Aerosol Dosimetry in Asthmatics: From MRI Data to Numerical Simulations

A Thesis Presented

By

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ABSTRACT

Reducing the frequency of exacerbations is the primary goal of asthma disease management. Severe asthmatics (~15% of asthmatics) are challenging to treat, as this cohort of patients do not respond well to inhaled therapeutics. Computational fluid dynamics and particle transport (CFD-PT) simulations provide unique insight on factors that may lead to abnormal airflow distributions and insufficient therapeutic delivery. CFD-PT has the potential to uncover structural/functional abnormalities beyond what can be feasibly measured in vivo. In this study, we perform CFD-PT simulations in six subjects by coupling image-based airway geometries with measurements of segmental ventilation defect percent (SVDP) collected from hyperpolarized (HP) 3He magnetic resonance images (MRI). Dosimetry is then predicted for each of the six subjects, which allows for the correlation between asthma severity and anatomical features to be quantified. The particle trajectories were calculated by numerically solving a reduced form of the Maxey-Riley equation. The influence of particle diameter coupled with initial time and location of particles on regional and total deposition was studied. Simulation results highlight the link between geometry, asthma severity, particle size, particle initial location, and particle release time with regional deposition concentration. At the end, we improved particle deposition in the lobe of interest of a severe asthmatic subject by using a modified release time and location of particles.
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I dedicate my thesis to my family for their love and support.
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Chapter 1: Introduction
1.1. Asthma

Asthma is a heterogeneous chronic airway disorder that affects 334 million people worldwide [1]. About 15% of asthmatic patients are considered as severe asthmatic, mostly based on symptoms and lung functions. Severe asthmatic care is particularly challenging, as these patients do not respond well to inhaled therapeutics [2]. The main goal of treatment is to control severe asthma by reducing the risk of future exacerbations. In recent years, significant attention has been directed towards understanding features of severe asthma [3], [4], enabling measurements of structure/function abnormalities [5], [6] such as inflammation and remodeling [7], [8], and helping to uncover links between these biomarkers and disease severity [9]. While these efforts have improved our understanding of severe asthma, knowledge gaps in treatment strategies remain.

1.2. Measuring Particle Deposition by Experiments

Measuring total dosimetry in healthy and pathological human lungs has been performed widely [11,12] as particle concentrations inhaled and exhaled may be readily measured with photometer techniques [13]. With these whole lung dosimetry methods, deposition fractions may be correlated to particle size and tidal volume. More recently, focus has turned to quantifying regional deposition patterns with SPECT [14,15], PET [16], or planner gamma scintigraphy [17] imaging methods. These data highlight subject variability in total and regional deposition, even in healthy lungs. However, sources of variability cannot be easily determined, mainly because of the data resolution and the impracticality of performing multiple and longitudinal studies on the same subjects.
1.3. Modeling State-of-the-Art

The benefit of computational fluid dynamics and particle tracking (CFD-PT) methods lie in their ability to virtually test a range of scenarios without conducting additional experiments. In addition, with simulations it becomes possible to identify major parameters that influence deposition and to pinpoint variability observed in experiments.

The level of sophistication of physiologically-based respiratory simulations have increased in recent years, enabling insight into factors that may contribute to abnormal airflow distributions and particle transport. While the majority of respiratory computational fluid dynamics (CFD) models have focused on resolving the airflow in healthy [18]-[25], recent works in modeling COPD [26-27] and asthmatic lungs [28]-[30] have emerged.

Despite wide variations in airway anatomy [31] in healthy and pathological lungs, most respiratory computational models predict aerosol fate in either a single representative patient [32] or in idealized airways created with classical morphometric data [33]. Until inter-subject variability is accounted for in lung modeling [34], it will remain impossible to translate model predictions into clinical practice (e.g. optimization of inhaled therapeutic delivery) or public-health policy (e.g. burden of airborne toxic materials) settings. In one study, Hussain et al. simulated particle deposition over a range of respiration conditions with a stochastic airway model and found that deposition predictions varied about 30% between the ten adult male subjects [35].

By correlating deposition patterns to patient-specific airway morphometric features, we may begin to understand which parameters play a key role in abnormal variances,
especially in the presence of disease. Furthermore, linking morphometric abnormalities with atypical distribution of particles in the lung may ultimately enable identification of subjects who may experience inadequate aerosol medication dosages.

1.4. Missing links: Introduction to Thesis

A major challenge of lung modeling is in the definition of boundary conditions, since neither time-dependent flow rate nor pressure may be measured at the terminal airways in vivo. To overcome this limitation, several groups [25,27,54,21] have developed frameworks that integrate lung mechanics into CFD simulations. While these methods enable realistic airflow distributions to be captured, it is challenging to parameterize these models and to distribute parameters in a meaningful way. This limitation may be alleviated by informing the CFD models with patient-specific imaging data.

