An *in silico* inter-subject variability study of extra-thoracic morphology effects on inhaled particle transport and deposition

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**ABSTRACT**

An understanding of human inter-subject variability is crucial for the implementation of personalized pulmonary drug delivery as well as exposure assessment of airborne hazardous materials. However, due to the lack of statistically robust data and subsequent comparisons, the influence of human respiratory morphology on inhaled nano-/micro-particle transport and deposition is still not fully known. Thus, focusing on identifying geometric parameters that significantly influence airflow and inhaled particle transport/deposition, an experimentally validated Computational Fluid-Particle Dynamics (CFPD) model based on the Euler-Lagrange method is developed. In analyzing deposition patterns to fill the knowledge gap, the particles are grouped into six diameter groups, i.e., 0.05, 0.1, 0.5, 2, 5, and 10 µm. To enhance the statistical robustness of the investigation, a virtual population group is created that contains seven distinct and widely used human upper-airway configurations, where the same tracheobronchial trees are extended to Generation 6 (G6). Numerical results and the inter-subject variability analysis indicate that the glottis constriction is the morphological parameter that significantly impacts the inhaled particle dynamics in the respiratory tract. For reasons of statistical robustness, anatomical features of the upper airways should be maintained to capture the personalized airflow and particle transport dynamics for particles smaller than 500 nm or larger than 2 µm. However, a single upper airway model, representing a basic subpopulation group, can be employed to evaluate the total deposition of particles in the diameter range of 500 nm < \(d_p\) < 2 µm. The present study provides an *in silico* lung-aerosol dynamics framework with detailed particle-deposition results and new physical insight. It may serve as a guide for implementing optimal targeting of inhaled drug-aerosols as well as for the assessment of hazardous aerosol exposure in distinct populations.

1. Introduction

Configurations and dimensions of human respiratory systems may vary significantly among individuals, thereby influencing airflow as well as inhaled particle transport and deposition. Studying such subject variability has several benefits for different applications. It can provide flow characteristics in common to different human respiratory systems with a better understanding of the...
influence of airway morphology on airflow structure, wall shear stress, and particle transport. For example, in the case of direct drug delivery to treat a patient’s lung and/or systemic disease (Kleinstreuer, Feng, & Childress, 2014; Longest & Hindle, 2017; Walenga, Longest, Kaviratna, & Hindle, 2017; Zarogoulidis et al., 2011), the accurate prediction of airflow and drug particle deposition is essential for targeting pulmonary drugs to predetermined lung sites (Burrowes, De Backer, & Kumar, 2017; Kleinstreuer et al., 2014).

Subject-variability studies also provide the relationship between geometric characteristics and airflow regime as well as particle dynamics, which can establish the foundation of the individualized health risk assessment for different subpopulation groups (e.g., children vs. adults, healthy vs. COPD patients, etc.). Furthermore, inter-subject variability studies are promising to generate insights into the respiratory system physiology and serve as a basis for the development of non-invasive diagnostic tools for different deep lung diseases by detecting different airflow and particle transport patterns in upper airways.

High-resolution local quantitative data are required and should be obtained from the inter-subject variability analysis, in order to generate in-depth understanding of the underlying physics of the morphological influence on particle deposition patterns. However, due to the limited imaging resolution and the invasive nature of clinical visualization in human bodies, it is impossible to use experimental or clinical tests to provide details of local particle transport characteristics through human respiratory tracts. Since it is difficult to characterize the geometric variabilities of subject-specific human respiratory system configurations using in vivo and in vitro methods, the combined effects from multiple morphological parameters need to be disseminated and investigated separately by credible in silico methodologies, i.e., Computational Fluid-Particle Dynamics (CFPD) models. They are capable of generating high-resolution deposition data based on physical principles in a noninvasive manner.

Past in silico studies include Choi, Tawhai, Hoffman, and Lin (2009) who numerically analyzed airflows in human airway configurations and pointed out that there are two factors that significantly affect the flow regime among individuals: the constriction ratio of the glottis with respect to the trachea and the curvatures and shapes of the airways. Farkhadnia, Gorji, and Gorji-Bandpy (2015) investigated the geometric influence on the laminar airflow field and particle transport in G3-G6 triple bifurcations with and without a partial blockage due to COPD. In parallel, Johari, Osman, Helmi, and Abdul Kadir (2015) compared airflow fields in realistic and simplified human airway models and found that over-simplified geometries can induce noticeable differences in numerical simulation results. They also stressed that the roughness of the realistic airway walls may have an influence on the airflow field. Xi et al. (2016) studied particle depositions in different mouth-throat models, which were reconstructed via modified morphological parameters of four prototypes. They discovered that the degree of realism of the airway models significantly affected particle deposition from the oral cavity to the glottis, while the effect of oral airway curvature was minor. Moreover, Xi, Kim, and Si, (2016) simulated particle transport in nasal cavities with different nostril orientations, and claimed that particle olfactory deposition (d₄₃ from 1 to 20 µm) constantly increases with the nostril angle. Recently, Koullapis, Nicolaou, and Kassinos (2017) studied the extra-thoracic influence on the particle deposition in tracheobronchial airway trees using three subject-specific human respiratory systems with a steady-state inhalation flow rate (30 L/min). They claimed that the extra-thoracic airway geometry has a negligible effect on the regional deposition patterns in the tracheobronchial trees for particles smaller than 6 microns. However, the statistical robustness of this conclusion needs further confirmation, as only three subject-specific geometries have been involved in their studies. Walenga et al. (2017) considered drug delivery in two mouth-nose-throat models with the aim to reduce inter-subject variability on deposition patterns. Again, concerns exist on the appropriate number of subjects to support the in silico study.
To obtain insightful and statistically robust conclusions on inter-subject variability effects, an experimentally validated CFD model with image-based subject-specific human respiratory configurations has been employed in the present study. Specifically, it focuses on the subject variability of mouth-to-glottis configurations, which is investigated using a computational fluid-particle dynamics method, i.e., a validated Euler-Lagrange model (Feng, Xu, & Haghnegahdar, 2016; Feng, Kleinstreuer, Nicolas, & Rostami, 2016). The research objective is to identify morphological parameters that significantly influence the airflow and inhaled particle transport characteristics. Simultaneously, it paves the way to develop a virtual framework for the design of pulmonary drug delivery therapy on a subject-specific level as well as to improve the knowledge of hazardous aerosol dynamics in human respiratory systems. The influence of combined morphological characteristics can be disseminated and quantified using the high-resolution numerical simulations.

