Numerical Modeling of Forced Expiratory Flow in a Human Lung

by

James Jang-Sik Shin

Submitted to the Department of Aeronautics and Astronautics on January 30, 1992, in partial fulfillment of the requirements for the degree of Master of Science in Aeronautics and Astronautics

Abstract

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In this thesis, a numerical model is developed, which extends previous models by incorporating unsteady inertia, branching asymmetry, and an “effective” airway liquid layer. The resulting model is capable of calculating flow conditions from the alveolar zone to the airway opening in a single calculation. The results indicate significant improvements over previous models in predicting the clinically-observed flow-volume curve, especially near low lung volume.

The model’s ability to deal with intrinsically unsteady flow led to the examination of other maneuvers such as cough, forced oscillation, and high frequency ventilation. The results elucidate the key features of these unsteady phenomena and show good agreement with the experimental findings. The current model can now be used as a foundation for more extensive studies.

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Chapter 1

Introduction

The lung is an asymmetric branching system with a complex geometry. During forced expiratory flow, coughing, high frequency ventilation, and a variety of other pulmonary maneuvers, the lung experiences large volume excursions accompanied by large changes in the geometry of the conducting airway network. In addition, flow is complicated by regions of unsteadiness, entrance effects, significant secondary flows, and airway compliance. Understanding these phenomena and their relationship to the state of health of the lung has been the object of numerous studies [18].

The numerical models presented here extend previous work to include the effects of unsteady inertia, branching asymmetries in the peripheral airways and the influence of changes in small airway caliber due to interstitial and airway edema. As in previous work, the present models rely on a number of simplifying assumptions in order to elucidate the key behavioral features. An attempt is made to incorporate the most critical fluid dynamical, structural, and geometric features based on current and reliable data to make the simulation as realistic as possible. In this thesis, four types of forced pulmonary flows are examined. Each is described below.

1.1 Forced expiration

Since the forced expiration is repeatable and reproducible for a given subject, it is an effective diagnostic measure of pulmonary function and is often used as an
early indicator of small airway disease. It is obtained by allowing the subject to inspire maximally and then to exhale as rapidly and completely as possible. This is referred to as forced vital capacity (FVC) maneuver, and the resulting graphical output is referred to as maximal expiratory flow volume (MEFV) curve (Figure 1-1). A reduction of flow, especially at the end of expiration, is accepted as an indication of small airway disease, and a variety of parameters computed from the MEFV curve are used to assess the severity and progression of the disease.

![Graph](https://via.placeholder.com/150)

**Figure 1-1:** Maximal expiratory flow volume (MEFV) curves for the human and for the dog (from Elad and Kamm, 1991).

Several key characteristics of the MEFV curve are worth discussing. For a given subject, the volume of expired air per unit time is independent of the intensity of the effort once a certain level of effort is reached. This phenomenon is attributed to wave-speed flow limitation which occurs when the fluid velocity ($U$) becomes equal to the wave speed ($c$) $^1$. The location in the lung at which flow limitation occurs is termed the flow limiting site (FLS). Downstream of FLS, the flow is thought to

$^1$The speed at which disturbances travel along the tube.
become supercritical, returning to subcritical speed via an elastic jump or a smooth transition [5]. The MEFV curve can be categorized into three sections:

**Volume near total lung capacity (TLC)** The respiratory muscles are incapable of producing sufficient force to reach the point of wave-speed limitation. Therefore, flow is highly dependent on the subject’s effort, increasing with pressure but without defined limit.

**Mid-range (45 – 85% TLC)** Once maximum flow is reached, flow no longer increases with pressure and hence becomes “effort-independent”.

**Low lung volume near residual volume (RV)** Studies by Leith and Mead [27] showed that at least in young normal subjects, the respiratory muscles cannot maintain sufficient force to produce flow limitation near RV. Effort-dependence is thought to prevail once again.

Note that TLC refers to total volume of air that the lung can hold when one takes the largest breath possible, and RV refers to volume of air remaining in the lung after a maximal expiratory effort.

Of the many theoretical studies aimed at elucidating the factors that determine maximal flow, perhaps the most comprehensive was that of Shapiro [38]^2^, who demonstrated that a change in flow behavior exists when the speed index \( S = U/c \), where \( U \) is the flow velocity and \( c \) is the local wave speed) undergoes a transition from sub-critical \( (S < 1) \) to super-critical \( (S > 1) \) speed. Attaining the critical condition \( (S = 1) \) at some point in the tube, the flow becomes independent of further reductions in downstream pressure and is thus said to be “choked”. Furthermore, Shapiro formulated the equations that describe how the area ratio \( \alpha = A/A_o \), where \( A \) is the actual cross-section area and \( A_o \) is some reference cross-sectional area) and the speed index vary in the streamwise direction. This has become the standard framework of the theoretical approach to forced expiration. Following Shapiro’s development of a new description for flow through collapsible tubes, many models were developed by

---

^2^Other key contributors include Oates [31], and Dawson and Elliot[4].
different researchers to investigate and better understand the various features of a FVC maneuver. Some of their efforts are described in section 1.5.

1.2 Cough

Cough initiates when excessive amounts of any foreign matter or irritation exist in the bronchi and the trachea. The impulse to cough originates in the respiratory passages and an automatic sequence of events follows. During coughing, the pressure in the lung rises to as high as 100mm Hg or more, and the air is expelled at extremely high velocity approaching the speed of sound. As a consequence, the strong compression of the lungs also collapses the bronchi and trachea causing the noncartilaginous parts to fold inward such that expiring air passes through bronchial and tracheal slits. The combined effects of high flow speed and airway collapse dislodge and propel mucus toward the mouth along with the offending substance. Since cough is a sign or symptom of well over 100 diseases and other medical conditions, its basis and related phenomena have been studied and reviewed extensively [15].

Our research is motivated by the fact that cough is another form of forced expiratory flow, the focus being the experimental finding of “supermaximal” flow above MEFV curve (Figure 1-2). The parametric origin of this phenomenon is examined.

1.3 Forced Oscillation

Forced oscillation is a common technique used to study the global mechanical properties of the lung such as respiratory system compliance and resistance, and local or distributed mechanical properties such as airway caliber and compliance. These parameters are deduced from the mechanical response to small time-dependent forces, generated either at the mouth or external to the chest wall. Further, the time history may be periodic, impulsive, steplike, or random. The scope of our research is limited to periodic forcing at the mouth at frequencies above and below the lowest natural frequency of the respiratory system.
In order to minimize the influence of nonlinearities, comparatively small inputs are used by researchers. A typical flow magnitude of ±0.5 liters is adopted here. The reason for using a periodic function such as a sine wave is that the frequency response can be easily obtained from oscillographs or from Lissajous figures. In short, the Lissajous figure is obtained by plotting airway opening pressure $P_{ao}$ versus airway opening flow rate $Q_{ao}$. A detailed explanation is given in Results and Discussion.

The focus of the simulation is to reproduce the respiratory impedance measurements so that the validity of our simulation can be tested. If a reasonable correlation can be established, the simulation will become the foundation of more extensive studies.

1.4 High Frequency Ventilation (HFV)

Since the first attempts at artificial respiration in the early period of this century, artificial ventilation has become increasingly important in the management of patients with respiratory failure. The conventional types of controlled mechanical ventilation such as intermittent positive pressure ventilation (IPPV) and continuous positive pressure ventilation (CPPV) are based on the traditional concept that the tidal vol-
volume \(^3 (V_T)\) must exceed the dead space \(^4 (V_D)\) for adequate gas exchange to take place. Although these techniques have been extremely useful, studies in the late 1930's showed that, due to the need for high intrapulmonary pressure, they can obstruct central and peripheral circulation and possibly increase the incidence of barotrauma and other pulmonary complications. For this reason, investigators have also studied alternate techniques for alveolar ventilation.

In 1915, Henderson et al. [16] first suggested that adequate gas exchange is possible using a tidal volume smaller than dead space. Many studies, beginning in the 1970's, have shown this to be true and have offered HFV as a new approach to the management of patients with respiratory failure. In the past 20 years, many different techniques, which as a group can be termed “high frequency ventilation” (HFV) have been developed. They are characterized by the use of small tidal volumes applied at high ventilatory frequencies.

Although specific techniques and principles vary considerably, HFV can be categorized broadly into pressure change generation at the airway opening or at the chest wall (or pleural surface). We are interested in HFV applied at the airway opening, of which three major techniques exist, differing in the frequency range of application. High frequency positive pressure ventilation (HFPPV) refers to ventilatory frequencies between 1 to 1.8 Hz, high frequency jet ventilation (HFJV) refers to 1.8 to 6.7 Hz, and high frequency oscillation (HFO) refers to frequencies up to 40 Hz [39]. Although the usefulness of HFV is not yet completely assessed, it does appear to hold promise as a means of achieving gas exchange with a minimal risk of developing pulmonary barotrauma; in several studies, it has proven particularly useful in the support of infants with respiratory distress syndrome.

The focus of this research is on sinusoidal oscillation with the objective of determining what factors limit the flow which can be introduced into the lung at a given frequency. It is clear that as the flow rate increases, pressure excursions increase, resulting in diminished gas passage down the airway due to central airway compliance.

---

\(^3\) volume of gas that is either inspired or expired during one ventilatory cycle.

\(^4\) the total volume of all non-gas-exchanging airways in the lung. This space normally consists of the upper airways and the bronchial tree down to, but not including, the respiratory bronchioles.
One hypothesis is that flow limitation is the cause, but it remains untested. These findings would also help to understand the effects of HFV in diseased lungs like in emphysema 8 and lungs with airway obstruction.

1.5 Previous Models

Forced expiratory flows result from complex interactions between the compliant structures of the airway tree and the flow of gas through it. In addition, the non-linear visco-elastic behavior of the airways and the irregular shape of their cross-sections when collapsed (which occurs when external pressure exceeds internal pressure) make an exact mathematical description of such fluid-structure interaction extremely difficult if not impossible. Consequently, success in modeling has come about only as a result of a series of simplifying assumptions which have gradually been relaxed as models become more sophisticated.

