OZONE TRANSPORT AND UPTAKE IN
ANATOMICALLY-ACCURATE MODELS OF THE RESPIRATORY TRACT

A Dissertation in
Chemical Engineering
by
Banafsheh Keshavarzi

© 2011 Banafsheh Keshavarzi

Submitted in Partial Fulfillment
of the Requirements
for the Degree of

Doctor of Philosophy

May 2011
The dissertation of Banafsheh Keshavarzi was reviewed and approved* by the following:

Ali Borhan
Professor and Graduate Program Chair of Chemical Engineering
Dissertation Advisor, Chair of Committee

James S. Ultman
Professor Emeritus of Chemical Engineering

Michael Janik
Assistant Professor of Chemical Engineering
Chair of the Brennan Clean Energy Early Career Professorship

Rebecca Bascom
Professor of Medicine
Penn State Milton S. Hershey Medical Center

*Signatures are on file in the Graduate School.
Abstract

Ozone ($O_3$) is a highly reactive gas and a harmful air pollutant. A reproducible pattern of tissue injury induced by inhalation of $O_3$ is believed to depend on the local dose delivered to the airway walls. To predict the local dose, we performed numerical simulations of ozone transport and uptake during inhalation in an anatomically-accurate geometrical model of the respiratory tract of a Rhesus monkey. The model geometry was created using three-dimensional reconstruction of MRI images of the respiratory tract, including the nasal passages, the larynx, and the first thirteen generations originating from the right bronchus. An unstructured mesh was generated for the resulting structure, and three-dimensional flow and concentration distributions were obtained through numerical solution of the Navier-Stokes, continuity, and species convection-diffusion equations. A quasi-steady diffusion-reaction model was used to account for the interaction between $O_3$ and endogenous substrates in the respiratory tract lining fluid.

The total rate of $O_3$ uptake within each section of the respiratory tract was determined, and hot spots of $O_3$ flux on the airway walls were identified. Hot spots of wall flux within the tracheobronchial tree are found to occur near the inlet of the trachea where the laryngeal jet impinges on the trachea wall, and at the bifurcations (especially the first bifurcation). The simulation results show that the structure of the upper airways has a significant effect on the distribution of ozone flux on the airway walls, by producing additional hot spots of ozone flux upstream of the trachea in the nasal vestibule, the dorsal and ventral parts of the middle turbinate, the medial part of the inferior turbinate, the ventral part of the inferior meatus, the medial part of the nasopharynx, and the larynx. In addition, the presence of the larynx leads to a more uniform wall flux distribution within the trachea, compared to the corresponding simulations in the same airway structure without the larynx.
Results of the three-dimensional simulations for ozone uptake along a single asymmetrically-branched airway path were also compared to the predictions of an axisymmetric single-path model. The axisymmetric model consisted of a series of tubular airway branches of decreasing cross-sectional area connected through leakage zones that emulated the flow split at each bifurcation. The dimensions of this path were determined from three-dimensional reconstruction of the actual airway structure. Single-path simulations of gas uptake were found to be comparable to the predictions of the more realistic (but more computationally-intensive) three-dimensional simulations. The effect of different boundary conditions imposed at the outflow boundaries were also examined. It was found that a simpler and less costly truncated geometry of the tracheobronchial tree can be used in the simulations to accurately predict ozone uptake and wall flux, provided that the flow distribution at the outflow boundaries of the truncated geometry is based on the total cross-sectional area of all of their downstream outflows in the complete geometry of the tracheobronchial tree.
# Table of Contents

List of Figures viii

List of Tables xiii

Acknowledgments xiv

Chapter 1
Introduction 1

Chapter 2
Background 4

2.1 The Respiratory Tract ........................................... 5
  2.1.1 Components of the Respiratory Tract ....................... 5
  2.1.2 Respiratory Tract Lining Fluid .......................... 6
  2.1.3 Site Specific Tissue Damage .............................. 7
  2.1.4 Mathematical Dosimetry Models ........................ 10
  2.1.5 Single-Path Models ................................. 10
  2.1.6 Three-Dimensional Models ............................. 11

Chapter 3
Methods 19

3.1 Geometry Construction and Meshing ....................... 19
  3.1.1 Anatomically-Accurate Geometry ..................... 19
  3.1.2 Axisymmetric Single-path Models ................... 22
3.2 Problem Formulation and Boundary Conditions ............ 23
3.3 Implementation in Fluent ............................... 26
Chapter 4
Comparison of Axisymmetric Single-Path and Truncated Three-Dimensional Models 34
4.1 CFD Simulations .............................................. 34
4.2 Simulation Results ........................................... 36
   4.2.1 Flow Field ............................................. 37
   4.2.2 Concentration Distribution ............................... 38
   4.2.3 Streaklines Color-labeled by Ozone Concentration ........ 40
   4.2.4 Flux Distribution ....................................... 41
   4.2.5 Mass Transfer Coefficient ............................... 41
4.3 Resolution and Accuracy ..................................... 51

Chapter 5
Simulation of Ozone Transport and Uptake in Three-dimensional Models of the Tracheobronchial Tree 66
5.1 Complete Three-Dimensional Model .................................. 67
   5.1.1 Specified Flow Rate at Outflow Boundaries ............... 67
       5.1.1.1 Flow Field ........................................ 68
       5.1.1.2 Concentration and Flux Distributions ............... 69
   5.1.2 Specified Pressure at Outflow Boundaries .................. 70
       5.1.2.1 Flow Field ........................................ 71
       5.1.2.2 Concentration and Flux Distributions ............... 71
   5.1.3 Comparison of the Simulation Results for Different Boundary Conditions .......... 72
       5.1.3.1 Flow Field ........................................ 72
       5.1.3.2 Concentration Field ................................ 74
       5.1.3.3 Ozone Flux at Airway Walls ......................... 75
5.2 Truncated Three-Dimensional Model ................................ 77
5.2.1 Simulation Results ........................................... 78

Chapter 6
Ozone Transport and Uptake in the Complete Three-Dimensional Model of the Respiratory Tract 114
6.1 Three-Dimensional Model of the Tracheobronchial Tree with the Larynx ................................. 114
   6.1.1 Model Geometry and Formulation .......................... 115
   6.1.2 Simulation Results ....................................... 116
       6.1.2.1 Flow Field ........................................ 116
       6.1.2.2 Concentration and Flux Distributions ............... 117
6.2 Complete Three-Dimensional Model of the Respiratory Tract ........................................... 119
List of Figures

2.1 The human respiratory tract [1]................................. 17
2.2 Respiratory Tract Lining Fluid ................................. 18
2.3 Physical and computational domains of axisymmetric single-path model [2]................................. 18

3.1 MRI images of the lung cast........................................ 29
3.2 (a) Three-dimensional reconstruction of the lung in AMIRA, and (b) The tracheobronchial tree geometry in GAMBIT................................. 30
3.3 Three-dimensional models of: (a) The tracheobronchial tree, (b) The tracheobronchial tree with the larynx, and (c) The complete respiratory tract of the rhesus monkey................................. 31
3.4 (a) Three-dimensional reconstruction of the tracheobronchial tree, and (b) The truncated geometry of the tracheobronchial tree (the right middle lobe), (c) Axisymmetric single-path model................................. 32
3.5 Serial ANSYS FLUENT architecture [3]............................. 32
3.6 Parallel ANSYS FLUENT architecture [3]............................. 33

4.1 $RTLF$ thickness and generation radius relationship in human conducting airways................................. 37
4.2 The axial lines of the airways........................................ 54
4.3 Color map of velocity magnitude in: (a) the anatomically-accurate truncated three-dimensional and (b) axisymmetric single path models, $Re_0 = 98$........................................ 55
4.4 Color map of $O_3$ concentration at various cross-sections for an infinitely fast reaction and $Re_0 = 98$: (a) the anatomically-accurate truncated three-dimensional model; (b) corresponding axisymmetric single path model................................. 56
4.5 Cross-sectional average of $O_3$ concentration in each generation of the axisymmetric single-path models for an infinitely fast reaction................................. 57
4.6 Cross-sectional average of $O_3$ concentration in each generation of the truncated three-dimensional models for an infinitely fast reaction................................. 57
4.7 Cross-sectional average of $O_3$ concentration in each generation of the truncated three-dimensional and axisymmetric single-path models, ($Re = 98$) and infinitely-fast reaction. .......................... 58
4.8 Cross-sectional average of $O_3$ concentration in each generation of the truncated three-dimensional model and the axisymmetric single-path model, ($Re = 98$), slow first-order reaction. ......................... 58
4.9 Streaklines of flow color-labeled by the local $O_3$ concentration, $Re_0 = 98$ and infinitely fast reaction. .......................... 59
4.10 Longitudinal distribution of the dimensionless wall flux in the axisymmetric single-path model, infinitely fast reaction. ............... 60
4.11 Longitudinal distribution of the dimensionless wall flux in the truncated three-dimensional model, infinitely fast reaction. ............... 60
4.12 Distribution of the dimensionless wall flux in the truncated three-dimensional model, infinitely fast reaction. .......................... 61
4.13 Local Sherwood number in each generation of the axisymmetric single-path models, infinitely fast reaction. .......................... 62
4.14 Local Sherwood number in each generation of the truncated three-dimensional models, infinitely fast reaction. .......................... 62
4.15 Local Sherwood number in each generation of the axisymmetric single-path model and the truncated three-dimensional model, $Re_0 = 98$ and infinitely fast reaction. .......................... 63
4.16 $Sh/Re^{0.5}$ in each generation of the axisymmetric single-path models, infinitely fast reaction. .......................... 63
4.17 $Sh/Re^{0.5}$ in each generation of the truncated three-dimensional models, infinitely fast reaction. .......................... 64
4.18 Comparison of $Sh/Re^{0.5}$ in each generation of the axisymmetric and truncated three-dimensional models, infinitely fast reaction. .......................... 64
4.19 Power-law fitting of Sherwood number versus Reynolds number. .......................... 65
4.20 The simulation results, asymptotic solutions for the entrance and fully-developed regions. .......................... 65

5.1 Major pathways in complete three-dimensional model of the tracheobronchial tree. .......................... 85
5.2 Contour maps of velocity distribution in the selected planes of the major pathways for the prescribed flow rate condition, Reynolds numbers of 98 and 392. .......................... 86
5.3 Streaklines of flow, color-labeled by the local velocity magnitude for the prescribed flow rate condition, Reynolds numbers of 98 and 392. 87
5.4 Contour maps of concentration distribution in the selected planes of the major pathways for the prescribed flow rate condition, Reynolds numbers of 98 and 392. .......................................................... 88
5.5 Color map of $O_3$ flux distribution on the wall of three-dimensional geometry of the tracheobronchial tree for the prescribed flow rate condition, Reynolds numbers of 98 and 392. ..................... 89
5.6 Streaklines of flow, color-labeled by the local $O_3$ concentration for the prescribed flow rate condition, Reynolds numbers of 98 and 392. ......................................................... 90
5.7 Contour maps of velocity distribution in the selected planes of the major pathways for the zero pressure condition, Reynolds numbers of 98 and 392. .......................................................... 91
5.8 Contour maps of concentration distribution in the selected planes of the major pathways for the zero pressure condition, Reynolds numbers of 98 and 392. .......................................................... 92
5.9 Color map of $O_3$ flux distribution on the wall of the three-dimensional geometry of the tracheobronchial tree for the zero pressure condition, Reynolds numbers of 98 and 392. ..................... 93
5.10 Streaklines of flow, color-labeled by the local $O_3$ concentration for the zero pressure condition, Reynolds numbers of 98 and 392. ......................................................... 94
5.11 Comparison of mass flow rates in the branches of pathways $RM$ and $RC$, Reynolds number of 98. .......................................................... 95
5.12 Comparison of mass flow rates in the branches of pathways $L$ and $R$, Reynolds number of 98. .......................................................... 96
5.13 Total pressure drop in the major pathways for both boundary conditions at the outflow boundaries, Reynolds numbers of 98 and 392. 97
5.14 Pressure drops in the airway branches of pathways $RM$ and $RC$, Reynolds number of 98. .......................................................... 98
5.15 Pressure drops in the airway branches of pathways $L$ and $R$, Reynolds number of 98. .......................................................... 99
5.16 Cross-sectional average of $O_3$ concentration in the planes of pathways $RM$ and $R$ for both boundary conditions at the outflow boundaries, Reynolds numbers of 98 and 392. ..................... 100
5.17 Bulk average $O_3$ concentration in the planes of pathways $RM$ and $R$ for both boundary conditions at the outflow boundaries, Reynolds numbers of 98 and 392. ..................... 101
5.18 Ozone uptake in the segments of pathways $RM$ and $RC$ for both boundary conditions at the outflow boundaries, Reynolds number of 392. ......................................................... 102
5.19 Ozone uptake in the segments of pathways $L$ and $R$ for both boundary conditions at the outflow boundaries, Reynolds number of 392. ......................................................... 103
5.20 Mean flux in the segments of pathways $RM$ and $RC$ for both boundary conditions at the outflow boundaries, Reynolds numbers of 98 and 392. .......................................................... 104
5.21 Mean flux in the segments of pathways $L$ and $R$ for both boundary conditions at the outflow boundaries, Reynolds numbers of 98 and 392. ......................................................................... 105
5.22 The truncated three-dimensional geometries. ............................. 106
5.23 Schematic of the local and global flow splits. ............................. 107
5.24 Color maps of $O_3$ flux distribution on the wall of pathway $RM$, Reynolds number of 392. .................................................................................................................. 108
5.25 Color maps of $O_3$ flux distribution on the wall of pathway $R$, Reynolds number of 392. .................................................................................................................. 109
5.26 Color maps of $O_3$ flux distribution on the wall of pathway $L$, Reynolds number of 392. .................................................................................................................. 110
5.27 Ozone uptake in the segments of pathway $RM$, Reynolds number of 392. .................................................................................................................. 111
5.28 Ozone uptake in the segments of pathway $R$, Reynolds number of 392. .................................................................................................................. 112
5.29 Ozone uptake in the segments of pathway $L$, Reynolds number of 392. .................................................................................................................. 113

6.1 Contour maps of velocity distribution in the selected planes of the major pathways for the tracheobronchial tree without the larynx and that with the larynx, tracheal Reynolds numbers of 183. ... 125
6.2 Streaklines of flow, color-labeled by the local $O_3$ concentration for the tracheobronchial tree with the larynx, tracheal Reynolds numbers of 183 and $Da = 15$. ................................. 126
6.3 Contour maps of concentration distribution in the selected planes of the major pathways for the tracheobronchial tree without the larynx and that with the larynx, tracheal Reynolds numbers of 183 and $Da = 15$. ................................. 127
6.4 Color map of $O_3$ flux distribution on the wall of three-dimensional geometry of the tracheobronchial tree with the larynx, tracheal Reynolds numbers of 183 and $Da = 15$. ................................. 128
6.5 Color map of $O_3$ flux distribution on the wall of three-dimensional geometry of the tracheobronchial tree without the larynx and that with the larynx, tracheal Reynolds numbers of 183 and $Da = 15$. ................................. 129
6.6 Nasal cavity of the rhesus monkey. MT: middle turbinate; IT: inferior turbinate; IM: inferior meatus; MS: maxillary sinus. .................. 130
6.7 Contour maps of velocity distribution in the selected planes of the major pathways for the tracheobronchial tree in the complete three-dimensional model of the respiratory tract, tracheal Reynolds numbers of 183.

6.8 Contour maps of velocity distribution in the selected planes of the nasal cavity, tracheal Reynolds numbers of 183.

6.9 Streaklines of flow, color-labeled by the local $O_3$ concentration for the complete three-dimensional model of the respiratory tract, tracheal Reynolds numbers of 183 and $Da = 15$.

6.10 Streaklines of flow, color-labeled by (a) the local velocity magnitude and (b) the local $O_3$ concentration for the nasal cavity, tracheal Reynolds numbers of 183 and $Da = 15$.

6.11 Contour maps of concentration distribution in the selected planes of the major pathways for the tracheobronchial tree in the complete three-dimensional model of the respiratory tract, tracheal Reynolds numbers of 183 and $Da = 15$.

6.12 Contour maps of concentration distribution in the selected planes of the nasal cavity, tracheal Reynolds numbers of 183 and $Da = 15$.

6.13 Color map of $O_3$ flux distribution on the wall of the complete three-dimensional model of the respiratory tract, tracheal Reynolds numbers of 183 and $Da = 15$.

6.14 Color map of $O_3$ flux distribution along the perimeter of the selected planes within the nasal cavity, tracheal Reynolds numbers of 183 and $Da = 15$.

6.15 Formaldehyde-induced lesion distribution in the selected levels of nasal passages (regions with cross-hatching) [24].

6.16 Color map of $O_3$ flux distribution along the perimeter of the selected planes within the nasal cavity, tracheal Reynolds numbers of 183 and infinitely-fast reaction.
List of Tables

4.1 \textit{RTLF} thickness and Airway Radius in the Conducting Airways \hspace{1em} 36
4.2 \textit{Da} and \textit{K} in each generation of the right middle lobe \hspace{1em} 38
4.3 Average Sherwood number for each branch in the axisymmetric single-path model \hspace{1em} 45
4.4 Average Sherwood number for each branch in the truncated three-dimensional model \hspace{1em} 45
4.5 Branch Reynolds numbers along the selected path in the right middle lobe \hspace{1em} 46
4.6 Constants of the power-law fit for the \textit{Sh} and \textit{Re} data in the axisymmetric single-path and truncated three-dimensional models \hspace{1em} 50
4.7 Average Sherwood numbers for the complete structure in the axisymmetric single-path and truncated three-dimensional models \hspace{1em} 51

5.1 Percentage of flow rate at the outlets of the pathway \textit{RM} \hspace{1em} 80
5.2 Percentage of flow rate at the outlets of the pathway \textit{R} \hspace{1em} 80
5.3 Percentage of flow rate at the outlets of the pathway \textit{L} \hspace{1em} 81
5.4 Mean flux errors in the truncated pathway \textit{RM} relative to the complete three-dimensional model of the tracheobronchial tree \hspace{1em} 82
5.5 Mean flux errors in the truncated pathway \textit{L} relative to the complete three-dimensional model of the tracheobronchial tree \hspace{1em} 83
5.6 Mean flux errors in the truncated pathway \textit{R} relative to the complete three-dimensional model of the tracheobronchial tree \hspace{1em} 84
Acknowledgments

First and foremost, I would like to express my sincere gratitude to my thesis advisors Professor Ali Borhan and Professor James Ultman for their guidance, patience, and encouragement during the course of my graduate studies and research. I could not have imagined having better advisors and mentors for my Ph.D studies. As a result of their endless support, research life became smooth and rewarding for me. I am specially indebted to Dr. Borhan whose energy, enthusiasm, and talent have inspired all of his students, including me.

I would like to thank Professor Rebecca Bascom for her valuable insights. I also wish to thank my colleagues and former research group members, Dr. Adekemi B. Taylor and Dr. Hongfei Wu, for helpful discussions and suggestions during this project.

Finally, I would like to thank my mother, Mahinbanoo Khodadadi, my father, Khosrow Keshavarzi, and my brother, Babak Keshavarzi, for their love and support throughout my life. And last, but not least, I would like to thank my husband, Pedram Hovareshti, for his friendship, encouragement, and support.
Chapter 1

Introduction

Ozone ($O_3$) is a highly reactive gas and a harmful air pollutant. Ground level ozone is formed primarily by the action of sunlight on molecular $O_2$ with hydrocarbon vapors and nitrogen oxides emitted by combustion of fossil fuels acting as catalyzing agents. The $O_3$-related adverse health effects range from decreased lung function and increased respiratory symptoms (e.g., increase the frequency of asthma attacks in populations suffering from asthma) to serious indicators of respiratory morbidity including emergency department visits and hospital admissions for respiratory causes, and possibly cardiovascular-related morbidity as well as total nonaccidental and cardiorespiratory mortality.

Adsorption of ozone occurs in all regions of the respiratory tract. It has been verified that $O_3$ exposure causes tissue damage in the upper as well as the lower airways [4]. More strikingly, recent observations have shown that exposure to ozone can produce intense remodeling in the developing lungs of infant primates, resulting in the loss of conducting airways [5]. A reproducible pattern of tissue injury induced by inhalation of $O_3$ is believed to depend on the local dose delivered to different tissue sites in the respiratory tract [6].

Previous analysis of transport and removal of $O_3$ in the lungs of guinea pigs, rabbits, and humans indicates the existence of a general similarity among these species in the shapes of the dose curves [7]. Thus, 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 predictive tools in the extrapolation of animal toxicological results to humans [8]. This study is the first of its kind on modeling of \( O_3 \) dose distribution in an immature respiratory system. The primary objective of this research is to model the exposure-dose relationship in the respiratory system of a 6-month-old rhesus monkey. In terms of human development, a 6-month-old rhesus monkey corresponds to a one or two year old child. Therefore, this study will lead to a better understanding of the potential effect that \( O_3 \) has on human infants and children. This is particularly important in light of the catastrophic rise in the incidence of asthma among children that may make them hypersensitive to inhaled \( O_3 \). The second objective of this project is to develop a two-dimensional single-path model of a selected path in the monkey lower airways. We will show that single-path simulations of gas uptake are comparable to the predictions of the more realistic (but more computationally-intensive) three-dimensional simulations.

The specific aims of this doctoral research are to:

- Simulate the spatial distribution of \( O_3 \) at specific sites in the respiratory tract such as nasal cavities, larynx, and airway bifurcations.

- Develop a two-dimensional single-path model that is capable of simulating longitudinal dose distribution.

- Compare \( O_3 \) uptakes in the axisymmetric single-path model and a truncated three-dimensional model.

- Compare the two different RTLF reaction models (the infinitely-fast and slow first-order reaction models) in the simulated structures.

- Investigate the effects of boundary conditions and Reynolds number on \( O_3 \) uptake.

