COMPUTATIONAL MODEL FOR OPTIMIZING PULMONARY DRUG DELIVERY ON THE HUMAN MISSIONS TO MARS. Mohammed Ali[1], Malay K. Mazumder[2], Rama N. Reddy[3], Mariofanna Milanova[4], Jing Zhang[5], and Alexandru S. Biris[6]. Address: Donaghey College of Information Science and Systems Engineering, University of Arkansas at Little Rock, ETAS 575, 2801 S. University Ave., Little Rock, AR 72204, USA. Email: [1]mxali, [2]mkmazumder, [3]rnreddy, [4]mgmilanova, [5]jxzhang1, [6]asbiris@ualr.edu.

Abstract: A computational model has been developed for *in-silico* studies of the optimum deposition of engineered respiratory drug aerosol particles in the human lungs while taking a flight to Mars. Since the lung is exquisitely sensitive to gravity, it is imperative, astronauts receive treatment if needed for pulmonary discomforts, while they are in the occupational settings of the Martian mission, where the medicinal drug aerosols inhalation conditions are fairly different than on ground. In such environmental circumstances, administration of respiratory drug aerosols to the flight crews in a conventional way would be problematic, and the targeted drug efficacy and bioavailability may not be achieved. Therefore, a precise control over the aerosol properties, such as drug particle size and electrostatic charge, would be necessary. With this in mind, the presented model employs an integrated approach which takes into account four deposition mechanisms, including inertial impaction, Brownian diffusion, interception, and electrostatic forces, as there is no or limited gravitational settling available during the flight due to zero or micro gravity. The model's application software has been developed using Visual C++ and is capable of handling polydispersed therapeutic drug particles with homogeneous distributions of particle size and electrostatic charge. In addition, it also offers users the freedom of studying the sensitivity of each property of the aerosols to the respiratory deposition. The results showed that by enhancing electrostatic charge 1.5 times, improvement in the deposition of drug aerosols in the respiratory airways can be achieved, which will compensate 67% of the reduction due to the absence of gravity.

Introduction: West et al. [15] reported greatly altered pulmonary functions to the astronauts while they were in microgravity. Inhalation therapy is required to treat such discomfort. Therapeutic drug aerosols delivery and deposition in the lung are strongly affected by several factors, including aerosol properties, breathing environment, gravitational acceleration, and physiochemical properties of the airways [10]. In the past, various studies developed computational models to study the respiratory drug deposition while the study subjects were on the ground (gravity G). No studies, however, have been done for the crews when they are situated in the flight to the Red Planet, Mars. It is well accepted that computer modeling is the most inexpensive and versatile method for analyzing a real life situation since it saves considerable time, effort and expense compared to studies relying solely on human subjects testing. Simulation of the lung deposition mechanisms would not only be faster using computational model but would be very responsive to controlling aerosol properties and inhalation parameters to deliver pharmaceutical drugs to cure pulmonary diseases.

The primary mechanisms of lung deposition of inhaled respirable drug aerosol particles in the human lung consist of five electromechanical processes: inertial impaction, Brownian diffusion, interception, gravitational settling and electrostatic force effects (Figure 1). Mathematical expressions that are widely accepted to calculate lung deposition efficiencies are:

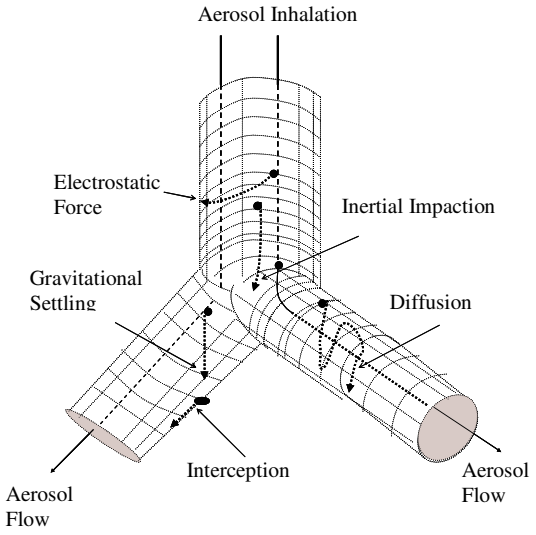

Fig. 1. Respiratory drug particle deposition mechanisms in the human lung.

