AN INTEGRATED MULTI-SCALE MULTI-PHYSICS COMPUTATIONAL MODEL OF THE RESPIRATORY SYSTEM.

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The transfer and deposition of particles in the respiratory system is of major interest for the development of targeted local and systemic drug delivery formulations (Illum, 2006; Azarmi et al., 2008). The effect of size on particle transfer and deposition has been well studied for smooth spherical particles. However, several issues remain to be elucidated including the deposition of non-spherical particles, dispersion and aggregation effects, changes in particle size, shape, and aggregation state as well as the effect of particle charge and surface properties. The fate of deposited particles is of major concern. Deposited particles can undergo disaggregation, can release beneficial drugs, and, if sufficiently small, can penetrate into the bloodstream. The effective transfer and deposition of particles depends on the physiological state of the respiratory system, e.g. diseased or normal. Diseased physiological states can present constricted airflows, increased mucous layer thickness (due to overproduction or decreased clearance) as well as acute and chronic inflammation. The effective and targeted delivery of drugs in such diseased states remains a challenge to this day.

To further improve the understanding of particle penetration and deposition, integrated multi-scale multi-physics models of the entire respiratory system can be developed that describe the flow of carrier particles/droplets through the nasal cavity and lungs (Martonen et al., 2002; Burrowes, 2008). In this work airflow through the nasal cavity, the nasopharynx, and the pulmonary system down to the alveolar sac and individual alveoli level is determined by dynamic and steady-state CFD simulations (Fig. 1). The deposition of particles is approximated by a Eulerian-fluid/Lagrangian-particle tracking scheme. Dissaggregation kinetics of solid particle aggregates, nanoparticle transfer through liquid carrier droplets, and drug release kinetics are taken into account to determine the total amount of drug released from a single inhalation. Lateral transfer of the deposited particles/droplets by the mucous layer limits the residence time in the pulmonary system and nasal cavities and is also taken into account.

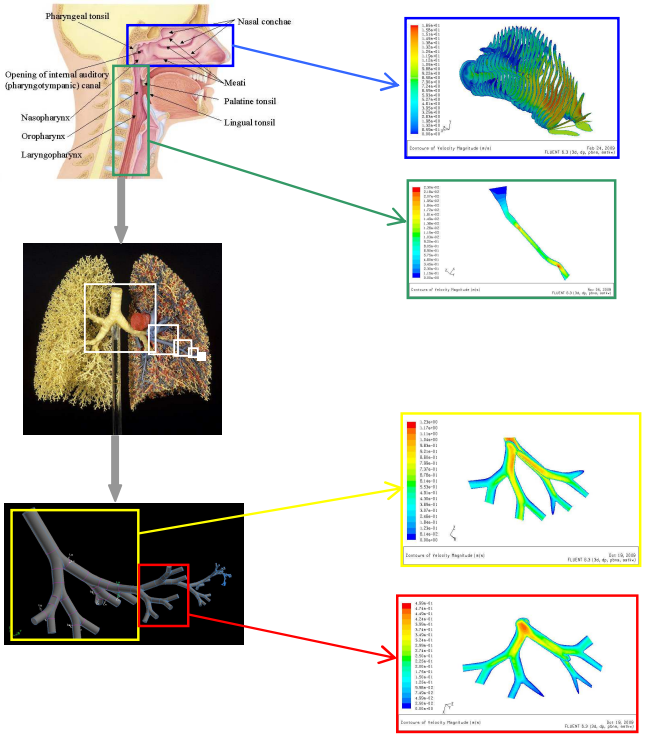

***Fig. 1** Block Computational Model of the Respiratory System*

The nasal cavity consists of two nasal air paths converging to a single pathway at the back of the cavity which is then directed downwards through the nasopharynx to the trachea (Cole, 2000). The two nasal air paths are highly curved and convoluted in shape providing a total surface area of about 150 cm^2. The nasal walls are covered by a mucous layer which moves to the posterior clearing deposited particles. The flow and deposition of particles in the nasal cavity has been investigated by several groups (Liu et al., 2007; Shi et al., 2008; Wen et al., 2008). In this work, the nasal cavity geometry is reconstructed based on a series of medical images. A number of different computational grids are then constructed (from 0.3 10^6 to 2.6 10^6 tetrahedral and/or polyhedral cells). Dynamic and steady-state CFD simulations of airflow during inspirations are performed in which turbulent flow is described with a transitional k-ω model (Fig. 2). Particle deposition in the nasal cavity increases with particle size, D, and volumetric flowrate, Q, and can be described in terms of the impaction parameter, QD^2 (Fig. 3). Inlet particles are assumed to be either single-sized or distributed (e.g., Rosin-Rammler distribution). Comprehensive information on the axial and size distribution of deposited particles can be obtained. It was found that larger particles were mostly deposited in the anterior region of the nasal cavity while smaller particles were deposited less and more evenly throughout the nasal cavity (Fig. 4).