The goal of the current study is to couple medical images with patient-specific CFD models to predict gas distributions and particle characteristics in asthmatics. Specifically, we incorporate CT imaging data to create realistic airway models, with segmental ventilation defect percentages (SVDP) calculated from HP $^3$He MRI to parameterize the flow boundary conditions. SVDP quantifies segmental lung regions that show reduced local signal and is computed as a low HP $^3$He MRI signal volume normalized by the total segmental volume [37]. Regions of high SVDP may be caused by mucus plugging and/or hyperresponsive airway smooth muscle, which in turn results in heightened airway resistance and reduction in quantity of gas delivered to distal lung regions. While incorporation of ventilation defects, quantified with HP $^3$He MRI, has been previously incorporated into network models [38-39], to the best of our knowledge we are the first to incorporate patient-specific models of gas flow with SVDP.
Beside the airflow characteristics, we study the particle deposition distribution in asthmatics and regional particle deposition for each lobe and variables affecting regional and total deposition. Targeted delivery may enable delivery of medications directly to areas in need, while alleviating adverse side effects. Here, we play with key variables to improve regional drug delivery to the lobes of interest (i.e. high SVDP). For example, we change the time that particles are released and the initial location of particles, optimizing drug delivery based on the needs of the individual subject.
Chapter 2: Methods
2.1. Overview

Unsteady CFD-PT simulations are performed in 6 human lungs (2 healthy, 1 mild, 1 moderate and 2 severe asthmatics, same subjects of our previous study [40]) to predict variability in total and regional particle deposition throughout inhalation. Anatomical 3D geometries are created based on the high resolution CT scans created with the open source software Simvascular [41]. Simulated ventilation distribution and particle tracking methods are executed by coupling our in silico framework [27,42] with ventilation assessed with HP\(^3\)He gas MRI based on measured ventilation defects. At the end, time and location of released particles have been studied to improve therapeutic deposition for severe asthmatics. Figure 1 shows the general pipeline of the modeling framework.
2.2. Image Data Acquisition and Calculation of SVDP

*Human Subjects:* The study was conducted in accordance with Health Insurance Portability and Accountability Act regulations and approved by the University of Wisconsin- Madison institutional review board under investigational new drug (IND) protocol No. 064867. Spirometry (EasyOne, ndd Medical Technologies, Andover, MA)
data was collected for each subject and reported as % of predicted values normalized for sex, age, and height based on Global Lung Function Initiative equations [43]. Asthma severity level was determined based on the American Thoracic Society Workshop on Refractory Asthma [2].

*CT and MRI Data Acquisition:* Hyperpolarization of the $^3$He gas was performed with a Polarean 9600 commercial polarizer (Polarean Inc., Durham, NC) using a spin-exchange optical pumping method [44]. Standard proton and $^3$He imaging were performed consecutively to minimize subject movement. Each subject inhaled approximately 1L of a mixture of 4.5 mmol=L of hyperpolarized $^3$He mixed with N2 while supine in a 1.5T MRI scanner (Signa HDx, GE Healthcare, Milwaukee, WI) coil (IGC Medical Advances, Milwaukee, WI) or a rigid-body single-channel volume coil (Rapid Biomedical, Columbus, OH) depending on patient size. $^3$He inhalation was performed over a period of approximately three seconds starting at functional residual capacity (FRC) and was followed by a 16-20s breath hold during which imaging was performed. To acquire the $^3$He images, a gradient echo sequence was used with the following imaging parameters: repetition time: 6.5ms, echo time: 2.9ms, flip angle: 14°, field of view: 40 x 40cm, matrix: 128 x 128, and slice thickness: 1.0cm with a typical range of 20-30 axial slices. Images were then reconstructed to a 256 square matrix with a voxel size of 1.56 x 1.56 x 10mm [45]. Further details on the imaging procedures may be found elsewhere: [10], [45], [46]. High resolution chest CT images were collected in all subjects at FRC with a 64 detector CT scanner (CT 750HD, GE Healthcare, Milwaukee, WI) with a pitch of 0.984, rotation time of 0.5 s, and tube current of 100-180 mAs adjusted based on subject’s body mass index. Resulting matrix size was 512 x 512 over a display field of
view adjusted to the lung volume (35 x 35 cm) with a slice thickness of 0.625 mm and interval of 0.5 mm yielding an approximately isotropic voxel size.

*Calculation of segmental volumes (\( V_S^M \)) and SVDP:* SVDP is a quantitative measure of regional ventilation defect located within each segment volume and is calculated as the percentage of defected volume with respect to the total segmental volume (\( V_S^M \)). Here, we define a segmental feeding airway (SFA) as the airway leading to a \( V_S^M \). There are 19 segments in total, 10 in the right lung and 9 in the left lung. \( V_S^M \) is estimated from CT images using VIDA Diagnostics software (VIDA Diagnostics, Coralville, IA). A binary ventilation defect mask is generated from the 3He images using an adaptive K-means method [45], Figure 2 with pulmonary vasculature excluded and with the lung boundary informed by proton MRI registered to \(^3\)He MRI using the ANTs software package (http://stnava.github.io/ANTs/). CT images and corresponding anatomical masks are registered to the already registered proton MRI (and thereby the \(^3\)He MRI) to determine segmental ventilation defect volume \( V_{VD}^M \), which is then divided by \( V_S^M \) to yield SVDP.
Figure 2. HP $^3$He MRI shown in panels (c) and (d); panel (c): raw image, panel (d): color-coded by a segment mask (i.e. sublobar regions) derived from the subject’s CT data at the axial location highlighted in panel (a). Labeled anatomical outlines of segment masks are shown in panel (b). Note the spatial overlap between the ventilation defects (red arrows) and the RB4, RB5, LB5, and LB8 segments.

