

An *in silico* laboratory for patient-specific treatment of asthma and COPD

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Summary

Predictive numerical capabilities have the potential for significant impact in the advancement of therapies for lung disease. Accurate and efficient numerical models can provide a valuable clinical aid to optimise therapies and to define the appropriate treatment, for example in severe asthma and chronic obstructive pulmonary disease (COPD). Geometric variations of the respiratory airways across subjects, however, have a pronounced effect on the airflow and aerosol deposition and, hence, pose a significant hurdle which motivates personalised treatment of respiratory diseases. An *in silico* framework for patient-specific predictions of the flow and aerosol deposition in the respiratory airways is presented. The proposed computational laboratory efficiently accommodates geometric variation and airway motion in order to optimise pulmonary delivery for patients with severe asthma and COPD. A non-rigid registration method is adopted to construct dynamic airway models conforming to the patient's breathing. The flow solver takes advantage of a novel immersed boundary (IB) approach which efficiently handles realistic airway geometries obtained from medical images of patients' lungs. A Lagrangian point particle-tracking scheme is adopted to model the transport and deposition of the aerosol particles in the airways. Using this method, the flow and aerosol deposition in realistic extrathoracic airways are examined and a patient-specific dynamic lung model is presented.

Introduction

The flow and particle dynamics in the respiratory system are the principal factors which determine the efficiency of aerosolized drug delivery in the treatment of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). The appreciable geometric variation across subjects has a significant effect on the flow and particle deposition [1, 2], and therefore motivates the need for patient-specific predictions. The ultimate goal is to develop capabilities for personalised medicine in order to provide optimal patient-specific drug delivery. Towards this goal, *in silico* / numerical models offer a cost-effective and non-invasive approach, compared to *in vitro* and *in vivo* testing.

Accurate and efficient simulations must, however, accommodate the complexity of the airway geometries and of the flow itself. Due to the bifurcating nature of the lung and the unsteady nature of the breathing cycle, flow patterns in the respiratory airways are complex even during quiet breathing. The flow is turbulent in the mouth and throat and the larger airways, before extensive branching increases the total cross-sectional area and therefore reduces the air velocity through each airway, causing laminarisation. In most of the tracheobronchial tree, the flow is intermittently turbulent with eddies forming at the branching points [3].

Most numerical investigations to date have examined idealised models of the airway geometries [4-9] and many have assumed laminar conditions [4, 6, 10] or employed Reynolds-averaged Navier-Stokes (RANS) turbulence models [5, 11, 12]. RANS models do not resolve the turbulence but rather model its influence on the mean velocity; These models are also often based on empirical data obtained from canonical and equilibrium flows. As a result, deposition predictions using RANS can be prone to large errors in the range of Reynolds numbers relevant to the extrathoracic airways [12, 13].

The *in silico* framework presented herein allows accurate and efficient modelling of (i) the realistic moving airway geometries, (ii) the complex flow, and (iii) the aerosol transport and deposition. An immersed boundary approach is adopted which efficiently handles the complex airway geometries and movement during breathing, and accommodates inter-subject geometric variations. A non-rigid registration method is employed to construct patient-specific dynamic lung models conforming to the patient's breathing. Accurate solution of the flow field is obtained by direct numerical simulations (DNS) which resolve all the flow scales in the airways. Finally, a Lagrangian particle-tracking scheme is adopted to model the transport and deposition of aerosol particles within the airways. Using the proposed method, the effect of geometric variation on the flow and aerosol deposition in the extrathoracic airways is examined and a patient-specific dynamic lung model is presented.

Numerical methodology

Airway geometries

Anatomically-accurate models of the airways are obtained from magnetic resonance imaging (MRI) or computed tomography (CT) scans at functional residual capacity (FRC) and total lung capacity (TLC). The medical images are converted to 3D volume files from which STL models of the airway walls at FRC and TLC are generated. An important

step is to establish a one-to-one mapping between the FRC and TLC geometry, despite the lack of scans at intermediate times and the difference in triangulation in the STL representations. A landmark-based non-rigid registration is therefore adopted to capture the non-uniform expansion of the lung (see [14] for the details of the Image Registration Toolkit). Once an accurate one-to-one mapping between the two triangulated surface meshes has been established, the time-variation of the geometry can be derived from the measured inhalation flow rate for the particular subject, thus prescribing a patient-specific airway movement.

