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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

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Nomenclature

Acronyms

B	Bifurcation
CFPD	Computational Fluid-Particle Dynamics
CR	Constriction Ratio
Cr	Circularity
DE	Deposition Efficiency
DF	Deposition Fraction
DNS	Direct Numerical Simulation
DPM	Discrete Phase Model
G	Generation
LLL	Left Lower Lobe
LUL	Left Upper Lobe
PIFR	Peak Inspiratory Flow Rate
RANS	Reynolds Averaged Navier-Stokes
RDE	Regional Deposition Efficiency
RLL	Right Lower Lobe
RML	Right Middle Lobe
RUL	Right Upper Lobe
SD	Standard Deviation
SST	Shear Stress Transport
TB	Tracheobronchial
TDE	Total Deposition Efficiency in the Upper Airway Configuration
VILI	Ventilator-Induced Lung Injuries
WSS	Wall Shear Stress

Greek symbols

κ	Curvature

Subscripts

air	Air
B	Boltzmann
BM	Brownian Motion
h	Hydraulic
p	Particle
ua	Upper Airway

Superscripts

BM	Brownian Motion
D	Drag
G	Gravity
L	Lift

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 (d_p 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.

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