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In silico assessment of mouth-throat effects on regional deposition in the upper tracheobronchial airways

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ABSTRACT

Regional deposition of inhaled medicines is a valuable metric of effectiveness in drug delivery applications to the lung. *In silico* methods are now emerging as a valuable tool for the detailed description of localized deposition in the respiratory airways. In this context, there is a need to minimize the computational cost of high-fidelity numerical approaches. Motivated by this need, the present study is designed to assess the role of the extrathoracic airways in determining regional deposition in the upper bronchial airways. Three mouth-throat geometries, with significantly different geometric and filtering characteristics, are merged onto the same tracheobronchial tree that extends to generation 8, and Large Eddy Simulations are carried out at steady inhalation flowrates of 30 and 60 L/min. At both flowrates, large flow field differences in the extrathoracic airways across the three geometries largely die out below the main bifurcation. Importantly, localized deposition fractions are found to remain practically identical for particles with aerodynamic diameters of up to $d_p = 4\,\mu m$ and $d_p = 2.5\,\mu m$ at 30 and 60 L/min, respectively. For larger particles, differences in the localized deposition fractions are shown to be mainly due to variations in the mouth-throat filtering rather than upstream flow effects or differences in the local flow field. Deposition efficiencies in the individual airway segments exhibit strong correlations across the three geometries, for all particle sizes. The results suggest that accurate predictions of regional deposition in the tracheobronchial airways can therefore be obtained if the particle size distribution that escapes filtering in the mouth-throat (ex-cast dose) of a particular patient is known or can be estimated. These findings open the prospect for significant reductions in the computational expense, especially in the context of *in silico* population studies, where the aerosol size distribution and precomputed flow field from standardized mouth-throat models could be used with large numbers of tracheobronchial trees available in chest-CT databases.

1. Introduction

Drug delivery *via* the pulmonary route is widely used for the treatment of pulmonary infections and respiratory diseases such as asthma, Chronic Obstructive Pulmonary Disease (COPD) and cystic fibrosis. More recently, the inhaled route has also emerged as a promising method for the systemic administration of drugs, due to the favorable absorption characteristics of the lungs (Smyth & Hickey, 2011).

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The amount of drug that deposits in different regions of the respiratory tract is an important factor that affects the efficacy of inhaled drug delivery. Knowledge of the regional deposition within the lungs can assist with drug dosing decisions and is valuable in assessing the effectiveness of drug targeting strategies and in optimizing patient maneuvering during inhalation. However, determining regional deposition accurately is not an easy task.

In vivo, deposition patterns can be determined using nuclear imaging techniques, such as 2D gamma scintigraphy, single photon emission computed tomography (SPECT), or positron emission tomography (PET), by the addition of a radiolabel to the aerosol formulation (Conway, 2012). These methods have the advantage of describing the real state, but remain limited by a number of challenges, such as insufficient spatial resolution and concerns from patient exposure to radiation.

In vitro, regional deposition in the tracheobronchial (TB) tree can be determined by using replicas of human airways derived from Computed Tomography (CT) scans, and because higher doses of radioactivity can be applied, they often provide better spatial resolution relative to *in vivo* methods. However, they are time-consuming and cannot easily be performed on a routine basis. As a result, the current industry standard is the use of pharmacopeial induction ports mounted on cascade impactors, which provides estimates of total lung deposition (Olson et al., 2013). However, when the bioavailability of the drug is less than 100%, the deposited lung dose is overpredicted due to mucociliary clearance of the dose fraction deposited in the TB region (Olsson & Backman, 2014). In this case, the efficacy of drug delivery depends, in part, on the site of deposition within the airways. Therefore, quantifying regional deposition is important in assessing and optimizing the systemic delivery of drugs with limited lung bioavailability, as well as in topical treatments requiring the targeting of specific lung sites.

In silico models can complement *in vivo/in vitro* tests and provide detailed information on regional deposition patterns. They can be used to perform repeated numerical experiments aiming to isolate the effect of a particular variable, something that is difficult to achieve *in vitro* or *in vivo*. A concise critical review of Computational Fluid Dynamics (CFD) techniques for *in silico* studies of the upper airways is given in Koullapis et al. (2017).