Since the pioneering computational work of Fry [14], most models have treated the airways as a symmetrical branching tree with a specified continuous distribution of mechanical (wall stiffness) and geometrical properties (area, number of branches, etc.). Most of the models have been successful in identifying the factors that are responsible for flow limitation, but no model has accurately predicted all features of the MEFV curve quantitatively. In fact, most of models including Lambert et al. ([24], referred as LW model) failed to calculate flow conditions downstream of the FLS. The lack of reliable data regarding key physiologic parameters is the primary reason for the failure of previous models. The lack of agreement between the theoretical and empirical suggests that we still have much to learn about flow limitation, especially near the end of expiration.

Lambert [23] introduced asymmetry into his model, but in a limited fashion, allowing asymmetric flows within a single generation, thus minimizing the increased computational requirements. Although this was a major step toward modeling a realistic lung, it is still inadequate to yield the satisfactory results.

---

8 the disease caused by regional destruction of the lung micro-structure.
The most recent and most rigorous model is that of Elad and Kamm [9]. Although their model reproduces many of the key elements of forced expiration and removes many limitations of previous models, the MEFV curve predicted by their analysis still deviates in several important respects from reality, especially near RV where the effects of small airways are most evident. The failure of their model at low lung volume has been tentatively ascribed to the combined effects in the peripheral airways of branching asymmetry, greater than anticipated airway narrowing, and obstruction due in part to the influence of the airway liquid lining.

Elad and Kamm's (EK) model, like other models, makes the assumption that lung-emptying may be described by a series of quasi-steady one-dimensional flows at successively decreasing fixed lung volumes. This assumption is valid, provided that the characteristic time over which the flow accelerates during expiration is much larger than the time required for waves of a fluid to traverse the bronchial network. This condition is satisfied at mid-range where the maximal expiratory flow is effort-independent. However, the validity of the assumption is questionable during the initial acceleration to peak flow rate where unsteadiness is significant. Furthermore, unsteadiness cannot be neglected for other expiratory flows of the type that are considered in this thesis.

1.6 The Present Model

Kimmel et al. [22] introduced the unsteadiness into their simulation and successfully identified many essential features of transient pulmonary flows. Following their approach, the present model has been developed to address several of the shortcomings of previous models. Starting with the EK model just described, unsteadiness is incorporated by introducing lung volume as a time-varying parameter and employing a numerical scheme that allows unsteady inertia to be included. By doing so, this allows us to compute the complete unsteady flow-volume curve in a single calculation resulting both in a more realistic simulation and a considerable reduction in compu-

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6this assumption implies that convective acceleration dominates over temporal acceleration.
tational time. Furthermore, attempts were made to overcome the limitations of the EK model with regard to symmetric branching and the greater apparent resistance of the small peripheral airways. As a result, further insights can be gained concerning the phenomena of flow limitation and lung behavior during large amplitude unsteady flows.
Chapter 2

Analysis

The main objective of this research is to develop a computational model that takes into account unsteadiness by introducing temporal inertia and by incorporating lung volume as a parameter. In addition, the method by which the peripheral airways are modeled includes the effects of asymmetric branching network and the presumed role of the airway liquid film. Many aspects of this model are similar to the EK model, and the readers are encouraged to refer to the previous publication [10] for a more detailed description.

2.1 The Lung Model

Figure 2-1 shows a schematic representation of the functional model of conducting airways. It indicates various pressures and parameters that are utilized in the computation. The bronchial tree is divided into two parts for the purpose of simulation. The peripheral airways are modeled as an asymmetric branching network whose area is a prescribed function of lung volume as described more fully in section 2.6. The central airways are assumed to be symmetric; the number of bronchi and their total cross-sectional area is represented by smooth and continuous functions of distance along the airway. This “trumpet” model replaces the complex geometry and sequence of discrete bifurcations, and it is based on the morphometric data of Weibel [47] for the first 17 generations of the lung. Note that Weibel’s data is obtained from a human
lung inflated to 75% of TLC. Curve fitting and the volume correction to TLC give the total cross-sectional area ($A_w$) and the number of branches ($N_w$) by following expressions 1.

\[
A_w(\xi) = 0.00023255(\xi + 0.01)^{-0.9} - 0.0014e^{(-3.9844\xi)}
\]

\[
N_w(\xi) = 1.0387(\xi + 0.01)^{-2.4} - 50.0e^{(-5.9766\xi)}
\]

where $\xi = z/L$ is a non-dimensional length.

Figure 2-1: A schematic representation of functional model of conducting airways indicating various pressures and parameters of computation (from Elad and Kamm, 1991).

The mechanical characteristics of the airway wall are described by a self-similar tube law which relates cross-sectional area to transmural pressure. Note that the  \footnote{all parameters are in SI units unless specified.}
effect of parenchymal tension is included in the tube law. The key assumption is that the dimensionless form of this constitutive relationship is the same for all generations and is independent of lung volume ($V_L$). Variation in airway compliance is introduced by making effective wall stiffness ($K_p$) a function of position. Based on data from Takashima [45], Elad et al. [12] arrived at the following relationship.

$$
\Pi = \frac{P_{aw} - P_{ext} - P_o}{K_p} = \alpha^{n_1} - \alpha^{-n_2}
$$

(2.3)

where

$$\alpha = A/A_o(\xi, \lambda)
$$

(2.4)

Here, $P_{aw}$ is the internal bronchial pressure, $P_{ext}$ is the external pressure (assumed equal to alveolar pressure for intrapulmonary airways but falling to atmospheric in the vicinity of the trachea), $A$ is the cross-sectional area of a single airway, $K_p$ is the effective wall stiffness at a given lung volume, and $A_o$ and $P_o$ are the respective inflection point values of the pressure-area curve. $A_o$, $P_o$, and $K_p$ depend on a dimensionless lung volume, $\lambda$, defined by

$$
\lambda = V_L/V_{Lo}
$$

(2.5)

where $V_L$ is lung volume, and $V_{Lo}$ is a reference volume corresponding to the condition at which the transpulmonary pressure ($P_A$ - pleural pressure $P_{pl}$) equals zero, assumed to correspond to 35% of TLC. By applying equations 2.3 and 2.4 to Takashima’s data, the values of the coefficients of the tube law are determined to be $n_1 = 0.5$ and $n_2 = 0.2$ [12]. Estimating from Takashima’s sparse data of bronchial pressure versus bronchial volumes, the lung volume dependence can be represented as follows:

$$
P_o(\xi, \lambda) = P_{oo}(\xi)(-1.33144(\lambda^{7.4} - 1))
$$

(2.6)

$$
A_o(\xi, \lambda) = 0.91588A_w(\xi)(1.0 + 0.01345(\lambda^{2.7} - 1))
$$

(2.7)

$$
K_{po}(\lambda) = K_{ppo}(1.0 + 0.078(\lambda^{7.4} - 1))
$$

(2.8)
$K_{po}$ is the effective wall stiffness of the most peripheral generation and estimated to be 1692 Pa from the data of Martin and Proctor [28]. $P_{oo}$ is the value at $V_L$ and is equal to 1 Pa.

There exist no precise physiological data of how wall stiffness $K_p$ varies along the airway tree. In lieu of more precise experimental data, we are free to adopt any distribution that yields a trachea that is about 10 times less compliant than the peripheral airways. The EK model used an exponential distribution given by

$$K_p(\xi,\lambda) = K_{po}(\lambda) e^{2.4\xi}$$

(2.9)

This distribution is somewhat unrealistic, however, since the tracheal (about $0.4 < \xi < 1.0$) wall stiffness is unlikely to vary significantly along its axis. Thus, we incorporate a stiffness distribution that has the form of a hyperbolic tangent, given by

$$K_p(\xi,\lambda) = K_{po}(\lambda)(1 + 5.0(1 + tanh(8.0(\xi - 0.4))))$$

(2.10)

Equation 2.10 yields a significant reduction of stiffness as lung volume decreases, consistent with the observation that airways become increasingly compliant due to the progressive relaxation of parenchymal stress. This is not true for the trachea and other extraparenchymal airways, however, where stiffness is primarily determined by structures within the airway wall that are essentially independent of $V_L$. To take this into account, $K_{po}(\lambda)$ is modified to introduce a dependence on nondimensional distance. Mathematically, we assume

$$K_p = (1 + 5.0(1 + tanh(8.0(\xi - 0.4))))K_{po}(\lambda)$$

$$= \mathcal{F}(\xi)(K_{po}(\lambda_o) + (1 - \xi)(K_{po}(\lambda) - K_{po}(\lambda_o)))$$

(2.11)

This ensures that the effect of $V_L$ will be small for large $\xi$. Note that $\lambda_o$ stands for conditions at TLC. In this research, both exponential and hyperbolic distributions are examined. The graphical representations of the two can be seen by figure 2-2.
2.2 Governing Equations

The simulation of dynamic emptying incorporates unsteady, incompressible flow, and an axial length of the tube assumed to vary with time $L(t)$. In order to simplify the analysis and make the computation more tractable, the one-dimensional formulation for fluid flow through collapsible tubes is used \(^2\). Note that implicit in this assumption is a neglect of any influence of complex flow patterns other than as reflected in the influence on the empirically-derived friction laws. In addition, gravity is neglected.

2.2.1 Theory

For fluid flow through the tube, two sets of coordinates are necessary to properly account for the fluid motion. Let $x$ represent the Eulerian coordinate system, which is fixed in space (laboratory frame), and $\xi$ be the Lagrangian coordinate, which is fixed to the tube wall (material frame). These two coordinate systems are related by

$$x = x(t, \xi) = L(t)\xi \quad (2.12)$$

\(^2\)original derivation by Dr. Elad.
and therefore,

\[
\left( \frac{\partial x}{\partial t} \right)_\xi = \xi \dot{L} \quad \left( \frac{\partial x}{\partial \xi} \right)_t = L(t)
\]  \hspace{1cm} (2.13)

where \( \xi \dot{L} \) is the speed of a material point at \( \xi \) in the laboratory frame.