Table 1. Subject demographics, spirometry results (collected post bronchodilator), and asthma severity level classification [2]. FEV1: forced expiratory volume in one second, FVC: forced vital capacity. % predicted values are calculated based on age, gender, and height-corrected standards.
2.3. Airways Geometry

Subject-specific conducting airway geometries are created directly from the FRC CT data with the open source software SimVascular (http://simvascular.github.io/) [41]. Models are created at FRC to be consistent with the lung inflation of HP ³He MRI (acquired at FRC + 14% of total lung capacity). When possible, geometries spanned from the trachea to one generation beyond the SFA, resulting in N=~38 subsegmental feeding airways (SSFA) per subject. For some subjects it was impossible to grow the tree to this extent, likely due to reduced airway size from remodeling, and therefore it was necessary to terminate the tree at the segmental airway level. To characterize the airway morphology, we measure each airway’s dimensions directly from the geometric model with custom-built MATLAB codes[53]. For each airway, we measure hydraulic diameter \( D_H = \frac{4A}{C} \), where \( A \) and \( C \) are the cross-sectional area and circumference, and length \( L \).

In addition, we characterize bifurcation angles \( \theta_B = \cos^{-1}\left[ \frac{P \cdot d}{L_p L_d} \right] \) where \( p \) and \( d \) are the parent and daughter vectors with lengths \( L_p \) and \( L_d \), respectively, and gravitational angles, \( \theta_G = \cos^{-1}\left[ \frac{g \cdot d}{L_d} \right] \), where \( g \) is the gravitational unit vector positioned parallel to the trachea. Deviation of airway’s cross-section from a perfect circle is quantified by its eccentricity

Equation 1

\[
e = \sqrt{1 - \frac{r_{min}^2}{r_{max}^2}}
\]

where \( r_{min} \) and \( r_{max} \) are the minimum and maximum radii, calculated for each branch within the airway tree. Note \( e = 0 \) for a perfect circle. When relevant, one-way ANOVA
with Bonferroni post-hoc test is employed to test for statistical significance \((p \leq 0.05,\) IBM SPSS Statistics software).

### 2.4. Calculating the Boundary Condition

*Simulation of 3He experimental conditions:* to simulate the gas employed during the HP \(^3\)He MRI imaging, we calculate the density \((8.55E-7 \text{ g/mm3})\) and viscosity \((1.99E-5 \text{ g/mms})\), assuming a 3:1 ratio of N2 and 3He \([47]\). Since subjects inhaled 14%TLC (i.e. 1000mL) of the gas mixture over approximately 3s, we set the flow rate at the trachea to 333.3mL/s, with a parabolic velocity profile. No slip (velocity = 0) is set at the airway walls.

*Inclusion of SVDP into gas simulations:* boundary condition definition at the terminal airways is challenging since it is not possible to measure the time-dependent flow or pressure at each of the terminal airways. Therefore, assumptions regarding the ventilation distribution is necessary. Here, we employ an iterative lung mechanics approach to achieve the desired gas distribution, leveraging the distal volume and SVDP measurements collected during the imaging protocol. Two final simulation results are achieved for each subject: “Normal Lung” \((\text{sim}_N)\) where gas distribution is based solely on distal lung tissue/gas volume, and “Ventilation Defect Lung” \((\text{sim}_{VD})\), where SVDP is incorporated to parameterize the gas distribution. \text{sim}_N and \text{sim}_{VD} are performed in series, Figure 1. \text{sim}_N is performed by first assuming an initial respiratory resistance
\( R_{res} = 7.0E - 3 \frac{cmH_2O-s}{ml} \) [48] and then distributing \( R_{res} \) to each segmental airway according to the distal volume fraction:

Equation 2

\[
R_S = \frac{R_{res} \sum_{S=1}^{N} V_S^M}{V_S^M}
\]

where \( V_S^M \) is calculated from the CT dataset. \( R_S \) is further decomposed to the SSFA (\( R_{SS} \)) branches according to the relative cross-sectional areas. 3D airway resistances (\( R_{3D} \)) are not negligible and cannot be predicted a priori due to the complex geometry and flow structures. Following each simulation, we update \( R_{SS} \), accounting for the 3D resistance, until the predicted \( V_S^P \) is within 5\% of the measured one, \( V_S^M \). As our geometric models expand one generation beyond the SVDP resolution, we choose to describe the larger and small daughter SSFA branches as diseased (D) and normal (N), respectively. \( R_{SS_N} \) remained the same for the normal branches. Resistance of the airway feeding a defected region \( R_{SS_D} \) is increased until the simulated volume minus the ventilation defect (\( V_{VD}^P \)) matches the experimentally-measured one (\( V_{VD}^M = V_S^M[1 - SVDP/100] \)), by at least 5\%.