- Study the effects of larynx and upper airways on \( O_3 \) uptake in the lower airways

This thesis is structured as follows: Chapter 2 provides background information for this research project. Chapter 3 describes the methodology for the three-dimensional reconstruction of the respiratory tract, the construction of the
single-path geometries, and solution of the governing equations and their associated boundary conditions. In Chapter 4, the simulation results of $O_3$ distribution in the axisymmetric single-path model are compared to those of the truncated three-dimensional model. Chapter 5 investigates the effects of the flow splits and Reynolds number on the simulation results of $O_3$ uptake in the full three-dimensional structure of the lung and also the truncated geometries. Chapter 6 considers the laryngeal effect on airflow, $O_3$ uptake and dose distribution. This chapter also investigates the effects of appending the nasal cavities to the larynx and lung structure on simulation results of $O_3$ uptake in the lower airways. A brief comparison between the simulation results of wall flux distribution and experimental observations of tissue injury induced by inhalation of a highly reactive gas is also included in this Chapter. Finally, a summary of the results and conclusions, as well as the suggestions for future works are given in Chapter 7.
Chapter 2

Background

Ozone ($O_3$) is a gas composed of three oxygen atoms. It exists both in the upper atmosphere (stratosphere) and at ground level (troposphere). Upper-level $O_3$, which is produced naturally, filters the sun’s ultra-violet radiation. In the Earth’s lower atmosphere, near ground level, $O_3$ is formed when oxygen and pollutants emitted by cars, power plants, chemical plants and other sources react chemically in the presence of sunlight. Ground-level $O_3$ is an air pollutant with harmful effects on the respiratory tract.

Based on the review of the air quality criteria for $O_3$ and related photochemical oxidants, the Environmental Protection Agency (EPA) set the 8-hour national ambient air quality standards (NAAQS) for $O_3$ at 0.075 parts per million ($ppm$) to protect both public health and the environment [9]. Based on this review, the detrimental effects of $O_3$ can be summarized as follows:

- **Health Effects of Ground-Level Ozone**

  People with lung disease, children, older adults, and people who are active can be particularly affected when ozone levels are high. Numerous scientific studies have linked ground-level ozone exposure to a variety of problems, including:

  - airway irritation, coughing, and pain when taking a deep breath;
  - wheezing and breathing difficulties during exercise or outdoor activities;
– airway inflammation, which is much like a sunburn on the skin;
– aggravation of asthma and increased susceptibility to respiratory illnesses like pneumonia and bronchitis;
– permanent lung damage with repeated exposures.

• **Environmental Effects of Ground-Level Ozone**

Ground-level ozone can have detrimental effects on plants and ecosystems. These effects include:

– interfering with the ability of sensitive plants to produce and store food, making them more susceptible to certain diseases, insects, other pollutants, competition and harsh weather;
– damaging the leaves of trees and other plants, negatively impacting the appearance of urban vegetation, as well as vegetation in national parks and recreation areas;
– reducing forest growth and crop yields, potentially impacting species diversity in ecosystems.

# 2.1 The Respiratory Tract

## 2.1.1 Components of the Respiratory Tract

The respiratory tract (Figure 2.1) is composed of the upper conducting airways, the lower conducting airways and the respiratory zone. The upper conducting airways contain several functional components such as the oral cavity, the nasal cavity, the pharynx, and the larynx. The anatomy of the upper airways includes an array of diverging and converging conduits which may lead to complicated gas transport in the region [10]. The total volume of the upper airways depends on the type of air access. For oral breathing in adult humans, volume estimates of the upper airways plus trachea range from 50 to 100 ml [11].

The lower conducting airways (tracheobronchial tree) include the trachea and a series of branching tubes which become narrower, shorter, and more numerous
before ending at the terminal bronchioles. These structures serve to transport the inhaled air to the respiratory region where gas exchange of oxygen and carbon dioxide takes place. The conducting airways warm and humidify the inhaled air before it reaches the lower respiratory tract. In addition, the walls of the conducting airways are lined with a layer of protective mucus which can clear out particles and absorb reactive gases before they can reach the delicate tissues in the respiratory zone [12].

In adult humans, the volume of the conducting airways is around 150 ml, while the volume of the respiratory zone is about 3 liters. The large volume of the respiratory zone is the result of the presence of expandable sacs called alveoli. Gas exchange occurs in the alveolar-capillary unit. The total number of alveoli in the respiratory zone has been quantified to be approximately $3 \times 10^8$ in adult humans [13], and an individual alveolus is roughly spherical with a characteristic diameter of about 0.3 mm [14]. The alveolar wall is a mesh of fine capillaries covered by a thin layer of epithelial tissue that is coated with a surfactant layer, with a total thickness of approximately 2 µm [10]. Therefore, unlike the much thicker conducting airways, the alveolar section expands during inhalation and contracts during exhalation, leading to the varying volume during the respiratory cycle [15].

Absorption of $O_3$ occurs in all regions of the respiratory tract. $O_3$ is not completely absorbed in the upper airways and therefore reaches the lower airways and air spaces. As a result, $O_3$ exposure causes tissue damage in the upper as well as the lower airways [16].

### 2.1.2 Respiratory Tract Lining Fluid

The inner walls of the respiratory tract are lined with a liquid referred to as the respiratory tract lining fluid (RTLF). The bronchial tree is lined with a thin film of mucus, while the alveolar region is lined with an even thinner layer of surfactant [17]. Inhaled gases initially contact the RTLF and must dissolve in and diffuse through it to gain access to the underlying pulmonary epithelial, endothelial, and vascular compartments (Figure 2.2). The RTLF layer is mainly aqueous, but it contains many types of biological substrates, such as proteins, carbohydrates,
amino acids, lipids, and antioxidants, which are capable of reacting with $O_3$ before it reaches the underlying epithelial cells.

The reaction between $O_3$ and substrate molecules has been studied rather extensively. Ozone is a relatively aqueous-insoluble but highly reactive oxidant gas [8]. It undergoes rapid peroxidation with biochemical substrates in the RTLF layer to produce a series of free radicals either through an $O_3$-carbonyl reaction or via an $O_3$-electron donor reaction. The first mechanism involves unsaturated fatty acids, cholesterol, and tryptophane molecules, while the second one depends on the presence of molecules such as glutathione, ascorbate, antioxidant, and thiosulfate [18]. The RTLF encounters both inhaled oxidants and oxidants released by inflammatory cells (e.g. $H_2O_2$ and $NO$). These extracellular oxidants or their reaction products contact cellular exteriors. Thus, they can initiate damage by pathways which differ from intracellular reactive species.

The toxicity of oxidant gases such as ozone is believed to be caused by peroxidation of membrane lipids, leading to destruction of the membrane integrity, which eventually leads to cell death. Ozone may also oxidize reduced sulfhydryl groups of proteins and peptides such as glutathione. Although membrane damage due to lipid peroxidation is a likely explanation for the toxicity of these compounds, other theories have also been proposed [19]. One of these is that peroxidation of membrane protein is more important than lipid peroxidation. Another is that the energy metabolism of the cell is compromised by a decrease in the NADPH concentration due to recycling of GSH by glutathione reductase. Yet another possibility is that key metabolic enzymes are inactivated by the oxidant [18].

### 2.1.3 Site Specific Tissue Damage

Tissue damage due to inhalation of ozone and other reactive gases occurs in a heterogeneous but reproducible manner throughout the respiratory tract. Experimental observations of these focal sites of epithelial injury in laboratory animals can be extrapolated to make predictions of risk to human health.

Fanucchi et al. [5] exposed 6 infant rhesus monkeys to cyclic episodes of 0.5 ppm ozone for 5 months and 6 monkeys to filtered air. This concentration of ozone is equivalent to high environmental concentrations found in Mexico city. Terminal
bronchioles of ozone-exposed monkeys were an average of 38% narrower and 45% shorter than terminal bronchioles of filtered-air control monkeys. The conducting airways in filtered-air control infants monkey are lined by a layer of continuous pseudostratified epithelium composed of mucous cells, ciliated cells, and basal cells and surrounded by a layer of smooth muscle. Following exposure to ozone, there were randomly scattered patches and longitudinal tracts in which ciliated cells had a shortened and less covering of cilia and an increase in the number of nonciliated cells [16, 20]. They observed that the conducting airways continued to generation 13 in filtered-air monkeys and only to generation 10 in ozone-exposed monkeys. This generation in ozone-exposed monkeys was lined by a discontinuous layer of epithelium punctuated by alveolar outpocketings and surrounded by a discontinuous layer of smooth muscle.

Bonnet monkeys were also exposed for 7 days, 8 hr/day to 0.2 and 0.35 ppm ozone by Castleman et al. [16]. They used bonnet monkeys for exposure with ozone concentration less than 0.5 ppm. The bonnet monkeys‘ terminal bronchioles are similar to those of man [21]. Pulmonary lesions were detected by light and electron microscopy in all monkeys exposed to ozone. The first and most consistently observed gradient of airway damage involved respiratory bronchioles where epithelial changes and macrophage accumulation were most extensive in proximal generations and decreased in severity in more distal generations. The second and more variable gradient of damage was located in the conducting airways where ciliated cells were affected most severely in the trachea and proximal bronchi and those in distal bronchi and terminal bronchioles were affected less severely. There was a gradient in severity of damage to ciliated cells in animals following exposure to either 0.2 or 0.35 ppm ozone.

Wilson et al. evaluated changes in light-microscopic, surface, and ultrastructural appearance of the tracheobronchioles epithelium of bonnet monkeys. One group of the monkeys was exposed to filtered-air, a second group to 0.64 ppm ozone continuously for 3 days, and a third group to 0.64 ppm ozone continuously for 7 days. The loss of ciliated cells and the presence of cells with attenuated cilia are the major changes in surface structures due to ozone exposure. Decreased density and altered morphology of secretory granules were the most consistent changes in mucous cells. Nuclei of mucous cells in ozone-exposed animals appeared larger,
less angular, and less electron-dense, with relatively more euchromatin. Apparent increase in epithelial extracellular space was also noted in ozone-exposed animals. The epithelium was more altered at 3 days and has less alteration after 7 days of exposure. It shows that the ciliated cell population becomes less susceptible to ozone-induced necrosis with continuing exposure.

Devlin et al. exposed 16 adult males to air and 0.4 ppm ozone for 2 hr/day on 5 consecutive days, and again a single time 10 or 20 days after the initial 5-day ozone exposure [22]. They concluded that increases in many cellular and biochemical mediators indicative of inflammation seen after a single exposure of humans to ozone are reduced after 5 consecutive days of exposure. However, markers of underlying cell damage and plasma extravasation are not reduced, suggesting that progressive damage to lung epithelial cells may continue to progress during the 5 days of exposure. Some mediators (polymorphonuclear leukocytes, interleukin-8, prostaglandin E$_2$, recovery of viable cells) showed at least partial reversal within 10–20 days, while others (total protein, α1) did not return to the normal response to ozone even after 20 days.

Plopper et al. [6] exposed adult male rhesus monkeys for 2 hours to filtered air, 0.4 or 1.0 ppm ozone. They concluded that there is a close association between site-specific O$_3$ dose, the degree of epithelial injury, and glutathione depletion at local sites in the tracheobronchial tree. Glutathione, an antioxidant, helps protect cells from reactive oxygen species such as free radicals and peroxides.

Lesion locations due to reactive gases other than O$_3$ have also been observed. Lesion distributions induced by formaldehyde differ between rats and primates due to interspecies differences in inspiratory airflow and uptake patterns [23, 24]. In rats, respiratory bronchioles are extremely poorly developed or nonexistent, and terminal bronchioles open distally into alveolar ducts where ozone-induced damage is most severe [16]. Moulin et al. [25] compared the lesion locations and regions of high H$_2$S flux predicted using a CFD model of a rat’s nasal passages. The rats were exposed by inhalation to 0, 10, 30, or 80 ppm H$_2$S for 6 hours per day over a 70 day period. They found that regions lined by olfactory epithelium showed a close correlation between H$_2$S flux and lesion incidence for the 30 and 80 ppm exposure groups. Kimbell et al. [26] also compared the reported distribution of
formaldehyde-induced nasal lesions observed in the F344 rat and concluded that the airflow driven uptake pattern may play an important role in determining the location of certain nasal lesions induced by formaldehyde.

2.1.4 Mathematical Dosimetry Models

Regional differences in tissue damage are hypothesized to be related to corresponding differences in the rates of $O_3$ delivery. Although local dose cannot be easily measured, mathematical dosimetry models can estimate site-specific dose and the exposure levels needed to produce the same dose at specific sites in different individuals of the same or different species [27]. Hence, site-specific dosimetry modeling is an important tool for interpreting the toxicological effects of inhaled compounds in animals, and predicting potential effects in humans.

2.1.5 Single-Path Models

The development of $O_3$ dosimetry models for laboratory animals and humans has mainly focused on the effects of $O_3$ in the lower respiratory tract ($LRT$) which includes the trachea and a series of branching tubes that become narrower, shorter, and more numerous before ending at the terminal bronchioles. Single-path models have been 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, the set of all alternative paths from the airway opening to the alveoli is replaced by a single representative path along which respired air is assumed to be laterally well-mixed and experiencing plug flow [28]. The one-dimensional single-path model was first developed to describe the transport of normal respiratory gases through the respiratory system [29], but was later modified by various investigators to examine the absorption of pollutant gases such as ozone [7, 8, 15, 17, 30, 31, 32]. Most of these studies found ozone absorption into the lining fluid decreased distally along a path in the tracheobronchial or pulmonary region, with a maximal tissue dose occurring in the terminal bronchioles.
A major shortcoming of one-dimensional single-path models is the implicit assumption of uniform cross-sectional profiles for both concentration and velocity at any given axial position. As a result, such models do not account for axial dispersion in the airways or boundary layer resistance at the airway wall in a fundamental manner. Instead, the models require the input of macroscopic parameters, namely effective diffusion coefficients and wall mass transfer coefficients to emulate dispersion and boundary layer resistance.

As an alternative approach, a two-dimensional axisymmetric single-path model was recently developed by Madasu et al. [2] to examine gas transport along a selected airway path within a branched airway system. As depicted in Figure 2.3, a transport path was modeled as a series of cylindrical airway branches that are connected with axisymmetric leaky transition regions corresponding to the bifurcation regions between parent and daughter branches. The leaky transition regions account for the loss (inspiration) or gain (expiration) in flow through the daughter branches that have been excluded from the selected airway path. The two-dimensional single-path model is advantageous compared to its one-dimensional counterpart in that axial dispersion and boundary layer resistance are automatically captured by solving the continuity, Navier-Stokes, and convection-diffusion equations for axisymmetric velocity and concentration distributions that depend on the radial as well as axial position.

Although single-path models are valuable tools for predicting the longitudinal dose distribution, they are inherently restricted to symmetrically branched airway systems. Recent advances in the implementation of reliable methods for three-dimensional imaging and computer reconstruction of complex geometries, combined with well-established computational fluid dynamics (CFD) strategies for the precise determination of velocity and concentration distributions in such geometries have paved the way for the development of more sophisticated dosimetry models based on anatomically-accurate geometries of the LRT.

2.1.6 Three-Dimensional Models

- *Air Flow Modeling*
Air flow is one of the primary mechanisms for transport of inhaled gases in the respiratory tract. Complex patterns of air flow can influence regional concentrations of inspired reactive gas throughout both URT and LRT and as a result affects local absorption and tissue damage. Three-dimensional modeling has been the focus of recent studies of both air flow in the human lower airways [33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43] and in the human nasal cavity [44, 45, 46, 23, 47], as well as particle deposition in the human respiratory tract [48, 49, 50, 51, 52, 53, 54, 55, 56, 57]. Obtaining knowledge of the airflow mechanism within the airways is the first step in understanding particle motion and deposition in the respiratory airflow network [58].

Simulating flow behavior inside human lower airways has been based on branching structures of the airways that vary from the symmetric Weibel model [13] to asymmetric models including the Horsfield model [11], the Schmidt model [59] and anatomically-accurate models. Accurate and realistic airway models are necessary for experimental or computational airflow, particle deposition, and gas absorption analysis. Modern imaging techniques allow for a detailed mapping of the respiratory tract. Cebral et al. and Backer et al. used CT-scan data to reconstruct the airways, while Tawhai et al. as well as Ma et al. reconstructed tracheobronchial tree from MRI images [33, 34, 40, 60].

To date, computational simulations have been performed in isolated sections of the lower airways of the human respiratory tract, using both the Weibel and Schmidt models [38, 54, 61] and anatomically-accurate models [34]. Both steady [34, 38, 54, 61] as well as unsteady [40, 51] laminar flow has been considered. However, at moderate to high breathing rates, the air flow from the larynx to generation G3 is transitional to turbulent, which may complicate flow structure [34, 36, 37, 39, 49]. The choice of boundary conditions for simulating flow has also been extensively studied [33, 34, 36, 38, 39, 40, 51].

Cebral et al. [33] simulated pressure and flow patterns through a few bronchi generations assuming both steady and unsteady conditions. They showed decreased pressure and increased shear stress in the region of a stenosis. During expiration, the flow pattern is less complicated, the pressure drop at the stenosis is less marked, and flow recirculation zones are not evident distal from the stenosis.
A three-dimensional reconstruction of the lower airway geometry up to the airway level where the airway diameter is around $1 - 2 \text{ mm}$ was done by Backer et. al [34]. They used CT images of the lung of a 73-year-old female suffering from chronic obstructive pulmonary disease. The simulation results showed that pressure distribution according to the right and left lung volumes corresponds well with the experimental observations of mass flow rates through the left and right lungs. They also concluded that turbulence has a negligible effect on the mass flow rates.

Gemci et al. [36] studied air flow in the 17-generation airway of the anatomical model of the human lung by Schmidt et al. [59]. They simulated steady inspiratory turbulent flow using large eddy simulation turbulence model imposing a uniform velocity at the tracheal inlet and constant $P = 0$ at the outlets. Despite Ma and Lutchen’s conclusions [40] regarding flow versus outlet pressure boundary conditions at the end of a 6-generation geometry, imposing zero pressure at the outlets of the 17-generation anatomical model which represents almost the complete anatomical replica of the tracheobronchial tree is clearly more appropriate. The simulation results of the flow field also showed that the anatomical characteristic of the branching conduits affects the nature of the secondary vortical flows.

Laminar steady inspiratory and expiratory flow in a symmetrical bifurcation was simulated by Zhao et al. [43]. Parabolic velocity profiles were imposed at the inlet of the parent branch for inspiration. For expiration, the parabolic profiles were specified at the inlets of the daughter branches and flow is pushed into the daughter branches. Skewed velocity profiles in the daughter branches during inspiration and a velocity peak in the parent tube during expiration were the important flow features.

Green [37] simulated wall shear stress in a model of the first three generations of the lung using $\kappa - \epsilon$ formulation for steady expiration flow. The geometry and the flow splits are based on Horsfield et. al [62]. In simulations of the expiratory flow, each bronchus was taken as an inlet and a zero-gradient boundary condition was imposed at the trachea outlet. The maximum values of wall shear stress were observed in the right main bronchus. The results of the simulations were compared to wall shear stress measurements within the bronchial network.
The effects of Reynolds number on the flow patterns and pressure drop through an asymmetric airway extracted from the 5th-11th branches of the Weibel model were studied by Liu et al. [38]. Computations were carried out for inspiratory laminar flow in the Reynolds number range 200 – 1600. A stationary parabolic velocity and a uniform static pressure were imposed at the inlet and at the outlets, respectively. It was concluded that the flow rate ratios through the medial branches to that of their mother branches are the same. This may explain why regular human breathing is not affected by airways of different sizes. They also showed that the pressure drop behavior is not affected the asymmetry of the geometry. Their study was extended to a 5-generation airway of a human lung [39]. The geometry was reconstructed from the CT images of a 60-year-old male patient in Mimics software. The simulations were done for a steady inspiratory flow in the Reynolds number range of 900 – 2100 using low Reynolds number (LRN) $\kappa - \epsilon$ turbulent model. The imposed boundary conditions are the same except the inlet velocity profile is biased towards the real wall [63]. It was concluded that in the real lung model, the flow patterns are much more complicated than those of symmetrical models and the secondary flow of turbulent flow is weaker than that of the laminar flow. They also concluded that the ratio of the air flow rate between left and right lobes does not depend on Reynolds number.

Nowak et al. [51] simulated airflow and aerosol deposition through a Weibel-based model and also a real geometry based on CT scan images. Flow conditions included both steady-state inhalation and exhalation conditions as well as time-dependent breathing cycles. Particle trajectories were calculated in each of these models by solving the equations of motion of the particle for the deterministic portion of particle displacement, and adding a stochastic Brownian term at each step. The results of this study suggest that under most conditions, an idealized model based on the Weibel dimensions is not sufficient to predict deposition, and an accurate model, such as those based on imaging techniques may be required.

Van Ertbruggen et al. [54] studied the gas flow and particle deposition in a realistic three-dimensional model of the bronchial tree, extending from the trachea to the segmental bronchi (seventh airway generation for the most distal airways), based on the morphometrical data of Horsfield et al. [11]. Considering symmetric double-bifurcation models, Longest and Vinchurkar [49] have recently assessed the
effects of upstream transition to turbulence on the flow field and particle deposition in the generations $G3G5$ of the respiratory tract. Turbulence was shown experimentally to influence the local deposition of 10 $\mu m$ diameter particles, primarily by influencing the initial velocity and particle profiles. Their results underline the importance of correct inlet conditions and the need to consider upstream effects in experimental and computational studies of the respiratory tract.

It has been generally shown that the flow in the nasal cavity is largely determined by inflow condition, the geometry of the cavity and the size and orientation of the internal nasal valve [44, 47]. The type of flow regime that exists over the breathing cycle, particularly through the inspiratory phase, significantly affects the overall pressure losses and the transport of inhaled species and even possibly the stimuli transmitted to the nasal mucus and epithelium.

• **Dosimetry Modeling**

Only a few dosimetry model studies have been carried out to predict the concentration and flux distributions of reactive gases in the respiratory tract. Kimbell et al. [23] used anatomically accurate, 3-dimensional computational fluid dynamics models of F344 rat, rhesus monkey, and human nasal passages to estimate regional inhaled formaldehyde uptake patterns. Estimates of regional nasal formaldehyde flux, including maximum flux, average flux, and flux in specific nasal regions, were compared among the 3 species. These results serve as input for risk modeling of formaldehyde carcinogenesis to help reduce uncertainty in human cancer risk estimates from formaldehyde exposure. The geometry of the nasal passages of F344 rat was also used for ozone dosimetry by Hubal et al. [64]. They added nasal-lining mass-transfer resistance to the CFD model. It was concluded that the mucus resistance is important for describing the dosimetry of ozone and the mucus thickness may play a role in determining patterns of ozone-induced lesions in the rat URT. In addition, a statistically significant correlation was found between predicted regional wall mass flux of ozone and measured regional cell proliferation.

Kepler et al. [65] examined the hypothesis that regions of high airflow-dependent uptake and lesions occur in similar nasal locations in the primates. Airflow and gas uptake patterns were simulated in an anatomically accurate computer model of
the right nasal airway of a rhesus monkey. Simulated airflow patterns agreed well with experimental observations, exhibiting secondary flows in the anterior nose and streamlined flow posteriorly. Results from the uptake simulations were compared with published observations of formaldehyde-induced nasal lesions in rhesus monkeys and indicated a strong correspondence between airflow-dependent transport patterns and local lesion sites.

