NUMERICAL SIMULATION OF TRANSPORT AND UPTAKE OF REACTIVE AIR POLLUTANTS IN HEALTHY AND DISEASED HUMAN LUNGS

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Abstract

Exposure to reactive air pollutants can initiate or exacerbate respiratory health problems, and absorption of inhaled toxicants can occur in all regions of the respiratory tract, from the nose to deep in the lung. It is believed that reactive gas-induced tissue injury depends on the local dose delivered to the airway walls. In order to determine whether individuals with disease-modified lung geometries are at higher risk of lung injury (compared to those with healthy lung geometries) as a result of exposure to harmful inhaled pollutants, numerical simulations of reactive gas transport and uptake were performed in anatomically-accurate human lung geometries reconstructed from high-resolution multidimensional computer tomography (MDCT) chest scans of two consenting adult males. The flow structures and toxicant concentration distributions within the proximal airways of the two lungs were determined via numerical solution of the governing equations, and hotspots of reactive gas flux on the airway walls were identified. For both quasi-steady inspiratory and quasi-steady expiratory flow, the flow structure and toxicant concentration distribution in the disease-modified lung were found to be qualitatively different from those in the healthy lung. The highly-deformed airway geometries in the disease-modified lung led to qualitatively different patterns of toxicant uptake and hotspot distributions on the airway walls. These differences were particularly prominent in the trachea and main bronchi, where development of complex secondary flow structures were observed in the disease-modified lung as a result of irregularities in the airway geometry.
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Chapter 1
Introduction

The National Toxicology Program demonstrated the importance of adverse health effects from inhaling over 200 chemicals because of their high volume use in industrial processes [2]. Similarly the U.S. Environmental Protection Agency (EPA) has identified numerous environmental air pollutants that exacerbate respiratory disease. According to the EPA, ground-level ozone ($O_3$), nitrogen oxides ($NO_x$), and sulfur oxides ($SO_x$) are three of the most common air pollutants. The nitrogen oxide of primary concern is nitrogen dioxide ($NO_2$), and it is used as the indicator for the larger group when standards are set by the EPA. Similarly, sulfur dioxide ($SO_2$) is used as the indicator for sulfur oxides. Nitrogen dioxide and sulfur dioxide are primarily emitted by the combustion of fossil fuels. Major sources of nitrogen dioxide include, vehicles, industrial facilities, and electric utilities. The primary sources of sulfur dioxide are industrial facilities such as power plants. Ground-level ozone is an air pollutant that is commonly encountered in metropolitan areas. It is a secondary pollutant in that it forms in the air rather than being emitted by a source. Ground-level ozone is formed by the reaction of volatile organic compounds with nitrogen oxides, in the presence of sunlight [3].

In addition to ambient air pollutants, there are several toxic industrial chemicals (TICs) that can cause harm to the respiratory tract. Chlorine ($Cl_2$) and formaldehyde ($CH_2O$) are examples of TICs that are known to cause respiratory problems and are designated with a high hazard index by the Occupational Safety and Health Administration (OSHA) [4-6]. Chlorine is used as an oxidizing agent in many chemical processes, such as water treatment, and formaldehyde is mainly
used in the synthesis of other chemicals [7, 8].

The EPA sets National Ambient Air Quality Standards (NAAQS) for air pollutants, while OSHA sets standards for workplace exposure to many toxic industrial chemicals. These standards, which are periodically reviewed and updated, are based on the effects of each air pollutant or TIC on public health and welfare, and specify the maximum allowable concentration of the given toxicant in ambient air. For example, the 8-hour ozone exposure limit (i.e. maximum allowable $O_3$ concentration measurement averaged over 8 hours) set by the EPA in 2008 was 75 parts per billion (ppb). Based on the 2012-2014 monitoring data, 224 counties in 25 states (home to about 40% of the U.S. population) were in violation of EPA’s 2008 ozone standard. In 2015, the EPA updated its ozone exposure limit to 70 ppb, and estimated (based on the 2012-2014 data) that at least 241 counties in 33 states would be in violation of its new standard [9].

Even though inhalation of ambient air pollutants and toxic industrial chemicals are known to exacerbate (and may even initiate) certain respiratory diseases, we lack critical information on how this comes about. In addition, a major challenge in respiratory science has been the difficulty in applying insights from animal studies to human pathophysiology. This study aims to overcome this difficulty by taking advantage of recent advances in medical imaging science that have allowed generation of detailed and accurate three-dimensional images of the airways in the human respiratory tract, and recent advances in engineering science that allow computer-simulated experiments in these virtual geometries. The long-term goal of this new interdisciplinary approach is to enable the incorporation of real-time, patient-specific, lung dosimetry models in the clinical diagnosis and treatment of common respiratory disorders. Achievement of this goal would fill a critical gap in individualized (precision) medicine, and would also be of use to a broad range of respiratory scientists.

The primary objective of this work is to determine the influence of airway geometry on reactive gas transport and uptake in the human lung. Specifically, this thesis aims to:

1. Develop three-dimensional numerical simulations of the flow fields and reactive gas concentration distributions in healthy and disease-modified human
lungs for inspiratory flow.

2. Compare the spatial distribution of reactive gas flux on the airway walls in the healthy lung to that in the disease-modified lung.

3. Develop the corresponding simulations and comparisons for expiratory flow in the healthy and disease-modified lungs.

This thesis is structured as follows: the remainder of Chapter 1 provides relevant background information, Chapter 2 describes the methods used to conduct this research, Chapter 3 presents and discusses the results, and Chapter 4 provides some concluding remarks and suggestions for future work.

1.1 The Respiratory Tract

The respiratory tract consists of the upper airways, the conducting airways (also known as the tracheobronchial tree), and the respiratory zone (see Fig. 1.1). The upper airways include the nasal cavity (nose), oral cavity (mouth), pharynx, and larynx. The larynx connects the upper airways to the conducting airways, which are a network of branched airways starting with the trachea and ending with the terminal bronchioles. The conducting airways and respiratory zone combined, consist of approximately 23 generations of airways, where the trachea is designated as generation 0 [10,11]. Each airway splits into two or more airways (typically two), with the diameter of the airways generally decreasing with increasing generation down the tracheobronchial tree [10,12,13]. The first branching in the tracheobronchial tree is a bifurcation that occurs at the bottom of the trachea, and is called the carina. The trachea is followed by approximately 10 generations of bronchi (beginning with the main bronchi), which are characterized as cartilage-containing branches. The bronchi are followed by the bronchioles, which are characterized as cartilage-free branches. The terminal bronchioles connect the conducting airways with the respiratory zone. The respiratory zone is characterized by the alveoli, which are responsible for the exchange of $O_2$ and $CO_2$ in the pulmonary capillaries. This thesis focuses on the conducting airways up to and including the third generation.
of airways, where there is a stark difference between the airway geometries in the healthy and disease-modified lungs.

1.2 The Respiratory Tract Lining Fluid

The respiratory tract lining fluid (RTLF) is a thin, heterogeneous aqueous layer that lines the respiratory tract. It is located between the airways (gas phase) and the respiratory tract wall tissue (epithelial cells), and serves as a protective layer to clear out particles and absorb reactive gases before they can reach the delicate tissues in the respiratory zone. The thickness of the RTLF can be significantly different in different regions of the respiratory tract. The RTLF thickness generally decreases down the respiratory tract, with its thickness falling in the range of about 5 – 10 μm in the nasal cavity, 1 – 10 μm in the airways, and 0.2 – 0.5 μm in the
alveoli [14]. The RTLF is composed of various biological substrates including low molecular weight antioxidants (e.g. uric acid, ascorbic acid, and glutathione), proteins (e.g. albumin), lipids (e.g. phosphatidylcholine), and high molecular weight glycoconjugates (e.g. mucin). Substrate concentrations vary depending on the region of the respiratory tract (i.e. nasal, proximal, and distal RTLF), but uric acid is the most abundant antioxidant in the proximal RTLF (which is the main region of interest in this work) [15,16]. Concentrations of uric acid, ascorbic acid, and glutathione in the proximal RTLF are typically in the range of $100 \text{−} 300 \, \mu M$, $20 \text{−} 45 \, \mu M$, and $50 \text{−} 200 \, \mu M$, respectively [16].

## 1.3 Health Effects of Reactive Gas Exposure

In this work, the term ‘reactive gas’ refers to any ambient air pollutant or toxic industrial chemical that reacts with endogenous substrates in the RTLF, as opposed to vapors such as methanol or ethanol, which are soluble in aqueous solutions but do not react in the RTLF. This terminology is standard in the literature (e.g. [17,18]).

