2008

Numerical Analysis of Respiratory Aerosol Deposition: Effects of Exhalation, Airway Constriction and Electrostatic Charge

Samir C. Vinchurkar
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NUMERICAL ANALYSIS OF RESPIRATORY AEROSOL DEPOSITION: EFFECTS OF EXHALATION, AIRWAY CONSTRUCTION AND ELECTROSTATIC CHARGE

A Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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Abstract

NUMERICAL ANALYSIS OF RESPIRATORY AEROSOL DEPOSITION: EFFECTS OF EXHALATION, AIRWAY CONSTRICITON AND ELECTROSTATIC CHARGE

By Samir C. Vinchurkar.

A Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2008

Advisor: Dr. P. Worth Longest
Assistant Professor, Department of Mechanical Engineering, and Department of Pharmaceutics

The dynamics of particle laden flows are integral to the analysis of toxic particle deposition and medical respiratory aerosol delivery. Computational fluid-particle dynamics (CFPD) can play a critical role in developing a better understanding of particle laden flows, especially in a number of under-explored areas. The applications considered in this study include both the numerical aspects and the physical phenomena of respiratory aerosol transport. Objective I: Considering the effects of mesh type and grid convergence, four commonly implemented mesh styles were applied to a double bifurcation respiratory...
geometry and tested for flow patterns and aerosol deposition. Results indicated that the mesh style employed had a significant effect on the transport and deposition of aerosols with hexahedral meshes being most accurate. Objective II: In order to evaluate the effects of bronchoconstriction under exhalation conditions, normal and constricted pediatric airway models were considered. Results include (i) a significant increase in deposition for constricted airways, and (ii) a novel correlation for deposition during exhalation based on the Dean and Stokes numbers. Objective IIIa: Considering evaluation of an aerosol size sampler, an eight-stage Andersen cascade impactor (ACI) was numerically analyzed. The numerical simulations indicated high non-uniformity and recirculation in the flow field. Numerical predictions of retention fraction matched well with existing experiments (0.5 – 11% error). Objective IIIb: As an extension to this study, numerical predictions of electrostatic charge effects on aerosol transport and deposition in the ACI were presented. Charges consistent with standard pharmaceutical pressurized metered dose inhalers and dry powder inhalers were considered. The numerical predictions indicated that charged aerosols deposit as if they were 5 – 85% larger due to electrostatic effects. Applications of the studies considered include (i) quantitative guidance in selecting numerical mesh styles and development of standard grid convergence criteria, (ii) the development of more accurate whole-lung deposition models that better evaluate exhalation conditions, (iii) improvements in the design of pharmaceutical assessment and delivery devices, and (vi) correction values to account for electrostatic charge on pharmaceutical aerosols.


1. Introduction

1.1 The Respiratory System

Two significant areas of study for which dosimetry modeling of the respiratory tract plays a vital role are toxicology, which includes radionuclide as well as pollutant exposure, and pharmacological studies, which primarily includes respiratory drug delivery. Studies in these areas require: (1) dosimetry analyses for individuals of all ethnic backgrounds and subpopulations (e.g., children), (2) data that could help establish regulatory standards for pollutant levels and predict deposition for given levels, (3) models to account for the effects of respiratory diseases, and (4) methods to predict the deposition of medical aerosols, pollutants and radioactive gases. The intricacy of the morphological characteristics of the respiratory tract is a key challenge in the development of dosimetry models, regardless of the approach of the study, i.e. analytical, experimental, or numerical.

Physiology and Functions

The human respiratory system can be subdivided in two regions, which are the extrathoracic and the thoracic airways. The extrathoracic region consists of the mouth, nasal passages, pharynx and larynx. The mouth and nose serve as alternative air passages for breathing and converge at the oropharynx (ICRP 1994). Nasal passages are considered as the ideal breathing path and serve two purposes, which include humidification of the
inspired air and filtration of particulate matter (Lumb 2000). The pharynx plays an important role in assisting breathing by filtering potential harmful aerosols. In addition to protection of airways, the larynx assists in functions such as speech and swallowing. The thoracic airway is divided in the bronchial, the bronchiolar, and the alveolar regions (Lumb 2000). The inhalation portion of the breathing cycle is characterized by air being pulled into the lung until it reaches the alveoli. Gas mixing and exchange takes place in the alveoli followed by the expiratory part of the breathing cycle, during which air is pushed out of the respiratory system through the nose or the mouth. A commonly used numbering system for the respiratory airways was developed by Weibel (1963). The trachea is numbered as G0 (generation 0) followed by G1, G2...G23, where G23 represents the entrance to the terminal alveolar sacs. The Weibel’s model gives an approximate formula for the numbering of dichotomous branching air passages in each generation as $2^N$, where $N$ is the generation number (Weibel 1963).

The bronchial region of the respiratory tract extends from the entrance of the trachea through generation 10 (ICRP 1994; Lumb 2000). The trachea (G0) and G1 are supported by U-shaped cartilaginous rings, whereas the subsequent generations are supported by helical, irregular cartilage bands and plates. The bronchiolar region extends from generation 10 through 15. Without any cartilage support, airway passages are directly embedded in the lung parenchyma. Both, the bronchial and the bronchiolar region have ciliated epithelial cells, which assist in flushing out foreign matter deposited on the mucus layer secreted by the goblet cells. In addition to particle clearance, the respiratory epithelium assists in humidification of inhaled air, acts as a chemical barrier, and provides
a defense mechanism against pathogens. The bronchial and bronchiolar regions of the lung primarily assist in transporting the inhaled air and protecting the alveolar region.

The alveolar interstitial region is comprised of the terminal bronchioles and the respiratory bronchioles. The terminal bronchioles represent G15, whereas the respiratory bronchioles represent G16 through G18. These regions are characterized by helical muscle bands, and the airway passages are directly embedded in the lung parenchyma. The terminal and respiratory bronchioles have a protective mucus layer, epithelial clara cells and smooth muscle layers. The gas exchange region of the lung begins here and extends to the deepest part of the lung, the alveolar ducts and sacs. In the alveolar region, which comprises of alveolar ducts and the alveoli, the mucus membrane is replaced by a very thin layer of surfactant on the order of a few nanometers. Goblet cells are replaced by the squamous alveolar epithelial cells. The average total number of alveoli is reported as 300 million with each alveolus being 0.2 mm in diameter, approximately. This region is primarily responsible for the gas exchange process in the lung.

The number of airway passages in the lung includes approximately 10,000 branches in the bronchiolar region and 8,000,000 alveoli. The surface area of the lung extends from less than 10 cm$^2$ for G0 – G5 to approximately 140 m$^2$ for the alveoli. As a morphologically asymmetric branching airway unit, the lung processes an air volume of approximately 0.5 liters per breathing cycle that lasts for 5 seconds under sedentary conditions (ICRP 1994; Lumb 2000). Figure 1.1 illustrates the primary regions of the lung including the nasopharyngeal region (N), tracheobronchial region (T), bronchiolar region
(B) and the alveolar region (A). In the Figure, P represents the pharynx whereas L represents the larynx.

1.2 Respiratory Fluid-Particle Dynamics

Respiratory airway modeling is important for evaluating exposure to pollutants and in the development and evaluation of respiratory drug delivery. The inherent intricacies of lung morphology make respiratory fluid dynamics modeling a challenging problem. Additionally, other factors affecting lung morphology and functionality, for example airway constriction, can complicate the analysis. The following section reviews experimental and numerical studies that have been highly important in our understanding of transport dynamics in the lung.

Preliminary Experimental and Mathematical Studies

The earliest studies in mathematical modeling of tracheobronchial airways were performed primarily by two researchers. Weibel (1963) developed a mathematical model to describe the geometry by classifying the airways in sequence starting from the trachea and proceeding to the alveolar region. Horsfield et al. (1968) developed a mathematical modeling technique of the tracheobronchial tree by numbering the branches in reverse order (starting from the last generation and going up to the trachea) following the branching sequence.

Ventilation parameters control how air travels in the lung and therefore govern particle deposition. Early studies on the evaluation of ventilation parameters in the lung were conducted in human subjects, lung casts, and idealized lung models. Pressure flow
relationships along intrathoracic and extrathoracic airways in subjects were conducted by Hyatt and Wilcox (1963). Their experiment was conducted on several subjects and results were presented in the form of centerline and near-wall velocities along the trachea, lung capacity, and flow resistance. The measured velocity profile at two locations along the trachea was observed to be flat throughout the central region, up to 1 mm away from the wall. This phenomenon was termed as unidentifiable from the pressure measurements made using two pitot tubes and was not attributed to either turbulent or laminar flow. In fact, the wall velocity data reported for three subjects exceeded the centerline velocity, which was presumed to be a random measurement error. The experiments were conducted on adult subjects for flow rates ranging from 0.5 to 4.5 liters per second. The pressure drop from the alveolus to the trachea was summarized as pressure losses due to friction and convective acceleration given by

$$\Delta P_{A-T} = \Delta P_{\text{friction}} + \Delta P_C \quad (2.1a)$$

and

$$\Delta P_C = K \rho v^2 / 2g \quad (2.1b)$$

where, $K$= constant varying from 1 for a perfectly blunt velocity profile to 2 for a parabolic shape, $\rho$ = density of the gas, $g$ = gravitational acceleration, and $v$ = average velocity across the trachea.

Schroter and Sudlow (1969) performed experiments on an airway model consisting of the first three generations of the airways. Velocity measurements were made using a hot wire anemometer in the plane of the junction as well as in the plane normal to it. All three cases showed that the peaks of the velocity profiles were located away from the centerline and inclined toward the inner edge of the branch. Based on these results, Pedley et al. (1969)
developed a mathematical model that calculates the pressure drop and viscous resistance provided by individual branches of the airways. The radial velocities obtained at the junctions illustrated a velocity peak near the edges and the velocity magnitude exceeded the centerline and near centerline velocities by a considerable extent. The velocity profile obtained was smooth and sagging across the centerline. Pedley et al. (1969) also reported non-uniform velocity profiles during inspiration. In another study by the Pedley et al. (1970), it was stated that expiration led to a flat velocity profile. Hardin et al. (1980) found that there was a drastic change in the pressure flow relationship at a Reynolds number Re = 4500 (average diameter based). Reynolds and Lee (1981) performed experiments on a latex canine airway model for inspiration as well as expiration and attributed the flattening of the velocity profile to turbulence. Reasons for sustaining laminar flow at a high Reynolds number were unclear, but were attributed to the geometry of the airways. Cohen et al. (1990) conducted flow experiments on hollow lung casts. The authors reported that unsteady velocities were observed in generations 5 to 10 of the tracheobronchial tree at flow rates of 30 and 60 L/min.

In addition to the ventilation parameters discussed above, other factors such as airway characteristics can significantly affect respiratory properties of the lung. Marshall and Holden (1963) analyzed the change in airway diameters in human respiratory airways during inhalation or exhalation along with the change in lung volume and concluded that the percent change varied between 5% for airways larger than 7 mm and 28% for smaller airways. Pedley et al. (1970) stated that the change in diameter in airways approximated to 5% for generation 1 through 2, 15% for 3 through 8 and 25% for generation 9 through 25. The effect of turbulence on bronchial pressure drop was well documented and it was reported that
boundary layers would always be laminar throughout the bronchi even at a flow rate of 240 L/min since the length of the bronchi was shorter than the developing length required for turbulent flow. Slutsky et al. (1980) conducted experiments on an airway model made of rigid latex and plotted the data in the form of a Moody chart. The slopes of the curves (friction loss) were observed to be -1 for \( \text{Re} < 500 \), 0 for \( \text{Re} > 10000 \) and between 0 and -1 for Reynolds numbers between 500 and 10000. The model followed the Zavala scheme of branching under inspiratory flow conditions alone. It was stated that the distribution of flow among branches was dependent on the tracheal Reynolds number. Also, the resistance due to the branching angles was flow-dependent and increased proportionally with the angle.

In addition to the above parameters, Jaffrin and Kesic (1974) performed dimensional analysis on the airway models, and developed laws of similitude, which allowed calculation of lung tissue resistance. It was stated that transition to turbulence occurred at a Reynolds number of 5000 and that \( \text{L/D} \), the ratio of length of a branch to its diameter had a significant effect on the resistance offered by that branch. The Reynolds numbers for a flow rate of 1 liter per second and 0.5 liter per second were reported to be \( \text{Re} = 4400 \) and \( \text{Re} = 2200 \), respectively, at their peak.

Olson et al. (1970) proposed a theoretical analysis predicting the pressure drop and flow regimes in the first 10 generations of airways for flow rates ranging from 30 to 120 liters per minute. For flow rates up to 60 liters per minute, a maximum Reynolds number of 3513 was quoted. The maximum Reynolds number for a flow rate of 120 liters per minute was found to be 8448, and although the nature of the flow was not reported, it can be concluded that the flow regime was turbulent. It was stated that periodic respiratory flows
had a negligible effect on the flow regimes under light inspiratory breathing conditions. Major simplifications were associated with neglecting the volume change of the airways during the breathing cycle and the morphological inaccuracy of the model analyzed.

Considering the transport and deposition of respiratory aerosols, primary contributions are found in the in vitro works of Chan and Lippmann (1980), Cohen et al. (1990), Kim and Fisher (1999) and Oldham et al. (2000). Chan and Lippmann (1980) performed experimental measurements of particle deposition in a hollow cast of a human larynx-tracheobronchial tree including the first seven generations (G0 – G7) and an in vivo study of twenty-six non-smoking human volunteers. This study reported a linear dependence of particle deposition efficiency on the Stokes number for particles larger than 2 μm. Maximum pulmonary deposition was reported for 3 μm particles, whereas minimum deposition was reported for 0.4 μm particles. A novel parameter representing an overall bronchial constriction index was proposed to classify individuals into sub-groups (e.g., mild constriction) based on the fraction of inhaled particles which deposit in their tracheobronchial airways. Cohen et al. (1990) performed experiments in a human central airway cast developed from the data of Schlesinger et al. (1977). Ultrafine particle deposition was reported for cyclic flow conditions at three inspiratory levels. Tracheal deposition rates exceeded predictions by a factor of 9, whereas the deposition for all other airways (G1 – G6) exceeded the predictions by a factor of 2. This increased deposition was attributed to strong secondary flows in the central airway region. A 20% increase in deposition was reported at the bifurcations relative to the airway lengths.
Kim and Fisher (1999) conducted deposition studies for 2.9 – 6.7 μm particles in symmetric and asymmetric double bifurcation models within a Re range of 283 – 4718. Deposition results were shown to be dependent on a single inertial parameter, the Stokes number. Relatively higher deposition was reported in the vicinity of the bifurcation. Novel impaction deposition correlations were proposed based on the Stokes number.

Oldham et al. (2000) performed experiments for deposition of 1 – 10 μm particles in an idealized three-generation (G3 – G5) hollow tracheo-bronchial model at a 60 L/min tracheal flow. The experiments, which were also considered using computational fluid dynamics (CFD) results showed heavy deposition at proximal and distal bifurcations, and a gradient of particle deposition from the outer airway wall to the inner airway wall for the airway generations considered.

**Preliminary Numerical Studies**

Numerical studies require validation with experimental and theoretical results obtained from realistic and idealized lung models. However, numerical studies are often better suited for realistic lung models because of their ability to better control and simulate outlet boundary conditions and transient respiration. Balashazy et al. (1996) performed simulations on tracheal bifurcation models to obtain flow structure and particle deposition patterns. The simulations were performed using a physiologically realistic carinal ridge geometry and a sharp (narrow) carinal ridge geometry. Two different CFD codes were employed, i.e., a finite difference code and a finite volume code. It was concluded that both CFD models yielded similar results. However, with the physically realistic model, it was
observed that the magnitude of secondary flow was lower in the daughter airways. The Reynolds number (based on airway diameter) used by the authors during their simulations was 851 with the maximum velocity in the trachea reaching 10.2 m/s. The maximum secondary velocities were reported to be 2.2 m/s for the model with narrow bifurcation. For the physically realistic model, the maximum secondary velocity was reported to be 0.86 m/s. The flow patterns for both geometries were reported to exhibit a double vortex structure. It was also concluded that particle deposition was very sensitive to local flow patterns in the vicinity of the surface of the bifurcation.

Guan and Martonen (1997) numerically simulated the flow in curved tubes using FIDAP. A comparison was made between the simulations and the analytical solution of Dean (1927), as well as the experimental data of Muguercia et al (1993). The flow structure was studied for the developing and fully developed region across the tube length. It was reported that the flow in a curved tube was different from that in a straight tube due to the secondary motion in a plane perpendicular to the centerline and the axial flow itself was skewed rather than parabolic. The skewness was observed to be inclined in such a way that the maximum velocities were observed closer to the outer walls of the bends. Also, the secondary motion in the cross sections formed a pair of symmetric vortices. A standard length for the flow to develop in curved tubes was estimated to be 12.5 times the inlet diameter. Muguercia et al (1993) stated that their experimental results consisted of four asymmetric vortices, reasons for which were not identifiable. The simulations by Guan and Martonen (1997) showed the presence of three symmetric pairs of vortices.
In addition to flow behavior, particle deposition studies of aerosol transport in the respiratory tract have been performed and compared with experimental results. A computational model was developed by Li and Ahmadi (1995) to study particle deposition in the upper tracheobronchial tree. A branching angle of 45° was used to model the airways. A turbulence model was used for higher inspiratory flow rates. Two cases, namely inhalation at 30 and 50 liters per minute were studied. It was assumed that a particle deposited upon surface contact. The tracheal bifurcation was symmetric with one plane of symmetry. The length and diameter of the trachea used in the simulation were 1.8 and 12 cm respectively. The grid used by the authors was a 2-D grid with 170 X 200 node points. The mean velocity reported in the trachea for a flow rate of 30 L/min was 2 m/s and the Reynolds number was 2400. Uniform profiles for mean velocities, turbulence kinetic energy and dissipation rate were specified at the inlet. The anisotropic turbulent model was solved using the STARPIC-RATE computational model, which was a modified version of the STARPIC code developed by Lilley and Rhode (1982). The maximum horizontal fluctuation velocity was reported to be 0.5 m/s near the carinal ridge wall. It was also stated that the turbulence intensity near the bifurcation region was controlled by the airway geometry and flow velocity. The turbulence intensity was reported to be higher near the bifurcation as compared to the trachea inlet.

Considering that 2-D models cannot be quantitatively compared to experimental results, Katz and Martonen (1999) simulated a 3-D model of the larynx through the trachea. The ventricular and vocal folds were simulated as two ellipses with the major axes being perpendicular to each other. The minor axis of the vocal folds was simulated as 0.7,
1.11 and 1.93 cm for sedentary (15 liters per minute), light (30 liters per minute) and heavy breathing (60 liters per minute) conditions, respectively. Results were presented only for the heavy breathing inspiratory flow conditions. The length of the larynx and trachea were 6 and 12 cm, respectively. The diameter of the trachea was specified as 1.8 cm. The flow was specified to be laminar for sedentary and light breathing activity. The Reynolds numbers that were reported for the 15, 30 and 60 liters/min case were 1155, 2310 and 4620, respectively. A uniform inlet velocity profile was used to simulate the flow. The 3-D grid constituted 34,037 nodes forming 35,200 3-D brick elements. The flow patterns observed by the authors included a central jet created by the restriction of the ventricular and vocal folds, a recirculation zone downstream of the vocal folds and circumferential secondary flow. The circumferential secondary flow was accredited to the perpendicular alignment of the major axes of the ventricular and vocal folds.

Comer at al. (2001a) performed computational fluid dynamics (CFD) analysis of planar and non-planar double bifurcation airway models (G3 – G5) for a Re range between 500 – 2000. Laminar, incompressible and steady flow conditions were employed. Results were reported in terms of velocity fields and vortex structure for planar and non-planar geometries. The effects of the shape of the carinal ridge were also reported. It was concluded that the shape of the carinal ridge negligibly affects the flow field. However, there were differences in the flow field and vortex structure between the planar and non-planar models. In a companion study, Comer et al. (2001b) report consequent effects of the flow field on particle deposition in bifurcating geometries. For a Stokes number range of 0.02 – 0.12, higher secondary flows were reported to be influential on particle transport.
Symmetric deposition in the first bifurcation and asymmetric depositions in the second bifurcations were reported. Significant changes in deposition patterns were observed for non-planar vs. planar geometries. However, negligible differences in deposition were reported for the different carinal ridge shapes considered.

Numerical simulations in a triple bifurcation airway model (G3 – G6) were performed by Zhang et al. (2002a). Deposition efficiency for a cyclic flow was reported to be higher than steady inspiratory flow (light activity) by as much as 50%. A novel matching Reynolds number lying between the maximum and mean Re was introduced to simulate quasi-steady flow conditions. Differences between steady flow at matching Re and cyclic flow were approximately 5%. In a subsequent study, Zhang et al. (2002c) report the effects of local tumors on airflow and particle deposition characteristics for a triple airway bifurcation. The Airway blockage considered was between 2 and 100% in terms of area. An increase in deposition was reported at the tumor site until the tumor blocked half the airway lumen. Further increases in tumor size decreased the deposition.

In addition to evaluating ventilation parameters associated with the respiratory system, numerical studies can be very useful when modeling the effects of physiological features such as the larynx on flow behavior in respiratory airways. These effects can be controlled by simulating the size, position and periodicity of the physiological features, which is often not practical with experimental or theoretical studies. For example, numerical simulations can simulate airway constriction, which is caused by chronic inflammation, or conduct simulations of pediatric airways by appropriately scaling the airway size. However, it is very important that numerical results are conducted with a
converged grid and validated with experiments. Grid convergence can be a difficult problem in such complex geometries. The following two sections will cover the literature available on grid convergence and constricted airway modeling for adult and pediatric subjects.

1.3 Effects of Mesh Style and Grid Convergence

Accurate assessment of the dose received from respiratory aerosols is critical in a number of applications including toxicology analysis of pollutant exposures and pharmacology analysis of inhaled medications (Jarabek 1995; Cohen et al. 1996; Frederick et al. 1998; Martonen et al. 2000; Kimbell et al. 2001). To assess respiratory aerosol dynamics within sub-regions of the lung, a number of researchers have employed computational fluid dynamics (CFD) analysis. Numerical simulations provide a powerful technique to assess the effects of geometric form and modifications, particles sizes, breathing patterns, and regional ventilation rates on local particle transport and deposition patterns both in the lung and in other biological systems. Computational fluid dynamics simulations have been employed to evaluate airflow patterns and the resulting particle deposition profiles in model geometries of the extrathoracic (Cohen et al. 1996; Kimbell and Subramaniam 2001; Schroeter et al. 2001; Martonen et al. 2003; Zhang et al. 2004; Zhang et al. 2005), bronchial (Balashazy and Hofmann 1995; Heistracher and Hofmann 1997; Comer et al. 2000; Zhang et al. 2000; Martonen et al. 2001; Zhang and Kleinstreuer 2001; Zhang and Kleinstreuer 2002; Balashazy et al. 2003; Hofmann et al. 2003) and pulmonary (Darquenne and Paiva 1996; Darquenne 2002; Karl et al. 2004) regions of the
lung. Simulations have been conducted for microscale (Martonen and Katz 1993; Heistracher and Hofmann 1997; Zhang and Kleinstreuer 2001; Martonen et al. 2002; Zhang et al. 2002; DeHaan and Finlay 2004; Zhang et al. 2004), submicrometer (Martonen and Musante 2000; Zhang et al. 2002; Balashazy et al. 2003; Martonen et al. 2003; Zhang et al. 2004) and nanoscale (Zhang and Martonen 1997; Hofmann et al. 2003; Shi et al. 2004; Zhang and Kleinstreuer 2004; Zhang et al. 2005) particle sizes. The influence of physical structures such as the larynx (Katz et al. 1999), various shapes of carinal ridges (Martonen et al. 1994), cartilaginous rings (Martonen et al. 1994) and lung tumors (Martonen and Guan 2001; Martonen and Guan 2001; Zhang et al. 2002) on the flow field have been assessed numerically. Computational simulations have also been employed to consider the effects of variable outflow division ratios to simulate different regional ventilation conditions (Zhang et al. 2000), asymmetric branching (Balashazy and Hofmann 1995), and transient flow (Zhang and Kleinstreuer 2002). In some cases, flow field validations of these models have often been performed by comparisons to in vitro results (Martonen et al. 2001; Zhang and Kleinstreuer 2002). Validations of particle depositions are widely based on comparisons to regional or branch-averaged values (Comer et al. 2000; Balashazy and Hofmann 2001; Comer et al. 2001; Zhang et al. 2001; Zhang et al. 2002; Shi et al. 2004; Zhang and Kleinstreuer 2004).

Very few studies have considered quantitative validations in comparison to more localized particle deposition patterns in single and double bifurcation models (Oldham et al. 2000). For a double bifurcation model, Longest and Oldham (2006) reported good agreement between simulations of local cumulative deposition fractions and the empirical
results of Oldham et al. (2000). These studies typically implement multiblock structured hexahedral grids and report relative errors of grid convergence on the order of 1% or less. Other mesh styles have also been employed to discretize the complex intricacies of the respiratory tract such as unstructured tetrahedral grids (Liu et al. 2002; Liu et al. 2003). The number and breadth of these studies is associated with a high degree of variability in the numerical method employed and the mesh style.

In addition to providing a better understanding of transport phenomena associated with respiratory aerosols, regional CFD models have also been employed to determine branch-level deposition functions and local deposition enhancement factors for use in whole-lung dosimetry modeling (Balashazy et al. 2003; Hofmann et al. 2003; Zhang et al. 2005). Improved model realism and the effects of upstream flow features, which have been shown to be important (Musante and Martonen 2001) but not fully quantified, require increasingly larger and more complex simulations. As such, numerical efficiency balanced with acceptable accuracy becomes evermore important in the simulation of regional respiratory aerosol dynamics and biological flows in general. However, methods that improve system efficiency while maintaining accuracy are difficult to identify considering that current CFD studies employ a large number of solution methods, mesh styles, and initial conditions and that particle deposition has been rarely validated at the sub-branch level.

When performing a CFD solution, generating the computational mesh often requires a significant amount of the total time and can affect the solution quality. As such, faster and automated mesh generation techniques can greatly enhance the total efficiency
of CFD solutions. Tetrahedral meshes, composed of four-sided triangle-faced elements, can be largely automated by current mesh generation software once a clean or seamless surface model is available. These meshes can be refined in regions of interest or automatically adapted to the flow field to provide increased resolution and reduced discretization errors. However, tetrahedral-based meshes are generally considered to be less accurate than hexahedral meshes due to a number of factors, including poor alignment with the primary flow direction and fewer control volume nodes (Ferziger and Peric 1999). Recently, hybrid meshes have also been introduced that are typically a combination of lower order internal elements surrounded by a layer of higher order pyramid, prism or hexahedral elements on the surface in order to better resolve the near-wall flow field. To assess the improved total efficiency in CFD solutions offered by tetrahedral and hybrid meshes in comparison to the higher accuracy that is typically associated with hexahedral meshes, comparison and validation studies are necessary. This is especially true for biological systems where the flow is predominantly oriented in one direction with superimposed secondary velocities arising from bifurcations and geometric curvature.

Several computational studies have considered the effects of various meshing styles on solution characteristics in biological systems with respect to *in vitro* validations, grid convergence, and other parameters either directly or indirectly. Liu et al. (2004) performed CFD simulations of the total cavopulmonary connection using structured and unstructured meshes. In this study, multi-block hexahedral meshes were considered structured and tetrahedral meshes were referred to as unstructured. For this bifurcating geometry, flow fields were reported to be similar between the structured and unstructured meshes;
however, the structured model resolved more secondary vortices. Furthermore, values of
the velocity-derived energy loss were reported to be significantly different based on the
two mesh styles. Validation of the velocity field with experimental measurements was not
reported. Prakash and Ethier (2001) conducted a mesh convergence study of blood flow in
a right coronary artery model using unstructured high-order tetrahedral meshes and a finite
element solution. Mesh-independent velocity fields for a solution adaptive tetrahedral
mesh were obtained based on a 5% cut-off criterion. However, mesh convergence of the
wall shear stress field was only observed to within 10% for the upper limit of elements
considered. Tambasco and Steinman (2002) employed a Lagrangian-based 3-D volumetric
residence time (VRT) model in stenosed carotid artery bifurcations. Theoretically the
VRT should approach unity as “Lagrangian mass conservation” is achieved. Using
uniform and adaptively refined tetrahedral meshes, Tambasco and Steinman (2002)
reported that a uniform VRT could not be achieved for the most refined tetrahedral mesh
considered. Similar to the VRT concept, Longest et al. (2004) calculated near-wall
residence time (NWRT) values of platelet-like spheres in an anastomotic model employing
hexahedral elements. In this model, the Lagrangian-based NWRT values were shown to
converge; however, the VRT criterion was not tested.

In addition to the appropriate mesh resolution, an uncertainty associated with
Lagrangian particle tracking in biofluid flows is the appropriate initial particle density or
seeding. The results of Tambasco and Steinman (2002) stress the importance of
appropriate particle seeding in determining path dependent quantities. With respect to
respiratory dynamics, Comer et al. (2001) and Zhang and Kleinstreuer (2001) initiated
parabolic particle seedings that were consistent with the initial velocity profiles employed in the corresponding \textit{in vitro} experiments. These simulations show good agreement with branch-averaged deposition efficiencies reported by Kim and Fisher (1999). Subsequent simulations employing initially parabolic particle profiles matched branch averaged deposition results very well (Zhang et al. 2001; Zhang et al. 2002; Zhang and Kleinstreuer 2004). However, Kim (2002) suggests that a constant initial profile may be most appropriate for respiratory dynamics simulations in some cases, as was employed for nanoparticle validation studies by Shi et al. (2004). Moreover, Longest et al. (2003) employed a parabolic particle profile multiplied by the local radial coordinate to account for cross-sectional area variation across local cylindrical geometries in an axisymmetric investigation of the potential for blood particle deposition.