Fig. 1. Configurations of human respiratory systems consisting of seven human upper airway geometries with cross-sections (Feng, Kleinstreuer, et al., 2016; Su & Cheng, 2006; Xi & Longest, 2007; Zhang et al., 2012): (a) Geometry A (b) Geometry B (c) Geometry C (d) Geometry D (e) Geometry E (f) Geometry F (g) Geometry G (h) Regional division.
data. To enhance the statistical robustness of the study, inter-subject variability analysis was performed for seven distinct and widely used human upper airways (Feng, Kleinstreuer, et al., 2016; Su & Cheng, 2006; Xi & Longest, 2007; Zhang, Kleinstreuer, & Hyun, 2012) with an identical lung-airway tree (Zhang et al., 2012). It is the largest virtual population group so far employed by existing numerical investigations. The morphological variabilities were measured via Mimics® and 3-matic STL® (Materialise N.V., Leuven, Belgium). Establishing a virtual population group is a novel idea that will significantly contribute to the creation of a noninvasive and cost-effective in silico clinical trial model, which is able to test drugs and devices across distinct virtual sub-populations. The study also attempts to provide a standard for in silico clinical trials by comprehensively analyzing variations in the general population.

The layout of this paper is as follows: Section 2 introduces the governing equations of the CFPD model adopted for the simulation of the airflow and particle transport dynamics. Section 3 presents the numerical set-up, which includes human respiratory tract configurations and mesh generation, initial conditions and boundary conditions. Following the model validations in Section 4, Section 5 contains the numerical results of airflow and particle transport and deposition patterns with parametric analyses. Finally, Section 6 summarizes the findings of the present study and Section 7 discusses future work.

2. Theory

Using commercial software enhanced with in-house C-programs, the Euler-Lagrange method has been employed to simulate airflow and micro/nano particle transport/deposition in human respiratory systems. The laminar-to-turbulence flow fields in the airways was assumed to be incompressible.

2.1. Airflow field equations

The airflow dynamics of the respiratory tract is always unsteady and driven by the pressure differences under the action of the cyclic breathing process. The conservation laws of mass and momentum can be written in tensor form as follows:

\[
\frac{\partial u_i}{\partial x_j} = 0
\]

\[
\frac{\partial u_i}{\partial t} + u_j \frac{\partial u_i}{\partial x_j} = -\frac{1}{\rho} \frac{\partial p}{\partial x_i} + \frac{1}{\rho} \frac{\partial \tau_{ij}}{\partial x_j} + g_i
\]

Fig. 2. Morphological parameters of the upper airway geometries.
where $u_j$ represents the fluid velocity, $p$ is the pressure, $g = (9.81, 0, 0)$ [m/s$^2$] is gravity (see Figs. 1 to 4 for the definition of the coordinate), and viscous stress tensor $\tau_{ij}$ in Eq. (2) is given by:

$$
\tau_{ij} = \mu \left[ \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} - \frac{2}{3} \delta_{ij} \frac{\partial u_k}{\partial x_k} \right]
$$

(3)

At typical breathing rates, airflow through the oral airway region and first few generations is incipient turbulent, becoming laminar again at the fourth to sixth generation and remaining so thereafter. Therefore, the shear stress transport (SST) transition model (Menter et al., 2006; Menter, Langtry, & Völker, 2006) is adapted in this study, based on its overall good performance, predicting “laminar-to-turbulent” transition onset, computational efficiency and reasonable accuracy when compared to large eddy simulation (LES). The use of the SST transition model was extensively validated for the first time with 3-D in-vitro velocity data in a subject-specific human respiratory system (Banko, Coletti, Schiavazzi, Elkins, & Eaton, 2015).

For turbulence simulation predicted by the RANS model, the fluctuating velocity component $u'_i$ were recovered by (Gosman & Loannides, 1983; Wang & James, 1999):

$$
u'_i = f_i \xi_i \sqrt{\frac{2}{3} k}
$$

(4)

$$
f_u = 1 + 0.285(y^+ + 6)\exp(-0.455(y^+ + 6)^{0.51})
$$

(5)

$$
f_v = 1 - \exp(-0.02 y^+)
$$

(6)

$$
f_w = \sqrt{\frac{3}{4} f_u^2 - f_v^2}
$$

(7)

where $\xi_i$ are the random numbers from standard normal distribution. In Eqs. (5)–(7), $f_i$ are the damping factors to reflect the anisotropic magnitudes of $u'_i$ in the near-wall region based on the Direct Numerical Simulation (DNS) results. In Eq. (5), $y^+$ is the dimensionless wall distance defined as:

$${\bar{y}} = \frac{y}{\nu}$$

where $\nu$ is the kinematic viscosity.

---

Fig. 3. Normalized velocity magnitude $u^* = \|\bar{u}\|/U_\infty$ at sagittal planes ($Q_{in} = 75$ L/min vs. $Q_{in} = 30$ L/min): (a) Geometry A (b) Geometry B (c) Geometry C (d) Geometry D (e) Geometry E (f) Geometry F (g) Geometry G.
where $y$ is the distance to the nearest wall, $\nu$ is the kinematic viscosity, and $\tau_w$ is the wall shear stress.

$$y^* = \frac{y\sqrt{\tau_w}}{\nu\sqrt{\rho}}$$

(8)
Table 1
Geometric parameters of all human upper airway configurations I.

<table>
<thead>
<tr>
<th>Name</th>
<th>Location [m]</th>
<th>Area [m²]</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
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<td>BB'</td>
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<td>6.62E−04</td>
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<td>CC</td>
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<tr>
<td>EE</td>
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</tr>
<tr>
<td>Glottis</td>
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<td>5.94E−05</td>
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<table>
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<th>Circularity</th>
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</thead>
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</tr>
<tr>
<td>JJ</td>
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<td>0.0624</td>
</tr>
</tbody>
</table>
2.2. Particle dynamics equations

A Lagrangian frame of reference for the trajectory computations can be employed for nano-to-micron-particle dynamics. Assuming nanoparticles to be spherical, and neglecting the thermophoretic forces in light of the large particle-to-air density ratio, the reduced particle trajectory equation reads:

\[
\frac{d}{dt}(m_p u_p) = F_D + F_L + F_{BM} + F_G
\]  
(9)

Here, \(u_p\) and \(m_p\) are the velocity and mass of the particle, respectively; \(F_D\) represents the drag force (Chen, Feng, Zhong, & Kleinstreuer, 2017), \(F_L\) is the gravity, \(F_{BM}\) is the Brownian motion induced force (Li and Ahmadi, 1993; Feng et al., 2016) and \(F_G\) is the Saffman lift force (Saffman, 1965).