Carey et al. [66] exposed 3 and 6-month-old rhesus monkeys to 0.5 ppm ozone for 5 consecutive days (8 hr/day). The principal nasal lesions observed in this primate model of ozone-induced nasal toxicology were neutrophilic rhinitis, along with necrosis and exfoliation of the epithelium lining the anterior maxilloturbinate. These lesions, induced by acute or cyclic (episodic) exposures, were examined by light microscopy, quantified by morphometric techniques, and mapped on 3-dimensional models of the nasal airways. The location and severity of the nasal epithelial injury were correlated with epithelial type, nasal airway geometry, and local biochemical and molecular changes on an individual animal basis. These correlations are critical for accurate predictive modeling of exposure-dose-response relationships in the nasal airways, and subsequent extrapolation of nasal findings in animals to humans for determining risk.

This thesis presents the results of three-dimensional CFD simulations of $O_3$ transport and uptake in an anatomically-accurate model of the respiratory tract of a 6-month-old rhesus monkey. To the author’s knowledge, this study represents the first three-dimensional CFD model of reactive gas dosimetry in the respiratory tract of a primate, and the only one of its kind to include the upper respiratory tract together with the first thirteen generations of the tracheobronchial tree. This study compares the results of the three-dimensional simulations to those of the corresponding single-path models, and also examines the effect of various boundary conditions used in the simulations on the predicted concentration and flux distributions.
Figure 2.1. The human respiratory tract [1]
Figure 2.2. Respiratory Tract Lining Fluid

Figure 2.3. Physical and computational domains of axisymmetric single-path model [2]
Methods

3.1 Geometry Construction and Meshing

3.1.1 Anatomically-Accurate Geometry

The respiratory tract of a rhesus monkey was selected as the platform for this computational study because experimental assessment of ozone-induced injury in the conducting airways of rhesus monkeys is being conducted concurrently by our collaborators, thereby allowing direct comparison between theoretical predictions and experimental observations.

- Complete geometry of the respiratory tract

  The anatomically-accurate airway geometry was created from three-dimensional reconstruction of the respiratory tract using MRI images of the casts of the lung and nasal cavities of a 6-month-old male rhesus monkey, and the larynx cast of a 3-month-old rhesus monkey. The MRI data of the lung consisted of 256 transverse slices depicting a square field of view of 10 cm on a side. The thickness of each slice and the resolution of its sides were both 391 microns. The raw data for the larynx was collected on a $256 \times 256 \times 256$ matrix showing a $3.5 \, cm \times 3.5 \, cm \times 3.5 \, cm$ field-of-view. Sampling resolution was therefore $136.7 \times 136.7 \times 136.7$ cubic microns. The field of view of the MRI images of the nasal cavity was $4.5 \, cm$ in the transverse ($xy$) plane and $5.12 \, cm$ in the $z$ direction. Linear interpolation was performed in the $xy$-plane, yielding an actual spatial resolution of 350 microns,
compared to a resolution of 200 microns in the z-direction. All slices were stored as 8-bit TIFF (Tagged Image File Format) files containing 256 × 256 pixels in DDV (Digital Data Viewer) format. Figure 3.1 shows one of the slices in DDV format. The dark regions represent the airways and the interior airspace.

The MRI images of the casts were separately imported as raw data into the three-dimensional visualization and volume modeling software AMIRA (Mercury Computer Systems, Chelmsford, MA). Open-ended triangulated surfaces of the lung, the larynx and the nasal cavities were created in AMIRA, and exported to the commercial meshing software GAMBIT (ANSYS, Canonsburgh, PA). The extraneous low-resolution parts of the small branches of the lung were cut off from the geometry, and the geometry was cleaned up by removing hard and short edges, as well as small faces. Due to lack of resolution, the final structure was obtained by eliminating the airways with diameter less than 1 mm. This resulted in a total of four main pathways (the major pathways in the right and left lobes, the right middle lobe, and the right cranial lobe). There were 13 generations (ranging from 0 to 12) along the major pathway in the right lobe of the final geometry. The reconstructed geometry of the lung in AMIRA and the final structure in GAMBIT are shown in Figure 3.2.

The lung geometry was scaled by a factor of 0.391 to give the lung geometry dimensions in millimeters. The trachea of the rhesus monkey is about 45 mm long. However, the entire trachea was not included in the imaging process. Therefore, the trachea was extended by reflective continuation about the inlet to obtain the required length. A closed surface of the lung was created by defining the faces of the inlet of the trachea and the outflow boundaries of the complete structure. The volume of the lung was then created from the closed surface of the lung geometry. Since the simulations were performed using dimensionless equations, the lung geometry was scaled by the hydraulic radius of the trachea.

Due to a lack of MRI images for the larynx of a 6-month-old monkey, the MRI images from a 3-month-old monkey larynx were used. The open-ended larynx surface in GAMBIT was scaled by a factor of 0.1367 to get the dimensions in millimeters. To fit the larynx geometry to the geometry of the respiratory tract of a 6-month-old monkey, it was scaled such that the hydraulic diameter of the
outlet surface of the larynx was equal to the hydraulic diameter of the inlet of the trachea. The scale factor was calculated as 1.58, which is a reasonable value for scaling a 3-month-old monkey larynx to a 6-month-old monkey larynx. A closed surface of the larynx was created by defining the inlet and outlet faces. The volume was then created from the closed surface, and scaled by the hydraulic radius of the trachea. The final structure of the larynx was attached to the lung geometry by mapping the outlet surface of the larynx to the inlet surface of trachea.

The rhesus monkey has a fairly simple nasal airways geometry, divided into symmetric halves by the nasal septum which extends from the nares to the pharynx. The MRI images were available only for the left side of the nasal cavity since the right side was used for observations of tissue injury. Therefore, the open-ended surface of the left side of the nasal cavity was first reconstructed in AMIRA, and imported to GAMBIT. The right side was then obtained as a mirror image of the left side and the two sides were attached to obtain a complete geometry. The geometry was scaled by a factor of 0.2 to convert the dimensions to millimeters, and again scaled by the hydraulic radius of the trachea. The URT geometry was connected to the larynx by mapping the outlet surface of the URT to the inlet surface of the larynx. The time required to reconstruct and process a surface model of the whole respiratory tract, which is the step that requires the most user interaction, was on the order of one month.

Following reconstruction of the geometry, zone types such as inflow, outflow, interior, and wall faces were assigned to the bounding surfaces in the resulting structure. To allow for useful output of information from the simulations, the tracheobronchial tree was split into a collection of airway branch and bifurcation regions. These regions were then meshed using tetrahedral elements of dimensionless size 0.016 – 0.05. The branches with smaller diameter were meshed using a smaller mesh size. The larynx and the upper airways were also meshed using the same type of elements of dimensionless size 0.01 and 0.06, respectively. Finally, the meshed geometry was exported to the commercial CFD software FLUENT 6.3 (ANSYS, Canonsburgh, PA) for the simulations. The generation of a finite-element mesh of about 12 million elements for the respiratory tract model requires about three days on a 2.99 GHz Pentium(R) PC with 3.5 GB of RAM.
Numerical simulations were performed in the following order: the tracheobronchial tree, the tracheobronchial tree plus the larynx, and the entire respiratory tract down to conducting airways with a hydraulic diameter of at least 1 mm. Numerical simulations were performed in this order because MRI images of the larynx and the nose were not available at the time the geometry of the tracheobronchial tree was reconstructed. (see Figure 3.3).

- **Truncated three-dimensional geometry**

To study the effects of flow splits on the simulation results and also for comparison between the axisymmetric single-path model and the truncated three-dimensional model, a truncated three-dimensional geometry was created from the lung geometry. To obtain a truncated geometry along a specified path, the extra branches coming out of the path were trimmed off (see Fig. 3.4-b). The geometry was cleaned up by eliminating short and dangling edges. The rest of the procedure is similar to what was done for the full geometry of the lung.

### 3.1.2 Axisymmetric Single-path Models

To create a corresponding axisymmetric single-path model, the volume, $V$, and wetted surface area, $S$, of a truncated geometry of the selected path in the three-dimensional geometry were first determined in FLUENT. Each branch was considered to begin at the outflow of its immediately-upstream bifurcation, and end at the outflow of its immediately-downstream bifurcation. The hydraulic radius, $R_h$, and the cylindrical-equivalent length, $L_c$, of each branch were calculated according to $R_h = \frac{2V}{S}$ and $L_c = \frac{S}{2\pi R_h}$. All lengths were then scaled by the hydraulic radius of the trachea. In the axisymmetric single-path model, branches and transition regions (corresponding to bifurcations) were respectively created as cylinders and frustums of cones. The length of each transition region was equal to the average of the radii of its adjacent branches (see Figure 3.4).

After creating the single-path geometry, boundary types were identified, and the geometry was meshed using quad elements of uniform dimensionless size 0.02.
The meshing process took 3 minutes on the same PC used for meshing the three-
 dimensional geometry. The resulting mesh was then exported to FLUENT 6.3 (ANSYS, Canonsburgh, PA) for the simulations.

3.2 Problem Formulation and Boundary Conditions

For incompressible laminar flow of a binary gas-mixture of air and ozone, the flow field is governed by continuity and Navier-Stokes equations given by

\begin{equation}
\nabla \cdot \mathbf{u} = 0
\end{equation}

\begin{equation}
\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} = -\nabla p + \frac{1}{Re} \nabla^2 \mathbf{u}
\end{equation}

where \( \mathbf{u} \) and \( p \) are the dimensionless velocity and dynamic pressure, respectively, and \( \nabla \) is the dimensionless gradient operator. All lengths are made dimensionless with the hydraulic radius of the trachea, \( R_0 \), velocities with \( U_0 = Q_0/\pi R_0^2 \), time with \( R_0/U_0 \), and pressure with \( \rho U_0^2 \), where \( \rho \) denotes the density of the gas mixture, and \( Q_0 \) denotes the volumetric flow rate through the trachea. The dimensionless parameter \( Re = U_0 R_0 / \nu \) appearing in Equation 3.2 represents the tracheal Reynolds number, with \( \nu \) denoting the kinematic viscosity of the gas mixture. Equations 3.1 and 3.2 were solved subject to the following boundary conditions:

- Uniform velocity (\( \mathbf{u} \cdot \mathbf{n} = 1 \)) normal to the inflow plane of the trachea.
- Zero velocity (\( \mathbf{u} = 0 \)) at the airway wall (no-slip condition).
- Zero viscous normal stress (\( \mathbf{n} \cdot (\nabla \mathbf{u} + (\nabla \mathbf{u})^T) = 0 \)) at the outflow boundaries.
- Prescribed pressure at the outflow boundaries, or alternatively prescribed volumetric flow rates with the flow splits among outflow boundaries proportional to their cross-sectional areas.
The $O_3$ concentration distribution is governed by the convection-diffusion equation, which can be written as

$$\frac{\partial C}{\partial t} + u \cdot \nabla C = \frac{1}{Pe} \nabla^2 C,$$

where the concentration $C$ is made dimensionless with the inlet $O_3$ concentration, $C_0$, $Pe = U_0 R_0 / D_g$ is the tracheal Peclet number, and $D_g$ denotes the gas phase diffusivity of $O_3$. The boundary conditions for this equation include:

- Uniform $O_3$ concentration ($C = 1$) at the inflow boundary.
- Zero diffusive flux, $n \cdot \nabla C = 0$, at the outflow boundaries
- An appropriate diffusion-reaction condition at the airway wall (two alternative models of the reaction of $O_3$ within the RTLF were used.).

Several different reactions can take place between $O_3$ and the RTLF components consisting of proteins, amino acids, carbohydrates and lipids. Due to a lack of reliable kinetic data for these reactions, we use simplified models for the reaction rates. The simplest model that is considered in our simulations is an infinitely fast reaction. In this model, the rate of reaction is so fast compared to the rate of $O_3$ transport to the RTLF that the $O_3$ concentration vanishes at the gas-RTLF interface, leading to the boundary condition $C = 0$ at the airway wall. Although using an infinite reaction rate overestimates the rate of $O_3$ uptake, it also magnifies the non-uniformity in the wall flux distribution, and facilitates the identification of hot spots of $O_3$ flux (which is one of the main objectives of this study).

In reality, the rate of reaction of $O_3$ in the RTLF is finite. Hence, a second model for the reaction between $O_3$ and RTLF substrates is formulated by considering the substrate concentrations in the RTLF to be much higher than the $O_3$ concentration that can result from any reasonable $O_3$ exposure. In that case, the reaction can be viewed as a pseudo-first order reaction with respect to $O_3$ concentration in the RTLF. Neglecting convection in the RTLF, the quasi-steady diffusion and reaction of $O_3$ within the RTLF is described by the species conservation equation
\[ \nabla^2 c = Da^2 c, \quad (3.4) \]

where \( c \) is the \( O_3 \) concentration in the RTLF (made dimensionless with \( C_0 \)) and the Damkohler number \( Da = \sqrt{\frac{k_r \Delta^2}{D_t}} \) represents the ratio of the characteristic time for diffusion to that for chemical reaction, with \( D_t \) denoting the diffusivity of \( O_3 \) in the RTLF, \( \Delta \) the thickness of the RTLF layer, and \( k_r \) the pseudo-first order reaction rate constant. The thickness of the RTLF layer is typically much smaller than the airway radius. In the human respiratory tract, it decreases with longitudinal position from about 10 \( \mu m \) in the upper airways to about 0.1 \( \mu m \) in the respiratory zone \([17]\), while the airway radii vary in the range 0.02 – 0.09 cm depending on the airway generation \([13]\). As such, a planar (rather than annular) view of the RTLF can be adopted in conjunction with the lubrication approximation to reduce Equation (3.4) to

\[ \frac{\partial^2 c(y, z)}{\partial y^2} = Da^2 c(y, z), \quad (3.5) \]

where \( y \) and \( z \) denote the coordinates (made dimensionless with \( \Delta \)) normal and tangent to the gas-RTLF interface, respectively. Solving this equation subject to boundary conditions consisting of vanishing \( O_3 \) concentrations at the RTLF-tissue interface and local equilibrium between the \( O_3 \) concentrations on the two sides of the gas-RTLF interface (i.e. \( c = \alpha C \) at the gas-RTLF interface, where \( \alpha \) is the equilibrium partition coefficient) yields the following \( O_3 \) concentration profile within the RTLF:

\[ c(y, z) = \frac{\alpha C(z) \sinh[Da(1 - y)]}{\sinh(Da)} \quad (3.6) \]

The resulting expressions for the dimensionless \( O_3 \) flux into the RTLF layer and the underlying tissue, respectively, are given by

RTLF: \[ \frac{\partial c}{\partial y} |_{y=0} = \alpha C(z) Da \coth(Da) \quad (3.7) \]

and
\[
\text{Tissue} : \quad \frac{\partial c}{\partial y} \bigg|_{y=1} = \frac{\alpha C(z) Da}{\sinh(Da)}
\]  

(3.8)

Using Equation (3.7) in conjunction with the requirement that the \(O_3\) flux be continuous across the gas-\textit{RTLF}\ interface then yields the effective wall reaction condition

\[
-\mathbf{n} \cdot \nabla C = KC ; \quad K = \left( \frac{D_1}{D_g} \right) \left( \frac{R_0}{\Delta} \right) \alpha Da \coth(Da),
\]  

(3.9)

which can be used as a boundary condition for the gas phase convection-diffusion equation (Equation (3.3)) in the computations based on the pseudo-first order reaction model.

The ozone flux to the tissue is an exponentially decreasing function of Damkohler number. Even for values of the pseudo-first order rate constant, at the low end of the wide range of values reported in the literature [15, 67, 17], the time scale for \(O_3\) diffusion across the \textit{RTLF}\ is larger than the time scale for reaction in all airways considered in this study, leading to values of the Damkohler number that are at least \(O(1)\) even in the smallest airways. As a result, the ozone flux to the tissue is essentially zero in all airway branches considered in this study, indicating that ozone is completely consumed under sequential reactions within the mucus layer before reaching the \textit{RTLF}-tissue interface.

### 3.3 Implementation in Fluent

FLUENT is a state-of-the-art computer program for modeling fluid flow, heat transfer, and chemical reactions in complex geometries. This powerful \textit{CFD}\ package provides the ability to solve flow problems using unstructured meshes in complex geometries. FLUENT uses a finite-volume-based technique to convert a general scalar transport equation to an algebraic equation that can be solved numerically. This control volume technique consists of integrating the transport equation about each control volume, yielding a discrete equation that expresses the conservation law on a control-volume basis. For a more detailed description of the numerical solution procedure, see FLUENT Documentation [3].
The FLUENT serial solver manages file input and output, data storage, and flow field calculations using a single solver process on a single computer. FLUENT also has a parallel solver which allows computing a solution using multiple processes that may be executing on the same computer, or on different computers in a network. Parallel processing in FLUENT involves an interaction between FLUENT, a host process, and a set of compute-node processes. FLUENT interacts with the host process and the collection of compute nodes using the cortex user interface utility. Cortex manages FLUENT’s user interface and basic graphical functions. Figures 3.5 and 3.6 illustrate the serial and parallel FLUENT architectures.

After a mesh has been read into FLUENT, all remaining operations are performed within FLUENT. These include defining fluid properties, setting boundary conditions, executing the solution, refining the mesh, and postprocessing and viewing the results. An important step in the setup of the model is to define the materials and their physical properties; FLUENT solves the equations in dimensional form. Therefore, to solve the dimensionless equations, density was set equal to 1, viscosity to $1/Re$ and diffusivity to $1/Pe$. The transport equations for steady laminar flow of a binary mixture of ozone and air was solved by FLUENT with constant properties (assuming the dilute mixture approximation). The species transport, and wall surface reaction options were enabled for the simulations with a first-order wall reaction. The rate of reaction was specified by using the laminar finite-rate model in FLUENT.

The three-dimensional forms of the governing equations and their corresponding boundary conditions were solved using FLUENTs segregated implicit solver, which solves the governing equations sequentially, in conjunction with the SIMPLE algorithm for pressure-velocity coupling. The flow and species conservation equations could be solved sequentially rather than simultaneously because changes in gas composition due to $O_3$ transport lead to negligible changes in density and viscosity of the gas mixture. A second-order accurate flux-limiting upwind scheme was implemented in FLUENT to reduce numerical diffusion while avoiding numerical instabilities in these convection-dominated simulations. The computations were started by initializing the flow and concentration fields throughout the domain to their respective values at the inflow boundary.
Convergence to steady state was achieved when successive changes in the dimensionless average velocity and \( O_3 \) molar flow rate at the outflow boundary did not exceed \( 10^{-4} \) for at least 100 iterations. At that point, the residuals for the continuity, Navier-Stokes, and convection-diffusion equations were all reduced to less than \( 10^{-5} \) (See FLUENT Documentation for the definition of the residuals). User-defined functions written in C++ were used to compute the flux of \( O_3 \) into the RTLF, where applicable [3].

Simulations for the single-path model were performed in FLUENT using a single processor. Each single-path model simulation took an average of 2 hours for 5000 iterations on a 2.99 GHz Pentium(R) PC with 3.5 GB of RAM. In contrast, the CFD calculations for the three-dimensional model of the complete respiratory tract required an average of 10 days for 5000 iterations running in shared memory parallel mode on 8 processors of a 20-node Beowolf clusters with dual 3.0 GHz Intel Xeon processors.
Figure 3.1. MRI images of the lung cast.
Figure 3.2. (a) Three-dimensional reconstruction of the lung in AMIRA, and (b) The tracheobronchial tree geometry in GAMBIT.
Figure 3.3. Three-dimensional models of: (a) The tracheobronchial tree, (b) The tracheobronchial tree with the larynx, and (c) The complete respiratory tract of the rhesus monkey.
Figure 3.4. (a) Three-dimensional reconstruction of the tracheobronchial tree, and (b) The truncated geometry of the tracheobronchial tree (the right middle lobe), (c) Axisymmetric single-path model.

Figure 3.5. Serial ANSYS FLUENT architecture [3]
Figure 3.6. Parallel ANSYS FLUENT architecture [3]
Chapter 4

Comparison of Axisymmetric Single-Path and Truncated Three-Dimensional Models

Simulation of gas transport through the first 13 generations along the right middle lobe of the monkey lung was performed using a two-dimensional axisymmetric single-path model to predict the longitudinal distribution of $O_3$ uptake into the mucus and underlying epithelium. The purpose of this chapter is to compare these simulation results to three-dimensional simulations in a more realistic truncated airway geometry with truncated side branches. We show that the axisymmetric single-path model results are in good agreement with the three-dimensional simulations. Thus, an axisymmetric single-path model can be developed to predict the dose distribution of an inhaled toxicant in the respiratory tract.

4.1 CFD Simulations

Simulations of $O_3$ transport and uptake were performed for the truncated geometry of the right middle lobe reconstructed from MRI images of the lung cast of a 6-month-old male rhesus monkey weighing 1.74 kg. The daily air intake, $I$ (in $m^3$), of a monkey based on its body weight, $W$ (in kg), has been reported as [68]:

[Note: The citation [68] is not included in the text as it is not provided in the given content.]
leading to an estimated inspiratory flow rate of 12.27 ml/s. Based on the hydraulic radius of the trachea (2.3938 mm), and $\nu = 0.17 \text{ cm}^2/\text{s}$, the calculated volumetric flow rate corresponds to quiet breathing conditions at a tracheal Reynolds number of 98. Simulations were performed for Reynolds numbers of 98, 392, and 784. Using a value of $Sc = 0.85$ for the $O_3$/air mixture [69], the corresponding values of Peclet number in the simulations were 83, 333, and 666.

For the flow simulations, the no-slip condition was imposed at the airway walls. Uniform velocity normal to the inflow plane, and zero viscous normal stress at the outflows were also imposed. The flow was split in proportion to the cross-sectional areas of the outflows. Equations 3.1 and 3.2 were solved subject to the above boundary conditions.

For $O_3$ transport simulations, zero $O_3$ concentration (corresponding to an infinitely-fast reaction) or a flux proportional to $O_3$ concentration (corresponding to the rate of a pseudo-first order reaction between $O_3$ and substrates in the RTLF) was imposed at the airway walls. The concentration and flux of $O_3$ are functions of $Da$, which depends on both the reaction rate constant, $k_r$, and RTLF thickness, $\Delta$.

The values of RTLF thickness, $\Delta$, and airway hydraulic radius ($R_H$) for each generation in the conducting airways of the human lung are shown in Table 4.1. The data in this Table were fit using a power law function (as shown in Figure 4.1) to estimate the RTLF thickness for any airway radius.