As discussed, a number of uncertainties exist with respect to the effects of mesh style and initial particle seedings on the efficiency and accuracy of biofluid flow simulations. While it is commonly accepted that hexahedral mesh solutions provide more accurate solutions than tetrahedral meshes at similar densities, this difference has not been quantified for bifurcating domains with comparison to experimental data. Quantitatively assessing the accuracy of various mesh styles in representative geometries is useful to help modelers choose the most effective mesh style for a given application. For instance, if the branch-averaged deposition rates are of interest, a rapidly generated tetrahedral mesh may be sufficient. In contrast, it is critical to quantify their associated accuracy in representative bifurcating geometries. Comparison to localized in vitro data is necessary to make these assessments. Moreover, quantitative comparisons of numerical results to sub-branch
particle deposition data has only been reported in one previous study by Oldham et al. (2000).

1.4 Effects of Asthma Induced Constriction

This section discusses the effects of asthma induced constriction on the deposition of respiratory aerosols in pediatric lung models. The sub-sections summarize inspiratory and expiratory breathing conditions under constricted airway conditions resulting from chronic inflammation or asthma. The supporting literature review includes applications of aerosol therapy in subjects suffering from long term asthma-induced airway adaption, improvement in efficacy of respiratory drug delivery, and physical mechanisms governing filtering efficiency for inspiratory and expiratory part of the breathing cycle.

Inhalation and Asthma

Urban development has created problems in the form of health hazards due to deteriorating air quality. Asthma has become a major health concern globally, especially for children between the ages 3 to 18 years (ALA 1998; Calmes et al. 1998; Mannino et al. 1998; Clark et al. 1999). Numerous studies associated with exposure to indoor and outdoor pollutants, congested urban environments, exposure to active or passive cigarette smoke, and evolution in the patterns of respiratory ailments have been performed for a better understanding of related effects on asthma. For example, Mortimer et al. (2002) report increased incidences of adverse effects of air toxins at pollution levels below current USA
air-quality standards in children between ages 4–9 years suffering from asthma and residing in urban areas. Pollutants including ozone, sulphur oxide, nitrogen oxide, and particulate matter below 10 μm in diameter (PM$_{10}$) caused respiratory dysfunction resulting in increments of 1.16, 1.32, 1.48 and 1.26 fold in adverse respiratory symptoms, respectively (Mortimer et al. 2002). A study involving a dense urban area in southern California has found that children with a prior diagnosis of asthma are more likely to develop chronic lower respiratory tract symptoms if exposed to PM in the range of 2.5~10 μm diameter (McConnell et al. 1999). Similar results have been confirmed for other dense urban areas, such as Seattle, where a 1.12 fold increase in asthma attacks in children for a 10 μgrams/m$^3$ increase in particulate matter less than 2.5 μm diameter (PM$_{2.5}$) was reported (Slaughter et al. 2003). A study involving children between ages 3 – 12 years, suffering from asthma, and residing in Singapore indicated a three to five fold increase in the number of hospitalizations or emergency room visits associated with an approximately 28% increase in the pollution level. It was also reported that such correlations were not observed for adolescents and young adults (13–21 years of age), who were a part of the study. Ambient air level during the course of this study was reported to be within air quality guidelines established by the World Health Organization (Chew et al. 1999). An increase of approximately 40% in asthma exacerbations and chest symptoms for children between the ages 7 – 13 years suffering from mild to severe asthma was reported for a corresponding increase of ozone (O$_3$) from 84 ppb to 164 ppb during the summer months (Thurston et al. 1997). Evolution of common pollutants over the past decade shows an increase in ultrafine particles, such as diesel exhaust particulate matter (Just et al. 2006). In
this study an associated increase in the allergic inflammation of the lung tissue and airway hyper-responsiveness was reported, eventually leading to greater incidences of asthma. Asthma is taking the form of a global epidemic which is influenced by various factors including common air-pollutants, subject age, and local exposure environment.

Predicting the deposition fraction and localization of inhaled aerosols is a critical component in determining the dose received and the resulting local and systemic responses (Isaacs et al. 2005; Martonen et al. 2005). With respect to inhaled pollutants and other hazardous particulate matter (i.e., inhalation toxicology), accurate assessment of the cellular-level dose is necessary to evaluate potential health effects and establish critical exposure limits (Hofmann et al. 2002; Goo and Kim 2003; Martonen and Schroeter 2003; Zhang et al. 2005). Similarly, knowledge of respiratory aerosol deposition rates and locations is necessary to design effective inhaled medications (i.e., aerosol therapy) that target specific lung regions (Martonen et al. 2000; Finlay 2001). It has been shown that critical subpopulations may receive doses of inhaled particulate matter at rates much higher than broader population groups of healthy adults (Hofmann et al. 1989; Musante and Martonen 2000; Segal, Martonen et al. 2002). Therefore, these critical groups may be more likely to suffer detrimental health effects associated with inhaled particulate matter. For instance, it has been shown that deposition rates of inhaled particulate matter are often much higher in children and people with asthma (Musante and Martonen 2000; Chalupa et al. 2004). Similarly, the effects of asthma have been shown to have a significant impact on the branch-averaged deposition rates of inhaled medical aerosols (Martonen et al. 2003; Sbirlea-Apiou et al. 2004).
Asthma Therapy

Asthma induces airway wall remodeling (Svärtengren et al. 1991; Kee et al. 1996; Kapsali et al. 2000; Amirav et al. 2001; Black et al. 2003; Brown and Mitzner 2003; Scichilone and Togias 2004; Boser et al. 2005). These remodeled airway conditions affect the airway morphology, which along with other factors including delivery device design and ventilation parameters play an important role in estimating particle deposition in airway models (Pauwels et al. 1997; Powell and Everard 1998; Wildhaber 1998; Segal et al. 2002; Martonen et al. 2003; Morishita et al. 2004; Sbirlea-Apiou et al. 2004; Roche et al. 2005).

Considering airway remodeling, significant differences have been observed in particle deposition studies associated with the effects of asthma induced remodeled boundary conditions including changes in flow rates, variations in geometry, and modifications of breathing cycles (Parry-Billings et al. 2003; Kamps et al. 2004; Isaacs and Martonen 2005; Longest et al. 2006). Particle deposition studies performed for morphologically detailed human respiratory airways and correct boundary conditions could improve the efficacy of respiratory aerosol delivery, which eventually can help better approximate the dose and location of targeted respiratory aerosols in the lungs.

Failure to deliver drugs to the lungs using inhaler devices remains the primary cause of respiratory morbidity associated with asthma (Powell and Everard 1998). Current therapies for asthma include inhaled medications from dry powder or metered dose inhalers, which target inflammation control and airway dilation (Ibsen and Bratton 1999).
Both experiments and computational simulations have been employed to investigate respiratory aerosol dynamics and deposition in subregions of the lung. Focusing on the numerical approach, computational fluid dynamics (CFD) simulations have been implemented to evaluate airflow patterns and the resulting particle deposition profiles in model geometries of the extrathoracic (Kimbell and Subramaniam 2001; Schroeter, Musante et al. 2001; Martonen et al. 2003; Zhang et al. 2004; Zhang, et al. 2005), bronchial (Comer et al. 2000; Martonen et al. 2001; Liu et al. 2002; Zhang and Kleinstreuer 2002; Balashazy et al. 2003; Hofmann et al. 2003) and pulmonary (Darquenne and Paiva 1996; Darquenne 2002; Karl et al. 2004) regions of the lung. These simulations highlight the effects of multiple physiological, geometric, and particle characteristics on flow fields and deposition patterns. Furthermore, a number of these studies have quantitatively validated the resulting velocity fields and particle deposition rates with in vitro data (Oldham et al. 2000; Martonen et al. 2001; Martonen et al. 2001; Liu et al. 2002; Zhang and Kleinstreuer 2002; Longest and Vinchurkar 2007b). While these efforts have investigated a broad range of respiratory conditions, very few studies have considered airflow patterns in pediatric airways (Segal et al. 2000). Similarly, regional simulations of airflow patterns in central airways have been conducted on a very limited basis. No studies were found that investigated the localized effects of asthma associated airway constriction on airflow fields, respiratory aerosol dynamics and sub-branch particle deposition profiles in pediatric airways except a previous study by Longest et al. (2006).
Whole-lung and regional models as well as experiments in respiratory casts have been used to assess branch-averaged particle deposition and airflow patterns in pediatric airways. Considering whole-lung models, which calculate deposition based on branch-averaged correlations, a number of studies have considered the pediatric respiratory tract. Hofmann et al. (1989) showed a significant increase in tracheobronchial and pulmonary deposition rates for pediatric airways with particles ranging from 0.001 – 10 μm. Musante and Martonen (2000) have also developed a whole-lung particle deposition model of the pediatric respiratory tract. This model predicts that the total deposition rate for 2 μm particles is approximately twice as high in a 7-month old compared to an adult subject. Similarly, particle deposition experiments in airway casts have highlighted elevated deposition rates and localizations for pediatric conditions. For example, Oldham et al. (1997) considered the deposition of dilute particle concentrations in tracheobronchial casts of adults and children. For the micrometer particle sizes considered, deposition efficiencies were found to be greatest in the pediatric models. Considering regional computational modeling of bifurcating pediatric airways, Segal et al. (2000) have investigated the effects of tumors on airflow dynamics. Similarly, Guan et al. (2000) considered the effects of ventilation parameters on airflow patterns in pediatric bifurcation models.

Very few studies were found on the effects of asthma on particle deposition. Recently, Chalupa et al. (2004) conducted inhalation experiments in adult asthma sufferers for ultrafine particles. It was found that the total number of particles retained in the lung was 74% greater in subjects with asthma than in healthy subjects. Martonen et al. (2003)
constructed a whole-lung model of particle deposition in adult normal and asthma constricted airways. Airway constrictions of 20 and 40% were considered for two breathing levels. For all conditions simulated, airway constriction consistently increased particle deposition in the affected areas. In a previous study by the authors on transport and deposition of respiratory aerosols in models of childhood asthma, an increase of up to an order of magnitude is reported for constricted airway conditions (Longest et al. 2006).

Exhalation and Pediatric Asthma

Among the few studies that have been performed on flow and particle dynamics for expiratory conditions in the respiratory airways, Kim et al. (1989) experimentally investigated the deposition of 3, 5 and 7 μm particles in a single bifurcating airway model with differing branching angles of 15, 30 and 45 degrees. In this study, particle deposition in representative upper respiratory airways for expiratory conditions was reported to be influenced by secondary flows rather than inertial impaction. Bennett and Smaldone (1987) conducted an experimental study investigating expiratory against inspiratory deposition of 0.9 μm particles in excised dog lungs. This study proposed that the nature of the flow profiles and differences in geometry could be the primary factors governing particle deposition. Smaldone (2000) analyzed the theory behind the observed differences during the expiration cycle and related this theory to secondary flow patterns and a constricted airway geometry during forced expiration. Zhao and Lieber (1994) conducted an experimental investigation of expiratory flow patterns for a central airway model with a branching angle of 35 degrees and Reynolds numbers of 518, 1036 and 2089 with
corresponding Dean numbers of 98, 196 and 395, respectively. This study reported that secondary flows for expiratory conditions cause a centrifugal effect on particles leading to dispersion. Fresconi and Wexler (2003) reported maximum values of secondary velocities at bifurcations. It was assumed that these secondary velocities generated maximum particle deposition due to impaction in the bifurcation region (Fresconi and Wexler 2003).

Dispersion is often considered to occur in lung airways as a result of a convective mixing process between the inhaled particles and the residual air (Heyder et al. 1988). Higher secondary flow during the expiratory part of the breathing cycle was reported by Scherer and Haselton (1982). Saranpani and Wexler (2000) have developed a mathematical model incorporating particle dispersion as a deposition mechanism in human airways. This study reported that dispersion affected the coarse (>1 μm) and ultra-fine (<100 nm) particle deposition considerably for the lower airways. Some of the studies refer to this type of dispersion mechanism as impaction for secondary flows, which is the terminology adopted in the current study.

The transport and deposition of particles in a pipe bend can assist in understanding the processes and governing mechanisms associated with expiratory flow. Respiratory airways can be represented by a complicated set of bifurcating pipes in series from the trachea to the alveoli. The effect of curvature of these tubes on particle deposition in the airways can be vital for expiratory flows. Secondary flows can be important at the pipe junctions (carina) and the surrounding vicinity due to mixing fluid streams during exhalation (Bennett and Smaldone 1987; Heyder et al. 1988; Kim et al. 1989; Balashazy and Hofmann 1993; Zhao and Lieber 1994; Fresconi et al. 2003). It has been shown that
particle transport for flow through pipe bends is a function of the Stokes number, Stk, and the Reynolds number, Re (Tsai and Pui 1990; Sato, Chen et al. 2002; Wang et al. 2002). For lower Reynolds numbers (Re < 250), particle deposition can be extremely sensitive to the bend geometry (Wang et al. 2002). This condition could be representative of sedentary breathing conditions. Furthermore, Sato et al. (2002) report that the contraction ratio in addition to the Stokes and Reynolds numbers affected particle deposition in a tube with an abrupt contraction. This condition can be representative of constricted airways. The study points to a critical flow Re = 100, below which Re effects become more important, and the deposition curve shifts to larger Stokes numbers. A particle deposition correlation was proposed for flow through tubes with a contraction, based on a $Stk_{50}$ parameter (Stokes number for the normalized deposition efficiency of 50%). For flow through a 90° bend, Wang et al. (2002) report a critical Re = 250, below which orientation and geometry of the pipe bend affects the deposition considerably. The overall deposition efficiency is reported as a function of the Reynolds number, Schmidt number and Dean number. Impaction losses were neglected due to a maximum Stokes number of $2 \times 10^{-5}$. Cheng and Wang (1981) report that the impaction efficiency of a 90° bend is mainly a function of the Stokes number and the flow Reynolds number. In this study the curvature ratio of the bend was within a range of 4 – 30 diameters, and the particle Reynolds number was less than one. These studies can assist in understanding the flow and particle transport mechanisms during expiratory breathing conditions.

Correlating the particle deposition efficiency in a 90° bend to a flow through two pipes merging together representing expiratory breathing conditions in the airways poses a
challenging problem. Primary impaction of particles is the dominant deposition mechanism during inspiratory flow (Chan and Lippmann 1980; Yeates, Gerrity et al. 1981; Gawronski and Krzysztof 1986; Bennett and Smaldone 1987; Balashazy and Hofmann 1993; Martonen and Katz 1993; ICRP 1994; Zhao and Lieber 1994; Heistracher and Hofmann 1997; Kim and Fisher 1999; Comer et al. 2001; Martonen et al. 2001), whereas secondary impaction of particles is considered important during expiration, as discussed earlier, for the respiratory particle size range. Kim et al. (1999) studied the effects of asymmetry and bifurcation angles on the deposition of 2.9 – 6.7 μm aerosols in sequentially bifurcating airway models under inspiratory conditions. The overall deposition was correlated to a single inertial parameter, Stk. In another study, Kim and Fisher (1989) propose a correlation for particle deposition during the expiratory phase as a function of the Stokes number and the branching angle. For a constant Stokes number, the deposition increased with increasing branching angle (Kim et al. 1989). Analytical correlations based on inertial impaction for curved tubes, and sedimentation and diffusion for straight tubes, have been proposed to evaluate total deposition in lung airways (Kim et al. 1989; Kim and Fisher 1999). Other studies have shown differences from these correlations based on physiological structures such as laryngeal jets and cartilaginous rings (Martonen 1982). Typically, the inclusion of dimensional parameters, such as branching angles, in a correlation makes it difficult to develop algebraic whole lung deposition models.

It has been shown that children are relatively more susceptible to allergic airway inflammation leading to asthma (Chew et al. 1999; Clark et al. 1999). Particle deposition profiles for inspiratory conditions in the lung of a subject suffering from asthma can differ
significantly from normal subjects (Svartengren et al. 1991; Longest et al. 2006). These deposition characteristics are also dependent on the age of the subject (Schillerscotland et al. 1994; Phalen and Oldham 2001). Very few numerical studies have concentrated on the remodeling of airway morphology for asthmatic conditions (Longest et al. 2006). After an exhaustive literature review, no studies were found focusing on particle deposition for expiratory conditions within an asthma-induced remodeled pediatric airway geometry. The current literature is also unclear on the effects of specific governing mechanisms for particle deposition in respiratory airways under expiratory conditions.

1.5 Pharmaceutical Particle Sampling

The role of particle size characterization is important in many fields, including pharmacology and toxicology. Particle size distribution is considered a core element in the analysis of pharmaceutical inhaler performance. A pharmaceutical aerosol could be in the form of a cloud discharged from a dry powder inhaler (DPI), a nebulizer or a spray discharged from a metered dose inhaler (MDI) (USP-601). Considering toxicology studies, characterizing the concentration and nature of pollutant particles in the environment has become an essential step for evaluating the quality of air required for safe and healthy respiration.

The human respiratory tract can be classified as a filtering mechanism which removes particles in the broad size range of 10 µm – 0.001 µm (ICRP 1994). The cut-off size below which a particle is considered to be respirable (i.e., inhalable) is approximately 7 – 10 µm (Finlay 2001). Decreasingly smaller sized particles are filtered through the
bifurcations of the respiratory system from the trachea to the alveolar region. Although the lung filtration process is governed by six different deposition mechanisms (inertial impaction, diffusion, gravitational settling, turbulent dispersion, interception and electrostatic precipitation), it is difficult to manufacture a prototype which can imitate the lung in all its aspects.

In vitro lung model deposition data has been used to model total in vivo lung deposition for respiratory aerosols (Snell and Ganderton 1998; Thiel 1998). Inertial impactors have also been recommended as a simple and reproducible system for simulating in vivo aerosol deposition (Flesch et al. 1967; Marple 1970; Marple 2004). When using an impactor, particle size distribution can be efficiently determined. An impactor is a size classification device, in which aerosol particles are passed through a nozzle and directed against a flat plate. Particles with inertia high enough to cross over the stream lines may result in impaction on the plate, depending on the aerodynamic diameter. For theoretical evaluations, it is assumed that a particle impacting on the plate sticks to the surface (Hinds 1998). Cascade impactors consist of multiple impactor stages arranged in series and are used for measuring particle size distributions.

The significant mechanisms affecting deposition and localization in the lung are defined by the particle aerodynamic size distribution. The most common way of studying particle size distribution is by using cascade impactors (Ranz and Wong 1952; Andersen 1966; Flesch et al. 1967; Lundgren 1967; Mercer and Stafford 1969; Marple 1970; Marple and Liu 1974; Marple and Liu 1975; Marple and Willeke 1976; Rader and Marple 1984; Vaughan 1989; Swanson et al. 1996; Hinds 1998; Marple et al. 2003; Marple 2004;
A few cascade impactors used for aerosol studies are the Andersen 1 ACFM non-viable (biologically inactive) particle sizing sampler (ACI) and the Next Generation Impactor (NGI). The flow rate for the ACI is usually maintained at 28.3 L/min, whereas for the NGI it can be adjusted in the range of 30 – 100 L/min (USP-601).

Cascade impactors have been studied based on the shape of jets, design criteria and flow conditions governing aerodynamic size distribution (Ranz and Wong 1952; Cohen and Montan 1967; Mercer and Chow 1968; Mercer and Stafford 1969; Marple and Liu 1974; Marple and Liu 1975). A few primary studies have lead to the development of new impactor models (Andersen 1966; Lundgren 1967). Subsequent studies focused on improving the performance of the impactors and testing the impactors with preliminary lung models (Marple and Liu 1974; Marple and Liu 1975; Marple and Willeke 1976; Rader and Marple 1984; Vaughan 1989; Swanson et al. 1996; VanOort et al. 1996).

In addition to entry losses and influences of electrostatic forces, several other factors were found to affect the performance and reliability of impactors. Swanson et al. (1996) numerically investigated a low flow single orifice cascade impactor called as the PC–2, for particle sizes ranging from 1 to 10 µm using commercial CFD software. The analysis included the effects of gravity, inertia and viscous friction. Sticking probability and restitution were defined for the model and S-shaped particle deposition curves were obtained. Particles within a critical size range were observed to be trapped in recirculation zones close to the impactor walls. These results highlighted potential problems with impactor data associated with losses and recirculating flow. Mitchell et al. (1988) experimentally studied the deposition of 10 µm particles in a calibrated Mark-II ACI
impactor attached to a calibrated preseparator. The authors concluded that for particles in the size range of 10 µm and above, wall losses could account for up to 20% of the total deposited mass, and that the wall losses increased significantly with moisture content of the aerosol particles. Vaughan (1989) conducted analytical computer simulations of various particle sizes in the ACI with greased and ungreased collection plates, and evaluated wall losses. An important assumption of this study was the entry efficiency curve. Size distribution curves were developed for particle deposition on individual stages and between stages. The study concluded that preceding stages reduced wall losses due to constrained flow, but negligibly affected size distribution. The most significant limitation of this study was the unknown actual entry efficiency of particles. The higher end of wall losses was reported to be in the range of 20 – 40% of the total mass of initial particles.

Dunbar et al. (2005) experimentally analyzed the effects of particle bounce, entrainment, and overload on uncoated impactor plates using large porous placebo particles and concluded that there were significant differences in mass median aerodynamic diameter and geometric standard deviation for the ACI (60 L/min flow) and the multistage liquid impinger (MLSI). The authors found that 20 µm porous glass plates inverted on the impactor collection plates minimized bounce effects and recommended the use of impaction substrate material and solvent. Roberts et al. (2005) studied the ACI and NGI for effective particle diameters as a measure of acceptance criteria. Regular mensuration of cascade impactors and development of acceptance criteria were recommended for new and used cascade impactors. Mensuration is defined as a periodic measurement of nozzle diameters on each stage of the impactor studied. Stein and Olson (1997) studied 14
samples of the ACI to test the reproducibility of particle size distribution results obtained experimentally, and compared the results to theoretically obtained data. The size distributions were significantly different for various Mark-II ACI impactors because of the differences in stage cutpoints. The current literature does not appear to consider the effect of electrostatic charge, hygroscopic growth, and evaporation on particle size cut-off values for standard cascade impactors. Based on these observations, it appears that numerical investigations are needed to improve impactor performance and reliability, standardize procedures for sampling, recommend design criteria, and report wall losses.

Considering dynamic properties, Janssens et al. (2003; 2004) report lung dose to be pMDI dependent, and flow as well as spacer independent. This can be assumed to indicate dependence on the ballistic component of the spray and particle size. Nichols et al. (1998) proposed a high flow rate ACI, which provides a ballistic component to DPIs to correlate in vitro particle size data with in vivo studies. Effects of drag parameters and interception mechanisms on impaction characteristics were reported by Rader and Marple (1984). The study reports that interception and particle density negligibly affect impaction characteristics. For a laminar Reynolds number range (500 – 1500), impaction characteristics are reported to be dependent on only the Stokes number. Marple and Liu (1974) report impactor design to be a function of the Reynolds number, the ratio of jet length to jet diameter, and the ratio of the distance between the jet exit and the impaction plate to the jet diameter. In a consequent study, Marple and Willeke (1976) report the Reynolds number alone as a design criteria for prespecified impactor length scale ratios. Additionally, true flow rates in the respiratory tract need to be considered when simulating
aerosol deposition using cascade impactors (Greenspan 1996; VanOort et al. 1996; Nichols et al. 1998; Nichols and Smurthwaite 1998). Effects of interception and drag characteristics of aerosols could also play a vital role in estimating particle sizes with cascade impactors (Rader and Marple 1984; Welty et al. 1984; Holzner and Muller 1995; Stein 1999; Menetrez et al. 2001; Dunbar and Mitchell 2005).

Although some studies have illustrated advantages of the NGI over the ACI (Marple et al. 2003; Kamiya et al. 2004), the ACI has been used prevalently for testing particle size distributions (Flesch et al. 1967; Mitchell et al. 1988; Vaughan 1989; Holzner and Muller 1995; VanOort et al. 1996; Stein and Olson 1997; Nichols et al. 1998; Nichols and Smurthwaite 1998; Stein 1999; Janssens et al. 2003; Marple 2004; Dunbar and Mitchell 2005). Additionally, the ACI is associated with the current food and drug administration (US FDA) guidelines. Availability of the extensive data in the literature and its prevalent use make the ACI suitable for a numerical study of cascade impactor performance.

1.6 Electrostatic Charge Effects

Electrostatic charge can affect the transport and deposition of aerosols, which is relevant in many fields including inhalation toxicology, pharmaceutics and micro-electromechanical systems. The influence of charge on the deposition of pollutants and pharmaceutical aerosols in the lung has been widely reported (Yu 1977; Chan and Yu 1981; Melandri et al. 1983; Balachandran et al. 1991; Ljepojevic and Balachandran 1993; Hashish et al. 1994; Cohen et al. 1995; Balachandran et al. 1997; Cohen et al. 1998; Hinds 1999; Koolpiruck et al. 2004; Saini et al. 2004; Jeffers 2005; Martonen et al. 2005).
Considering pharmaceutical aerosols, inhalation therapy typically employs pressurized metered dose inhalers (pMDI), dry powder inhalers (DPI) and nebulizers to disperse medications through the extrathoracic airways to the deeper portions of the lung. The current study will not consider medications discharged from nebulized aerosols. Several studies have reported charge effects on the characterization of particles associated with inhaler devices (Byron et al. 1997; Thiel 1998; Peart and Byron 1999; Peart et al. 2002; Rahmatalla et al. 2002; Glover and Chan 2004; Mikkanen et al. 2004; Noakes 2004; Kwok et al. 2005; Telko et al. 2007). Additionally, pharmaceutical aerosols have been studied to evaluate the effects of external factors like humidity (Ratz et al. 2002; Kwok and Chan 2007; Young et al. 2007).

In order to characterize the dominant transport mechanism and the location of deposition associated with the lung or an inhaler device, it is essential to study the particle size distribution of an aerosol sample (USP-601). The most common experimental method for studying these particle characteristics is by using cascade impactors (Ranz and Wong 1952; Andersen 1966; Flesch et al. 1967; Lundgren 1967; Mercer and Stafford 1969; Marple 1970; Marple and Liu 1974; Marple and Liu 1975; Marple and Willeke 1976; Rader and Marple 1984; Vaughan 1989; Swanson et al. 1996; Hinds 1998; Marple et al. 2003; Marple 2004; Dunbar and Mitchell 2005). Quantifying the amount of charge on both, environmental and pharmaceutical aerosols is an important step towards determining the expected deposition characteristics. Measurements of charge quantity and interactions for aerosols have been conducted to quantify the amount of charge (Makin; Liu and Pui 1974; Rowley 2001; Balachandran et al. 2003). Although in vitro studies report that a
considerable effect of electrostatic charge on the size distribution results from cascade impactors is expected, the literature does not quantify the effects of static charge on deposition.

The challenge in standardizing the quantity and effect of charge on deposition is hindered by the fact that charge characteristics vary with the pharmaceutical blend and the inhaler device used. For example, DPIs and MDIs are known to produce significantly different charge levels. The literature available on the amount of charge carried by DPIs and MDIs is summarized below.

**DPI Charge**

Triboelectricity of pharmaceutical powders for large particle sizes (> 50 µm) are reported by Rowley (2001). For metallic contact surfaces, particles in the size range 90 – 120 µm are negatively or positively charged exhibiting an approximate magnitude of 90 nC/g. For PVC and polypropylene contact surfaces, a maximum charge magnitude of 100 nC/g and 15 nC/g are reported, respectively (Rowley 2001).

The electric low pressure impactor (ELPI) is widely used for measuring particle size specific charges. A comprehensive investigation of DPI electrostatics is possible due to electrical isolation of individual stages for a particle size range extending down to 30 nm. Telko et al. (2007) studied two different DPIs, the Rotahaler® (GlaxoSmithKline, RTP, NC) and the Inhalator® (Boehringer Ingelheim, Germany). Averaged values were employed for electrostatic charge because non-uniformity in distribution with respect to
particle size and formulation were expected. The polarity varied between negative for larger particles and positive for smaller ones (Telko et al. 2007). Irrespective of polarity, inhalers, and other parameters, a highest charge of approximately $4 \times 10^5$ fC was observed for Stages 7 and 8 of the ELPI with cut-off sizes of 0.63 and 0.97 µm, respectively. It was reported that the choice of capsule, although affected the polarity of the charge, had only a minor effect on charge magnitude. A maximum charge of 1.5 nC/30 mg actuations with 1% drug load for sieved lactose and 2.5 nC/30 mg for milled lactose were reported, both using the Inhalator. The maximum charge using the Rotahaler was 0.4 nC/30 mg (Telko et al. 2007). Overall, the maximum charge reported in this study was comparable to a range of 0.5 – 400 elementary charges for 1 – 13 µm particles, respectively.