TICs with a high toxicity can result in adverse health effects immediately upon exposure [4]. For example, exposure to chlorine or formaldehyde can cause severe tissue damage to mucous membranes, particularly those of the upper respiratory tract [5,6]. Health effects that are associated with short-term chlorine and formaldehyde exposure include irritation of the respiratory tract, coughing, shortness of breath, and chest pains [5–8].

Exposure to reactive air pollutants can initiate or exacerbate respiratory health problems, and absorption of inhaled toxicants can occur in all regions of the respiratory tract, from the nose to deep in the lung. For example, it has been verified that ozone exposure causes tissue damage in the upper airways (e.g. the nose) as well as in the conducting airways. Short-term health effects include coughing, inflammation of airways, and shortness of breath. Although short-term effects are reversible, repeated exposure can lead to permanent lung damage and long-term exposure can lead to decrease in lung functionality, airway remodeling, and loss of conducting airways [19]. Recent observations have shown that exposure to $O_3$ can produce intense remodeling in the developing lungs of infant primates, resulting in
dramatic loss of conducting airways in the form of substantial reductions (of up to 40\%) in airway diameter and length [20]. In addition, $O_3$ and $NO_2$ exposure have been found to be associated with exacerbations of respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and idiopathic pulmonary fibrosis (IPF) [21–23]. Adverse health effects as a result of environmental exposure to air pollutants are particularly severe among children who can suffer impaired lung development [19].

The toxicity of inhaled oxidant gases such as ozone is believed to be due to peroxidation of membrane lipids, leading to destruction of membrane integrity and eventual cell death. Reactive gases are also capable of reacting with biochemical substrates in the RTLF before reaching the underlying tissue. For example, ozone can undergo rapid peroxidation to produce a series of free radicals either through an $O_3$-carbonyl reaction involving unsaturated fatty acids, cholesterol, and tryptophane molecules or via an $O_3$-electron donor reaction in the presence of molecules such as glutathione, ascorbate, and thiosulfate [14, 24, 25]. Thus, lung tissue injury as a result of reactive gas exposure can occur via two mechanisms [25]:

1. Inhaled oxidants react with biochemical substrates in the RTLF to form harmful products, which subsequently contact cellular exteriors to initiate tissue injury.

2. Unreacted inhaled oxidants in the RTLF reach the underlying tissue and cause tissue injury by directly reacting with the cell membrane.

Regardless of which mechanism is dominant (and even if both are equally important), the overall extent of tissue injury can be expected to correlate with the flux of the inhaled toxicant into the RTLF at the gas-RTLF interface (i.e. at the airway wall). Hence, regional differences in tissue injury are attributed to differences in the local rate of reactive gas delivery (local dose), and it is the reactive gas flux at the airway wall that will be the main quantity of interest in this study.
1.4 Dosimetry Modeling

Dosimetry refers to the estimation or measurement of the amount of a compound (or its toxic metabolites or reaction products) that reaches specific target sites after exposure to a given concentration of the compound. Although local dose cannot be easily measured in a site-specific manner, mathematical dosimetry models can provide predictions of the uptake and distribution of absorbed reactive gases in the respiratory tract that can be used to estimate site-specific dose and the exposure levels [26–28]. Hence, accurate dosimetry models that incorporate physical, biological and chemical properties of the respiratory tract, as well as the nature of gas transport in the lumen and air spaces, can serve as invaluable tools for interpreting the toxicological effects of inhaled reactive gases.

Several different dosimetry models have been used to date (e.g., [26,28–30]). Single-path models were developed as a simple mathematical tool to predict the longitudinal distribution of reactive gas absorption in the human respiratory system. In the one-dimensional single-path model of the respiratory system, all airway paths are replaced by a single path with well-mixed airflow [29]. The major shortcoming of one-dimensional single-path models is their inability to predict axial dispersion or boundary layer resistance at the airway wall, due to the assumption of uniform cross-sectional profiles for both velocity and concentration. A two-dimensional single-path approach was developed by Madasu et al. [30], wherein flow and species conservation equations are solved assuming axisymmetric velocity and concentration profiles over cross-sections, both being dependent on axial as well as radial position within the axisymmetric single-path. Single-path models of the lower respiratory tract provided insight into the longitudinal distribution of reactive gas concentration along a path in the tracheobronchial tree [29,31,32]. Recent advances in the development of reliable procedures for three-dimensional reconstruction of complex geometries, combined with well-established computational fluid dynamics (CFD) strategies for the computation of flows in complex geometries, have led to the development of more sophisticated dosimetry models based on anatomically-accurate geometries of the respiratory tract. Such three-dimensional simulations have recently been used to predict the distribution of inhaled ozone in
the lung of an infant rhesus monkey [28,33].

Advances in imaging science have revolutionized the diagnostic approach to lung disease, creating new opportunities for developing dosimetry models in a disease-specific and patient-specific manner. This study aims to develop three-dimensional dosimetry models to predict the patient-specific distribution of reactive gases such as ozone or chlorine in the proximal airways of healthy and disease-modified human lungs. Three-dimensional numerical simulations will be developed using anatomically-accurate airway geometries reconstructed from multidimensional computerized tomography (MDCT) scans of the respiratory tract of a healthy individual and that of a patient with lung disease. The dosimetry models will be applied for characteristic toxicants (high and low reactivity) under quiet breathing conditions, and the uptake distribution patterns will be compared to examine the impact of the disease-modified lung geometry on the exposure-dose relationship.
Investigation of the effect of lung geometry on reactive gas transport and uptake requires the construction of airway models suitable for use in CFD simulations. This chapter provides information on the construction and meshing of airway structures, the governing equations and boundary conditions used in the simulations, and the implementation of the numerical simulations.

2.1 Airway Construction and Meshing

High-resolution multidimensional computerized tomography (MDCT) scans of the chests of two consenting adult males (one with a healthy lung geometry and one with a disease-modified lung geometry) were used to obtain three-dimensional reconstructions of the airway geometries (Fig. 2.1) at the Pennsylvania State University Milton S. Hershey Medical Center. The high-resolution MDCT scans had a resolution of 1 mm, which allowed reconstruction of the lung geometries down to at most the sixth generation of airways. The resulting airway geometries were then cleaned, segmented, and meshed using the commercial meshing software ICEM CFD (Ansys, Inc., Canonsburg, PA).

First, the reconstructed airway geometries were cleaned by removing low resolution airways and artifacts of the MDCT scans. Airways past the fourth generation had very poor resolution, and were therefore eliminated from both lung geometries. Planes were created at the ends of the fourth (and in some cases the third) generation of airways, defining the outlet boundaries of the airway system, and a
plane was created near the entrance of the trachea to specify the inlet boundary. In addition, planes were created at each bifurcation (each time a new generation was introduced) to specify the inlets of its downstream (daughter) branches. This was done to allow for uptake calculations to be performed between the planes bounding a single airway segment. All planes were created such that the normal to each plane was locally tangent to the airway wall.

Once the airway geometries were cleaned and segmented, they were ready to be meshed. Initially, the lung geometries were meshed using tetrahedral elements. A tetrahedral mesh was generated in each airway segment, using smaller tetrahedral elements in higher generation airways. The mesh structures in successive airway generations were then joined together at the segment boundaries. Due to the roughness of the airway wall on a length scale comparable to the resolution of the MDCT scans, tetrahedral mesh elements in many wall regions were skewed and the resulting tetrahedral mesh could not achieve sufficiently high mesh quality for accurate numerical simulations. Refining the tetrahedral mesh (i.e. decreasing the
mesh element size) did not lead to a significant improvement in the resulting mesh quality. This led to the conclusion that a more sophisticated, but time-intensive, meshing procedure using hexahedral elements had to be implemented. Using a hexahedral mesh provided the flexibility of locally refining the mesh in the wall regions as necessary, albeit at the significant additional cost of manually performing the procedure.