By employing this procedure, we are allowing the gas to redistribute from the defected regions to regions that are otherwise normal. Note that the same procedure is employed for the models where it is impossible to include all the SSFA (AS2 and AS4), with the only difference being that the sub segmental branches are modeled by parallel resistance network pairs.

\textit{Results for this part:} This steady CFD simulation met convergence after 1000 time steps; each time step is 0.0001s. Three to five iterations are necessary for the simulations to match both \( V_S^M \) and \( V_{VD}^M \), and in general, more iterations are needed for larger, or more
heterogeneous distributions of, SVDPs. Measured SVDPs (mean $\pm$ standard deviation of all the segmental airways) are presented for each subject in Table 2. Measured SVDP are largest for the two severe asthmatics (AS3 and AS4). As suggested by the standard deviation, defects are more heterogeneously distributed in AS4; two of AS4’s airways have SVDP greater than 15% (an airway in middle right lobe (16.6%) and the inferior left lobe (20.6%) and five airways did not have any defects, mostly located within the inferior right lobe. Subject AS3 only has one airway with SVDP greater than 15%, also located in the inferior left lobe (20.4%) and only one airway with no defects, similarly located within the inferior right lobe. To match the measured ventilation defect, prescribed resistances ($R_{SSD}$) increases (Table 2), and consequently largest changes in $R_{SSD}$ from baseline, are also found for the two severe asthmatic subjects. Likely linked to the heterogeneous distribution of SVDP, achieving a resistance that enabled matching of $V_{VD}^{P}$ and $V_{VD}^{M}$ required ten simulation iterations for AS4. The largest change in $R_{SSD}$ is found for AS4’s airway with 20.6% SVDP; resistance increased by 4.7 times baseline. Total respiratory resistance, $R_{res}$, increases with incorporation of SVDP, Table 2. Note, increase in $R_{res}$ may be a combination of increases in both airway and tissue resistance and it is not possible within our current framework to distinguish between the two.

Table 2. Measured ventilation defects (SVDP) and resulting simulated resistances for each distal airway ($R_{SSD}^{P}$), total respiratory Resistance ($R_{res}$) and resistance within the modeled conducting
airways \((R_{3D})\). SVDP and \(R_{SS}^D\) are reported as mean ± the standard deviation across all SSFA for each subject.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>SVDP (%)</th>
<th>(R_{SS}^D)</th>
<th>(R_{res})</th>
<th>(R_{3D}) (cm (H_2O)-s/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS1</td>
<td>0.03 ± 0.09</td>
<td>0.03 ± 0.09</td>
<td>0.01</td>
<td>4.1E-3</td>
</tr>
<tr>
<td>AS2</td>
<td>0.43 ± 0.59</td>
<td>0.44 ± 0.60</td>
<td>0.21</td>
<td>8.9E-3</td>
</tr>
<tr>
<td>AS3</td>
<td>4.30 ± 5.22</td>
<td>7.32 ± 7.28</td>
<td>4.40</td>
<td>1.1E-3</td>
</tr>
<tr>
<td>AS4</td>
<td>3.54 ± 5.98</td>
<td>30.2 ± 83.6</td>
<td>12.2</td>
<td>17.3E-3</td>
</tr>
<tr>
<td>HS1</td>
<td>0.02 ± 0.10</td>
<td>0.02 ± 0.10</td>
<td>0.02</td>
<td>4.5E-3</td>
</tr>
<tr>
<td>HS2</td>
<td>1.13 ± 1.55</td>
<td>1.16 ± 1.66</td>
<td>0.66</td>
<td>5.3E-3</td>
</tr>
</tbody>
</table>

2.5. Airflow Simulation

After the iterative steady simulation is done and we found the 3D resistances, since the 3D resistances are a function of geometry not a wave form nor flow rate, we can use them for the unsteady airflow simulation which simulate one using the Dried powder Inhaler (DPI). Airflow velocities and pressures during the inhalation time are calculated by solving the Navier- Stokes equations with an open source finite element solver, Simvascular. Slow-and-Deep realistic inhalation waveform is used here based on the
study of Lognest et. al and Khajeh-Hosseini [49,50]. They described the inhalation waveform by these equations:

Equation 3

\[ Q(t) = \frac{PIFR}{T_{PIFR}} t, \quad 0 \leq t \leq T_{PIFR} \]

Equation 4

\[ Q(t) = PIFR \cos \left( \frac{2\pi(t - T_{PIFR})}{4(1 - T_{FPIFR})} \right) \quad T_{PIFR} < t \leq T \]

Where \( Q(t) \) is the transient inhalation flow rate, \( PIFR \) is the peak inhalation flow rate which is 61.4 L/min, \( T_{PIFR} \) is the time to peak inhalation flow rate which is 1.22 sec and \( T_{PIFR} \) is the time fraction of peak inhalation flow rate which is 1/4.