The partials of any physical quantity \( Z = Z(x, t) = Z(\xi, t) \) of two coordinates can be related by the chain rule as

\[
\left( \frac{\partial Z}{\partial \xi} \right)_t = \left( \frac{\partial Z}{\partial x} \right)_t \left( \frac{\partial x}{\partial \xi} \right)_t + \left( \frac{\partial Z}{\partial t} \right)_x \left( \frac{\partial t}{\partial \xi} \right)_t = L \left( \frac{\partial Z}{\partial x} \right)_t
\]  \hspace{1cm} (2.14)

\[
\left( \frac{\partial Z}{\partial t} \right)_\xi = \left( \frac{\partial Z}{\partial x} \right)_t \left( \frac{\partial x}{\partial t} \right)_t + \left( \frac{\partial Z}{\partial t} \right)_x \left( \frac{dt}{dt} \right)_t = \xi \dot{L} \left( \frac{\partial Z}{\partial x} \right)_t + \left( \frac{\partial Z}{\partial t} \right)_x
\]  \hspace{1cm} (2.15)

From the above, conservation of mass and momentum formulated in Eulerian coordinates can be easily transformed to Lagrangian coordinates for cross-sectional area (\( A \)), fluid pressure (\( P \)) and cross-sectional average velocity (\( U \)).

### 2.2.2 Continuity

For an incompressible fluid flowing through a compliant tube, mass conservation gives

\[
\left( \frac{\partial A}{\partial t} \right)_x + \left( \frac{\partial (UA)}{\partial x} \right)_t = \left( \frac{\partial A}{\partial x} \right)_x + U \left( \frac{\partial A}{\partial t} \right)_t + A \left( \frac{\partial U}{\partial x} \right)_t = 0
\]  \hspace{1cm} (2.16)

Introducing equations 2.14 and 2.15 into this gives,

\[
\left( \frac{\partial A}{\partial t} \right)_\xi + (U - \xi \dot{L}) \frac{1}{L} \left( \frac{\partial A}{\partial \xi} \right)_t + A \left( \frac{\partial U}{\partial \xi} \right)_t = 0
\]  \hspace{1cm} (2.17)

With the assumption that \( U \gg \xi \dot{L} \),

\[
L \left( \frac{\partial A}{\partial t} \right)_\xi + \left( \frac{\partial (UA)}{\partial \xi} \right)_t = 0
\]  \hspace{1cm} (2.18)
2.2.3 Momentum Equation

In the Eulerian frame, the momentum balance can be expressed as

\[
\left( \frac{\partial U}{\partial t} \right)_x + \frac{\partial}{\partial x} \left( \frac{U^2}{2} + \frac{P_{aw}}{\rho} \right) + F \left( U - \left( \frac{\partial x}{\partial t} \right)_x \right)^2 = 0 \tag{2.19}
\]

Performing a similar analysis to that which led to 2.17 above, we obtain

\[
\left( \frac{\partial U}{\partial t} \right)_x + \left( U - \xi \dot{L} \right) \frac{1}{L} \left( \frac{\partial U}{\partial \xi} \right)_t + \frac{1}{L} \frac{\partial}{\partial \xi} \left( \frac{P_{aw}}{\rho} \right)_t + F(U - \xi \dot{L})^2 = 0 \tag{2.20}
\]

For \( U \gg \xi \dot{L} \),

\[
L \left( \frac{\partial U}{\partial t} \right)_x + \frac{\partial}{\partial \xi} \left( \frac{U^2}{2} + \frac{P_{aw}}{\rho} \right) + LFU^2 = 0 \tag{2.21}
\]

To reiterate, \( A \) is the total cross-sectional area of the bronchial branches at any axial distance \( \xi \), \( U \) is the cross-sectional average gas velocity, \( t \) is time, \( \rho \) is the density of the gas, and the shear stress contribution at the wall is represented by \( F = \frac{f_T S}{2A} \). \( f_T = \frac{2\tau_w}{\rho U^2} \) is the friction coefficient where \( \tau_w \) is wall shear stress and \( S \) is airway perimeter. \( L \) is the total length of the airway tree and is also a function of lung volume \( L = L_o(\lambda^{1/3}) \), where \( L_o \) is the values of \( L \) at lung volume \( V_{Lo} \); Weibel's data gives \( L_o = 26.5 \text{cm} \). For oscillatory flows, the frictional dissipation term must be written as \( FU|U| \) to ensure that friction does not feed energy into the fluid.

2.3 Friction Laws

Dissipation due to friction may be represented by the data from Reynolds [36], who measured the contribution of friction to the total pressure drop across a cast of the first 10 generations of a human bronchial tree. It is given by,

\[
f_T = 16\left( \frac{1.5}{Re} + 0.0013 \right) \tag{2.22}
\]

\( Re = \frac{UD_e}{\nu} \) is the Reynold's number based on hydraulic diameter \( (D_e) \) and \( \nu \) is the kinematic viscosity. The simulation is assumed to be carried out at a temperature of
$37\degree C$, normal body temperature.

Another form of the friction law was obtained Collins [3] who conducted in vitro experiments to determine the expiratory pressure drop across a single bifurcation in a lung-like model. This relationship is given by,

$$f_T = \begin{cases} \frac{16}{Re} (0.556 + 0.067\sqrt{Re}) & Re \geq 50 \\ \frac{16}{Re} & Re < 50 \end{cases}$$

(2.23)

Note that both forms exhibit laminar flow behavior when $Re$ is small ($f_T \propto Re^{-1}$) and take on turbulent characteristics when $Re$ is large ($f_T = \text{const}$). In addition, the Collins form accounts for a domain of intermediate behavior in which $f_T \propto Re^{-\frac{1}{3}}$ indicative of curvature and entrance-type behavior. Elad and Kamm [9] examined both laws in their simulation and found that there exist only slight differences between the two in terms of the MEFV curve. In this research, both laws are examined to confirm these previous findings.

2.4 Forcing Function

For forced expiration, the flow is driven mouthward by the pressure gradient resulting from the contraction of the expiratory muscles and the muscles of diaphragm producing a pressure difference between the pleural pressure $3$ and atmospheric pressure of 0 to 12000 Pa. In the simulation, we assumed pressure acting on the outer surface of the airways is equal to alveolar pressure $(P_A)$. In reality, $P_A$ exceeds $P_{el}$ by the elastic recoil pressure $(P_{el})$, which depends on $V_L$. The magnitude of $P_{el}$ is small, however, compared to the total driving pressure and therefore we assumed $P_{el} \simeq P_A$. The rapid rise of $P_{el}$ was simulated by specifying the external pressure as

$$P_{ext}(\xi, \lambda) = 12000(1.0 - e^{-10\xi})\cos \left( \frac{\pi(3 - \lambda)}{7.2} \right) (0.5\tanh(20(0.85 - \xi)) + 0.5)$$

(2.24)

$^3$Pressure acting outside surface of the lung and is usually assumed equal to the pressure within the thorax.
The dependence on time was necessary to account for the rise time required for
the expiratory muscles to contract, and the dependence on distance represents the
fact that $P_{est}$ is different for extra- and intra-thoracic airways. The transition from
maximal $P_A$ to zero is centered at a location $\xi = 0.85$. The volume dependence
was based on data by Hyatt and Flath [19], who examined the relationship between
esophageal pressure and the rate of change of lung volume during maximal effort at
various levels of lung inflation.

Cough is associated with dynamic airway collapse and can be thought of as an
explosive expiratory effort. This can be easily simulated by specifying a time-varying
impulse-type transpulmonary pressure decrease at the mouth with respect to up-
stream pressure as shown in the figure 2-3. This is justified because the flow rate
through the bronchial system depends primarily on the transmural pressures acting
at the upstream ($\xi = 0$) and downstream ($\xi = 1$) ends, and it is only slightly influ-
enced by the gradient in effective external pressure at the point where the trachea
leaves the thorax. This means that the same condition prevails whether increasing
$P_{pl}$ with mouth pressure fixed or holding $P_{pl}$ fixed and reducing mouth pressure below
atmospheric by means of vacuum. Mathematically, the forcing is generated by,

$$
P_{max} = \begin{cases} 
-P_c e^{-(150(t-0.2))^2} & 0.00 \leq t < 0.02 \\
-P_c & 0.02 \leq t < 0.05 \\
-P_c e^{-(60(t-0.05))^2} & 0.05 \leq t < 0.1 
\end{cases}
$$

(2.25)

where $P_c$ stands for the maximum possible pleural pressure that can be generated at
given lung volume.

Following the approach of Kimmel et al. [22], lung emptying can be easily incor-
porated into the simulation by subtracting the cumulative gas volume that leaves the
conducting airways from the initial lung volume, updating lung volume constantly.
Since most of the parameters depend on $V_L$, this means that those parameters must
also be updated. The equation for lung volume is given by

$$
V_L(t+\Delta t) = V_L(t) - \frac{V_{out}}{V_{L_{max}}} 
$$

(2.26)
Figure 2-3: Impulse-type transpulmonary pressure reduction at the mouth for coughing at $V_L = 75\%$.

where $V_{out} = Q_{exit} \Delta t$ is the volume leaving the airway in time $\Delta t$ and $V_{Lmax}$ is the maximum lung volume, which is estimated to be 6 liters [9].

2.5 Upper Airway Resistance

Previously, it has been assumed that pressure at the end of the trachea ($\xi = 1$) equals $P_{atm}$. In reality, a pressure drop exists across the glottis and mouth, and the extra $\Delta P_g$ from $\xi = 1$ to mouth is now incorporated into the simulation. Jaeger and Matthys [20] showed that the resistance of the upper airways (from mid-trachea to the mouth) is similar to the resistance of a venturi tube. It can be described by a nondimensional loss coefficient

$$C_d = \frac{Q}{A} \left( \frac{\rho}{2 \Delta P_g} \right)$$

(2.27)

where $A$ is the cross-sectional area of the glottis. From Jaeger’s data, the dependence of $C_d$ on $Re$ can be represented by

$$lnC_d = -3.394 + 0.776lne - 0.0495(lnRe)^2 + 0.000813(lnRe)^3$$

(2.28)

Stanescu et al. [44] concluded that the glottis tends to be more open at high
volumes and higher flows. Based on their sparse data, the lung volume dependence of
the glottal aperture can be represented as a hyperbolic function ($A \approx .000353\lambda^{-1}$).
Knowing $V_L$ and $Re$ dependence, the final equation becomes

$$\Delta P_y = \frac{1}{(C_d)^2} \frac{\rho u^2}{2} \frac{0.000353}{\lambda}$$

(2.29)

where $Re$ and $u$ are computed based on the velocity and opening width of the glottis.

