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Development of an infant complete-airway *in vitro* model for evaluating aerosol deposition

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ABSTRACT

A complete-airway *in vitro* model would be very useful for toxicological dosimetry testing and for developing targeted inhaled medications in cases where conducting *in vivo* experiments are exceedingly difficult, as with infants. The objective of this study was to determine whether packed bed *in vitro* models, which contain spheres as the primary repeating unit, provide a realistic representation of aerosol deposition in the tracheobronchial region of infant lungs based on computational fluid dynamics (CFD) predictions. The packed bed (PB) CFD model contained an inlet consistent with airway bifurcation B3 (~lobar bronchi) leading to a spherical array with voids between the spheres forming a divided flow pathway. The hydrodynamic diameter of the voids was approximately matched to the diameter of bifurcations in various lung regions. For comparison, a CFD stochastic individual pathway (SIP) geometry with realistic bifurcations extending from B4-B15 (terminal bronchioles) was selected as an anatomically accurate model. The CFD-SIP model predictions were benchmarked with existing algebraic correlations for aerosol deposition in the lungs and found to be reasonable. Unfortunately, the CFD-PB model did not provide a good representation of aerosol deposition in the tracheobronchial region of human lungs. Through careful selection of the PB sphere size and inlet conditions, total deposition in the CFD-PB model matched CFD-SIP deposition within 10% absolute error across a range of relevant aerosol sizes. However, regional deposition within the CFD-PB model was very different from the CFD-SIP case. Therefore, the PB approach cannot be recommended for determining spatial or temporal distribution of aerosol transport and impaction deposition through the lungs.

1. Introduction

In vitro airway models provide a convenient and scientifically useful testing platform for determining aerosol delivery to and deposition within the lungs [1–4]. These models can be used to determine inhaled dose of airborne pollutants and bioaerosols arising from environmental exposures. Considering infants, a number of studies have implemented *in vitro* models to evaluate aerosol deposition in a portion of the airways. Widely used infant nasal models based on a single subject scan have been reported for preterm [5] and 9-month-old [6] infants. Javaheri et al. [7] developed a characteristic infant nasal model based on 10 previously published geometries in the age range of 3–18 months. Xi et al. [8] developed a set of pediatric nasal models across an age range from infant to 5-years-old. The studies of Storey-Bishoff et al. [9] and Golshahi et al. [10] provide examples of implementing *in vitro* infant nasal models to determine the lung delivery efficiency of inhaled aerosols. Carrigy et al. [3] further reviews the development of infant and pediatric extrathoracic models with applications to determining lung delivered dose from inhaled pollutants and inhaled pharmaceutical aerosols. For soluble drugs, multiscale methods are available [11] that go beyond determining bio-availability from particle deposition by modeling the absorption process, from dissolution in the airway surface liquid to systemic circulation.

A hybrid-style *in vitro* lung model can be defined as containing a geometrically realistic upper airway structure and an approximation of the remaining lung anatomy. As reported by Carrigy et al. [3], pediatric extrathoracic models typically connect to a filter or aerosol impactor to evaluate total lung delivery and particle size distribution (PSD) of the lung delivered dose. More detailed hybrid-style *in vitro* lung models also contain some of the upper tracheobronchial bifurcating airways. For example, Delvadia et al. [4] report small, medium, and large adult upper airway geometries through the third respiratory bifurcation with the airway outlets contained in a lung Plexiglas chamber with a filtered outlet. Studies by Longest et al. [12,13] have implemented a hybrid-style *in*

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vitro model and sized the lung chamber prior to an impactor to reproduce realistic lung aerosol residence time in order to study hygroscopic aerosol growth during a respiration cycle. While providing additional information about respiratory aerosol transport, these hybrid-style lung models have not attempted to capture the mechanisms of particle deposition in the lower lung and, therefore, are not capable of capturing exhaled aerosol dose and regional aerosol deposition.

Packed beds, also known as glass bead media or granular beds, are a form of porous media composed of spheres or beads in a tightly packed arrangement [14]. Fluids can move between the spheres and the spherical surfaces providing a high surface-area to volume ratio. Packed beds are traditionally used for gas or liquid flows with surface reactions, as with component extraction or purification applications, but have also been characterized for aerosol filtration. Gebhart et al. [15] initially characterized diffusional and sedimentation deposition in a packed bed structure. Subsequent studies characterized aerosol deposition by interception [16] and impaction [17] in packed beds.