The following steps were taken in order to generate a hexahedral mesh for each lung geometry:

1. Blocking of the geometry
2. Generation of the mesh in each block
3. Adjustment of the mesh to improve overall mesh quality

The first step in generating a hexahedral mesh was 'blocking' the lung geometry, i.e. subdividing the airway geometry into blocks. This was done by starting with a single bounding box, then splitting the block and fitting the block segments to the lung geometry, one generation at a time (moving down the lung). Figure 2.2 shows the fully-blocked lung geometries. After the geometry was captured using blocks, the mesh was generated. The initial surface mesh was adjusted by changing the total number of surface mesh elements, and the distribution of the elements, such that a nearly uniform surface mesh (with small/gradual changes in mesh size) was achieved and the number of stretched elements was minimized. Once the surface mesh was complete, an O-grid was applied and the mesh was converted to an unstructured mesh. The mesh quality was improved by adjusting the mesh where low quality elements were present, as determined by the following two criteria: $2 \times 2 \times 2$ determinant and orthogonal quality. These two metrics were improved such that a minimum mesh quality of 0.15 was achieved. Figure 2.3 shows magnified regions of the final refined mesh structures for the healthy and diseased lungs, which consist of 16 million and 13 million hexahedral mesh elements, respectively.
2.2 Problem Formulation

For incompressible flow of a dilute binary mixture of a reactive gas in air, the flow field is governed by the continuity and Navier-Stokes equations, which can be written in dimensionless form as

\[ \nabla \cdot \mathbf{u} = 0 \quad (2.1) \]

\[ \frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} = -\nabla p + \frac{1}{Re_0} \nabla^2 \mathbf{u} \; ; \quad Re_0 = \frac{U_0 R_0}{\nu_g} \quad (2.2) \]

where \( \mathbf{u} \) and \( p \) represent the velocity and dynamic pressure, respectively, \( \nabla \) is the dimensionless gradient operator, and the dimensionless parameter \( Re_0 \) is the tracheal Reynolds number. In these equations, all lengths are made dimensionless with the hydraulic radius of the trachea, \( R_0 \), and all components of velocity with the magnitude of the tracheal inlet velocity, \( U_0 \equiv Q_0/A_0 \), where \( Q_0 \) is the volumetric flow rate.
Figure 2.3. Hexahedral mesh structures of the healthy and diseased lungs
flow rate through the trachea and $A_0$ is the cross-sectional area of the inlet of the trachea. Time is made dimensionless with $R_0/U_0$ and pressure with $\rho_g U_0^2$, where $\rho_g$ is the density of the gas mixture. The quasi-steady inspiratory and expiratory flow fields were obtained by solving the time-dependent Navier-Stokes equation using an iterative method.

For inspiratory flow, Equations (2.1) and (2.2) were solved subject to the following boundary conditions:

- Uniform velocity normal to the inlet of the trachea, $\mathbf{u} \cdot \mathbf{n} = 1$.
- Vanishing viscous normal stress at the distal ends of the airway structure, $\mathbf{n} \cdot (\nabla \mathbf{u} + (\nabla \mathbf{u})^\top) = 0$.
- Flow split among the distal ends proportional to their cross-sectional areas.
- Vanishing velocity at the airway wall (no-slip and no-penetration conditions), $\mathbf{u} = 0$.

For expiratory flow, the inlet and outlet boundary conditions were reversed while keeping the flow split among the distal ends proportional to their cross-sectional areas. Namely,

- Uniform velocity normal to the distal ends of the airway structure, $\mathbf{u} \cdot \mathbf{n} = A_0/A_{tot}$, equal to 0.61 and 0.66 for the healthy and disease-modified lungs, respectively, where $A_{tot}$ is the total cross-sectional area of the distal ends of the airway structure.
- Vanishing viscous normal stress at the inlet of trachea, $\mathbf{n} \cdot (\nabla \mathbf{u} + (\nabla \mathbf{u})^\top) = 0$.

The reactive gas concentration distribution is governed by the dimensionless convection-diffusion equation given by

$$\frac{\partial C_g}{\partial t} + \mathbf{u} \cdot \nabla C_g = \frac{1}{Pe_0} \nabla^2 C_g ; \quad Pe_0 = \frac{U_0 R_0}{D_g} \quad (2.3)$$

where $C_g$ is the reactive species concentration in the gas phase made dimensionless with that at the tracheal inlet, $C_{g,0}$. The dimensionless parameter $Pe_0$ is the
tracheal Peclet number, and $D_g$ is the diffusivity of the reactive species in the gas phase. For inspiratory flow, the boundary conditions for Equation (2.3) include:

- Uniform reactive gas concentration at the inlet of the trachea, $C_g = 1$.
- Zero diffusive flux at the distal outlet planes, $\mathbf{n} \cdot \nabla C_g = 0$.
- An effective wall reaction condition resulting from a quasi-steady diffusion-reaction model in the RTLF.

For expiratory flow, the inlet and outlet boundary conditions were reversed as follows:

- Uniform reactive gas concentration at the distal ends of the airway structure, $C_g = 1$.
- Zero diffusive flux at the inlet of the trachea, $\mathbf{n} \cdot \nabla C_g = 0$.

Depending on the reactivity of the inhaled toxicant, many different reactions can take place between the toxicant and RTLF components. Two different wall reaction models are used to represent the rates of these reactions for toxicants with high and low reactivity. The simplest model considered in the simulations for inhaled toxicants with high reactivity (such as chlorine) is that of an infinitely fast reaction. In this model, the reaction rate is assumed to be so fast (compared to the rate of reactive gas transport to the RTLF) that instantaneous reaction between the toxicant and RTLF substrates occurs at the gas-RTLF interface. In this case, the toxicant concentration vanishes at the gas-RTLF interface, and the condition $C = 0$ is imposed at the airway walls. Although using an infinite reaction rate overestimates the rate of reactive gas uptake, it also magnifies the non-uniformity in the wall flux distribution and facilitates the identification of hot spots of toxicant flux. A second model for the reaction between RTLF substrates and toxicants with low reactivity (such as ozone) is based on the premise that typical substrate concentrations in the RTLF are much higher than toxicant concentrations (e.g., about $100 \mu M$ for uric acid compared to $0.03 \mu M$ for $0.075 \text{ ppm} O_3$ in the gas phase). In that case, the reaction rate can be considered to be pseudo-first order with respect to toxicant concentration in the RTLF. Table 2.1 lists some reported values for rate
Table 2.1. Reported values of rate constants for select reactive gas-antioxidant pairs

<table>
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<tr>
<th>Reactive Gas ; Substrate</th>
<th>Second-Order Rate Constant ( (M^{-1}s^{-1}) )</th>
<th>Pseudo First-Order Rate Constant ( (s^{-1}) )</th>
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<tr>
<td>ozone ; uric acid</td>
<td>( 1.4 \times 10^6 ) [34]</td>
<td>420</td>
</tr>
<tr>
<td>ozone ; glutathione</td>
<td>( 2.5 \times 10^6 ) [35]</td>
<td>500</td>
</tr>
<tr>
<td>ozone ; ascorbic acid</td>
<td>( 4.8 \times 10^7 ) [35]</td>
<td>2160</td>
</tr>
<tr>
<td>nitrogen dioxide ; uric acid</td>
<td>( 2 \times 10^7 ) [36]</td>
<td>6000</td>
</tr>
<tr>
<td>nitrogen dioxide ; glutathione</td>
<td>( 2 \times 10^7 ) [36]</td>
<td>4000</td>
</tr>
<tr>
<td>hypochlorous acid ; uric acid</td>
<td>( \sim 3 \times 10^5 ) [37]</td>
<td>( \sim 90 )</td>
</tr>
<tr>
<td>hypochlorous acid ; glutathione</td>
<td>( \sim 4 \times 10^7 ) [37]</td>
<td>( \sim 8000 )</td>
</tr>
<tr>
<td>hypochlorous acid ; ascorbic acid</td>
<td>( &gt; 1 \times 10^7 ) [37]</td>
<td>( &gt; 450 )</td>
</tr>
</tbody>
</table>

constants of the reactions between toxicant gases and typical antioxidants. Since the reactivity of chlorine with substrates is greater than that of hypochlorous acid, the rate constants of the reactions of hypochlorous acid with substrates can be taken as lower limits for those of chlorine with the same substrates [37].

Neglecting convection in the RTLF and noting that the thickness of the RTLF is typically much smaller than the airway radius, the quasi-steady diffusion and reaction of the inhaled toxicant with the RTLF substrates can be described by a planar (rather than annular) representation of the species conservation equation. Namely,

\[
\frac{\partial^2 C_l}{\partial x^2} + \left( \frac{\delta}{L} \right)^2 \frac{\partial^2 C_l}{\partial z^2} = Da^2 C_l ; \quad Da = \left( \frac{k\delta^2}{D_t} \right)^{1/2}
\]

(2.4)

where \( C_l \) is reactive gas concentration in the liquid phase (RTLF) made dimensionless with \( C_{g,0} \), and \( x \) and \( z \) denote the coordinates normal and tangent to the
air-RTLF interface, made dimensionless with the RTLF thickness, $\delta$, and the length of the airway, $L$, respectively. The dimensionless parameter $Da$ is the Damkohler number representing the ratio of the diffusion time scale to the reaction time scale in the RTLF, where $k$ is the pseudo-first order rate constant and $D_l$ is the diffusivity of the reactive gas in the liquid phase.