3D Resistances from last section has been used to parametrize the boundary condition. Zero pressure has been set on the trachea face and no slip condition for the airway walls. It is assumed that the air is incompressible and Newtonian with fluid density of \( \rho_f = 1.2E-6 \, \frac{g}{mm^3} \) and viscosity of \( \mu = 1.81E-5 \, \frac{g}{mm \cdot s} \). The walls have been assumed to be rigid. To solve the unsteady airflow, in average 6M tetrahedral mesh elements were created for each model with MeshSim [41], featuring refinements in boundary layers to capture near-wall flow gradient.

2.6. Particle Transport Simulation

Following the unsteady airflow simulation, particles with diameter of 1, 3 and 5 micron were tracked throughout inhalation. The particles were released at the trachea face proportional to the local flow rate of the cell they are releasing from [52]. This method
simulates the fact that more particles are inhaled during times and locations of peak flow rates. About 4M particle trajectories were calculated by solving a reduced form of Maxey-Riley equation by neglecting the Faxen and Basset history term (Eq 5), where \( v(X_p) \) is the particle velocity, \( X_p \) is the position of the particle at any given time, \( g \) is the gravitational vector, and \( u(X_p) \) is the fluid velocity obtained from the 3D Navier-Stokes equation. First term of right side of equation 5 is Buoyancy force, the second term is Force of fluid on sphere, and the last term is Stokes drag force, see [51] and [42] for discussion.

As the particle's Stokes numbers \( Stk = \frac{\rho_p d_p^2 w}{18 \mu d_c} \) where \( d_p \) is the particle diameter, \( \rho_p \) the particle density, \( w \) the mean speed of fluid, and \( d_c \) the diameter of the airway) are much smaller than one; we may assume that the computationally intensive memory terms may be neglected as they scale to the square root of the particle's Stokes number. The Faxen term are ignored because \( \frac{d_p}{d_c} \ll 1 \).

Equation 5
\[
\frac{\partial v(X_p)}{\partial t} [\rho_p + \frac{1}{2} \rho_f] = [\rho_p - \rho_f] g + \frac{3}{2} \rho_f \left[ \frac{\partial u(X_p)}{\partial t} + (u(X_p).\nabla)u(X_p) \right] - 18 \frac{\mu}{d_p^2} \left[ v(X_p) - u(X_p) \right].
\]

We assume one-way coupling which means that particles cannot affect the airflow distribution because the volume fraction of the particles are much smaller than the carrier fluid. Also because of this, it is appropriate to ignore any interaction between particles. These rigid, spherical particles are going through the lung, floating in air and they may deposited on the airway walls or exit out one of the distal airways.
2.6.1. Variables affecting Particle Deposition

Time of releasing particles and their location on the trachea at the release time, are two important variables that can affect the faith of particles, also total and regional deposition [36]. To identify times of enhanced deposition efficiency, we recorded particle deposition over inhalation time (4.8s) and correlated with the particle bolus injection time.

For initial location of particles, we record initial location of all particles and study the link between the location they started and where they deposited. At the end, some changes have been made on these two factors to see whether by changing initial time and location of particles, the total or regional deposition can be improved for severe asthmatic subjects.
Chapter 3: Results
3.1. Airway Geometries and Morphometric Analyses

Representative geometries for a healthy, moderate, and severe asthmatic subject are shown in Figure 3 and rotating videos for all subjects are provided in the supplementary materials. Most airway geometries spanned from the trachea to the SSFA, resulting in \( \sim 38 \) terminal branches. It is impossible to grow the trees to this extent for AS2 (moderate asthma) and AS4 (severe asthma), perhaps due to mucus plugging or airway remodeling. Therefore, parallel resistive elements are substituted for branches within AS2's lower left lobe and AS4's upper left lobe and lower right lobe.

Figure 3. Constructed airway geometries of healthy (HS1, panel A), moderate (AS2, panel B), and severe asthmatic (AS4, panel C).
Airway diameters, as shown in Figure 4A, did not vary significantly between subjects.

As AS3 and AS4’s dimensions represent the extremes, and both subjects are classified as severe, we choose to analyze these two subjects in depth. As highlighted in Figure 4A, AS3’s and AS4’s airway diameters are larger and smaller than the mean, respectively.

Airway eccentricity is calculated for each generation, as presented in Figure 4B. Per generation, AS3’s and AS4’s airway eccentricity tend to be smaller (more circular) and larger (more elliptic) than the mean values, respectively. AS3’s airway eccentricity (Eqn.1) is significantly smaller than all other subjects (p < 0.05), except AS1 (Figure 4B).
Mean bifurcation ($\theta_B = 29.2 \pm 1.5^\circ$) and gravitational angles ($\theta_c = 75.7 \pm 2.7^\circ$) did not vary significantly between subjects.

### 3.2. Airflow Characteristics

Streamlines are shown in Figure 5 for each subject at the time of mean flow rate, during deceleration ($t = 3.6s$); color coded based on the velocity magnitude. Also, time averaged wall shear stress (TAWSS) for each subject, averaged over the entire simulation are shown within each panel.