Mikkanen et al. (2004) performed a particle mass, number, and charge size analysis for DPIs with an ELPI. A charge level range of 1 – 300 units per particle as an approximately linear monotonic function of the particle size range of 0.1 – 10 µm was reported. Byron et al. (1997) studied electrostatic properties of fine powders of processed pure micronized terbutaline sulfate and budesonide in commercially available Bricanyl and Pulmicort Turbolahers. These were compared to powders aerosolized using the prototype Dryhalers. Fine particle dose (FPD) for terbutaline sulfate and budesonide were approximately 0.15 and 0.03 mg. A range of 0 – 800 pC/mg was reported for the Turbolaher and Dryhaler used in this study. The study reported approximately 200 elementary charges per particle with mean aerodynamic diameter of less than 5.8 µm. Balachandran et al. (2003) conducted net bipolar charge measurements of pharmaceutical powders in the size range 1 – 10 µm using a method which separates charged particles of
opposite polarity. A maximum charge of $3.5 \times 10^{-10}$ and $2.5 \times 10^{-9}$ C per 125 mg of powder mass using a precipitator and wire electrodes, respectively was reported by a study on charged bipolar pharmaceutical powders in the absence of an external electric field (Balachandran et al. 2003). Ali et al. (2007) studied three different DPIs – Spiriva, Advair and Pulmicort, and reported a net charge to mass ratio of 0.76, 0.49 and 0.46 μC per gram for particle sizes (MMAD) of 4.99, 5.29 and 3.65 μm, respectively. However, the maximum charge for three DPIs was approximately 6.6 μC per gram, which is similar to 0.003, 3.2 and 7000 elementary charges for 0.1, 1 and 13 μm particles, respectively (Ali et al. 2007).

For dry powders, factors like frequent collisions and neutralization or loss of charge with time affects the nature and behavior of different charging mechanisms. Particle Doppler anemometry extends the use of conventional laser Doppler velocimetry to measure the particle size and charge of aerosols. In a study by Kulon et al. (2003), naturally charged aerosols indicated an average charge to mass ratio of 0.24 μC per gram and a maximum of 91 μC per gram for a particle size range of 1.9 – 2.5 μm. In addition, the average charge per particle was reported as a linear fit with a maximum level of $5 \times 10^{-17}$ C for a particle size range of 0.5 – 4 μm. These translate to a maximum charge of approximately 315 and 65 electronic charges per particle for 4 μm and 1.5 μm particles, respectively (Kulon et al. 2003).

Aerosol properties in terms of fine particle dose (FPD), fine particle fraction (FPF) and static charge levels may be influenced by relative humidity (RH) levels for pharmaceutical powders. A RH value of 60% may be considered critical for change in the
profile pattern of FPD and FPF in DPIs. Both FPF and FPD show a decrease at RH levels above 60%. A maximum charge of 30,000 fC per µg is typical for DPIs with micronised salbutamol sulphate particle size of 1.48 µm and sieve fractioned lactose carrier of particle size 88.78 µm (Young et al. 2007). At 60% RH, a mean electrostatic charge of – 419 pC was reported by Young et al. (2007). Although, there is a difference in the reported charge levels, the range of charge reported is the focus of the present literature review. Usually, it is reported that RH tends to monotonically decrease the triboelectric effect, which may vary with the inhaler used. A maximum difference of 20% in the absolute specific charge levels for a RH level range of 15 – 90% is reported in a study on two separate DPIs (Pulmicort and Bricanyl Turbohaler) by Kwok et al. (2007). The study reports a mean charge level range of 20 – 35 pC and a maximum specific charge level of 25 µC/g for a particle diameter of 0.388 µm. For particle sizes below 1.62 µm, the maximum specific charge was below 3 µC per gram. For particle sizes of 0.621 and 0.96 µm, the maximum charge levels were approximately 8.5 and 5 µC per gram, respectively. Irrespective of the polarity, the maximum number of elementary charges per particle was reported for a RH of 15% as approximately 650, 205, 80, 34, 11, 5 and 4 for ELPI stages 12 – 6, respectively (Kwok and Chan 2007). These charge levels are consistent with cut-off diameters of 6.06, 4.04, 2.42, 1.62, 0.96, 0.621 and 0.388 µm, respectively. However, RH reportedly has negligible effects on the charging of particles with low hygroscopicity (Rowley and Mackin 2003).

The average charge associated with DPIs is reported to be on the order of 1 up to a few hundred elementary charges, depending on particle size. The saturation charge limit
provides good approximation to DPI charge levels. Specifically, the saturation charge level results in an elementary charge range of 4 – 531 unit charges for a particle size range of 0.2 – 13 μm, respectively (Hinds 1999). Although the range of saturation limit charge for particles lower than 1 μm diameter is higher than that reported in the literature, it is well known that the existing charge measurement systems are not exact, and may be inefficient particularly for sub-micrometer particles. On the other hand, the saturation limit is a theoretical range of charge levels based on the material properties and surface area of the particles in addition to the applied electric field strength. The present study employs zero or no externally applied field strength. The material properties and aerodynamic diameters considered in the present study are typical of pharmaceutical powders.

**MDI Charge**

Electrostatic forces may be weak for distant drug particles on the order of a few millimeters from the surface of a delivery device, but increase as the square of the distance decreases. For MDIs, the degree and polarity of charging is affected by the choice of propellant, delivery device characteristics, polymer material based surface properties, and interactions between the drug and the carrier liquid. Bespak (Bespak Inc.) evaluated a range of commercially available MDIs and DPIs for charge conditions. It was concluded that ranges of 1 – 200 and 2 – 25 elementary charges per particle were observed for the MDIs and DPIs, respectively (Bespak Inc.). Peart and Byron (1999) studied electrostatic properties of fine particles from commercial MDIs (Ventolin and Airomir). Maximum
charge levels of 165 pC per 65 µg for Ventolin and 175 pC per 40.2 µg for Airomir were reported, corresponding to 300 and 500 elementary charges per particle, respectively.

Electrostatic charge levels of aerosol particles from commercially available MDIs may be studied using the ELPI. Glover and Chan (2004) studied Ventolin and Flixotide aerosols for their charge characteristics confirming reproducibility of the results within 12.5% for a total of 10 actuations. Charge per unit mass was reported for individual stages of the ELPI, which assisted in correlating charge levels to the particle sizes studied. For Ventolin, a maximum charge of approximately 210 pC per 7.25 µg with a single peak in the particle size range of 0.3 – 0.5 µm was reported. For Flixotide, 300 pC per 35 µg with the first peak in the particle size range of 0.3 – 0.5 µm and a second peak of - 310 pC per 5 µg in the particle size range of 6 – 7 µm particle size range were reported. A maximum charge level of 1500 pC per actuation was reported for all cases analyzed (Glover and Chan 2004). In a subsequent study (Kwok et al. 2005) the ELPI was used to study five different MDIs for electrostatic properties of the fine particle dose. Absolute averaged maximum unit charges reported in this study as a function of particle size were approximately 16000, 2630, 375, 128, 25, 40, 142, 338, 67, 17.5, 8 and 0 for particle diameters of 6.06, 4.04, 2.42, 1.62, 0.96, 0.621, 0.388, 0.266, 0.159, 0.0948, 0.0552 and 0.028, respectively. Dastoori et al. (2005) suggested a range for electrostatic charges on particles based on the production mechanism and material properties. A charge range of $10^{-3}$ to $10^{1}$ C/kg was reported for liquid droplets created by atomization as well as for organic solids created using ball milling or spray drying. To generate these estimates, an upper limit of the maximum charge which can be transferred to a particle was evaluated
theoretically and related to the time dependence of the charging. Typical charge densities reported for pipe transport of powders were $10^{-4} - 10^{-5}$ C/kg, and for spraying of liquids were $10^{-3} - 10^{-5}$ C/m$^3$ (Dastoori et al. 2005). These represent a difference of one order of magnitude between solid particles and liquid droplets.

Various physiochemical mechanisms and material properties including hygroscopicity, amorphous content, resitivity, shear stress, deaggregation of drug agglomerates, and movement of particles in the turbulent airstream affect triboelectrification as well as contact charging of DPI and MDI dispersions. As described for dry powders, the saturation charge limit is the closest theoretical approximation to the DPI charge values quoted in the literature. The saturation limit is in good agreement to particles larger than 0.5 μm, but underestimates the charge level for particles smaller than 0.5 μm.

The literature reports that MDIs typically show a charge level of 13 to 20 fold of the charge levels associated with DPIs due to a significant difference in the level of triboelectrification (Rowe et al. 2003; Kwok et al. 2005). This increase in charge value is assumed to be due to a cumulative or isolated effect of one or more triboelectrification parameters mentioned above. In addition, the increased charge level for MDIs could be due to a relatively more dynamic system as compared to DPIs. For example, the liquid droplets are evaporating, which can concentrate the charge over a smaller surface area. Furthermore, there is significant movement of the liquid between the core and the periphery of the aerosol. As a result of these observations, MDI charge levels employed in
the present study are selected to be an order of magnitude higher than the DPI charge values (saturation limit charge).
Fig. 1.1. Primary regions of the human respiratory system illustrating the location of the Nasopharyngeal region including the larynx and the pharynx, the tracheobronchial region, the bronchiolar region and the pulmonary region (Vinchurkar 2004).
2. Objectives

The overall goal of this project is to investigate under-explored areas of respiratory aerosol transport and deposition in the lung and in pharmaceutical testing devices. For the evaluation of respiratory aerosols, computational fluid dynamics (CFD) simulations have been applied with frequent comparisons to available experimental data sets. The applications considered in this project include both the numerical aspects and the physical phenomena of respiratory aerosol transport and deposition. The specific applications considered address the effects of mesh type and grid convergence on flow field and aerosol deposition in the lung, the effects of bronchoconstriction and exhalation on aerosol deposition, an evaluation of a pharmaceutical particle sampler, and the effect of electrostatic charge on aerosol deposition in pharmaceutical testing devices. These applications are further described below in the form of objectives.

**Objective 1:** Characterize the effects of commonly used mesh styles and grid convergence criteria on flow field and aerosol deposition patterns in idealized respiratory airways.

Current numerical studies of respiratory dynamics apply arbitrarily selected mesh styles and unjustified criteria to establish grid convergence. The objective of this study is to
better evaluate the effects of mesh generation techniques and grid convergence on velocity and local particle deposition fields in representative bifurcating geometries. To achieve this objective, a set of commonly implemented mesh styles has been considered. These mesh styles include structured hexahedral, unstructured hexahedral, prism, and hybrid tetrahedral-hexahedral. Mesh independence of the results has been tested in these systems using a seldom implemented but theoretically sound grid convergence index (GCI) approach that accounts for cases where true grid halving is not feasible. A velocity dependent or secondary variable in the form of particle deposition profiles has been evaluated for each mesh on a local basis and compared to the empirical results of Oldham et al. (2000) for an identical bifurcating geometry. It is expected that both the degree of grid independence and the mesh style used will significantly affect the numerical results of the flow field and particle deposition patterns in the respiratory geometry considered. This study is intended to serve as a basis for modeling broader regions of the lung where multiblock structured hexahedral meshes may be prohibitively complex.

**Objective 2: Investigate the effects of exhalation on aerosol deposition in healthy and constricted models of pediatric airways.**

In current whole-lung models of particle transport, deposition during exhalation is approximated using the same correlations applied for inhalation conditions. Moreover, a recent study by Longest et al. (2006) has shown that bronchoconstriction due to asthma can
have a dramatic impact on regional and local aerosol deposition. The objective of this study is twofold:

2.1 *The first objective is to characterize the effects of exhalation on regional and local deposition of aerosols in the branching airways.*

2.2 *The second objective is to characterize regional and local deposition characteristics during exhalation in models of childhood asthma*

Micron sized particles ranging from 1 – 7 μm have been considered, which are consistent with the distribution of typical medical aerosols (Finlay 2001), as well as coarse atmospheric and exhaust particulate matter (Kittelson 1998; Friedlander 2000). The computational model employed has been validated with comparisons to branch-averaged and sub-branch deposition profiles. For this study, particle depositions have been evaluated with respect to both branch-averaged deposition rates and sub-branch focal accumulations, which are referred to as hot spots. Results of branch-averaged deposition rates have been compared to predicted values from sample analytic and empirical correlations. The formation of hot spots has been quantified with a novel microdosimetry deposition factor ($\chi$). Geometries considered include double bifurcation models of upper (G3 – G5) and central (G7 – G9) airways for a four-year-old child under healthy and 30% constricted conditions. Steady exhalation flow rates consistent with sedentary, light and heavy activity levels have been employed. At these flow rates, laminar and low Reynolds number (LRN) k-ω flow solutions were necessary. Results for normal and constricted airways are presented in terms of velocity fields, branch averaged deposition rates, and microdosimetry
deposition factors. It is expected that deposition correlations will be developed for branch-averaged deposition during exhalation. In future studies, these correlations can be applied to whole-lung algebraic models of particle deposition in order to improve performance.

**Objective 3:** (a) Evaluate fluid-particle dynamics in an inertial impactor, and (b) Determine the effects of electrostatic charge on the deposition of common DPI and pMDI generated pharmaceutical aerosols.

Particle size characterization is vital for the evaluation of inhaler performance, and for obtaining information on the mechanisms effecting deposition in the lung, as well as the potential deposition locations. Cascade impactors are commonly used as particle samplers to test size distributions of aerosols (Ranz and Wong 1952; Andersen 1966; Flesch et al. 1967; Lundgren 1967; Mercer and Stafford 1969; Marple 1970; Marple and Liu 1974; Marple and Liu 1975; Marple and Willeke 1976; Rader and Marple 1984; Vaughan 1989; Swanson et al. 1996; Hinds 1998; Marple, Olson et al. 2003; Marple 2004; Dunbar and Mitchell 2005). These impactors with applications to the fields of pharmacology and toxicology need to be evaluated for their performance in order to establish accurate particle size distribution results. Additionally, aerosols from common pharmaceutical delivery devices such as pressurized metered dose inhalers (pMDI) and dry powder inhalers (DPI) may be significantly charged (Byron et al. 1997; Thiel 1998; Peart and Byron 1999; Peart, Orban et al. 2002; Rahmatalla et al. 2002; Glover and Chan 2004; Mikkanen et al. 2004; Noakes 2004; Kwok et al. 2005; Telko et al. 2007). However, these
static charges are typically not considered in cascade impactors used to study particle size characteristics. The image charge force may result in a change in the estimation of the actual particle cut-off size measured in impactor studies. The objective of this study is twofold:

3.1. Numerically investigate a high flow-rate impactor- The Andersen Mark II cascade impactor.

3.2 Evaluate charge effects on the deposition of typical pharmaceutical aerosols in an inertial cascade impactor.

The current study presents a numerical analysis of the multi-stage, multi-orifice Andersen cascade impactor (ACI). The flow rate for the ACI is maintained at 1 ACFM (28.3 L/min) and its functionality is limited to non-viable (biologically inactive) particles. Specifically, the particle sampler considered is the Mark II ACI with 0 – 8 stages and a particle size range of 0.2 – 12 μm. The upper limit for total particulate mass on any of the stages is 10 mg. The assumptions for the numerical model include no-slip wall boundary conditions and adherence of the aerosol particles to the collection plate upon impaction for a laminar to transitional incompressible flow. Results are presented in the form of velocity profiles, recirculation and dead zones, stage retention fraction and wall losses. Results for retention fraction are validated with available data from the literature as well as from the manufacturer. It is expected that significant recirculation zones and non-uniformity in flow distribution will result in higher numbers of suspended particles and increased wall losses.
The second part of this study addresses the effects of electrostatic charge on particle deposition in a typical pharmaceutical sampler, the Andersen Mark II cascade impactor. The image charge component of the electrostatic force is considered, whereas the space charge component is assumed to negligibly affect the results due to dilute discrete flow conditions. The electrostatic force UDF is validated with the theoretical formula proposed by Chen and Yu (1993). The results obtained for particle retention in the Andersen cascade impactor stages under electrostatic charge effects are presented for two charge levels, i.e., the saturation limit charge and ten times the saturation limit charge representative of DPI (dry powder inhaler) and MDI (metered dose inhaler) aerosols. These representations are based on comparisons to the values quoted in the literature. Overall, the present study is focused on the numerical assessment of charge effects in an inertial cascade impactor for typical pharmaceutical aerosols. This study provides correction curves to standard impactor data tables to account for the effect of particle charge on deposition and sizing. The electrostatic model is validated with theory, and is ready to be established as an integral part of particle deposition analyses in respiratory airway models for future studies. It is expected that these charge levels will significantly affect particle size distribution results in the impactor used.
3. Methods

3.1 Continuous Phase Transport

The incompressible and isothermal flows of interest are simulated using both a laminar assumption and the low Reynolds number (LRN) k-ω turbulence model. The LRN k-ω model has been validated in previous studies for accurate and numerically efficient solutions under transitional and turbulent flow conditions (Zhang and Kleinstreuer 2003; Zhang and Kleinstreuer 2004).

The Reynolds averaged governing equations for the conservation of mass and momentum are (Wilcox 1998)

\[
\frac{\partial \bar{u}_i}{\partial x_i} = 0
\]

\[
\frac{\partial \bar{u}_i}{\partial t} + \bar{u}_j \frac{\partial \bar{u}_i}{\partial x_j} = -\frac{1}{\rho} \frac{\partial p}{\partial x_i} + \frac{\partial}{\partial x_j} \left[ \nu + \nu_T \left( \frac{\partial \bar{u}_i}{\partial x_j} + \frac{\partial \bar{u}_j}{\partial x_i} \right) \right]
\]

where \( \bar{u}_i \) is the time-averaged velocity in three coordinate directions, i.e., \( i = 1, 2, \) and \( 3, \) \( p \) is the time-averaged pressure, \( \rho \) is the fluid density, and \( \nu \) is the kinematic viscosity. For the two-equation turbulence model considered, the turbulent viscosity \( \nu_T \) is (Wilcox 1998)

\[
\nu_T = \alpha \frac{k}{\omega}
\]
Transport equations for the turbulent kinetic energy \((k)\) and the specific dissipation rate \((\omega)\) are

\[
\frac{\partial k}{\partial t} + \mathbf{u} \cdot \nabla k = \tau_{ij} \frac{\partial u_i}{\partial x_j} - \beta_k^* k \omega + \frac{\partial}{\partial x_j} \left[ \nu + 0.5 \nu_T \left( \frac{\partial k}{\partial x_j} \right) \right]
\] (3.4)

\[
\frac{\partial \omega}{\partial t} + \mathbf{u} \cdot \nabla \omega = \frac{13}{25} \frac{\omega}{k} \tau_{ij} \frac{\partial u_i}{\partial x_j} - \beta_\omega \omega^2 + \frac{\partial}{\partial x_j} \left[ \nu + 0.5 \nu_T \left( \frac{\partial \omega}{\partial x_j} \right) \right]
\] (3.5)

In Eq. (3.4), the dissipation of \(k\) is modeled as \(\beta_k^* k \omega\) where

\[
\beta_k^* = \frac{9}{100} f_\beta^* \\
f_\beta^* = \begin{cases} 
1 & \chi_k \leq 0 \\
1 + 680 \chi_k^2 & \chi_k > 0
\end{cases} \quad \chi_k = \frac{1}{\omega^3} \frac{\partial k}{\partial x_j} \frac{\partial \omega}{\partial x_j}
\] (3.6)

In Eq. (3.5) the dissipation of \(\omega\) is modeled as \(\beta_\omega \omega^2\) where

\[
\beta_\omega = \frac{9}{125} f_\beta \\
f_\beta = \frac{1 + 70 \chi_\omega}{1 + 80 \chi_\omega} \quad \chi_\omega = \frac{\Omega_{ij} \Omega_{jk} S_{ki}}{(0.09 \omega)^3}
\] (3.7)

In the above equations, \(\tau_{ij}\) is the shear stress tensor, \(\Omega_{ij}\) represents the mean rate of rotation tensor and \(S_{ki}\) represents the mean strain rate tensor. For the LRN \(k-\omega\) approximation, which models turbulence through the viscous sublayer, the \(\alpha^*\) parameter in Eq. (3.3) is evaluated as:

\[
\alpha^* = \frac{0.024 + k / 6 \nu \omega}{1.0 + k / 6 \nu \omega}
\] (3.8)

For laminar flow, \(\nu_T\) is zero.
The Reynolds number (Re) is defined as the ratio of the viscous forces to the inertial forces experienced by the fluid. The Re is the most significant dimensionless number affecting flow behavior, and is given by:

\[ \text{Re} = \frac{\rho ud}{\mu} \quad (3.9) \]

where \( d \) is the diameter of the conduit and \( \mu \) is the dynamic viscosity of the fluid. For flow through curved pipes, the Dean number (De) is also a significant non-dimensional number. The De is defined as the product of the Reynolds number and square root of the length scale ratio \( a/R \). The Dean number is given by

\[ \text{De} = \frac{\rho ud}{\mu} \left( \frac{a}{R} \right)^{1/2} \quad (3.10) \]

Where \( a \) is the radius of the pipe and \( R \) is the radius of curvature of the path of the channel.

### 3.2 Discrete Phase Transport

For the discrete phase transport of 0.2 – 12 \( \mu \)m aerosols, one-way coupled trajectories are calculated using a Lagrangian model. Dimensional and material details for the aerosols studied include a particle density \( \rho_p = 1.00 \text{ g/cm}^3 \), a density ratio \( \alpha = \rho / \rho_p \approx 10^{-3} \), a Stokes number range \( \text{St} = \rho_p d_p^2 C_c U / 18 \mu D \approx 0.001 - 2.0 \), and a particle Reynolds number \( \text{Re}_p = \rho u |u - v| d_p / \mu \leq 20 \). The governing transport equation is written as

\[ \frac{dv_i}{dt} = \alpha \frac{Du_i}{Dt} + \frac{f}{\tau_p} (u_i - v_i) + g_i (1 - \alpha) + f_{i,\text{lubrication}} + f_{i,\text{lift}} \quad \text{and} \quad \frac{dx_i}{dt} = v_i(t) \quad (3.11a \& b) \]
where \( v_i \) and \( u_i \) are the components of the particle and local fluid velocity, respectively, and \( g_i \) denotes gravity. The characteristic response time for particles is denoted by \( \tau_p = \rho_p \frac{d_p^2}{18\mu} \) and the drag factor \( f \), which represents the ratio of the drag coefficient to Stokes drag, is given by (Morsi and Alexander 1972)

\[
f = \frac{C_D \text{Re}_p}{24} = \frac{\text{Re}_p}{24} \left( a_1 + \frac{a_2}{\text{Re}_p} + \frac{a_3}{\text{Re}_p^2} \right)
\]

(3.12)

where the \( a_i \) coefficients are constant for smooth spherical particles over the range of particle Reynolds number considered in the current study, i.e. \( 0 \leq \text{Re}_p \leq 20 \). The effect of Saffman lift is included for \( 1 - 12 \mu m \) aerosols, whereas Brownian motion effects are included for particles smaller than \( 1 \mu m \) diameter.

To predict turbulence effects on the discrete phase, a random walk model is employed that represents the fluid velocity during the time spent by a particle in an eddy. The instantaneous velocity is composed of the time averaged and fluctuating components.

\[
u_i = \bar{\nu}_i + \nu_i'
\]

(3.13)

The eddy entrainment time is the minimum of the eddy crossing time \( (T_c) \) and the random eddy lifetime \( (T_e) \) given by

\[
T_c = -\tau_p \ln \left[ 1 - \frac{\ell}{\tau_p |\bar{u} - \bar{v}|} \right] \quad T_e = -\frac{0.15}{\omega} \log(r)
\]

(3.14a & b)

where \( \ell \) is the characteristic eddy length scale taken to be \( 0.15 \kappa^{0.5}/\omega \) and \( r \) is a uniform random number between 0 and 1.
For the discrete phase, the Stokes number (Stk) is considered to be a significant dimensionless parameter. The Stk is defined as the ratio of the stopping distance of a particle to the characteristic dimension of the geometry, and is given by

$$\text{Stk} = \frac{\tau_p U_0}{d_c}$$

where $\tau_p$ is the electrostatic response time of the particle, $U_0$ is the fluid velocity and, $d_c$ is the characteristic dimension of the geometry.

### 3.3 Grid Convergence

The performance of hexahedral and hybrid meshes as described in Objective 1 is calculated based on grid convergence. All mesh schemes are implemented for a particle size range of 0.2 – 12 μm. The geometry selected to evaluate the mesh styles of interest is a double bifurcation model representative of respiratory generations G3 – G5 (Fig. 1.1). This model is generated from the “Physiologically Realistic Bifurcation” (PRB) geometry specified by Heistracher and Hofmann (1995). For the PRB geometry, Heistracher and Hofmann (1995) provide a complete mathematical description of a single symmetric or asymmetric bifurcation based on a set of 11 geometric parameters and two sigmoid functions. Specific parameters for the double bifurcation model of generations G3 – G5 for Objective 1 are identical to the values used in the work of Heistracher and Hofmann (1997) and the localized particle deposition measurements of Oldham et al. (2000). The inlet diameter of G3 in the model is 0.56 cm. Further geometric details of this configuration have been reported in (Longest and Vinchurkar 2007a).
To determine grid convergence and establish grid independence of the velocity field solutions for Objectives 1, 2 and 3, successive refinements of each mesh have been considered. For each refinement, grid convergence is evaluated using a relative error measure of velocity magnitude between the coarse and fine solutions

$$\varepsilon = \frac{|u_{i,\text{coarse}} - u_{i,\text{fine}}|}{u_{i,\text{fine}}}$$  \hspace{1cm} (3.16)

A vector of relative error values was determined for 1,000 consistent points located in the region of interest. The root-mean-square of the relative error vector was used to provide an initial scalar measure of grid convergence for the points considered

$$\varepsilon_{\text{rms}} = \left(\frac{\sum_{i=1}^{10^3} \varepsilon_i^2}{10^3}\right)^{1/2}$$  \hspace{1cm} (3.17)

Rigorously, grid convergence measures should be based on refining the grid by a factor of two, i.e., grid halving. However, dividing hexahedral elements by a factor of two in three dimensions is often not practical due to the significant increase in the number of control volumes. As such, relative error values must be adjusted to account for cases in which grid reduction factors less than \( r = 2 \) are employed. To extrapolate \( \varepsilon_{\text{rms}} \) values to conditions consistent with true grid halving, the grid convergence index (GCI) has been
suggested by Roache (1992). This method is based on Richardson extrapolation and can be applied as

\[ GCI = F_s \frac{\varepsilon_{rms}}{r^p - 1} \]  

(3.18)

In the above equation, \( r \) represents the grid refinement factor and \( p \) is the order of the discretization method. Based on second-order discretization of all terms in space, \( p = 2 \) for the systems of interest. Refinement of the meshes was performed to maintain a constant reduction value in the three coordinate directions. The associated \( r \) value has been calculated as the ratio of control volumes in the fine and coarse meshes

\[ r = \left( \frac{N_{\text{fine}}}{N_{\text{coarse}}} \right)^{1/3} \]  

(3.19)

To limit errors arising from the extrapolation procedure, \( r \) values of approximately 1.5 or greater have been considered. A factor of safety \( F_s \) equal to 3 has been selected to provide a GCI value equal to the \( \varepsilon_{rms} \) value when \( r = 2 \) and \( p = 2 \). As such, the GCI value represents a scaled version of \( \varepsilon_{rms} \) to account for mesh refinement factors less than 2.

To evaluate grid convergence for each mesh style considered, low, medium and high resolution comparisons between coarse and fine grids have been considered. Results of this comparison in the form of grid convergence values and required simulation times are reported in Table 4.1, and are discussed in the Section 4.3. The number of grid cells required is based on the presence of one symmetry plane, i.e., one-half of the geometry is meshed for Objective 1 and 2. For Objective 3, two planes of symmetry are considered resulting in a converged mesh ranging from 400,000 control volumes for impactor stage 0
up to 2.5 million control volumes for impactor stage 6. As described, grid convergence has been based on comparisons between coarse and fine grid solutions at 1,000 points concentrated in the region of interest. A layer of near-wall comparison points was positioned to be less than 5% of the internal radius away from the wall. Selections of other sets of 1,000 points as well as doubling the number of points considered had a negligible (i.e., less than 1%) impact on the grid convergence values reported.

3.4 Electrostatic Effects and the Image Force

Triboelectrification is defined as the buildup of charge from the separation of two insulating materials that are in contact with each other. These materials can inherit a net measurable charge on their surfaces with one of the polarities dominating the other. The process is also referred to as frictional charging. Some of the materials which illustrate this phenomenon need only touch each other before a significant charging of the surface occurs (Cross 1987). Metered dose inhalers (MDIs), which are used as storage and delivery devices for respiratory aerosols, exhibit the triboelectric effect (Peart et al. 1995; Byron, Peart et al. 1997; Peart and Byron 1999; Peart 2001; Kwok et al. 2005). Dry powder inhalers (DPI) also exhibit similar static charges. As a result, pharmaceutical aerosols delivered using MDIs and DPIs may be characterized by significant electrostatic effects (Peart and Byron 1999; Kwok et al. 2005).

Charged respiratory aerosols act as point entities, which induce an equal and opposite static charge in a surrounding conductor. Under the influence of the field created by the aerosol particles, an image force is developed between the surface and the aerosol
particles. These image forces are always in the form of attraction, since equal and unlike charges are induced on the surface. If the material of the wall is not a conductor, then the static charge on the particles interacts with the static charge of the material and can result in attractive or repulsive forces between the wall and the particle depending on the polarity and distribution of the charges.