### 2.6 Peripheral Airway Resistance

The motivation behind this section is to introduce a more realistic means of comput-
ing the influence of small airways, especially at low lung volumes. Typically about
15% of the total pressure drop from alveoli to the trachea is attributed to small air-
ways. A recent study by Wiggs et al. [50], however, has shown that their relative
contribution can increase significantly as lung volume decreases. Collins [3] has shown
that one factor that contributes to this tendency is the asymmetric branching found
in the periphery. In addition, none of the previous models for forced expiration have
directly accounted for the effects of airway liquid to partially obstruct the flow pas-
sages although Elad and Einav [7] have introduced the effects of small airway closure.
Based on these observations, there is reason to believe that the EK model may have
underestimated the resistance contributed from the small airways. Furthermore, it
appears to be advantageous to treat small airways as a “lumped” resistance, because
of the rapid gradients in geometrical parameters which introduce considerable error
and potential instability into the numerical calculation.

The airway tree can be divided into two parts: one representing the central air-
ways extending from trachea to the point somewhere beyond segmental bronchi, and
another representing the peripheral airways. The effect of pressure drop in the pe-
ripheral airways will be included via an upstream boundary condition. Simulation
results will be shown later to demonstrate that this new approach, which eliminates
the potential influence of small airway compliances per se, does not compromise the
realism of the simulation.

2.6.1 Lung Descriptions

Due to the geometrical complexity of the actual lung, all previous models have assumed symmetric branching to make the simulation more tractable. This simplification is known to deviate significantly from reality. One relatively simple way to introduce asymmetry, at least in the small airways, is to treat these airways as a resistance network thereby making it possible to "lump" these resistances together. In doing so, we make airway cross-sectional area independent of $P_{aw}$ and thereby neglect airway compliance. This is based on the observation that the pressure drop in the periphery is typically quite small leading to transmural pressures no larger than about $-900$ Pa. Given this low value and the presumed stiffness of these airways, the degree of collapse produced in the periphery can be shown to be small and should have little influence on flow in the larger airways in the vicinity of the FLS.

Symmetric models, such as the Weibel model, assume that each airway bifurcation can be represented by a parent airway splitting into two identical daughter branches. The particular airway can be identified in terms of generations or order. For example, the trachea is defined as generation 1 and order 35. In the Weibel model, the difference in order number between parent and daughter branches is 1. Further, the model implies that the total number of airways in any particular generation $n$ is $2^{n-1}$.

A more realistic representation was produced by Horsfield [17], which accounts for asymmetric branching. In this model, a parent airway does not necessarily give rise to two identical daughters. The two daughters are allowed to differ in order by a maximum of three, thus allowing for a more complicated asymmetric structure. In what follows, we employ both the Weibel and Horsfield models of lung structure 4.

4The complete description of morphometric data of the lung models is in Appendix.
2.6.2 Resistive Circuit Analysis

The basic relationship between pressure drop ($\Delta P$) and resistance $R$ is given by

$$\Delta P = Q \ast R$$

(2.30)

and therefore, knowing the resistance and flow rate, we can easily determine the corresponding $\Delta P$.

With the assumption of fully developed Poiseuille flow, the resistance of a particular airway is given by:

$$R_p = \frac{8\pi \mu L}{A^2}$$

(2.31)

this was deemed to be valid for $Re < 60$ (Collins [3]).

For $Re > 60$,

$$R_v = (0.556 + 0.06Re^{1/2})R_p$$

(2.32)

where $R_p$ stands resistance calculated with the Poiseuille flow assumption. Knowing the airway dimensions and the local flow rate, the resistance of each airway can, in principle, be calculated.

The resistances of the airways can be effectively represented as electrical resistors, and therefore “lumped” resistance can be determined through analogue electric network theory. Figure 2-4 shows the situation for symmetric branching. For two resistors in parallel,

$$R_{eq} = \frac{R_n}{2}$$

(2.33)

where $R_n$ is the resistance of a single airway of order $n$, and $R_{eq}$ is the equivalent resistance for two resistors in parallel. If we define $S_n$ as the equivalent resistance of airway $n$ and all the airways upstream of $n$ (i.e. toward alveoli) and $T_n$ as the equivalent resistance of two $S_n$ in parallel, the following expressions are obtained.

$$T_n = \frac{S_n}{2}$$

(2.34)

$$S_n = T_{n-1} + R_n$$

(2.35)
For asymmetric branching, let \( \delta \) specify the difference in order between two daughter branches. Figure 2-5 shows the situation for \( \delta = 2 \). A similar analysis then gives,

\[
R_{eq} = \frac{R_n \times R_{n-\delta}}{R_n + R_{n-\delta}}
\]  

(2.36)

\[
T_n = \frac{S_n \times S_{n-\delta}}{S_n + S_{n-\delta}}
\]  

(2.37)

\[
S_n = T_{n-1} + R_n
\]  

(2.38)

With the above equations, the value of \( T_n \) and \( S_n \) can be determined for all generations.

Once \( S_n \) is determined for all order \( n \), the corresponding pressure drop from the alveoli to an airway of order \( n \) is given by,

\[
\Delta P_n = P_A - P_n
\]  

(2.39)

This is shown in Figure 2-6, and the techniques developed in 2.6.2 allow us to reduce the more complex circuit to the one in Figure 2-7. Note that \( Q_n \) is the flow passing

Figure 2-4: Analogue electrical representation of symmetric branching (from Prasad, 1991).

2.6.3 Upstream Pressure Drop

Once \( S_n \) is determined for all order \( n \), the corresponding pressure drop from the alveoli to an airway of order \( n \) is given by,

\[
\Delta P_n = P_A - P_n
\]  

(2.39)

This is shown in Figure 2-6, and the techniques developed in 2.6.2 allow us to reduce the more complex circuit to the one in Figure 2-7. Note that \( Q_n \) is the flow passing
through one particular airway of order $n$, and due to asymmetric branching, this is not the same flow that passes through the trachea. The relationship is given by

$$Q_n = \frac{N_e Q_{total}}{N_{total}}$$

(2.40)

where $N_e$ is the number of alveolar endings that each airway of order $n$ results in, and $N_{total}$ is the total number of endings. The explicit assumption is that flow is distributed according to number of endings. The final equation becomes

$$\Delta P = S_n Q_n$$

(2.41)

This now constitutes the upstream boundary condition for the computational scheme. In principle, we can now set the upstream point at any location along the airway tree as long as the simulation is stable and provided the effects of compliance can still be neglected.

### 2.6.4 Coordinate Shift

Care must be given to the fact when a portion of the airway tree is modeled in the manner just described, the domain of calculation utilizing the distributed equations
no longer ranges from 0 to 1. In addition, the location of the transition is not uniquely defined since the Horsfield model is used in one region and the Weibel model in the other. The boundary matching of the two models is accomplished by locating position in the two models that has the approximately the same diameter and number of airways. This effectively determines $X_{\text{boundary}}$, defined as the location of the upstream boundary. We introduced a new coordinate system $\eta$, which goes from 0 to 1, in the new computational domain. Note that if $X_{\text{boundary}}$ is zero, $\xi$ is same as $\eta$. Consequently, distributed parameters retain accurate values in the new coordinate system $\eta$, only if the effect of $X_{\text{boundary}}$ is taken into account such that the particular location in the lung is independent of the coordinate systems.

2.6.5 Airway Narrowing

In the small airways, the thickness of the liquid lining layer combined with the inner, non-structural components of the airway wall, represent a significant fraction of the airway diameter, increasingly so as lung volume falls. If we assume that some diameter representative of the load-bearing portion of the wall varies in proportion to $V_L^{\frac{1}{3}}$ as would be the case if geometric similarity pertained as assumed by many, this non-load bearing region is simply squeezed into a smaller and smaller area as $V_L$ decreases. This view is viewed as consistent with the observations of Wiggs et al. [50] in their studies of airway wall with and without smooth muscle constriction.

Since the combined effects of the liquid lining and non-structural tissue reduces the effective diameter of the airway, an increase in resistance is expected, especially for small airways where it is a larger percentage of the actual diameter. Since the dimensions of the load-bearing structure (i.e. length and diameter) are assumed to vary as of $V_L^{\frac{1}{3}}$, the importance of the airway liquid increases with decreasing $V_L$. From the volume conservation of liquid thickness,

$$L(\pi R^2 - \pi (R - H)^2) = \text{constant}$$  \hspace{1cm} (2.42)

where $H$ is the liquid thickness.
With the assumption that $H \ll \text{diameter}$, the volume can be approximated by the product of length, circumference of the airway, and the liquid thickness.

$$L \times 2\pi R \times H = \text{constant}$$  \hspace{1cm} (2.43)

Let the subscript 0 stand for values at TLC, it follows from equation 2.43 that,

$$H = H_o \times \frac{D_o}{D} \times \frac{L_o}{L}$$  \hspace{1cm} (2.44)

Since linear dimensions vary as $V_L^{\frac{1}{2}}$, the equation below calculates the effective airway diameter as a function of $V_L$:

$$D_{eff} = D - 2H = D - 2H_o \left(\frac{V_{Lo}}{V_L}\right)$$  \hspace{1cm} (2.45)

Equation 2.45 shows that $D_{eff}$ decreases significantly as $V_L$ falls and reaches zero at some $V_L > 0$.

### 2.7 Tissue Effect for Forced Oscillation and HFV

In modeling the effects of oscillations forced at the mouth, one needs to take into account the additional effects associated with lung tissue and the chest wall. These effects include those associated with the mass of the tissue, its elastance or ability to resist to static deformation, and its resistance or opposition to dynamic deformations.

Since DuBois [6] in 1956, electrical analogue models have been used widely to simulate pulmonary function. This is advantageous since a complex interconnection of solid and fluid components can be usefully thought of in terms of three simpler types of primitive passive elements called elastances, inertances, and resistances. Figure 2-8 shows the general model for respiratory dynamics. The compliance of the lung and chest wall (tissue) are represented by capacitor $C_t$, the resistance by resistor $R_t$, and inertance by $I_t$. The resistor $R_{aw}$ accounts for the flow resistance of the airways, and
inertance by $I_{aw}$. $C_g$ takes account of gas compression effects. Following the electrical circuit analogy, flow is analogous to current and pressure to voltage. Many more components can be added, but the above description is often considered adequate. For a comprehensive review, see Peslin [33].