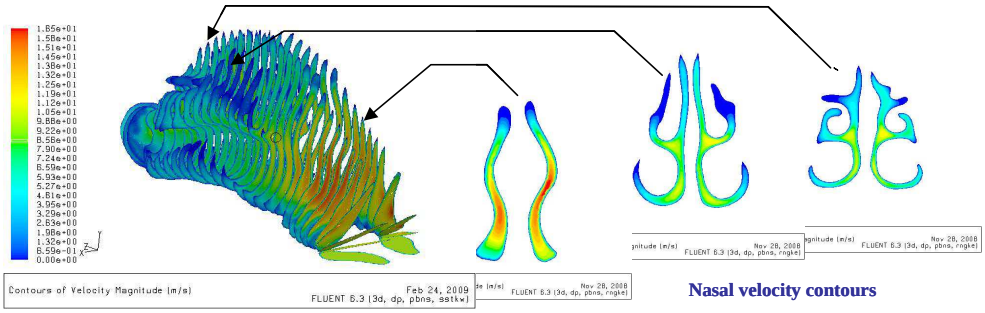

Fig. 2 *Velocity magnitude in the nasal cavity. Coronal sections. Inlet velocity V_{in}=2m/s.*

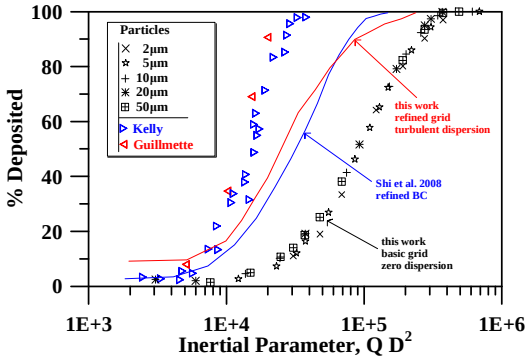

Fig. 3 *Particle Total Deposition Efficiency*

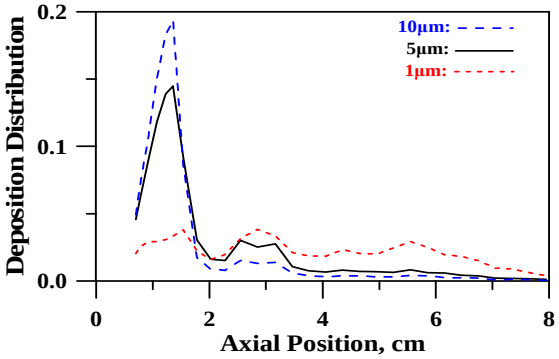

Fig. 4 *Particle deposition profiles in the nasal cavity. V_{in}=2m/s.*

The pulmonary system consists of a multitude of nonsymmetrical branches of progressively smaller diameter. There are a total of 23-24 branch generations leading to about 10^7 simple branches in the entire pulmonary system (Finlay, 2004). This limits the number of branch generations that can be completely simulated to around 5-6 (Longest and Vinchurkar, 2007; van Ertbruggen et al., 2005; Zhang et al., 2002). However, if a single pathline down to the alveolar sacs is considered, a successive simulation approach can be followed (Nowak et al., 2003). In the present work, a model of the pulmonary tract is developed based on 7 consecutive "blocks" of the pulmonary system plus the alveoli-sacs. Each block consists of 4 generations of symmetrical branches with one side rotated 90 degrees relative to the other and is discretized into 2 10^5 tetrahedral cells. The inlet flow and particle motion conditions of each block are obtained from the outlet conditions of the previous block and the inlet conditions of the first block are obtained from the outlet conditions of the nasal cavity. Steady and Dynamic CFD simulations were performed for each block employing the k-ω model for turbulence (Fig. 5). Particle depositions in the pulmonary tract again favored the larger particles (i.e., 100nm-1µm), and only the smallest of particles (i.e., <100nm) could reach the lower respiratory tract and alveolar sacs at significant concentrations (Fig. 6). Drug release from deposited particles and penetration through the underlying mucosal layer is described using a stochastic diffusion model which accounted for the mucosal layer motion as well as the deposition location.