Moreover, the regional deposition of particles in human airways can be quantified in terms of deposition fraction (DF) and deposition efficiency (DE), which can be defined as:

\[
DE = \frac{Number\ of\ deposited\ particles\ in\ a\ specific\ region}{Number\ of\ particles\ entering\ this\ region}
\]

(10)

\[
DF = \frac{Number\ of\ deposited\ particles\ in\ a\ specific\ region}{Number\ of\ particles\ entering\ the\ mouth}
\]

(11)

3. Numerical setup

3.1. The virtual population group and in silico inter-subject variability study framework

To obtain statistically meaningful relationships between particle transport/deposition patterns and inter-subject variability, a virtual population group consisting of seven geometries with different anatomical features was established. In general, the virtual population group (VPG) should be a set of high-resolution anatomical models created from CT/MRI data of human subjects. In this study, the VPG is so far the largest digital cohort to determine the impact of key morphological parameters on inhaled particle deposition efficiency (DE), which can be defined as:

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Specifically, seven widely used human upper airway geometries were selected and connected to a subject-specific tracheobronchial tree from the mid of trachea to Generation 8 (G8) (see Figs. 1 and 2). Each human upper airway geometry contains a 20-mm inhaler inlet, oral cavity, pharynx, larynx and a portion of the trachea. Inlet centers are all located at \((x,y,z) = (0,0,0)\), and the upper airway geometries ends in the plane at \(x = 0.12\) m. To provide 3D respiratory system geometries ready for CFD simulations, we merged upper airway configurations with the tracheobronchial tree using 3-matic STL® (Materialise N.V., Leuven, Belgium) to construct Geometries A to G. As shown in Figs. 1 and 2, Geometry A and Geometry B are the upper airway geometries from two in-house subjects (Zhang et al., 2012). The tracheobronchial tree employed for all upper airway configurations is from the same set of computed tomography (CT) scans of Geometry A (see Fig. 1(a)). Geometry C, i.e., the idealized human upper airway shown in Fig. 1(c), was created based on the geometric dimensions measured by Cheng, Zhou, and Chen (1999). The stereo-lithography files (STL) (Geometries D & E (see Fig. 1(d) & (e))) were reconstructed via NextEngine’s Desktop 3D Scanner and processed by ScanStudio software (NextEngine Inc., Santa Monica, CA 90401) based on Replica A and Replica B employed by Su and Cheng (2006). Additionally, Geometry F and Geometry G were created based on the Realistic Model and Elliptical Model respectively, used by Xi and Longest (2007). Geometry F is the realistic model of human upper airway created and smoothed (see Xi & Longest, 2007) based on the CT data of a healthy adult. Geometry G consists of the elliptic model of the human upper airway (Xi & Longest, 2007), which is a simplified version of the realistic model. Cross-sectional segments of the elliptical model are all ellipses with the same local

Table 2

| Geometric parameters of all human upper airway configurations II. |
|-------------------|----------------|----------------|----------------|
|                   | A              | B              | C              | D              |
| Average Cross-section Circularity from AA’ to HH’ (\(C_{AA'}\)) | 0.8975          | 0.8569          | 0.9700          | 0.8929          |
| Average Hydraulic Diameter from AA’ to HH’ (\(D_h\)) [mm] | 10.1075         | 10.0759         | 8.2384          | 10.9835         |
| Axial Length from AA’ to HH’ (\(L_{ax}\)) [mm] | 196.8815        | 213.7903        | 204.128         | 196.4703        |
| Constriction Ratio (CR) | 0.5188         | 0.1892          | 0.1750          | 0.2688          |
| Mouth-to-Throat Curvature (\(\alpha\)) [m⁻¹] | 22.8467         | 28.1770         | 28.6368         | 29.7974         |
| Angle (\(\theta\)) [°] | 134.99          | 172.48          | 176.75          | 142.98          |
|                   | E              | F              | G              |
| Average Cross-section Circularity from AA’ to HH’ (\(C_{AA'}\)) | 0.8843          | 0.9775          | 0.9029          |
| Average Hydraulic Diameter from AA’ to HH’ (\(D_h\)) [mm] | 11.2692         | 10.4214         | 10.8949         |
| Axial Length from AA’ to HH’ (\(L_{ax}\)) [mm] | 168.2582        | 169.8856        | 170.0283        |
| Constriction Ratio (CR) | 0.2366         | 0.2517          | 0.3625          |
| Mouth-to-Throat Curvature (\(\alpha\)) [m⁻¹] | 26.2812         | 23.9120         | 22.3514         | 29.7974         |
| Angle (\(\theta\)) [°] | 118.18          | 147.25          | 138.07          | 142.98          |
hydraulic diameter and flow area as the realistic model (Xi & Longest, 2007). The axial curvatures of both the realistic and elliptical models are identical. Morphological parameters of the configurations are listed in Tables 1 and 2.

Furthermore, to enhance the general statistical robustness of in silico research, a systematic investigation framework is proposed for computational lung aerosol dynamics with data analysis of inter-subject variability, literally the CFPD simulations with error bars (Feng et al., 2017). For regional deposition efficiency (RDE) comparison, the geometries are divided into multiple regions, i.e., oral cavity, pharynx+larynx, trachea, B1, B2.1, B2.2, left upper lobe (UL), left lower lobe (LL), right upper lobe (RUL), right middle lobe (RML), and right lower lobe (RL) (see Fig. 1 for details). It worth mentioning that all lobe symbols represent branch segments leading to the five lobes respectively.

3.2. Mesh generation and independence test

Computational meshes were generated for the seven human respiratory system configurations, using the commercial software ICEM CFD v. 18.0 (ANSYS Inc., Canonsburg, PA). A multi-layer region consisting of dense hybrid tetrahedral/pentahedral elements were generated near the wall surface to fully contain the viscous sub-layers and to resolve any geometric features present there. Local element size was adjusted according to the local airway diameters. Such high local mesh resolution is also necessary to accurately calculate near-wall derivative values. The thickness of the first prism layer guarantees \( y^+ < 1 \) in order to capture the laminar and transitional boundary layers correctly for the testing cases, where \( y^+ \) is the dimensionless wall distance (or local near-wall Reynolds number). Specifically, \( y^+ < 1 \) is for resolving the viscous sub-layer for optimum accuracy using SST transition model (Menter, 1994). If the \( y^+ \) is too large, then the transition onset location will not be accurately predicted and will move upstream with increasing \( y^+ \).