Air flow

Due to the complexity of the respiratory airway geometries, an immersed boundary (IB) method is adopted [2]: The airways geometry is immersed within the grid, and boundary conditions are enforced on the surface rather than on grid points. The IB approach therefore allows the use of relatively simple structured grids to model the complex airways (in contrast to unstructured body-fitted grids), circumvents the need to remesh at every time step in the case of moving airways and accommodates geometric variations on the same grid. As a result, the IB approach leads to a more efficient computational algorithm compared to unstructured body-fitted approaches commonly adopted in the literature. An example of a structured curvilinear grid for IB simulations of flow in the extrathoracic airways is shown in figure 1.

Aerosol particles

A Eulerian-Lagrangian approach is adopted to model the transport and deposition of the aerosol particles: The dispersed phase (the aerosol) is treated as individual particles in a continuous carrier phase (the air). For micron-sized aerosol particles, the aerodynamic drag and the gravitational force are dominant. The mucus layer on the inner walls of the airways avoids reflection and re-suspension of particles that collide with the surface. Therefore, in the computational model, deposition is assumed to occur once a particle comes in contact with the airways walls.

Results

Flow and aerosol deposition in the extrathoracic airways

The *in silico* framework presented herein has been applied to the first fully-resolved simulations of the flow in realistic extrathoracic airways [2]. Through realistic geometric representation of the airways and detailed flow fields, the effect of geometric variation on the mean flow and the turbulent fluctuations was examined. Comparison of the main flow features with PIV measurements in the same geometries [15] showed good agreement with our numerical predictions.

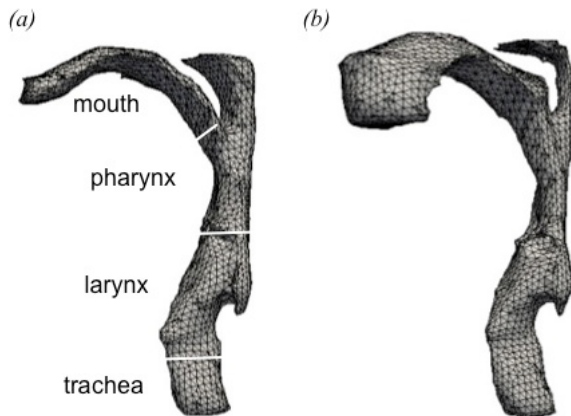


Figure 2 STL triangulated surface models of the mouth-throat geometries: (a) S1b; (b) S1a.

The mean flow fields and deposition patterns in both geometries are contrasted in figure 3. When the tongue is pushed forward (geometry S1b), the velocity profiles in the mouth are highly skewed towards the inner wall due to the airway curvature (A-A). The flow accelerates at the back of the mouth due to the restriction in cross-sectional area, developing a pharyngeal jet which impinges onto the posterior wall (B-B). Due to the bend in the airway, the flow shifts towards the outer wall, separating from the inner wall and leading to a recirculation region (C-C). When the tongue is pulled back (geometry S1a), a larger oral cavity results in lower velocities in the mouth (A-A), and therefore no pharyngeal jet is formed. Instead, the flow accelerates farther downstream due to the narrower nasopharynx (B-B), leading to a more pronounced separated shear layer in the trachea (D-D).

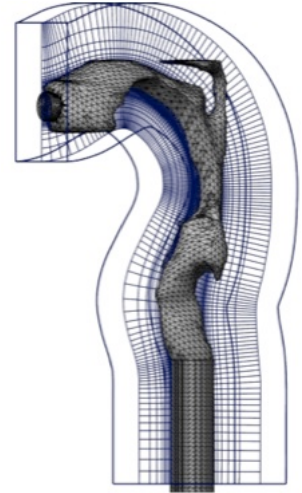


Figure 1 Example of a curvilinear grid for realistic extrathoracic airways.

Models of two realistic geometries obtained from MRI scans in STL format were employed. The geometries belong to the same subject in different configurations: In geometry S1b the tongue is pushed forward touching the back of the teeth (figure 2a), whereas in S1a the tongue is pulled back creating a larger oral cavity and narrower nasopharynx (figure 2b).