![Diagram of analogous electric representation of the lung](image)

Figure 2-8: Analogous electric representation of the lung (from Peslin and Fredberg, 1986).

### 2.7.1 Constitutive Equations for Tissue Components

In respiration mechanics, it is common to characterize the various elements in terms of pressure differences across the element and associated flow rates passing through the element. The relationship depends only on geometry and the properties of the physical material and is often referred to as a constitutive relation. To avoid the complexities associated with nonlinear systems, we approximate linearity by concentrating only in the immediate neighborhood of the reference state. By doing so, simple relations can be obtained, but we need to exercise caution when applying these models to simulate large amplitude flow.

Resistance is attributed to dissipation by means of friction, and corresponding pressure difference is specified simply as

$$\Delta P_{resist}(t) = R \cdot Q(t)$$  \hspace{1cm} (2.46)

where resistance is the constant of proportionality between pressure and flow (or, in
the case of the chest wall, the rate of expansion). Inertance is given by

$$\Delta P_{\text{in}}(t) = I \frac{dQ(t)}{dt}$$  \hspace{1cm} (2.47)

where \( I = \frac{e_l}{A} \). It is important when flow rate changes rapidly.

Compliance has pressure difference in inverse proportion to volume, and therefore the relationship can be represented as

$$\Delta P_c(t) = \frac{1}{C} \int_0^t Q(t) dt$$  \hspace{1cm} (2.48)

These three constitutive relations provide a means of including tissue effects in the simulation for forced oscillation and HFV. Note that tissue contributions are ignored in forced expiration and cough due to the fact that we are assuming that the forcing functions in that they are based on measurements of pleural pressure, which effectively take into account the contribution of the chest wall as they are based on measurements of pleural pressure. Also, \( C_g \) is ignored on the basis that it is negligible for frequencies less than about 20 Hz. As a result, the model reduces to a simple LRC circuit with distributed \( R_{aw} \) and \( I_{aw} \). Furthermore, it can be assumed that ventilation occurs around Functional Residual Capacity (FRC) such that equilibrium between the elastic recoil of the lung and chest wall prevails. Therefore, the muscles of respiration are relaxed and additional pressure need not be considered.

The most reliable estimation of parameters comes from Peslin et al. [34] who carried out their study at small tidal volume and over a wide range of frequencies. From their averaged value of 15 subjects, we used \( R_t = 1.10 \times 10^{-3} \text{cmH}_2\text{O} / \text{ml/s} \), \( I_t = 2.1 \times 10^{-6} \text{cmH}_2\text{O} / \text{ml/s}^2 \), and \( C_t = 20.8 \text{cmH}_2\text{O} / \text{ml} \).

## 2.8 Numerical Method

Equations 2.18 and 2.21 constitute a set of hyperbolic differential equations that give rise to discontinuities similar to shock waves in compressible gas dynamics. This similarity is the main reason that many researchers (Elad et al. [8], Cancelli and
Pedley [2] etc.) used the two-step MacCormack scheme, which is easy to program and effective in dealing with internal discontinuities. The scheme consists of predictor and corrector steps and is second order accurate in both space and time. Note that equations 2.18 and 2.21 are in the form of

\[
\frac{\partial A}{\partial t} + \frac{\partial B}{\partial \xi} + C = 0
\]  

Therefore, numerics are done by,

**First Step (Predictor):**

\[
A_i^{n+1} = A_i^n - \frac{\Delta \tau}{\Delta \xi}(B_{i+1}^n - B_i^n) - \Delta \tau C_i^n \equiv \frac{A_i^n + A_i^{n+1}}{2}
\]  

**Second Step (Corrector):**

\[
A_i^{n+1} = \frac{1}{2} \left( (A_i^n + A_i^{n+1}) - \frac{\Delta \tau}{\Delta \xi}(B_{i+1}^{n+1} - B_{i-1}^{n+1}) - \Delta \tau C_i^{n+1} \right)
\]

where the values at the end of first step are indicated by \(n+1\), and the subscript \(i\) identifies the particular spatial grid location. In order to increase stability, the above scheme is modified by reversing the spatial differencing at each time step. This is a preferable technique for the non-linear case, and there is no penalty in time since the same amount of computation is involved.

The numerical stability is satisfied when the time step is less than or equal to the time required for a perturbation to travel two successive grid points. This means,

\[
\Delta \tau = \frac{\eta \cdot \Delta \xi \cdot L}{|u + c|_{\text{max}}}
\]

where \(\eta\) is the coefficient between 0 and 1. Following EK model, \(\eta = 0.8\).
2.9 Boundary Conditions and Initial Conditions

The physics of the flow is represented through governing equations, and the tube law effectively relates transmural pressure to nondimensional area of the tube. Proper specification of initial conditions and boundary conditions is very important in solving hyperbolic partial differential equations, and they are specified and marched forward in time until the desired solution is obtained. Figure 2.9 shows the simplified representation of the computational domain.

![Figure 2-9: Simplified representation of the computational domain.](image-url)

At the periphery (location 1), the airways merge into the alveolar zone. At location 4, mouth pressure equals atmospheric pressure. The techniques we have developed easily determine the equivalent pressure drops across the resistors. Consequently the boundary conditions for forced expiration and cough are,

\[
P_{aw} = P_A \quad \text{at location 1}
\]
\[
P_{aw} = P_{atm} \quad \text{at location 4}
\]

(2.53)

Once the pressures at location 2 and 3 are determined, the tube law effectively determines \( \alpha \), from which cross-sectional area and fluid velocity can be determined through the governing equations.

For oscillatory flows, the airway opening pressure \( P_{ao} \) does not equal to \( P_{atm} \) because of external forcing at the mouth. Since the flow rate is specified at location 4, the conditions at location 3 can be obtained by properly accounting for \( \Delta P_r \) to
ensure that $P_{ao}$ is greater than $P$ at location 3 when flow is forced into the lung. Opposite situation holds for outflow. For initial conditions, we assumed that fluid velocity is zero and pressure inside the tube equals to $P_{atm}$ everywhere.
Chapter 3

Results and Discussion

As mentioned in Chapter 2, the purpose of this thesis is to extend a previously developed model for pulmonary airflow to include:

1. unsteady inertial effects that are important during early stages of a forced expiration, a cough, and oscillatory flows.

2. branching asymmetry in the lung periphery.

3. the effects of airway liquid and associated wall tissue that tend to obstruct the airways, especially at low lung volumes.

For this purpose, the numerical code was extensively modified. The results presented in this chapter fall into two categories: the first section describes parametric studies that were conducted to compare the present model with that of Elad and Kamm [9] (hereinafter referred to as EK). In the second, results are presented for cases in which unsteady flow is an important factor, including forced expiration, cough, forced oscillation, and HFV. The results show that the new model represents a considerable improvement over previously published models and provides a useful tool in the study of a wide variety of forced, unsteady pulmonary flows.

The examples are chosen such that the comparison can be directly made with the EK model, and also such that new insights can be gained concerning the nature of flow during various maneuvers. The general agreement with EK implies that the
computational approach is valid; deviations can be attributed to fundamental differences in the model and are discussed in some detail. For simulations of coughing and HFV, there exist no other computational source of direct comparison. Nevertheless, the agreement of these predictions with experimental data provide some degree of corroboration. These provide a good starting point for further research in this field. In all simulations reported here, it was assumed that the gas was air at $37^\circ$ with $\rho = 1.2 \text{ kg/m}^3$ and $\nu = 0.000015 \text{ m}^2/\text{s}$.

### 3.1 General Characteristics of Forced Expiration

The general behavior of the model for unsteady forced expiration was examined by performing the same parametric studies reported by Elad and Kamm [9] for their quasi-steady model. The effects of airway liquid film and branching network asymmetry were purposely omitted at this stage to facilitate a direct comparison. Two wall stiffness distributions and two types of friction law were used, as explained in section 2.1 and 2.3, to reproduce the results of the EK model. The four cases examined are described in Table 3.1.

<table>
<thead>
<tr>
<th>Case</th>
<th>Wall Stiffness</th>
<th>Friction Law</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>hyperbolic</td>
<td>Collins</td>
</tr>
<tr>
<td>2</td>
<td>hyperbolic</td>
<td>Reynolds</td>
</tr>
<tr>
<td>3</td>
<td>exponential</td>
<td>Collins</td>
</tr>
<tr>
<td>4</td>
<td>exponential</td>
<td>Reynolds</td>
</tr>
</tbody>
</table>

Table 3.1: The description of the cases examined.

Figure 3-1 shows the MEFV curves of the four runs. Case 1 resulted in a slight instability around $V_L$ of 80% TLC, however all the cases gave results that are in general agreement with the EK model. Significant differences are only seen at early times during which unsteady inertia is certain to be important. Generally speaking, Collins' friction law resulted in larger maximal flow in the region of effort-dependence (as much as 15 %) than with the Reynolds friction law, but the difference becomes small as lung volume decreases. Previously published results from the EK model
did not exhibit this difference due to the fact that their simulations were performed for the quasi-steady region (lower lung volumes) only. One possible explanation for this finding is that Collins' friction law provides lower friction dissipation resulting in larger supercritical flow. Presumably, as a consequence of these high values of $S$ and the resulting increase in jump strength, the solution exhibits some minor tendency for instability.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3-1.png}
\caption{MEFV curves for the cases examined.}
\end{figure}

The hyperbolic tangent wall stiffness distribution gave a slightly higher flow than the exponential distribution, but the difference is minimal. All curves approached an asymptotic value of 6 liter/s at low $V_L$, much higher than is observed experimentally. At low $V_L$, the reduction in flow rate is typically attributed to small airways resistance, where the coupling between viscous losses and tube compliance causes the flow limitation site to move upstream. This suggests that in all four cases shown in Figure 3-1, the simulation lacks the ability to mimic the actual viscous pressure drops in the peripheral airways and requires further modification in modeling as discussed below.
Even though different wall stiffness distributions have a negligible effect on the MEFV curve, the difference in location of FLS is quite significant. Figure 3-2 shows the distribution of speed index along the tube for all four cases at $V_L = 65\%$, and figures 3-3 to 3-6 show the effect of decreasing lung volume from 95% TLC to 45% TLC for individual cases. Table 3.2 shows the lung volumes at which the curves are generated.