The mesh topology was determined by refining the mesh until grid independence of the flow field solutions was achieved. As an example, the final mesh of Geometry A contains 11,601,350 elements and 3,403,103 nodes. As an example, mesh details of Geometry A has been documented by Feng et al. (2017).

3.3. Particle size range and particle number independence test

In analyzing deposition patterns to fill the knowledge gap, the particles are grouped in distinct diameters, i.e., 0.05, 0.1, 0.5, 2, 5, and 10 µm. The particle density \( \rho_p = 1000 \text{ kg/m}^3 \) is used as a representative density for lung cancer drugs. For steady-state simulations, 1,000,000 particles were released at random locations at the inlet plane for all cases with particle-number independence guaranteed.

3.4. Brownian motion discrete phase model (DPM) time step

In regard to modeling the Brownian motion effects accurately using the white noise process model (Gupta & Peters, 1985), the particle time step \( \Delta t_p \) can be estimated by:

\[
\Delta t_p \approx \frac{C_mC_p}{3\pi\mu_{air}d_p^3} \tag{12}
\]

where \( \mu_{air} \) is the air viscosity and \( C_C \) is the Cunningham correction factor which is given as:

\[
C_C = 1 + \frac{2\lambda}{d_p}(1.257 + 0.4e^{-1.1}\frac{d_p}{\lambda}) \tag{13}
\]

in which \( \lambda \) is the mean free path of air. Specifically,

(1) The DPM time-step should be much larger than the time interval between two successive collisions between the particle and surrounding air molecules, because the white noise process simulated Brownian motion force is a result of sufficient number of collisions. Hence, the DPM time step \( \Delta t_p \) should be much larger than \( \tau_{BM} \), which is calculated based on the collision frequency estimated from kinetic theory:

\[
\tau_{BM} = \frac{1}{\pi (d_p + d_{air})^2} \frac{\rho_{air}}{\rho_p d_p^2} \tag{14}
\]

(2) The DPM time step should be approximately equal to or a slightly larger than the value dictated by Eq. (12), which is the momentum relaxation time. Actually, the white noise process model requires that two successive random Brownian-force magnitudes, obtained via a Gaussian random number generator, should be independent of each other. To guarantee that, the DPM time step must be equal to or a slightly larger than Eq. (12), so that the energy and momentum the particle obtained during \( \Delta t_p \) due to Brownian motion can be damped by the dissipation forces.

(3) The DPM time step should be much less than the large-scale particle-residence time, because the frequency of Brownian motion induced fluctuations is much higher so that the number of fluctuations numerically generated during the transport of the particle should be high enough.
3.5. Boundary conditions

The boundary conditions can be summarized as follows (also see Table 3):

1. Uniform gauge pressure was applied at the terminal outlets.
2. A random-parabolic particle distribution was used at the inlet, where the random particle positions were generated from an in-house MATLAB code.
3. Particle-wall interaction boundary condition was assumed to be a “100% trapped wall”, meaning the airway capture particles at initial contact.

3.6. Numerical solution

The numerical solution of the governing equations with appropriate boundary conditions was achieved by using a user-enhanced, commercial finite-volume based program, i.e., ANSYS Fluent and CFX 18.0 (ANSYS Inc., Canonsburg, PA). All variables, including velocity components, pressure, turbulence variables and particle trajectories and deposition data are calculated and located at the centroids of the discretized mesh cells. An improved Rhie-Chow interpolation method was employed to obtain the velocity components, pressure, turbulence and scalar variables on the control volume faces from those at the control volume centers. A Quadratic Upwind (QUICK) differencing scheme, which is third-order accurate in space, was used to model the advective terms of the transport equations. Numerical simulations were performed on a local 64-bit Dell Precision T7910 workstation with 128 GB RAM and sixteen 3.1GHz CPUs and the supercomputers in the High Performance Computing Center at Oklahoma State University (e.g., Cowboy cluster machine with 252 standard compute nodes with dual Intel Xeon E5-2620 “Sandy Bridge” hex core 2.0 GHz CPUs, with 32 GB of 1333 MHz RAM). The user-enhanced programs are able to perform the following tasks:

1. Defining realistic inhalation waveforms.
2. Recovering anisotropic correction on turbulence fluctuation velocities to reflect the realistic unsteadiness of the flow in human airways (Bernate, Geisler, Padhy, Shaqfeh, & Iaccarino, 2017).
3. Modeling Brownian motion induced fluctuation velocities of particles in the submicron size range (Feng & Kleinstreuer, 2013; Mansour, Rhee, & Wu, 2009).
4. Post-processing particle deposition data in human respiratory systems.

4. Model validations

The Lagrange model for particle transport dynamics has been validated with experimental deposition data on micro-/nano-scales and documented in previous publications (Feng & Kleinstreuer, 2013, 2014; Feng, Xu, et al., 2016; Feng, Kleinstreuer, et al., 2016). The additional in-house CFPD model validations with benchmark in vitro deposition data in human upper airway configurations have been performed recently with good agreements (Haghnegahdar, Feng, Chen, & Lin, 2018).

The SST k-ω transition model has been claimed as an accurate and time-saving Reynolds-averaged Navier–Stokes (RANS) model to be employed to simulate laminar-to-turbulence transitional airflow regime compared to Large Eddy Simulation (LES) models (Elcner, Lizal, Jedelsky, Jicha, & Chovancova, 2016; Zhang & Kleinstreuer, 2011a, 2011b). Still, debates exist on the effectiveness of using RANS models for the prediction of complex 3D airflow regimes in human respiratory tracts (Ball, Uddin, & Pollard, 2008; Bernate et al., 2017; Mina, Ghorbaniasl, & Lacor, 2017). So, due to the importance of correct predictions of transitional and turbulent flows in human upper airways, the airflow field calculated using the SST transitional model has been validated with the most advanced experimental measurements in the same subject-specific human upper airway geometry (Fig. 1(a)). Recently, the in-house SST transition model has been validated (Feng et al., 2017) by comparing for the first time numerical results with 3-D in vitro data of airflow velocity contours in a subject-specific human respiratory system (i.e., Geometry A shown in Fig. 1(a)) using Magnetic Resonance Velocimetry (MRV) (Banko et al., 2015). Good agreements can be observed between the present numerical studies and the experimental measurements in both cases for the 3D airflow field in the human upper airway. It indicates that the SST transition model is capable of predicting the transition and separation locations in the complex respiratory tracts with acceptable accuracy.