Assuming that the dependence of the RTLF thickness on airway radius in each generation is the same for the human and rhesus monkey lungs, and based on a hydraulic radius of 2.3938 mm for the trachea, the thickness of the mucus layer in generation 0 (trachea) of the rhesus monkey lung was estimated to the 6.35 $\mu$m. For this value of the RTLF thickness, the value of $Da = 3$ used in the simulations with the pseudo-first order reaction model, corresponds to a rate constant on the order of 1000 s$^{-1}$ which represents the lower end of the values reported in the literature [15, 67, 17]. Based on values of $D_l = 2.66 \times 10^{-5} \text{ cm}^2/\text{s}$ [17], $R_h/\Delta = 900$ [17, 13], and $\alpha = 0.145$, Equation 3.3 was solved subject to wall boundary condition to determine the $O_3$ concentration field.
Table 4.1. *RTLF* thickness and Airway Radius in the Conducting Airways

<table>
<thead>
<tr>
<th>Generation</th>
<th>$R_h$ (cm) [13]</th>
<th>$\Delta$ [$\mu$m] [17]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.9</td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>0.61</td>
<td>8.6</td>
</tr>
<tr>
<td>2</td>
<td>0.415</td>
<td>7.2</td>
</tr>
<tr>
<td>3</td>
<td>0.28</td>
<td>6.81</td>
</tr>
<tr>
<td>4</td>
<td>0.225</td>
<td>6.41</td>
</tr>
<tr>
<td>5</td>
<td>0.175</td>
<td>6.02</td>
</tr>
<tr>
<td>6</td>
<td>0.14</td>
<td>5.63</td>
</tr>
<tr>
<td>7</td>
<td>0.115</td>
<td>5.23</td>
</tr>
<tr>
<td>8</td>
<td>0.093</td>
<td>4.84</td>
</tr>
<tr>
<td>9</td>
<td>0.077</td>
<td>4.45</td>
</tr>
<tr>
<td>10</td>
<td>0.065</td>
<td>4.06</td>
</tr>
<tr>
<td>11</td>
<td>0.0545</td>
<td>3.66</td>
</tr>
<tr>
<td>12</td>
<td>0.0475</td>
<td>3.27</td>
</tr>
<tr>
<td>13</td>
<td>0.041</td>
<td>2.88</td>
</tr>
<tr>
<td>14</td>
<td>0.037</td>
<td>2.48</td>
</tr>
<tr>
<td>15</td>
<td>0.033</td>
<td>2.09</td>
</tr>
<tr>
<td>16</td>
<td>0.03</td>
<td>1.70</td>
</tr>
</tbody>
</table>

As mentioned in Chapter 3, the effect of *RTLF* thickness on $O_3$ uptake is characterized by Damkohler number. Table 4.2 shows the hydraulic radius, *RTLF* thickness, $Da$, and $K$ (the rate of the wall reaction defined in Equation 3.9) in the airway generations of the truncated geometry of the right middle lobe. Although $Da$ changes from generation to generation, $K$ remains almost constant in all generations. The largest percentage difference (6%) occurs in the last generation. These calculations show that the rate of uptake is generally insensitive to the thickness of *RTLF* except at very low $Da$ ($Da << 1$).

### 4.2 Simulation Results

In order to facilitate the presentation of results for the truncated three-dimensional geometry, axial position within each branch was specified using a line (hereafter referred to as the branch axis) connecting the centers of mass of the inlet and outlet cross-sections of the branch, as shown in Figure 4.2.
4.2.1 Flow Field

Contour maps of the dimensionless velocity magnitude for $Re = 98$ are presented in Figure 4.3 for both the axisymmetric single-path and three-dimensional models. More than 75% of the flow leaves the central airway through the first three outlets (first outlet: 32%, second outlet: 17%, and the third outlet: 28%). As flow enters the right middle lobe, dramatic reduction in the airway cross-sectional area (by 85%) causes the velocity to increase immediately after the third bifurcation within branch IV (between planes 6 and 8).

In the three-dimensional geometry, the velocity distribution is not symmetric over the cross-sections. It is skewed toward one side of the branch, because of the asymmetry in the airway geometry. For example, in the bifurcation at the junction of major pathway in the right lobe and the right middle lobe, the flow distribution in plane 6 (inlet of branch IV) is skewed toward the outer wall of the right middle
In the axisymmetric single-path model, the velocity profile is symmetric over branch cross-sections. As we move to the downstream branches, the local Reynolds number of the flow decreases and the velocity profile approaches the fully-developed parabolic profile more quickly as the boundary layer on the airway wall grows more rapidly with axial distance from the inlet.

### 4.2.2 Concentration Distribution

The distributions of dimensionless $O_3$ concentration for the axisymmetric single-path and the truncated three-dimensional models are shown in Figure 4.4 for the case of the infinitely-fast reaction at $Re = 98$. The computed $O_3$ concentration distribution is qualitatively similar to the corresponding distribution of the velocity magnitude. In the axisymmetric single-path model, the concentration profile over each cross-section is symmetric, whereas the concentration distribution in the three-dimensional model is skewed toward one side of the airway because of the significant asymmetry in the airway geometry.

As shown in Figure 4.4, the high $O_3$ concentration portion of the flow leaves the truncated three-dimensional geometry through the third outflow as the flow enters the right middle lobe from the major pathway in the right lobe. Almost all

<table>
<thead>
<tr>
<th>Generation</th>
<th>$R_h(cm)$</th>
<th>$\Delta(\mu m)$</th>
<th>$Da$</th>
<th>$K$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.3348</td>
<td>6.27</td>
<td>3.00</td>
<td>0.0222</td>
</tr>
<tr>
<td>2</td>
<td>2.2990</td>
<td>6.23</td>
<td>2.98</td>
<td>0.0222</td>
</tr>
<tr>
<td>3</td>
<td>1.9423</td>
<td>5.81</td>
<td>2.78</td>
<td>0.0223</td>
</tr>
<tr>
<td>4</td>
<td>0.9354</td>
<td>4.28</td>
<td>2.05</td>
<td>0.0228</td>
</tr>
<tr>
<td>5</td>
<td>0.8199</td>
<td>4.05</td>
<td>1.94</td>
<td>0.0230</td>
</tr>
<tr>
<td>6</td>
<td>0.7784</td>
<td>3.96</td>
<td>1.90</td>
<td>0.0231</td>
</tr>
<tr>
<td>7</td>
<td>0.7594</td>
<td>3.92</td>
<td>1.88</td>
<td>0.0232</td>
</tr>
<tr>
<td>8</td>
<td>0.6731</td>
<td>3.73</td>
<td>1.78</td>
<td>0.0234</td>
</tr>
<tr>
<td>9</td>
<td>0.6315</td>
<td>3.63</td>
<td>1.74</td>
<td>0.0235</td>
</tr>
<tr>
<td>10</td>
<td>0.6683</td>
<td>3.72</td>
<td>1.78</td>
<td>0.0234</td>
</tr>
<tr>
<td>11</td>
<td>0.5830</td>
<td>3.51</td>
<td>1.68</td>
<td>0.0237</td>
</tr>
</tbody>
</table>

**Table 4.2.** $Da$ and $K$ in each generation of the right middle lobe

lobes. In contrast, the flow distribution in planes 7 and 8 within branch IV were skewed toward the inner wall.
of the \( O_3 \) is consumed when the flow reaches plane 16 at the end of the airway geometry in the right middle lobe.

The axial distribution of the cross-sectional average of \( O_3 \) concentration within each branch in the three-dimensional structure is shown in Figure 4.6 for the case of an infinitely fast reaction at Reynolds numbers of 98, 392, and 784. The axial position of any cross-section within a branch was defined as its distance from the inlet plane of the branch along the branch axis. This distance was normalized by the length of the branch (the distance between the centers of mass of the inlet and outlet planes of the branch).

In this Figure, the \( O_3 \) concentration is averaged over cross-sections normal to the branch axis, and the length of each branch is normalized by scaling with the length of the branch axis. As Reynolds number increases, the average concentration within each branch increases. At higher Reynolds numbers, the flow leaves each branch more quickly, and there is less time for \( O_3 \) to react with the components of the \( RTLF \) layer.

In the three-dimensional model, the asymmetry and bending of the airway in conjunction with the non-uniformity in the cross-sectional area of each branch cause changes in the local flow pattern. As a result, the average \( O_3 \) concentration is not reduced monotonically along the branches in contrast to the behavior predicted by the axisymmetric single-path model. The sudden drop in \( O_3 \) concentration after the third bifurcation occurs because of the prominent bend in the geometry of the airways where the gas moves from the major airway into a minor airway.

The corresponding axial concentration profiles for the axisymmetric single-path model are shown in Figure 4.5. The average \( O_3 \) concentration along each branch decreases monotonically because of the nature of the airways and the uniform cross-sectional area of each branch. At the end of each branch, a large amount of low \( O_3 \)-concentration fluid near the airway wall leaves the branch through the leaky transition region representing the flow through the missing daughter branches. This leads to a sudden increase in average \( O_3 \) concentration at the beginning of the next branch as reflected by the apparent discontinuity in the average \( O_3 \) concentration at the beginning of each branch in Figure 4.5. The same effect is observed in the simulation results shown in Figure 4.6 for the three-dimensional
Comparison of the simulation results for the axisymmetric single-path and three-dimensional models are shown in Figures 4.7 and 4.8, respectively for the infinitely fast and pseudo-first order reaction models at $Re = 98$. The minimum values of the vertical axis in two Figures are different. Ozone concentration in the infinitely-fast reaction varies in the range of $0 - 1$ while in the first-order reaction, it varies between 0.95 and 1.00. There is good agreement between the average concentration profiles for both reaction models, specially in the trachea with its nearly cylindrical shape. As expected, the average $O_3$ concentration for the pseudo first-order reaction model is much higher than that for the infinitely-fast reaction. In the case of the pseudo first-order reaction, most of the $O_3$ is transported to the airways beyond the distal end of the path considered in the simulated structure.

4.2.3 Streaklines Color-labeled by Ozone Concentration

The computed velocity and concentration fields for the infinitely-fast reaction model with $Re$ of 98 were imported to FIELDVIEW (Intelligent Light, Rutherford, NJ) for visualization. To visualize the results in the three-dimensional model, a set of seeds was introduced into the flow at the inlet of the trachea. The motion of the seeds within the airway structure was then followed to produce streaklines shown in Figure 4.9. The streaklines are color-labeled according to the local $O_3$ concentration, with red representing high concentration and blue denoting zero concentration.

It is interesting to note that the dramatic bending of the three-dimensional structure near the first and third bifurcations causes a significant amount of high-ozone-concentration gas to leave the main path through the daughter branches excluded from the main path. This is consistent with the results presented earlier for the $O_3$ concentration profile in the truncated three-dimensional model. Development of swirling flow near the walls of the trachea and the next two generations along the the major pathway in the right lobe causes the low-ozone-concentration fluid to leave the airway geometry. Other computations at high Reynolds numbers show that flow separation along the outer wall of the right middle lobe results in region of backflow.
4.2.4 Flux Distribution

In the axisymmetric single-path model, a local maximum in the $O_3$ wall flux appears after each transition region (see Figure 4.10). A new concentration boundary layer begins to develop on the airway wall as the flow enters each branch. Large local wall fluxes develop near the inlet of each branch, where the thickness of the boundary layer is very small (compared to the airway radius). The highest wall flux appears right after the third bifurcation. This is due to a significant reduction in the airway cross-sectional area as the gas moves from a major path into a minor path. This leads to a much higher local $O_3$ concentration in the vicinity of the airway wall on which a new concentration boundary layer begins to develop.

In the truncated three-dimensional model, hot spots of $O_3$ wall flux occur at the carina of the bifurcations, specially in the first and third bifurcations along the major path as shown in Figures 4.11 and 4.12. The prominent bend in the air flow path causes a stream of high concentration gas near the center of the airway to come into near contact with the airway wall over which the reaction occurs. Spikes in $O_3$ wall flux appear downstream of each bifurcation, with the magnitude of the spikes decreasing with each successive branching generation. The appearance of the spikes in wall flux downstream of bifurcations is due to the development of a thin concentration boundary layer on the airway wall, starting from the carina. As the flow enters the downstream branches, the local Reynolds number of the flow decreases. At lower Reynolds numbers, the thickness of the concentration boundary layer on the airway wall at any fixed distance downstream of the carina will be larger, thereby leading to a smaller $O_3$ flux on the airway wall.

4.2.5 Mass Transfer Coefficient

- Local Sherwood Number

A local mass transfer coefficient can be used to characterize the interphase transport of $O_3$ between the RTLF and air at any point on the airway wall. Empirical relationships for the dependence of local mass transfer coefficients on flow parameters have been widely investigated for both laminar and turbulent flow through conduits. The local mass transfer coefficient, $h$, is defined
as

\[ h = \frac{-D_g (\mathbf{n} \cdot \nabla C)}{(C_{avg} - C_w) R_0} \]  \hspace{1cm} (4.2)

where \( C_{avg} \) is the dimensionless average \( O_3 \) concentration over any cross-section normal to branch axis, and \( C_w \) and \( -(\mathbf{n} \cdot \nabla C) \) denote the dimensionless circumferential averages of \( O_3 \) wall concentration and flux over the cross-section, respectively. It follows from Equation (4.2) that

\[ Sh = \frac{h R_0}{D_g} = \frac{(\mathbf{n} \cdot \nabla C)}{C_{avg} - C_w} \]  \hspace{1cm} (4.3)

The local Sherwood number, \( Sh \), is a dimensionless local mass transfer coefficient. For the case of an infinitely fast reaction, \( C_w = 0 \) and the local Sherwood number is given by

\[ Sh = \frac{-\mathbf{n} \cdot \nabla C}{C_{avg}} \]  \hspace{1cm} (4.4)

The circumferential average of wall flux is computed by isoclipping the airway wall into equal bands in the axial coordinate direction. The area weighted average of wall flux for each band is then computed. As the size of the axial band is reduced, the area weighted average of flux over the band reduces to the circumferential average of wall flux over the cross-section corresponding to the infinitesimally thin band. The average concentration, \( C_{avg} \), was computed as an area-weighted average over the inlet plane of each band according to

\[ C_{avg} = \frac{1}{A} \int C \, dA \]  \hspace{1cm} (4.5)

where \( C \) and \( A \) are the local \( O_3 \) concentration over the inlet plane and the area of the inlet plane, respectively.

Local Sherwood numbers based on the hydraulic radius of the trachea were calculated for each generation along the selected path in the axisymmetric
single-path and three-dimensional models. The axial profiles of the local Sherwood number are plotted in Figures 4.13 and 4.14 for the two models, respectively. As mentioned before, the largest $O_3$ flux on the airway wall is found right after the third bifurcation. The large reduction in the cross-sectional area causes the high concentration gas jetting through the center of the airway to come into near contact with the airway wall over which the reaction occurs. In effect, this leads to a larger driving force for mass transfer across the concentration boundary layer. In the three-dimensional model, asymmetry of the flow and $O_3$ concentration distributions leads to significant asymmetry in the wall distribution of $O_3$ flux, and thus the local Sherwood number, along the selected path.

At higher Reynolds numbers, the thickness of the concentration boundary layer on the airway wall at any given distance downstream of the carina will be smaller, thereby leading to a larger $O_3$ flux on the airway wall. As a result, the local Sherwood number increases as the Reynolds number becomes larger, even though the average $O_3$ concentration on any cross-section increases with increasing $Re$. Figure 4.15 shows a comparison of the values of the local Sherwood number for the truncated three-dimensional and axisymmetric single-path models at tracheal Reynolds number of 98. It is remarkable that despite the large qualitative difference in airway configuration between the two models, the local mass transfer coefficients are comparable in magnitude and show qualitatively similar variation with airway generation.

- **Average Sherwood Number**

The average Sherwood number, $\bar{Sh}$, for each branch based on the hydraulic radius of the branch is determined by integrating Equation (4.4) over the wall surface area of the branch. It is related to the dimensionless $O_3$ uptake, $M$, in each branch according to

$$\bar{Sh} = \frac{R}{R_0} \cdot \frac{M}{A_w C_{avg}}$$  (4.6)

where $\frac{R}{R_0}$ is the ratio of the hydraulic radius of the branch to that of the trachea, $A_w$ is the dimensionless wall area of the branch, and $C_{avg}$ denotes
the average $O_3$ concentration over the entire volume of the branch, which is calculated by integrating of the cross-sectional average, $C_{avg}$ over the length of the branch. The dimensionless rate of $O_3$ uptake is calculated from the overall mass balance of $O_3$ over each branch according to

$$M = Pe_0 \left\langle \int C \, u \cdot n \, dA \right\rangle$$

(4.7)

where the brackets around the integral denote the difference between the values of the integral over the inflow and outflow boundaries of the branch, and the Peclet number $Pe_0 = \frac{u_0 R_0}{D_g}$ is defined based on the hydraulic radius of the trachea.

The computed values of average Sherwood number for each branch are presented in Tables 4.3 and 4.4 for the axisymmetric single-path and truncated three-dimensional models, respectively. The Reynolds numbers shown in these Tables are based on the hydraulic radius of the trachea. For these Reynolds numbers, the flow in the trachea is expected to be of boundary layer type namely, the flow can be divided up into two unequally large regions; the inviscid bulk flow where viscosity can be neglected, and a very thin boundary layer near the wall where the effect of viscosity must be taken into account. A similar boundary layer for mass transfer develops near the wall wherein the effect of the wall reaction (i.e. zero concentration at the wall) is experienced by the gas mixture. For large Schmidt number ($SC >> 1$) and laminar flow within the boundary layer, the average Sherwood numbers within a parallel plate channel with an infinitely-fast wall reaction is given by

$$Sh_l = 0.664 \, Re_l^{1/2} \, Sc^{1/3}$$

(4.8)

where $Sh_l$ and $Re_l$ are based on the length ($l$) of the channel [70].

Equation (4.8) is based on a linearization of the velocity profile within the concentration profile within the concentration boundary layer. It can also be applied to flow in a tube provided that the boundary layer thickness
Table 4.3. Average Sherwood number for each branch in the axisymmetric single-path model

<table>
<thead>
<tr>
<th>branch</th>
<th>$Re_{R_0} = 98$</th>
<th>$Re_{R_0} = 392$</th>
<th>$Re_{R_0} = 784$</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>3.13</td>
<td>4.38</td>
<td>5.50</td>
</tr>
<tr>
<td>II</td>
<td>3.02</td>
<td>5.38</td>
<td>8.44</td>
</tr>
<tr>
<td>III</td>
<td>2.83</td>
<td>4.82</td>
<td>7.00</td>
</tr>
<tr>
<td>IV</td>
<td>2.93</td>
<td>4.62</td>
<td>6.16</td>
</tr>
<tr>
<td>V</td>
<td>2.51</td>
<td>3.69</td>
<td>5.09</td>
</tr>
<tr>
<td>VI</td>
<td>2.69</td>
<td>3.92</td>
<td>5.59</td>
</tr>
<tr>
<td>VII</td>
<td>2.39</td>
<td>3.21</td>
<td>4.38</td>
</tr>
<tr>
<td>VIII</td>
<td>2.60</td>
<td>3.58</td>
<td>4.94</td>
</tr>
<tr>
<td>IX</td>
<td>2.59</td>
<td>3.41</td>
<td>4.56</td>
</tr>
<tr>
<td>X</td>
<td>2.60</td>
<td>3.09</td>
<td>3.88</td>
</tr>
<tr>
<td>XI</td>
<td>2.50</td>
<td>3.15</td>
<td>4.09</td>
</tr>
</tbody>
</table>

Table 4.4. Average Sherwood number for each branch in the truncated three-dimensional model

<table>
<thead>
<tr>
<th>branch</th>
<th>$Re_{R_0} = 98$</th>
<th>$Re_{R_0} = 392$</th>
<th>$Re_{R_0} = 784$</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>3.06</td>
<td>5.62</td>
<td>8.17</td>
</tr>
<tr>
<td>II</td>
<td>3.90</td>
<td>8.35</td>
<td>9.93</td>
</tr>
<tr>
<td>III</td>
<td>2.76</td>
<td>6.43</td>
<td>8.08</td>
</tr>
<tr>
<td>IV</td>
<td>2.69</td>
<td>5.35</td>
<td>9.15</td>
</tr>
<tr>
<td>V</td>
<td>2.86</td>
<td>7.49</td>
<td>10.30</td>
</tr>
<tr>
<td>VI</td>
<td>2.84</td>
<td>6.25</td>
<td>9.34</td>
</tr>
<tr>
<td>VII</td>
<td>2.36</td>
<td>5.01</td>
<td>5.87</td>
</tr>
<tr>
<td>VIII</td>
<td>2.10</td>
<td>3.66</td>
<td>4.44</td>
</tr>
<tr>
<td>IX</td>
<td>1.84</td>
<td>3.31</td>
<td>4.08</td>
</tr>
<tr>
<td>X</td>
<td>2.25</td>
<td>4.58</td>
<td>7.46</td>
</tr>
<tr>
<td>XI</td>
<td>1.58</td>
<td>2.95</td>
<td>4.51</td>
</tr>
</tbody>
</table>

remains small compared to the tube radius so that the wall curvature can be neglected. In that case, Equation (4.8) can be rewritten for flow and mass transfer in a tube as

$$\bar{Sh} = 0.664 \left( l \right)^{-1/2} Re^{1/2} Sc^{1/3}$$

(4.9)

where $l$ is the dimensionless length of the tube (made dimensionless with the tube radius), and both $\bar{Sh}$ and $Re$ are based on the tube radius. According to
Equation (4.9), the rate of uptake in a tube is expected to depend on $Re^{1/2}$. Hence, the value of $\bar{Sh}/Re^{1/2}$ should be independent of Reynolds number for tube-like branches if the flow is of boundary layer type.

Table 4.5 shows the Reynolds number in each branch based on the hydraulic radius of the branch.

