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Prediction of particle deposition in the lungs based on simple modeling of alveolar mixing

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ABSTRACT

A simplified model of particle deposition in the lungs has been developed and implemented, based on the hypothesis that perfect mixing takes place in the alveolar volume of each airway generation. This key idea is combined with purely convective transport along airways, driven by steady alveolar expansion and contraction, and results in an analytically tractable model. Predictions of the model, and in particular pulmonary deposition, are found in very good agreement with detailed benchmark data in the literature for particle diameters $d \geq 0.1$ μm. The success of this simple model provides indirect evidence in favor of the role of alveolar mixing in the deposition process.

1. Introduction

Accurate prediction of spatio-temporal variation of aerosol deposition in the respiratory tract has been a long-term research goal of the past decades (see for example the reviews by Kleinstreuer and Zhang (2010) and Longest and Holbrook (2012)), motivated by efforts to assess the consequences of air-born pollutants (Bailey et al., 2008) and also by the desire to optimize the location of inhaled drug delivery (Heyder, 2004).

The geometric complexity of the respiratory tract and the multitude of physical and biochemical phenomena involved in the process of particle transport, deposition and internalization necessitates a series of simplifying assumptions. This necessity become imperative when modeling the entire respiratory system. Particles are assumed to travel independently and deposit as soon as their trajectory touches the wall. The airways are described by generations of symmetrically bifurcating tubes and the length and diameter of each generation at functional residual capacity FRC are provided by various morphometric models (Weibel, 1963; Finlay, 2001; Weibel et al., 2005). Transverse variations of air velocity and particle concentration are neglected and the only spatial variation considered is along the respiratory tract (one-dimensional models). Particle fractions deposited inside each generation by inertial impaction, gravitational settling and Brownian diffusion are taken to depend on respective dimensionless numbers defined in terms of the generation dimensions and the mean air velocity (Finlay, 2001).

Several key modeling issues have been identified over the years in the literature and remedial efforts have been implemented. As the present contribution aims at a systemic approach, we will not elaborate on questions related to detailed simulation of specific sub-regions of the respiratory tract but will concentrate on a rather global picture of the deposition process. One such issue is the reference frame used to describe air and particle motion. A Lagrangian approach -where specific air masses are followed along the airways- is intuitively appealing and has led to the first solid models (see for example Kim et al., 1983; Martonen, 1993). Higher flexibility to describe time-varying breathing patterns is provided by Eulerian models, where velocities and concentrations are referred to fixed locations along the flow path and their variation is described by differential balances (Nixon and Egan, 1987).

Concerning the larger scales of the respiratory tract, it has been known for some time that deposition in the extrathoracic cavities as well as in the trachea and the first bronchial generations varies significantly with the patient-specific morphometric characteristics (Kleinstreuer et al., 2008). Thus, systematic research has been undertaken to combine tomographic techniques for recording the individual's characteristics with computational fluid dynamics (CFD) simulations of particle transport inside the specific airway geometry (see for example Fleming et al., 2011). However, escalation of computational time and decreasing reliability of tomographic data combine to limit the present application of this approach to the first few airway generations.

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At the other end of the respiratory tract (and of the relevant length scales), concerns over proper modeling of the alveolar acinus have culminated over the years (Sznitman, 2009). A widely used approach in systemic simulations is to consider the alveoli at each generation as additional volume contributing an area on top of the airway cross-section (Egan et al., 1989). Evidently, in such models particle concentration in the alveoli is not differentiated from the local airway concentration.

A major improvement has been the consideration by Choi and Kim (2007) of a more realistic transport scheme that differentiates between airway and alveolar volumes and includes radial exchange of particles between the two. However, the actual flow conditions inside the alveoli were not incorporated in the model and particle deposition was treated by these authors in an average sense.

About two decades ago, it was discovered that the flow inside an alveolus may result in chaotic mixing despite the very small velocities involved. Chaotic mixing is the outcome of combination of axial flow due to expansion/contraction with shear flow along the airway. The original simulations were given by Tsuda et al. (1995) and Henry et al. (2002), and an experimental demonstration was provided by Tsuda et al. (2002). Alveolar flow was reviewed by Tsuda et al., 2008 and discussed -with emphasis on the physics rather than the mathematics involved- by Tsuda et al. (2011).

Though the original simulations were two-dimensional, chaotic mixing in the acinus was repeatedly confirmed by three-dimensional simulations (see for example Sznitman et al., 2009). In a recent study of three-dimensional flow in rhythmically expanding models of alveolated ducts, Henry et al. (2012) showed that each individual alveolus acts simultaneously as flow mixer and flow feeder. A direct consequence of the above is that alveoli constitute efficient mixing units and promote increased residence time of particles in the acinus (kinematic irreversibility). Alveolar mixing was included in a computational particle deposition model by Muller (2011), which was based on detailed flow considerations and provided moderately encouraging results.