In summary, the good agreements between experimental observations and numerical predictions instill confidence that the
The proposed computer simulation model is sufficiently accurate to analyze laminar-to-turbulent fluid flow as well as particle deposition in 3D human upper airways.

5. Results and discussion

5.1. Morphological characterizations of human upper-airway configurations

In order to determine the influence of subject variability on the transport and deposition of particles in human lung-airway models via an efficient parametric analysis plan, we evaluated the geometric variabilities of the upper airways of the seven virtual population groups. Following previous publications (see Choi et al., 2009, 2015; Xi et al., 2016), five sets of morphological parameters were selected (Fig. 2):

1. Circularity (Cr) and hydraulic diameter (Dh) at different cross sections.
2. Constriction ratio (CR = Amin/Ain) between glottis and mouth inlet openings.
3. Curvature (κ) and axial length (Lmax) of the upper airway centerlines (from mouth to x = 0.12 m).

These critical parameters may significantly influence airflow and hence particle deposition. Specifically, the circularity Cr is defined as:
5.2. Airflow fields

The understanding of airflow structures in the human airways underlies the basis for analyzing particle transport and deposition. For example, data of local pressure drop and wall shear stress are of interest to clinicians to prevent ventilator-induced lung injuries (VILI) when mechanical ventilation is applied to patients (Wunsch et al., 2010). Thus, the focus is on the following airflow pattern:

1. Mainstream and secondary flows at multiple cross-sections (see Figs. 3 to 5 for details), i.e., standard deviation of the velocity;
2. Length and deviation of laryngeal jet cores from the centerline (see Fig. 4 & Table 4);
3. Local pressure drop and total pressure drops from mouth to trachea (see Fig. 6); and
4. Turbulence intensities (TIs) at different cross-sections AA’ to LL’ (see Fig. 7).

5.2.1. Secondary flow patterns at sagittal planes and cross-sections

To investigate the morphological effect of upper airways on regional and local airflow patterns in the identical tracheobronchial tree, the normalized velocity contours and secondary flow streamlines at sagittal planes and cross-sections are shown in Figs. 3 to 5 (Q_{in} = 30, 52, and 75 L/min). The coordinates of cross-sectional planes in the seven upper airway models can be found in Fig. 1 and Table 1. Specifically, as the upper airways end at x = 0.12 m, cross-sections HH’ to LL’ are the same in all upper airway models (see Fig. 4). Additionally, seven extra cross-sections were created from the tracheobronchial tree (see Fig. 5(a)) for the evaluation of the velocity profile variabilities induced by the upper airway morphological differences.

General flow patterns include: (1) Recirculation regions (i.e., flow separation) exist at the locations with high curvatures and steep lumen changes; and (2) a laryngeal jet core is generated in each geometry at the glottis (see Fig. 3).

Nevertheless, local airflow regimes in the upper airways and the induced flows in the tracheobronchial tree are distinguished from each other (see Figs. 3 to 5). Fig. 3(a) to (g) visualize the normalized velocity contours (\(u^* = \|\mathbf{u}\|/U_{in}\)) and high-velocity laryngeal jet cores in different upper airway models under two inhalation flow rates (Q_{in} = 30 and 75 L/min). Specifically, the deviation of high-velocity laryngeal jets depends on the connecting angle of the centerlines of pharynx and trachea. The associated recirculation regions are induced by the high-velocity jet in the trachea, which will potentially influence local particle deposition patterns (see Section 5.3). Surprisingly, the influence of inhalation flow rate on the normalized velocity distributions is negligible (see Fig. 3).

The conclusion drawn by Koullapis et al. (2017) concerning the influence of the upper airway morphology on airflow patterns is questionable. Specifically, Koullapis et al. (2017) stated that the upper airway morphology has a negligible influence on the airflow patterns from G1 to airway outlets. In contrast, as shown with the secondary velocity contours at JJ’ in Fig. 4(d) and velocity profiles in Fig. 5(b) to (d), inter-subject variabilities are significant. Indeed, secondary flows and jet core position at JJ’ among the seven upper airway geometries are distinct and can be readily observed (see Fig. 4(d)). The opposite conclusions drawn by Koullapis et al. (2017) may be due to the special geometric features in the three upper airway models they employed. An interesting common geometric feature in the three airway models (Koullapis et al., 2017) is the contraction at the middle of the trachea, as shown in Figs. 9 and 15 in their paper (Koullapis et al., 2017). Therefore, it is possible that the contraction in the trachea serves as a “flow regulator” which is the main reason why the airflow patterns are similar from G1. Thus, a larger cohort is necessary to be employed to solve the inconsistent findings in this study and the publications of other research groups.

Further comparisons in B1, B2.1, and B2.2 indicate that the flow rates entering the five lobes are significantly influenced by the geometric parameters of the upper airways. Velocity profiles distributions in Fig. 5(b) to (d) has demonstrated the local velocity distributions from B1 to G6 depends on the laryngeal jet flow regime, i.e., the impaction patterns on the first bifurcation (see Figs. 3 and 4 for more details), which is affected by the geometric characteristics of the upper airways. Similar laryngeal jet flow regimes result in similar local velocity and flow rate distributions. Velocity profiles at OO’ (see Fig. 5(d)) show that inter-subject variabilities of the upper airways at G6 become less important, except for the average flow rate difference in each airway induced by the upper airway variabilities. Based on the abovementioned observations, we propose the following principle to facilitate the construction of a fully 3D whole-lung model:

Table 4

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 L/min</td>
<td>0.1148 m</td>
<td>0.1733 m</td>
<td>0.1525 m</td>
<td>0.1807 m</td>
<td>0.1809 m</td>
<td>0.1473 m</td>
<td>0.1407 m</td>
</tr>
<tr>
<td>75 L/min</td>
<td>0.0720 m</td>
<td>0.1788 m</td>
<td>0.1877 m</td>
<td>0.1861 m</td>
<td>0.1866 m</td>
<td>0.1678 m</td>
<td>0.1349 m</td>
</tr>
</tbody>
</table>
Fig. 6. Pressure distributions and the pressure drop trends with the constriction ratio: (a) Geometry A  (b) Geometry B  (c) Geometry C  (d) Geometry D  (e) Geometry E  (f) Geometry F  (g) Geometry G  

(h) $\frac{\Delta p}{\rho \| \vec{u} \|^2}$ vs. Constriction Ratio

$\frac{\Delta p}{\rho \| \vec{u} \|^2} = 0.3415(CR)^{-1.341}$

- $A_{min}/A_{in} = 0.52$
- $A_{min}/A_{in} = 0.19$
- $A_{min}/A_{in} = 0.17$
- $A_{min}/A_{in} = 0.27$
- $A_{min}/A_{in} = 0.24$
- $A_{min}/A_{in} = 0.31$
- $A_{min}/A_{in} = 0.23$
Subject-specific upper airway anatomical features from nose/mouth to G6 need to be accurately reconstructed from the CT/MRI scanning data, to guarantee the inter-subject variabilities are maintained correctly.