![Graph showing speed index distribution](image)

Figure 3-2: Speed index distribution for the cases examined at $V_L = 65\%$ TLC.

<table>
<thead>
<tr>
<th>Curve</th>
<th>Lung Volume [% TLC]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
</tr>
</tbody>
</table>

Table 3.2: The legend for speed index graphs in this section.
Figure 3-3: Speed index distribution at successively decreasing $V_L$ for case 1.

Figure 3-4: Speed index distribution at successively decreasing $V_L$ for case 2.
Figure 3-5: Speed index distribution at successively decreasing $V_L$ for case 3.

Figure 3-6: Speed index distribution at successively decreasing $V_L$ for case 4.
Defining the FLS as the location where $S$ passes from sub- to super-critical, the FLS is positioned further upstream with the hyperbolic tangent distribution than with the exponential distribution. This is due to the steep gradient in stiffness associated with the hyperbolic distribution in the vicinity of the second to fifth generations. Collins’ friction law gives higher supercritical flow and displaces FLS slightly more upstream. Our results are in general agreement with those obtained by the EK model; however, our simulation gives significantly higher supercritical velocities when the Collins’ friction law is used as compared to their result ([9], Fig.3) perhaps due to the influence of unsteady inertia in the present calculations. Note that Collins’ friction law results in stronger elastic jumps than the Reynolds’ law.

Table 3.3 shows the approximate $\xi$ location of the generations according to Weibel. For case 1 and 2, the FLS is located within the third generation and moves into the fourth generation at low $V_L$; for case 3, FLS moves from the second to third generation; for case 4, the FLS is located in the trachea at large $V_L$ and moves into the second generation at around 50% of TLC. These predictions are consistent with the findings of Smaldone and Smith [42] who reported that the FLS always resides within the central airways and does not move beyond the proximal subsegmental bronchi (generation 5). Continuous movement of the FLS can be seen in all four cases, and this is confirmed by experimental studies.

<table>
<thead>
<tr>
<th>Generation</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.547 1.000</td>
</tr>
<tr>
<td>2</td>
<td>0.368 0.546</td>
</tr>
<tr>
<td>3</td>
<td>0.296 0.367</td>
</tr>
<tr>
<td>4</td>
<td>0.271 0.295</td>
</tr>
<tr>
<td>5</td>
<td>0.230 0.270</td>
</tr>
</tbody>
</table>

Table 3.3: $\xi$ locations for first 5 generations according to Weibel.

Since the hyperbolic distribution is introduced to produce a relatively constant tracheal stiffness, we have reason to believe that it is a more accurate representation than the exponential distribution. However, the steeper gradients associated with the hyperbolic distribution tend to aggravate the stability problem. Similarly, Collins’
friction law which properly takes into account the bifurcation and entrance effects and, unlike the Reynolds' form, yields more reasonable values for high and low values of Re, also contributes to the instability. Despite these difficulties, case 1 is accepted as the standard case in subsequent calculations, unless otherwise specified. It will be used as the basis for the further modifications into the simulation. The discrepancy between prediction and experiment at low lung volumes is, as yet unresolved, but will be discussed in subsequent sections.

3.2 Effect of Upper Airway Resistance

The effect of the upper airway resistance can be seen in Figure 3-7. Note that these results include the modified upstream resistance calculation described in section 3.3. The upper airway resistance resulted in flow reduction in the effort-independent region, but at lung volumes for which the flow is wave-speed limited, the flow rates are virtually unaffected. Figure 3-8 shows the variation of ΔP_g, which exhibits a shape similar to that of the MEFV curve. This indicates that the dependence of ΔP_g on Re is greater than on V_L. The upper airway inertance is purposely excluded in the simulation, because even in the region of initial acceleration, where the largest contribution of inertia would be found, the magnitude is significantly smaller (maximum value of 100 Pa) than ΔP_g.

3.3 Upstream Resistance Calculation

Including the effects of asymmetry is a crucial step toward realism since the experiments have shown that inhomogeneity associated with airway resistance and lung emptying is a significant factor, especially at low lung volumes. Asymmetry thus cannot be ignored. Computationally, it is difficult to model these effects, however, due to lack of understanding of fluid dynamics at the bifurcation where two streams of unequal velocity meet, and due to the increase in computational time required to proceed up a large number of parallel pathways [10]. In a limited fashion, Lambert
Figure 3-7: The comparison between with or without upper airway resistance.

Figure 3-8: The upper airway resistance contribution.
introduced asymmetry by allowing asymmetric flow within a single generation. Clearly, the complete incorporation of asymmetry is a formidable task, and some simplification must be made.

In this thesis, we introduce a more realistic representation of asymmetry in the form of a “lumped” peripheral resistance. This is motivated by the previous findings that the peripheral airways undergo little area change, due to the negative transmural pressure that must exist, even though they are more compliant than central airways [10]. This reasoning is based on the observation that, despite their small caliber, the total pressure drop in the peripheral airways is relatively small. Consequently, the change in area due to compliance is likely to be small compared to that associated with changes in lung volume. The approach used here is to introduce the area change as a function of lung volume in the most realistic way possible, but to ignore the comparatively small changes associated with compliance.

In principle, the technique we have developed (as described in section 2.6) allows us to move the upstream boundary between the lumped periphery and the distributed symmetric system to virtually any position in the lung, but care must be taken to ensure that by ignoring the compliance of small airways, we are not significantly altering the numerical result. Provided the elimination of compliance is plausible, it is advantageous to move the boundary up as much as possible such that asymmetry is incorporated over the greatest possible fraction of the conducting airways.

The cases examined are listed in Table 3.4. Note that “order” refers to the Horsfield classification of the location in the lung, and \( X_{\text{boundary}} \) is given in terms of \( \xi \), and hence represents a fractional distance along the airway tree. \( X_{\text{boundary}} \) is the point of attachment of Horsfield and Weibel model that was determined by matching the number of airways and diameter data of the two models. Since the number of airways poses greater uncertainty than diameter, we chose to weigh 75% accuracy to the diameter matching. Note that order 7 is the natural matching of the two lung models.

Figure 3-9 shows the resulting MEFV curves for the cases examined. The case with the boundary at order 31 is omitted since it resulted in a numerical instability.
that terminated the calculation. Except for a small instability present for the case with the boundary at order 25, moving up the boundary resulted in a decrease in flow rate at low lung volumes. We had originally anticipated an increase in flow rate, reasoning that making the airways non-compliant in the presence of a negative transmural pressure, would cause a relative increase in area and a consequent reduction in resistance. The behavior in this case, however, is complicated by several factors. First, as the boundary is moved toward the mouth, more and more of the symmetric structure is being replaced by an asymmetric structure which has been shown in a previous study (Collins [3]) to be more resistive. Secondly, variations in area due to changes in lung volume are modeled differently in the two regions: the behavior of the symmetric system is based on an extrapolation of experimental measurements in the central airways of dogs (Takashima [45]) while the asymmetric system is based on the assumption that the linear dimensions of the structural components of the airway wall vary as \( V_L^{1/4} \). The combined effects of these two, apparently produce an increase in total resistance when the boundary is moved mouthward, overwhelming the effect of making the airways non-compliant.

While there is very little information on which to base our decision, it seems likely that the asymmetric model with dimensions varying as \( V_L^{1/4} \) is more realistic; hence we have greater confidence in those prediction obtained when the boundary moves closer to the mouth and would, if anything, expect the actual flow rate to be somewhat lower yet due to the additional influence of compliance. Figure 3-10 shows how transmural pressure varies with the lung volume. It grows in magnitude when the boundary is moved mouthward, but the magnitude is only -900 Pa when the boundary is at order 25. This is relatively small, therefore justifying neglect of the compliance effect.

<table>
<thead>
<tr>
<th>Horsfield Order</th>
<th>NB Matching</th>
<th>Diameter Matching</th>
<th>( X_{critical} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>0.000</td>
<td>0.000</td>
<td>0.0000</td>
</tr>
<tr>
<td>16</td>
<td>0.077</td>
<td>0.055</td>
<td>0.0605</td>
</tr>
<tr>
<td>24</td>
<td>0.210</td>
<td>0.149</td>
<td>0.1643</td>
</tr>
<tr>
<td>31</td>
<td>0.473</td>
<td>0.341</td>
<td>0.3740</td>
</tr>
</tbody>
</table>

Table 3.4: The classification of different upstream boundary locations.
Figure 3-9: MEFV curves produced by placing the upstream boundary at different locations corresponding to the 7th, 16th, and 24th order in the Horsfield lung model.

The peripheral airway pressure drop ($P_d$) at different upstream conditions is shown in Figure 3-11. The largest magnitude is about 1000 Pa and, when compared to $P_{pl}$, constitutes only about 10% of the driving pressure. With the introduction of airway liquid, the resistance of the peripheral airways will play a more important role.
Figure 3-10: Transmural pressures produced by placing the upstream boundary at locations corresponding to the 7th, 16th, and 24th order in the Horsfield lung model.

Figure 3-11: Peripheral pressure drops produced by placing the upstream boundary at locations corresponding to the 7th, 16th, and 24th order in the Horsfield lung model.
3.4 Effect of Airway Narrowing

When incorporating in the model the effects of airway narrowing, the key question is how thick the airway liquid should be. Studies have indicated that airway liquid itself is about 10 microns thick. In addition, however, the inner wall epithelium and some fraction of the wall tissues should probably be included in an estimate of the "effective" thickness of the liquid layer. The rationals for this can be explained by reference to the simplified cross-sectional area of the airway as shown on Figure 3-12. Beyond the inner gas-liquid interface, there exists not only airway liquid but also a layer of epithelium, sub-mucosal tissues, and the smooth muscle layer. If the $V_L^{1/3}$ dependence holds for some representative airway diameter, say the smooth muscle layer, we can effectively incorporate the thickness between lumen and this representative diameter as part of the airway liquid in the sense that as this representative diameter decreases. The tissues and liquid within are packed into a smaller and smaller volume. In subsequent discussion, we refer to this tissue/liquid combination as the "effective" liquid layer thickness, $H_e$.