An aerosol particle carrying a charge $q$ is considered. The image charge induced on the impactor surface will then be equal to $-q$ which will yield an image force $F_e$ between the particle and the surface as follows:

$$F_e = \frac{qq}{4\pi d^2} \frac{1}{\varepsilon_0\varepsilon_{air}}$$

where $F_e$ is the force of attraction between the particle and the surface, $d$ is the distance separating the particle and the surface, $\varepsilon_0 = 8.854 \times 10^{-12}$ and $\varepsilon_{air} \approx 1$ are the permittivity of free space and relative permittivity of air, respectively.

It is reported that respiratory aerosols exhibit a static charge ranging between 200 and on the order of 40,000 electron charges per particle (Peart et al. 1995; Peart and Byron 1999; Kwok et al. 2005). Assuming the aerosol particle to be spherical in shape, a viscous drag force is given by

$$F_d = (3\pi\mu)d_pV_{slip}$$

where $V_{slip}$ is the particle slip velocity and $\mu$ is the dynamic viscosity of air. The ratio of $F_e$ to $F_d$ can be used to estimate the importance of particle charge on transport and deposition near a wall boundary.
4. Effects of Mesh Style and Grid Convergence

4.1 Introduction

Recently, Longest and Vinchurkar (2007a) have considered the effects of various common mesh styles on the grid convergence, velocity fields and particle deposition profiles of a bifurcating respiratory model. The meshes considered included a structured multiblock hexahedral style, an unstructured tetrahedral mesh, a flow-adaptive tetrahedral design, and a hybrid style consisting of tetrahedral and prism elements. To evaluate solution quality, the grid convergence index (GCI) was employed as well as comparisons to empirical velocity fields (Zhao and Lieber 1994) and cumulative particle depositions (Oldham et al. 2000). As expected, construction of the structured multiblock mesh for a double bifurcation geometry was highly time consuming and required the creation of 178 blocks without a symmetry plane. In contrast, tetrahedral meshes including flow adaption could be created very rapidly. The structured hexahedral mesh was shown to have a GCI value of approximately 1%, which was an order of magnitude below values for the other mesh styles considered. Moreover, the flow field solution on the structured hexahedral mesh was approximately three times faster than the solution for the other meshes and provided the best match to empirical cumulative particle deposition results. As a result, Longest and Vinchurkar (2007a) quantified the advantages of a multiblock structured
hexahedral mesh in a branching respiratory model. However, difficulties associated with generating the multiblock mesh in a complex geometry and the excess construction time required remain significant shortcomings of this approach. As an extension to Longest and Vinchurkar (2007a), this study will determine if unstructured hexahedral and higher-order hybrid methods can maintain the advantages of the structured hexahedral scheme while saving mesh construction time and effort.

Inhaled pharmaceutical aerosols include a wide particle size range typically from 1 through 10 µm (Hinds 1999; Finlay 2001). Effects of particle size on the cumulative deposition of respiratory aerosols in the planar physiologically realistic bifurcation (PRB) airway model will be evaluated in the form of deposition fractions. Considering that realistic lung airways are three dimensional, a non–planar geometry will be considered as well. The non-planar PRB model is achieved by rotating the second bifurcation region (airway G4 through G5) by 90 degrees in the radial plane of airway G4. Several studies have reported higher secondary flows for non-planar lung models (Comer et al. 2000; Caro, Schroter et al. 2002). However, a correlation between high secondary flows in non-planar geometries and related effects on local and cumulative particle deposition is not well defined in the literature.

Accurate deposition estimates of targeted respiratory aerosols and toxic particles require better evaluation of the effects of mesh generation techniques and grid convergence on velocity and local particle deposition fields in bifurcating respiratory geometries. In order to improve computational accuracy, different meshes need to be studied to evaluate performance with respiratory airway models. Justified grid convergence criteria need to be
established. Accuracy of the simulations may be assessed by comparisons to experimental \textit{in vitro} data available in the literature. Finally, benchmark studies are intended to serve as a basis for future improvements in accuracy and computational efficiency, and to facilitate modeling broader regions of the respiratory tract.

As discussed above, this part of the study explores meshes that may maintain the advantages of the structured hexahedral style while providing significant savings in construction complexity. The objective of this study is to evaluate the performance of hexahedral and hybrid meshes based on grid convergence and local particle deposition fractions in a bifurcating model of the respiratory tract. To achieve this objective, mesh styles considered include the multiblock structured hexahedral mesh (as a base case), an unstructured hexahedral mesh, an unstructured prism mesh, and a tetrahedral-hexahedral hybrid mesh. All mesh schemes are implemented for a particle size range of 1 through 10 µm in the planar PRB model, which is illustrated in Fig. 1.1. For the out-of-plane model, all schemes will be implemented for particle sizes of 3 µm and 10 µm. The GCI has been implemented in order to assess grid convergence in cases where true grid halving is not feasible. A velocity dependent or secondary variable in the form of particle deposition profiles has been evaluated for each mesh on a local basis and compared to the empirical results of Oldham et al. (2000) for an identical bifurcating geometry. This study is intended to serve as a basis for modeling broader regions of the lung where multiblock structured hexahedral meshes may be prohibitively complex.
4.2 Methods

4.2.1 Bifurcation Model and Boundary Conditions

The geometry selected to evaluate the mesh styles of interest is a double bifurcation model representative of respiratory generations G3 – G5 (Fig. 4.1). This model is generated from the “Physiologically Realistic Bifurcation” (PRB) geometry specified by Heistracher and Hofmann (1995). For the PRB geometry, Heistracher and Hofmann (1995) provide a complete mathematical description of a single symmetric or asymmetric bifurcation based on a set of 11 geometric parameters and two sigmoid functions. Specific parameters for the double bifurcation model of generations G3 – G5 employed in this study are identical to the values used in the work of Heistracher and Hofmann (1997) and the localized particle deposition measurements of Oldham et al. (2000). The inlet diameter of G3 in the model is 0.56 cm. Further geometric details of this configuration have been reported in Longest and Vinchurkar (2007a). In this study, grid convergence, velocity fields, and local particle deposition profiles will be evaluated for an in-plane configuration, as implemented in the experimental study of Oldham et al. (Oldham et al. 2000) (Fig. 4.1a). For comparison, local deposition patterns will also be considered in an out-of-plane model where the second bifurcation has been rotated by an angle of 90° (Fig. 4.1b).

The steady inspiratory flow rate employed in the PRB model results in an inlet Reynolds number of 1788. For respiratory generations G3 – G5, this is consistent with an inhalation flow rate in the trachea of 60 L/min and represents a state of heavy exertion
(ICRP 1994). The flow rate in generation G3 is 125 ml/sec, as specified in the experimental study of Oldham et al. (2000).

Both inlet velocity and initial particle profiles are expected to have a significant impact on the flow field and particle deposition locations. For comparisons to *in vitro* deposition data, these profiles may be largely influenced by upstream effects in the experimental particle generation system. Longest and Vinchurkar (2007b) have shown that upstream transition to turbulence results in a relatively blunt initial velocity field and particle profile at the model inlet. However, the flow within the PRB model can be approximated as laminar. As such, fully-developed blunt turbulent profiles of velocity and initial particle distributions have been assumed at the model inlet. Within the model, laminar flow is assumed. Outlet flow is assumed to be evenly divided between the left and right symmetric branches, i.e., homogeneous ventilation. Gravity has been included in the flow field and particle trajectory calculations of the PRB model with the gravity vector oriented in the negative z-direction, i.e., normal to the plane of the bifurcation, to remain consistent with the experiments of Oldham et al. (2000).

### 4.2.2 Mesh Styles

For comparisons to the structured hexahedral base case, three unstructured mesh styles have been considered (Fig. 4.2). Unstructured meshes are defined as having at least one face or block surface on which the gridlines do not remain continuous. For the structured hexahedral mesh, four-sided blocks are used (Fig. 4.3a), which allows the
gridlines to remain continuous within each block. For the unstructured hexahedral mesh, blocks with one triangular face have been implemented (Fig. 4.3b). On the triangular cross-sectional faces, the gridlines become discontinuous at the center of each triangle (Fig. 4.2b Slice 1). As a result, this blocking structure produces an unstructured hexahedral mesh. The other unstructured meshes considered include prismatic and hybrid styles (Fig. 4.2). All meshes were created using the integrated solid modeling and meshing program Gambit 2.2 (Ansys Inc.)

The structured base case mesh consists of 6-sided hexahedral elements arranged in a system of interconnected rectangular blocks. The blocks have been arranged in a butterfly blocking design which minimizes control volume distortions while aligning a higher percentage of elements with the local flow direction (Fig. 4.3a). Moreover, mesh density is increased near the wall and near the bifurcation points. This multiblock structure is difficult to develop because gridlines may be distorted, but must remain continuous throughout the geometry. Designing a high quality block-structured meshing configuration for a geometry with multiple branches in which hexahedral elements largely align with streamlines is a user intensive nontrivial task. However, this style of mesh is often associated with reduced numerical errors, as described further in Longest and Vinchurkar (2007a).

As with the structured mesh, the unstructured hexahedral configuration requires the creation of sub-blocks within the geometry. However, the unstructured hexahedral design allows for two faces on each block to have a non-continuous grid (Fig. 4.2b). Furthermore,
blocks with one pair of triangular faces may be accommodated. As a result, the planes forming these blocks may pass entirely through the geometry (Fig. 4.3b). These planes are much easier to construct than the planes in the structured hexahedral configuration that only partially bisect the geometry. In addition, the blocking structure for the unstructured hexahedral mesh reduces the number of required blocks by over 50% (Fig. 4.3). Once the geometry is divided into the required blocks, non-continuous meshes are created on cross-sectional surfaces. These meshed faces are then swept through the geometry in the axial direction to generate the volumetric mesh. As a result, this mesh style retains the advantage of aligning mesh elements in the predominate direction of flow.

The prismatic mesh consists of five-sided elements which are composed of two triangles joined together by a longitudinal section of three rectangular faces. Generation of this mesh style requires four-sided faces to be constructed on the surface of the PRB (Fig. 4.2c). However, subdivision of the geometry into blocks is not required. The prismatic elements are arranged such that their triangular faces fill the axial slices (Fig. 4.2c). This allows for the rectangular sections of each prismatic element to be aligned with the direction of predominate flow.

In order to improve the accuracy of the tetrahedral mesh style (Longest and Vinchurkar 2007a), an unstructured hexahedral-tetrahedral hybrid mesh has been created (Fig. 4.2d). As with the prismatic mesh, four-sided faces are required on the surface of the PRB geometry. These faces are used to construct structured quadrilateral surface meshes, which form the basis for a layer of near-wall hexahedral cells. The hexahedral elements
are intended to better resolve the flow field near the walls where velocity gradients are typically highest. The inner core of the flow field is then meshed with randomly oriented tetrahedral elements. A layer of prismatic elements is used to join the hexahedral and tetrahedral cells. In this configuration, the thin near-wall layer of hexahedral elements is aligned with the predominate direction of flow. However, it is not possible for the randomly oriented tetrahedral elements, which comprise a majority of the flow field, to be aligned with the axial flow direction.

4.2.3 Numeric Method

To solve the governing mass and momentum conservation equations in each of the geometries and for each mesh style, the CFD package Fluent 6.2 has been employed. This commercial software provides an unstructured control-volume-based solution method for multiple mesh styles including structured hexahedral, unstructured hexahedral, prismatic and hybrid meshes. User-supplied FORTRAN and C programs have been employed for the calculation of initial particle profiles, particle deposition locations, grid convergence, and post-processing. All transport equations were discretized to be at least second order accurate in space. For the convective terms, a second order upwind scheme was used to interpolate values from cell centers to nodes. The diffusion terms were discretized using central differences. To improve the computation of gradients for the tetrahedral elements of the hybrid mesh, face values were computed as weighted averages of values at nodes, which provides an improvement to using cell center values for these meshes. Nodal values
for the computation of gradients were constructed from the weighted average of the surrounding cells, following the approach proposed by Rauch et al. (1991). A segregated implicit solver was employed to evaluate the resulting linear system of equations. This solver uses the Gauss-Seidel method in conjunction with an algebraic multigrid approach to solve the linearized equations. The SIMPLEC algorithm was employed to evaluate pressure-velocity coupling. The outer iteration procedure was stopped when the global mass residual had been reduced from its original value by five orders of magnitude and when the residual-reduction-rates for both mass and momentum were sufficiently small. To ensure that a converged solution had been reached, residual and reduction-rate factors were decreased by an additional order of magnitude and the results were compared. The stricter convergence criteria produced a negligible effect on both velocity and particle deposition fields. To improve accuracy, cgs units were employed, and all calculations were performed in double precision. To further improve resolution in the particle deposition studies, geometries were scaled by a factor of 10 and the appropriate non-dimensional parameters were matched.

4.2.4 Validation Studies

Validations of velocity field values for the structured hexahedral mesh scheme applied to a bifurcation geometry have been reported in a previous study (Longest and Vinchurkar 2007a). Briefly, a single bifurcation model was considered with a characteristic Reynolds number of 518 and results were compared to the empirical velocity
field data of Zhao and Lieber (1994). For steady inhalation flow, the velocity field results of Longest and Vinchurkar (2007a) indicate good quantitative agreement with the empirical data of Zhao and Lieber (1994).

4.3 Results

4.3.1 Grid Convergence

To evaluate grid convergence for each mesh style considered, low, mid- and high resolution comparisons between coarse and fine grids have been considered for the planar geometry. Results of this comparison in the form of grid convergence values and required simulation times are reported in Tables 4.1 – 4.4 and are discussed below. The reported grid convergence results are for the planar bifurcation model (Fig. 4.1a). Similar grid convergence results were observed for the out-of-plane configuration (Fig. 4.1b). The number of grid cells required is based on the presence of one symmetry plane, i.e., one-half of the geometry is meshed. As described, grid convergence has been based on comparisons between coarse and fine grid solutions at 1,000 points concentrated in the region of the bifurcation. A layer of near-wall comparison points was positioned to be less than 5% of the internal radius away from the wall. Selections of other sets of 1,000 points as well as doubling the number of points considered had a negligible (i.e., less than 1%) impact on the grid convergence values reported.

For the structured hexahedral mesh, successive grid refinements resulted in an effective reduction of $\varepsilon_{\text{rms}}$ values (Table 4.1). For the high resolution case, an $\varepsilon_{\text{rms}}$ of 1.99% was obtained. In comparison to other relative error estimates, this value is
relatively high. However, the selection of 1,000 points with many locations near the wall and in low velocity positions produces a very rigorous condition for testing grid convergence. Moreover, errors on the order of 1% are expected to arise from the linear interpolation algorithm used to calculate values at the positions of interest for comparisons of the course and fine grid solutions. Therefore, achieving \( \varepsilon_{\text{rms}} \) values below 1% may not be possible with the rigorous grid convergence method employed. In this study, values of \( \varepsilon_{\text{rms}} \) on the order of approximately 1% have been considered to represent a well converged solution. Accounting for the grid reduction factor used in the high resolution case results in a GCI value of 4.27% for the structured hexahedral mesh with 214,000 control volumes.

Grid convergence estimates for the unstructured hexahedral mesh are reported in Table 4.2. These results are highly similar to the grid convergence values observed for the base case. That is, an \( \varepsilon_{\text{rms}} \) value of 1.95% is achieved for the high resolution case. However, the number of grid cells required to achieve this level of grid convergence was increased from 214,000 for the structured hexahedral mesh to 318,000 for the unstructured hexahedral mesh. This increase in cell number resulted in a 10% increase in solution time.

To graphically evaluate the implications of these reported GCI values, velocity profiles at Slice 1 (Fig. 4.2) are shown in Fig. 4.5 for various mesh resolutions. Grid convergence index values on the order of 10%, as observed for the medium-level resolution, are shown to result in visible differences between velocity profiles. For the high resolution case, which is characterized by a GCI of 4.32%, differences in the velocity profiles are much less discernable.
For the prismatic mesh configuration, \( e_{\text{rms}} \) and GCI values are comparable to those observed for the hexahedral style meshes (Table 4.3). However, to achieve this level of grid convergence, grid resolution had to be increased by approximately 30 – 40% for each case considered. This increase in grid density produces an associated increase in simulation time of approximately 20%. Furthermore, it is observed that the medium-level resolution case of the unstructured prism mesh results in a GCI value of approximately 6.6%, which is consistent with the high resolution prismatic case and significantly lower than with the medium resolution hexahedral meshes.

Grid convergence values for the hybrid meshes are significantly higher than values reported for the other configurations (Table 4.4). The minimum GCI value for the hybrid style was 17.7% and occurred with medium-level grid density. For the high-level resolution condition, the GCI value increased to 21.3%. Further increases in grid density resulted in an increasing GCI value. This increase may be a result of round-off errors arising from an over-resolved grid. Furthermore, this level of grid convergence is consistent with GCI values observed for purely tetrahedral meshes with and without flow adaption (Longest and Vinchurkar 2007a). As a result, the hybrid mesh style results in GCI values that are significantly higher than observed for the other meshes considered in this study and appears to provide little advantage to purely tetrahedral style meshes. The higher GCI values of the hybrid configuration may largely be a result of mesh elements not aligning with the direction of predominate flow.
4.3.2 Velocity Fields

Velocity vectors, contours of velocity magnitude and streamlines of secondary motion are presented in Fig. 4.6 for the high resolution cases of the four mesh styles considered in the planar bifurcation model. Midplane velocity fields appear highly similar among the hexahedral and prismatic meshes (Figs. 4.6a – c). However the hybrid mesh results in a significant reduction in midplane velocity gradients, which may arise from artificial or numerical dissipation (Fig. 4.6d). Similarly, secondary motions viewed at cross-sectional slice locations appear similar among the first three mesh styles considered (Fig. 4.6a – c). A single vortex is observed for the upper half of the geometry at Slice 1. The second carinal ridge produces a pair of counter rotating vortices for the inner branch of G5, as observed in Slice 2 (Fig. 4.6a – c). However, due to the highly dissipative conditions of the hybrid mesh, only one fully formed vortex is observed in each of the three cross-sectional planes considered (Fig. 4.6d). In summary, midplane velocity vectors appear relatively consistent among the four meshes considered, with some variations observed for the hybrid configuration. Secondary velocity profiles appear similar between the two hexahedral mesh styles. However, secondary velocity profiles are significantly different for the non-hexahedral meshes with the largest variations occurring for the hybrid configuration.

In order to better evaluate differences among the solutions of the meshes considered, midplane velocity profiles have been plotted at Slices 1 – 3 for high resolution conditions in the planar model (Fig. 4.7). At each location, velocity profiles for the hexahedral and prismatic meshes are similar. However, minor differences among the first three solutions
are discernable. This observation highlights the fact that a high level of grid convergence does not ensure an exact match among solutions of different mesh types. In contrast to the hexahedral and prismatic solutions, the hybrid configuration results in significantly different velocity profiles. Velocity values for the hybrid solution again appear to be influenced by a high degree of dissipation. Considering Slice 3, differences between the first three solutions and the hybrid configuration vary between approximately 30% to one order of magnitude (Fig. 4.7c).

4.3.3 Particle Deposition

Deposition locations for the four mesh styles considered and the planar geometry with 10 μm particles are shown in Fig. 4.8. The 10 μm aerosols considered deposit primarily by impaction. Qualitatively, the observed deposition locations are very similar between the structured and unstructured hexahedral meshes. Furthermore, the hexahedral mesh styles exhibit very distinct divisions between regions of deposition and areas devoid of particle-wall interactions. In contrast, particle deposition locations for the prismatic and hybrid meshes appear more diffuse. This effect may be the result of fewer mesh elements aligned with the flow, especially for the hybrid configuration. Nevertheless, each of the mesh styles considered emphasizes local accumulations of particles, referred to as hotspots, occurring just upstream of the bifurcation points and continuing downstream for approximately one-half the branch lengths.

Cumulative deposition percentages as a function of distance in the y-direction are shown in Fig. 4.9 for the planar geometry. For 10 μm particles, the structured hexahedral,
unstructured hexahedral and prismatic high resolution meshes all match the experimental data of Oldham et al. (2000) to a very high degree (Fig. 4.9a). For these three solutions, variations from the cumulative particle deposition experimental data are within 2 – 3%. Furthermore, these solutions result in a final deposition fraction that is within approximately 1% of the experimentally reported value of 81%. Differences in cumulative deposition values among the solutions for the hexahedral and prismatic meshes vary by less than 1%. In contrast, cumulative deposition results for the high-resolution hybrid mesh and 10 μm particles are significantly lower than the experimental data. The hybrid mesh considered is observed to under-predict cumulative deposition by approximately 20% (Fig. 4.9a).

As particle size decreases, larger differences are observed among the cumulative deposition predictions for the mesh styles considered. For 5 μm aerosols, the structured and unstructured hexahedral meshes are in close agreement with a final deposition fraction between 5 and 6% (Fig. 4.9b). In contrast, the prismatic mesh predicts a cumulative deposition of 11%, which is approximately double the hexahedral mesh estimates. Results for the hybrid mesh and 5 μm particles are even higher, with a total deposition fraction of 12%. Considering 3 μm particles, close agreement is observed between the hexahedral mesh predictions with a total deposition fraction of 0.3% (Fig. 4.9c). In contrast, the prismatic and hybrid configurations predict a deposition rate of approximately 1.8%. A similar trend is observed for 1 μm aerosols (Fig. 4.9d). Again, results for the structured and unstructured hexahedral configurations are in close agreement with a total deposition
fraction ranging between 0.12 and 0.17%. However, predictions of the prismatic and hybrid meshes are significantly higher by a factor of approximately five.

In general, cumulative deposition results are consistent between the structured and unstructured hexahedral meshes for the planar geometry (Fig. 4.9). Results for the prismatic and hybrid meshes differ from the hexahedral results by values ranging from 20% (10 μm) to a factor of five (1 μm). Deposition predictions of the prismatic and hybrid meshes are also generally higher than for the hexahedral models. Differences in deposition results between the hexahedral and prism/hybrid meshes appears to increase with decreasing particle size. For all particle sizes considered in respiratory generations G3 – G5, impaction is the primary deposition mechanism. However, the smaller particles considered have less inertia and are influenced to a greater extent by the secondary velocity patterns. Significant differences in secondary velocity profiles were observed between the hexahedral and other mesh styles considered in Fig. 4.6. Therefore, it is concluded that differences in secondary motion patterns associated with mesh style are partially responsible for increased differences in deposition patterns as particle size is reduced. Furthermore, increase in secondary motion associated with out-of-plane bifurcations may induce additional discrepancies among the models considered.

Cumulative deposition results for the out-of-plane geometry and particle sizes of 3 and 10 μm are shown in Fig. 4.10. As with the planar geometry for 10 μm particles, close agreement is observed between the hexahedral and prismatic mesh configurations with a total deposition rate of approximately 90% (Fig. 4.10a). The hybrid mesh results in an 85% deposition value, which is in relatively close agreement with the other mesh styles
considered. However, significant differences in model predictions are again observed as the particle size is decreased. For 3 μm aerosols, results for the structured and unstructured hexahedral meshes appear to be in close agreement with a total deposition rate of approximately 1.8% (Fig. 4.10b). Deposition results for the prismatic and hybrid meshes are approximately six times higher than the other model predictions with a total deposition fraction of 11%.

### 4.4 Discussion

In this study, the effects of mesh style have been evaluated with respect to grid convergence, velocity fields and particle deposition values in a double bifurcation model of the respiratory tract. Mesh styles considered include structured hexahedral, unstructured hexahedral, prismatic and hybrid configurations. Particles ranging from 1 to 10 μm have been evaluated in planar and out-of-plane geometries. Deposition results for 10 μm particles in the planar geometry were found to be in close agreement with the experimental deposition data of Oldham et al. (2000) on a highly localized basis. In general, grid convergence, velocity fields, and local particle deposition values were consistent between the structured and unstructured hexahedral meshes. Both hexahedral meshes considered resulted in GCI values of approximately 5% and nearly identical midplane and secondary velocity patterns. Furthermore, local particle deposition profiles were largely similar for the hexahedral meshes across the range of particle sizes evaluated. Considering the prismatic mesh, GCI values were comparable to the hexahedral configuration with only a moderate increase in control volume number. Prismatic velocity fields were consistent
with the hexahedral results, with some minor variations in the secondary velocity profiles. However, the prismatic mesh resulted in significant differences in local deposition profiles for particles less than 10 μm. The hybrid mesh resulted in a GCI value that was significantly higher than observed for the other meshes. This increase in GCI occurred despite a significant increase in the number of cells in the hybrid mesh. The velocity field for the hybrid configuration differed from the hexahedral and prismatic solutions by up to an order of magnitude at some locations with significant differences in the secondary vortex patterns. Moreover, deposition results for the hybrid mesh differed from the hexahedral results by values ranging from 20% (10 μm) to a factor of five (1 μm). For the out-of-plane bifurcating geometry, local deposition results were generally consistent for 10 μm aerosols, but differed significantly for 3 μm particles among the mesh styles considered.

This study highlights the effects of mesh style on grid convergence and related solution variables for an internal biofluid flow field. For any CFD problem, the required quality of the solution is often weighted against the time and resources available for mesh development. Structured hexahedral meshes are often thought to provide the highest quality solution, but the associated mesh construction time may be prohibitively extensive. In this study, structured hexahedral and unstructured hexahedral mesh schemes have been shown to provide highly comparable grid convergence values, velocity fields and particle deposition profiles. Moreover, both of these mesh styles predicted deposition results in very close agreement with experimental data for 10 μm aerosols in a planar geometry. As illustrated in Figs. 4.2 and 4.3, construction of the unstructured hexahedral mesh requires a
less complex blocking schemes than for the structured hexahedral configuration. For example, construction of the structured hexahedral mesh requires the creation of 178 blocks in comparison to 80 blocks for the unstructured hexahedral mesh. Therefore, the unstructured hexahedral mesh offers a significant savings in construction time without an appreciable loss in solution performance.

Compared with the purely tetrahedral meshes considered in Longest and Vinchurkar (2007a), the hybrid mesh employed in this study showed no improvement in performance. Construction of the hybrid mesh did require subdivision of the PRB surface geometry into rectangular faces. In contrast, construction of purely tetrahedral meshes does no require subdividing the surface into rectangular faces. As a result, purely tetrahedral and flow adaptive tetrahedral meshes may be advantageous in comparison to the hybrid mesh considered in this study. Furthermore, the use of tetrahedral meshes may be preferred when rapid approximate solutions are the top priority. This scenario may arise for patient-specific modeling in the clinical setting. That is, approximate solutions with rapidly generated tetrahedral meshes may be necessary in order to make true patient-specific modeling a reality in the clinical setting (Martonen, Burton et al. 2005). However, results of this study indicate that implementing a hybrid scheme with near-wall hexahedral elements does not necessarily result in an improvement in solution accuracy and performance.

In this study, hexahedral and prismatic meshes were found to provide adequate grid convergence and similar velocity fields. For particle deposition, hexahedral mesh configurations appear to provide the best solution. The observed better performance of the
hexahedral and prismatic meshes in comparison to the hybrid mesh may occur for two reasons. First, both hexahedral and prismatic meshes can be aligned with the predominate direction of flow. This alignment is reported to reduce numerical diffusion errors (Ferziger and Peric 1999). Furthermore, discretization errors partially cancel on opposite hexahedral faces. In contrast, mainly tetrahedral meshes cannot be aligned with the direction of predominate flow, thereby increasing the potential for numerical diffusion. Therefore, numerical diffusion errors associated with randomly oriented tetrahedral faces are one likely cause of the higher grid convergence values observed for these meshes. The occurrence of these errors is enhanced in the unidirectional flow system considered. The second possible factor responsible for the improved performance of the hexahedral solutions is the use of higher order elements. The hexahedral elements implemented provide more nodes per face for improved predictions of flux values and particle tracking. Some commercial CFD packages provide an increased number of nodes per face to account for this problem. However, the effect of increasing the number of nodes per face has not been quantified for internal biofluid flows. Furthermore, the effects of nodes per face on solution performance is expected to be a secondary factor in comparison to aligning the grid with the predominate direction of flow in the long and thin conduits of interest.

Limitations of the current study include calculation of the GCI parameter at linearly interpolated points, the evaluation of a single software package, and the construction of only one style of hybrid mesh. The grid converged parameter was evaluated at 1,000 representative points throughout the flow field. These points include near-wall locations
where minor variations in flow field velocities can result in very large relative errors. Modifying the number and location of these randomly selected points did not appreciably change the GCI value provided at least 1,000 points were included. However, interpolation errors are present in determining values at comparison points. These errors are estimated to be on the order of approximately 1%. Nevertheless, the grid convergence algorithm employed provided an effective strategy for evaluating relative performance among the mesh styles considered that includes low velocity and near-wall regions.

In this study, only one commercial software package was evaluated. Other software may improve the solution quality of the hybrid configuration. Moreover, many other hybrid mesh styles are possible. Nevertheless, evaluation of this representative state-of-the-art software provides a valuable basis of comparison for various styles of meshes. Furthermore, this study highlights the advantages of aligning mesh elements with the predominate direction of flow, which is independent of the computational package considered.

In conclusion, structured and unstructured hexahedral meshes have been shown to provide acceptable grid convergence values, comparable velocity fields and good agreement with experimental 10 μm particle deposition data in a branching respiratory geometry. Generation of the unstructured hexahedral mesh provided a significant time savings in pre-processing with an associated minimal increase in computational run time. In contrast, a hybrid mesh configuration of tetrahedral cells surrounded by multiple layers of near-wall hexahedral elements resulted in significantly higher grid convergence values and provided largely different velocity and particle deposition results. These results
emphasize the importance of aligning control volume gridlines with the predominate direction of flow and using higher order elements in biofluid applications with long and thin conduits. Future work is needed to better assess modified flux interpolation schemes, other hybrid configurations and the use of polyhedral elements.
Table 4.1. Grid convergence for the structured hexahedral scheme.