Due to the diminished inter-subject variabilities starting from G6, it is relatively more feasible to employ a representative airway tree as the unified lower airway model for deeper airway geometry reconstruction, without sacrificing the accuracy of airflow and particle deposition pattern predictions.

Additionally, other distinguished local airflow patterns are observed and can be summarized as follows:

1. There are two counter rotating vortices following the mainstream at both sides in the oral cavities in Geometries A, B, D, E, and G, due to the non-circular geometry effect (see AA’ and DD’ in Fig. 4(a) & (b)). However, no similar structures exist in the idealized upper airway (Geometry C) with perfect circular outlines at those cross-sections.

2. Due to the large constriction ratio CR and low circularity at the glottis in Geometry B and E, high flow resistance around the glottis region breaks up the jet core and spreads it towards the wall (see the contour in sagittal plane in Fig. 3). Recirculation is generated at the upper trachea. However, no such flow patterns are observed in the other geometries.

3. Although the lung-airway tree employed in the seven geometries are the same, mass flow distributions to the left and right lobes are different because of geometric differences among upper airways. For example, Dean’s flows can be observed at RR’ and LL’. However, the local mass flow rate distributions are different, which will potentially influence the fraction of particles moving into different lung branches.

5.2.2. Laryngeal jet core structures

To visualize the laryngeal core structures for $u^* = ||\vec{u}||/U_{in}$, Fig. 4(a)-(d) show the high-velocity jets in the seven geometries for a
steady-state inhalation flow rate $Q_{in} = 30$ L/min. Laryngeal jet length statistics for two steady-state inhalation flow rates, i.e., $Q_{in} = 37$ L/min and $Q_{in} = 75$ L/min, are listed in Table 4. In contrast to the conclusion drawn by Choi et al. (2009), i.e., “at a higher flow rate, the jet core is found to be shorter and detaches from the tracheal wall”, no decrease in jet-core length was detected between $Q_{in} = 30$ L/min and $Q_{in} = 75$ L/min in Geometries B, C, D, E, and F (see Table 4). However, in Geometries A and G, jet core length reduction was found, i.e., higher flow rate induced shorter length of the laryngeal jet core due to the energy dissipation of the impingement effect. Specifically, higher inhalation flow rates (e.g., $Q_{in} = 75$ L/min) will lead to stronger impact on the tracheal wall, which may or may not induce break-up of the jet core. Additionally, jet-core break-up depends not only on the inhalation flow rate, but also on the jet core orientation with the trachea centerline. For example, Geometries D and E jet core length did not change too much, because of the stronger splash along the theta direction.

Furthermore, Fig. 3(a) to (g) and Fig. 4(c) & (d) indicate that laryngeal jet cores deviate from the trachea centerlines with highly distinguished patterns in all seven geometries (red regions in cross-sections). For example, the jet core impacts the front right trachea in Geometry C, the front left trachea in Geometry B, the front middle tracheas in Geometry F and G, the back left trachea in Geometry D, and the back middle trachea of Geometry E, respectively (also see velocity contours From GG to JJ’ in Fig. 4). No common characteristics were discovered because of the highly different geometric characteristics among the three geometries. Furthermore, Table 4 demonstrates that the constriction ratio has an impact on the length of the jet core. Specifically, a large constriction ratio generates a stronger jet core with a longer core length (Geometry C vs. Geometry A). It is reasonable to expect that the impingement location and the length of the laryngeal jet core can significantly influence the local depositions of particles. Another interesting observation is that, despite the axisymmetric shape of the idealized upper airway of Geometry C, the laryngeal cores shown in Fig. 4 is not axisymmetric. This is due to the influence of the reverse flow in the trachea, which conveys the non-axisymmetric geometric effect of the lower lung airways towards the upstream region.

In summary, the laryngeal jet core structures depend significantly on the inter-subject upper airway morphological variability, having a strong impact on local particle transport and deposition in the tracheobronchial tree (see Section 5.3). The dependence of core length and inhalation flow rate is not monotonic in the virtual population group, due to the coupled impacts from other geometric parameters in the upper airways.

5.2.3. Upper airway inspiratory resistance

For different inhalation flow rates local pressure distributions in the seven geometries are visualized in Fig. 6, as well as the correlations between $\Delta p/\rho \parallel \overrightarrow{u} \parallel^2$ and the constriction ratio CR (see Eq. (15) and Fig. 6(h)). The $R^2$ coefficients of determination indicate the relevance of all geometric parameters of the human upper airways (see Table 2 for the parameter values). Except when $R^2 > 0.67$ for the constriction ratio CR, the $R^2$-values for all the other geometric parameters are all less than 0.2. Therefore, it can be concluded that CR is the dominant geometric parameter that influences the pressure drop in human upper airways. A correlation is provided as follows:

$$\frac{\Delta p}{\rho \parallel \overrightarrow{u} \parallel} = 0.3415(CR)^{-1.341}$$

Fig. 6(a) to (h) also demonstrate that sudden pressure drops occur when the airflow passes the glottis because of the constriction effect. Due to the limitation of the size of the virtual population group used in this study, the relevance of the pressure drop and other geometric parameters cannot be determined, implying that the influence of inter-subject variabilities on flow patterns is complex. Therefore, it is again necessary to build a large cohort to enhance the statistical robustness of the investigation. With the low $R^2$-values, trends can still be observed and summarized as follows:

1. the pressure drop increases with the increase of mouth-to-throat curvature and angle, and upper airway length; and
2. the pressure increase with the decrease of cross-section circularity and average hydraulic diameters in the upper airway.