![Figure 3-12: Simplified cross-section of a peripheral airway.](image)

Figure 3-13 shows the result of using different values for $H_e$. The larger values of $H_e$ increase the resistance by reducing the lumenal area, in turn making the MEFV
curve closer to the experimental. The difference is most significant near RV where small airway resistance is important. The current simulation is designed to terminate when lumenal area reduces to zero (i.e. infinite resistance), and this effectively represents airway closure. Note that this occurs simultaneously in all branches representing a highly non-realistic situation. We can also think of increasing thickness as a means of simulating obstructive lung disease, in which, excess liquid is present. Compared to MEFV curve, the results obtained with a value for $H_e$ of 50 microns matches the best, although the shape of the MEFV curve is still somewhat unphysiologic. The presence of airway liquid did not result in any significant movement of FLS.

![Graph](image)

Figure 3-13: The effect of airway narrowing to the MEFV curve.

As an alternative approach to correcting the discrepancies at low lung volumes, Elad and Einav [7] applied progressive airway closure by reducing $A_o$ and $N_o$ starting from closing volume (CV) \(^1\). Due to a lack of knowledge concerning at what lung volume closure occurs, these simulations were necessarily based on somewhat arbitrary assumptions concerning the pattern and distribution of airway closure. On the

\(^1\)lung volume at which onset of airway closure is assumed to occur.
other hand, LW model made peripheral airways extremely compliant and varied their
cross-sectional area in an arbitrary manner so as to produce results that matched
experiments. They were able to achieve significant flow reduction at low $V_L$, however
the justification of their model is somewhat questionable.

The current research gives yet another possible explanation for the observed flow
reduction by introducing airway liquid that was missing in previous models. Together
with asymmetry, this model gives a fairly realistic result and is based on a model
that might be more easily verified. The simulation is relatively at primitive stage,
however, and several improvements are still possible. The assumptions of a uniform
liquid thickness at TLC is probably not correct. Recent methods involving the use of
low temperature scanning electron microscopy [52] promise to yield some information
concerning this question. Also, differences due to natural variability from branch
to branch should also be considered. Further, the exact dimensional dependence on
lung volume and understanding of lumenal area change due to “folding” of epithelium
should enhance the realism of the simulation.

3.5 Cough

The cough reflex was simulated at lung volumes equal to of 95%, 75%, 55%, and
35% of TLC. Figure 3-14 shows the cough simulations superimposed on top of the
MEFV curve under the same conditions. At 95% TLC, the flow was actually below
the MEFV curve. Since this corresponds to the range of effort-dependence, flow
is not determined by wave-speed limitation, but rather, by the maximum possible
pressure generated by muscle contraction. For other cases, “supermaximal” flows
(flows that exceed those observed during a FVC maneuver) were clearly evident and
were consistent with experimental findings. Following the initial peak, however, flow
rates fell to nearly the same level as during a forced expiration.

“Supermaximal” flow as predicted here, can be directly attributed to the volume
expelled by transient collapse of the central airways. Figure 3-15 shows the area
distribution of the 75% TLC case showing the collapse of the conducting airway
Figure 3-14: The cough reflex at different lung volumes superimposed with MEFV curve.

Note that the tracheal region collapses about by 40% of the original dimension, despite the fact that it is relatively stiff. The maximum deformation occurred at $\zeta = 0.4$ where 80% reduction of the original area is observed. Figure 3-16 shows the difference between inflow and outflow for the simulated cough at 75% TLC. The initial peak in outflow, surpassing flow into the conducting airway, represents volume displaced from the collapsing airway network. Near the end of the cough, inflow is greater than outflow implying that the airways are expanding back to their original dimension. The time integral of both flows representing the total volume expelled, was estimated, and no difference was found.
Figure 3-15: Area distribution during cough at $V_L = 75\%$ TLC.

Figure 3-16: The comparison of inflow and outflow during cough for $V_L = 75\%$ TLC.
Figure 3-17 shows the distribution of speed index during a cough and for a forced expiration at $V_L = 55\%$ TLC. The results indicate that $S$ is somewhat lower during cough, confirming the results of Kimmel et al. [22]. This contradicts the conclusion reached by Pederson et al. [32] that super-maximal flows are not due exclusively to airway collapse but instead, are a result of higher critical flows occurring in an airway at a higher, but unstable area. Coughing does not seem to alter the location of the FLS. It is important to keep in mind, however, that these simulations ignore the effects of tissue mass and tissue visco-elasticity that could be an important factor in this highly transient event.

![Figure 3-17: The comparison of Speed Distribution at $V_L = 55\%$.](image)

**3.6 Forced Oscillation**

The forced-oscillation technique is currently used as a convenient tool to estimate total respiratory resistance, and is a potentially powerful method in detecting and interpreting lung diseases through parameter estimation. It is especially applicable
to young children, because it does not require cooperation on the part of the patient.

The ratio of the pressure $P_{ao}$ to the flow $Q_{ao}$ at a frequency $w$ is called the respiratory system impedance, $Z_{rs}(w)$. It is easily calculated from the ratio in the complex plane as,

$$Z_{rs}(w) = \frac{P_{ao}(t)}{Q_{ao}(t)} = \frac{P_{ao}(w)e^{j(wt+\phi_{rs})}}{Q_{ao}(w)e^{jwt}} = \frac{P_{ao}(w)}{Q_{ao}(w)}e^{j\phi_{rs}} = |Z_{rs}|e^{j\phi_{rs}} \quad (3.1)$$

where $j$ is the unit imaginary number and $\phi_{rs}$ is the phase angle difference between pressure and flow. Furthermore, the impedance can be divided into the real and the imaginary components as

$$Z_{rs}(w) = R_{rs} + j[wI_{rs} - \frac{1}{wC_{rs}}] \quad (3.2)$$

Note that $R_{rs}$, $I_{rs}$, and $C_{rs}$ stand for total respiratory system resistance, inertance, and compliance, respectively. The real part of impedance is called the equivalent resistance and the imaginary part of the impedance is referred to as the equivalent reactance. Impedance can be thought of as the impediment the element poses to oscillatory flow.

A Lissajous figure is obtained when an oscilloscope is used to plot flow versus pressure. Because only sinusoidal forcing at the mouth is considered, both pressure and flow are periodic, and impedance can be easily deduced from them. Figure 3-18 shows the coefficients $(a,b,c,e)$ that can be determined from the Lissajous figure. Once they are known, the components of impedance correspond to,

$$|Z_{rs}| = b/c$$
$$|\Phi_{rs}| = \cos^{-1}(a/b)$$
$$\text{Real}[Z_{rs}] = a/c$$
$$|\text{Imag}[Z_{rs}]| = e/c \quad (3.3)$$

Note that when the ellipse is traced clockwise, the phase angle and imaginary part are both positive.
Figure 3-18: The Lissajous figure showing the coefficients from which the different components of the impedance are deduced.

Figures 3-19 to 3-22 show the predictions obtained by forcing at the mouth with $\pm 0.5 \text{liters/sec}$ at $V_L$ equal to FRC along with the experimental results of Michealson et al. [30] obtained at FRC and at TLC. For each frequency, Lissajous figures were constructed and the components of impedance were calculated through the coefficients mentioned above. Our results match fairly well, except for the $\text{real}|Z_{re}|$, which is significantly lower than theirs. This, in turn, causes the overall magnitude of the impedance ($|Z_{re}|$) to be small. The results appear to matched the experimental data at TLC quite well for no apparent reason. This suggests that the present model underpredicts flow resistance at FRC and this could account for the overprediction of maximal flow in the region of mid-lung volumes. Nevertheless, the key features of the total respiratory impedance were successfully identified in the simulation. They are:

- At low frequency, the impedance is dominated by compliance, and pressure lags flow by an amount approaching $90^\circ$ at zero frequency.

- At resonance (about 10Hz in simulation and experiment), pressure and flow are in phase. The impedance magnitude is minimized at this point, as the compliant impedance and inertive impedance exactly cancel, and only the resistive
contribution remains.

- At higher frequencies, the contribution of inertance increases, and the pressure increasingly leads the flow.

The above description fits the characteristics of a second order system; previous studies have shown that the lung behaves roughly like a second order linear system with constant coefficients. According to our simulation, the resonant frequency is about 10 Hz, and the experimental value ranges anywhere from 7 to 11 Hz [33], further supporting the validity of our simulation.

Since our simulation is based on a simplified model of the lung, there exist numerous possible sources of error that may have caused the under-estimation of $\text{Real} |Z_{r+s}|$. First, our simulation uses the tissue coefficients (i.e. $R_t$, $I_t$, and $C_t$) that are derived from transfer impedance measurements of the pressure forcing at the chest. The values may be different for forcing at the mouth, although this is unlikely to be a large effect. Second, alveolar gas compression $(C_g)$ is ignored in the simulation. Even though the contribution of $C_g$ should be small for $f < 20$ Hz, its influence on $Z_{r+s}$ cannot be ignored completely. Third, the nonuniformity associated with the lung tissue is completely ignored. The inhomogeneity is difficult, if not impossible to model, and it may be the biggest source of error. More complicated electric analogous models were proposed by investigators [33], and more extensive simulations may be necessary to produce greater realism. Fourth, our simulation might also be improved by including other factors such as shunt impedance of the upper airways and mouth. And finally, at these frequencies, the Wormersley number is high in much of the lung, and the unsteady boundary layers are consequently small. Hence, our use of steady flow relations for the frictional pressure drop will underestimate the true resistance, perhaps considerably. The error will grow as the frequency increases.
Figure 3-19: Impedance modulus \(|Z_{re}|\) versus frequency for Forced Oscillation.

Figure 3-20: Phase angle \(\phi_{re}\) versus frequency for Forced Oscillation.
Figure 3-21: Equivalent resistance ($\text{Real}|Z_{rs}|$) versus frequency for Forced Oscillation.

Figure 3-22: Equivalent reactance ($\text{Imag}|Z_{rs}|$) versus frequency for Forced Oscillation.
3.7 High Frequency ventilation

The goal of this section is to produce a realistic model of flows generated by the application of high frequency ventilation (HFV) and, more specifically, to examine the mechanisms that limit the rate at which a given lung can be ventilated. For this purpose, a frequency range of 1 to 11 Hz was studied for tidal volumes ranging from 20 to 200 ml. The simulations were carried out at a mean lung volume equal to FRC, which corresponds roughly to 47% TLC. The corresponding MEFV curve predicts the maximum flow rate to be about 5.8 liters/sec.