<table>
<thead>
<tr>
<th>Grid sizes</th>
<th>r value</th>
<th>$\varepsilon_{\text{rms}}$ (%)</th>
<th>GCI (%)</th>
<th>Run time for fine grid (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15k to 73k</td>
<td>1.69</td>
<td>4.73</td>
<td>7.58</td>
<td></td>
</tr>
<tr>
<td>73k to 214k</td>
<td>1.43</td>
<td>3.82</td>
<td>10.93</td>
<td></td>
</tr>
<tr>
<td>214k to 798k</td>
<td>1.55</td>
<td>1.99</td>
<td>4.27</td>
<td>210</td>
</tr>
</tbody>
</table>

Table 4.2. Grid convergence for the unstructured hexahedral scheme.

<table>
<thead>
<tr>
<th>Grid sizes</th>
<th>r value</th>
<th>$\varepsilon_{\text{rms}}$ (%)</th>
<th>GCI (%)</th>
<th>Run time for fine grid (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30k to 122k</td>
<td>1.59</td>
<td>3.66</td>
<td>7.088</td>
<td></td>
</tr>
<tr>
<td>122k to 318k</td>
<td>1.38</td>
<td>2.90</td>
<td>9.728</td>
<td></td>
</tr>
<tr>
<td>318k to 1148k</td>
<td>1.53</td>
<td>1.95</td>
<td>4.32</td>
<td>240</td>
</tr>
</tbody>
</table>

Table 4.3. Grid convergence for the prismatic scheme.

<table>
<thead>
<tr>
<th>Grid sizes</th>
<th>r value</th>
<th>$\varepsilon_{\text{rms}}$ (%)</th>
<th>GCI (%)</th>
<th>Run time for fine grid (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>52k to 142k</td>
<td>1.40</td>
<td>3.62</td>
<td>10.36</td>
<td></td>
</tr>
<tr>
<td>142k to 510k</td>
<td>1.53</td>
<td>2.94</td>
<td>6.55</td>
<td></td>
</tr>
<tr>
<td>510k to 1422k</td>
<td>1.40</td>
<td>1.79</td>
<td>5.47</td>
<td>285</td>
</tr>
</tbody>
</table>

Table 4.4. Grid convergence for the hybrid scheme.

<table>
<thead>
<tr>
<th>Grid sizes</th>
<th>r value</th>
<th>$\varepsilon_{\text{rms}}$ (%)</th>
<th>GCI (%)</th>
<th>Run time for fine grid (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>124k to 266k</td>
<td>1.29</td>
<td>4.30</td>
<td>19.46</td>
<td></td>
</tr>
<tr>
<td>266k to 608k</td>
<td>1.39</td>
<td>4.33</td>
<td>17.67</td>
<td></td>
</tr>
<tr>
<td>608k to 1144k</td>
<td>1.40</td>
<td>3.71</td>
<td>21.28</td>
<td>245</td>
</tr>
</tbody>
</table>
Fig. 4.1. Isometric view of the physiologically realistic bifurcation (PRB) surface models for (a) planar and (b) out-of-plane configurations.
Fig. 4.2. Four characteristic meshing styles of the PRB model including (a) structured hexahedral, (b) unstructured hexahedral, (c) prismatic, and (d) hybrid configurations. The hybrid style consists of tetrahedral elements throughout the interior surrounded by three layers of hexahedral control volumes on the surface. The internal block divisions have been shown in the cross-sectional slices of the structured and unstructured hexahedral meshes.
Fig. 4.3. Geometric blocking patterns used to construct meshes for the (a) structured
hexahedral design (178 blocks) and (b) unstructured hexahedral configuration (80
blocks).
Fig. 4.4. Specification of the initial particle profile at the model inlet. (a) The inlet mass flow rate for the blunt inlet velocity profile, and (b) the resulting spatial distribution of initialized particles. The x-axis has been non-dimensionalized by the inlet radius R.
Fig. 4.5. Midplane velocity profiles for three resolutions of the planar unstructured hexahedral mesh at Slice 1.
Fig. 4.6. Velocity vectors, contours of velocity magnitude, and in-plane stream traces at the mid-plane and selected slice locations for the planar PRB model including the (a) structured hexahedral mesh with 214,000 control volumes, (b) unstructured hexahedral mesh with 318,000 control volumes, (c) prismatic mesh with 510,000 control volumes, (d) hybrid mesh with 608,000 control volumes.
Fig. 4.7. Comparisons of midplane velocity profiles for the planar geometry at high-level resolutions: (a) Slice 1, (b) Slice 2, and (c) Slice 3.
Fig. 4.8. Deposition locations for 10 µm particles in the planar geometry for the (a) structured hexahedral mesh, (b) unstructured hexahedral mesh, (c) prismatic mesh, and (d) hybrid mesh.
Fig. 4.9. Cumulative deposition fraction vs. linear distance in the y-direction for the planar geometry with (a) 10 μm, (b) 5 μm, (c) 3 μm, and (d) 1 μm particles.
Fig. 4.10. Cumulative deposition fraction vs. linear distance in the y-direction for the out-of plane geometry with (a) 10 μm and (b) 3 μm particles.
5. Effects of Exhalation and Asthma

5.1 Introduction

The current literature lacks an adequate model for local aerosol deposition in respiratory airways under expiratory conditions. Additionally, it is becoming essential to study particle deposition for constricted airway conditions due to the prevalence of chronic respiratory inflammation and asthma in the modern world (ALA 1998; Calmes et al. 1998; Mannino et al. 1998; Clark et al. 1999). Since children are most susceptible to these ailments, pediatric lung models should be considered (Hofmann et al. 1989; Musante and Martonen 2000; Segal et al. 2002). To achieve this, it is essential to analyze the effects of asthma induced airway constriction on fluid-particle dynamics in airway models under expiratory conditions for pediatric subjects. Theoretical explanations of the mechanisms governing fluid-particle dynamics in flows where two conduits merge into one (for example, expiratory flow) as opposed to inspiratory conditions (flow from one parent branch separates into two daughter branches) are required for better lung deposition modeling. Additionally, whole lung deposition models are based on inhalation conditions, and do not consider the entire breathing cycle. A valid correlation is required for exhalation conditions to complete the breathing cycle in order to obtain accurate deposition estimates using whole lung dosimetry models.
The objective of this study is to investigate the effects of asthma-induced airway constriction on aerosol dynamics and particle deposition patterns in bifurcating models of pediatric airways for expiratory conditions. Micron sized particles ranging from 1 – 7 μm have been considered. The computational model employed has been validated in previous studies with comparisons to branch-averaged and sub-branch deposition profiles (Longest, Vinchurkar et al. 2006; Longest and Vinchurkar 2007a; Longest and Vinchurkar 2007b). For this study, particle depositions have been evaluated with respect to both branch-averaged deposition rates and the formation of sub-branch focal accumulations, which are referred to as hot spots. Results of branch-averaged deposition rates have been compared to predicted values from sample analytic and empirical correlations. The formation of hot spots has been quantified with a novel microdosimetry deposition factor (χ). Geometries considered include double bifurcation models of upper (G3 – G5) and central (G7 – G9) airways for a four-year old child under healthy and 30% constricted conditions, as illustrated in Fig. 5.1. Steady inhalation flow rates consistent with sedentary, light and heavy activity levels have been employed. At these flow rates, laminar and low Reynolds number (LRN) k-ω flow solutions were necessary. Results for normal and constricted airways are presented in terms of velocity fields, branch averaged deposition rates, and microdosimetry deposition factors. A valid correlation is provided for the expiratory phase of the breathing cycle based on a combination of the branch Dean numbers and the Stokes numbers for pediatric airway models.
5.2 Methods

5.2.1 Models and Boundary Conditions

To study the effects of asthma or inflammation induced chronic airway constriction on fluid-particle characteristics of respiratory aerosols, four pediatric airway models are considered. Airway generations modeled include 3 through 5 (G3 – G5), representing upper airways, and 7 through 9 (G7 – G9), representing central airways based on Weibel’s convention (Weibel 1963). These airways include An, Ac, Bn and Bc as illustrated in Fig. 5.1. The subscripts \( n \) and \( c \) represent normal and constricted airway conditions, respectively, of a four-year old child. Airway constriction is modeled based on a 30% reduction of the airway lumen diameter. Hofmann et al. (1989) provide a description of the dimensional features for airway generations G4 and G8. Upper and lower airways are constructed using a parent to daughter diameter scaling factor of 1.245 and a length scaling factor of 1.19. Additionally, the surface geometries are based on the physiologically realistic bifurcation (PRB) model proposed by Heistracher and Hofmann (1995). Anatomic data for these models has been provided by Hammersley and Olson (1992) and Horsfield et al. (1971). Branch angles and lengths for normal and constricted conditions are identical. Tables 5.1 and 5.2 provide details on the mathematical description of the pediatric airways, Reynolds numbers, and surface parameters for the PRB model employed in this study. Further details on the models considered are provided in a previous study by Longest, Vinchurkar et al. (2006).

Exhalation flow rates are calculated as

\[
Q_{Ex} = 2 f V_T
\]  

(5.1)
where $f$ is the breathing frequency converted to breaths per second and $V_T$ is the tidal volume (cm$^3$/breath). Hofmann et al. (1989) provided tidal volumes and breathing frequencies for a four-year old child. Flow rates considered are representative of sedentary, light and heavy activity conditions. A matching Reynolds number approach, defined by $Re_{match} = 0.5(Re_{mean} + Re_{max})$ is employed for all breathing conditions based on a study by Zhang et al. (2002), where $Re_{max} = 0.75(Re_{mean}/Re_{max})$ (ICRP 1994). The Reynolds number range for this study is between 100 – 5200, requiring laminar, transitional and fully developed turbulent conditions. Identical flow rates are considered between constricted and normal airway models. Symmetric expiratory flow from all four branches is considered. Mass conservation is employed, so that for all models considered, the net flow rate during inhalation is equal to the net flow rate during expiration.

In previous studies (Longest and Vinchurkar 2006; Longest and Vinchurkar 2007a), good agreement was observed between branch-averaged and highly localized in vitro deposition data for a blunt inlet velocity profile. This blunt inlet velocity profile was employed in previous studies to account for a higher Reynolds number, and to simulate the effects of upstream flow conditions. However, a parabolic inlet velocity profile is more suited for this study since the Reynolds number is in the low range of 40 – 680 except in two cases where $Re = 1410$ and 2020, in which a blunt inlet velocity profile is employed.

The blunt inlet profile is defined as

$$u(r) = 1.2244u_m \left( \frac{R-r}{R} \right)^{1/7}$$

and

$$Re_{match} = 0.5(Re_{mean} + Re_{max})$$

(5.2)

the parabolic profile is defined as
\[ u(r) = u_m \left( 1 - \frac{r^2}{R^2} \right) \]  

(5.3)

where \( r \) is the inlet radial coordinate, \( u_m \) is the mean velocity and \( R \) is the outer radius of the inlet. Homogenous inflow is assumed at the four inlets, modeled in terms of equal mass flow for each inlet. The no-slip wall boundary condition was applied and particles were assumed to deposit at initial wall interception. The inlet particle profiles were matched with the inlet mass flow rate profiles and are given as

\[ \dot{m}_{p,\text{ring}} \sim \dot{m}_{\text{ring}} = \int_{r_1}^{r_2} \rho u(r) 2\pi r dr \]  

(5.4)

where \( \dot{m}_{p,\text{ring}} \) is a finite ring of particles, \( r_1 \) and \( r_2 \) define the extent of the ring and \( u(r) \) is the inlet velocity profile.

5.2.2 Numerical Methods

The commercial CFD software Fluent 6 is based on a finite volume scheme and has been employed to solve the governing mass and momentum equations of the 3-D expiratory flows simulated in the PRB model. User-supplied Fortran and C programs have been employed for the calculation of initial particle profiles, particle deposition locations, grid convergence, and post processing. A segregated implicit solver was employed to solve the linear set of equations using a Gauss-Seidel method, and the SIMPLIC algorithm was employed to solve the pressure-velocity coupling. To improve accuracy, cgs units were employed, and all calculations were performed in double precision. A multiblock structured grid was employed, and was validated in a previous study (Longest and
Vinchurkar 2006) for inhalation. Grid convergence was reported on the order of 2% using the GCI approach as proposed by Roache (1992). For the laminar and LRN k-ω turbulent solutions, the largest meshes resulted in a root-mean-square relative velocity error of approximately 0.4% with a mesh size of 325,000 and 650,000, respectively.

5.2.3 Deposition Factors and Model Validations

Particle trajectories were calculated for the steady flow field using an integration scheme that solves Eq. 5.4 with a trapezoidal rule. The number of particles required was determined by adding additional groups of 10,000 until the local deposition results varied by less than 1%. Specifically, for the 1, 3, 5 and 7 μm aerosols considered the numbers of particles simulated were 100,000, 50,000, 20,000 and 20,000, respectively.

Branch averaged deposition is reported for individual bifurcations as

\[ \eta_i = \frac{\text{number of particles depositing in bifurcation } i}{\text{number of particles entering bifurcation } i} \] \hspace{1cm} (5.5)

Whereas, local deposition is represented by a microdosimetry factor given by

\[ \chi = \frac{\text{number of particles within 75 μm of a point}}{(\text{initial number of particles}) \cdot A_{\text{crit}}} \] \hspace{1cm} (5.6)

where \( A_{\text{crit}} \) is a local critical area with an assumed diameter of 150 μm, or approximately 15 lung epithelial cells, which represents the local area required for the desorption of many moderately soluble compounds from deposited respiratory aerosols into the mucus. The resulting increase in deposition is mapped by the deposition enhancement factor (DEF) where
\[ \text{DEF} = \frac{\chi}{\chi_{\text{mean}}} \quad \text{and} \quad \chi_{\text{mean}} = \frac{\sum \chi}{N} = \frac{\eta_i}{SA_i} \]

In these Eqns., \( N \) is the number of non-overlapping sample locations, \( \eta_i \) is the filtering efficiency of bifurcation \( i \), and \( SA_i \) is the surface area of bifurcation \( i \).

Validations of velocity field patterns and grid convergence for the multiblock mesh scheme applied to the PRB bifurcation geometry have been reported in Chapter 4 and in a study by Longest and Vinchurkar (2007a). This validation study was performed for inspiratory phase of the breathing cycle. The present study is consistent in all aspects of the previous studies except the direction of the flow, which is reversed in order to represent the expiratory phase of the breathing cycle.

5.3 Results

Results are reported for flow patterns as well as local and cumulative particle deposition under sedentary, light and heavy activity conditions. Deposition enhancement factors (DEF) and microdosimetry factors (\( \chi \)) for 1 and 5 \( \mu \)m aerosols are illustrated for light activity conditions. Effects of constriction on particle deposition and localization are discussed along with an explanation of the governing physical mechanisms. Maximum microdosimetry factors and filtering efficiencies for the airway models considered are also reported as a function of particle diameter and Stokes number. Finally, a correlation is proposed to capture particle deposition during expiration based on the reported deposition data.
5.3.1 Flow Patterns

Plots of mid-plane velocity contours, velocity vectors and cross-sectional velocity slices at approximately half-way of each bifurcation are illustrated in Figs. 5.2, 5.3 and 5.4 for sedentary, light, and heavy activity conditions, respectively. For all figures shown, results are arranged for (a) An, (b) Ac, (c) Bn and (d) Bc airway models. Velocities are approximately doubled by a 30% decrease in airway diameter for all models and flow conditions, which is apparent from the continuity equation. Reynolds numbers for models An, Ac, Bn and Bc are reported in Table 5.1. Considering all models with a single pair vortex structure, one counter clockwise and one clockwise vortex is observed. For a 2-pair vortex structure (4 vortices total), two counter clockwise and two clockwise vortices are observed. Directions of secondary flows are consistent for all models considered. In general, airway constriction results in sharper (skewed towards the center) velocity profiles and higher hydrodynamic instabilities, which lead to splitting of velocity fronts. Splitting is defined as a phenomenon leading to multiple peaks in the velocity profile along the primary flow direction.

For most models under the three breathing conditions considered, an asymmetrical flow pattern was observed in the secondary velocity fields of airways G4 and G8 (Slice 1). An exception to this pattern is the Bn model under sedentary conditions. The streamlines for secondary flow in this model appear as vertical lines directed from the core of the airway towards the top and bottom walls. This occurs when the vortex structure disintegrates due to a lack of energy, resulting in an asymmetrical flow structure. It can be concluded that a Reynolds number greater than 30 is essential to maintain a vortical flow
pattern from one bifurcation to the next. For all models under heavy activity, upper airway models under light activity, and the Ac model under sedentary conditions, a 2-pair vortex structure is observed for airway generations G3 and G7, and a 1-pair vortex structure is observed for airways G4 and G8. The central airway models under light activity and all models except Ac and Bn under sedentary conditions show a single pair vortex pattern for airways G4 and G8 as well as G3 and G7. Based on these observations it can be concluded that Re >230 was essential to maintain a 2-pair vortex structure for merging tubes representing expiratory breathing conditions.

5.3.2 Particle deposition

Particle deposition locations for 1 μm aerosols are illustrated in Figs. 5.5, 5.7 and 5.9 under sedentary, light and heavy activity conditions, respectively. Figures 5.6, 5.8 and 5.10 illustrate particle deposition for 5 μm aerosols for sedentary, light and heavy activity conditions, respectively. Total deposition results are reported as a percentage in the figures. Particle deposition occurs as a result of primary impaction, secondary impaction and turbulent dispersion. Primary impaction is defined as the deposition of a particle due to its inertia in the primary flow direction, whereas secondary impaction may be defined as the deposition of a particle due its inertia in the secondary flow direction. Turbulent dispersion refers to particle motion arising from interactions with turbulent eddies. Gravity and electrostatic forces are considered to be negligible in this study. For exhalation, primary impaction results in aerosol deposition on a bifurcation wall facing the exit of an airway generation. Secondary impaction during exhalation results in deposition patterns on the top
and bottom of the airway walls as well as on the sides of the airway walls. Primary and secondary impaction result in areas of high localized deposition, which are referred as hotspots. Turbulent dispersion results in a relatively uniform deposition pattern along an airway generation, which is apparent from the results obtained for heavy activity (high Reynolds number) conditions.

Under sedentary conditions, constriction decreases the deposition of 1 \( \mu m \) aerosols by approximately 1.5 and 3 times for upper and central airway models, respectively, as illustrated in Fig. 5.5. For 5 \( \mu m \) aerosols, constriction increases deposition by approximately 5 times for the upper airway models and decreases it by approximately 20 times for central airway models, as illustrated in Fig. 5.6. These deposition patterns imply secondary impaction. A very important point to be noted is that under certain conditions during exhalation, deposition actually decreases with an increase in particle diameter for the central airways (Figs. 5.5c and 5.5d vs. Figs. 5.6c and 5.6d). For the normal upper airway, particle deposition is roughly equal for both particle sizes considered under expiratory conditions. Sedentary conditions are representative of a low Reynolds number flow, yielding lower inertial forces. It is understood that deposition due to primary impaction is a function of particle size. However, this trend is not observed for the particle sizes considered under sedentary expiratory conditions. It can be concluded that deposition for low Reynolds number flow occurring in long thin conduits is affected by several other mechanisms. In this case, secondary impaction may be considered the most significant factor affecting particle deposition, since the deposition follows a fixed pattern in an inclined plane on the outer walls of the airways across either bifurcation.
Similar trends are observed for light activity conditions. As shown in Fig. 5.7, for 1 μm aerosols, constriction actually decreases the deposition by approximately 2.5 times for the upper and by 1.1 times for the central airway models, respectively. Although the deposition patterns do not clearly point at a specific mechanism, the patterns suggest deposition due to secondary impaction. Constriction increases deposition of 5 μm particles by approximately 2.5 times for the upper and by 4.5 times for the central airway models, respectively. This is illustrated in Fig. 5.8 and is caused primarily by secondary impaction for the An and Bn models. For the constricted geometries, both primary and secondary impaction appear to affect deposition.

Constriction increases particle deposition by 1.1 to 2 times for 1 and 5 μm diameter aerosols under heavy activity conditions for all but one case considered. For the central airway model with 1 μm aerosols, constriction increases the deposition by approximately 6 times. For the upper airways, namely An and Ac, secondary impaction and turbulent dispersion play a major role in deposition of 5 μm aerosols, as illustrated in Fig. 5.10a and 2.10b. Secondary impaction is responsible for the significant deposition observed on the top and bottom walls of the airways due to one pair of counter–rotating vortices. The second pair of vortices results in deposition on the sides of the airway walls, which can be observed for model An. As a result, it is observed that deposition due to secondary impaction can result in hotspot formations on the top and bottom as well as on the sides of airway walls. The deposition pattern in the Bc model for 5 μm aerosols is well pronounced on the sides (x-y plane) of generation G8, as illustrated in Fig. 5.10d. However, this pattern is similar to deposition from primary impaction, where particles from either airways of G9
impact on the opposite walls of G8. The deposition pattern that occurs due to primary impactation is different in terms of the location of hotspots compared with secondary impactation patterns. The deposition occurring on the sides of airway walls due to secondary impactation is not aligned with the flow emerging out of the airway, whereas the deposition occurring due to primary impactation is well aligned with the flow emerging from the airways as shown in Fig. 5.10d. For the Bn model, the 5 µm aerosols deposit on the upper and lower sides of G8, as illustrated in Fig. 5.10c, suggesting secondary impactation. For the same case, scarce but uniform particle deposition along G8 suggests that dispersion may have a small role in deposition as well. It is observed that the effect of dispersion in upper airway models is greater than the central airway models. This is due to higher Reynolds numbers leading to more turbulence and stronger eddies.

Cumulative deposition fractions of 1 and 5 µm aerosols for sedentary and light breathing conditions are illustrated in Fig. 5.11a and 5.11b, respectively. Under sedentary conditions, the upper airway models yield a deposition fraction of approximately 11% for 5 µm aerosols. All other models yield a deposition fraction in the range of 0 – 2% for both particle sizes. Under light activity conditions, a deposition fraction range of 0 – 4% is observed for 1 µm aerosols. The 5 µm aerosols show relatively increased deposition for constricted conditions. The constricted upper airway, Ac, under light activity shows a maximum deposition fraction of approximately 83% against the normal model, An, which yields an approximate deposition fraction of 35%. For the central airway models, constriction increases the deposition fraction from 12% for the Bn model to 54% for the Bc
model, approximately. Deposition fractions for heavy conditions yield a similar increase in deposition for constricted conditions and are not included.

5.3.3 Local Deposition functions

Microdosimetry factors ($\chi \text{ cm}^{-2}$) for 1 $\mu$m and 5 $\mu$m diameter aerosols under light activity conditions are illustrated in Fig. 5.12 and Fig. 5.13, respectively. Constriction is observed to increase the $\chi_{\text{max}}$ values for 1 $\mu$m aerosols by approximately 4 and 1.5 times for the upper and central airway models, respectively. In addition to an increase in the $\chi$ values, it is also observed that there is an increase in the area covered by the higher $\chi$ values. For 5 $\mu$m aerosols under light activity, $\chi$ values for the upper airway models actually decrease with constriction by approximately half, whereas for the central airway models it increases by a negligible percentage (Fig. 5.13). Nevertheless, contours of $\chi$ values for constricted conditions cover more area of the bifurcation. In general, contours of $\chi$ values at specific locations may provide information about the dominant mechanism governing deposition and can be used to quantify the localized deposition of particles.

Deposition enhancement factors (DEF) for 1 $\mu$m and 5 $\mu$m aerosols are illustrated in Fig. 5.14 and 5.15, respectively, for light activity conditions. For 1 $\mu$m aerosols, constricted conditions increase the DEF by an order of magnitude for the upper airway models. For the central airways, constriction negligibly affects the DEF values. For 5 $\mu$m aerosols, constriction decreases the DEF by approximately an order of magnitude.
5.3.4 Deposition Curves

Filtering efficiency vs. particle diameter is plotted for the first (G3 & G7) and second (G4 & G8) bifurcations in Fig. 5.16. Differences in deposition fractions between upper and central airways approach an order of magnitude for some cases. It is also observed here that well-defined correlations can be obtained between normal and constricted conditions, except for the central airways under heavy activity, and the upper airways under light activity conditions. For sedentary conditions, a consistent decrease in deposition with increasing particle diameters is observed. Therefore, it can be concluded that Stokes number alone may not be sufficient to entirely capture the deposition data during exhalation. In general, deposition fraction differences between normal and constricted conditions appear to be between of 5% and a factor of five.

Filtering efficiency as a function of the particle Stokes number for the first and second bifurcation is illustrated in Fig. 5.17 for the three flow conditions considered. Branch-averaged filtering efficiencies are plotted against Stokes numbers, and compared to the inhalation empirical correlation of Kim and Fisher (1999), the inhalation analytic deposition correlation of Martonen (1982) and the exhalation empirical correlation of Kim, Antonio et al. (1989). The expiratory data obtained in the present study compares moderately well to the exhalation correlation of Kim (1989) for the normal airway models under light and heavy activity conditions. The filtering efficiency results obtained in this study are in agreement with the inhalation correlation of Kim and Fisher (1999) and the empirical correlation of Martonen (1982) for light and heavy activity conditions. However, some differences are observed; for example, under heavy activity conditions, the first
bifurcation results tend towards a linear profile, while the existing correlations are exponential in nature.

Maximum values of the microdosimetry factor ($\chi_{\text{max}}$) are plotted against particle diameter and Stokes number in Figs. 5.18 and 5.19, respectively. A matching trend is obtained between the normal and constricted conditions with a maximum difference of an order of magnitude. The $\chi_{\text{max}}$ factor follows a similar profile between normal and constricted conditions when plotted against the Stokes number as shown in Fig. 5.19. The maximum difference between the normal and constricted conditions is observed to be slightly less than an order of magnitude. Similar profiles with varying magnitude for the $\chi_{\text{max}}$ factor imply dependency on the Stokes number, which is a function of the particle diameter. Maximum values of the $\chi_{\text{max}}$ factor are reported on the order of 200 for the constricted airways, except for the sedentary flow case, and on the order of 20 for the normal airways.

5.3.5 Novel Correlation for Deposition

Exhalation deposition is observed to be influenced by the Stokes number (Kim et al. 1989), Reynolds number (Zhang and Kleinstreuer 2002) and the Dean number (present study). The Dean number is defined as the ratio of the square root of the product of the inertial and centrifugal forces to the viscous force. The effect of branch Dean number on deposition during exhalation is shown in Fig. 5.20. For a constant Stokes number, the figure shows an increase in deposition with an increase in the branch Dean number. Based on these results, a novel correlation for the expiratory phase in pediatric upper and central
airway models is presented for a particle size range of 1 – 7 μm. Data presented in Figs. 5.21a, b and c represent sedentary, light activity and heavy activity conditions, respectively. The sedentary data and light activity data are represented by

\[ Y = 0.758 - 0.258X + 8X^{1.5} \quad \text{(sedentary)} \]  \hspace{1cm} (5.7)

\[ Y = 54.52 \exp(-6.47/X) \quad \text{(light)} \]  \hspace{1cm} (5.8)

where \( X = \text{De}^a \text{Stk}^b \). The values of \( a \) and \( b \) are 1 for sedentary conditions, and 0.5 and 0.75, respectively for light activity conditions.

For heavy activity conditions, an adequate correlation could not be found using a combination of the Stokes, Reynolds, and Dean numbers. The lack of an adequate curve fit indicates that not all physical mechanisms are being captured in the correlation. To illustrate that considering Stokes number alone is inadequate, a Stokes number correlation is presented as

\[ Y = 6.5\text{Stk} + 14.9 \]  \hspace{1cm} (5.9)

A regression analysis of the three correlations results in \( R^2 \) values of 0.91, 0.92 and 0.27 for the sedentary, light activity and heavy activity correlations, respectively. Considering sedentary and light activity results together, a single correlation results in a \( R^2 \) value of 0.9, and is represented by the equation

\[ Y = 1 + 55.75 \exp(-6.86/X), \text{ where } X = \text{De}^{0.5}\text{Stk}^{0.75} \]  \hspace{1cm} (5.10)

The quality of Eq. (5.10) is illustrated in Fig. 5.22. Although the \( R^2 \) value shows good agreement with the data for a joint sedentary and light activity correlation, it is recommended to use the sedentary correlation for representative breathing conditions to capture the entire data set.
5.4 Discussion

For sedentary conditions, model Bn showed secondary velocity streamlines aligned diagonally (along the x-z plane) for airway G8 (Fig. 5.2). This unusual phenomenon occurs when the initial two vortices emerging out of the upstream bifurcation (G8) collapse due to lack of energy associated with low Reynolds numbers. For models Ac and An, a similar trend can be observed slightly upstream of the 7th bifurcation, however, this trend is disturbed when the flows emerging from either airway passage of generation G8 meet at the 7th bifurcation. This phenomenon is not pronounced for light and heavy activity conditions because of the high Reynolds numbers, which provide sufficient momentum to maintain the vortices.