Streamlines and velocity magnitudes vary between subjects, especially between the asthmatic subjects. AS4 has very high velocity magnitude in its distal airways while the peak velocity of AS1 is located at the main left and right bronchi regions. Although AS4 and AS3 are both severe asthmatics (see Table 1), velocity distribution is different between these two. Mostly because AS4’s conductive airways are smaller than those of AS3 (Fig 4). Another interesting result is that there are more helical streamlines for the asthmatic subjects in comparison to the healthy subjects. This is perhaps because airways of asthmatic subjects are not as smooth as the healthy subjects and some of the asthmatics subjects seem to have signs of airway collapse, because the backside of the trachea is flat.

Time Average Wall Shear Stress (TAWSS) which is a measure of average of wall shear stress of whole model during the inhalation time, varies amongst the subjects as well. Since AS3 has bigger conductive airways compare to the others, it has the lowest TAWSS and lowest velocity magnitudes. TAWSS peaks at the main carina and at the main left and right bifurcation regions of subject AS1. In subjects AS2 and AS4 high TAWSS is located at the terminal airways; AS4 has the highest TAWSS since it has the smallest distal airways.
in comparison to the other subjects. Note, AS3 and AS4 are both severe asthmatics, but again we see significant difference in gas flow behavior, as exhibited by TAWSS.

**Figure 5.** Stream lines are shown for each subject at the time of mean flow rate during flow deceleration (t=3.6s); color coded based on the velocity magnitude (mm/s). Also, time averaged wall shear stress ($g/mm - s^2$) (TAWSS) for each subject during the whole simulation time are shown within each panel.

### 3.3. Particle Deposition

Normalized number of deposited 3 micron particles for all six subjects are shown in Figure 6. In addition, deposited particle locations are shown within each panel and the particles are color coded based on the lobe they deposited in. Values in each panel show the percent of deposited particles in each region with respect to total deposition, and the values beside each model shows the total 3 micron particle deposition. Normalized number of deposited particles is
\[ NP = \frac{N_e \sum T}{N_T \sum e}, \]

where \( N_e \) is the number of particles that deposit within a surface element, \( N_T \) is the total number of deposited particles, \( \sum e \) is the element’s surface area and \( \sum T \) is the total surface area of the 3D model.

The regional deposition varies between subjects, no matter if they are in the same asthma severity group or not. For instance, there is large variability amongst the healthy subjects, as within the Lower Left lobe, which is represented by green. Percentage of deposited particles in Lower Left lobe varies from 6.2\% to 25.3\% between the subjects. This is also true for AS3 and AS4, we can see the distribution of deposited particles varies between these two.

In our previous study, we showed that the regional deposition could vary between healthy subjects while the total depositions remain the same [18], which remains true here. For the two healthy subjects (HS1 and HS2), although total deposition is the same, regional deposition is different. Right lung regional deposition of AS1 and AS2 are quite similar but NP is different between them in the right lung, which means even when the regional deposition is the same, concentration and distribution of deposited particles can be different. In AS1 high concentration regions (high NP) are located around the main bifurcation. In AS2 high NP regions are located mainly in the distal airways. That’s because of the small right and left main bronchi of AS1 which we can see in Figure 4, resulting in high velocity magnitude in the main bifurcation (Figure 5), causing the particles to deposit there due to inertial forces, instead of going further like AS2. Everything is different between AS3 and AS4 even though they are in a same severity
group. Total deposition, regional deposition and Np are different between these two subjects.
Figure 6. Normalized number of deposited particles ($d_p = 3\mu m$) for the six subjects, in addition location of deposited particles are shown within each panel and they are color-coded based on the
region they deposited in. The numbers show the percent of regional particles deposited in each lobe with respect to total particle deposition. Total particle deposition is shown beside each model.

Total particle deposition percentages are shown in Table 3 for all six subjects for particle diameter of 1, 3 and 5 microns. In addition, Table 3 represents total concentration of deposited particles, which means percent of deposited particles divided by total surface area of that subject. Total deposition can vary across different subjects and different sizes. For bigger particles we saw more deposition, likely because the bigger particles have more inertia compared to the smaller ones, so they cannot follow the airflow at the bifurcations or when the flow changes its path due to the geometric changes. Also, gravity can have a greater influence on bigger particles (e.g. more mass) in comparison to small ones since it’s a body force. To sum up, more impaction and more sedimentation lead to more deposition.

Table deposition between healthy subjects are the same with minimum variation, but in asthmatic subjects it can vary considerably.

