elasticity stated by King and Macklem [12]. In the work of Foster et al. [15] it is stated that increased volume of mucus production and decreased mucociliary clearance may cause accumulation of mucus in the airway tree.

4.2.1. Angle with constant velocity values

Simulations in this section have been performed with constant velocity values (i.e., 5, 10, and 15 m/s) and different angles in order to see the effect of two variables on clearance shown in Figure 3. We observed that when angle increases the clearance decreases and at higher velocities the clearance increases. It is also observable that velocity variation has a larger effect at low angles but less effect at larger angles on clearance. It is clear that the relationship between two variables is non-linear.

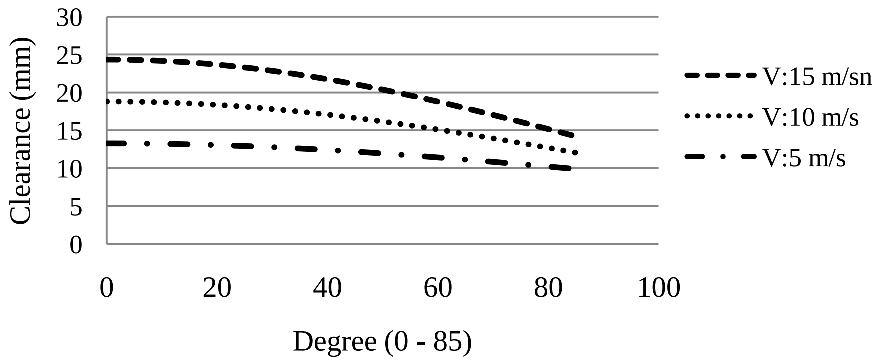

Figure 3. Angles with constant velocity values

4.2.2. Velocity with constant angle degrees

Simulations in this section have been performed with constant angle ranges (i.e., 0, 30, 45, and 60 degrees) and increasing velocity shown in Figure 4. It is also clear that when angle increases the clearance decreases and it is worth mentioning that the relationship between the two variables is linear and higher velocity rates increase the impact of angle variation on clearance.

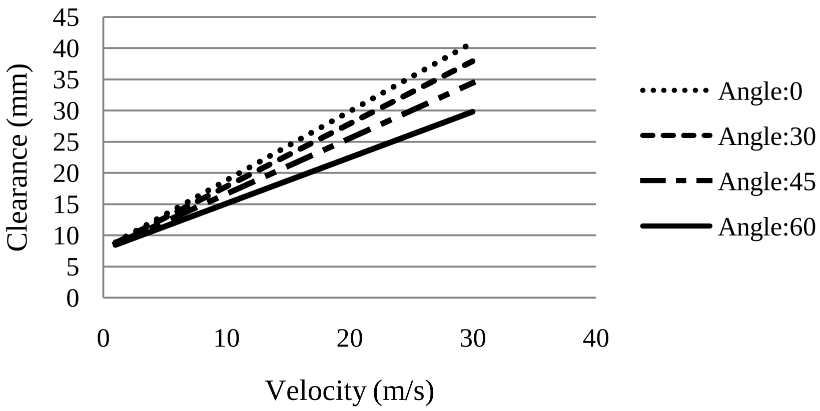

Figure 4. Velocity with constant angle values

4.2.3. Angle with constant mucus simulant parameters

Simulations in this section have been performed with constant mucus simulant values (i.e., 0.25, 0.5, 0.75, and 1.00) and increasing angle shown in Figure 5, for mucus simulant coefficient values see Table I. In order to see that effect of mucus simulant on clearance, the velocity has been decreased to the lowest value. We have observed that 12% mucus simulant has higher impact on clearance rather than 3% because it is more solid in nature.