(i) Impaction by Yu [16]; (ii) Laminar diffusion by Ingham [6]; (iii) Turbulent diffusion by Landahl [8]; (iv) Gravitational settling by Heyder [4], Pich [11]; (v) Space and image charge forces by Yu [17]. Balachandran et al. [2] proposed a simplified mathematical model based on the above contributions with focus on electrostatic effect. Among all the mechanisms, inertial impaction and gravitational settling are the dominant causes for particle deposition in the head airways [5]. The terminal settling velocity, inertial impaction and electrostatic forces are approximately proportional to the square of the particle

diameter [13]. Therefore, they favor deposition in the lower respiratory airways. In order to test mathematical models, researchers employed Weibel's lung morphometry model which has been regarded as a standard of the human lung anatomy [1,14]. It divides human respiratory tract into 24 generations, providing specific length, diameter, area and volume for each generation. Our computational model adopted Weibel's data as well. In addition, the model investigated the sensitivity of aerosol's electrostatic charge property to the total respiratory drug deposition in the absence of gravitational settling.

Methodology: The application software of the computational model was coded in Microsoft Visual C++. Since the mathematical expressions were based on the contributions from several researchers as cited in the introduction section, it is well recognized that algebraic complexity of equations in their original form are unable to imply in a general manner. Any well behaved (smooth, continuous) mathematical expression can be re-expressed as an infinite polynomial, or approximated by finite polynomial. Balachandran et al. [2] made such approximations to leave each original equation with single variable term. Both algorithm and code were realized from that simplified form to calculate deposition efficiency due to impaction, laminar and turbulent diffusion, gravitational settling, and electrostatic image and space charge forces. The model assumed tabular airway, and did not include alveolar sacs. Each airway generation was represented progressively by a cylinder whose length increased and diameter deceased. It considered inhalation only, and a constant aerosol flow rate of 500 ml/s which is the average light activity breathing condition of a healthy adult.

Deposition efficiency (η) is the ratio of the particles deposited in the particular generation to those entering the respiratory tract. The mathematical expression to calculate deposition efficiency due to the intertial impaction is shown in equation 1,

$$\eta_i = \left\{1.5\,x10^{6}\right\}\left\{d_a^2 q_v\right\}\left\{\frac{L_i}{N_i D_i^4}\right\} \qquad (1)$$

where d_a = aerodynamic diameter, D_i = diameter of the airways, q_v = airflow rate, L_i and N_i are the length and number of the airways in the i_{th} generation respectively.

Liu and Wang [9] modeled the aerosol particle interception efficiency and their investigations showed that the particle interception mechanism does not have significant impact on deposition efficacy. Instead, Brownian diffusion and gravitational settling take care of interception for drug particles. Mathematical expressions to calculate the deposition efficiencies due to turbulent diffusion (TD), laminar diffusion (LD), gravitational settling (GS), electrostatic image (EI) charge and electrostatic space (ES) charge forces are shown in equation 2–6,

$$\text{TD, } \eta_t = \left\{1.9\,x10^{-8}\right\}\left\{d_a q_v\right\}^{-\frac{1}{2}}\left\{L_i N_i\right\}^{\frac{1}{2}} \qquad (2)$$

$$\text{LD, } \eta_l = \left\{5.18\,x10^{-11}\right\}\left\{d_a q_v\right\}^{-\frac{2}{3}}\left\{L_i N_i\right\}^{\frac{2}{3}} \qquad (3)$$

$$\text{GS, } \eta_g = \left\{3x10^{7}\right\}\left\{\frac{d_a^2}{q_v}\right\}\left\{L_i N_i D_i\right\} \qquad (4)$$

$$\text{EI, } \eta_{im} = \left\{3.9\,x10^{-8}\right\}\left\{\frac{n^2}{d_a q_v}\right\}^{\frac{1}{3}}\left\{\frac{L_i N_i}{D_i}\right\}^{\frac{1}{3}} \qquad (5)$$

where n = number of electronic charges per particle.