Momentum is transferred from a velocity front, which behaves as a momentum source, to regions with lower momentum through viscous diffusion. A velocity front tends to disperse or dissipate momentum through a vortex structure with equal numbers of vortices across one or two symmetry planes. Multiple velocity fronts are reported for the velocity field in G3 and G7 for all models under heavy activity conditions. For light activity, models An and Ac have Reynolds numbers high enough to split the velocity front into 2 peaks, whereas for sedentary conditions, a dual velocity front was observed only for the Ac model. As a general guide, a cut-off Reynolds number of 230 was necessary to split the velocity front. Furthermore, for an airway model with one symmetry plane, a dual-front velocity pattern would result in a 2-pair vortex structure. However, it should be noted that the dual-front velocity profile is an unstable mode, which decays due to the transfer of momentum. This dual-front phenomenon is reported for low Reynolds number flows in
thin, long conduits merging into a single conduit. Further studies are needed before these conclusions can be extended to other flow domains.

The present study shows a single pair vortex structure for airways G4 and G8 with all models under light activity conditions (Fig. 5.3). These results agree well with the available literature on single bifurcation studies related to the direction and vortex structure of the flow (Balashazy and Hofmann 1993; Zhao and Lieber 1994; Hofmann et al. 2001; Fresconi et al. 2003). As stated in the existing literature, secondary flow effects are important for particle deposition during expiratory breathing. The present study is an extension of existing work and considers a double bifurcation model. A 2-pair vortex structure is reported for the farthest downstream airway (G5 and G9) with one plane of symmetry for the higher Re flows. Dual-front velocity profiles are observed for G5 and G9 in all models under heavy breathing conditions due to the 2-pair vortex structure. The present study reports a critical Reynolds number of 230 to maintain a 2-pair vortex structure. This effect can be observed in a separate study on flow in a bend section for $38 > \text{Re} > 198$ (Tsai and Pui 1990). In this study, a single vortex pair was observed for a single bend-pipe. In the same study, it was reported that particle deposition increases for increased Dean numbers until it remains relatively constant at $\text{De} > 200$. Additionally, it was mentioned that the curvature of the bend continues to affect particle deposition. Other studies on particle deposition in bent tubes have reported similar numbers below which the Dean and Reynolds numbers as well as the geometry shape plays a more significant role in deposition (Sato et al. 2002; Wang et al. 2002). Berger and Talbot showed that a vortex flow structure is introduced in a curved pipe at $150 > \text{De} > 200$ (1983). These results
correlate well to the proposed deposition formula in the present study, which defines particle deposition as a function of the Stokes number and the Dean number, considering that the Dean number itself is a function of the Re and the curvature ratio of the pipe. Additionally, the present results agree with the lower Re criteria quoted in the literature. However, the expiration data did not match well to the existing analytical and expiratory correlations, especially for sedentary conditions.

Deposition decreases with an increase in the particle diameter due to the effects of secondary flow under sedentary breathing conditions for constricted airways (Fig. 5.5 vs. Fig. 5.6) This occurs due to additional time required by the 5 μm particles to cover the distance to the outer (away from the bifurcation) airway wall as compared to the 1 μm particles. The 1 μm particles follow the flow streamlines better than 5 μm particles, and as a result cover this distance in less time. In contrast, the 5 μm particles require more time to cover this distance. Eventually, a majority of the 5 μm particles are pulled back by the primary flow stream before they deposit on the outer airway wall due to the secondary current. This effect is observed for the central airway models with low Reynolds numbers.

The deposition correlations proposed by most studies on exhalation and inhalation report particle deposition as a function of the Stokes number alone (Martonen 1982; Balashazy and Hofmann 1993; Kim and Fisher 1999). The expiratory data from the present study for light activity conditions is in partial agreement with the analytical correlation proposed by Martonen (1982). The agreement occurs for relatively high Re when primary impaction takes over as the dominant deposition mechanism. Although the analytical model considers inertial deposition in curved tubes, it is assumed that for lower Re flows
the model does not capture the interactions between centrifugal and inertial forces acting on the flow, i.e., when secondary impaction becomes the dominant mechanism governing deposition. Additionally, for particle deposition the Stokes number introduces a time delay in the effect of these parameters on the discrete flow. This could result in the particles depositing a short distance downstream of the expected deposition sites. Under these conditions, a large fraction of the particles may not deposit since they are pulled back into the core by the primary flow. It is assumed that this could be the reason for not capturing deposition data for secondary impaction by the analytical correlation of Martonen (1982). The exhalation correlation proposed by Kim and Fisher (1989) found that the expiratory data was a function of the bifurcation angle and the Stokes number. In a sense, the present study converts the bifurcation angle effect to a dimensionless number, De, which can assist in developing whole lung deposition models. Li et al. (1994) analyzed particle deposition in an obstructed turbulent duct flow and showed deposition to be a linear function of the Stokes number. The present study agrees with the nature of the correlation profile of Li et al. (1994) for heavy activity conditions. In addition to parameters analyzed in this study including the Reynolds number, Stokes number, Dean number and turbulent intensity for high activity conditions, it is intended to study particle relaxation times and particle Reynolds numbers (Zhang and Ahmadi 2000) to find an appropriate correlation for heavy activity turbulent flow conditions. These parameters will be included in future studies.

In conclusion, particle deposition and flow structures for expiratory breathing conditions in upper and central pediatric airway models under healthy and constricted states were presented. A critical Reynolds number of Re = 30 was reported to maintain a
vortex flow structure and Re = 230 to sustain a 2-pair vortex structure. These critical Re numbers can be considered as threshold values above which a significant deposition can be expected. In general, inspiratory flow is directed into sequentially lower Reynolds number regimes, whereas expiratory flow is directed into sequentially higher Re regimes. It can be concluded that due to cumulative addition of general upstream flow disturbances, expiratory flow tends to be a relatively unstable phase of the breathing cycle. The deposition patterns and hotspots for expiratory flow are dependent on the flow rate and the dominant mechanism for particle deposition. For sedentary conditions the dominate deposition mechanism was secondary impaction, for light activity conditions the dominate deposition mechanism was primary as well as secondary impaction, and for heavy activity conditions turbulent dispersion controlled deposition. A novel correlation based on explicit factors (Stokes and Dean numbers) for expiratory breathing was proposed showing good agreement with the sedentary and light activity data. Further studies are essential to find a correlation that can better predict the heavy activity deposition data. The resulting correlations can provide an algebraic formula for whole lung deposition over the exhalation part of the breathing cycle.
Table 5.1. Description of upper and lower bifurcation models for a pediatric (4-year-old) lung geometry.

<table>
<thead>
<tr>
<th>Model</th>
<th>Dimensions (mm)</th>
<th>Activity</th>
<th>Flow Rate (cm$^3$/s) and Re</th>
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<tr>
<td>G3 – G5 Healthy 4 year old $A_N$</td>
<td>$L_3 = 6.65$</td>
<td>$D_3 = 3.44$</td>
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<td></td>
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<td></td>
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<td>$Q_3 = 39.15$ $Re_3 = 1411$</td>
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<td>G3 – G5 Constricted 4 year old $A_C$</td>
<td>$L_3 = 6.65$</td>
<td>$D_3 = 2.40$</td>
<td>$Q_3 = 4.08$ $Re_3 = 90$</td>
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<tr>
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<tr>
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<td>$L_5 = 4.70$</td>
<td>$D_5 = 1.55$</td>
<td>$Q_3 = 39.15$ $Re_3 = 2022$</td>
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<td>G7 – G9 Healthy 4 year old $B_N$</td>
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<td>$D_9 = 0.731$</td>
<td>$Q_9 = 2.45$ $Re_9 = 268$</td>
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<td>G7 – G9 Constricted 4 year old $B_C$</td>
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<td>$D_9 = 0.512$</td>
<td>$Q_9 = 2.45$ $Re_9 = 384$</td>
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Table 5.2: Geometry parameters for the physiologically realistic double bifurcation (PRB) model.

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<th>Second</th>
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</tr>
<tr>
<td>Length ratio</td>
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<td>$1.19$</td>
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Fig. 5.1 Pediatric respiratory airway models of Generations G3 – G5 for (a) normal and (b) 30% constricted conditions, Generations G7 – G9 for (c) normal and (d) 30% constricted conditions.
Fig. 5.2 Contours of velocity magnitudes, velocity vectors, and in-plane streamtraces for the (a) An, (b) Ac, (c) Bn, and (d) Be models under sedentary conditions.
Fig. 5.3 Contours of velocity magnitudes, velocity vectors, and in-plane streamtraces for the (a) An, (b) Ac, (c) Bn, and (d) Bc models under light activity conditions.
Fig. 5.4 Contours of velocity magnitudes, velocity vectors, and in-plane streamtraces for the (a) An, (b) Ac, (c) Bn, and (d) Bc models under heavy activity conditions.
Fig. 5.5 Deposition locations for 1 μm particles in model (a) An, (b) Ac, (c) Bn, and (d) Bc under sedentary conditions.
Fig. 5.6  Deposition locations for 5 μm particles in model (a) An, (b) Ac, (c) Bn, and (d) Bc under sedentary conditions.
Fig. 5.7  Deposition locations for 1 μm particles in model (a) An, (b) Ac, (c) Bn, and (d) Bc under light conditions.
Fig. 5.8 Deposition locations for 5 μm particles in model (a) An, (b) Ac, (c) Bn, and (d) Bc under light conditions.
Fig. 5.9  Deposition locations for 1 μm particles in model (a) An, (b) Ac, (c) Bn, and (d) Bc under heavy conditions.
Fig. 5.10 Deposition locations for 5 μm particles in model (a) An, (b) Ac, (c) Bn, and (d) Bc under heavy conditions.
Fig. 5.11 Local cumulative deposition results including 1 and 5 μm particles for An, Ac, Bn and Bc models under (a) sedentary and (b) light activity conditions.
Fig. 5.12  Microdosimetry factors ($\chi$) for 1 $\mu$m aerosols in models (a) An, (b) Ac, (c) Bn and (d) Bc under light activity conditions.
Fig. 5.13  Microdosimetry factors ($\chi$) for 5 $\mu$m aerosols in models (a) An, (b) Ac, (c) Bn and (d) Bc under light activity conditions.
Fig. 5.14 Deposition enhancement factors (DEF) for 1 μm aerosols under light activity conditions in models (a) An, (b) Ac, (c) Bn and (d) Bc.
Fig. 5.15 Deposition enhancement factors (DEF) for 5 μm aerosols under light activity conditions in models (a) An, (b) Ac, (c) Bn and (d) Bc.
Fig. 5.16 Filtering efficiencies (η) vs. particle diameters under sedentary (a & b), light (c & d), and heavy (e & f) activity conditions for the third and fourth bifurcations.
Fig. 5.17 Branch-averaged filtering efficiencies ($\eta$) vs. Stokes number for sedentary (a & b), light (c & d), and heavy (e & f) activity conditions.
Fig. 5.18 Maximum microdosimetry factors ($\chi_{\text{max}}$) vs. particle diameter for (a) sedentary, (b) light and (c) heavy activity conditions.
Fig. 5.19 Maximum microdosimetry factors ($\chi_{\text{max}}$) vs. Stokes number for (a) sedentary, (b) light and (c) heavy activity conditions.
Fig. 5.20. Effect of branch Dean number on particle deposition efficiency at various Stokes numbers. Deposition efficiency increases as a function of Dean number.
Deposition efficiency vs. X

(a) Deposition efficiency vs. X

(b) Deposition efficiency vs. X
Fig. 5.21. Novel correlation for particle deposition during exhalation for (a) Sedentary, (b) light activity and (c) heavy activity breathing conditions. Good agreement is observed with the expiratory data for sedentary and light activity conditions.
Fig. 5.22. A single correlation for particle deposition during exhalation for sedentary and light activity conditions.
6. Fluid-Particle Transport and Wall Losses in the Andersen Cascade Impactor

6.1 Introduction

Evaluating particle size distribution characteristics for pharmaceutical inhalers is a primary component in judging inhaler performance. The particles can be in the form of an aerosol cloud discharged from a dry powder inhaler (DPI) or a liquid spray discharged from a metered dose inhaler (MDI). Determining the particle size distribution provides information on the mechanisms affecting deposition in the lung, as well as potential deposition locations. A cascade impactor acts as a filtering mechanism for a polydisperse particle size sample. Inertial impactors are widely used to perform particle size distribution measurements with applications to pharmacology and toxicology (Ranz and Wong 1952; Andersen 1966; Flesch et al. 1967; Lundgren 1967; Mercer and Stafford 1969; Marple 1970; Marple and Liu 1974; Marple and Liu 1975; Marple and Willeke 1976; Rader and Marple 1984; Vaughan 1989; Swanson et al. 1996; Hinds 1998; Marple et al. 2003; Marple 2004; Dunbar and Mitchell 2005). Furthermore, cascade inertial impactors may be useful in simulating in vivo lung deposition. Evaluating the impactor and the intricate parameters affecting its performance has become an essential step toward validating particle size distribution measurements.

Considering inertial impactors, a number of questions remain unanswered including the degree of flow distribution among jets, recirculation and dead zones in the impactor
body, visualization of airflow and particle dynamics, amount of turbulence, mechanisms responsible for wall losses, and the effects of electrostatic charge, hygroscopic growth and evaporation on deposition. Computational fluid dynamics (CFD) can help to better resolve these issues. Very few numerical studies have addressed inertial cascade impactors (Vaughan 1989; Swanson et al. 1996), and no CFD studies could be found that simulated inertial impactors.

The current study presents a numerical CFD analysis of the multi-stage, multi-orifice inertial Andersen cascade impactor (ACI). The flow rate for the ACI is maintained at 1 ACFM (28.3 L/min) and its functionality is limited to non-viable (biologically inactive) particles. The particle sampler considered is a Mark II ACI with 0 – 8 stages and a particle size range of 0.2 – 12 μm. The upper limit for total particulate mass on any of the stages is 10 mg. The assumptions for the numerical model include no-slip wall boundary conditions, bounce and no-bounce nozzle-wall conditions, and adherence of the aerosol particles to the collection plate upon impaction for a laminar to transitional incompressible flow. Results are presented in the form of velocity profiles, recirculation and dead zones, stage retention fraction and wall losses. Results for retention fraction are validated with available data from the literature as well as from the manufacturer.

6.2 Methods
6.2.1 Impactor Characteristics

A Mark II Andersen cascade impactor consisting of eight stages is shown with the induction port (IP) in Fig. 6.1. The ACI is assembled such that all stages are arranged in
descending order of nozzle diameters from Stages 0 through 7. Stage 8 is a collection stage only, which traps all particles that escape Stages 0 – 7. The orifices on Stages 0 – 7 range from 0.1004 inches to 0.01 inches in diameter, respectively. Every stage has a collection plate made of stainless steel, which is 3.25 inches in diameter. Particles that fail to impact on the collection plate pass through to the next stage. For ambient particles above 10 µm, a preseparator is essential to capture larger aerosols, and to reduce particle bounce and re-entrainment. A vacuum pump is attached to the air sampler which is calibrated for a flow rate of 1 ACFM (1 ACFM = 28.3 actual liters per minute). The vacuum pump is attached to the outlet of the base stage (stage 8) using the rubber hose supplied with the sampler.

An important parameter for studying the ACI is the Stokes number, which is defined as the stopping distance of a particle suspended in a flow to the characteristic dimension of the object. The ACI sampler operates on the principle of particle impaction, which is governed by the Stokes number with the characteristic length being the jet (nozzle or orifice) radius. The Stokes number at which 50% of the particles impact and are collected is expressed as $Stk_{50}$. The aerodynamic cut-point or cut-off diameter of a stage, $d_{50}$, is the particle diameter at which $Stk = Stk_{50}$. The Stages 0 through 7 of the ACI sampler are arranged in decreasing order of the cut-off sizes. The first two stages have 96 nozzles each and a center hole in the collection plate (Fig. 6.2a and b). As shown in Figs. 6.2d and 6.3, Stages 3 – 6 consist of 400 nozzles each, whereas Stage 7 consists of 201 nozzles with a solid collection plate. The distance between the jet outlets and the collection plate is one of the significant length scales, and is equal to 1.02 mm for Stages 0 and 1, and 2.15 mm, approximately, for the remaining Stages. Other ACI specific impaction
characteristics are presented in Table 6.1. All values with subscript $n$ represent measurements at the ACI nozzle. In Table 6.1, $S$, $L$ and $d_n$ represent nozzle exit to impaction plate distance, nozzle length of impactor and diameter of the nozzle, respectively.

Determining the material of the collection surface and its coating is application specific, and can include glass or stainless steel. The deposition efficiency (DE) of particulate matter on each stage is obtained by dividing the number of particles collected on that stage by the total number of particles approaching the plate. This method is consistent with the study of Vaughan (1989). Particle concentration for any size range can be obtained by plotting the effective cut-off diameter and cumulative percent on log probability graph paper or with the help of numerical algorithms. The Reynolds numbers, Stokes numbers and dimensional characteristics for the ACI with 1 ACFM flow are reported in Table 6.2. As quoted in Table 6.2, $A_{\text{total}}$ represents the total area of all nozzles at an ACI stage.

Particle deposition in the ACI is primarily governed by the process of impaction. As explained earlier, a particle with inertial forces large enough to cross the flow streamlines strikes the collection plate, and sticks to the plate depending on its diameter. This process can be evaluated using a force equilibrium method. The distance $\Delta$ traveled by the particle towards the plate and perpendicular to the flow after the particle has passed the flow stagnation point defines whether or not a particle will strike the collection plate. However, the deposition efficiency curve for an impactor can be affected by the
distribution of particles at the nozzle exit. The distance \( \Delta \) can be shown to be equivalent to \( (Stk) \pi/2 \) where,

\[
Stk = \frac{\rho_p d_p^2 U C_C}{9 \eta D_j}
\]

and,

\[
d_{s0} = \frac{(9 \pi \eta D_j^3 Stk_{s0} N)^{1/2}}{(\rho_p QC_C)^{1/2}}
\]  \( (6.1) \)

The Stokes number, \( Stk \) is calculated using the particle diameter \( d_p \), particle density \( \rho_p \), average nozzle exit velocity \( U \), slip factor \( C_C \), absolute viscosity \( \eta \) and nozzle jet diameter \( D_j \) as shown above. For Eqn. 6.1, which gives the cut-off diameter, the flow rate is given by \( Q \) and the numbers of orifices are given by \( N \) (Hinds 1999).

6.2.2 Numerical Model and Boundary conditions

The numerical model for the ACI is three dimensional, with two planes of symmetry. The computational mesh employed is shown in detail in Fig. 6.4 for Stages 2 and 3. The figure illustrates a very fine mesh used in the vicinity of the collection plate and the nozzle sections. The mesh is relatively coarse away from the nozzles and the collection plate. The number of control volumes employed for the numerical model ranged from approximately 400,000 cells for Stage 0 to 2.5 million cells for Stage 7.

The inlet flow profile for the IP is parabolic, defined as

\[
u(r) = u_m \left(1 - \frac{r^2}{R^2}\right)
\]  \( (6.2) \)
where $r$ is the inlet radial coordinate, $u_m$ is the mean velocity and $R$ is the outer radius of the inlet. All stages are analyzed independently for particle distribution results. The inlet flow profile for Stage 0 is imported from the IP, whereas for Stage 1, the inlet flow profile is imported from Stage 0. For the remaining stages, it is assumed that the upstream flow exiting the IP has negligible effects on the particle deposition profiles in the ACI. The 180° bend at the beginning of a stage except for Stage 0 modifies the profile of the upstream velocity, resulting in a profile that is independent of the upstream flow. Inlet profiles for Stages 2 – 7 were simulated as a parabolic profile upstream of the 180° bend leading to the actual stage inlet. Simulating the flow upstream of the 180° bend can help in simulating the effects of the upstream stage to a considerable extent because the flow profile entering each stage is primarily governed by the profile of the bend.

For particles, the no-slip wall boundary condition was applied and particles were assumed to deposit at initial wall interception for the case with no bounce at the nozzle walls. For the case with bounce at the nozzle walls, reflective conditions were implemented. The inlet particle profiles were matched with the inlet velocity profiles based on the equation

$$\dot{m}_{p,ring} \sim \dot{m}_{ring} = \int_{r_1}^{r_2} \rho u(r)2\pi r dr$$

(6.3)

where $\dot{m}_{p,ring}$ is a finite ring of particles, $r_1$ and $r_2$ define the extent of the ring and $u(r)$ is the inlet velocity profile.

Fractional retention for individual stages is given by
\[ R = \frac{n_d}{N_d} \] (6.4)

and is adapted from the study of Vaughan (1989). Vaughan defines the retention fraction (deposition efficiency) for a single stage as the ratio of the number of particles deposited on the collection plate to the number of particles approaching the plate. Wall losses are calculated by subtracting the number of particles deposited in the impactor body (excluding the collection plate) from the total number of particles injected in the impactor, and dividing this by the total number of particles simulated for that stage.

6.3 Results

6.3.1 Velocity Fields

Flow patterns in the ACI are presented for the induction port (IP) and all stages of the ACI excluding the filter. The IP, Stage 0, Stage 1 and Stages 2 and 3 are shown in Fig. 6.5, and Stages 4, 5, 6 and 7 are shown in Fig. 6.6. Nozzle Reynolds numbers for Stages 0 through 7 lie in the range 150 – 800, approximately, with a Stokes number range of 0.001 – 1. Asymmetric entry flow is observed for the IP as shown in Fig. 6.5a. It is assumed that the asymmetry of the flow negligibly affects particle deposition because the mass distribution is nearly equal across the lines of symmetry. As the flow enters Stage 0 of the ACI, recirculation zones are observed upstream of the nozzle inlets. The maximum Reynolds number within the IP is reported to be 1250. This value is expected to increase in the recirculation zones upstream of the nozzles in Stage 0. Therefore, it can be predicted that some turbulence is expected in this region. The Reynolds number starts decreasing
thereafter, and reaches a minimum of 150 in the nozzle sections. The recirculation zones and initial asymmetry of the flow introduced by the IP may result in variable mass distribution among the individual nozzles. This can be observed as differences in the flow patterns for individual nozzles shown in Fig. 6.5b. Incurring differences on the particle deposition on the collection plates are discussed in the next sub-section. In addition to these differences, the recirculation zones can increase dead zones, wherein some particles remain suspended, and fail to deposit. Specifically, the number of suspended particles was observed to be on the order of 50% or more for submicrometer sized particles. Additionally, recirculation zones were observed below the collection plate, and along the passage of the flow to the next stage. These recirculation zones could affect wall losses and reliability of size distribution data. Furthermore, less sharp cut-off curves could be obtained for individual stages due to recirculation. The relative degree and distribution of recirculation zones is less pronounced for Stage 1. As a result, flow distribution is comparatively more uniform among the individual nozzles as shown in Fig. 6.5c. Nevertheless, increased recirculation is observed in the vicinity of the collection plate, which is apparent from the uniformity of mass distribution among the nozzles. The uniform distribution of mass tends to force an equal amount of flow through the nozzles hindering the exit flow from intermediate nozzles passing over the collection plate. This leads to recirculation zones in the region between nozzle exits and along the collection plate.

Stages 2 and 3 are constructed such that the effects of the upstream stage (Stage 2) can be studied on flow and particle dynamics of the subsequent stage (Stage 3). Due to an
increased number of nozzles, Stages 2 and 3 show decreased differences in flow
distribution as observed in Fig. 6.5d. Increased flow is observed for nozzles near the wall
compared with central nozzles. This trend tends to diminish for downstream stages. This
increased flow results in increased recirculation zones in the vicinity of the collection plate
in Stage 3. Some differences in the nature of the recirculation zones below the collection
plate are observed between Stage 2 and Stage 3. The effects of this on particle deposition
and distribution are discussed in the following sub-sections. Similar results are obtained for
Stages 4, 5, 6 & 7 in terms of recirculation zones, whereas the degree of non-uniformity in
flow distribution between nozzles decreases for further stages downstream as shown in
Fig. 6.5. For all stages, entry flow causes recirculation zones upstream of the nozzles with
a similar profile. Recirculation zones in the vicinity of the collection plates increase as the
nozzle Re increases from Stage 4 to Stage 7 (Table 6.2).

Figure 6.5 illustrates vector plots of the IP, and Stages 0, 1 and 2 – 3. Vectors
represent only direction of the flow. Figs. 6.5 b and c show that vectors are not normal to
the inlet of the nozzles for Stages 0 and 1, whereas Fig. 6.5d shows that the vectors are
normal to the entrance of the nozzles for Stages 2 and 3. This could be due to an increased
number of nozzles for Stages 2 & 3 resulting in more uniform flow distribution. The
normal alignment of vectors to the nozzle entrances remains consistent for the vector plots
of Stages 4 through 7 shown in Fig. 6.6.

Boundary layer flow in the vicinity of the collection plates for Stages 3 and 6 are
illustrated by Figs. 6.7a and b, respectively. The nozzle diameters for these stages are 0.71
mm and 0.25 mm, respectively. It is apparent from the figures that high uniformity between nozzles is attained for these Stages.

6.3.2 Retention Fraction

Three dimensional, 5 μm particle traces within Stage 1 are illustrated in Fig. 6.8. Particle traces show greater recirculation upstream of the nozzle inlets as compared to near the collection plate. It is observed that the particle distribution is skewed towards the center and the walls of the ACI for this stage due to the center hole in the upstream collection plate. Significant fractions of the particles are observed to be trapped in recirculation zones potentially leading to higher wall losses and errors in size distribution results.

Numerical predictions of retention fraction for Stages 0 through 7 are compared with the experimental results of Vaughan (1989) and the calibration curves of the manufacturer in Figs. 6.9a, b, c and d for Stages 0 – 1, Stages 2 – 3, Stages 4 – 5 and Stages 6 – 7, respectively. These numerical predictions for Stages 0 through 7 are in good agreement with the S-shaped curves reported by the experiments and the manufacturer. The retention data is plotted for bounce conditions at the nozzle walls. The $d_{50}$ values for the numerical predictions are reported together with the experimental data and the manufacturer values in Table 6.3. These values are in good agreement with the available literature and the manufacturer’s data. Numerical predictions show a maximum difference of 20% and 11% relative to the manufacturer and the experiments by Vaughan (1989), respectively. Some discrepancies are observed due to limitations over computational power and particles that remained suspended in the flow field due to recirculation.
6.3.3 Wall Losses

Visualization of predicted wall losses and particle deposition patterns for Stage 0, Stages 2 – 3 and Stage 6 are illustrated in Fig. 6.10 for particle sizes of 8 μm, 3.5 μm and 0.6 μm, respectively. Nozzle walls are numerically modeled to simulate particles to bounce on contact due to high shear stress. Considerable wall losses are observed for Stage 0 with 8 μm particles as well as for Stages 2 & 3 with 4 μm particles at the exit of the collection plate along the wall, where the flow direction changes by 180°. For Stage 6 as shown in 6.10c, the losses are significant behind the upstream collection plate due to the effect of recirculation zones.

Figure 6.11 illustrates numerical losses and deposition patterns for the same stages and particle sizes shown in Fig. 6.10 with no bounce effects at the nozzle walls. Negligible differences are observed between bounce and no-bounce effects in terms of deposition patterns on collection plates. However, simulating bounce effects at the nozzle walls are in better agreement to the experimental results for retention fractions. The wall losses reported in the present study are based on the number of particles depositing in the 180° bend passage between two stages. As discussed above, the effects of bounce are considered for nozzle walls. However, losses at walls upstream of the nozzle plates are not considered in this study. Some discrepancy in the results for wall losses in this study as compared to the literature is attributed to this approach. The range of numerical wall losses with bounce effects at the nozzle walls are approximately 7 – 9% for Stage 0, 4 – 11% for Stage 2, 0 – 2% for Stage 3, and 2 – 4% for Stages 5 and higher as reported in Table 6.4. The presence
of an upstream stage has a considerable effect on wall losses in the subsequent stage. This is observed for Stages 2 & 3 with wall losses decreasing from approximately 10% for Stage 2 to 1% for Stage 3.

6.4 Discussion

Numerical predictions of airflow, retention fraction and wall losses were presented for a typical pharmaceutical particle sampler, the Mark II Andersen cascade impactor. This particular impactor was selected for analysis because of its prevalent use and the availability of particle deposition and wall loss data. The numerical model includes the IP attached to an eight stage impactor model. Stages 0 – 7 were analyzed for particle size distribution, flow patterns and wall losses for a range of 12 – 0.2 μm diameter particles. Retention fraction for all stages analyzed was reported together with the experimental results and the manufacturer’s data. Excellent agreement was observed between the numerical predictions and available literature as well as the manufacturer’s data. Results showed significant recirculation zones, which could affect particle deposition and distribution data as well as wall losses. Additionally, non-uniform flow distribution among nozzles was observed for the upper stages (Stage 0 – 2), which decreased for lower stages due to the higher number of openings.

Maximum wall losses on the order of 11% were reported for the lower stages (Stage 2 and below). These numerical results agreed well with wall losses previously reported in the experimental study of Vaughan (1989) under similar conditions. However, Vaughan (1989) reported a decrease in wall losses for decreasing particle size. This trend
was not observed for the numerical predictions because of individual stage analysis in the present study. Whereas, Vaughan (1989) studied wall losses for individual particle size in the entire ACI. Specifically, Vaughan (1989) reported wall losses on the order of 5 – 11% for particles larger than 9 µm, 1 – 5% for particles between 4 and 9 µm, and less than 1% for particles smaller than 4 µm. These values agreed well with the wall losses reported in the present study as 0.3 – 11.5% for Stages 0, 2, 3 and 5 as shown in Table 6.4. As reported by Vaughan (1989), the upstream stages affect the flow of the lower stages by constraining the flow field. The effect of upstream stage on flow and particle dynamics reported in the present study is in agreement with the study of Vaughan (1989). The present study reported a reduction in wall losses by an order of magnitude for Stage 3, which is numerically attached to the upstream Stage 2. However, other stages of the ACI were individually analyzed. The effect of upstream stage on subsequent stages was reduced by simulating the flow inlet for individual stages just upstream of the 180° bend passage connecting adjoining stages. This bend passage requires the flow to negotiate a 180° change in flow direction through a restricted space. As a result, the flow characteristics were predominantly affected by the geometry of the bend passage as compared to upstream flow fields.