Table 3. Total deposition and concentration (percent deposition/surface area) for the six subjects for 3 different sizes.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Surface Area</th>
<th>% of deposition</th>
<th>Concentration (%/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1mic</td>
<td>3mic</td>
</tr>
<tr>
<td>HSI</td>
<td>107</td>
<td>4.4</td>
<td>26.7</td>
</tr>
<tr>
<td>HS2</td>
<td>125</td>
<td>4.4</td>
<td>26.6</td>
</tr>
<tr>
<td>AS1</td>
<td>121</td>
<td>5.6</td>
<td>33.4</td>
</tr>
<tr>
<td>AS2</td>
<td>116</td>
<td>7.8</td>
<td>40.3</td>
</tr>
<tr>
<td>AS3</td>
<td>183</td>
<td>2.6</td>
<td>5.9</td>
</tr>
<tr>
<td>AS4</td>
<td>105</td>
<td>8.7</td>
<td>56.3</td>
</tr>
</tbody>
</table>
We recorded initial time of all the particles we studied to understand the effect of the time that the particles are released on their fate in the lung. Figure 7 shows the transient 3µm particle deposition for AS3, AS4, and HS1. The grey area represents the flow rate during the time of inhalation; simulating one using an inhaler in a slow-deep way [50]. Although total deposition of these 3 subjects are different, they have the same transient particle deposition which indicates that this is not a subject specific issue. For all of these three subjects more deposition will occur for particles released near the peak of the flow (1.2s to 2.4s). the reason behind this is: high velocity leads to more inertia of particles and causes them to deposit more in the bifurcation regions or where there is a change in direction of airflow.

Figure 7. Transient 3µm particle deposition of AS3, AS4 and HS1. Airflow rate is shown by the grey area.
Particles are released all over the trachea cross section area, but the results have shown that there are specific regions on the trachea, that if particles start from there, will deliver into each specific lobe. Initial location of $3\mu$m particles which deposited in each lobe of AS3 and AS4 are shown in Figures 8 and 9. These figures show the cross section of the trachea with initial location of deposited particles in each lobe. We can see that there is a link between initial location of particles and the lobe that they deposit into. The colors represent the particle location hot spot on the trachea inlet, based on the lobe that it goes into, calculated by dividing the number of particles in each element divided to total particles deposited in each lobe.
Figure 8. Initial location of 3μm particles, deposited in each lobe of AS3. Colors show the percentage of number of particles in each element with respect to the total number of deposited particles in each lobe.
3.4. Improved Particle Deposition

In this section we show how we can improve drug delivery in asthmatic subjects by modifying initial location and initial time of particles. Initial location can be used to improve regional deposition for the lobe of interest, while the release time of particles can be used to increase total deposition. Furthermore, by changing the initial time of particles we can decrease total deposition, which gives particles the chance to bypass the conducting airways and deliver into deeper regions of that lobe.
3.4.1. Release time Improved

In this section, we changed the release time of particles in order to make particle deposition greater in AS3, HS1, and HS2. Instead of releasing the particles during the whole breathing time, we released them between 1.2s and 2.5s. This means that if someone is using the Dried Powder Inhaler, he/she would press the button about 1 second after they begin inhalation. Figure 10 Panel A Shows the results of how the total deposition of 3µm particles increased by changing the initial time of particles.

For AS1, AS2, and AS4, which had high particle deposition percentages, we changed the releasing time to be between 3.2s and 4.5s. Figure 10 Panel B Shows how much deposition can be decreased by changing the initial time for these subjects.

Decreasing total deposition is much easier than increasing them, since we are not changing the flow rate or geometry, we just release the particles when the flow rate is high instead of all the time. That means we can get close to the maximum deposition with that geometry, size of particles and flow rate, and not any further. On the other hand, we can release particles when the flow rate is low to prevent them from depositing in the conducting airways. This gives them enough time to go deeper in lung and deposit in the periphery regions.
Figure 10. Increase and decrease in 3µm particle deposition by modifying the releasing time of particles. Panel A shows increase in particle deposition once the particles are released between 1.2s to 2.5s (grey area). Panel B shows decrease in particle deposition once the particles are released between 3.2s to 4.5s (grey area).

3.4.2. Release location Improved

In figure 8, we showed the link between the initial location of particles in the trachea and the lobe they deposit in. By using these results, we changed the initial location of 3µm particles of AS3 to deliver them to the right middle lobe. We chose right middle lobe of AS3 because the SVDP of that lobe was highest amongst all lobes. This means that lobe is affected more by asthma and should be our target lobe. Figure 11 shows the regional deposition percentages for 3µm particles of AS3 before and after modification on initial location. By releasing the particles in the region related to right middle lobe (Fig 8, Panel D), regional deposition of the right middle lobe doubled. Regional deposition of the right lower lobe increased along with right middle since they have overlap in the area of figure.
8. Also, we can see particle deposition of rest of lung decreased and no particle deposition in the left lower lobe.

We are driving particles toward the right middle lobe and it is important to know how much particles are delivering into that lobe. Figure 12 shows the percent of particle that left the 3D domain through each lobe before and after modification on initial location. We can see significant improvements happened by changing the initial location for more efficient delivery to the right middle lobe. Not only did deposition in this conducting airway increase for the right middle lobe, but also about 45 percent of particles went through that lobe and they have the chance to deposit further in that lobe. Thus, we are delivering more therapeutic particles to the lobe of interest.