$$\text{ES, } \eta_{sp} = \left\{1.2x10^{-24}\right\}\left\{\frac{n^2}{d_a q_v}\right\}\left\{L_i N_i D_i^2 C_{oi}\right\} \qquad (6)$$

where C_{oi} = coefficient of space charge effects.

In order to integrate interactive effects of each mechanism as well as their superposition principle, we adopted Landahl's [8] realistic numerical method. For calculation simplicity both laminar and turbulent diffusions can be combined to a single term of diffusion ($\eta_d = \eta_l + \eta_t - \eta_l\eta_t$), and both space and image charge forces can be combined into electrostatic force ($\eta_e = \eta_{im} + \eta_{sp} - \eta_{im}\eta_{sp}$). These results in the total deposition efficiency are shown in equation 7.

$$\eta_T = \eta_i + \eta_d + \eta_g + \eta_e + \eta_i\eta_d\eta_g\eta_e - \eta_i\eta_d\eta_g - \eta_d\eta_g\eta_e - \eta_i\eta_g\eta_e - \eta_i\eta_d\eta_e \qquad (7)$$

Figure 2 shows the module structure chart of the computational model for determining deposition efficiencies due to the different deposition mechanisms.

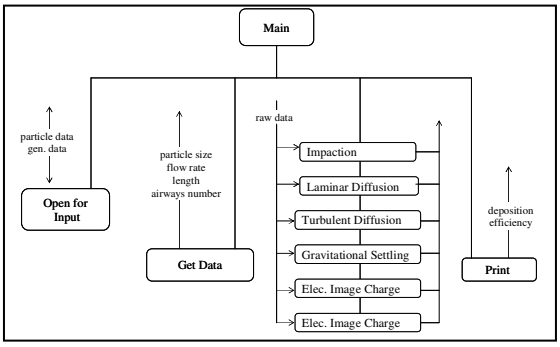

Fig. 2. Module structure chart of the computation model to determine the deposition efficiencies due to various deposition mechanisms.

Simulation Results: Many simulations were performed using the proposed computational model, with varying aerosol parameters (homogeneous distributions of size and/or charge). The particles were considered unipolarly charged with an inhalation flow

rate of 30 L/m. We assumed that the particles were solid spheres, have a unit density of 1000 kg/m^3, and that they instantly achieved the velocity of the air inside the respiratory tract. The particles' aerodynamic diameters (d_a) were in the range of 0.1 to 10 µm.

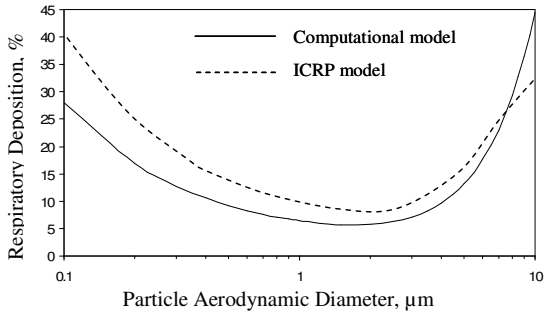

Fig. 3. Predicted total respiratory drug aerosol depositions for light physical activity based on ICRP model and computational model.

Using the computational model we developed, predictions of the total respiratory drug aerosol depositions for light physical activity is presented in the Figure 3. Also included in figure 3 are the predictions based on the International Commission on Radiological Protection (ICRP66) model [7].