To mimic the experimental setup [1], the simulations were performed at a steady flow rate, $Q = 30$ L/min. Particles of three different sizes, $d_p = \{3, 5, 6.5\} \mu\text{m}$, were distributed uniformly at the inlet and released at regular intervals. They were advected until either deposited or exited the domain.

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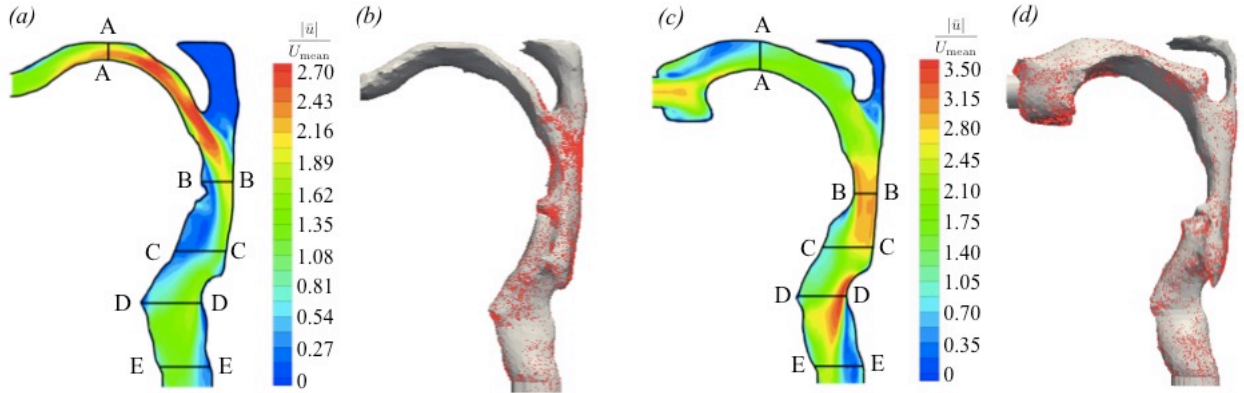


Figure 3 Mean flow field (a,c) and deposition patterns (b,d) in the extrathoracic airways: (a,b) S1b; (c,d) S1a.

The flow field has an appreciable effect on the particle deposition as demonstrated in figures 3b,d. With the tongue pushed forward, a deposition hot-spot is observed at the posterior wall of the upper pharynx where particles deposit via impaction due to the pharyngeal jet. When the tongue is pulled back, qualitatively different deposition patterns are recorded. The regions of highest deposition are now at the front of the tongue due to impingement of the incoming flow from the inlet pipe, and in the sharp step in the larynx due to the high velocity and sudden change in the flow direction. The accuracy of the *in silico* model is established by favourable comparison with *in vitro* data [1].

This study serves two objectives: Firstly, it demonstrates the ability of the current in-silico model to handle complex anatomical geometries; Secondly, it highlights the large effect of geometric variation on the flow and deposition patterns in the airways. Even within the same subject, a change in the position of the tongue can have a large effect on the extrathoracic losses, and therefore the efficacy of the inhaled dose. These results therefore reaffirm the need for patient-specific models which can accommodate geometric variation in the optimisation of inhaled drug delivery.

Dynamic model of lung geometry

Here we consider lung geometries consisting of extra- and intra-thoracic airways, which undergo expansion and contraction during the breathing cycle. We demonstrate our methodology for providing a patient-specific dynamic model using the airway images at FRC and TLC, along with the inhalation flow-rate profile for the subject.

The STL representations of the lungs at FRC and TLC are shown in figures 4a and b, respectively. A landmark-based non-rigid surface registration is applied to map the geometry at TLC onto the geometry at FRC. This transformation yields a one-to-one mapping between the two surface triangulations. The FRC geometry that is obtained via the registration procedure, $\text{FRC}_{\text{Registered}}$, is shown in figure 4c. A measure of the registration error can be obtained by computing the distance between the registered and the original FRC geometries. The resulting surface distance map is shown in figure 4c. A very good agreement between the $\text{FRC}_{\text{Registered}}$ and the original FRC geometry is observed.