<table>
<thead>
<tr>
<th>branch</th>
<th>$Re_{R_0} = 98$</th>
<th>$Re_{R_0} = 392$</th>
<th>$Re_{R_0} = 784$</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>98</td>
<td>393</td>
<td>787</td>
</tr>
<tr>
<td>II</td>
<td>68</td>
<td>273</td>
<td>546</td>
</tr>
<tr>
<td>III</td>
<td>61</td>
<td>245</td>
<td>489</td>
</tr>
<tr>
<td>IV</td>
<td>58</td>
<td>232</td>
<td>465</td>
</tr>
<tr>
<td>V</td>
<td>51</td>
<td>206</td>
<td>412</td>
</tr>
<tr>
<td>VI</td>
<td>45</td>
<td>178</td>
<td>356</td>
</tr>
<tr>
<td>VII</td>
<td>39</td>
<td>158</td>
<td>316</td>
</tr>
<tr>
<td>VIII</td>
<td>33</td>
<td>134</td>
<td>267</td>
</tr>
<tr>
<td>IX</td>
<td>31</td>
<td>123</td>
<td>246</td>
</tr>
<tr>
<td>X</td>
<td>26</td>
<td>106</td>
<td>211</td>
</tr>
<tr>
<td>XI</td>
<td>18</td>
<td>70</td>
<td>141</td>
</tr>
</tbody>
</table>

Table 4.5. Branch Reynolds numbers along the selected path in the right middle lobe

Computed values of $\bar{Sh}/Re^{1/2}$ for the branches in the axisymmetric single-path and truncated three-dimensional models are shown in Figures 4.16 and 4.17, respectively. As shown in Figure 4.16, values of $\bar{Sh}/Re^{1/2}$ are almost the same for tracheal Reynolds numbers of 392 and 784 in the axisymmetric single-path model. This is not surprising since all branches are straight tubes in this model. The values of $\bar{Sh}/Re^{1/2}$ for the tracheal Reynolds numbers of 98 are larger than those at higher Reynolds numbers because the branch Reynolds numbers are all too small (less than 100 as can been seen from Table 4.5) for the flow to be of boundary layer type.

In the three-dimensional model, the asymmetry of the airway structure (including bending of airways, and these non-uniform cross-sections) leads to the development of secondary flow, specially at high Reynolds numbers. The secondary flow appears in the form of a swirling flow near the airway wall and the direction of a superimposed field of flow in the boundary layer deviates
from that in the external flow. The three-dimensional nature of the resulting boundary layer flow is qualitatively different from boundary layer flow on a flat plate which was the basis for Equation (4.9) [71]. Nevertheless, the computed values of $\bar{Sh}/Re^{1/2}$ at different Reynolds numbers in each branch are about the same.

A comparison of the computed values of $\bar{Sh}/Re^{1/2}$ in the axisymmetric single-path and truncated three-dimensional models is shown in Figure 4.18 for $Re_0$ of 392. In nearly all branches, the values in the truncated three-dimensional model are larger than those in the axisymmetric single-path model indicating the average $O_3$ concentration in the three-dimensional model is lower than that in the axisymmetric single-path model.

- **Mass, Energy, and Momentum transfer analogies**

The Schmidt number and the computed values of the Sherwood number in the respiratory tract are within the allowable range [72] for application of the Chilton-Colburn analogy [73]. This analogy exists between heat and mass transfer such that the corresponding j-factors are equal. Chilton and Colburn suggested a simple variation of the Reynolds analogy that allows its application to situations where the Schmidt and Prandtl numbers are other than unity. The Chilton-Colburn analogy between steady heat, mass, and momentum transfer (when drag is negligible) states that

$$ j_D = j_H = f/2 $$

(4.10)

where $f$ is the friction factor. For a given geometry, $f$ is only a function of $Re$; thus the j-factors ($j_D$ and $j_H$) are also functions of $Re$. For viscous flow in a tube, the j-factors are defined in terms of the Sherwood and Nusselt numbers ($Sh$ and $Nu$, respectively) as [74]:

$$ j_D = \frac{Sh}{Re \cdot Sc^{1/3}} $$

$$ j_H = \frac{Nu}{Re \cdot Pr^{1/3}} $$

(4.11)
The Sherwood and Nusselt numbers can therefore be expressed as

\[ Sh = A \ g(Re)Sc^{1/3} \]
\[ Nu = A \ g(Re)Pr^{1/3} \]  \hspace{1cm} (4.12)

where \( A \) is a constant and \( g \) represents a function of Reynolds number. These relationships can be put into the following empirical form used for heat transfer within pipes

\[ Nu = A \ Re^NPr^{1/3} \]  \hspace{1cm} (4.13)

where \( N \) is a constant.

The dependence of the Sherwood number on Reynolds number can thus be inferred from a knowledge of the local heat transfer characteristics in airways. For the human upper respiratory tract, mean convective heat transfer coefficients in the nasal and oral passages have been determined during quasi-steady inspiratory and expiratory flow [75]. The results show that the Nusselt number scales as the 0.854 power of Reynolds number for nasal inhalation, and Equation (4.12) is of the form:

\[ Nu = 0.023Re^{0.854}Pr^{1/3} \]  \hspace{1cm} (4.14)

where the Reynolds and Nusselt numbers are both defined based on the diameter of the trachea. Values of \( A \) and \( N \) were also determined for oral inhalation and oral expiration. Ingenito et al. [76] determined heat transfer coefficients in the trachea and the first three generations of the human tracheobronchial tree for steady inspiratory flow. They expressed the Nusselt number in the form \( Nu = A \ (Re \cdot Pr)^b \) where \( Re \) is the tracheal Reynolds number, and the values of \( A \) and \( b \) are provided below.
Other empirical relationships have been reported by Cheng et al. [77] for inhalation and exhalation through the human oral cavity:

\[ Nu = 15.3Re^{0.812}Pr^{-0.986} \]  \hspace{1cm} (4.15)

and for the laryngeal-tracheal region

\[ Nu = 25.9Re^{0.861}Pr^{-1.37} \]  \hspace{1cm} (4.16)

where \( Re \) is based on the average hydraulic diameter of the airway passage.

To obtain relationships of the form \( \bar{Sh} = ASc^{(1/3)}Re^n \) (suggested by Equation (4.13)) between the Sherwood number and Reynolds numbers, the average Sherwood number in each branch was plotted versus the Reynolds number based on the hydraulic radius of the branch. A power-law curve-fitting routine was then utilized to obtain a least-squares fit of the form to the data. The computed values of \( A \) and \( n \) for each branch in the two models are presented in Table 4.6.

The power-law fit was also applied to the data points for all branches. The results of overall power-law fit for both the axisymmetric single-path and truncated three-dimensional models are shown in Figure 4.19. The calculated powers of Reynolds number are 0.30 and 0.50 for the axisymmetric single-path and truncated three-dimensional models, respectively. The power of \( Re \) in the axisymmetric single-path model is in good agreement with the predicted dependence of average Nusselt number in a tube with a specified wall temperature, based on the Lévéque approximation [78]. This approximation assumes that the thermal boundary layer is so thin that the curvature in
Table 4.6. Constants of the power-law fit for the $Sh$ and $Re$ data in the axisymmetric single-path and truncated three-dimensional models

<table>
<thead>
<tr>
<th>branch</th>
<th>Single-path model</th>
<th>3-D model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$A$</td>
<td>$n$</td>
</tr>
<tr>
<td>I</td>
<td>0.91</td>
<td>0.96</td>
</tr>
<tr>
<td>II</td>
<td>0.38</td>
<td>0.40</td>
</tr>
<tr>
<td>III</td>
<td>0.48</td>
<td>0.51</td>
</tr>
<tr>
<td>IV</td>
<td>0.69</td>
<td>0.73</td>
</tr>
<tr>
<td>V</td>
<td>0.67</td>
<td>0.71</td>
</tr>
<tr>
<td>VI</td>
<td>0.72</td>
<td>0.76</td>
</tr>
<tr>
<td>VII</td>
<td>0.84</td>
<td>0.88</td>
</tr>
<tr>
<td>VIII</td>
<td>0.89</td>
<td>0.94</td>
</tr>
<tr>
<td>IX</td>
<td>1.04</td>
<td>1.09</td>
</tr>
<tr>
<td>X</td>
<td>1.40</td>
<td>1.47</td>
</tr>
<tr>
<td>XI</td>
<td>1.28</td>
<td>1.35</td>
</tr>
</tbody>
</table>

The parabolic velocity profile for fully-developed laminar flow within a tube is negligible, and therefore the velocity profile can be linearized within the thermal boundary layer near the tube wall [78]. The average Nusselt number in the tube is thus found to be:

$$Nu = 1.357 L^{-1/3} Re^{1/3} Pr^{1/3}$$

(4.17)

where $Nu$ and $Re$ are based on the tube diameter, $L$ is the dimensionless length of the tube (made dimensionless with the tube radius). For mass transfer from a dilute solution to the wall of a tube on which the concentration is fixed at a prescribed value, the result for the average Sherwood number is entirely analogous to that given by Equation (4.17) for the Nusselt number, i.e. $Sh = 1.357 L^{-1/3} Re^{1/3} Sc^{1/3}$. The power of $Re$ in the truncated three-dimensional model is almost the same as that predicted by Equation (4.9) for boundary layer flow over flat plates. It indicates that developing momentum boundary layer is much thicker than developing concentration boundary layer. Computed values of the average Sherwood number in the complete axisym-
metric single-path and truncated three-dimensional geometries were also regressed with tracheal Reynolds number according to a power-law relation. The average Sherwood number for the complete structure was calculated as

\[
\bar{Sh} = \frac{M_{\text{total}}}{A_{w_{\text{total}}}C_{\text{avg}}}
\]

where \( M_{\text{total}} \) and \( A_{w_{\text{total}}} \) are equal to the sum of branch uptakes and wall areas, respectively, and \( C_{\text{avg}} \) is the average \( O_3 \) concentration in the whole geometry. The value of \( C_{\text{avg}} \) was determined according to:

\[
C_{\text{avg}} = \frac{\sum C_{i_{\text{avg}}} l_i}{\sum l_i}
\]

where \( l_i \) is the length of the \( i \)-th branch. The average Sherwood numbers for the complete structure are presented in Table 4.7 for different tracheal Reynolds numbers in the two models.

<table>
<thead>
<tr>
<th>Model</th>
<th>( Re_{R_0} = 98 )</th>
<th>( Re_{R_0} = 392 )</th>
<th>( Re_{R_0} = 784 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-path</td>
<td>4.16</td>
<td>5.96</td>
<td>7.91</td>
</tr>
<tr>
<td>3-D model</td>
<td>4.19</td>
<td>8.12</td>
<td>11.36</td>
</tr>
</tbody>
</table>

Table 4.7. Average Sherwood numbers for the complete structure in the axisymmetric single-path and truncated three-dimensional models

Based on these values of the average Sherwood number, values of 0.30, and 0.48 were found for the power \( n \) in Equation (4.13) for the axisymmetric single-path and the truncated three-dimensional models, respectively.

4.3 Resolution and Accuracy

The resolution of the simulations was tested by performing mesh refinement for the highest tracheal Reynolds number of 784 in both the axisymmetric single-path and the truncated three-dimensional models assuming infinitely-fast reaction between \( O_3 \) and the RTLF substrates. The original dimensionless mesh size for the axisymmetric single-path simulation was 0.02 and the mesh consisted of 67,695 elements. In the mesh refinement studies, the mesh size was reduced by a factor
of 2, leading to a mesh with 270,129 elements. The sensitivity of the simulation results to mesh size was examined by comparing the results for the dimensionless \( O_2 \) uptake in the branches. The maximum observed variation between the calculations was about 0.2\%, and it occurred in the trachea. For the truncated three-dimensional model, computations were performed with an original mesh of 2,486,025 tetrahedral elements. The refined mesh consisted of 6,947,270 elements with element sizes in the range of 0.016 - 0.05. The maximum observed variation in the computed value of uptake in the trachea was about 0.01\%.

The accuracy of the numerical method was also tested by performing computations for steady laminar flow of a fluid through a straight tube with the same boundary conditions as those used in the simulations. The diameter and length of the test tube were the same as the hydraulic diameter and length of the trachea. The comparison between numerical predictions and analytical results was made in terms of local Sherwood number which is the main quantity of interest in this study. The simulation results for the local Sherwood number in the trachea of the axisymmetric single-path model were calculated using Equation (4.4).

The asymptotic solution for the local Sherwood number in the entrance region of a tube with constant concentration at the wall is given by Equation (4.17). The calculation of \( Sh \) in the fully-developed region of a tube with specified concentration shows that Sherwood number becomes a constant in this region \((Nu = 3.65)\) [78]. For long enough tubes, \( Sh \) approaches a constant, even though the concentration may continue to change in the axial direction, \( z \). The position at which \( Sh \) becomes essentially constant separates the entrance region from the fully-developed region for mass transfer. Figure 4.20 shows the simulation results for local Sherwood numbers as well as the asymptotic results for both the entrance and the fully-developed regions of a tube. The entrance region results are quite accurate for \( z/R < 5 \), whereas the fully developed values are satisfactory for most purposes when \( z/R > 13.5 \) [78]. The intermediate values were reported by Shah and London [79].

As can been seen in Figure 4.20, there is good agreement between the simulation results and the asymptotic results. The maximum deviation from the analytical solution for the local Sherwood number occurred at the tube entrance due to the
presence of a singularity in the local mass transfer coefficient at the tube entrance where the thickness of the concentration boundary layer tends to zero. This singularity at \( z = 0 \) is evident in the analytical expression given by Equation (4.17) for the local Sherwood number. The lack of a sufficiently refined mesh to resolve the thin concentration boundary layer near the tube entrance eventually led to errors in the computed fluxes as \( z \to 0 \). The same source of error was present in numerical simulations of flow through a bifurcation since boundary layer development in the immediate vicinity of the flow inlet at a bifurcation is identical to that in a straight tube.
Figure 4.2. The axial lines of the airways.
Figure 4.3. Color map of velocity magnitude in: (a) the anatomically-accurate truncated three-dimensional and (b) axisymmetric single path models, $Re_0 = 98$. 
Figure 4.4. Color map of $O_3$ concentration at various cross-sections for an infinitely fast reaction and $Re_0 = 98$: (a) the anatomically-accurate truncated three-dimensional model; (b) corresponding axisymmetric single path model.
Figure 4.5. Cross-sectional average of $O_3$ concentration in each generation of the axisymmetric single-path models for an infinitely fast reaction.

Figure 4.6. Cross-sectional average of $O_3$ concentration in each generation of the truncated three-dimensional models for an infinitely fast reaction.
Figure 4.7. Cross-sectional average of $O_3$ concentration in each generation of the truncated three-dimensional and axisymmetric single-path models, ($Re = 98$) and infinitely-fast reaction.

Figure 4.8. Cross-sectional average of $O_3$ concentration in each generation of the truncated three-dimensional model and the axisymmetric single-path model, ($Re = 98$), slow first-order reaction.
Figure 4.9. Streaklines of flow color-labeled by the local $O_3$ concentration, $Re_0 = 98$ and infinitely fast reaction.
Figure 4.10. Longitudinal distribution of the dimensionless wall flux in the axisymmetric single-path model, infinitely fast reaction.

Figure 4.11. Longitudinal distribution of the dimensionless wall flux in the truncated three-dimensional model, infinitely fast reaction.
Figure 4.12. Distribution of the dimensionless wall flux in the truncated three-dimensional model, infinitely fast reaction.
Figure 4.13. Local Sherwood number in each generation of the axisymmetric single-path models, infinitely fast reaction.

Figure 4.14. Local Sherwood number in each generation of the truncated three-dimensional models, infinitely fast reaction.
Figure 4.15. Local Sherwood number in each generation of the axisymmetric single-path model and the truncated three-dimensional model, $Re_0 = 98$ and infinitely fast reaction.

Figure 4.16. $Sh/Re^{0.5}$ in each generation of the axisymmetric single-path models, infinitely fast reaction.
Figure 4.17. $Sh/Re^{0.5}$ in each generation of the truncated three-dimensional models, infinitely fast reaction.

Figure 4.18. Comparison of $Sh/Re^{0.5}$ in each generation of the axisymmetric and truncated three-dimensional models, infinitely fast reaction.
Figure 4.19. Power-law fitting of Sherwood number versus Reynolds number.

Figure 4.20. The simulation results, asymptotic solutions for the entrance and fully-developed regions.
Chapter 5

Simulation of Ozone Transport and Uptake in Three-dimensional Models of the Tracheobronchial Tree

We have simulated ozone transport and uptake using the complete three-dimensional model of the tracheobronchial tree and the truncated three-dimensional geometries (the left lobe, the right middle lobe, and the major pathway in the right lobe). The purpose of this chapter is to present the simulation results of the velocity and concentration fields and to investigate the effect of imposing different boundary conditions at the outflow boundaries. In this chapter, simulation results of the complete lung geometry using the specified flow rate condition for two tracheal Reynolds numbers (98 and 392) are presented. These results are compared to those of the case imposing zero pressure at the outflow boundaries.

The second part focuses on the effects of different procedures for flow splits in the truncated three-dimensional models. We were looking for a procedure that would allow us to get the simulation results of the complete three-dimensional geometry of the tracheobronchial tree (specially wall flux distribution and ozone uptake) using only the three-dimensional truncated geometries.
5.1 Complete Three-Dimensional Model

5.1.1 Specified Flow Rate at Outflow Boundaries

Numerical simulation of ozone transport and uptake was performed for the complete three-dimensional geometry of the tracheobronchial tree of the Rhesus monkey lung mentioned in section 3.1.1. The complete three-dimensional geometry of the tracheobronchial tree includes up to 13 generations originating from the right primary bronchus and 7 generations originating from the left primary bronchus, that terminates in a total of 78 truncated distal bronchioles that constituted the outflow boundaries of the model. The geometry was meshed using tetrahedral elements of dimensionless size 0.016 - 0.05, and consisted of about 18 million mesh elements. Simulations were performed for Reynolds numbers of 98 and 392 based on the hydraulic radius of the trachea. For the flow simulations, uniform velocity normal to the inlet cross-section of the trachea and the no-slip condition at the airway walls were imposed. The boundary condition imposed at the outflow boundaries was zero viscous normal stress in conjunction with a specified flow rate. Flow was partitioned proportional to the cross-sectional areas of the outflow boundaries. The latter condition was based on the assumption that the flow at each outlet is proportional to the total distal lung volume for that outlet, and that the distal lung volume for each outlet is itself proportional to the cross-sectional area of the outlet. This flow partitioning is supported by Balashazy [80] who showed that flow division at a bifurcation between two daughter branches was determined by the ratio of their cross-sectional areas if the ratio of their diameters was less than 3. For the concentration field, uniform ozone concentration at the inlet of the trachea, zero ozone concentration on the airway walls (corresponding to the infinitely-fast reaction), and zero diffusive flux normal to the outflow boundaries were imposed. Based on the gas properties mentioned in Chapter 4, Equations 3.1, 3.2, and 3.3 were solved subject to the above boundary conditions.

Simulation results are compared for the set of four pathways: right cranial (RC), right middle (RM), and the major pathways in the right and left lobes (R and L, respectively). In order to facilitate the comparison of results and also the calculation of ozone uptake in each generation, planes were introduced at the
inlet and outlet of each branch normal to the branch axis. Each plane is identified according to its position in one of the major pathways ($RC, RM, R$, and $L$). For example, the planes along the major pathway in the right lobe are labeled as $R_1$ (the inlet of the right lobe after the first bifurcation) to $R_{15}$ (the outlet of the major pathway in the right lobe). Other planes along the right cranial, right middle, and left lobes are labeled as $RC_1$ to $RC_{13}$, $RM_1$ to $RM_9$, and $L_1$ to $L_{14}$, respectively. Each branch is designated based on its inlet and outlet planes. For example, the first generation airway along the left lobe is labeled as $L_1L_2$. The trachea is identified as $T_0T_1$, with $T_0$ and $T_1$ denoting the inlet and outlet planes of the trachea, respectively. The various pathways, branches, and planes are shown in Figure 5.1.

### 5.1.1.1 Flow Field

Contour maps of the dimensionless velocity magnitude in selected planes along the major pathways are presented in Figure 5.2 for tracheal Reynolds numbers of 98 and 392. The non-circular shape of the trachea inlet and the asymmetry of the trachea geometry cause the velocity distribution in the trachea to be skewed toward the left bronchus. Kabilan et al. [81] suggested that the skewness of the velocity profile in the trachea is also due to the volume difference between the right and left lung lobes. In our simulations, mass flow rate through the trachea is not equally partitioned at the first bifurcation (59% through the right lobe and 41% through the left lobe) because of the asymmetry of the lung geometry and the alignment of pathway $R$ with the trachea. It is also found that the average velocity is consistently greater in pathway $R$ than in pathway $L$ at any corresponding cross-sections. This result is consistent with the finding of Kabilan et al. [81].

The flow path and velocity distribution are basically determined by the geometry. After each bifurcation, the velocity distribution becomes skewed toward the inner wall of the downstream branches. This is clearly shown in planes $R_1$, $L_1$, $RC_1$, $RM_1$, and $R_5$ of Figure 5.2. One notable exception to this pattern occurs at plane $R_3$, where velocity profile is skewed toward the outer wall of branch $R_3R_4$. Due to the pronounced asymmetry in the preceding bifurcation, this branch recieves 71% of the flow through pathway $R$. 
Increasing the tracheal Reynolds number affects the flow structure, especially in the trachea and pathway $L$ where complex secondary flow develops at high Reynolds number. This is reflected in Figure 5.3 which shows the streaklines color-labeled by velocity magnitude. This change in flow structure with Reynolds number is the reason for the small difference between the maximum dimensionless velocities of corresponding cross-sections for the two tracheal Reynolds numbers as seen in Figure 5.2.

The trachea, and $L_1 L_2$, and $R_1 R_2$ branches are not sufficiently long for the flow within these airways to become fully-developed at a tracheal Reynolds number of 98.

### 5.1.1.2 Concentration and Flux Distributions

Contour maps of $O_3$ concentration in selected planes along the different pathways are presented in Figure 5.4 for tracheal Reynolds numbers of 98 and 392. The computed $O_3$ concentration distributions are qualitatively similar to the corresponding distributions of the magnitude of velocity presented earlier, as can be seen from a comparison of Figures 5.2 and 5.4. The concentration distribution is asymmetric in the branches and skewed toward the inner walls in the downstream branches after each bifurcation. The average $O_3$ concentration in the fluid leaving the branches increases with increasing tracheal Reynolds number, due to the reduction in the residence time of $O_3$ in the airways.

As shown in Figure 5.5, corresponding $O_3$ flux distribution on the airway walls is asymmetric at both tracheal Reynolds numbers. Hot spots of $O_3$ wall flux occur at the carina of each bifurcation, with the hot spots in the first and second bifurcations of pathway $R$ being most pronounced. The magnitude of these hot spots decreases with successive branching generations. The appearance of the hot spots is due to the development of new concentration boundary layers on the inner airway walls of a bifurcation just after the flow is split at the carina. In general, increasing the tracheal Reynolds number leads to the development of thinner concentration boundary layers, which in turn produces larger $O_3$ flux on the airway walls.