ICRP66 Human Respiratory Tract Model was ideally developed for determining radiological particle deposition. It is an empirical model based on the theoretical model and mathematical formalism. Its recursive convolution of deposition efficiencies were calculated for extrathoracic (ET), tracheobronchial (BB), bronchiolar (bb), and alveolar-interstitial (AI) deposition. Our model however does not take into account ET deposition, since Finlay [3] pointed out that the empirical model usually differs considerably from reality (for ET airways) when inhaling respiratory drugs. As a result, our model predicted slightly lower percent deposition (5 ± 2%) for particles in the size rage of 0.1 to 6 µm than the ICRP model. The difference can be the result of different assumptions and methods used in the derivation of the formula. The increased deposition of particles larger than 6 µm complies with Swift's [13] observation (calculational model predicts high large particle deposition efficiency in the alveolar region). Overall, our model predicted depositions were fairly consistent with the ICRP depositions for the particle size range of 0.1 to 10 µm.

The contribution of different deposition mechanisms to the total deposition is presented in Figure 4. The modeling results estimated that the deposition efficiency due to: (a) impaction was extremely small for smaller (d_a <1 µm) particles, (b) gravitational settling was higher for larger (d_a > 3 µm) particles, (c) diffusion and electrostatic force were decreased with increasing particle sizes.

A comparison between the depositions due to different electrostatic charge forces is presented in Figure 5. It clearly demonstrated that 50% increase in the elementary charge approximately doubled the deposition for each size.

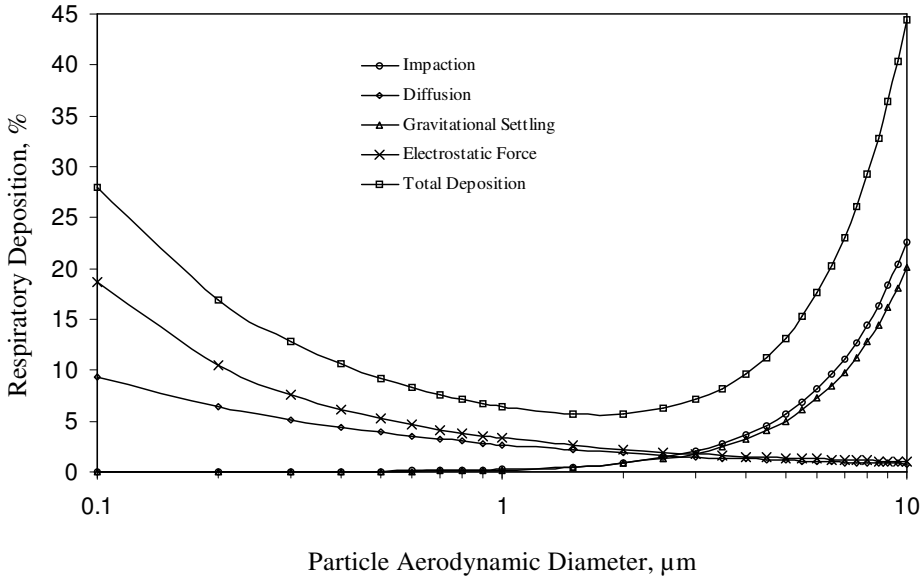

Fig. 4. Effects of deposition mechanisms and total deposition (on Earth surface) for light physical activity.

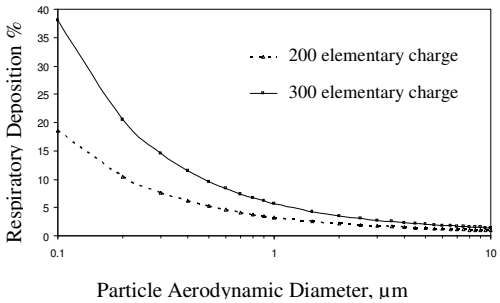

Fig. 5. Comparison of electrostatic charge force deposition efficiencies for different charged aerosols.