Flow patterns in this study showed recirculation zones in the impactor body upstream of the nozzles for Stage 0. For the other stages, recirculation was observed in the vicinity of the collection plates and below the collection plates. These result did not agree with the streamlined flow patterns hypothesized in the study by Vaughan (1989). On the contrary, the flow patterns for all stages showed recirculation zones that adversely affected the
performance of the ACI. These regions of recirculation can result in entrained particles and high residence times, non-uniform flow distribution among nozzles, high wall losses and substandard particle size distribution results. Recirculation in the vicinity of the collection plate could yield poor results for particle size cut-off values. Additionally, for submicrometer-sized particles, diffusive forces can significantly affect deposition as compared to particles larger than 1 µm (Longest and Xi 2007). Therefore, particle deposition results for sub-micrometer particles could be severely affected by recirculation zones in the vicinity of the collection plate.

Non-uniform flow patterns leading to skewed particle distributions were observed for Stages 1 and 2. It appeared that the particle distribution was skewed towards the center and the walls of the ACI for these stages due to the center hole in the collection plate of upstream Stages 0 and 1. Due to this center hole in the plates, the flow field was different for these two stages. Apart from differences in the nature of the flow field, higher recirculation occurred in the vicinity of the collection plate for Stage 2. For Stage 1 the change in the flow field due to the presence of the upstream collection plate center hole assisted in maintaining the uniformity of the flow among the nozzles without increasing recirculation significantly. For all lower stages (Stage 2 through Stage 7), the degree of recirculation was maximum at the farthest end of the collection plate away from the center. Deposition profiles on the collection plates were more evenly distributed for bounce conditions at the nozzle walls. Without bounce conditions, these profiles represented normally exiting particles impacting on the collection plate. Nozzle bounce conditions
assisted in simulating realistic conditions, and provided a better fit to the experimental results and the manufacturer’s data.

Predicted wall losses for the ACI were observed to be much higher than acceptable values recommended by the United States and European Pharmacopoeias (USP-601; EP 2002). These results related well qualitatively with the study of Kamiya et al. (2004), in which the authors reported higher wall losses for the ACI compared to the NGI. Mitchell et al. (1988) reported that wall losses for the ACI could be higher for large particles (> 5 μm). These losses were incurred at the top stages (Stage 0). For small (< 5 μm) particles, the losses were distributed over a number of stages. This could be one reason for lower losses reported for smaller particles. Specifically, particle losses were reported to be on the order of 20 – 40% for larger particles and 8 – 15% for smaller particles. Results in the present study agreed well with the larger particle losses. Particle losses were observed in the pathway between stages, where the particles were unable to follow the 180° change in flow direction at the edge of the collection plates. A significant amount of small particle losses was reported on the bottom side of the collection plate due to the effect of the recirculation zones. Individual stage analysis as opposed to analyzing the ACI assembly as a unit could be a reason for this discrepancy. Additionally, the present study does not perform particle simulations for the induction port. The induction port is used to only determine the entry flow conditions for Stage 0. This could result in reduced deposition on the walls of the ACI assembly. Nevertheless, predicted wall losses in the ACI are much higher than the 5% criteria recommended by the USP. Simulating bounce on the nozzle walls is observed to have negligible effects on wall losses. However, simulations with bounce effects at the
nozzle walls compared well with the experimental and manufacturer’s data for retention fraction. No attempt was made to incorporate particle bounce on the collection plate in this study, which may be of interest in future work. As such, this study provides insight into the flow field within inertial cascade impactors, predictions of particle characterization and wall losses, and provides a basis for implementing other parameters that could affect the internal workings of impactor systems.

In conclusion, results were presented for numerical predictions of particle size distribution, flow patterns and wall losses for an inertial cascade impactor. Numerical predictions were validated with the experimental results and the manufacturer’s data for retention fraction in the ACI for Stages 0 – 7. Retention fraction is in excellent agreement with the available literature and the manufacture’s data. Predictions for wall losses were higher than those reported earlier due in part to exclusion of the IP and the absence of full continuity between stages. Results indicated non-uniformity in the flow distribution among nozzles and the occurrence of recirculation zones within the flow field. It is proposed that these recirculation zones can affect wall losses and increase the number of suspended particles. Additionally, these zones could severely affect deposition characteristics of sub-micrometer particles due to their time dependent diffusive properties making them relatively more susceptible to being suspended in dead zones. Although the Reynolds numbers for the nozzles were well within the laminar regime, some areas of the flow field could experience turbulence, affecting particle dynamics. This study is intended to form a basis for studying the effect of other parameters like electrostatic charge, evaporation and hygroscopic growth on particle size distribution characteristics in cascade impactors,
eventually leading to better technology and products in the fields of inhaled pharmaceutics, environmental sampling and toxicology.
Table 6.1 Andersen Mark II cascade impactor jet characteristics. $S$, $L$ and $d_n$ represent nozzle exit to impaction plate distance, nozzle length of impactor, and diameter of the nozzle, respectively.

<table>
<thead>
<tr>
<th>Stage</th>
<th>$d_n$ [mm]</th>
<th>$S/d_n$</th>
<th>$L/d_n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>USP IP</td>
<td>13.5</td>
<td>1.26</td>
<td>3.19</td>
</tr>
<tr>
<td>0</td>
<td>2.55</td>
<td>0.4</td>
<td>1.78</td>
</tr>
<tr>
<td>1</td>
<td>1.88</td>
<td>0.54</td>
<td>2.4</td>
</tr>
<tr>
<td>2</td>
<td>0.91</td>
<td>2.37</td>
<td>1.46</td>
</tr>
<tr>
<td>3</td>
<td>0.71</td>
<td>3.05</td>
<td>1.9</td>
</tr>
<tr>
<td>4</td>
<td>0.53</td>
<td>4.07</td>
<td>2.46</td>
</tr>
<tr>
<td>5</td>
<td>0.34</td>
<td>6.32</td>
<td>3.85</td>
</tr>
<tr>
<td>6</td>
<td>0.00025</td>
<td>8.54</td>
<td>5.2</td>
</tr>
<tr>
<td>7</td>
<td>0.00025</td>
<td>8.54</td>
<td>5.2</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 6.2 Reynolds numbers and Stokes number reported for individual stages of the Andersen Mark II cascade impactor (ACI). Stokes numbers are based on the nozzle diameters and velocities.

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of nozzles</th>
<th>(d_n) [m]</th>
<th>Area_{n} [m²]</th>
<th>Area_{total} [m²]</th>
<th>Flow rate_{n} [m³/s]</th>
<th>vel_{n} [m/s]</th>
<th>Re_{n} Mach no.</th>
<th>Stk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>96</td>
<td>0.00255</td>
<td>5.1 E-6</td>
<td>4.9 E-4</td>
<td>4.87 E-6</td>
<td>0.955</td>
<td>154</td>
<td>0.002</td>
</tr>
<tr>
<td>1</td>
<td>96</td>
<td>0.00188</td>
<td>2.77 E-6</td>
<td>2.66 E-4</td>
<td>4.87 E-6</td>
<td>1.758</td>
<td>208</td>
<td>0.005</td>
</tr>
<tr>
<td>2</td>
<td>400</td>
<td>0.00091</td>
<td>2.62 E-7</td>
<td>2.62 E-4</td>
<td>1.17 E-6</td>
<td>1.8</td>
<td>104</td>
<td>0.005</td>
</tr>
<tr>
<td>3</td>
<td>400</td>
<td>0.00071</td>
<td>1.59 E-7</td>
<td>1.59 E-4</td>
<td>1.17 E-6</td>
<td>2.939</td>
<td>132</td>
<td>0.008</td>
</tr>
<tr>
<td>4</td>
<td>400</td>
<td>0.00053</td>
<td>8.9 E-7</td>
<td>8.9 E-5</td>
<td>1.17 E-6</td>
<td>5.246</td>
<td>176</td>
<td>0.015</td>
</tr>
<tr>
<td>5</td>
<td>400</td>
<td>0.00034</td>
<td>3.67 E-8</td>
<td>3.67 E-5</td>
<td>1.17 E-6</td>
<td>12.72</td>
<td>274</td>
<td>0.036</td>
</tr>
<tr>
<td>6</td>
<td>400</td>
<td>0.00025</td>
<td>2.02 E-8</td>
<td>2.02 E-5</td>
<td>1.17 E-6</td>
<td>22.94</td>
<td>367</td>
<td>0.066</td>
</tr>
<tr>
<td>7</td>
<td>201</td>
<td>0.00025</td>
<td>1.01 E-8</td>
<td>1.01 E-5</td>
<td>2.32 E-6</td>
<td>45.49</td>
<td>728</td>
<td>0.132</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 6.3 Comparison of errors between the numerical predictions of stage cut-off diameters (\(d_{50}\)) with the experiments of Vaughan et al. (1989) and the manufacturer’s data in \(\mu\)m.

<table>
<thead>
<tr>
<th>Stage no.</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted neutral (\mu)m</td>
<td>8.79</td>
<td>5.43</td>
<td>5.67</td>
<td>3.3</td>
<td>1.86</td>
<td>1.00</td>
<td>0.59</td>
<td>0.44</td>
</tr>
<tr>
<td>Vaughan (\mu)m</td>
<td>9.0</td>
<td>6.0</td>
<td>5.7</td>
<td>3.1</td>
<td>2.06</td>
<td>0.9</td>
<td>0.6</td>
<td>-</td>
</tr>
<tr>
<td>% difference</td>
<td>2.3</td>
<td>9.5</td>
<td>0.52</td>
<td>6.4</td>
<td>9.2</td>
<td>11.1</td>
<td>1.6</td>
<td>-</td>
</tr>
<tr>
<td>Manufac. (\mu)m</td>
<td>9.0</td>
<td>5.8</td>
<td>4.7</td>
<td>3.3</td>
<td>2.1</td>
<td>1.1</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>% difference</td>
<td>2.3</td>
<td>6.3</td>
<td>20.6</td>
<td>0</td>
<td>10.9</td>
<td>9.0</td>
<td>15.7</td>
<td>10.0</td>
</tr>
</tbody>
</table>
Table 6.4 Wall losses in representative stages of the Andersen Mark II cascade impactor for neutral particles. The particle diameter is given by $d_P$.

<table>
<thead>
<tr>
<th>ACI Stage no.</th>
<th>$d_P$ (μm)</th>
<th>Particle diameter</th>
<th>Wall losses (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>9.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>8.3</td>
<td></td>
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<tr>
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<td>7</td>
<td>7.4</td>
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</tr>
<tr>
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<td>6</td>
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<tr>
<td></td>
<td>5</td>
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</tr>
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<td>4</td>
<td>11.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>11.19</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.5</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.9</td>
<td></td>
</tr>
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<td>3.2</td>
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<tr>
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<td>0.7</td>
<td>4.2</td>
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Fig. 6.1. ACI (Andersen Mark II eight Stage cascade impactor), showing Stage 0, Stage 1 and the IP separated from the assembly.
Fig. 6.2. Numerical models of (a) IP, (b) Stage 0, (c) Stage 1 and (d) Stages 2 – 3. For the impactor stages, 2 planes of symmetry were implemented based on approximately symmetric flow. The number of nozzles reported are based on the actual ACI.
Fig. 6.3. Numerical models of (a) Stage 4, (b) Stage 5, (c) Stage 6 and (d) Stage 7. Symmetry and number of nozzles reported are consistent with Fig 4.2.
Fig. 6.4. Numerical model of ACI Stages 2 and 3 illustrating the computational grid. The total number of control volumes for these stages was approximately 2 million cells.
Fig. 6.5. Contours of velocity magnitude and velocity vectors for the (a) IP and the upper stages of the ACI assembly: (b) Stage 0, (c) Stage1, and (d) Stages 2 – 3. The velocity unit vectors represent direction only.
Fig. 6.6. Contours of velocity magnitude and velocity vectors for the lower ACI stages including (a) Stage 4, (b) Stage 5, (c) Stage 6, and (d) Stage 7. The velocity unit vectors represent direction only.
Fig. 6.7. Boundary layer flow at the collection plate shown for ACI (a) Stage 3 and (b) Stage 6 with different jet diameters of 0.71 and 0.25 mm, respectively.
Fig. 6.8. Three dimensional, 5 μm particle traces for Stage 1 showing the effect of the upstream collection plate on particle trajectories.
Fig. 6.9. Predictions of retention fraction for (a) Stages 0 and 1, (b) Stages 2 and 3, (c) Stages 4 and 5, and (d) Stages 6 and 7 compared with the experimental results of Vaughan (1988) and the manufacturer’s data.
Fig. 6.10. Visualization of numerical wall losses and collection plate deposition patterns for (a) Stage 0, (b) Stages 2 – 3, and (c) Stage 6 employing particle bounce for the nozzles walls. The three particle sizes studied were 0.6, 3.5, and 8 μm.
Fig. 6.11. Visualization of numerical wall losses and collection plate deposition patterns for (a) Stage 0, (b) Stages 2 – 3, and (c) Stage 6 without particle bounce effects for the nozzle walls. The three particle sizes studied were 0.6, 3.5, and 8 μm.
7. Effects of Particle Charge in the Andersen Cascade Impactor

7.1 Introduction

Effects of electrostatic charge on particle size distribution studies for pharmaceutical aerosols are widely reported in the literature. The available literature reports significant effects of charge on deposition characteristics in devices (Byron et al. 1997; Thiel 1998; Peart and Byron 1999; Peart et al. 2002; Rahmatalla et al. 2002; Glover and Chan 2004; Mikkanen et al. 2004; Noakes 2004; Kwok et al. 2005; Telko et al. 2007) and in the lung (Yu 1977; Chan and Yu 1981; Melandri et al. 1983; Balachandran et al. 1991; Ljepojevic and Balachandran 1993; Hashish et al. 1994; Cohen et al. 1995; Balachandran et al. 1997; Cohen et al. 1998; Hinds 1999; Koolpiruck et al. 2004; Saini et al. 2004; Jeffers 2005; Martonen et al. 2005). The lung behaves as a chamber with a low applied voltage that can enhance the effect of particle charge on deposition characteristics and locations. Size distribution governs the mechanism affecting ventilation parameters of particles inhaled either as medications or as harmful pollutants. Inertial impactors are routinely used to evaluate particle size distribution. Over the last two decades it has become evident that effective inertial impactors are essential for accurate and consistent particle size distribution studies. There are very few studies in the literature that focus on the evaluation
of particle size classification instruments and procedures. Additionally, electrostatic charge effects need to be quantified and associated corrections need to be applied to size distribution instruments that are susceptible to charge effects. In order to evaluate size classification instruments, purely experimental studies alone are not sufficient to visualize the internal flow dynamics, evaluate wall losses, and quantify charge effects.

Numerical analysis can be very useful when performing studies related to the effects of electrostatic charge on the transport and deposition of pharmaceutical powders and droplets in an inertial cascade impactor. Numerical models permit visualization of the flow field inside the impactor and offer better control over boundary conditions. The present study addresses the effect of electrostatic charge as a body force on the particles in addition to the commonly considered mechanisms of impaction, sedimentation and diffusion. This additional body force is implemented in the form of a user-defined function (UDF) that is attached to the solver. The image charge component of the electrostatic force is considered, whereas the space or field charge component is assumed to negligibly influence the results due to dilute discrete flow conditions. The electrostatic force UDF is validated with the theoretical deposition formula proposed by Chen and Yu (1993) for tubular flow. The results obtained for particle retention in the Andersen cascade impactor under electrostatic charge effects are presented for two charge levels, i.e., the saturation charge level and ten times the saturation charge level representative of DPI (dry powder inhaler) charge and MDI (metered dose inhaler) charge, respectively (Section 2.6). The present study does not consider charge effects on aerosols discharged from nebulizers. Overall, the present study evaluates the charge effects on particle dynamics in an inertial cascade impactor for typical
pharmaceutical aerosols. This study provides correction values to standard impactor cut-off curves to account for the effect of particle charge on deposition and sizing. The electrostatic model is validated with theory and is capable of becoming an integral part of particle deposition analyses in respiratory airway models for future analyses.

7.2 Methods

7.2.1 Electrostatic Forces

Triboelectrification is defined as the buildup of charge from the separation of two insulating materials, which are in contact with each other. These materials can inherit a net measurable charge on their surfaces with one of the polarities dominating the other. The process is more frequently referred to as frictional charging. Some of the materials which illustrate this phenomenon need only touch each other before a significant charging of the surface occurs (Cross 1987). Metered dose inhalers (MDIs), which are used as storage and delivery devices for respiratory aerosols, exhibit the triboelectric effect (Peart et al. 1995; Byron et al. 1997; Peart and Byron 1999; Peart 2001; Kwok et al. 2005). Dry powder inhalers (DPIs), used for respiratory drug delivery, also exhibit similar static charges. As a result, pharmaceutical aerosols delivered using MDIs and DPIs may be characterized by significant static charge (Peart and Byron 1999; Kwok et al. 2005).

The mechanism of inducing charge in a conductor influenced by an external electric field is known as induction charging. Charged respiratory aerosols act as point entities, which induce an equal and opposite static charge in the surrounding conductor. The conductor may be the liquid lining of the lung, an impactor, or a medical inhalation
device. Under the influence of the field created by the aerosol particles, an image force is developed between the charged conductor and the aerosol particles, which are in the vicinity of the conductor. These image forces are always in the form of attraction, since equal and unlike charges are induced in the conductor. Materials that are not a conductor carry their own static charge, which can influence the particle deposition by either attractive or repulsive forces, depending on the polarity and distribution of charge on the wall.

An aerosol particle carrying a charge \( q \) is considered. The image charge induced on the impactor surface will then be equal to \(-q\) which will yield an image force \( F_e \) between the particle and the surface as follows

\[
F_e = -\frac{qq}{4\pi d^2} \frac{1}{\varepsilon_0 \varepsilon_{air}}
\]

(7.1)

where \( F_e \) is the force of attraction between the particle and the surface, \( d \) is the distance separating the particle and the surface, \( \varepsilon_0 = 8.854 \times 10^{-12} \) and \( \varepsilon_{air} \approx 1 \) are the permittivity of free space and relative permittivity of air, respectively (Cross 1987).

It is reported that respiratory pharmaceutical aerosols exhibit a static charge ranging between 200 and on the order of 40,000 electron charges per particle (Peart et al. 1995; Peart and Byron 1999; Kwok et al. 2005). Assuming the aerosol particle to be spherical in shape, a net viscous drag force of \( F_d \) acts on it, which is given by

\[
F_d = (3\pi\mu)d_p V_{slip}
\]

(7.2)

where \( V_{slip} \) is the particle slip velocity and \( \mu \) is the dynamic viscosity of air.
The effect of electrostatic charge is modeled as an additional body force on the particles in addition to the viscous and gravitational forces. This additional body force is implemented in the form of a user-defined function (UDF), which was written in-house and is attached to the FLUENT 6 commercial CFD solver employed in this study. The image charge component of the electrostatic force is considered, whereas the space charge component is assumed to negligibly influence the results due to the assumption of dilute discrete flow conditions. The saturation charge employed in this study is given by (Hinds 1999)

\[
n_s = \left( \frac{3\varepsilon}{\varepsilon + 2} \right) \left( \frac{Ed^2}{4K_Ee} \right)
\]  

(7.3)

where \( \varepsilon \) is the relative permittivity of the material of the particle, \( E \) is the electric field strength, \( K_E \) is a constant of proportionality, \( e \) is the charge on an electron, and \( d \) is the diameter of the particle.

Chen and Yu (1993) conducted a theoretical study on the effects of image charge force on particle deposition in a horizontal duct with a conducting wall under fully developed laminar flow conditions. A formula to calculate the deposition efficiency in the duct by electrostatic precipitation was proposed in this study. The electrostatic force UDF is validated with the theoretical formula proposed by Chen and Yu (1993) for an electrostatic charge of 500 elementary charges per particle over a size range of 0.05 – 10 \( \mu m \). The formula for deposition efficiency due to electrostatic forces in a tubular geometry under laminar conditions is given by

\[
n_e = \left\{ 1 - \exp \left[ - \left( 4 \left( \frac{k}{2} \right)^{1/2} \right)^{1.74} \right] \right\}^{1.74}
\]

(7.4)
where
\[ k = \frac{q^2LC_s}{48\pi^2\varepsilon_0\mu d_P R^3U} \]  
(7.5)

In Eqns. 7.4 and 7.5, \( \eta_e \) is the deposition efficiency due to electrostatic image force, \( k \) is an electrical parameter, \( L \) is the tube length, \( U \) is the mean velocity, \( C_S \) is the slip correction factor, \( \varepsilon_0 \) is the permittivity of the medium, \( \mu \) is the viscosity of the medium, \( d_P \) is the diameter of particles, and \( R \) is the radius of the tubular duct.

7.2.2 Numerical Model and Boundary Conditions

In this study, an eight stage (excluding the filter) Andersen Mark II impactor is simulated as shown in Fig. 7.1. The numerical model for the ACI is three dimensional, with two planes of symmetry. The computational mesh employed is shown in detail in Fig. 7.2 for Stages 2 and 3. The figure illustrates a fine mesh used in the vicinity of the collection plate and the nozzle sections. The mesh is relatively coarse away from the nozzles and the collection plate. The number of control volumes employed for the numerical model ranged from approximately 400,000 control volumes for Stage 0 to approximately 2.5 million control volumes for Stages 6 and 7.

The ACI geometry was preceded by an induction port (IP). The inlet flow profile for the IP was parabolic, defined as

\[ u(r) = u_m \left(1 - \frac{r^2}{R^2}\right) \]  
(7.6)

where \( r \) is the inlet radial coordinate, \( u_m \) is the mean velocity, and \( R \) is the outer radius of the inlet. All stages are analyzed independently for particle distribution results except
Stage 3. Stage 3 is connected to the upstream Stage 2 to study upstream stages on flow behavior. The flow profile for Stage 0 is imported from the IP, whereas the inlet profile for Stage 1 is imported from Stage 0. For the remaining stages, it is assumed that the upstream flow has negligible effects on particle deposition profiles. Inlet profiles for Stages 2 – 7 are simulated as parabolic profiles upstream of the 180° bend leading to the actual stage inlet. Initializing the flow upstream of the 180° bend assists in simulating the effects of the upstream stage because the flow profile entering each stage is primarily governed by the profile of the bend. The no-slip wall boundary condition is applied, and particles are assumed to deposit at initial wall interception. For the case with bounce at the nozzle walls, reflective conditions were implemented. The inlet particle profiles are matched with the inlet velocity profiles and are given as

$$m_{p,ring} \sim m_{ring} = \int_{r_1}^{r_2} \rho u(r) 2\pi r dr$$  \hspace{1cm} (7.7)$$

where $m_{p,ring}$ is a finite ring of particles, $r_1$ and $r_2$ define the extent of the ring and $u(r)$ is the inlet velocity profile.

Retention fractions (deposition efficiencies) for individual stages are given by

$$R = \frac{n_d}{N_d}$$  \hspace{1cm} (7.8)$$

and are adapted from the study of Vaughan (1989). Vaughan (1989) defines the retention fraction for a single stage as the ratio of the number of particles deposited on the collection plate to the number of particles approaching the plate. Wall losses are defined by the ratio
of the particles depositing in the 180° bend passage between two stages to the total number of particles injected in the impactor for individual stages.

7.3 Results

7.3.1 Velocity Fields

Three dimensional flow patterns for Stages 1 and 4 are shown in Figs. 7.3a and b, respectively, with two-planes of symmetry. These figures illustrate velocity at the symmetry planes together with the location of the collection and nozzle plates. Flow characteristics are shown for the ACI interior including mid-planes of the nozzle sections. The contours indicate velocity magnitude of the flow. Flow patterns for other stages are illustrated in the previous chapter. The isometric view of the flow field suggests high recirculation zones upstream of the nozzle inlets and considerable recirculation zones in the vicinity of the collection plate. The flow Reynolds numbers in the nozzles and the particle Stokes numbers for the ACI stages are in the range of 104 – 730 and 0.0001 – 1, respectively. Stages 0 and 1 are characterized with a center hole in the collection plate resulting in a different flow pattern as compared to the remaining stages (Fig. 7.3a). Non-uniformity in flow distribution among the nozzles is observed for the upper ACI stages considered. The resulting effects on particle deposition characteristics are discussed in the previous chapter.

7.3.2 Validation of DPI and MDI Charge Levels
The in-house electrostatic UDF was tested for a tubular geometry under laminar flow conditions as described in Chen and Yu (1993). Numerical predictions of deposition efficiencies were compared with theoretical values as proposed in the study by Chen and Yu (1993). The validation was performed for a charge of 500 elementary units on a particle diameter range of 0.5 – 10 \( \mu \)m. Figure 7.4 shows that the numerical predictions obtained using the electrostatic UDF are in good agreement with the theoretical formula of Chen and Yu (1993). The validation for the electrostatic UDF is performed for a tubular geometry flow under fully developed laminar flow conditions as shown in Fig. 7.4 together with velocity vectors for the flow profile.

Representative DPI and MDI charge levels used in this study together with the Rayleigh charge limit are illustrated in Fig. 7.5. Representative experimental values from Byron et al. (1997) and Kwok et al. (2005; 2007) are also shown. During field charging of a particle, it collects ions from the surrounding environment. The saturation charge level is reached when no further ions can be collected by the particle from the adjoining field, and incoming field lines cease to converge on the particle. The saturation charge is defined by Eqn. 7.3. As described in Section 2.6, the saturation charge was selected as a representative value for DPI aerosols. In comparison, 10 times the saturation charge was used to represent the charge on typical MDI aerosols. In comparison to the values in the literature (Rowe et al. 2003; Kwok et al. 2005), the MDI charge level is approximately 13 – 20 times the DPI charge level. The present study employs a conservative approach by representing the MDI aerosols by 10 times the saturation charge. The Rayleigh limit for liquid droplets is reached when mutual repulsion of electric charges within a droplet exceeds the confining force of
surface tension resulting in an explosion that shatters the droplet into smaller droplets (Hinds 1999). As shown in Fig. 7.5, both the MDI and DPI charge values are significantly below the Rayleigh limit.

7.3.3 Retention Fraction and Wall Losses

Numerical predictions of particle deposition locations in the ACI under the effects of electrostatic charge for DPI particles are visualized in Fig. 7.6 for Stages 0, 1, 2 – 3 and 6, with particle sizes of 8, 5, 2.5 and 0.6 μm, respectively. The deposition on collection plates covers a larger area as compared to the results reported in the previous chapter for neutral particles. This is because of the increased uniformity in deposition on the collection plate. The increased uniformity is a result of the cumulative effect of inertial impaction and electrostatic forces. In the present study, charge effects on wall losses are not considered. An increase in collection plate deposition due to charge effects is observed to reduce wall losses as compared to neutral particles. This can be observed for Stages 0 and 1 along the passage of the flow between stages. Although Stage 2 in Fig. 7.6c shows considerable wall losses along the 180° bend passage, Stages 3 and 6 are consistent with the overall reduced wall losses observed in this region. However, wall losses on the nozzle plate and sections are expected to increase under the influence of charge due to lower characteristic length scales, which increase the relative effect of electrostatic forces. Representative DPI charge levels resulted in a maximum increase of an order of magnitude in the deposition efficiency on the collection plate as compared to neutral particles. For example, deposition
of 2.5 μm particles on the Stage 3 plate without charge was 1.57%, whereas with charge, the deposition efficiency was 23.43%. For 0.9 μm particles on Stage 5 plate, charge increased the deposition efficiency from 39.47% to 70.23%.

Typical charge levels associated with MDIs are represented by a charge equivalent to 10 times the saturation charge. This conservative representation of the typical charge observed on MDI particles is shown to affect particle deposition in the ACI in Fig. 7.7 for Stages 0, 1, 2 – 3 and 6 with particle sizes 8, 5, 2.5 and 6 μm, respectively. The MDI charge level increased deposition in a manner similar to the DPI charge. Nevertheless, increase in the charge level for MDIs resulted in a small increase in the magnitude and area covered by the particles deposited on the collection plate. Specifically, the MDI charge resulted in an increase in deposition on the collection plate within a range of 0 – 6 % relative to the DPI charge, which is equivalent to more than an order of magnitude as compared to neutral particles. The effect of MDI charge relative to the DPI charge level resulted in an increase of 2 – 30% in wall losses in the ACI for all particle sizes considered. However, wall losses in the passage connecting two stages are slightly lower for the MDI charge levels. This can be attributed to stronger electrostatic forces on the MDI particles that cancel out the inertial forces to a greater extent than the DPI particles resulting in reduced deposition on the walls of the passage.