Figure 5.6 shows the streaklines colored-labeled according to the local $O_3$ concentration, with red representing high concentration and blue denoting zero concen-
tration. The streaklines were created by randomly introducing virtual fluid particle “seeds” on the inlet of the trachea, and calculating the particle trajectories based on the computed velocity distribution. At each point along their trajectories, the particles are assigned by the local $O_3$ concentration computed earlier. The streaklines are consistent with the results presented earlier for the flow field and the $O_3$ concentration distribution. Development of swirling flow within the trachea and the first 2–3 generations along the main path in the right and left lobes is clearly shown by the streaklines, particularly at the higher Reynolds number (tracheal $Re$ of 392). In addition, at the higher Reynolds number, boundary layer separation along the outer walls of the first generation airways results in the development of regions of backflow. The resulting flow structure in the first bifurcation at the higher Reynolds number causes a larger of portion of high concentration fluid near the axis of the trachea to find its way into the left lobe (pathway $L$), as can been seen from the red streaklines in the first generation airway of the left lobe in Figure 5.6. Furthermore, the pronounced swirling flow within the first 2–3 airway generations causes more of the low-concentration fluid from the trachea to enter minor branches that are oriented at large angles relative to the main right and left pathways (e.g., pathway $RC$).

5.1.2 Specified Pressure at Outflow Boundaries

In this section, the simulation results obtained by imposing zero pressure at the outflow boundaries of the complete three-dimensional airway structure are presented. Based on the results of their computations for a 6-generation airway model of a human lung, Ma and Lutchen [40] concluded that using a zero-pressure condition at the outflow boundaries is unacceptably inaccurate in predicting the flow field. Since the three-dimensional airway structure considered here is a more complete anatomical model of the tracheobronchial tree that includes up to 13 generations along the main pathway in the right lobe, and more than 6 generations along all pathways, imposing a zero-pressure boundary condition at the outflows may be more appropriate, as supported by the results of Gemci et al. [36].
5.1.2.1 Flow Field

Contour maps of the dimensionless velocity magnitude in selected inlet and outlet planes along the major pathways in the three-dimensional airway structure are presented in Figure 5.7 for tracheal Reynolds numbers of 98 and 392. The velocity distributions are qualitatively similar to those reported earlier for the specified flow rate boundary condition. Namely, the velocity distributions over the inlet and outlet planes are asymmetric, with the maximum velocities skewed toward the inner wall of the downstream branches after each branch (except in the $R_3 R_4$ branch, as mentioned in section 5.1.1.1). The flow rate through the trachea is not equally partitioned at the first bifurcation; about 59% passes through the right lobe, and 41% passes through the left lobe at a Reynolds number of 98. As the Reynolds number increases to 392, the mass flow rate through the left lobe increases changing the flow split at the first bifurcation to 57% and 43% through the right and left lobe, respectively. At a tracheal Reynolds number of 98, the magnitude of average velocity is consistently larger in pathway $R$ than in pathway $L$ at corresponding cross-sections, as was also the case for the prescribed flow rate condition. At Reynolds number of 392, the magnitude of average velocity in the first two generations along the left lobe is higher than that over corresponding cross-sections in the right lobe.

Increasing the tracheal Reynolds number produces some changes in the flow structure, especially in the trachea and the $L_1 L_2$ branch, leading to difference in the velocity contour maps with increasing Reynolds number. Flow in the trachea, and $L_1 L_2$ and $R_1 R_2$ airways is not fully-developed at either of the tracheal Reynolds numbers considered. Thus, as the Reynolds number increases, the magnitude of the maximum velocity at the outlet of these airways is increased.

5.1.2.2 Concentration and Flux Distributions

Contour maps of $O_3$ concentration over selected inlet and outlet planes along the different pathways are presented in Figure 5.8 for tracheal Reynolds numbers of 98 and 392. The computed $O_3$ concentration distributions are qualitatively similar to the corresponding distributions of the magnitude of velocity. The bulk-average $O_3$ concentration over branches outlets increased with increasing tracheal Reynolds
number as a result of the reduction in the residence time of $O_3$ to react with the RTLF substrates.

The $O_3$ flux distribution on the airway walls is shown in Figure 5.9 for both Reynolds numbers. The wall flux distribution is asymmetric in all airway branches. Hot spots of wall flux occur at the carina of the bifurcations due to the development of a new concentration boundary layer on the inner walls of the daughter branches downstream of each carina. Increasing the tracheal Reynolds number leads to thinning of the concentration boundary layer everywhere and hence a larger $O_3$ flux in the vicinity of each bifurcation downstream of the carina.

The streaklines colored-labeled by the local $O_3$ concentration are shown in Figure 5.10. Due to the swirling flow, a significant amount of low-ozone concentration fluid leaves the major pathways through the first bifurcations along the right and left lobes.

### 5.1.3 Comparison of the Simulation Results for Different Boundary Conditions

The velocity, concentration, and flux distributions for the simulations with prescribed flow rate or zero pressure boundary conditions at the outlets had several common features, as described in the previous sections. Several differences were also observed, however, as detailed in following sections.

#### 5.1.3.1 Flow Field

At a tracheal Reynolds number of 98, the maximum velocities obtained using the two outlet boundary conditions are nearly the same (with a difference of less than 2%) over cross-sections in the trachea ($T_1$), the first two generations along the right lobe ($R_1, R_2, R_3,$ and $R_4$), and the first generation along the left lobe ($L_1$ and $L_2$). Contour maps of velocity magnitude over these planes are also nearly the same for the two outlet conditions. This result is consistent with the observations of Nowak et al. [51] who simulated airflow and aerosol deposition through a Weibel-based model of a human lung, as well as in a reconstructed three-dimensional geometry based on CT images of the first 9 generations along the left lobe. These
investigators segmented both geometries into subunits and applied flow boundary conditions similar to those used in this study. Their results show that there is no significant difference between the velocity fields computed using specified flow rate or pressure boundary conditions at the outlets.

As flow enters the downstream generations, contours of velocity magnitude in the two cases become different. For example, the velocity magnitudes over corresponding cross-sections of pathways $RC$ and $RM$, as well as generations 2 and higher of pathway $L$ are higher for the prescribed flow rate condition compared to those for the zero-pressure condition. Conversely, the velocity magnitudes in generations 3 and higher of pathway $R$ are higher for the zero-pressure condition compared to those for the prescribed flow rate condition. Since the geometries for the computations using the two different boundary conditions are identical, differences in mass flow rate distribution among the various branches can be used to examine the effect of the outlet boundary condition on velocity distribution.

Mass flow rates in the branches of pathways $RM$, $RC$, $L$, and $R$ are shown in Figures 5.11 and 5.12 for Reynolds number of 98. Mass flow rates through pathways $RC$, $RM$, and $L$ are higher for the prescribed flow rate condition than those for the zero-pressure condition. Conservation of mass thus requires the mass flow rates through generations 3 and higher of pathway $R$ to be higher for the zero-pressure condition than those for the prescribed flow rate condition. As a result, the average velocities in pathway $R$ should be larger for the zero-pressure boundary condition.

As the Reynolds number increases to 392, the difference in maximum velocities in planes $T_1$, $L_1$, $L_2$, $R_1$, $R_2$, and $R_3$ between the two different boundary conditions grows to a maximum of about 4%. Maximum velocities in plane $R_4$ (at the exit of the second generation along the right lobe) show about 10% variation between the two boundary conditions. Contour maps of velocity are substantially different in all other planes due to a change in flow structure at higher Reynolds number.

The computed pressure variations along the different branches are consistent with the simulation results for the mass flow rate. As shown in Figure 5.13, the computed pressure drops across pathways $RC$, $RM$, and $L$ (from the inlet of the trachea to the outflow boundaries) are higher for the prescribed flow rate
condition compared to those for the zero-pressure condition. The opposite happens in pathway \( R \), where specifying zero pressure at the outflow boundaries produces a larger pressure drop along the pathway compared to that resulting from a specified flow rate boundary condition. As the Reynolds number increases, the pressure drop along all pathways decreases.

As shown in Figures 5.14 and 5.15 for Reynolds number of 98, the pressure drops in corresponding airway branches of pathways \( L \), \( RC \), and \( RM \) are higher for the prescribed flow rate condition than those for the zero-pressure condition. Increasing the Reynolds number increases the percentage difference between the computed pressure drops using the two boundary conditions. For example, the discrepancy between the pressure drops computed for the trachea using the two boundary conditions is 0.01% to 9.6% at Reynolds numbers of 98 and 392, respectively.

### 5.1.3.2 Concentration Field

The effect of the outlet boundary condition on the computed concentration distributions is similar to its effect on the velocity distributions. The percentage difference between the maximum concentrations computed for planes \( T_1, L_1 - L_4 \), and \( R_1 - R_5 \) using the two outlet conditions is less than 2% at a Reynolds number of 98. The corresponding percentage differences at the inlets of pathways \( RC \) and \( RM \) are 1.3% and 12%, respectively. As the Reynolds number increases to 392, the difference between the two results decreases along pathways \( R \) and \( L \), but increases along pathways \( RC \) and \( RM \). For example, the percentage difference increases to 10% and 13% in planes \( RC_1 \) and \( RM_2 \), respectively at \( Re = 392 \).

Figure 5.16 shows the cross-sectional average concentration of \( O_3 \) in the specified planes along pathways \( RM \) and \( R \). For a specific Reynolds number, the average ozone concentrations over planes in pathway \( RM \) are higher for the prescribed flow rate condition than those for the zero-pressure condition. On the other hand, the average \( O_3 \) concentration in the planes of pathway \( R \) are generally higher in the case where zero pressure is imposed at the outlets. It is interesting to note that the percentage difference between the average concentrations for the two boundary conditions grows with increasing Reynolds number in planes \( R_1 - R_4, L_1 - L_4 \),
$RM_1 - RM_2$, and $RC_1$, but is reduced over planes in other branches. As shown in Figure 5.17, the bulk-average concentration exhibits a dependence on the boundary condition that is similar to that of the cross-sectional average $O_3$ concentration in the major pathways for pathways $RM$ and $R$. As the Reynolds number increases, the percentage difference between bulk-average concentrations computed using the two boundary conditions increases in planes $T_1$, $R_1 - R_6$, $L_1 - L_5$, $RM_1 - RM_2$, and $RC_1 - RC_4$. At a Reynolds number of 392, the difference is less than 2\% in the trachea, the first generation along the right lobe, and the first two generations along the left lobe.

5.1.3.3 Ozone Flux at Airway Walls

A comparison of the $O_3$ flux distributions on the airway walls in Figures 5.5 and 5.9 shows that the imposed condition at the outflow boundaries has very little effect on the wall flux distributions in the trachea, the first two airway generations along the right lobe and the major airways in the left lobe for both Reynolds numbers. In the airways beyond the second generation in the right lobe, however, some changes do occur in the flux pattern as the outlet boundary condition is changed, specially at Reynolds number of 392. In particular, additional hot spots of $O_3$ flux occur on the airway walls of generations three and higher in pathway $R$ for the zero-pressure condition. In contrast, a smaller $O_3$ flux is found on the airway walls of pathways $RC$ and $RM$, and also in all minor branches in the right and left lobes.

The forgoing observations of wall flux distribution are also confirmed by comparing the amounts of ozone uptake in each airway segment for the two outlet conditions. Figures 5.18 and 5.19 show the amount of ozone uptake in each airway generation along pathways $RM$, $RC$, $L$, and $R$ for a Reynolds number of 392. The amount of uptake in the airways of pathways $RM$, $L$, and $RC$ is higher for the prescribed flow rate condition than that for the zero-pressure condition. The opposite trend is observed in the airways of pathway $R$. The difference in the uptake behavior can be explained by the flow distribution in the different pathways. As was mentioned earlier, the flow rate in the major pathway of the right lobe is higher for the zero-pressure condition than that for the prescribed flow rate condition. As
a result, a larger fraction of incoming ozone passes through pathway $R$, leading to higher uptake along that pathway. For both Reynolds numbers, the percentage difference between the amounts of $O_3$ uptake resulting from the application of the two boundary conditions is less than 5% in the trachea, the first three generations in the right lobe, and the first two generations both in the left lobe and the right cranial pathway.

Interpretation of the differences between $O_3$ uptake in different airways, as well as their relation to the presence of local hot spots of $O_3$ wall flux is made difficult by the variations in the wall surface area among the different airways. To eliminate the contributions of wall surface area and identify the effect of changes in flow structure and concentration distribution on the uptake patterns in the different airways, the mean flux in each airway segment is defined as the total uptake in the segment divided by the area of the segment. The mean flux also provides a simple quantitative tool for detecting hot spots of flux on the walls of an airway segment.

Figures 5.20 and 5.21 show the mean flux in each segment of pathways $RM$, $RC$, $L$, and $R$ for Reynolds numbers of 98 and 392. As can been seen in these Figures, the mean flux in all generations of pathways $RM$, $RC$, and $L$ increases with increasing Reynolds number. In pathway $R$, the mean flux decreases with increasing Reynolds number in all but the last five segments. The larger mean flux resulting from the increase in Reynolds number is caused by changes in flow structure, specially in the airway paths with prominent bends.

The effect of the imposed boundary condition at the outlets on the mean flux in various airway segments can been seen in Figures 5.20 and 5.21 for the two Reynolds numbers considered. For both Reynolds numbers, the mean flux in the airway segments of pathways $RM$ and $RC$ is higher for the prescribed flow rate condition than that for the zero-pressure condition. In the left lobe, the mean fluxes in the first 4 segments are nearly the same (to within 1.5%) for the two boundary conditions at $Re = 98$, while the mean fluxes in generations 5 and beyond are larger for the prescribed flow rate condition compared to those for the zero-pressure condition. For $Re = 98$ in pathway $R$, the mean fluxes for the two boundary conditions are the same in the trachea and the next 4 airway segments. In all remaining airway segments of pathway $R$ except the second bifurcation,
the zero-pressure condition leads to a larger mean flux than the prescribed flow rate condition. For a Reynolds number of 392, mean flux in the first 6 airway segments of pathway $L$ is higher for the the zero-pressure condition than that of the prescribed flow rate condition. In other segments, the opposite trend is observed. This again indicates the effect of the change in flow structure as the Reynolds number increases. For Reynolds number of 392, mean fluxes for the two boundary conditions are the same in the first two generations of pathway $R$ except the second bifurcation. The mean flux in generations 3 and higher of pathway $R$ is higher for the zero-pressure condition compared to that of the prescribed flow rate condition.

Since we are ultimately interested in determining the ozone flux distribution on the airway walls in the lung geometry, these results suggest that imposing either a prescribed flow rate or zero pressure at the outflow boundaries will lead to quantitatively comparable results in the trachea and the first two generations along the right and left lobes.

5.2 Truncated Three-Dimensional Model

Accurate numerical simulations of steady ozone transport and uptake in the complete three-dimensional geometry of the tracheobronchial tree at $Re = 392$ required a minimum of about 18 million mesh elements and 120 hours of CPU time running in parallel on 8 dual-processors Linux cluster. This translates into an estimated of memory requirement of about 32 GB. Hence, the memory and CPU requirement associated with simulations in the complete three-dimensional structure can be prohibitory expensive. In this section, numerical simulation using a truncated three-dimensional geometry and a modified outflow condition will be introduced as an effective tool to reproduce realistic uptake patterns over selected portion of the full structure without the computational cost of using the complete structure.

To demonstrate the effectiveness and accuracy of the truncated three-dimensional model, numerical simulations of ozone transport and uptake were performed along selected pathways in the tracheobronchial tree of the Rhesus monkey lung. The major pathways in the left and right lobes, as well as the right middle lobe were con-
sidered, and truncated three-dimensional geometries for all three pathways were generated, as shown in Figure 5.22. All branches and planes in this Figure are labeled according to the scheme described earlier in section 5.1. For the flow simulations, two different boundary conditions were imposed at the outflow planes of the truncated geometry. In the first (local) scheme, the flow rates at the outflow boundaries of the truncated geometry were specified in proportion to the cross-sectional areas of those boundaries. In the second (global) scheme, the flow rate at an outlet of the truncated geometry was specified in proportion to the total cross-sectional area of outflow boundaries of the complete model that were located downstream of that truncation point. In the latter scheme, the flow distribution among the airways in the selected pathway is guaranteed to be the same as that in numerical simulation in the complete three-dimensional geometry even though the complete three-dimensional structure of the tracheobronchial tree is not used in the computations. Figure 5.23 shows the schematic of the local and the global flow splits. The remaining boundary conditions were the same as those described earlier in section 5.1. For each selected pathway, three separate numerical simulations were performed with the following characteristics: the complete three-dimensional geometry with the specified flow rate outflow condition, the truncated three-dimensional geometry with a locally specified flow rate outflow condition based on outflow boundaries of the truncated model, and the truncated three-dimensional geometry with a globally specified flow rate outflow condition based on outflow boundaries of the complete geometry. The results of these simulations are compared in the following section.

5.2.1 Simulation Results

Numerical predictions of $O_3$ flux distribution on the airway walls resulting from the three different simulations for each selected pathway are presented in Figures 5.24-5.26 for a tracheal Reynolds number of 392. The color maps of wall flux in these Figures are labeled as $TR$ (truncated right lobe), $TL$ (truncated left lobe), $TRM$ (truncated right middle lobe), and $F$ (full geometry). Each alphabetical label is followed by two numbers, the first one indicating the number of outflow boundaries of the model, and the second one denoting the number of outflow boundaries
on which the specified flow rate conditions are based. For example, \textit{TRM-8-8} in Figure 5.24 corresponds to the computations performed on the truncated three-dimensional model of the right middle lobe which has 8 outflow boundaries, using the local specified flow rate condition at those 8 outflows based on the areas of those same outflows. Similarly, \textit{TRM-8-78} in Figure 5.24 refers to the computations in the same truncated three-dimensional geometry, but with the global specified flow rate condition based on the cross-sectional area of the 78 downstream outflow boundaries in the complete three-dimensional structure. The label \textit{F-78-78} corresponds to the results of numerical simulations performed with the complete three-dimensional geometry and a specified flow rate outflow condition.

As can been seen from the color maps of Figures 5.24-5.26, there is very good agreement between the predicted flux distribution resulting from the simulation with the complete three-dimensional structure \((F-78-78)\) and those obtained from simulations \textit{TRM-8-78}, \textit{TR-13-78}, and \textit{TL-8-78} based on the truncated geometries. The predicted wall fluxes in the \textit{TRM-8-8}, \textit{TR-13-13}, and \textit{TL-8-8} simulations are generally higher than those in the \textit{TRM-8-78}, \textit{TR-13-78}, and \textit{TL-8-78} simulations, especially for the minor branches. The truncated model simulations with a global specified flow rate condition are guaranteed to produce the same flow distributions as in the simulations with the complete structural model, whereas the truncated model simulations with a local specified flow rate condition are not. This, in conjunction with the results in Figures 5.24-5.26, suggests that the mass flow rate distribution among the airways is the key factor in causing differences in \(O_3\) flux distribution on the airway walls.

A comparison of the predicted flow distributions among the airways in each selected pathways is shown in Tables 5.1-5.3. Each column in these Tables shows the percentage of total flow rate passing through different outflow boundaries, as predicted by the indicated simulation scheme. In these Tables, outlet "m" refers to the outflow boundary at the "m-th" bifurcation along each pathway. Clearly, the percentage of mass flow rate passing through each branch in the \textit{TRM-8-78}, \textit{TR-13-78}, and \textit{TL-8-78} simulations is identical to that predicted by the \textit{F-78-78} simulation in the complete three-dimensional geometry. In the \textit{TRM-8-8}, \textit{TR-13-13}, and \textit{TL-8-8} simulations, however, the percentage of mass flow rate going into the minor branches is larger than that predicted by the \textit{F-78-78} simulation. As
can be inferred from the results in Tables 5.1-5.3, for all truncated geometries, a
larger portion of flow leaves the pathway through the first outlet where the flow is
split according to the cross-sectional areas of the downstream outflow boundaries.

<table>
<thead>
<tr>
<th>Outlet</th>
<th>TRM-8-8</th>
<th>TRM-8-78</th>
<th>F-78-78</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35.1</td>
<td>41.4</td>
<td>41.4</td>
</tr>
<tr>
<td>2</td>
<td>20.9</td>
<td>17.2</td>
<td>17.2</td>
</tr>
<tr>
<td>3</td>
<td>29.9</td>
<td>32.4</td>
<td>32.4</td>
</tr>
<tr>
<td>4</td>
<td>4.9</td>
<td>3.1</td>
<td>3.1</td>
</tr>
<tr>
<td>5</td>
<td>2.1</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>7</td>
<td>2.9</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>8</td>
<td>2.9</td>
<td>1.8</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Table 5.1. Percentage of flow rate at the outlets of the pathway RM

<table>
<thead>
<tr>
<th>Outlet</th>
<th>TR-13-13</th>
<th>TR-13-78</th>
<th>F-78-78</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29.6</td>
<td>41.4</td>
<td>41.4</td>
</tr>
<tr>
<td>2</td>
<td>17.6</td>
<td>17.2</td>
<td>17.2</td>
</tr>
<tr>
<td>3</td>
<td>10.3</td>
<td>9.0</td>
<td>9.0</td>
</tr>
<tr>
<td>4</td>
<td>5.0</td>
<td>8.2</td>
<td>8.2</td>
</tr>
<tr>
<td>5</td>
<td>6.0</td>
<td>2.9</td>
<td>2.9</td>
</tr>
<tr>
<td>6</td>
<td>8.1</td>
<td>7.1</td>
<td>7.1</td>
</tr>
<tr>
<td>7</td>
<td>3.9</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>8</td>
<td>0.7</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>9</td>
<td>5.1</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>10</td>
<td>1.5</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>11</td>
<td>2.5</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>12</td>
<td>4.9</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>13</td>
<td>4.9</td>
<td>3.7</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Table 5.2. Percentage of flow rate at the outlets of the pathway R

A more quantitative comparison of the results of the numerical simulations
based on the truncated and complete three-dimensional geometries can be made
in terms of the predicted $O_3$ uptake in different airway segments. Figures 5.27-
5.29 show the predicted ozone uptake in all airways of the right middle lobe, and
generations three and higher of the right lobe, and generations two and higher of
the left lobe for the three simulations along each path. The predicted values of
$O_3$ uptake obtained from the TRM-8-78, TR-13-78, and TL-8-78 simulations for
Table 5.3. Percentage of flow rate at the outlets of the pathway $L$

<table>
<thead>
<tr>
<th>Outlet</th>
<th>$TL-8-8$</th>
<th>$TL-8-78$</th>
<th>$F-78-78$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45.8</td>
<td>58.5</td>
<td>58.5</td>
</tr>
<tr>
<td>2</td>
<td>19.8</td>
<td>17.8</td>
<td>17.8</td>
</tr>
<tr>
<td>3</td>
<td>6.7</td>
<td>3.6</td>
<td>3.6</td>
</tr>
<tr>
<td>4</td>
<td>8.0</td>
<td>6.5</td>
<td>6.5</td>
</tr>
<tr>
<td>5</td>
<td>7.4</td>
<td>5.7</td>
<td>5.7</td>
</tr>
<tr>
<td>6</td>
<td>2.6</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>7</td>
<td>2.8</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>8</td>
<td>6.9</td>
<td>4.5</td>
<td>4.5</td>
</tr>
</tbody>
</table>

all airway segments are in excellent quantitative agreement with those obtained from the $F-78-78$ simulation. The largest difference between the amounts of uptake values predicted by the two simulation schemes is 12%, which occurs for a Reynolds number of 392 in the airway segment between generations 3 and 4 in the left lobe.