Both packed beds and the alveolar region of the lung have a high surface-area to volume ratio, which in the case of a packed bed can be tuned to equal that of the lung [18]. As a result, several studies have used simple packed bed models as an approximate surrogate of the human lung for deposition in the sedimentation and diffusion regimes [19–21]. Very few studies have previously generated a hybrid *in vitro* airway model by combining a realistic extrathoracic airway model with a packed bed model of the lower lungs. This interesting idea was originally suggested by Gebhart and Heyder [18]. As shown in Figure 1 of their study, they approximated the mouth-throat as a 90-degree bend and reproduced the first several bronchi leading to a packed bed. Modifications to the packed bed length and bead size allowed the model to capture deposition by diffusion and sedimentation consistent with *in vivo* experiments. In a short conference paper by Saini et al. [22], a hybrid model is reported consisting of a larynx cast and glass bead model in a triangular geometry containing three different glass bead sizes. This model could theoretically capture impaction, sedimentation and diffusion deposition mechanisms similar to lung airways. However, comparisons to *in vivo* data of lung aerosol deposition are not provided. Similar to Gebhart and Heyder [18], an appealing approach for creating a complete airway *in vitro* model is to combine a realistic 3D printed upper airway geometry with a packed bed structure.

The envisioned hybrid-style complete-airway model for an infant consists of a realistic upper airway geometry derived from a CT scan together with a shell of the plural region. The plural cavity is filled with monodisperse beads. Of interest is whether the packed bed region can capture correct total deposition similar to the lung airways and if the model can capture regional (spatial) deposition distributions. Matching both total and regional deposition will require correctly capturing impaction, sedimentation and diffusion mechanisms at the appropriate time scales and flow rates of respiration. More advanced complete-airway models will implement multiple bead sizes, as with Saini et al. [22]. However, the first challenge is to determine if a packed bed of spheres can capture impaction similar to the bronchi and bronchioles of the respiratory airways. Therefore, the objective of this study was to determine whether packed bed *in vitro* models, which contain spheres as the primary repeating unit, provide a realistic representation of aerosol deposition by impaction in the tracheobronchial region of infant lungs based on computational fluid dynamics (CFD) predictions.

2. Methods

An overview of the systems considered in this study is shown in Fig. 1. The infant complete-airway *in vitro* model integrates a CT-scan-based upper airway geometry through bifurcation B3 with a packed bed structure to represent the remainder of the lungs (Fig. 1a). The realistic model is truncated at approximately B3 based on resolution of the CT scan and structural integrity of the model. The TB airways extend beyond B3 through bifurcation B15, which contains the terminal bronchioles and leads to the respiratory bronchioles containing alveoli. A stochastic individual pathway model, as developed by Longest et al. [23–25], is shown in Fig. 1b extending from B4 through B15. The respiratory airways contain approximately 300,000 bronchi/bronchioles (including the respiratory bronchioles) and 480 million alveoli [26], which is not practical to reproduce with current 3D printing technologies. To represent the conducting airways, this study implements a packed bed (PB) model as shown in Fig. 1c. The tube shown in the PB model is the transition between the outlet of B3 and the sphere array. It is expected that this transition region will have an important impact on performance of the PB model.

2.1. Infant complete-airway model

The infant complete-airway *in vitro* model [27] was originally developed to evaluate the improved compliance of the lung while administering surfactants to infants. The upper airways (MT-B3) of the infant complete-airway model were based on an adult model [28] referred to as Model D. This model was scaled so that the average outlet diameter from B3 matched infant morphometric data [29]. The lower airways (B4 onwards) are represented by a pleural cavity shell, constructed from an infant computed tomography (CT) scan, that was completely filled with 6 mm diameter spheres. The pleural cavity was scaled so that the Functional Residual Capacity (FRC) was 150 mL of airspace after the spheres were added. The 6 mm spheres were initially selected for the infant complete-airway model because the hydraulic diameter of the triangular void between three connected spheres (0.62 mm) is a reasonable approximation of the number average diameter of the remaining infant tracheobronchial airways from B4 to B15 (0.45 mm). However, this sphere diameter may not be ideal, and the current study intends to determine whether alternative sphere sizes may be more suitable for matching deposition in the infant lung. To represent the airway surface liquid, 12 mL of water was added to the pleural cavity to form liquid bridges between the connected spheres. Administration of surfactant to the model reduced the surface tension of these liquid bridges and improved lung compliance in a realistic way [27].

2.2. CFD-Packed bed (PB) model

A CFD model was constructed to represent the PB region of the complete-airway model with a focus on the junction between the B3 outlet and surrounding spheres (CFD-PB model; Fig. 1c). The sphere arrangement is a hexagonal close packed formation, which gives the maximum packing density of 0.74 for equal diameter spheres. Note that packing density is determined by the sphere arrangement only, and does not change when sphere diameter is adjusted. To account for the water added to the infant complete-airway model, filleted surfaces represent the liquid bridges between each connected sphere. The 0.29 mm radius of these fillets (see Fig. 2) determines the added volume of the liquid bridges, which matches the 12 mL of water used in the infant complete-airway model.

The inlet duct of the CFD-PB model is equivalent to the outlet of the upper airways in the infant complete-airway model.