Since the RTLF thickness is much smaller than the length of an airway ($\frac{\delta}{L} \ll 1$), partial differential equation (2.4) can be reduced to the second-order ODE

$$\frac{d^2C_l}{dx^2} = Da^2C_l,$$  \hspace{1cm} (2.5)

which can then be solved subject to the following boundary conditions:

- At the gas-RTLF interface: $C_l = \alpha C_g$
- At the RTLF-tissue interface: $C_l = 0$

where $\alpha$ is the partition coefficient at the gas-RTLF interface. The boundary condition at the gas-RTLF interface imposes local equilibrium between the gas phase and RTLF concentrations of the inhaled toxicant. The boundary condition at the RTLF-tissue interface is imposed based on the assumption that any unreacted toxicant that reaches the RTLF-tissue interface will instantaneously react with the underlying tissue (i.e. via an infinitely fast reaction) to yield zero toxicant concentration at the RTLF-tissue interface.

Analytical solution of Equation (2.5) subject to the aforementioned boundary conditions yields

$$C_l = \left[ \frac{\alpha \sinh(Da\, x)}{\sinh Da} \right] C_g|_{int}, \hspace{1cm} (2.6)$$

where the subscript ‘$\text{int}$’ denotes the gas-RTLF interface. Flux continuity at the gas-RTLF interface requires

$$\left( \frac{D_g}{R_0} \right) \mathbf{n} \cdot \nabla C_g|_{int} = \left( \frac{D_l}{\delta} \right) \frac{dC_l}{dx}|_{int} \hspace{1cm} (2.7)$$

Substituting Equation (2.6) into Equation (2.7) then results in the following effective wall reaction condition for convection-diffusion equation (2.3) in the gas
\[ \mathbf{n} \cdot \nabla C_g|_{\text{int}} = K C_g|_{\text{int}} \quad ; \quad K \equiv \left( \frac{D_l}{D_g} \right) \left( \frac{R_0}{\delta} \right) \alpha Da \coth Da \]  

(2.8)

In the limit of an infinitely fast reaction, the effective wall reaction condition (2.8) reduces to \( C_g|_{\text{int}} = 0 \) since

\[ \lim_{Da \to \infty} K = \infty \implies C_g|_{\text{int}} = \lim_{Da \to \infty} \left( \frac{1}{K} \right) \mathbf{n} \cdot \nabla C_g|_{\text{int}} = 0 \]  

(2.9)

### 2.3 Numerical Simulation

After the airway geometries were meshed, the hexahedral mesh structures were imported into FLUENT (Ansys, Inc., Canonsburg, PA), a state-of-the-art commercial CFD software [38]. In FLUENT, fluid properties were defined, the reaction mechanism was specified, and boundary conditions were set. FLUENT solves the governing equations in dimensional form. In order to obtain the solution to the dimensionless equations defined earlier in this chapter, the airway geometries were scaled by \( R_0 \) and fluid property values were adjusted. Specifically, in FLUENT, density was set equal to 1, viscosity to \( 1/Re_0 \), and gas-phase diffusivity to \( 1/Pe_0 \). As a result, the effective wall reaction rate constant used in the simulations was also set to the value of \( K \) in Eq. (2.8) normalized by the tracheal Peclet number.

The three-dimensional form of Equations (2.1)-(2.3) and their corresponding boundary conditions were then solved using FLUENT’s parallel segregated implicit solver. This solver uses the finite volume method in conjunction with the SIMPLE predictor-corrector algorithm [38] for pressure-velocity coupling to solve the flow and species conservation equations sequentially rather than simultaneously. This approach is justified because changes in gas composition due to reactive species transport lead to negligible changes in density and viscosity of the gas mixture. A second-order accurate upwind scheme was implemented in FLUENT to reduce numerical diffusion while avoiding numerical instabilities in the convection-dominated regime.

The computations were started by initializing the flow and concentration fields throughout the computational domain (i.e. in all airways) to their respective inlet
values. The steady-state solution was obtained by marching the time-dependent forms of Equations (2.2) and (2.3) in pseudo-time using an explicit scheme. Convergence to steady state was achieved when successive variations in the dimensionless maximum velocity and toxicant molar flow rate at the outflow boundaries did not exceed 1% for at least 50 iterations. At that point, the scaled residuals for the continuity, Navier-Stokes, and convection-diffusion equations were all reduced to less than 0.001%. Computations were performed in parallel on 26 processors of an Atipa Linux cluster (Atipa Technologies, Lawrence, KS) with 20 compute nodes (80 processors). Typically, each numerical simulation required about 3-4 days of run time.

Numerical simulations were performed in the airways of the healthy and disease-modified lungs for each of the following cases:

- Quasi-steady inspiratory flow with a slow pseudo first-order reaction
- Quasi-steady inspiratory flow with an infinitely fast reaction
- Quasi-steady expiratory flow with an infinitely fast reaction

The quasi-steady assumptions for the flow and concentration fields are reasonable for quiet breathing at small Womersley numbers for momentum and species transport, defined as $W_o \equiv \omega R^2/\nu$ and $W_{om} \equiv \omega R^2/D_g$, respectively, where $R$ is the hydraulic radius of an airway and $\omega$ is the breathing frequency. Under these conditions, the time scales for diffusive transport of momentum and reactive species are much smaller than the time scale of breathing oscillation, thereby rendering the time derivatives in Equations 2.2 and 2.3 negligible. Figure 2.4 summarizes the parameter values used in the simulations. The rate constant and gas mixture properties used in the simulations with a slow pseudo first-order reaction correspond to the range of reported values in the literature for the reaction of ozone with uric acid. Numerical simulations for the healthy and disease-modified lungs were performed for the same volumetric flow rate of the binary gas mixture. Respiratory rates associated with quiet breathing range from 15 breaths/min to 30 breaths/min [39,40]. The maximum tracheal Reynolds number of $Re_0 = 1500$ used in the simulations represents the high end of the range of flow rates for breathing under rest conditions in the human lung.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy Lung</th>
<th>Diseased Lung</th>
<th>Slow Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal Volume (mL)</td>
<td>500</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td>Respiratory Rate (breaths/min)</td>
<td>15 - 30</td>
<td>15 - 30</td>
<td></td>
</tr>
<tr>
<td>Q₀ (mL/s)</td>
<td>236 - 473</td>
<td>236 - 473</td>
<td></td>
</tr>
<tr>
<td>ν (m²/s)</td>
<td>1.73 x 10⁻⁵</td>
<td>1.73 x 10⁻⁵</td>
<td></td>
</tr>
<tr>
<td>D_g (m²/s)</td>
<td>2 x 10⁻⁵</td>
<td>2 x 10⁻⁵</td>
<td></td>
</tr>
<tr>
<td>D_l (m²/s)</td>
<td>2 x 10⁻⁹</td>
<td>2 x 10⁻⁹</td>
<td></td>
</tr>
<tr>
<td>δ (µm)</td>
<td>8.6</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>R₀ (mm)</td>
<td>5.8</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>Re₀</td>
<td>750 - 1500</td>
<td>679 - 1358</td>
<td></td>
</tr>
<tr>
<td>Pe₀</td>
<td>638 - 1275</td>
<td>577 - 1154</td>
<td></td>
</tr>
<tr>
<td>k (s⁻¹)</td>
<td></td>
<td>420</td>
<td>420</td>
</tr>
<tr>
<td>α</td>
<td></td>
<td>0.145</td>
<td>0.145</td>
</tr>
<tr>
<td>Da</td>
<td></td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>K</td>
<td></td>
<td>0.04</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Figure 2.4.** Simulation Parameters
Chapter 3 | Results and Discussion

Recent three-dimensional numerical simulations of ozone uptake in the respiratory airways of a rhesus monkey have shown the existence of distinct regions of high local ozone flux on the airway walls, referred to as hotspots of wall flux [33, 41]. These hotspots have been observed mainly in regions where the airway structure exhibits abrupt topological changes, such as the airway bifurcations (e.g. the carina) and the larynx. The purpose of this chapter is to examine the influence of disease-modified airways on the pattern of reactive gas uptake and hotspot formation in the proximal airways of the human lung.