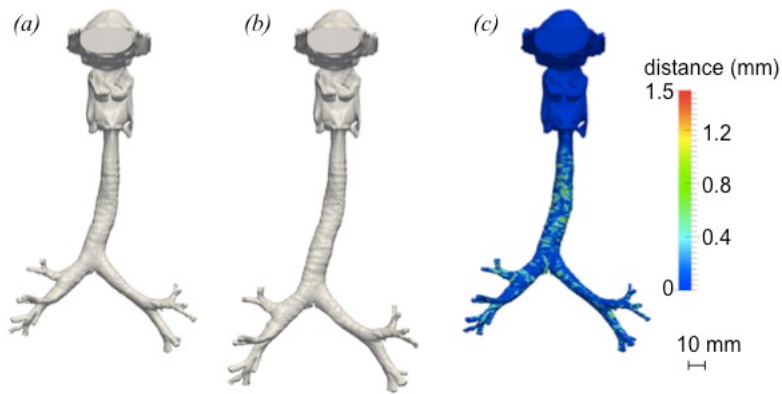


Figure 4 Airway geometries employed for the dynamic lung model: Original geometries reconstructed from CT scans at (a) FRC and (b) TLC; (c) $\text{FRC}_{\text{Registered}}$ geometry coloured by surface distance to original FRC model.

The time-varying airway model is then constructed based on the subject's inhalation flow-rate profile. The dynamic lung geometry is shown in figure 5. Five time points in the breathing cycle are plotted, $t/T = \{0, 1/8, 2/8, 3/8, 4/8\}$, where T is the breathing period and $t/T = 0$ and $4/8$ correspond to FRC and TLC, respectively. The time-resolved patient-specific model of the airways, combined with the flow solver, form an *in silico* laboratory for the assessment and optimisation of inhaled-drug delivery in the treatment of severe asthma and COPD.

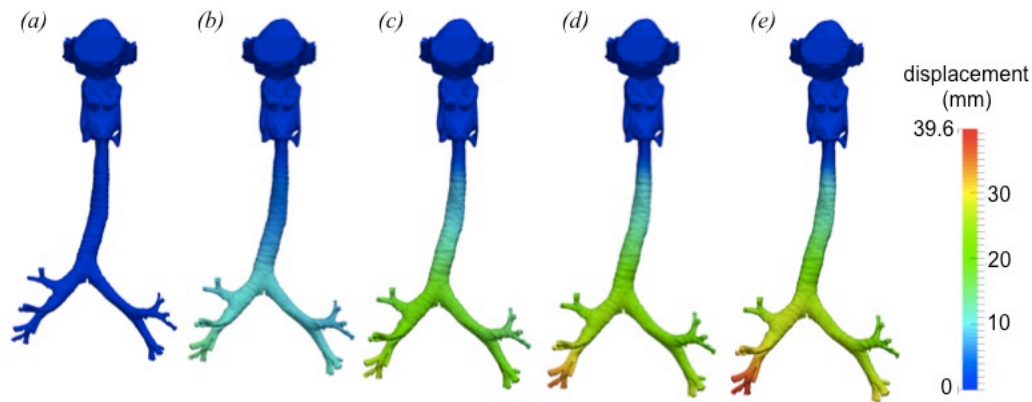


Figure 5 Dynamic model of airway geometry coloured by the magnitude of local displacement: (a) $t=0$; (b) $t=T/8$; (c) $t=T/4$; (d) $t=3T/8$; (e) $t=T/2$.

Conclusion

An *in silico* framework for accurate and efficient patient-specific predictions of flow and deposition in the respiratory airways was developed for the optimisation of inhaled drug delivery. The computational approach accommodates geometric variations across subjects and airway movement during breathing. Two case studies were presented to demonstrate the ability of the numerical approach to handle anatomical geometries, accurately model the flow and determine particle deposition. First, realistic extrathoracic airways were considered. This case highlights the pronounced effect of geometric variation on the flow and deposition in the airways and reaffirms the importance of patient-specific modelling. Next, a dynamic model consisting of the extra- and intrathoracic airways was presented to demonstrate the treatment of airway movement during breathing. The long-term goal of this work is the development of a cost-effective *in silico* model for clinical use in patient-specific treatment of respiratory illnesses.

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