**Figure 11.** Regional particle deposition percentages (3µm) of AS3 before and after modification on the initial location.
**Figure 12.** 3\(\mu\)m particle delivery (percentages) of each lobe of AS3 before and after modification on the initial location.
Chapter 4: Conclusion and Discussion
4.1. Discussion:

Asthma is a heterogeneous chronic disorder that causes airway closure (from airway remodeling and/or mucus plugging) in various regions of the lung; thus, disease pathologies and presence are highly variable among asthmatic subjects. Current treatment strategies are not based on the affected regions in patients. This means that treatment is not yet targeted, therefore patients do not necessarily get enough particles delivered to diseased regions of the lungs. Perhaps this is the reason why some patients do not respond well to inhaled therapeutics and lung function continues to decline throughout life.

Because of advancements in imaging techniques, specifically MRI, we can now visualize ventilation maps in addition to creating realistic 3D geometric models of the airway tree. Using the SVDP results of MRI gives us the ability to parametrize the boundary conditions. Therefore, we are able to model the asthmatic patients and can perform multiple studies and try different strategies to better understand asthma and drug delivery without conducting further experiments.

Since it is not possible to measure the flowrate or pressure at the distal airways of the lung in vivo, we have introduced a novel method to translate segmental ventilation defects percentages to resistances as boundary conditions. This enables us to predict airflow distribution and particle characteristics in healthy and asthmatic subjects. In this thesis, we showed that velocity distributions and peak regions vary between subjects, for example: AS1 and AS2 vary significantly. We also showed the particle deposition is different for individual asthmatic subjects, even when they are in the same severity group. For example, 3-micron particle deposition varies between 5.9% and 56.3% which
the lowest and highest are for AS3 and AS4 respectively (Table 3). We also studied regional deposition and regional concentration, which together indicate that regional particle deposition varies between all subjects. For instance, in the left superior lobe, deposition for the 3 micron diameter particles varies between 9.1% and 27.6% among all subjects.

Variation in regional deposition between all subjects, highlights that drug delivery methods should be designed for each subject in order to deliver drug to the lobe of interest. To this end, we linked the particle initial location with the lobe that they deposit in. For example, in figure 8 panel D, we can see that only the particles released from the green-red region deposited in the right middle lobe of AS3. This means that if we want to deliver particles in that specific lobe, we should release them within this region of the trachea face. Figure 12 shows that we can increase the number of particles going to the right middle lobe of AS3 from 10 to 45 percent by changing the release location of particles. In addition, we showed that the particle release time matters in term of total deposition. Figure 10 shows that we can increase or decrease total deposition by changing the release time. This can ultimately be used when doctors/nurses show asthmatic patients how to use asthma inhalers. The ultimate goal of these studies is to optimize drug delivery based on which lobe is affected by asthma on a per patient basis. Then treatment could be more effective, and the dosage of drug could be decreased, resulting in a reduction in dose-related side effects.

Since we are the first ones to combine the HP $^3$He MRI and CT imaging with computational fluid dynamics and particle transport, there are some limitations in this work that we must acknowledge. First, we only had thoracic CT images and we have
created our 3D models from the trachea downwards. We did not have access to the CT scans of upper airways of our patients. While having these airways can capture the laryngeal jet and associated turbulence, we do not expect this flow physics to significantly impact our overall conclusions. Indeed, asthma obstructions are generally located within the conducting bronchi and small bronchioles, where the flow is laminar and is likely not influenced by flow far upstream. Second, SVDPs are measured only at the FRC +14%TLC and we are not sure how much geometry (diameter of distal airways) can change during the time of breathing. This variable may cause the resistance values to be overestimated. Third, we chose one diseased airway and one normal at each segment, and we assumed all defection of asthma located along the diseased one; but in reality, there might be some diseased regions after few generations of the normal airway. Perhaps we can overcome this challenge by using dynamic imaging of gas distribution [55]. Fourth, we showed the link between the location of particles at the trachea face and the lobe they go into, but patients inhale the drugs from their mouth. Thus, we need to consider the extrathoracic in future studies to examine the particle fate in the upper airways. While with CFD-PT we can predict high resolution particle deposition patterns and concentrations, which are not able to be obtained from clinical setups, computational simulations have their own limitation. We assume that particle are rigid spheres and that their size or shape do not change during the time of simulation. Also, we are just looking into the drug delivery from an engineering perspective, and we do not consider type of drug particles or what happens and how effective they are after they deposit on the airway’s wall. Furthermore, we are not modeling the mucus or the cilia of the walls. We assume walls are rigid and stationery and its material properties are not taken into
account. The walls of the lung periphery airways are compliant, but we did not have any data of their compliance, so we had to model them by a resistance lump parameter. This method is not as accurate as having a resistance-compliance lump parameter. Finally, we need to acknowledge the uncertainty of numerical simulation caused by meshing and residuals.

4.2. Conclusion:

The vast differences in total and regional particle deposition and concentration between healthy and asthmatic subjects are highlighted with a novel method by combining the clinical dataset with computational framework. Conflicting findings from the two severe asthmatic simulations highlight the importance of integrating computer simulations to predict flow distribution and drug delivery, beyond what can be measured within the clinical setting. Also, variability in regional deposition between all subjects indicates the significance of subject-specific treatment strategies. Changing the release time and initial location of particles has the ability to improve the regional deposition and ultimately may enable targeted treatment strategies.
REFERENCES