3.1 Steady Inspiratory Flow

3.1.1 Flow Structure and Toxicant Concentration Distribution

This section presents the simulation results for quasi-steady inspiratory flow in the proximal airways of the healthy and disease-modified lungs. Computational results will be shown for different pathways in the left and right lobes of each lung. All relevant airway segments are labeled in Figures 3.1 and 3.2. The labels used for the trachea, the right main bronchus, and the left main bronchus are \( T \), \( R \), and \( L \), respectively. At each bifurcation past the first airway generation, the daughter airway with the higher flow rate is assigned a suffix 1, and the daughter airway with the lower flow rate is assigned a suffix 0. For example, segment \( R1 \) represents a second generation airway along the main path in the right lobe, whereas \( L0 \) denotes a minor second generation airway in the left lobe. In the case of a
Figure 3.1. Front and side views of the healthy lung with labeled airway segments

trifurcation, subscript ‘1’ (‘0’) is used on the 0 daughter branch to identify the minor segment with the higher (lower) flow rate. The number of ‘digits’ (not including subscripts) in the segment identifier indicates the generation number for the given airway segment.

In order to visualize the flow structure in the airways, streaklines were generated by placing 200 seed particles at the inlet of the trachea and allowing them to flow with the fluid through the airway structure. Seed particles are passive in that they do not interfere with the flow. Hence, the particle paths provide a convenient way of visualizing the flow field. Figure 3.3 shows front, back, and side views of the healthy lung with streaklines color-labeled by dimensionless flow speed. The gas mixture in the healthy lung flows straight down the trachea in a nearly unidirectional manner before splitting into two streams at the carina. The flow appears to remain streamlined in the left main bronchus, but experiences the onset of weak
secondary flow in the right main bronchus. In addition, inhaled air flows at much higher speeds through the left main bronchus compared to the right main bronchus, due to the former’s smaller hydraulic diameter.

Figure 3.4 shows the distribution of flow among the airways at each generation in the healthy lung, as well as the local $Re$ and $Pe$ values corresponding to the flow in each airway segment. The fraction of flow is computed based on all airways of the same generation in the entire lung, and provides a snapshot of the flow split at each generation. For example, the flow is almost equally distributed between the main bronchi, with 48% of the flow entering the left main bronchus and 52% going into the right main bronchus. It is also uniformly distributed among the second generation airways. However, the third generation airways $L_{11}$, $L_{01}$, and $R_{11}$ receive nearly twice as much flow as the other third generation airways, with all of these other airways receiving about the same flow rate. The local airway Reynolds numbers decrease from a maximum of 1500 in the trachea to the minimum value
Figure 3.3. Streaklines of inspiratory flow color-labeled by dimensionless velocity magnitude in the healthy lung.
Figure 3.4. Flow distribution by airway segment in the healthy lung of 277 in the L00 segment, indicating that convection is the dominant gas phase transport mechanism in the proximal airways considered in this study.

The corresponding distribution of flow among airways of the same generation in the disease-modified lung is shown in Figure 3.5. In contrast to the nearly symmetric partitioning of flow at the carina of the healthy lung, the disease-modified lung has a flow split between the left and right main bronchi of 39% and 61%, respectively. Hence, at each generation, the airways in the right lobe altogether receive 50% more flow than their counterparts in the left lobe. The flow is split almost equally among the second generation airways in each lobe (e.g. R1 versus R0), i.e. the second bifurcations along each path appear to be nearly symmetric in terms of flow split. However, the third bifurcations are all highly asymmetric, resulting in a nearly 2-to-1 flow split among their major and minor daughter airways (e.g. R01 versus R00 or L11 versus L10). The local Reynolds numbers for airways in the right lobe of the disease-modified lung are generally larger than those in the healthy lung due to the substantially higher flow rate in the right main bronchus of the disease-modified lung arising from the highly asymmetric flow split at the carina.

<table>
<thead>
<tr>
<th>Lung Segment</th>
<th>Flow Rate Fraction</th>
<th>Re</th>
<th>Pe</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>1</td>
<td>1500</td>
<td>1275</td>
</tr>
<tr>
<td><strong>Generation 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>0.48</td>
<td>1100</td>
<td>935</td>
</tr>
<tr>
<td>R</td>
<td>0.52</td>
<td>912</td>
<td>775</td>
</tr>
<tr>
<td><strong>Generation 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1</td>
<td>0.24</td>
<td>704</td>
<td>598</td>
</tr>
<tr>
<td>L0</td>
<td>0.24</td>
<td>713</td>
<td>606</td>
</tr>
<tr>
<td>R0</td>
<td>0.25</td>
<td>704</td>
<td>598</td>
</tr>
<tr>
<td>R1</td>
<td>0.28</td>
<td>649</td>
<td>552</td>
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<tr>
<td><strong>Generation 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L11</td>
<td>0.17</td>
<td>623</td>
<td>529</td>
</tr>
<tr>
<td>L10</td>
<td>0.07</td>
<td>357</td>
<td>304</td>
</tr>
<tr>
<td>L01</td>
<td>0.16</td>
<td>577</td>
<td>490</td>
</tr>
<tr>
<td>L00</td>
<td>0.07</td>
<td>277</td>
<td>236</td>
</tr>
<tr>
<td>R00r</td>
<td>0.08</td>
<td>351</td>
<td>298</td>
</tr>
<tr>
<td>R000</td>
<td>0.07</td>
<td>305</td>
<td>259</td>
</tr>
<tr>
<td>R01</td>
<td>0.09</td>
<td>395</td>
<td>335</td>
</tr>
<tr>
<td>R10</td>
<td>0.09</td>
<td>344</td>
<td>292</td>
</tr>
<tr>
<td>R11</td>
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<td>513</td>
<td>436</td>
</tr>
<tr>
<td>Lung Segment</td>
<td>Flow Rate Fraction</td>
<td>Re</td>
<td>Pe</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>T</td>
<td>1</td>
<td>1358</td>
<td>1154</td>
</tr>
<tr>
<td><strong>Generation 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>0.39</td>
<td>834</td>
<td>709</td>
</tr>
<tr>
<td>R</td>
<td>0.61</td>
<td>1004</td>
<td>853</td>
</tr>
<tr>
<td><strong>Generation 2</strong></td>
<td></td>
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<tr>
<td>L1</td>
<td>0.21</td>
<td>592</td>
<td>503</td>
</tr>
<tr>
<td>L0</td>
<td>0.18</td>
<td>604</td>
<td>514</td>
</tr>
<tr>
<td>R1</td>
<td>0.31</td>
<td>1239</td>
<td>1053</td>
</tr>
<tr>
<td>R0</td>
<td>0.30</td>
<td>859</td>
<td>730</td>
</tr>
<tr>
<td><strong>Generation 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L11</td>
<td>0.15</td>
<td>556</td>
<td>473</td>
</tr>
<tr>
<td>L10</td>
<td>0.06</td>
<td>363</td>
<td>309</td>
</tr>
<tr>
<td>L01</td>
<td>0.11</td>
<td>466</td>
<td>396</td>
</tr>
<tr>
<td>L00</td>
<td>0.07</td>
<td>449</td>
<td>381</td>
</tr>
<tr>
<td>R11</td>
<td>0.15</td>
<td>797</td>
<td>677</td>
</tr>
<tr>
<td>R100</td>
<td>0.06</td>
<td>340</td>
<td>289</td>
</tr>
<tr>
<td>R101</td>
<td>0.10</td>
<td>626</td>
<td>532</td>
</tr>
<tr>
<td>R00</td>
<td>0.10</td>
<td>582</td>
<td>495</td>
</tr>
<tr>
<td>R01</td>
<td>0.19</td>
<td>708</td>
<td>602</td>
</tr>
</tbody>
</table>

**Figure 3.5.** Flow distribution by airway segment in the disease-modified lung

The local airway Reynolds numbers in the disease-modified lung decrease from a maximum of 1358 in the trachea to the minimum value of 340 in the $R10_0$ segment. The lower tracheal Reynolds number in the disease-modified lung (compared to the healthy lung) is caused by the larger hydraulic diameter of the disease-modified trachea which deviates substantially from a cylindrical shape.