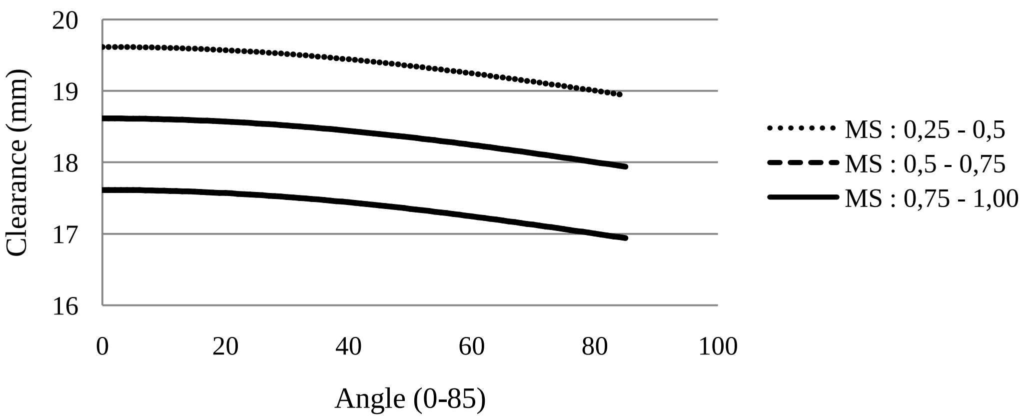

Figure 5. Angle with constant mucus simulant values

4.2.4 Angle with constant surface parameters

Simulations in this section have been performed with constant surface values (i.e., 0.25, 0.5, 0.75, and 1.00) and increasing angle is shown in Figure 6, for surface coefficient values refer Table 1. In order to see the effect of surface on clearance, the velocity has been decreased to the lowest value. We have observed that the clearance increases when surface becomes adhesive, because this type of surface prevents the mucus simulant from going backward and lower clearance for slippery surface, because when the angle increases mucus simulants tend to slide down. King et al. [16] stated that samples with higher elasticity cleared less well. An increased amount of mucus seems to improve clearance stated by Svartengren et al. [17]. From our studies, we observed that generally an adhesive surface has higher impact and slippery surface has lower impact whereas a dry surface is in-between. Because we studied the model generally the error rate is higher for lower angles in this section, in future we shall develop methods that will rectify such problems in more accurately.

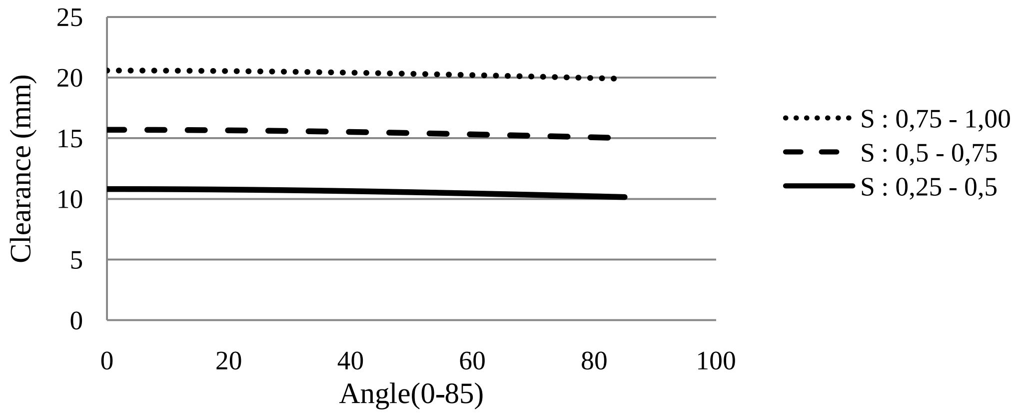

Figure 6. Angle with constant surface values

5. CONCLUSION

A linear multivariate regression model for mucus clearance in pulmonary airways is generated using experimental data obtained from in-vitro tracheal model tests. The regression model is tested by several simulations for different parameters. Four variables are used in multiple regression analysis (i.e., mucus simulant – MS, surface – S, velocity – V and CV – transformed variable). It is important to state that strong correlations between dependent and independent variables result in better linear model and higher R and R^2 statistical parameters. We have observed that when the angle increases the clearance decreases and with high velocity the clearance increases and 12% mucus simulant has higher impact on clearance rather than 3% due to its solid nature. In addition, we observed that generally the adhesive surface has a higher impact on clearance and the slippery surface has lower impact whereas the dry surface is in between. Simulations revealed several important data like the direct relation between velocity and clearance and indirect relation between angle and clearance.

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