5.2.4. Turbulence Intensity (TI)

Averaged turbulence intensities (TIs) at multiple cross-sections are shown in Fig. 7(a) to (c) in different geometries under different inhalation flow rates. TI is defined as:

$$TI = \frac{\sqrt{\sum^k_{ij} u_{ij}^2}}{\| \overrightarrow{u} \|}$$

Fig. 7(a) to (c) show the averaged TIs at cross-sections AA’ to JJ’ of the seven upper airway geometries with different inhalation flow rates ($Q_{in} = 30$ and 75 L/min). Noticeable inter-subject variabilities of TI can be observed among the seven geometries. However, there are common trends such as the abrupt increase of the average TI when flow passed the constriction at the glottis. Transitions from laminar to turbulence can be observed in the upper airways at locations where sudden lumen contraction or expansion occur. Also, the maximum average TI in trachea is dependent on the constriction ratio CR. For example, Geometries B and C have similar maximum average TI values after the airflow passes the glottis contractions (see data at FF’ in Fig. 7(a) and (b)). In contrast, with a higher constriction ratio (CR), the maximum average TI in Geometry A is lower. To further determine the statistically robust influence of inhalation flow rate on TI, we plotted the mean TIs at different cross-sections with standard deviations (see Fig. 7(c)), despite the significant variabilities observed from Fig. 7(a) and (b). As it is shown in Fig. 7(c), higher inhalation flow rate generates higher mean TIs at cross-sections upstream to the glottis, i.e., from AA’ to FF’ approximately. In contrast, higher inhalation
flow rate leads to lower mean TIs in trachea downstream to the glottis. However, to our surprise, low inhalation flow rate \( Q_{in} = 30 \) L/min induces larger regions of turbulence. This phenomenon can be interpreted as follows:

In laminar-to-turbulence transitional flow, eddies usually occupy more room because they have more time for diffusion and expansion under low Reynolds number inlet condition. With stronger inhalation flow rates and higher Reynolds number, the turbulent area gets narrower but with eddies containing more energy. Such an observation is consistent with the empirical correlation between TI and Reynolds number for pipe flow (Russo & Basse, 2016).

5.3. Inter-subject variability on particle transport and deposition

To fully investigate the inter-subject variability on nano-/micro- particles sizes and common inhalation flow rates, this paper focuses on simulating the transport and deposition of particles with diameters from 50 nm to 10 µm at steady-state inhalation flow rates, i.e., 30, 52, and 75 L/min. Total deposition efficiency (TDE), regional deposition efficiency (RDE) and local deposition patterns of the upper airway configurations are visualized with extensive statistical analyses. The definition of deposition efficiency (DE) is documented in Zhang, Kleinstreuer, and Kim (2008).

5.3.1. Total Deposition Efficiency (TDE)

For particles with diameters from 50 nm to 10 µm, the total deposition efficiencies (TDEs) with different inhalation flow rates \( Q_{in} = 30, 52, \) and 75 L/min are shown in Fig. 8(a) to (d). Although inter-subject variabilities on TDEs are significant, common U-shape TDE curves can be observed for all geometries. Indeed, particles with \( d_p \) approximately equal to 1 µm generate minimum TDEs from mouth to G6, because of their relatively good capability to follow the airflow streams and avoid inertial impactions and relatively low intensity of Brownian motion compared to nanoparticles \( (d_p = 50 \text{ nm}) \). For particles smaller than 1 µm, TDE increases with the

![Fig. 8. Total deposition efficiencies (TDE) of different particle size and inhalation flow rates: (a) \( Q_{in} = 30 \) L/min (b) \( Q_{in} = 52 \) L/min (c) \( Q_{in} = 75 \) L/min (d) Mean TDEs with standard deviations (SD) for different particle sizes.](image-url)
decrease of \(d_p\) induced by the enhanced Brownian motion induced deposition. While for particles larger than 1 µm, TDE increases with the increase of \(d_p\), which is majorly influenced by the enhanced inertial impaction and gravitational sedimentation effects. The TDE data shown in Fig. 8(a) to (c) lead to the conclusion that particles with \(d_p = 1\) µm are the best drug candidates to target lesions in lower lung airways. In order to assess the extra-thoracic morphological variability on particle deposition in the whole upper airway and tracheobronchial tree, average and standard deviations (SDs) are calculated and shown in Figs. 8(d) and 9(d). With the increase of inhalation flow rates, TDEs of particles with \(d_p < 1\) µm decrease accordingly, because of the reduced residence time and reduced chance of deposition due to the dominant Brownian motion effect. In contrast, TDEs of particles with \(d_p > 1\) µm increase with the increase of inhalation flow rate, which is due to the stronger inertial impaction effect. Another finding from Fig. 8(d) is that intersubject variabilities on TDEs are small for particles with \(d_p\) from 500 nm to 2 µm since SDs are small. However, for small particles (\(d_p < 500\) nm) or large particles (\(d_p > 2\) µm), inter-subject variability is significant.

To further determine the influence of upper airway morphological variability on particle depositions from B1 to G6, regional deposition efficiencies (RDEs) in the tracheobronchial tree are plotted in Fig. 8(a) to (d). For particles with \(d_p < 1\) µm, RDE in the tracheobronchial tree also decreases with the increase of inhalation flow rates. For particles with \(d_p > 1\) µm, an opposite dependence can be observed. Such phenomena are also because of the different dominant deposition mechanisms. It can be observed that the subject-variability is negligible of lung deposition for particles with \(d_p\) from 500 nm to 2 µm with the small SDs (see Fig. 9(d)). The conclusion is inconsistent with Koullapis et al. (2017).

Therefore, it can be assumed that a single upper airway model can be used to evaluate the total deposition of particles (500 nm < \(d_p < 2\) µm) in the whole tracheobronchial tree with the statistical robustness to represent a subpopulation group. However, a virtual population group is necessary for the investigation of transport dynamics for particles with size out of that range.

5.3.2. Regional Deposition Efficiency (RDE)

Fig. 10–12 plotted RDEs in different regions (see Fig. 1(h)) for different particles (\(d_p = 50\) nm, 500 nm, and 5 µm) with different

![Diagram](image-url)
flow rates ($Q_{in} = 30, 52,$ and $75 \text{ L/min}$). For small particles ($d_p = 50 \text{ nm}$), RDEs have major decreasing trends when $Q_{in}$ increases from $30 \text{ L/min}$ to $75 \text{ L/min}$ in oral cavity, pharynx + larynx, trachea, B1, B2.1, B2.2, as well as the 5 lobes with exceptions due to subject variabilities (see Fig. 10(a) to (c)). The reduced RDEs indicate that the Brownian motion is the dominant deposition mechanism for nanoparticles, which is diminished due to the less residence time induced by the higher inhalation flow rate. In contrast, RDEs for large particles ($d_p = 5 \mu m$) at those regions increase when the flow rate increases because of the enhanced direct impaction (see Fig. 12(a) to (c)). It is worth mentioning that the increasing trend of RDEs is mild in tracheobronchial airways, since direct impaction induced deposition in lower airways is less important compared to upper airways. For mid-size particles ($d_p = 500 \text{ nm}$), mixed trends are observed because of the combined influence on Brownian motion and direct impaction (see Fig. 11(a) to (c)). Specifically, most RDEs increase in upper airways with the enhanced intensity of inhalation flow rates, while most RDEs in deeper
Fig. 12. Regional Deposition Fraction Comparisons ($d_p = 5 \mu m$): (a) $Q_{in} = 30$ L/min, (b) $Q_{in} = 52$ L/min, and (c) $Q_{in} = 75$ L/min.