Figure 3.6 shows front, back, and side views of the disease-modified lung with streaklines color-labeled by dimensionless flow speed. It is clear that there is a significant qualitative difference in the flow structure between the healthy and disease-modified lungs, particularly in the trachea. The air flow in the disease-modified trachea is far from being streamlined or unidirectional. The flow is forced to turn as it jets into the tracheal deviation, giving rise to onset of an extensive secondary flow pattern downstream of the tracheal bend. Fluid flow around the bend leads to a swirling motion that propagates downstream into the main bronchi, particularly into the right main bronchus. This is evident from a comparison of the vorticity isocontours (computed from $\nabla \times \mathbf{u}$) at the inflow boundaries of airway segments in the right lobe of the disease-modified lung with those in the healthy lung.
Figure 3.6. Streaklines of inspiratory flow color-labeled by dimensionless velocity magnitude in the disease-modified lung
shown in Figures 3.7-3.9. These figures show that vorticity is mostly confined to a thin near-wall region in airways of the healthy lung, whereas in the airways of the disease-modified lung, vorticity is present throughout the cross-section. The difference between the healthy and disease-modified contours is most prominent at the entrance to the right main bronchus. The larger vorticity in the disease-modified airways indicates stronger circulation in planes normal to primary flow, which can have a significant impact on mass transfer to the airway wall.

Figures 3.10 and 3.11 show front/back and side views of the healthy and disease-modified lungs with streaklines color-labeled by dimensionless reactive gas concentration for the infinitely fast reaction and red and blue indicating high and low toxicant concentrations, respectively. The gas mixture flowing in the trachea of the
healthy lung consists of a toxicant-rich core that jets into the carina and remains in the vicinity of the inner wall of the main bronchi downstream of the carina. Similarly, in downstream bifurcations, the toxicant-rich gas comes into close contact with the airway wall. The concentration profiles in the trachea and at the carina of the healthy lung are very similar to those reported for an ideal symmetric bifurcation consisting of cylindrical airways [42]. In the disease-modified lung, the toxicant-rich core jets into the tracheal deviation before reaching the carina. As previously discussed, one of the most prominent differences between the flow fields in the healthy and disease-modified lungs is the presence of extensive secondary flow in the disease-modified trachea. Secondary flow results in mixing of the fluid and movement of higher concentrations of reactive gas to the airway wall.

Figure 3.12 shows contours of reactive gas concentration at the inflow boundaries.
Figure 3.10. Streaklines of inspiratory flow color-labeled by dimensionless reactive gas concentration for an infinitely fast reaction (front/back views)
Figure 3.11. Streaklines of inspiratory flow color-labeled by dimensionless reactive gas concentration for an infinitely fast reaction (side views)
of generation 1 airways. Looking at the concentration contours at the inflow boundaries of the main bronchi, it is clear that there is a shift in the high-concentration region of flow towards the inner airway wall near the carina in both lungs. However, in the healthy lung, the toxicant-rich core remains nearly intact in the daughter branches, with reactive gas concentration decreasing radially outward from the high-concentration core, whereas in the disease-modified lung, the effects of mixing due to secondary flow are clearly visible in that the high-concentration core loses its integrity. Mixing in the disease-modified lung results in larger concentration gradients near the outer walls of the daughter airways, which in turn leads to larger toxicant flux to the outer walls.

The computed concentration distributions for a low reactivity toxicant with a pseudo first-order reaction rate are qualitatively similar to those shown for the infinitely fast reaction, but with much smaller concentration gradients. It is clear from these results that the flow fields and concentration distributions in the proximal airways of the disease-modified lung are qualitatively different from those in the healthy lung. These differences lead to qualitatively different toxicant flux distributions at the airway wall, as will be discussed in the next section.

Figure 3.12. Isocontours of dimensionless concentration at the inlet of generation 1 airways for inspiratory flow with an infinitely fast reaction.
3.1.2 Toxicant Uptake and Wall Flux Distribution

The dimensionless rate of toxicant uptake, $M$, in an airway segment is calculated from the following expression:

$$M = Pe_0 \langle \int C_g u \cdot n \, dA \rangle$$

(3.1)

where the angled brackets, $\langle \rangle$, denote the difference between the values of the enclosed quantity over inflow and outflow boundaries of the airway segment. Fractional uptake is then defined as the fraction of toxicant entering an airway segment that is absorbed in that airway segment. For inspiratory flow uptake calculations, an airway segment is defined as an airway plus its downstream bifurcation (trifurcation), so that each airway segment is defined by one inflow boundary and two
Figure 3.14. Isocontours of dimensionless concentration at the inlet of generation 3 airways in the left lobe for inspiratory flow with an infinitely fast reaction (three) outflow boundaries.

Figures 3.16 and 3.17 present comparisons of fractional uptake by airway segment between the healthy and disease-modified lungs for the the pseudo first-order and infinitely fast reactions, respectively. The fractional uptakes in airway generations 0, 1, and 2 are shown in these figures, where $R$ and $L$ refer to the right and left lobes of the lung, respectively. The expiratory flow data in Figure 3.17 will be discussed in Section 3.2. Under both reaction conditions, the values of fractional uptake corresponding to the trachea and the main bronchi in the disease-modified lung are much greater than those in the healthy lung. In particular, under the infinitely fast reaction condition, the values of fractional uptake for the trachea and the main bronchi in the disease-modified lung are about twice the corresponding values in the healthy lung. In order to identify the largest local contributions to uptake, and therefore gain insight into why the fractional uptake in the healthy and diseased lungs are so different, the toxicant wall flux distributions are examined.
Figure 3.15. Isocontours of dimensionless concentration at the inlet of generation 3 airways in the right lobe for inspiratory flow with an infinitely fast reaction.

Figure 3.16. Comparison of fractional uptake by airway segment for inspiratory flow and a slow pseudo first-order reaction.
Figures 3.18 and 3.19 show front/back and side views, respectively, of the dimensionless wall flux distribution (computed as $-\mathbf{n} \cdot \nabla C_g$) in the healthy and diseased-modified lungs for an infinitely fast reaction. The hotspots of toxicant wall flux for the healthy lung occur primarily at the carina and subsequent bifurcations. In contrast, hotspots in the disease-modified lung are not confined to bifurcations, but are distributed along the airway walls as determined by the flow structure. This is particularly evident in the trachea, where hotspots exist at and distal to the tracheal deviation, and in the main bronchi. In addition, due to the contorted nature of some of the bifurcations in the disease-modified lung, hotspots at those bifurcations are asymmetric. For example, the bifurcation at the end of the right main bronchus in the disease-modified lung, which is much wider (i.e. with a larger branching angle) than its counterpart in the healthy lung, has hotspots only on one side of the bifurcation. Another example of this is the hotspot at the carina of the disease-modified lung, which is skewed to the right side of the lung (front view).

Figures 3.20 and 3.21 show front and side views, respectively, of the dimensionless toxicant wall flux distribution in the healthy and diseased-modified lungs for the slow pseudo first-order reaction. Although the magnitudes of the wall flux for
Figure 3.18. Dimensionless wall flux distribution for inspiratory flow and an infinitely fast reaction (front and back views)
Figure 3.19. Dimensionless wall flux distribution for inspiratory flow and an infinitely fast reaction (side views)
Figure 3.20. Dimensionless wall flux distribution for inspiratory flow and a slow pseudo first-order reaction (front and back views)
Figure 3.21. Dimensionless wall flux distribution for inspiratory flow and a slow pseudo first-order reaction (side views)
Figure 3.22. Dimensionless wall vorticity distribution for inspiratory flow and an infinitely fast reaction (front and back views)
Figure 3.23. Dimensionless wall vorticity distribution for inspiratory flow and an infinitely fast reaction (side views)
an infinitely fast reaction are much greater than those for the slow reaction, the
distribution of hotspots are qualitatively similar in the two cases. In other words,
the non-uniformity of the toxicant wall flux distribution (and therefore the hotspots
of wall flux) is magnified under the infinitely fast reaction condition, and is deter-
mined by the flow structure. The influence of the flow structure becomes more
evident by noting the similarity between the wall flux patterns in Figures 3.18-3.19
and the distributions of wall vorticity shown in Figures 3.22 and 3.23. The pattern
of hotspots of wall flux correlates well with regions of high vorticity on the airway
walls, both of which are strongly affected by the airway geometry. This correlation
is also noticeable at the top of the trachea in the healthy lung, where the rings of
elevated wall vorticity, arising from surface roughness produced by cartilage rings,
coincide with rings of elevated wall flux resulting from the surface topology of the
cartilage rings.