The goal of the present work is to test the hypothesis that intense alveolar mixing is a key ingredient in the process of particle deposition in the lungs. To this end, a highly simplified model of transport and deposition is constructed, which consists of plain convection with a sharp front (no axial mixing) in the conducting airways, combined with fast mixing leading to spatially uniform concentration in the alveolar volume of each generation. In-line with the simplicity of this approach, air flow is modeled by a steady mean volumetric rate resulting from the uniform expansion of distal alveolar volumes. Advantages of this approach are analytic tractability and straightforward modeling of deposition in the alveoli. The present simple model appears to agree very satisfactorily with detailed benchmark data in the literature (Chan and Lippmann, 1980; Heyder et al., 1986) that cover a wide range of particle sizes and breathing patterns. This agreement provides indirect evidence in favor of the role of mixing in the alveolar volumes.

2. Methods

2.1. Modeling of air flow

We consider the transport and deposition of monodisperse, spherical particles of density ρ and diameter d during one breathing cycle. Breathing patterns are described in terms of the tidal volume, V_T and inhalation time, t_b, assuming equal durations of inhalation and exhalation and no breath-holding. Thus, the mean volumetric air flow rate is $Q_0 = V_T/t_b$ and the mean velocity through generation i is $U_i = 4Q_0/N_i \pi D_i^2$ where $N_i = 2^i$. The length, L_i, and diameter, D_i, of the airways of generation i are taken from the model developed by Finlay (Finlay, 2001), which also provides the volume of

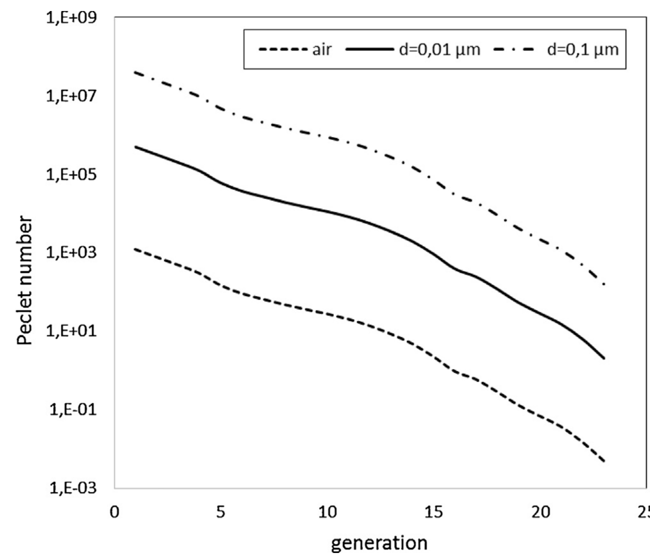

Fig. 1. The Peclet number as function of the airway generation for particles with diameters d_p = 0.1 μm, 0.01 μm, and for O_2 diffusing into air.

airways, $V_{p,i}$, and alveoli, $V_{a,i}$, per generation, normalized to a functional residual capacity (FRC) of 3000 ml. In this model, respiratory bronchioles start at the 15th generation and -according to the recommendation of Tsuda et al. (2008)- the fractional coverage with alveoli is taken as $f_i = 0$ for $i < 15$, $f_{15} = 0.2, f_{16} = 0.4$, $f_{17} = 0.7$, and $f_i = 1.0$ for $i > 17$.

Air flow is driven by the uniform expansion of distal alveolar volumes, thus neglecting the flexibility of small airways. Concerning particle transport, and for particles with diameters above a few tenths of nm, the air may be considered to move with a sharp concentration front. This assumption -which neglects axial dispersion- is reasonable at the present level of approximation and is supported by the values of Peclet number, $\mathrm{Pe} = U_i L_i / D_{\mathrm{diff}}$, calculated for each airway using the particle diffusivity, D_{diff}. The Peclet number indicates the significance of convection as compared to diffusion (Sznitman, 2009), and representative results are shown in Fig. 1 for the diffusion of particles with diameters d = 0.01 μm, d = 0.1 μm and for diffusion of oxygen in air. It is evident from Fig. 1 that for $d \geq 0.01$ μm convection dominates diffusion along the entire respiratory tract.

Based on the assumption of a sharp front, we can determine the time, t_i, for the particle front to reach generation i. This is simply the summation of the time intervals, τ_i, taken by the front to cross each of the previous airway generations. If we denote by $Q_{p,i}$ the total air flow rate entering generation i and by $Q_{a,i}$ the flow rate entering the alveoli of generation i, we readily have

$$Q_{p,i} = Q_{a,i} + Q_{p,i+1} \quad (1)$$

If we further assume linear variation of local flow rate along the airway, i.e. $Q(x) = Q_{p,i+1} + Q_{a,i}(1 - x/L_i)$, then by a straightforward integration using the definition of velocity, $U(x) = dx/dt = Q(x)/A_i$, we obtain the time lag, τ_i, to cross the airways of generation i

$$\tau_i = \left(\frac{V_{p,i}}{Q_{a,i}}\right) \ln\left(1 + \frac{Q_{a,i}}{Q_{p,i+1}}\right) \quad (2)$$

In the limit of $Q_{a,i} \ll Q_{p,i+1}$, we obtain from Eq. (2) the expected result for non-alveolated airways, $\tau_i = \left(V_{p,i}/Q_{p,i+1}\right) = \left(V_{p,i}/Q_0\right)$. The time, t_i, for the particle front to reach generation i is then calculated as the sum of τ_k, k = 0 to i-1.