The amount of $O_3$ uptake in each airway segment is overpredicted by the $TRM-8-8$, $TR-13-13$, and $TL-8-8$ simulations. The percentage difference between the amounts of uptake predicted by these simulations and those obtained from the $F-78-78$ simulation grows with increasing airway generation (for example, from 15% in the segment between generations 3 and 4 to 220% in the last generation of pathway $R$). The discrepancy between the two sets of results decreases with increasing Reynolds number. The amount of $O_3$ uptake predicted for the trachea is the same for all three simulation schemes.

Tables 5.6, 5.5 show the percent deviations of the computed values of mean wall flux in different airway segments from the corresponding values obtained in the $F-78-78$ simulation. It is evident from these Tables for both Reynolds numbers, the relative errors in the $TRM-8-78$, $TR-13-78$, and $TL-8-78$ simulations are less than the corresponding errors in the $TRM-8-8$, $TR-13-13$, and $TL-8-8$ simulations, especially for the last airway generations in each pathway. The calculated errors in pathways with prominent bends are larger than those in other branches. For example, the relative errors in the corresponding segments of pathway $R$ are smaller than those for pathway $RM$. As the Reynolds number increases, the relative error in mean wall flux increases in the right middle lobe and the left lobe, but decreases in the major pathway of the right lobe. This is consistent with the notion that
variations in the mean wall flux in each airway are caused by changes in the flow structure within that airway. Since the flow structure is basically determined by the airway geometry, increasing the Reynolds number can be expected to produce larger errors in the pathways with sharp turns.

The results presented in this section indicate that accurate prediction of $O_3$ flux distribution on the airways walls can be obtained using a truncated geometry that includes the pathway of interest, provided that the outflow boundary condition is imposed such that it captures the correct flow distribution in the complete three-dimensional structure. This can be achieved by specifying the flow rates at the outlets of the truncated geometry in proportion to the total cross-sectional area of all outflow boundaries of the complete structure that are downstream of each truncated outflow boundary. The truncated three-dimensional model represents an effective method for accurate prediction of uptake distribution while avoiding the prohibitively high computational costs associated with three-dimensional numerical simulations in the complete airway structure. It can also prove useful when detailed structural information is not available. For example, if the resolution of MRI images from a lung cast is not sufficient for three-dimensional reconstruction

<table>
<thead>
<tr>
<th>Airway segment</th>
<th>$RM - 8 - 78$</th>
<th>$RM - 8 - 8$</th>
<th>$RM - 8 - 78$</th>
<th>$RM - 8 - 8$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_0T_1$</td>
<td>0.2</td>
<td>0.2</td>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td>$T_1R_1$</td>
<td>2.9</td>
<td>3.5</td>
<td>10.8</td>
<td>11.1</td>
</tr>
<tr>
<td>$R_1R_2$</td>
<td>2.0</td>
<td>-0.4</td>
<td>-0.2</td>
<td>2.1</td>
</tr>
<tr>
<td>$R_2R_3$</td>
<td>2.3</td>
<td>1.6</td>
<td>1.6</td>
<td>2.1</td>
</tr>
<tr>
<td>$R_3R_4$</td>
<td>2.2</td>
<td>2.0</td>
<td>2.8</td>
<td>0.6</td>
</tr>
<tr>
<td>$R_4RM_1$</td>
<td>9.8</td>
<td>2.5</td>
<td>9.5</td>
<td>1.0</td>
</tr>
<tr>
<td>$RM_1RM_2$</td>
<td>3.9</td>
<td>51.1</td>
<td>3.7</td>
<td>22.3</td>
</tr>
<tr>
<td>$RM_2RM_3$</td>
<td>5.4</td>
<td>77.3</td>
<td>8.0</td>
<td>69.7</td>
</tr>
<tr>
<td>$RM_3RM_4$</td>
<td>4.3</td>
<td>111.6</td>
<td>1.9</td>
<td>60.7</td>
</tr>
<tr>
<td>$RM_4RM_5$</td>
<td>5.5</td>
<td>145.1</td>
<td>6.5</td>
<td>72.7</td>
</tr>
<tr>
<td>$RM_5RM_6$</td>
<td>3.8</td>
<td>181.6</td>
<td>4.9</td>
<td>85.6</td>
</tr>
<tr>
<td>$RM_6RM_7$</td>
<td>4.2</td>
<td>213.7</td>
<td>8.3</td>
<td>87.6</td>
</tr>
<tr>
<td>$RM_7RM_8$</td>
<td>3.7</td>
<td>284.3</td>
<td>6.0</td>
<td>86.8</td>
</tr>
<tr>
<td>$RM_8RM_9$</td>
<td>4.0</td>
<td>504.9</td>
<td>7.0</td>
<td>124.2</td>
</tr>
</tbody>
</table>

Table 5.4. Mean flux errors in the truncated pathway $RM$ relative to the complete three-dimensional model of the tracheobronchial tree.
of the complete airway structure, but the diameters of the branch outlets in the lung cast can be measured, truncated simulations can be used to predict flux distributions on selected pathways for which sufficient resolution for three-dimensional reconstruction is available.

<table>
<thead>
<tr>
<th>Airway segment</th>
<th>$L - 8 - 78$</th>
<th>$L - 8 - 8$</th>
<th>$L - 8 - 78$</th>
<th>$L - 8 - 8$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_0T_1$</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>$T_1L_1$</td>
<td>2.9</td>
<td>3.5</td>
<td>3.7</td>
<td>13.1</td>
</tr>
<tr>
<td>$L_1L_2$</td>
<td>1.5</td>
<td>15.6</td>
<td>0.4</td>
<td>5.9</td>
</tr>
<tr>
<td>$L_2L_3$</td>
<td>1.2</td>
<td>21.5</td>
<td>3.5</td>
<td>17.8</td>
</tr>
<tr>
<td>$L_3L_4$</td>
<td>0.3</td>
<td>15.9</td>
<td>3.2</td>
<td>4.5</td>
</tr>
<tr>
<td>$L_4L_5$</td>
<td>1.0</td>
<td>27.8</td>
<td>3.3</td>
<td>15.1</td>
</tr>
<tr>
<td>$L_5L_6$</td>
<td>1.3</td>
<td>39.4</td>
<td>1.2</td>
<td>22.0</td>
</tr>
<tr>
<td>$L_6L_7$</td>
<td>0.7</td>
<td>53.0</td>
<td>11.6</td>
<td>46.1</td>
</tr>
<tr>
<td>$L_7L_8$</td>
<td>1.4</td>
<td>71.7</td>
<td>2.1</td>
<td>50.4</td>
</tr>
<tr>
<td>$L_8L_9$</td>
<td>3.7</td>
<td>88.1</td>
<td>3.4</td>
<td>48.2</td>
</tr>
<tr>
<td>$L_9L_{10}$</td>
<td>2.0</td>
<td>110.6</td>
<td>4.9</td>
<td>20.0</td>
</tr>
<tr>
<td>$L_{10}L_{11}$</td>
<td>4.2</td>
<td>93.9</td>
<td>0.5</td>
<td>44.9</td>
</tr>
<tr>
<td>$L_{11}L_{12}$</td>
<td>1.7</td>
<td>135.9</td>
<td>3.3</td>
<td>33.8</td>
</tr>
<tr>
<td>$L_{12}L_{13}$</td>
<td>4.4</td>
<td>188.1</td>
<td>1.7</td>
<td>47.4</td>
</tr>
<tr>
<td>$L_{13}L_{14}$</td>
<td>2.5</td>
<td>284.5</td>
<td>5.2</td>
<td>52.6</td>
</tr>
</tbody>
</table>

**Table 5.5.** Mean flux errors in the truncated pathway $L$ relative to the complete three-dimensional model of the tracheobronchial tree.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_0 T_1$</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>$T_1 R_1$</td>
<td>2.9</td>
<td>3.5</td>
<td>6.9</td>
<td>13.2</td>
</tr>
<tr>
<td>$R_1 R_2$</td>
<td>2.0</td>
<td>0.4</td>
<td>0.5</td>
<td>2.5</td>
</tr>
<tr>
<td>$R_2 R_3$</td>
<td>2.3</td>
<td>1.6</td>
<td>0.4</td>
<td>5.0</td>
</tr>
<tr>
<td>$R_3 R_4$</td>
<td>2.2</td>
<td>2.0</td>
<td>1.4</td>
<td>3.2</td>
</tr>
<tr>
<td>$R_4 R_5$</td>
<td>4.3</td>
<td>5.7</td>
<td>7.0</td>
<td>9.4</td>
</tr>
<tr>
<td>$R_5 R_6$</td>
<td>2.3</td>
<td>14.6</td>
<td>1.3</td>
<td>22.5</td>
</tr>
<tr>
<td>$R_6 R_7$</td>
<td>1.8</td>
<td>31.7</td>
<td>2.8</td>
<td>18.2</td>
</tr>
<tr>
<td>$R_7 R_8$</td>
<td>4.2</td>
<td>25.8</td>
<td>3.5</td>
<td>12.8</td>
</tr>
<tr>
<td>$R_8 R_9$</td>
<td>3.4</td>
<td>40.1</td>
<td>2.1</td>
<td>19.0</td>
</tr>
<tr>
<td>$R_9 R_{10}$</td>
<td>3.7</td>
<td>53.6</td>
<td>1.7</td>
<td>31.5</td>
</tr>
<tr>
<td>$R_{10} R_{11}$</td>
<td>4.4</td>
<td>79.7</td>
<td>1.8</td>
<td>43.4</td>
</tr>
<tr>
<td>$R_{11} R_{12}$</td>
<td>2.1</td>
<td>109.3</td>
<td>-0.5</td>
<td>33.5</td>
</tr>
<tr>
<td>$R_{12} R_{13}$</td>
<td>2.9</td>
<td>135.7</td>
<td>1.0</td>
<td>38.9</td>
</tr>
<tr>
<td>$R_{13} R_{14}$</td>
<td>8.1</td>
<td>171.9</td>
<td>4.7</td>
<td>49.8</td>
</tr>
<tr>
<td>$R_{14} R_{15}$</td>
<td>1.2</td>
<td>223.9</td>
<td>3.1</td>
<td>51.2</td>
</tr>
</tbody>
</table>

**Table 5.6.** Mean flux errors in the truncated pathway $R$ relative to the complete three-dimensional model of the tracheobronchial tree
Figure 5.1. Major pathways in complete three-dimensional model of the tracheobronchial tree.
Figure 5.2. Contour maps of velocity distribution in the selected planes of the major pathways for the prescribed flow rate condition, Reynolds numbers of 98 and 392.
Figure 5.3. Streaklines of flow, color-labeled by the local velocity magnitude for the prescribed flow rate condition, Reynolds numbers of 98 and 392.
Figure 5.4. Contour maps of concentration distribution in the selected planes of the major pathways for the prescribed flow rate condition, Reynolds numbers of 98 and 392.
Figure 5.5. Color map of $O_3$ flux distribution on the wall of three-dimensional geometry of the tracheobronchial tree for the prescribed flow rate condition, Reynolds numbers of 98 and 392.
Figure 5.6. Streaklines of flow, color-labeled by the local $O_3$ concentration for the prescribed flow rate condition, Reynolds numbers of 98 and 392.
Figure 5.7. Contour maps of velocity distribution in the selected planes of the major pathways for the zero pressure condition, Reynolds numbers of 98 and 392.
Figure 5.8. Contour maps of concentration distribution in the selected planes of the major pathways for the zero pressure condition, Reynolds numbers of 98 and 392.
Figure 5.9. Color map of $O_3$ flux distribution on the wall of the three-dimensional geometry of the tracheobronchial tree for the zero pressure condition, Reynolds numbers of 98 and 392.
Figure 5.10. Streaklines of flow, color-labeled by the local $O_3$ concentration for the zero pressure condition, Reynolds numbers of 98 and 392.
Figure 5.11. Comparison of mass flow rates in the branches of pathways $RM$ and $RC$, Reynolds number of 98.
Figure 5.12. Comparison of mass flow rates in the branches of pathways $L$ and $R$, Reynolds number of 98.
Figure 5.13. Total pressure drop in the major pathways for both boundary conditions at the outflow boundaries, Reynolds numbers of 98 and 392.
Figure 5.14. Pressure drops in the airway branches of pathways RM and RC, Reynolds number of 98.
Figure 5.15. Pressure drops in the airway branches of pathways L and R, Reynolds number of 98.
Figure 5.16. Cross-sectional average of $O_3$ concentration in the planes of pathways $RM$ and $R$ for both boundary conditions at the outflow boundaries, Reynolds numbers of 98 and 392.
Figure 5.17. Bulk average $O_3$ concentration in the planes of pathways $RM$ and $R$ for both boundary conditions at the outflow boundaries, Reynolds numbers of 98 and 392.
Figure 5.18. Ozone uptake in the segments of pathways RM and RC for both boundary conditions at the outflow boundaries, Reynolds number of 392.
Figure 5.19. Ozone uptake in the segments of pathways $L$ and $R$ for both boundary conditions at the outflow boundaries, Reynolds number of 392.
Figure 5.20. Mean flux in the segments of pathways $RM$ and $RC$ for both boundary conditions at the outflow boundaries, Reynolds numbers of 98 and 392.
Figure 5.21. Mean flux in the segments of pathways $L$ and $R$ for both boundary conditions at the outflow boundaries, Reynolds numbers of 98 and 392.
Figure 5.22. The truncated three-dimensional geometries.
Figure 5.23. Schematic of the local and global flow splits.
Figure 5.24. Color maps of $O_3$ flux distribution on the wall of pathway RM, Reynolds number of 392.
Figure 5.25. Color maps of $O_3$ flux distribution on the wall of pathway $R$, Reynolds number of 392.
Figure 5.26. Color maps of $O_3$ flux distribution on the wall of pathway $L$, Reynolds number of 392.
Figure 5.27. Ozone uptake in the segments of pathway $RM$, Reynolds number of 392.
Figure 5.28. Ozone uptake in the segments of pathway \( R \), Reynolds number of 392.
Figure 5.29. Ozone uptake in the segments of pathway L, Reynolds number of 392.
In the preceding chapter, simulation results for ozone transport and uptake in a three-dimensional model of the tracheobronchial tree were presented. Numerical simulations were further developed using a more complete geometry of the respiratory tract. For this purpose, three-dimensional models of the larynx and the nasal cavities were reconstructed and attached to the lung geometry. Simulations were performed for the following three-dimensional geometries: the tracheobronchial tree and the larynx, and the entire respiratory tract from the nose down to the airways with diameters on the order of 1 millimeter.

In this chapter, the simulation results for ozone transport and uptake in the above geometries will be presented. The effect of the inlet boundary condition on the simulation results are revealed by these simulations.

6.1 Three-Dimensional Model of the Tracheobronchial Tree with the Larynx

The larynx is a part of the respiratory tract containing the vocal cords which produce vocal sound. It is located between the pharynx and the trachea. Airflow
for both speech and respiration travels through the cavity of the larynx, a conduit in which the rima glottidis produces a sharp and sudden airway constriction [1]. The influence of this laryngeal constriction on pulmonary airflow has been the focus of several investigations. Studies of flow structure near the laryngeal constriction have shown the presence of a laryngeal jet. In the human respiratory tract, increases in Reynolds number near the laryngeal constriction causes a laminar-to-turbulent transition to occur in the flow. The resultant jet turbulence in some cases persists until the first bifurcation [82].

The larynx geometry is therefore essential to studies of pulmonary transport phenomena. The effect of the larynx on the transport of inhaled reactive gases such as ozone has been the focus of only a single investigation [82]. The goal of this section is to examine the influence of the larynx on ozone transport and uptake in the three-dimensional model of the tracheobronchial tree, and to determine the flux of ozone in the larynx relative to that in the other airways.

6.1.1 Model Geometry and Formulation

The three-dimensional model of the tracheobronchial tree used in the following simulations was reconstructed from the MRI images of the same 6-month-old monkey as described in Section 3.1.1, but is different from the three-dimensional model of the tracheobronchial tree studied in Chapter 5. This three-dimensional geometry has 68 outlets, and fewer generations along the minor branches of the left lobe and the right middle lobe. The geometry was meshed in GAMBIT using tetrahedral elements of dimensionless size 0.016 – 0.064, and consisted of about 8 million mesh elements. The full length of the trachea was reconstructed as described in Section 3.1.1 and the three-dimensional model of the larynx was then reconstructed and attached to the geometry of the tracheobronchial tree. The three-dimensional geometry of the larynx was meshed with 1,620,000 tetrahedral elements of dimensionless size 0.01. A pair of simulations (for the infinitely-fast and first order reactions) were performed for the three-dimensional models of the tracheobronchial tree with and without the larynx attached, in order to investigate the impact of the presence of the larynx on ozone uptake.

Numerical simulations were performed for a Reynolds number of 183 based on
the hydraulic radius of the trachea. For the simulations in the three-dimensional model of the tracheobronchial tree without the larynx, uniform velocity and concentration profiles were imposed at the inlet of the trachea. When the larynx was attached to the tracheobronchial tree, uniform velocity and concentration profiles were imposed at the inlet plane of the larynx. The uniform velocity normal to the inlet of the larynx was determined by using the same flow rate for both models. The resulting dimensionless velocity at the inlet of the larynx was about one-third of the dimensionless velocity imposed at the inlet of the trachea for the simulations without the larynx. The no-slip condition was imposed at the airway walls for both three-dimensional models. The imposed boundary condition at the outflow boundaries was a specified flow rate.

For the concentration field, zero $O_3$ concentration (corresponding to an infinitely-fast reaction) or a pseudo-first order reaction between $O_3$ and substrates in the $\text{RTL}_F$ with $Da = 15$ was imposed at the airway walls. Based on a Reynolds number of 135 at the inlet of the larynx, the highest local Reynolds number reached at the larynx constriction was 420 leading to laminar flow through the geometry. Based on the gas properties mentioned in Chapter 4, Equations 3.1, 3.2, and 3.3 were solved subject to the above boundary conditions.

### 6.1.2 Simulation Results

Simulation results are compared for the four following major pathways: right cranial ($RC$), right middle ($RM$), right ($R$) and left ($L$) lobes. In order to facilitate the comparison of results, one or two planes were introduced in each branch normal to the branch axis. Each plane is identified according to its position in one of the major pathways ($RC$, $RM$, $R$, and $L$), as was described in Section 5.1. The plane at the outlet of the trachea is labeled as $T_1$. The three-dimensional model of the tracheobronchial tree with larynx, branches, and planes is shown in Figure 3.3.

#### 6.1.2.1 Flow Field

Contour maps of the dimensionless velocity magnitude in selected planes along the major pathways of the tracheobronchial tree are presented in Figure 6.1 for both geometries (i.e. without the larynx and with the larynx). Overall the flow structure
in both geometries is asymmetric. Velocity distributions in the corresponding planes look completely different. Nearly circular contours are observed in plane $T_1$ in the geometry without the larynx, whereas two high velocity regions are present over the same plane in the presence of the larynx. The locations of high velocity regions, especially in planes $R3 - R7$, are also different. The change in flow structure resulting from the addition of the larynx to the geometry is reflected by the change in the location of the high velocity regions within the trachea in the corresponding planes.

Figure 6.2 shows the streaklines colored-labeled according to the local $O_3$ concentration. As mentioned before, the structure of the larynx significantly affects the resulting flow pattern in the trachea. The larynx geometry includes a narrow opening between the vocal cords (rima glottidis) where a sharp and sudden change in the cross-sectional area of the larynx occurs. The sudden reduction in the cross-sectional area of the larynx just upstream of the rima glottidis leads to the formation of a curved sheet-like laryngeal jet that impinges on one side of the tracheal wall a short distance downstream of the larynx (see the magnified image in Figure 6.2). The bending of the laryngeal jet causes asymmetry in the flow structure extending to the distal trachea. It produces a complex flow with skewed velocity profiles and recirculation regions in the trachea. It should be noted that the complex secondary flow patterns observed in the trachea are produced based on laminar flow simulations.

6.1.2.2 Concentration and Flux Distributions

Contour maps of dimensionless concentration in selected planes along the major pathways of the tracheobronchial tree are presented in Figure 6.3 in both geometries (i.e. without the larynx and with the larynx) for the case of a first-order reaction. The concentration distributions are qualitatively similar to the corresponding velocity distributions shown in Figures 6.1 and 6.3. The average ozone concentration over each plane in the geometry without the larynx is higher than that over the corresponding plane in the geometry with the larynx. For example, the bulk-average ozone concentrations over the $T_1$ plane are 0.96 and 0.92, respectively in the model without the larynx and that with the larynx. The percentage
The difference between the average ozone concentrations in the two models increases, as the rate of reaction between $O_3$ and the RTLF substrates increases. For an infinitely fast reaction, the bulk average $O_3$ concentrations over the $T_1$ plane are 0.61 and 0.17 for the model without the larynx and that with the larynx.