Figure 6 shows the total respiratory aerosols deposition in the lung. Curve (a) indicates the deposition pattern (DP) in the lung when the subject is situated at zero gravity. Curve (b) indicates DP when the subject is situated on Earth's surface. Curve (c) indicates DP at zero gravity with enhanced electrostatic charge from 200 to 300 elementary charges. Since the gravitational settling is absent in the zero gravity environment, the amount of respiratory drug delivery to the lung will be 30 % lower than usual. The deposition efficiency can be increased by 23% by increasing the electrostatic charge in the aerosols by 50%. Thus it is logical to conclude that, a substantial amount (about two third) of the reduction in respiratory drug aerosol delivery in the lung due to zero gravity can be recovered by increasing the electrostatic charge of the aerosols.

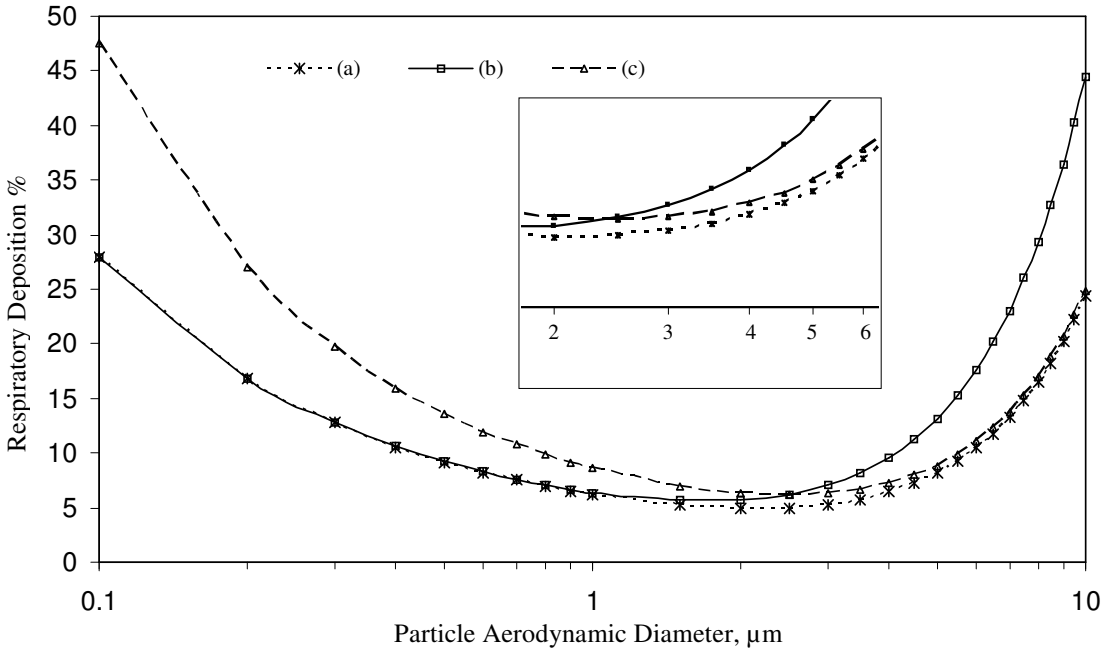

Fig. 6. Total respiratory aerosols deposition in the lung, (a) at zero gravity, (b) on Earth's surface, and (c) at zero gravity with enhanced elementary charge from 200 to 300. Inset shows deposition patterns of ideal therapeutic size range (2 to 6 µm) particles.

Conclusion: A flexible integrated computational lung deposition model for zero gravity environments which incorporated the effects of all four deposition mechanisms has been developed. The model is in good agreement with the mathematical model proposed by the international commission on radiological protection. The influences of different deposition mechanisms have been examined. Analysis indicated that drug aerosol particle's size and charge were very sensitive to the deposition efficiencies. The administration of respiratory aerosolized drugs to the Martian mission flight crews will suffer from lower amount of delivery due to the absence of gravity. A substantial portion of that reduction can be recovered by controlling the electrostatic charge property of drug aerosols.

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