The effect of DPI charge on particle retention fractions in the ACI are reported together with the experimental results and the numerical predictions for neutral particles in Fig. 7.8 for all stages considered. The results for Stages 0 – 1 illustrate that DPI particle charge increases the retention fraction by 5 – 25% in comparison with neutral particles.
The increase in retention fraction for charged particles over uncharged experimental results is greater since the numerical predictions slightly under predicted the retention fraction for neutral particles. For Stages 2 – 3 as shown in Fig. 7.8b, the retention fraction for charged particles increases between 10% and an order of magnitude. For Stages 4 – 5 as well as Stages 6 – 7, the increase in retention fraction for charged particles is observed to reach an order of magnitude. For examples, the deposition efficiency of 2.5 μm aerosols for Stage 3 increases from 1.5% for neutral particles to 23.4% for DPI particles, whereas for 0.7 μm aerosols for Stage 5, the retention efficiency increases from 2.5% for neutral particles to 57% for DPI particles.

The effects of MDI charge on particle retention fractions in the ACI are reported together with the experimental results and the numerical predictions for neutral particles in Fig. 7.9 for all stages considered. Relative to neutral particles, the MDI particles result in an increase of 30% to 2 fold for particle retention fraction in Stages 0 – 1. For Stages 2 – 3 the MDI particles increase the deposition efficiency between 10% and an order of magnitude as compared to neutral particles. Similar to the DPI particles, for Stages 6 – 7, the MDI particles increase the retention fraction for charged particles by more than an order of magnitude. The differences between the DPI and MDI particles are approximately 5% for Stages 0 – 1. This difference is reduced for downstream stages, and is negligible for particle sizes below 0.7 μm as shown in Figs. 8.9c and d.
7.3.4 Correction Curves

Correction curves to account for the effects of charge on particle size distribution studies of DPI particles are illustrated in Fig. 7.10. The overall effect of DPI charge on particle retention is plotted as a function of the particle size for neutral (CFD) and charged (CFD DPI) particles. The figures show that effects of charge on size distribution studies are increasingly more pronounced for smaller particle sizes and lower stages. It is observed that the effects of charge on retention fraction range from 5% for Stages 0 – 1 to an order of magnitude for Stages 6 – 7. Similarly, Fig. 7.11 illustrates correction curves for all stages considered at MDI charge levels. The results show that DPI and MDI charge levels affect the retention fraction of particles in a typical pharmaceutical sampler by as much as an order of magnitude for particles smaller than 3.5 μm and by 5 – 90% for particles larger than 3.5 μm. The difference between DPI and MDI charge levels on particle retention fraction is more pronounced for lower particle sizes, and ranges between approximately 2.5% for Stages 0 – 1 to a maximum of 6% for Stages 2 – 3. For Stages 4 – 5, these differences start decreasing and are negligible for Stages 6 – 7.

Correction curves to account for DPI and MDI associated charge levels are illustrated in Fig. 7.12. The figure compares d$_{50}$ values of neutral and charged particles. As shown in Fig 7.12, the d$_{50}$ value is plotted as predicted aerodynamic diameter (PAD) on the ordinate and electrostatic diameter (ACI measured) on the abscissa. The PAD describes how a particle will deposit under the influence of charge and maps the measured diameter to the actual diameter. For example, a 3 μm measured diameter aerosol will behave and deposit like a 2.5 μm diameter aerosol. Table 7.1 compares d$_{50}$ values for ACI Stages 0 – 7.
with neutral particles and for ACI Stages 0 – 5 with DPI and MDI particles. For Stages 6 and 7, the \( d_{50} \) values could not be established because the deposition efficiency was above 95% for all particle sizes considered. The Table 7.1 illustrates a difference of approximately 10% in \( d_{50} \) values of neutral and charged particles for the upper ACI stages and between 40 – 85% difference in \( d_{50} \) values of neutral and charged particles for the lower ACI stages (particle size < 3.5 \( \mu m \)). As observed in Fig. 7.12, the saturation charge level representing DPIs affected the change in particle diameter by as much as 85% compared to neutral particles. The percent difference between the \( d_{50} \) values obtained in the present study and the study of Vaughan et al. (1989) as well as the manufacturer’s data is presented in Tables 7.2 and 7.3 for neutral and charged particles, respectively. Negligible differences are observed between the correction curves for DPI vs. MDI charge levels. For example, a maximum difference of less than approximately 2% is observed for 5 \( \mu m \) particles. The effect of charge on the equivalent or actual diameter is more pronounced for lower sized particles (< 3.5 \( \mu m \)). For the particle size range of 3.5 – 5.5 \( \mu m \), the effect of charge is relatively less significant, and starts increasing again for particles larger than 5.5 \( \mu m \).

### 7.4 Discussion

This study presents numerical predictions of particle charge effects on deposition characteristics in an inertial cascade impactor for typical pharmaceutical aerosols. Representative charge levels are established from the available literature for DPI and MDI particles. The DPI particles are represented by the saturation charge limit. The MDI
particles are represented by 10 times the saturation charge. A numerical model of the Andersen Mark II cascade impactor is simulated to evaluate the effects of charge on retention fraction and the consequent effect on particle size distribution. The electrostatic force is modeled using a user-defined function (UDF), which is attached to the commercial solver employed to solve the Navier-Stokes equations. The UDF employed in this study is validated with the theoretical formula proposed by Chen and Yu (1993). Fractional retention is analyzed for all stages of the ACI under both charge levels to obtain particle size distributions. Results for flow patterns, recirculation, and deposition of neutral particles in the ACI are presented in the previous chapter. This study presents the results for numerical retention in the ACI for charged particles leading to the effects on the predicted size distribution. Results are presented as numerical predictions of retention fraction for all stages of the ACI under charged and neutral conditions. The retention fractions for neutral particles are validated with experiments and the manufacturer’s data in the previous chapter. This study provides correction curves to account for DPI and MDI associated charge levels on typical pharmaceutical aerosols.

In the present study, charge effects are more pronounced for lower particle sizes (< 3.5 μm). For a particle size range of 3.5 – 5.5 μm, charge effects are relatively less significant. Above 5.5 μm, the effects start to increase again. Chan et al. (1978) report substantial increases in deposition of particles smaller than 5 μm in a larynx-tracheobronchial hollow cast for a particle size range of 2 – 7 μm. For these charged particles, with 360 – 1100 elementary charges per particle, approximately 10% to an order of magnitude increase in deposition is reported by Chan et al. (1978). Additionally, Chan
et al. (1978) reported negligible effects of electrostatic charge for the heavy activity case of 60 L/min. This can be assumed to occur due to higher turbulent dispersion effects at this flow rate. However, it should be noted that the study by Chan et al. (1978) focuses on deposition in the lung, whereas the present study focuses on the effects of charge in cascade impactors. Lower particle sizes experience lower inertial and drag forces. Therefore, the magnitude of electrostatic charge becomes comparable to drag and gravitational forces. As the particle size increases resulting in higher inertia and drag, the electrostatic forces becomes less significant. However, for particle sizes above 1 μm diffusive forces become negligible, and due to gravity the particles come much closer to the ACI collection plate, where electrostatic forces are stronger. Bailey et al. (1998) report a 10% increase in deposition of 0.5 and 5 μm particles with 200 charges per particle in the pulmonary region. For singly charged particles, Cohen et al. (1995) report an increase of up to an order of magnitude in deposition of ultrafine particles in the trachea. The effects of charge on particle deposition efficiency reported in the present study are in qualitative agreement with these studies.

The present study reports that differences in retention fraction between charged and neutral particles is up to an order of magnitude for smaller particles, and up to 90% for larger particles (>3.5 μm). However, the differences in the retention fraction between DPI and MDI particles are on the order of 2 – 6% for Stages 0 through 4. For Stages 5 through 7, these differences disappear since the retention fraction reaches above 95% for charged particles. These results relate well to the study by De Juan et al. (1997) and Saini et al. (2004). Saini et al. (2004) studied the ACI for charge effects on deposition of 3.4 μm
particles. This study reports an increase in deposition by 50 – 120% for approximately 40 elementary charges per particle. De Juan et al. (1997) report an approximately 2% change in the effects of highly charged particles as compared to singly charged 74 nm particles in terms of the square root of the Stokes number.

In the present study, as particle retention starts increasing for charged particles, wall losses in the 180° bend passage connecting two stages start to decrease. In the previous chapter, wall losses in this region are reported to be on the order of 2 – 10% for neutral particles. Considering DPI particles, these losses can decrease to the extent of being negligible. This effect is visualized in Fig. 8.6. Similar results are obtained for MDI particles. The effect of charge on wall losses is not directly studied as the charge UDF is employed for the collection plate only. However, it is expected that particle charge will increase deposition on the nozzle plate and sections due to relatively smaller characteristic length scales. In terms of consequent changes in particle diameters, the saturation charge level representing DPIs affected the change in particle diameter by a range of 40 – 85% compared with neutral particles. These results agree well with the study by Ali et al. (2007), which reports an increase of three fold in particle deposition for a significant increase in the number of charged particles (DPI II vs. DPI III). Additionally, Ali et al. (2007) report comparatively lower wall losses, on the order of 7%, for charged particles. Although these values correlate well to the wall losses reported in the present study, space charge and image charge effects were together responsible for this change in deposition efficiency and wall losses in the in vitro study by Ali et al. (2007).
It is observed that the deposition of charged particles associated with Stage 4 shows 85% difference with neutral particles, whereas the charged particles associated with Stage 5 show 40% difference relative to neutral particles for DPIs. This behavior is not observed for any of the stages upstream of Stage 4. This discrepancy, which is reported for Stages 4 – 5 and Stages 6 – 7 can be attributed to higher residence times for particles associated with the upstream stage (Stage 4 and Stage 6) as plotted in Fig. 7.10 and 7.11, respectively. The residence times for Stage 4 particles are higher than Stage 5 particles due to lower jet velocities (Table 6.2). The electrostatic charge being temporal in nature increases the deposition with increasing particle residence times. However, this effect was not observed for Stage 0, 1, 2 and 3 because the effect of electrostatic force on particle deposition was relatively less significant as compared to the inertial forces for the particles associated with these upper stages. The increase in deposition for Stage 6 as compared to Stage 7 can be explained in a similar manner. The significant increase in deposition of charged particles observed at the aerodynamic diameter of 1.86 µm for DPI and MDI (Fig. 7.12) particles is attributed to increased deposition arising from electrostatic forces for low particle sizes with lesser inertia and higher residence times (Stage 4 and 6 compared to Stages 5 and 7, respectively).

Correction curves for typical pharmaceutical aerosols showed negligible differences for DPI vs. MDI particles. This illustrates that the effect of a small initial increase in particle charge is most significant, and the characteristic curve for deposition as a function of different charge levels follows a potentially logarithmic profile. These correction curves can be employed when determining particle size for DPI and MDI applications. The
inevitable charge carried by powders and sprays in pharmaceutical applications can be accounted for by changing the particle diameter in order to obtain the expected deposition results. These results can be further extended to the effects of charge on deposition in lung regions with smaller diameters, for example the pulmonary region is expected to observe enhanced deposition due to electrostatic charge.

In conclusion, this study has presented the effects of electrostatic charge on particle size distribution for pharmaceutical aerosols in a typical inertial cascade impactor. Results were presented for charge effects on retention fraction in the impactor stages and the changes in \( d_{50} \) values for charged and neutral particles. The retention fraction was reported to be affected by an order of magnitude for smaller particles (\(< 3.5 \mu m\)) and approximately 10 – 90% for larger particles. The consequent changes in \( d_{50} \) values for charged particles compared with neutral particles are approximately 5 – 85%. The effects of charge on wall losses were not considered directly, whereas the indirect effects of charge associated with the collection plate on wall losses were studied for representative stages. Furthermore, additional parameters not studied include the effects of evaporation, hygroscopic changes, cloud effects and condensation on deposition efficiency of pharmaceutical aerosols. Numerical predictions for retention fraction under two charge levels representative of DPIs and MDIs were reported. These results were in qualitative agreement with the available literature. This study provided correction curves to standard impactor data tables to account for the effect of particle charge on deposition and sizing.
Table 7.1 Stage cut-off diameters ($d_{50}$) obtained by numerical predictions of neutral and charged particles for the ACI.

<table>
<thead>
<tr>
<th>ACI Stage no.</th>
<th>$d_{50}$ Neutral</th>
<th>$d_{50}$ DPI</th>
<th>$d_{50}$ MDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8.79</td>
<td>7.98</td>
<td>8.02</td>
</tr>
<tr>
<td>1</td>
<td>5.43</td>
<td>5.27</td>
<td>5.12</td>
</tr>
<tr>
<td>2</td>
<td>5.67</td>
<td>5.38</td>
<td>5.26</td>
</tr>
<tr>
<td>3</td>
<td>3.30</td>
<td>3.05</td>
<td>2.97</td>
</tr>
<tr>
<td>4</td>
<td>1.86</td>
<td>0.33</td>
<td>0.3</td>
</tr>
<tr>
<td>5</td>
<td>1.00</td>
<td>0.6</td>
<td>0.66</td>
</tr>
<tr>
<td>6</td>
<td>0.59</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>0.44</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 7.2 Comparison of numerical predictions of stage cut-off diameters ($d_{50}$) associated with neutral particles with the results of Vaughan et al. (1989) and the manufacturer’s data.

<table>
<thead>
<tr>
<th>Stage no.</th>
<th>Predicted Neutral $\mu$m</th>
<th>Vaughan $\mu$m</th>
<th>% difference</th>
<th>Predicted $\mu$m</th>
<th>Vaughan $\mu$m</th>
<th>% difference</th>
<th>Predicted $\mu$m</th>
<th>Vaughan $\mu$m</th>
<th>% difference</th>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8.79</td>
<td>9.0</td>
<td>2.3</td>
<td>0.59</td>
<td>0.6</td>
<td>1.6</td>
<td>0.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5.43</td>
<td>6.0</td>
<td>9.5</td>
<td>0.33</td>
<td>3.1</td>
<td>6.3</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5.67</td>
<td>5.7</td>
<td>0.52</td>
<td>1.86</td>
<td>2.06</td>
<td>11.1</td>
<td>1.1</td>
<td>0.9</td>
<td>10.9</td>
</tr>
<tr>
<td>3</td>
<td>3.30</td>
<td>3.1</td>
<td>6.4</td>
<td>1.00</td>
<td>0.9</td>
<td>10.9</td>
<td>2.1</td>
<td>1.1</td>
<td>9.0</td>
</tr>
<tr>
<td>4</td>
<td>1.86</td>
<td>2.06</td>
<td>9.2</td>
<td>0.59</td>
<td>0.6</td>
<td>10.9</td>
<td>0.7</td>
<td>0.4</td>
<td>9.0</td>
</tr>
<tr>
<td>5</td>
<td>1.00</td>
<td>0.9</td>
<td>11.1</td>
<td>0.44</td>
<td>-</td>
<td>10.9</td>
<td>15.7</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.59</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>0.44</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 7.3 Comparison of numerical predictions of stage cut-off diameters ($d_{50}$) associated with charged particles with the numerical predictions for neutral particles.

<table>
<thead>
<tr>
<th>Stage no.</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted neutral</td>
<td>8.79</td>
<td>5.43</td>
<td>5.67</td>
<td>3.3</td>
<td>1.86</td>
<td>1.00</td>
<td>0.59</td>
<td>0.44</td>
</tr>
<tr>
<td>CFD DPI</td>
<td>7.98</td>
<td>5.27</td>
<td>5.38</td>
<td>3.05</td>
<td>0.33</td>
<td>0.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>% difference</td>
<td>9.2</td>
<td>2.9</td>
<td>5.1</td>
<td>7.5</td>
<td>82.2</td>
<td>40</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CFD MDI</td>
<td>8.02</td>
<td>5.12</td>
<td>5.26</td>
<td>2.97</td>
<td>0.30</td>
<td>0.66</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>% difference</td>
<td>8.9</td>
<td>5.7</td>
<td>7.2</td>
<td>10</td>
<td>83.8</td>
<td>34</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Fig. 7.1. ACI (Andersen Mark II eight stage cascade impactor), showing Stage 0, Stage 1 and the USP induction port separated from the assembly.
Fig. 7.2. Representative numerical model of ACI Stages 2 and 3 illustrating the computational grid. The total number of control volumes for these two stages was approximately 2 million cells.
Fig. 7.3. Contours of velocity magnitude for ACI (a) Stage 0 and (b) Stage 4. The location of the collection and nozzle plates are highlighted.
Fig. 7.4. Validation of the electrostatic charge UDF (user-defined function) employed in this study compared to the theoretical model of Chen and Yu (1993) for a particle size range of 0.5 μm through 10 μm. A charge level of 500 elementary units was used to perform the validation study. The tubular geometry employed in the study is shown together with the flow profile.
Fig. 7.5. Particle charges on DPI and MDI aerosols compared with the Rayleigh charge limit. Droplets explode due to the effect of static charge at the Rayleigh limit.
Fig. 7.6. Deposition of particles with a saturation limit (Hinds, 1999) charge in the ACI (a) Stages 0, (b) Stage 1, (c) Stage 3, and (d) Stage 6. The saturation charge limit is a good representation of the typical charge observed on particles delivered using a DPI (Kwok, 2007). The particle size range considered was 300 nm through 12 μm.
Fig. 7.7. Deposition of particles with ten times the saturation charge limit in the ACI (a) Stage 0, (b) Stage 1, (c) Stage 3, and (d) Stage 6. A charge equivalent of 10 fold the saturation charge limit is a conservative representation of the typical charge observed on particles delivered using a MDI (Glover and Chan, 2004; Rowe et al., 2003; Kwok et al., 2005). The particle size range considered was 300 nm through 12 μm.
Fig. 7.8. Static charge effects on numerical predictions of retention fraction for Stages 0 through 7 for DPIs in comparison with retention fraction of neutral particles reported by experiments, CFD and the ACI manufacturer.
Fig. 7.9. Static charge effects on numerical predictions of retention fraction for Stages 0 through 7 for MDIs, in comparison with retention fraction of neutral particles reported by experiments, CFD and the ACI manufacturer.
Fig. 7.10. Particle size correction curves for individual stages of the ACI accounting for the effect of static charge found on typical DPI aerosols.
Fig. 7.11. Particle size correction curves for individual stages of the ACI accounting for the effect of static charge found on typical MDI aerosols.
Fig. 7.12. Comparisons of $d_{50}$ values between neutral and charged particles. Correction curves for DPIs and MDIs are based on predicted $d_{50}$ values. Two examples of effects of charge levels on particle sizes measured in the ACI vs. actual particle sizes (PAD) are shown.
8. Conclusion and Future Work

The three objectives stated in Chapter 1 (Objectives) have been achieved. In conclusion: (1) effects of numerical mesh styles and grid convergence criteria were evaluated for respiratory air flow and particle deposition; (2) transport and deposition of respiratory aerosols were evaluated for models of childhood asthma under expiratory conditions; (3a) fluid-particle dynamics in an inertial cascade impactor were numerically analyzed; and (3b) the effects of particle charge on deposition for typical pharmaceutical aerosols in a particle sampler were numerically assessed.

8.1 Effects of Numerical Mesh Styles and Grid Convergence

A fundamental study of a novel grid convergence technique and numerical mesh styles was conducted to fulfill the first objective. Structured and unstructured hexahedral meshes were shown to provide the best grid convergence values, comparable velocity fields and good agreement with experimental 10 μm particle deposition data on a local basis in a branching respiratory geometry. Generation of the unstructured hexahedral mesh provided a significant time savings in pre-processing with an associated minimal increase in computational run time. In contrast, a hybrid mesh configuration of tetrahedral cells surrounded by multiple layers of near-wall hexahedral elements resulted in significantly higher grid convergence values (poor convergence) and provided largely different velocity...
and particle deposition results. These findings emphasize the importance of aligning control volume gridlines with the predominate direction of flow and using higher order elements in biofluid applications with long and thin conduits, when possible. Future work is needed to better assess modified flux interpolation schemes, other hybrid configurations, and the use of polyhedral elements.

Background work for this study (not included) indicated that the numerical errors initially start decreasing with mesh refinement. After the number of control volumes exceeded an upper limit, depending on the geometry and boundary conditions, further mesh refinement resulted in an increase in numerical errors. Although the grid convergence index (GCI) method applied in this study is an improvement in the evaluation of grid convergence, there are limitations to its use. In general, the GCI introduces a bias proportional to the difference in control volumes between the fine and coarse grids studied. Based on Richardson’s extrapolation and the GCI, a novel grid convergence criterion was established to reduce this limitation of the basic GCI approach. The new grid convergence criterion reduces the GCI bias by measuring grid convergence in a computational grid per unit control volume for the fine mesh. This restricts the user from employing bigger differences in the fine and coarse meshes. However, the more advanced GCI was not employed in the current study because it is still in the evaluation phase.

The mesh styles and GCI approach developed in this study can be applied to any internal flow problem. These may include general biofluid applications such as microdosimetry analysis, evaluation of lung cancer formation, cardiovascular blood flow, and electrostatics in multiphase flows. Future studies may consider re-evaluating the new
grid convergence index and analyzing other mesh styles that could be more efficient, user-friendly and time saving.

8.2 Constricted Pediatric Airways and Exhalation

As outlined in the second objective, which outlines transport and deposition of respiratory aerosols in pediatric airway models for normal and constricted airway conditions, a novel correlation was developed for exhalation based on non-dimensional numbers that describe the flow characteristics. Particle deposition and flow structures for expiratory breathing conditions in upper and central pediatric airway models under healthy and constricted states were presented. A critical Reynolds number of Re = 30 was reported to maintain a vortex flow structure and Re = 230 to sustain a 2-pair vortex structure. These critical Reynolds numbers can be considered as threshold values above which a significant deposition can be expected. In general, inspiratory flow is directed into sequentially lower Reynolds number regimes, whereas expiratory flow is directed into sequentially higher Reynolds number regimes. It can be concluded that due to cumulative additions of general upstream flow disturbances, expiratory flow tends to be a relatively unstable phase of the breathing cycle.

The deposition patterns and hotspots for expiratory flow are dependent on the flow rate and the dominant mechanism for particle deposition. For sedentary conditions, the dominate deposition mechanism was secondary impaction. For light activity conditions, the dominate deposition mechanism was primary as well as secondary impaction. Considering heavy activity conditions, turbulent dispersion controlled deposition. A novel
correlation based on explicit factors (Stokes and Dean numbers) for expiratory breathing was proposed showing good agreement with the sedentary and light activity data. Further studies are needed to find a correlation that can better predict the heavy activity deposition data.

The correlations developed in this study can be directly applied in whole-lung algebraic deposition models. This may be useful for accurate dosimetry modeling in the whole lung, which will lead to better evaluation of pollutant exposure and inhalation therapy techniques. Additionally, the results of this study may be useful in analyzing two or more flows merging together. For examples, the wake of an object immersed in a low Reynolds number pipe flow and two blood flow conduits merging together. The junctions of such flows are vital to the performance of the flow system. For biological flows, these regions are significant from the perspective of injury or blockage. Future studies are needed to include the effects of fluid-structure interactions and unsteady breathing conditions.

8.3 Particle Size Distribution and Electrostatic Charge Effects

(a) Size distribution: As outlined in Objective 3a, fluid-particle dynamics in an inertial cascade impactor were numerically analyzed. Particle samplers are vital in evaluating the size characteristics of an aerosol. The Andersen Mark II cascade impactor (ACI) was selected for numerical analysis because it is one of the most commonly used aerosol instruments, and due to the availability of size distribution data in the literature and from the manufacturer.
Results were presented for numerical predictions of size-dependent deposition, flow patterns, and wall losses for the ACI. Numerical predictions were validated with experimental results and manufacturer’s data for retention fraction in the ACI stages 0 – 7. The retention fraction was in excellent agreement with the available literature and the manufacturer’s data. Predictions for wall losses were higher than those reported in the literature due to exclusion of the USP induction port and the absence of full continuity between the stages. Results indicated non-uniformity in flow distributions among nozzles and the occurrence of recirculation zones within the flow field. These recirculation zones affected wall losses and increased the number of suspended particles. Additionally, these zones were observed to severely affect the deposition characteristics of sub-micrometer particles due to their diffusive properties making them relatively more susceptible to being entrained. Although the Reynolds numbers for the nozzles were well within the laminar regime, some areas of the flow field were observed to experience turbulence, which affected particle dynamics. Wall losses were shown to decrease with decreasing particle diameters and reached a maximum of 11% for Stage 2. For the upper stages, wall losses of particles > 1 μm are predicted to be on the order of 7% or more. Predicted cut-off diameters for 50% retention fraction agreed well with the literature and the manufacturer’s data.

The current literature is reconsidering the particle size distribution results associated with the ACI. Particle sampler performances need to be evaluated to standardize sampling techniques. For example, wall losses and non-uniform flow distributions in a sampling device are known to affect particle size distribution results (Sections 2.5 and 2.6). Particle
samplers with sharper cut-off curves and more consistent retention fractions have been developed. Two examples are the (1) next generation impactor (NGI), which claims to incur lower wall losses than the ACI, and (2) the electrical low pressure impactor (ELPI), which can simultaneously measure particle charge and size. The United States Pharmacopoeia and the European Pharmacopoeia recommend a set of criteria to endorse better impactor performance. Although these criteria are not impactor specific, it is necessary to correlate characterization values between different impactors in order to make inhaler performance standards independent of the impactor used. The current study is intended to serve as a basis for studying the effect of parameters like electrostatic charge, evaporation and hygroscopic growth on particle size distribution characteristics in cascade impactors, eventually leading to better technology and improved products in the fields of inhaled pharmaceutics, respiratory and environmental sampling, and toxicology. Future studies may consider re-evaluating the ACI along with the NGI and ELPI to compare their performances and better standardize the particle size distribution results.

(b) Electrostatic effects: As outlined in Objective 3b, this study presented the effects of electrostatic charge on measured particle size distribution for pharmaceutical aerosols in the ACI. Numerical predictions for retention fraction under two charge levels representative of DPIs and MDIs were reported. This study reported that differences in retention fraction between DPI representative charged particles and neutral particles can approach an order of magnitude. However, differences in retention fraction between DPI and MDI charged particles are on the order of 2 – 6%. As particle retention increased for
charged particles, wall losses in the $180^\circ$ bend passages connecting successive stages decreased. Wall losses in the $180^\circ$ bend region are reported to be on the order of 2 – 10% for neutral particles (Chapter 6). Considering DPI charge levels, these wall losses can be negligible because of the interactions between electrostatic and inertial forces. Considering charge effects, the saturation charge level representing DPI aerosols affected the change in measured particle diameter (aerodynamic diameter) by 5 to 85%. That is, charged particles depositing in the impactor deposited as if they were 5 – 85% larger than their measured diameter. This new diameter, termed the predicted aerodynamic diameter (PAD), is defined as the particle diameter after removing the effects of charge. However, correction curves for typical pharmaceutical aerosols showed negligible differences for DPI vs. MDI charge levels. Parameters not addressed in this study include the effects of evaporation, hygroscopic growth, condensation and cloud effects on the deposition efficiency of pharmaceutical aerosols.

The charged particle correction curves can be employed when evaluating particle size for DPI and MDI applications. The inevitable charge carried by powders and sprays in pharmaceutical applications can be accounted for by converting from the virtual electrostatic diameter (VED) to the aerodynamic diameter (AD) using Figure 7.12. These results can be further extended to the effects of charge on deposition in regions of the lung. For example, the pulmonary region is expected to observe enhanced deposition due to electrostatic charge. In addition to quantifying the effects of particle charge, it is essential to evaluate the effects of other external factors such as humidity and evaporation on particle size distribution results. This can include the development of numerical models to
optimize impactor standardization. For example, numerical models could be used to quantify effects of various parameters like humidity, evaporation and hygroscopic growth. These quantifications can help find a range within which impactors may be effectively operated. Additionally, these quantifications can help in deciding which parameters would negligibly affect impactor performance. In conclusion, considering external factors using computational fluid dynamics can help standardize particle size distribution results and correct for external parameters when testing an aerosol sample.

8.4 Final Remarks

Three studies were performed as a part of this project underlining the importance of under-explored areas in the field of respiratory fluid dynamics and pharmaceutical particle sampling. These studies show that these under-explored areas, i.e., grid convergence and numerical mesh styles, exhalation and constricted airways, and impactor dynamics can significantly affect the transport, deposition and characterization of aerosols. Novel contributions include (1) development of a grid convergence technique, (2) evaluation of normal and constricted pediatric respiratory airways during exhalation, (3) evaluation of a high flow-rate particle sampler and 4) assessment of the effects of electrostatic charge on particle size distribution results for pharmaceutical aerosols. Future applications of this research include patient specific lung modeling, improved whole-lung algebraic models, medical device design, respiratory drug delivery, toxicology and pharmaceutical/environmental particle size assessment. Future recommendations include evaluating the modified grid convergence criteria, developing standard grid convergence
procedures, and testing these procedures under diverse boundary conditions with wide applications. These grid convergence techniques can be atomized with the numerical solver to reduce the current time required. Considering the development of a correlation for deposition during exhalation, integration into a whole-lung model such as ICRP (1994) or NCRP (1997) is recommended. Furthermore, a correlation for deposition during exhalation at 60 L/min and above is needed. These correlations can help in better predicting the fate of pollutants as well as inhaled medications. Electrostatic charge may affect the deposition results significantly in the deeper part of the lung (pulmonary region) due to shorter length scales and extended residence times. Considering impactor performance, it is highly recommended to re-evaluate the performance of the ACI and compare it to other existing samplers. Impactor designs need to be modified to obtain sharper cut-off curves and consistent results by reducing wall losses and recirculation zones. Finally, it is suggested to incorporate the effects of evaporation, hygroscopic growth, condensation and humidity in addition to static charge within numerical models to better evaluate the fate of pharmaceutical aerosols in impactors, obtain improved particle size distribution results, and eventually develop better inhalation products.
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List of References


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