Fig. 13. Local deposition patterns of the virtual population group colored by particle residence time ($Q_{in} = 30$ L/min, $d_p = 50$ nm, 500 nm, and 5 $\mu m$): (a) Geometry B (b) Geometry C (c) Geometry D (d) Geometry E.
airways decrease accordingly. However, trend exceptions exist in all regions. Therefore, it is necessary to build an even larger virtual population group to enhance the statistical robustness.

5.3.3. Local deposition distribution patterns

Employing Geometry B, C, D, and E as examples, local particle deposition patterns are shown in Figs. 13 and 14. Common local deposition features can be summarized as follows:

1. “Hot spots” of particle deposition include pharynx, glottis, and bifurcating points, due to direct impaction, secondary flow, and gravitational sedimentation, respectively.
2. Distributed deposition patterns can be observed for small particles ($d_p = 50$ nm) due to the Brownian motion effect without preferential directions.
3. Concentrated deposition patterns exist for larger particles ($d_p = 500$ nm and 5 $\mu$m), because of the dominant effects of direct impaction and gravitational sedimentations. For large particles, due to the enhanced gravitational sedimentation and diminished Brownian motion, nearly no particles deposit at the upper palates but more concentrated particles deposit at lower palates. Significant subject variabilities of local deposition in upper airways and the tracheobronchial tree are discovered and presented as follows:

1. Laryngeal core and induced recirculation zone in trachea, B1, B2.1, and B2.2 can determine the localized deposition patterns. For example, the laryngeal core of Geometry D strikes the back of trachea and generates a recirculation zone at the front of trachea (see Figs. 3(d) and 4(d)). Correspondingly, particles entering the recirculation region stay in the zone longer and have a higher chance to deposit on the airway wall either due to the Brownian motion or direct impaction (see the red circles in Fig. 14(c)). Different deposition patterns can be observed at B1 due to the different impaction areas and the “extending splashes” of laryngeal cores into the tracheobronchial tree (see red circles in Figs. 13 (a), 14(b) and (c)).
2. A special particle deposition pattern is found in Geometry E for particles with $d_p = 5$ $\mu$m and $Q_{in} = 30$ L/min (see the red circle in Fig. 13(d)). Particles depositing at the lower palate have longer residence time compared to other particles depositing in the oral cavity. Such an observation demonstrates the deposition is influenced by the local recirculation flow and gravitational sedimentation effects. Indeed, particles enter the recirculation zone near the lower palate, and gradually sediment on the wall. However, nanoparticles can follow the mainstream well and avoid jumping into the recirculation zone, which indicates that the
recirculation flow may enhance the deposition of large particles but serve as a blocking zone to keep nanoparticles from touching the covered airway wall.

5.3.4. DE vs. Stokes Number

Deposition data are reorganized and plotted vs. the Stokes Number $St$, which is defined as:

$$St = \frac{\rho_p d_p^2 U_m}{18 \mu_{air} D_m}$$

(20)

As shown in Fig. 15(a) and (b), inter-subject variability of the upper airway on tracheobronchial tree deposition is trivial when $1e^{-5} < St < 0.08$. However, for TDE shown in Fig. 15(c) and (d), the inter-subject variability of the upper airway is significant across all St-values.

6. Conclusions

In this study, numerical inter-subject variability studies were performed for airflows at typical drug-inhalation flow rates. An exemplary pipeline of the virtual simulation tool for pulmonary drug delivery optimization and personalized health risks assessment are discussed. It can be concluded that the upper-airway morphology has a significant influence on local airflow pattern as well as particle transport and deposition in the tracheobronchial region. Based on the numerical results presented, the conclusions are as follows:

1. Morphological parameters of the upper airways, such as cross-section circularity, constriction ratio (CR) between the glottis and mouth inlet, mouth-to-throat curvature, and connecting angle between pharynx and trachea have different levels of influence on airflow patterns, pressure drops, and particle deposition distributions. Most important appears to be the level of constriction at the glottis, i.e., the local CR-value, on the pressure drop in the upper airways. A pressure-drop correlation is provided (see Eq. (18)) based on the geometric parameter values of the subject-specific upper airway configuration. The influence of other

![Fig. 15. Deposition efficiencies vs. Stokes number: (a) RDEs in the tracheobronchial tree vs. St (b) Mean RDEs in the tracheobronchial tree with SDs vs. St (c) TDEs vs. St (d) Mean TDEs with SDs vs. St.](image-url)
geometric parameters are comparatively less important.

(2) For particles with diameters from 500 nm to 2 µm, inter-subject variabilities of regional DEs can be negligible. It indicates that a single upper airway model can be used to evaluate the total deposition of particles in the whole tracheobronchial tree, thus with a statistical robustness to represent a subpopulation group.

(3) Statistical robustness needs to be guaranteed by introducing subject-specific virtual population groups for particles with dp < 500 nm and dp > 2 µm. In other words, patient-specific pulmonary disease treatment needs to be accompanied by the maintenance of realistic geometric complexities of human upper airway geometries.

7. Future Work

The ultimate goal of the in silico inter-subject variability is to pave the way to develop a non-invasive tool for “personalized medicine”, i.e., to have the right drug with the right dosage for the right patient at the right time and location. Accordingly, future work includes:

(1) Extended inter-subject variability studies with:(a) accurate laminar-transitional-turbulent flow simulations with transient breathing waveforms (“Normal Breathing”, 2016; Huang & Zhang, 2011; Olsson, Borgström, Lundbäck, & Svensson, 2013), employing a whole lung-airway model; and (b) additional virtual population groups with increased resolution of 3D respiratory systems, representing more specific subgroups, to meet different needs of investigations, e.g., personalized pulmonary disease treatment as well as potential health risk assessment on a patient specific level.

(2) An open-source in silico investigation framework for personalized pulmonary disease treatment planning, i.e., “individualized medical digital twin”, which will pave the way for the paradigm shift to realize personalized medicine faster.

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Disclaimer

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