Figure 3-23 shows the simulation results. For tidal volumes smaller than the dead space (about $V_T < 140$ ml), the peak pressure increases slightly with increasing frequency, but the frequency dependence is minimal. On other hand, for $V_T$ greater than $V_D$, pressure excursions increase significantly. For the case of $V_T = 200$ ml, $P_{pp} (11 \text{ Hz}) \approx 15952$ Pa and the pressure excursion increases about 30 fold between 3 Hz and 11 Hz. The key point is that only for this case, does the peak flow rate (6.9 liters/sec) exceed the maximal expiratory flow as predicted by the MEFV curve. In addition, the ratio of flow into the airway to flow out of airway is less than one ($|\frac{Q_{in}}{Q_{scl}}| = .8966$) implying that flow at the mouth is not getting all the way down to the alveolar zone resulting in a decrement in alveolar ventilation. This means that the airways are collapsing to satisfy the flow requirement at the mouth, a finding consistent with the observation of Lehr et al. [25], who identified "upper airway shunting" in excised lungs in the form of large amplitude excursions in airway cross-sectional area. This may be the basis for the limitations of HFV. We have tried the case for $V_T = 220$ ml at the 11 Hz, but it resulted in program termination indicating the fact that pressure excursions were enormous and, perhaps, that there was insufficient volume to compensate for the difference between limited inflow and specified outflow.

Figure 3-24 shows the area distribution along the tube for forcing above flow limitation. It clearly shows both expansion and collapse of the airway during the ventilatory cycle. Symmetry with respect to the rest area is not observed due to
Figure 3-23: Pressure excursion versus frequency for different tidal volumes.

... choking associated with the maximum flow out of the lung. Note that there exists an incipient instability occurring at the point of maximum flow into the lung, the exact cause of which is not known.

Investigators have found that inadvertent gas trapping can occur in the lung during HFV [41]. The simulations suggest that the mechanism responsible for this phenomenon is related to flow limitation, which sets an upper bound on outflow rate. When attempting to exceed this limit, pressures at the mouth must be extremely large and negative during expiration. If the ventilator is incapable of producing such pressures, the expired volume will be somewhat less than inspired volume on each stroke, and lung volume will rise, leading to progressively greater lung inflation.

For HFV, flow excursions are large enough to reveal nonlinearities in the pressure-flow relation. Therefore, our assumption of linearity breaks down with large amplitude flow and high frequency, and equations derived in section 2.7 describing tissue and chest wall effects must be modified to incorporate nonlinearities. Nevertheless, the results given here provide a sufficiently accurate picture to reveal the essential features...
Figure 3-24: The area distribution for case of $V_T = 220\text{ml}$ and $f = 11\ \text{Hz}$.

of this type of flow.
Chapter 4

Conclusion

The goal of this thesis was to extend a previous model so that greater insight could be obtained concerning forced unsteady pulmonary airflows. This was accomplished by including factors that were absent in previous models, specifically unsteady inertial effects, asymmetry branching, and the effects of airway liquid obstructions. The numerical model still lacks some key physiologic characteristics, but results have shown a considerable improvement over previous models and provided a useful tool to study forced unsteady flows such as cough, forced oscillation, and HFV. The accomplishments of this thesis along with key findings are summarized here.

A comparison was made with the EK model by imposing the same parametric condition in terms of effective wall distributions and friction laws. The general agreement thus obtained indicated the validity of the current computational model, even though fundamental differences exist between two models. The current model was successful in identifying the location of the FLS, continuous movement of FLS as lung volume falls, reproducing the results of the EK model. Significant differences were only seen during the initial time period of rapid acceleration, where the unsteadiness plays a significant role. This finding reinforces the belief that unsteadiness must be taken into account when attempting to simulate the full regime of forced expiratory flows. As with the EK model, the MEFV curve obtained with the present simulation appears to be relatively insensitive to significant variation in system parameters.

With with the EK model, the present model initially predicted flows at low volume
for in excess of what is typically observed. As a first step toward eliminating this discrepancy, asymmetry was incorporated in our model of the peripheral airways by treating them as a “lumped” resistance. In order to do so, both Weibel (for central airways) and Horsfield (peripheral airways) lung models were introduced. In the process, the compliance of these small airways was ignored; the effect of this was explored in detail. Contrary to our anticipation, the new results demonstrated a decrease in flow rate at low lung volumes, implying an increase in total resistance despite the neglect of peripheral compliance. The magnitudes of both transmural pressure and small airway resistance were small even when the non-compliant region extended up to order 24, further justifying the incorporation of asymmetry.

To further enhance realism, the effect of airway narrowing was introduced. We considered airway obstruction due to all components of the airway wall that might contribute; this includes airway liquid, the inner wall epithelium, and some fraction of the wall tissues. The “effective” liquid layer increased the peripheral resistance resulting in reduction of flow particularly at low lung volumes, more so with a thicker layer. Together with asymmetry, the current model resulted in one of the most realistic results currently available.

Cough simulations confirm the experimental findings of “supermaximal” flows. These were found to be due to transient collapse of those airways mouthward of the FLS. The results has shown that portion of the conducting airway, a subject to severe collapse, was as large as 40% in the trachea. Furthermore, the results indicated that the speed index is somewhat lower, but the location of FLS was not altered during cough.

For forced oscillation, the key features of the total respiratory impedance were identified, confirming the studies that the lung behaves roughly like a second order linear system. The resonance frequency was determined to be about 10 Hz. Some differences were observed in the magnitude of the real part of the impedances when compared to the experimental data, suggesting that further study is warranted.

Results obtained with HFV suggested that there exists a clear relationship between maximal flow during HFV and flow limitation. The results indicated that empasis
should be placed not on whether forcing is greater or less than the dead space, not rather on the maximal flow attainable as measured in the FVC maneuver. The current model for unsteady maneuvers has formed a basis for further research resulting in more realistic simulation with increasing degree of realism.

4.1 Future Considerations

The ultimate goal of modeling forced expiratory flows is to simulate the pathological states such that a fundamental understanding can be attained that will enhance the diagnosis and treatment of many respiratory diseases. While these simulations already exhibit impressive capabilities, more physiological understanding is required. Even though the current model made significant improvements compared to previous ones, there are many aspects that can be improved. Possible extensions and additional aspects, subject to incorporation into the model, are discussed here.

For forced expiration, more reliable physiological data will help to raise our confidence in the results by removing uncertainties that are embedded in the simulation. In order to do so, more extensive experimental studies are required. One such limitation is the existence of simultaneous multiple serial choke points. Solway et al. [43] predicted that they might exist as demonstrated by some experiments in canine airways. In the experiment, two plateaus in the static pressure distribution were observed at small negative airway opening pressures and three plateaus were observed at larger negative values. Previous models [9] [22] interpreted this phenomenon as due to "weak spots", one presumably occurring at the tracheal carina, and imposed perturbations to mimick the effect. When the current model incorporated similar perturbations, it was also possible to obtain two FLS's. The results are subject to great uncertainty, however, lacking not only physiological data, but also due to large gradients that arise in the solution that are prone to numerical error.

On the other hand, there are some experimental findings that the model cannot currently simulate. This raises questions concerning the validity of the assumptions made and the limitations that the model has to overcome. One such example is the
existence of violent oscillations often coincident with flow limitation that appear to originate near the site of the sub-to-supercritical transition. The nature of this wall oscillation ("flutter") has been the subject of numerous studies, but their influence on expiratory flow in the lung is not well understood. Recent experiential results obtained in our laboratory have shown that oscillations cause a reduction in maximal flow rate. Currently, our models cannot predict flutter due to the assumption of a massless tube; the validity of this assumption is questionable. To improve the current model, wall mass and the visco-elastic nature of lung tissue should be taken into account. Further, "folding" of the epithelium together with a better understanding of small airway collapse will simulate airway obstruction and narrowing more realistically.

For other unsteady flows, the incorporation of wall mass will also improve the model significantly. Furthermore, the under-estimation of magnitude of impedance of forced oscillation suggest that other effects might need to be considered such as more complicated electrical model including gas compression effect, shunt impedance of mouth and upper airways, and unsteady flow resistance. For HFV, the situation is somewhat different due to highly nonlinear behavior associated with large volume excursions and high frequency. In principle, constitutive relations describing tissue and chest wall nonlinearities can be used in place of the present linear ones. In addition, wall mass, unsteady friction, and upper airway asymmetry will need to be considered at some future time.
Appendix A

Conducting Airway Data

The following table provides the dimensions of conducting airways from a symmetric airway model developed by Weibel [47]. Generations between 0 (trachea), and 17 (respiratory bronchiole) are represented.

Table A.1: Dimensions for the first 17 generations of symmetric branching (from Ultman, 1985).

<table>
<thead>
<tr>
<th>Generation</th>
<th>Branch radius r(mm)</th>
<th>Branch length l(mm)</th>
<th>Summed cross-section A(cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0(trachea)</td>
<td>9.0</td>
<td>120</td>
<td>2.5</td>
</tr>
<tr>
<td>1(primary bronchi)</td>
<td>6.1</td>
<td>47.6</td>
<td>2.3</td>
</tr>
<tr>
<td>2(secondary bronchi)</td>
<td>4.15</td>
<td>19.0</td>
<td>2.1</td>
</tr>
<tr>
<td>3(bronchioles)</td>
<td>2.4</td>
<td>6.5</td>
<td>1.5</td>
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<td>4</td>
<td>1.95</td>
<td>10.9</td>
<td>1.8</td>
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<td>9.2</td>
<td>2.3</td>
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<td>4.6</td>
<td>7.0</td>
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<td>9.8</td>
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<td>3.3</td>
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</table>
Appendix B

Horsfield Lung Model

The following table provides the dimensions of conducting airways from an asymmetric airway model developed by Horsfield [17]. Order 35 (trachea) to order 0 (alveolar sacs) are presented. Order 8 is terminal bronchioles, and Delta specify the difference in order between the 2 daughter branches arising from a parent of order $n$. Number of endings is number of order 1 branches supplied by a branch of order $n$. 
Table B.1: Horsfield Lung Model for asymmetric branching (from Horsfield, 1986).

<table>
<thead>
<tr>
<th>Order (n)</th>
<th>Delta</th>
<th>Diameter (mm)</th>
<th>Length (mm)</th>
<th>Number of Endings</th>
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Bibliography