3.1.3 Effect of Reynolds Number

The results reported so far correspond to numerical simulations for flow rates at
the high end of the quiet breathing range, namely 30 breaths/min at a tidal vol-
ume of 500 mL. In order to determine whether decreasing the Reynolds number
qualitatively affects the distribution of hotspots of wall flux, numerical simulations
were also performed for a respiratory rate of 15 breaths/min (and the same tidal
volume of 500 mL). This corresponds to a volumetric flow rate of 236 mL/s and
tracheal Reynolds numbers of 750 and 679 in the healthy and disease-modified
lungs, respectively. Figures 3.24 and 3.25 show front/back and side views, re-
spectively, of the reactive gas wall flux distributions for an infinitely fast reaction
and the aforementioned values of $Re_0$. From these figures, it is clear that toxicant
wall flux distributions for respiratory rates at the low end of the quiet breathing
range are qualitatively similar to those presented earlier for larger $Re_0$, indicating
that the flow structures in the healthy and disease-modified lungs are not signifi-
cantly affected over the entire range of tracheal Reynolds numbers associated with
quiet breathing. While the distribution of hotspots of wall flux remains nearly un-
changed with the reduction in tracheal Reynolds number, the hotspot intensities
are reduced for smaller $Re_0$ as a result of the increased thickness of concentration
Figure 3.24. Dimensionless wall flux distribution for inspiratory flow with $Re_0 = 750$ and an infinitely fast reaction (front and back views)
Figure 3.25. Dimensionless wall flux distribution for inspiratory flow with $Re_0 = 750$ and an infinitely fast reaction (side views)
boundary layers on the airway walls.

3.2 Steady Expiratory Flow

3.2.1 Flow Structure and Toxicant Concentration Distribution

Figures 3.26 and 3.27 show front/back and side views of the healthy and disease-modified lungs, respectively, with streaklines color-labeled by dimensionless flow speed. One of the most striking features of the expiratory flow structure in the disease-modified lung is the appearance of a high speed fluid stream jetting down from the third generation of airways in the upper right lobe of the lung. The sudden increase in flow speed is due to the abrupt contractions in the airway geometry in that region. The high velocity fluid entering the second generation ($R_1$) airway bends sharply into the right main bronchus, diverting the fluid stream from the $R_0$ airway in the lower right lobe and creating a pronounced swirling motion. This creates a complex secondary flow structure in the right main bronchus that persists well into the trachea, as is evident from the vorticity distributions over the outflow boundaries of the airways in the right lobe, shown in Figures 3.28-3.29. The comparison with the corresponding airway cross sections in the healthy lung (for which the absence of vorticity over the bulk of the cross-section is evident) shows the substantial effect of the airway topology on flow structure in the disease-modified lung. The effect of the resulting secondary flow structure is clearly present even at the outflow boundary of the trachea.

The corresponding comparisons of toxicant concentration over the same airway cross-sections are shown in Figures 3.30-3.31. Toxicant concentrations on the outflow cross-sections of the trachea and the main bronchi (generation 0 and 1 airways) are generally much lower in the disease-modified lung (compared to their counterparts in the healthy lung). For example, a large toxicant-rich core is still clearly visible on the outflow cross-section of the trachea in the healthy lung, whereas toxicant concentration is more than 50% depleted throughout the same cross-section in the disease-modified lung. A substantial reduction in reactive gas concentration at the outflow boundary of the right main bronchus in the disease-modified lung is
Figure 3.26. Streaklines of expiratory flow in the healthy lung color-labeled by dimensionless flow speed
Figure 3.27. Streaklines of expiratory flow in the disease-modified lung, color-labeled by dimensionless flow speed
**Figure 3.28.** Isocontours of dimensionless vorticity at the outlet of generation 0 and 1 airways for expiratory flow with an infinitely fast reaction

**Figure 3.29.** Isocontours of dimensionless vorticity at the outlet of generation 2 airways in the right lobe for expiratory flow with an infinitely fast reaction
For steady expiratory flow through an ideal symmetric bifurcation consisting of cylindrical airway segments, the fluid streams from the upstream daughter branches merge to form a sheet of high-speed, toxicant-rich fluid [42]. This ideal behavior is not observed in either of the two lungs. Starting at the second generation of airways in the healthy lung, when two streams from the upstream daughter branches meet at a bifurcation, the asymmetry of the bifurcation causes the streams to spiral around one another as they flow in the parent branch. The presence of the two swirling streams can be detected (particularly in the disease-modified lung) from the vorticity and concentration contours shown in Figures 3.28 and 3.30, respectively, for the outflow boundary of the trachea in the two lungs. The resulting swirling flow structure can bring more toxicant-rich fluid close to the airway wall, as can be seen in Figures 3.32 and 3.33 where the streaklines of flow are color-labeled by
3.2.2 Toxicant Uptake and Wall Flux Distribution

Figure 3.17 shows comparisons of fractional uptake by airway segment between the healthy and diseased lungs, as well as between inspiratory and expiratory flow, for an infinitely fast reaction. For expiratory flow uptake calculations, an airway segment is defined as an airway plus its upstream bifurcation (trifurcation), so that each airway segment is defined by two (three) inflow boundaries and one outflow boundary. The same airway segments are examined for inspiratory and expiratory
Figure 3.32. Streaklines of expiratory flow color-labeled by dimensionless toxicant concentration (front/back view)
Figure 3.33. Streaklines of expiratory flow color-labeled by dimensionless toxicant concentration (side view)
flow. Similar to inspiratory flow, the values of fractional uptake corresponding to the trachea and main bronchi in the disease-modified lung are greater than those of the healthy lung. However, the difference in fractional uptake between the two lungs is less pronounced in the trachea and left main bronchus, and more pronounced in the right main bronchus, for expiratory flow than for inspiratory flow. In particular, the fractional uptake in the right main bronchus of the disease-modified lung is more than twice that of the healthy lung.

The aforementioned differences when shifting from inspiratory to expiratory flow can be explained by the toxicant wall flux distributions. Figures 3.34 and 3.35 show front/back and side views, respectively, of the dimensionless wall flux distributions in the healthy and diseased-modified lungs for an infinitely fast reaction. The effect of the spiraling secondary flow structure on the wall flux distribution is clearly visible in the trachea and main bronchi of the healthy lung. In contrast to inspiratory flow in the healthy lung, expiratory flow does not produce hotspots of wall flux at bifurcations. Instead, streaks of hotspots are present on the airway walls, with the most intense hotspots occurring immediately downstream of bifurcations, where the fluid streams from upstream daughter branches merge.

Several hotspots are present on the tracheal wall of the healthy lung, which were not observed under inspiratory flow conditions. Fewer hotspots appear on the tracheal wall of the disease-modified lung for expiratory flow than for inspiratory flow. These observations are consistent with the smaller difference in tracheal fractional uptake between the two lungs for expiratory flow (compared to inspiratory flow). The right main bronchus of the disease-modified lung is a region with a high density of hotspots. The hotspots present in this segment of the lung are more intense in the disease-modified lung than in the healthy lung, consistent with earlier observations of development of a complex secondary flow structure in the right main bronchus of the disease-modified lung. This observation also visually supports the quantitative data, which show that fractional uptake in the diseased right main bronchus is more than twice that of the healthy right main bronchus under the same expiratory flow conditions.
Figure 3.34. Dimensionless wall flux distribution for expiratory flow and an infinitely fast reaction (front and back views)
Figure 3.35. Dimensionless wall flux distribution for expiratory flow and an infinitely fast reaction (side views)
<table>
<thead>
<tr>
<th>L/(R Pe)</th>
<th>Lung Segment</th>
<th>L/(R Pe)</th>
<th>Lung Segment</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td>Disease</td>
</tr>
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<td>R0</td>
<td>0.0020</td>
<td>R1</td>
</tr>
<tr>
<td>0.0051</td>
<td>L1</td>
<td>0.0043</td>
<td>R</td>
</tr>
<tr>
<td>0.0055</td>
<td>R</td>
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<td>L01</td>
<td>0.0052</td>
<td>L0</td>
</tr>
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<td>0.0105</td>
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<td>R000</td>
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<td></td>
</tr>
</tbody>
</table>