Due to the geometrical complexity and high Reynolds numbers, especially at flowrates that are relevant to drug delivery *via* Dry Powder Inhalers (DPIs), airflow in the upper airways usually transitions to turbulence (Tawhai & Lin, 2011). Three different methods can be applied to solve the turbulent flow: direct numerical simulations (DNS), Reynolds averaged Navier-Stokes (RANS) and large eddy simulations (LES). DNS resolves the turbulent fluctuations at all scales, providing the most accurate picture of the flow (Nicolaou & Zaki, 2013), but still remains exceedingly costly to perform on current computers. Presently, most CFD studies solve only for the averaged (or mean) flow using the RANS equations. A large reduction in computational cost is achieved in comparison to DNS, however accurate prediction of the laminar-turbulent-laminar flow transition that occurs in the TB airways is challenging for RANS (Kleinstreuer & Zhang, 2010). A more robust choice is the method of Large Eddy Simulations (LES), where only the smallest scales of motion are discarded and accounted for *via* a model. The computational expense of LES is considerably higher than that of RANS, but it retains significantly more elements of the underlying turbulence physics (Radhakrishnan & Kassinos, 2009; Koullapis et al., 2016).

With increasing gains in computing power, LES has become affordable for research purposes, but its application remains challenging for both population studies, where a large sample would need to be simulated, and for routine clinical use on a patient-specific basis. Therefore, there is a need to reduce the computational times required to predict regional deposition. Moreover, whereas CT-reconstruction of the imaged TB airways is straightforward and semi-automated in specialized imaging softwares (Miyawaki & Tawhai, 2016), reconstruction of the extrathoracic airways is more challenging due to the complexity of the structures in this region. Therefore, *in silico* assessments of regional deposition in the TB region can be accelerated further if reconstruction of a patient's MT geometry is not required. In addition to this, a large number of chest CT-scans, which typically exclude the extrathoracic airways (Miyawaki, Hoffman, & Lin, 2017), are available and could potentially be used for population studies of lung deposition.

The pronounced effect of geometric variation on deposition in the extrathoracic airways is well documented in the literature (Burnell et al., 2007; Grgic, Finlay, Burnell et al., 2004; Heenan, Finlay, Grgic, Pollard, & Burnell, 2004; Nicolaou & Zaki, 2013). Grgic, Finlay, Burnell et al. (2004) performed measurements in several realistic MT geometries at flowrates of 30 and 90 L/min for particle diameters of 3–6.5 μm. They found that both total and regional deposition exhibit large inter-subject differences, as well as intra-subject variability to a lesser extent. Deposition was found to occur primarily *via* impaction, and the mouth area was identified as the largest obstacle for inhaled aerosols. An empirical Reynolds number correction, $Re^{0.37}$, was applied to the Stokes number (Grgic, Finlay, & Heenan, 2004), which reduced scatter in the reported deposition efficiencies, and provided better collapse of their data onto a single curve.

In a later study, Nicolaou and Zaki (2013) examined the flow in a subset of four MT geometries used by Grgic, Finlay, Burnell et al. (2004). Adopting an immersed boundary method to simplify the task of grid generation for the realistic airway geometries (Nicolaou, Jung, & Zaki, 2015), the authors performed DNS of the flow and related the predicted flow to the variations in deposition observed in the *in vitro* measurements. It was found that geometric variation, even within the same subject, has a large impact on both the mean velocity profiles and the turbulence intensities. Their analysis revealed that the empirical correlation $StkRe^{0.37}$ arises due to the fact that deposition in the airways occurs *via* both impaction and turbulent diffusion. More recently, the authors proposed the use of an instantaneous Stokes number, based on the local properties of the flow field, for a more accurate representation of particle transport and deposition in the airways (Nicolaou & Zaki, 2016).

In an effort to identify key geometric parameters governing MT deposition, Burnell et al. (2007) investigated retention of drug aerosols inhaled from four delivery devices in 12 physical MT models *in vitro*. They found that deposition in the 12 models was dependent on the inhalation delivery system and that the most influential factor in MT deposition was the total volume. The airway geometries were ranked based on their retention efficiency and three models that represent high, median and low oropharyngeal filtration were identified. They suggested that these three models may reasonably cover the range of MT dimensions in the adult population and could therefore be used to indicate the expected range of MT deposition.