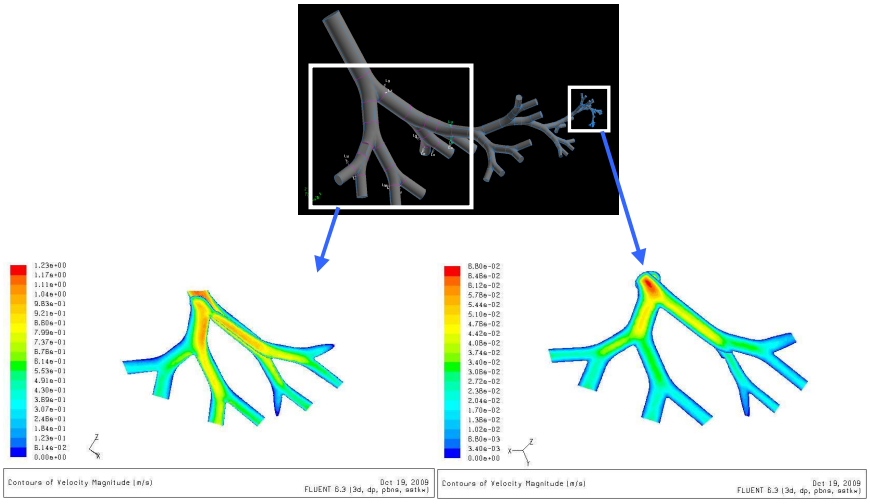

Fig. 5 *Velocity magnitudes for different blocks, V_{in}=2.7m/s.*

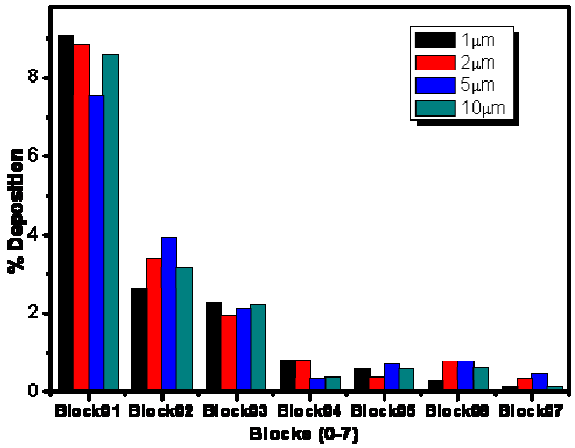

Fig. 6 Local Particle Deposition, V_{in}=2.7m/s.

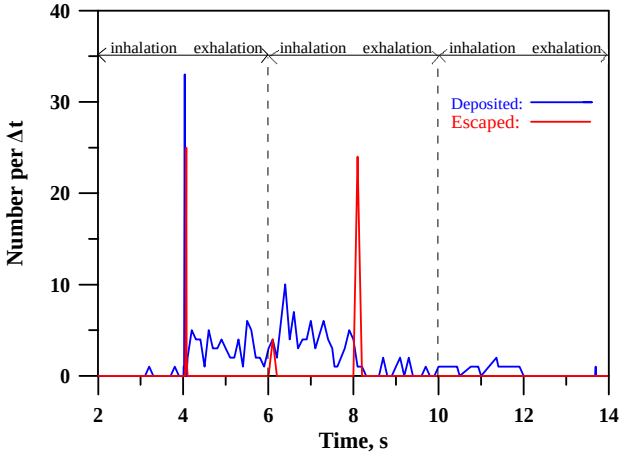

Fig. 7 Dynmaic particle deposition in an alveoli.

The alveolar sac model was integrated with the pulmonary model. Specifically, the outflow from the last block of the pulmonary model is taken as the inflow to an alveolar sac. Although each alveolar sac contains a number (i.e., 10-50) of alveoli, the description of flow to the alveolar sac and to the individual alveoli is simplified by considering a model of single alveoli which consists of a spherical volume which changes in size during inhalation due to inflow from the alveoli mouth. During inhalation particles enter the alveoli and their deposition is controlled by Brownian motion and gravitational forces. Fig. 7 depicts the dynamic deposition during a series of inhalation cycles.

The proposed integrated respiratory model describes the flow, penetration, and deposition of drug-laden particles and droplets in the respiratory system accounting for the influence of the nasal cavity and the 23-24 generations of pulmonary branches including the alveolar sacs. The present integrated model will be employed to describe the spatial distribution of deposited particles in the respiratory system under healthy as well as different scenarios of diseased states.

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