Figure 3.36. Airway segments identified by their L/(RPe) values

### 3.3 Mass Transfer Coefficient

The interphase transport of reactive gas from air to the RTLF in each airway segment can be characterized by the average Sherwood number, $\overline{Sh} = 2\overline{h}_m \left( \frac{R}{R_0} \right)$, where $\overline{h}_m$ is the average dimensionless mass transfer coefficient and $R$ is the hydraulic radius of the airway segment. The average mass transfer coefficient is calculated from simulation results according to:

$$\overline{h}_m = \frac{\int \int_{\text{wall}} \mathbf{n} \cdot \nabla C_g \, dA}{C_{LM} \int \int_{\text{wall}} dA} = \frac{Pe_0 \langle \int \int_{\text{wall}} C_g \mathbf{u} \cdot \mathbf{n} \, dA \rangle}{C_{LM} \int \int_{\text{wall}} dA} = \frac{M}{C_{LM} \overline{S}} \tag{3.2}$$

where $S$ is the dimensionless wall area and $C_{LM}$ is the dimensionless log-mean average concentration difference in the airway segment. For an infinitely fast reaction, the latter is defined as

$$C_{LM} = \frac{\langle \bar{C} \rangle}{\langle \ln \bar{C} \rangle} \tag{3.3}$$

The average Sherwood number was calculated for airway segments in generations 0 – 3 in both the healthy and the disease-modified lung under an infinitely
fast reaction condition. Theoretical values of average Sherwood number were also calculated using two different correlations. For each airway segment, these correlations were applied to an equivalent tube with the same hydraulic radius and wall area as the airway. The equivalent tube length, $L$, for each airway segment was thus calculated from $L = S/(2\pi R)$. The first correlation, provided by Hausen [43] for fully-developed flow in tubes of arbitrary length, has the form

$$\overline{Sh} = 3.66 + \frac{0.2672 \, Pe \, (R/L)}{1 + 0.1134 \, [Pe \, (R/L)]^{2/3}} \quad (3.4)$$

where $Pe$ is the Peclet number based on hydraulic radius. As the length of the tube increases for fixed $Pe$ (i.e. as $L/R \, Pe$ increases), theoretical predictions for $\overline{Sh}$ based on the Hausen correlation approach a constant value of 3.66. This constant value is associated with the fully-developed concentration region, since most of the mass transfer occurs in that region for sufficiently long airways (much longer than the entrance length). The second theoretical prediction is obtained based on an asymptotic expression for mass transfer in developing flow over a plane [44], and has the form

$$\overline{Sh} = \frac{4}{\sqrt{\pi}} \, Pe^{1/2} \, (\frac{R}{L})^{1/2} \quad (3.5)$$

This planar asymptotic result can be used for sufficiently short tubes (much shorter than the entrance length) in which the assumption of fully-developed flow is not justified and both the momentum and concentration boundary layers are sufficiently small that the wall curvature can be neglected.

Figure 3.37 shows the computed values of $\overline{Sh}$ for each airway segment in the healthy and disease-modified lungs, respectively, under inspiratory flow conditions. The corresponding theoretical predictions based on Equations (3.4) and (3.5) are shown by dotted and solid lines, respectively, in this figure. Each airway segment is identified with its value of $L/(R \, Pe)$ (see Fig. 3.36), where $L$ is the length of the equivalent tube. The average Sherwood numbers for the trachea and main bronchi are larger in the disease-modified lung than the healthy lung. For the healthy lung, there is good quantitative agreement between the values of $\overline{Sh}$ computed from simulation results and predictions of the planar asymptotic model. This is consistent with the nearly unidirectional nature of inspiratory flow in the proximal
Figure 3.37. Comparison of the average Sherwood number, $\bar{Sh}$, in the healthy and disease-modified lungs for inspiratory flow and an infinitely fast reaction.

Airways of the healthy lung, for which regular boundary layer development and growth along the airway walls can be expected. Theoretical predictions from the Hausen correlation are consistently lower than the simulation results for the healthy lung. However, the computed average Sherwood numbers in the disease-modified lung are in better agreement with predictions of the Hausen correlation, with the exception of the trachea and the main bronchi. The average Sherwood numbers in these three airway segments of the disease-modified lung more closely follow the planar asymptotic predictions.

The corresponding values of the average Sherwood number for expiratory flow in the healthy and disease-modified lungs are shown in Figure 3.38. With the exception of the trachea and main bronchi, the average Sherwood numbers for expiratory flow in airways of the healthy lung are in better agreement with predictions of the Hausen correlation than those of the planar asymptotic model. The computed average Sherwood numbers in the disease-modified lung are in surprisingly good agreement with predictions of the Hausen correlation. As in the case of inspiratory
Figure 3.38. Comparison of the average Sherwood number, $\overline{Sh}$, in the healthy and disease-modified lungs for expiratory flow and an infinitely fast reaction flow, the average Sherwood numbers in the trachea and main bronchi of the disease-modified lung are better approximated by predictions of the planar asymptotic model. It is interesting to note that these three airway segments are characterized by complex secondary flow structures that apparently resulted in much higher mass transfer coefficients. Overall, the Hausen approximation appears to provide a good estimate for the average mass transfer coefficient under expiratory flow conditions in both lungs.
Chapter 4  |  Concluding Remarks

The primary goal of this thesis was to study the effect of airway geometry on reactive gas transport and uptake in the human lung. Since tissue injury caused by the inhalation of reactive air pollutants is expected to depend on the local dose delivered to the airway walls, the principle quantity of interest in this study was the distribution of toxicant flux at the airway wall. Reconstructed airway geometries of two consenting adult males (one with a healthy lung geometry and one with a disease-modified lung geometry) obtained from the Penn State Hershey Medical Center were used to numerically simulate the flow structures and concentration distributions in the healthy and disease-modified lung geometries. The spatial distribution and uptake of the reactive gas in the proximal airways were determined for both quasi-steady inspiratory and quasi-steady expiratory flow (under quiet breathing conditions) and hotspots of toxicant flux were identified.

For both inspiratory and expiratory flow, the flow and concentration distributions in the disease-modified lung were found to be qualitatively different from those in the healthy lung, which led to significantly different hotspot patterns, particularly in the trachea and main bronchi. For example, under inspiratory flow conditions, hotspots of toxicant flux on the airway walls of the healthy lung occur primarily at the carina and subsequent bifurcations, whereas hotspots in the disease-modified lung are not confined to bifurcations, and are distributed along the airway walls as determined by the flow structure. These differences are attributed to the development of prominent secondary flow structures in the disease-modified lung, arising from the highly asymmetric nature of the airway cross-sections and the
presence of geometrical irregularities such as the tracheal deviation. In addition, the fractional uptake of toxicant in the trachea and main bronchi were found to be larger in the diseased-modified lung than in the healthy lung, for both inspiratory and expiratory flow. The results of this study suggest that lung geometry can have a significant impact on the local dose delivered to the airways, and that individuals with disease-modified lung geometries can be at higher risk of tissue injury associated with the inhalation of toxicants.

The numerical simulations in this study have assumed that laminar flow conditions exist in all airway segments. The local Reynolds numbers in airway generations 1-3 are generally within the laminar range for flow in a cylindrical tube. However, the tracheal Reynolds numbers for the high end of the respiratory rate fall outside the laminar regime for tube flow. In addition, the turbulence generated in the upper airways (e.g. by the laryngeal jet) can persist past the carina, well into the regions where smaller Reynolds numbers are expected [41]. This turbulence can potentially affect reactive gas transport and uptake in ways that have not been considered in this work. Thus, addition of the upper airways, particularly the larynx, to the airway structure and inclusion of a turbulence model in the numerical simulations both represent important directions for future study.

The availability of computer simulations to reveal internal airway sites that are particularly susceptible to tissue injury can be extremely valuable. Knowledge of these patient-specific, high-risk sites can guide diagnostic procedures, particularly bronchoscopy, and in tailoring treatment modalities such as targeted drug delivery. The long-term goal of an interdisciplinary approach such as the one used here would be to enable the incorporation of real-time, patient-specific, lung dosimetry models in the clinical diagnosis and treatment of common respiratory disorders. Because of a limitation in resolution of the MDCT scans, this procedure currently requires extensive human interaction to complete the process. In particular, since the existing procedure does not produce simulation-ready airway structures, any small surface defects in the airway walls (which can be detrimental to the performance of numerical simulations) must be removed by post-processing the resulting airway structures. This is not practical during patient-specific diagnosis and treatment procedures where near real-time geometric reconstruction will be necessary. Thus,
a major focus of future work in this direction must be to rapidly convert MDCT scans to a virtual geometry that is suitable for numerical simulation.
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