The ozone flux distribution for the first-order reaction case in the three-dimensional model with the larynx is shown in Figure 6.4. The scale for the color map ranges from 0.22 (blue) to 0.26 (red). The $O_3$ flux distribution on the trachea wall is significantly affected by the complex flow pattern created within the trachea due to the presence of the larynx. In particular, the impingement of the laryngeal jet on the tracheal wall produces a hot spot of ozone flux in the vicinity of the impingement region. Overall, the secondary flow produced in the trachea by the presence of the larynx results in a more uniform $O_3$ wall flux distribution within the trachea, compared to the corresponding $O_3$ wall flux in the same airway structure without the larynx. This is clearly shown by the comparison of flux distributions on the walls of the tracheobronchial tree in the two geometries. Figure 6.5 compares the wall flux distribution in the presence and absence of the larynx for $Da = 15$. In the absence of the larynx, local maxima in $O_3$ wall flux occur just downstream of the carina of each bifurcation (specially in the first three bifurcations of the conducting airways), with the magnitudes of the spikes in $O_3$ flux decreasing with each branching generation. As the flow enters downstream branches, the local Reynolds number of the flow decreases. At lower Reynolds numbers, the thickness of the concentration boundary layer on the airway wall is larger at any given distance downstream of the carina, thereby leading to a smaller $O_3$ wall flux at the airway wall. As expected, the magnitudes of the hot spots of $O_3$ flux for the infinitely-fast reaction are much larger than those for the slow first-order reaction. While the hot spots of $O_3$ wall flux just downstream of the airway bifurcations persist even in the presence of the larynx, their intensities are reduced due to both the substantial uptake of ozone within the larynx, and the effect of the larynx on the downstream flow pattern.
6.2 Complete Three-Dimensional Model of the Respiratory Tract

The nasal cavity of the rhesus monkey consists of two airways separated by a septum, which extends from the tip of the nostrils to the posterior limit of the soft palate in the nasopharynx. There are three geometrically distinct regions of the nasal airway: nasal vestibule, central nasal passages, and nasopharynx, as shown in Figure 6.6. The nasal vestibule is defined as the region that extends from the tip of the nostrils to the beginning of the middle turbinate. The middle and inferior turbinates were bony extensions covered by nasal mucosa, which protrude from the lateral wall and divide the nasal airway into the superior, middle and inferior meatus [24]. This region of the nasal airway is characterized by the elongation of the cross sections.

The central nasal passages start with the beginning of the middle turbinate and extend posteriorly for the full extent of the middle and inferior turbinates. This region of the airway is characterized by long, narrow cross sections. The nasopharynx region begins at the point of attachment of the middle turbinate to the nasal wall. The two halves of the nasal cavity join at the point where the septum ends. The termination of the septum occurs simultaneously with the bending of the airway toward the larynx and the joining of the oral cavity. In this region, the cross sections more closely resemble sections of a circular tube. In the nasopharynx/pharynx, the airway makes a 90 bend toward the larynx [65].

6.2.1 Model Geometry and Formulation

A three-dimensional model of the left nasal cavity was reconstructed from the MRI images, and then mirrored to create a model for the right nasal cavity. The two sides were connected to the three-dimensional airway structure containing the tracheobronchial tree and the larynx (explained in Section 3.1.1). Each side of the three-dimensional geometry of the nasal passages was meshed with about 1.2 million tetrahedral elements of dimensionless size 0.06.

Numerical simulations were performed for a Reynolds number of 183 based on the hydraulic radius of the trachea, corresponding to quiet breathing condition
for the rhesus monkey. Thus, airflow remained laminar throughout the entire airway structure, including the nasal passages. Uniform velocity and concentration distributions were imposed at the inlet of the nasal passages. The inlet velocity normal to the inlet planes was determined assuming the same flow rate as that used earlier for the simulations in the two geometries of the tracheobronchial tree with and without the larynx. It was assumed that the flow rate is equally partitioned between the two sides of the nasal cavity. Hence, the resulting dimensionless velocity normal to the inlet of one side of the nasal cavities was about twice that imposed at the inlet of the larynx for the simulations reported earlier for the model of the tracheobronchial tree with the larynx. The no-slip condition was imposed at the airway walls, and a specified flow rate was imposed at the outflow boundaries. For the concentration field, either zero $O_3$ concentration (corresponding to an infinitely-fast reaction) or a pseudo-first order reaction (with $Da = 15$) between $O_3$ and substrates in the RTLF) was imposed at the airway walls. Using the gas properties mentioned in Chapter 4, Equations 3.1, 3.2, and 3.3 were solved subject to the above boundary conditions.

### 6.2.2 Simulation Results

Results of the numerical simulations are presented for the $RC$, $RM$, $R$, and $L$ pathways, as well as for one side of the nasal cavity in the upper respiratory tract ($URT$) of the complete three-dimensional model. Planes along the four major pathways of the tracheobronchial tree were defined normal to the local airway axis at exactly the same locations as those defined for the three-dimensional models discussed in section 6.1. Similar planes across the nasal passages were defined by cutting the nasal cavity with equidistant planes parallel to the inlet planes located at the nostrils. The planes along the nasal cavity are labeled as $URT_0$ (nostril- the inlet of the nasal cavity at the nostrils) to $URT_{14}$ (the outlet of nasopharynx), as shown in Figure 6.6.

#### 6.2.2.1 Flow Field

Contour maps of the dimensionless velocity magnitude in selected planes along the major pathways of the tracheobronchial tree are presented in Figure 6.7 for
a tracheal Reynolds number of 183. As expected from the irregular upstream
gonometry, the velocity distributions over these planes are asymmetric. After the
first bifurcation, the maximum velocities are clearly skewed toward the inner wall
of the $T_1R_1$ and $T_1L_1$ airways. The flow rate through the trachea is not equally
partitioned at the first bifurcation with about 60% passing through the right lobe
and 40% passing through the left lobe. At a tracheal Reynolds number of 183,
the average velocity magnitudes over corresponding cross-sections are consistently
larger in pathway $R$ than in pathway $L$.

Contour maps of the dimensionless velocity magnitude in magnified selected
planes within the nasal cavity are presented in Figure 6.8. The computed veloc-
ity distribution exhibits the largest average velocities and the most complex flow
patterns with vortices and swirls within the nasal vestibule. It also predicts the
presence of a jet emanating from points near the front of the nostril and passing
through the dorsal and medial parts of the airway in the nasal vestibule. Mass
flow rate through the nostril is distributed at the septal wall into ventral, medial,
and dorsal airways in the central nasal passages. The magnitude of velocity in the
dorsal part of the airway is smaller than those for the medial and ventral parts.
The dorsal meatus disappears as the middle turbinate joins the nasal wall at the
interface between the nasal passages and the nasopharynx. In the nasopharynx,
the velocity distribution is skewed toward the ventral side of the nasal cavity.
Planes $URT_7$ and $URT_8$ are the only planes that intersect the maxillary sinus. As
observed in Figure 6.8, the velocity magnitude is zero over the two cross-sections
in the maxillary sinus. This indicates that there is essentially no flow through the
maxillary sinus. This result is consistent with the experimental observations of
flow in hollow acrylic molds of rhesus monkey nasal airways performed by Morgan
et al. [83].

The computed velocity distribution in the nasal cavity is consistent with the
simulation results of Kepler et al. [65], who also computed the local Reynolds num-
bers within the passages of the nasal cavity of a rhesus monkey. These investigators
concluded that the Reynolds numbers in the central nasal passages are generally
smaller than those in the nasal vestibule. In the simulations presented here, a
tracheal Reynolds number of 183 corresponds to a local Reynolds number of about
100 at the inlet of the nasal cavity. Calculations of the local Reynolds numbers
in the nasal vestibule indicate that the highest local Reynolds number achieved in
the nasal vestibule is about 900. Therefore, the airflow within the nasal cavity is
expected to remain laminar, consistent with the governing equations used in the
simulations.

Figure 6.9 shows the streaklines color-labeled according to the local \( O_3 \) con-
centration in the complete three-dimensional model of the respiratory tract. Fig-
ure 6.10 shows magnified images of the streaklines color-labeled by velocity mag-
nitude and ozone concentration in one side of the nasal cavity, respectively. The
jet originating at the nostril is observed at the beginning of the nasal vestibule.
It produces a complex secondary flow pattern with recirculation regions in the
nasal vestibule. The channel-like geometries of the ventral and middle turbinates,
and the small hydraulic diameters in the central nasal passages, cause the flow
to become more streamlined. In the nasopharynx section with its nearly circular
cross-section, the flow is completely streamlined. As the flow enters the larynx,
it evolves into a planar jet that impinges on the tracheal wall. Because of the
orientation of the larynx, the impinging laryngeal jet creates a strong swirling flow
in the upper part of the trachea which persists down to the first bifurcation.

6.2.2.2 Concentration and Flux Distributions

Contour maps of the dimensionless concentration distribution in selected planes
over the major pathways of the tracheobronchial tree, as well as within the nasal
cavity are presented in Figures 6.11 and 6.12 for the case of first-order reaction
with \( Da = 15 \). It should be noted that the scales for the color maps are different
in these two Figures. The computed \( O_3 \) concentration distributions are again
qualitatively similar to the corresponding distributions of the velocity magnitude.
The bulk-average ozone concentration in planes \( URT_{14} \) and \( T_1 \) are 0.80 and 0.72,
respectively, indicating that about 10\% of \( O_3 \) leaving the nasopharynx is taken
up by the larynx and the trachea. The bulk-average ozone concentration at the
outflow boundary of the major pathway in the right lobe is calculated as 0.62.

The resulting \( O_3 \) flux distribution on the airway walls of the complete three-
dimensional model of the respiratory tract is shown in Figure 6.13 for a first-order
reaction with \( Da = 15 \). The high-flux regions within the upper respiratory tract
are located in the nasal vestibule, the medial part of the nasopharynx, and the larynx. Hot spots of \( O_3 \) wall flux within the tracheobronchial tree occur near the inlet of the trachea where the laryngeal jet impinges on the trachea wall, and at the bifurcations (especially the first bifurcation). Due to the complex geometry of the nasal cavity, the wall flux distribution in the nasal passages is only shown along the perimeter of the selected planes within the nasal cavity, as shown in Figure 6.14. As shown in this Figure, the high flux regions appear in the dorsal and ventral parts of the middle turbinate, the medial part of the inferior turbinate, and the ventral part of the inferior meatus. For the first-order reaction, the fractional uptakes in the nasal cavity, the larynx, and the tracheobronchial tree were calculated to be 21.2\%, 1.1\%, and 14.4\%, respectively. Hence, the nasal cavity removes about a quarter of the ozone entering the respiratory tract.

### 6.3 Comparison with Experimental Observations

Experimental assessment of ozone-induced injury in the conducting airways of rhesus monkeys is being currently made by our collaborators at UC Davis, Michigan State University, and University of Alabama. Since these experimental observations are not yet available, we have used experimental observations of formaldehyde-induced injury in the nasal passages of a rhesus monkey for validation of our simulation results. The locations of formaldehyde-induced lesions in the nasal passages of a rhesus monkey were determined by Monticello et al. [24]. The monkey was exposed to 6 ppm formaldehyde, 5 days per week for 6 weeks. Figure 6.15 shows the lesion distribution based on data derived from histological examination of multiple cross-sections of the nasal passages. Locations of formaldehyde-induced lesions involve the nasal atrium, mid-septum, lateral wall, floor of the inferior meatus, dorsal and ventral angles of the middle turbinate, and the medial aspect of the inferior turbinate.

Since formaldehyde is a highly reactive and water-soluble gas, the reaction between formaldehyde and the \( RTLF \) components can be considered as an infinitely-fast reaction [65]. To examine the hypothesis that nasal lesions and regions of high wall flux occur in similar locations, the simulated wall flux distribution for an infinitely-fast reaction was determined along the perimeter of cross-sections
considered to be equivalent to levels A through E in Figure 6.15, and high flux regions were compared to reported lesion locations. The wall flux distribution for an infinitely-fast reaction and a tracheal Reynolds number of 183 is shown in Figure 6.16 for different cross-sections along the nasal passages. Although the experimental and simulation results are not compared over identical cross-sections, the high flux regions tend to coincide with the locations of lesions. Specifically, high flux regions and lesions both occur in the dorsal and ventral parts of the middle turbinate, the medial part of the inferior turbinate, and the ventral part of the inferior meatus. These results suggest that patterns of tissue injury induced by inhalation of a highly reactive gas can be predicted by determining the flux distribution at the airway walls. Further validation of this hypothesis for ozone must await the availability of experimental observations of ozone-induced tissue injury in the conducting airways of rhesus monkeys.
Figure 6.1. Contour maps of velocity distribution in the selected planes of the major pathways for the tracheobronchial tree without the larynx and that with the larynx, tracheal Reynolds numbers of 183.
Figure 6.2. Streaklines of flow, color-labeled by the local $O_3$ concentration for the tracheobronchial tree with the larynx, tracheal Reynolds numbers of 183 and $Da = 15$. 
Figure 6.3. Contour maps of concentration distribution in the selected planes of the major pathways for the tracheobronchial tree without the larynx and that with the larynx, tracheal Reynolds numbers of 183 and $Da = 15$. 

Without larynx

With larynx
Figure 6.4. Color map of $O_3$ flux distribution on the wall of three-dimensional geometry of the tracheobronchial tree with the larynx, tracheal Reynolds numbers of 183 and $Da = 15$. 
Figure 6.5. Color map of $O_3$ flux distribution on the wall of three-dimensional geometry of the tracheobronchial tree without the larynx and that with the larynx, tracheal Reynolds numbers of 183 and $Da = 15$. 
Figure 6.6. Nasal cavity of the rhesus monkey. MT: middle turbinate; IT: inferior turbinate; IM: inferior meatus; MS: maxillary sinus.
Figure 6.7. Contour maps of velocity distribution in the selected planes of the major pathways for the tracheobronchial tree in the complete three-dimensional model of the respiratory tract, tracheal Reynolds numbers of 183.
Figure 6.8. Contour maps of velocity distribution in the selected planes of the nasal cavity, tracheal Reynolds numbers of 183.
Figure 6.9. Streaklines of flow, color-labeled by the local $O_3$ concentration for the complete three-dimensional model of the respiratory tract, tracheal Reynolds numbers of 183 and $Da = 15$. 
Figure 6.10. Streaklines of flow, color-labeled by (a) the local velocity magnitude and (b) the local $O_3$ concentration for the nasal cavity, tracheal Reynolds numbers of 183 and $Da = 15$. 
Figure 6.11. Contour maps of concentration distribution in the selected planes of the major pathways for the tracheobronchial tree in the complete three-dimensional model of the respiratory tract, tracheal Reynolds numbers of 183 and $Da = 15$. 
Figure 6.12. Contour maps of concentration distribution in the selected planes of the nasal cavity, tracheal Reynolds numbers of 183 and $Da = 15$. 
Figure 6.13. Color map of $O_3$ flux distribution on the wall of the complete three-dimensional model of the respiratory tract, tracheal Reynolds numbers of 183 and $Da = 15$. 
Figure 6.14. Color map of $O_3$ flux distribution along the perimeter of the selected planes within the nasal cavity, tracheal Reynolds numbers of 183 and $Da = 15$. 
Figure 6.15. Formaldehyde-induced lesion distribution in the selected levels of nasal passages (regions with cross-hatching) [24].
Figure 6.16. Color map of $O_3$ flux distribution along the perimeter of the selected planes within the nasal cavity, tracheal Reynolds numbers of 183 and infinitely-fast reaction.
Chapter 7

Summary and Future Work

The goal of this thesis was to study $O_3$ dose distribution in the respiratory tract, and investigate the effects of different factors on $O_3$ uptake into the respiratory tract lining fluid (RTLF). This study was based on the hypothesis that the reproducible pattern of tissue injury induced by inhalation of $O_3$ depends on the local dose delivered to different tissue sites in the respiratory tract. The respiratory tract of a rhesus monkey was selected as the platform for this computational study because of the parallel experimental study being carried out by our collaborators at UC Davis, the Michigan State University, Pacific Northwest National Laboratory (PNNL), and the University of Alabama. Three-dimensional reconstruction of the airway geometries using MRI images of the tracheobronchial tree, the larynx, and the nasal cavities was performed in Amira (Mercury Computer Systems, Chelmsford, MA). Unstructured volume meshes for the geometries were then generated in GAMBIT (ANSYS, Canonsburg, PA). Three-dimensional flow and concentration distributions in the resulting structure were subsequently obtained through numerical solution of the Navier-Stokes, continuity, and species convection-diffusion equations for steady inspiratory flow at physiologically relevant tracheal Reynolds numbers using FLUENT (ANSYS, Canonsburg, PA).

The first study compared the simulation results for $O_3$ transport and uptake through the first 13 generations along the right middle lobe of the monkey lung to those of the axisymmetric singel-path model. The simulations were performed at the tracheal Reynolds numbers of 98, 392, and 784. In the three-dimensional model, spikes in $O_3$ wall flux appeared downstream of each bifurcation, with the magnitude
of the spikes decreasing with each successive branching generation. The appearance of the spikes in wall flux downstream of bifurcations is due to the development of a thin concentration boundary layer on the airway wall, starting from the carina. In the axisymmetric single-path model, a local maximum in the $O_3$ wall flux appeared after each transition region. Large local wall fluxes developed near the inlet of each branch, where the thickness of the boundary layer was very small (compared to the airway radius). The highest wall flux appeared right after the third bifurcation, due to a significant reduction in the airway cross-sectional area as the gas moved from a major path into a minor path. The axisymmetric single-path model results were found to be in good agreement with the corresponding results for three-dimensional simulations. Thus, an axisymmetric single-path model can be used to predict the dose distribution of an inhaled toxicant along a specified pathway in the tracheobronchial tree.

The second study examined the influence of the imposed boundary condition at the outflow boundaries of the complete and truncated three-dimensional models of the tracheobronchial tree. To investigate the effect of the imposed outlet boundary condition, simulations were performed for the two outlet boundary conditions of (1) prescribed flow rate and (2) zero pressure. The simulation results for $O_3$ uptake and wall flux distribution indicated that imposing either a prescribed flow rate or zero pressure at the outflow boundaries led to quantitatively comparable results in the trachea and the first two generations along the right and left lobes. The second part of the study focused on using a truncated three-dimensional geometry in conjunction with a modified boundary condition at the outflow boundaries as to reproduce realistic uptake patterns over selected portion of the full structure without the computational cost of using the complete structure. The simulation results at tracheal Reynolds number of 392 indicated that accurate prediction of $O_3$ flux distribution on the airways walls can be obtained using a truncated geometry that includes only the pathway of interest, provided that the outflow boundary condition is imposed such that it captures the correct flow distribution in the complete three-dimensional structure (i.e. using a global flow split).

In the final study, the effect of upper airways on ozone transport and uptake was examined by performing numerical simulations at a tracheal Reynolds number of 183 in the following three-dimensional geometries: the tracheobronchial tree with
the larynx, and the complete geometry of the respiratory tract from the nose down to the airways with diameters on the order of 1 millimeter. It was found that the $O_3$ wall flux distribution in the trachea was significantly affected by the complex flow pattern created within the trachea due to the presence of the larynx. In particular, the impingement of the laryngeal jet on the tracheal wall produced a hot spot of ozone flux in the vicinity of the impingement region. While the hot spots of $O_3$ wall flux just downstream of airway bifurcations persisted even in the presence of the larynx, their intensities were reduced due to both the substantial uptake of ozone within the larynx and the effect of the larynx on the downstream flow pattern. In the simulations with the complete geometry of the respiratory tract, hot spots of $O_3$ wall flux within the tracheobronchial tree were found to occur near the inlet of the trachea, where the laryngeal jet impinged on the tracheal wall, and at the bifurcations (especially the first bifurcation). In the nasal cavities, the high flux regions appeared in the dorsal and ventral parts of the middle turbinate, the medial part of the inferior turbinate, and the ventral part of the inferior meatus. The fractional uptakes in the nasal cavity, the larynx, and the tracheobronchial tree were calculated to be 21.2%, 1.1%, and 14.4%, respectively, for the first-order reaction. This indicated that the nasal cavity removed about a quarter of the ozone entering the respiratory tract, and that more than 60% of the inhaled ozone survived past the 13th generation.

The work presented in this thesis demonstrates the successful use of Computational Fluid Dynamics (CFD) to predict reactive gas transport and uptake in the complete geometry of the respiratory tract of a rhesus monkey. The results of this study suggest the following directions for future work:

- Since it was found that over 60% of the inhaled ozone was transported to the airways beyond generation 13 for the first-order reaction, $O_3$ transport and uptake in a more complete geometry, including small airways will be necessary to predict the depth of penetration of ozone in the lung. This would require imaging the lung cast with better resolution.

- Although under quiet breathing conditions, flow can be considered to be quasi-steady throughout much of the respiratory tract, flow in the nasal cavities and the larynx, especially during exercise, is not likely to be quasi-steady.
In this case, it will be important to conduct time-dependent simulations of $O_3$ uptake during cyclic breathing (pulsatile flow). Furthermore, at high respiratory flow rates, the turbulent jet resulting from flow through the larynx can be expected to propagate further into the lower respiratory tract. Therefore, including flow through the larynx in such simulations becomes critically important.

- An important missing feature of this study was the direct validation of the simulation predictions using experimental observations of local tissue injury. The respiratory tract of a rhesus monkey was selected as the platform for this computational study because of the expected availability of relevant experimental data for this species. Experimental assessment of ozone-induced injury in the conducting airways of rhesus monkeys is being made concurrently by our collaborators at UC Davis, Michigan State University, Pacific Northwest National Laboratory (PNNL), and University of Alabama. Finding correlations between the location and severity of the epithelial injury with the $O_3$ flux distribution on the airway walls is critical for accurate predictive modeling of exposure-dose-response relationships in the respiratory tract, and subsequent extrapolation of the findings in animals to humans for determining risk.

- Finally, the end purpose of using CFD simulations to predict $O_3$ dose distribution in the RTL$F$ and tissue is to eventually predict the tissue response. In order to accomplish this goal, knowledge of the nature of the reactions occurring between $O_3$ and RTL$F$ substrates, including knowledge about reaction products, RTL$F$ reaction kinetics, and possible interactions between RTL$F$ substrates is crucial. Unfortunately, these details have not been well-established yet. The kinetic rate constants for the relevant biochemical reactions involving $O_3$ in the RTL$F$ are going to be experimentally characterized by our collaborators at the University of Alabama, and must be incorporated into the simulations when they become available.
Bibliography


Vita
Banafsheh Keshavarzi

Education:

• Ph.D. in Chemical Engineering: The Pennsylvania State University, May 2011
• M.Sc. in Chemical Engineering: Sharif University of Technology, Tehran, Iran, 2004
• B.Sc. in Chemical Engineering: Sharif University of Technology, Tehran, Iran, 2001

Publications:


2. N. F. Baril, B. Keshavarzi, J. R. Sparks, M. Krishnamurthy, I. Temnykh, P.J.A. Sazio, A. Borhan, V. Gopalan, and J. V. Badding, ”High-pressure chemical deposition for void-free filling of extreme aspect ratio templates,” Advanced Materials, 22(41): 4605-4611, 2010
