CHAPTER 1

INTRODUCTION

1.1 ANATOMY OF RESPIRATORY SYSTEM

Acquisition of oxygen from external medium and the discharge of carbon dioxide into the same milieu is the primary role of respiration (Maina et al. 2014). The respiratory tract provides passageway for airflow to the gas exchange regions of pulmonary alveoli in the lungs. Periodic pumping of gas in and out of the lungs is controlled by contractions of the respiratory muscles that rhythmically change the thoracic volume and produce the pressure gradients required for airflow. Respiratory system is therefore a complex combination of the physiological processes of ventilation, pulmonary blood flow, gaseous diffusion along with biomechanical performance of respiratory muscles and chest wall mechanics.

Respiratory diseases are lung conditions with symptoms of inability to inhale or exhale normally. It has been reported that, globally, 4 million deaths has occurred due to chronic respiratory diseases. It still remains as one of the largest contributor to the overall disease burden measured in terms of disability-adjusted life-years (DALYs) loss (World Health organisation, 2014).

Chronic respiratory diseases (CRDs) affect the airways and cause alteration in structures of the lung. An early diagnosis and appropriate treatment reduce the burden of CRDs. It also has major effects on the quality of life of the affected individuals. Assessment of respiratory mechanics is
therefore essential to understand the pathophysiology of the disease as well provide guidelines for further therapeutic measures.

The anatomy of the respiratory system comprises of three major divisions namely the airways, the lungs and the muscles of respiration. The conducting airway begins from the nose and mouth, extends through the head connecting to the trachea and concludes at the alveoli inside the lungs (Figure 1.1). The gas exchange takes place between the alveoli and the capillary blood flowing around them.

![Figure 1.1 Structure of the respiratory system](http://legacy.cnx.org)

(Source: http://legacy.cnx.org)

**Figure 1.1 Structure of the respiratory system**
The conducting airways of the respiratory system is subdivided into two modules namely the upper respiratory tract and the lower respiratory tract. The upper respiratory tract includes the nose, mouth, pharynx and larynx. The function of the upper respiratory tract is to prevent dust, debris enter the respiratory tract, other than being a simple conduit for air, food and drink. Its cough reflex protects the lungs from the inhalation of foreign material. The upper airway has a significant role in respiration as it warms, humidifies and filters air passing into the lungs.

The lower respiratory tract arises from the trachea and is partitioned into 23 generations of dichotomous branching to the terminal or respiratory bronchioles (Patwa & Shah, 2015). Tiny sacs like structures called alveoli are attached to these bronchioles. The prime function of alveolus is to deliver oxygen ($O_2$) to blood passing through the capillaries (Figure 1.1). The dense network of alveolar capillaries highlights the structural, functional relationship of the respiratory and circulatory systems.

The lungs are located inside the thorax and are protected by the bony thoracic cage. The main respiratory muscle called the diaphragm and the intercostal muscles of the chest wall under the control of the central nervous system generate the pumping action on lungs.

A regular, healthy functioning lung depends on many mechanical and physiological factors. There are pathologies that disturb the symmetry of this natural organisation. Respiratory diseases are largely classified as obstructive and restrictive conditions. An obstructive disorder is a disproportionate reduction of maximal airflow from the lung in relation to the maximal volume that can be displaced (Bates 1989). This is due increased expiratory resistance to airflow caused in the conducting airways. There are three common clinical
characteristics associated with obstructive pulmonary diseases: airway inflammation, airway obstruction and Bronchial Hyperresponsiveness (BHR). Due to their large interdependencies, many obstructive diseases present complexity in disease diagnosis.

Restrictive lung diseases are heterogeneous group of conditions characterized with a reduction in total lung capacity. When the bellow action of the lungs or chest wall disrupts it leads to restrictive disorder. The etiologies can be intrinsic with lung parenchyma involvement as in interstitial lung diseases or extrinsic to the lung as in obesity and neuromuscular disorder (Robinson, 2016).

1.2 PULMONARY FUNCTION TEST

Respiratory mechanics are associated with the interaction of resistive, elastic and inertial forces of breathing. The mechanical properties of the respiratory system are evaluated with Pulmonary Function Tests (PFT). Vital information relating to the large and small airways, pulmonary parenchyma is identified with the aid of these tests. They supplement diagnosis along with clinical history and physical examinations. PFTs therefore yield valuable findings in the investigation of individuals with suspected respiratory pathology or monitoring therapeutic intervention in previously diagnosed pulmonary impairment (Franca et al. 2016).

Spirometry is a universally accepted, gold standard lung function test used in the assessment and detection of pulmonary function alterations in adults, adolescents and paediatrics (Beydon, 2009). It is a forced breathing maneuver that measures individual exhalation and inhalation lung volumes as a function of time. The measurement reflects the mechanical properties of the
respiratory system due to the phenomenon of airflow limitation caused in a forced expiration (Golczewski et al. 2012).

The interrelationship of flow and volume obtained during various time intervals from spirometer are displayed as graphical loop patterns called spirogram (Figure 1.2). The flow-volume curve represents inspiratory and expiratory phases of breathing (Veezhinathan et al. 2007). The highest flow rates are obtained during the first one-third part of expiration. The curve rises rapidly to a peak point known as Peak Expiratory Flow (PEF) (Figure 1.2). It represents approximately 25-33% of vital capacity of the lung and is effort dependent.

Due to the presence of dynamic compression of large airways, above a certain threshold level of effort, no increase in the flow occurs.
Consequently, maximum flow attained during forced expiration, begins to decrease progressively as lung volume falls. This is evident in the linear part of the curve after 1/3 of expiration and is also effort independent. The flow volume during this portion represents the changes either in the recoil pressure of the lungs or the resistance in the airways.

Expiratory flow volumes of Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV₁), the ratio of FEV₁/FVC, Peak Expiratory Flow (PEF) and Forced Expiratory Flow (FEF) at time instants of 25%, 50%, 75% and the average between 25-75% are the flow volume indices recorded from spirometer. The flow parameters of the spirometry are derived from the vital capacity.

FVC is the maximum volume of air that can be exhaled during forced maneuver. It is the difference between Total Lung Capacity (TLC) and the minimal volume inaccessible to spirometer called Residual Volume (RV) (Pellegrino et al. 2005). The FEV₁ is the volume exhaled during the first one second of forced expiratory maneuver from the level of total lung capacity. It is an index of the average flow over the initial two thirds or more of FVC (Manoharan et al. 2008). The FEV₁ index reflects the lung size as well as the rate of lung emptying.

Spirometry have proven to be a useful tool for characterizing the pattern and extent of airway obstruction with global lung function measures, principally FVC, FEV₁ and the ratio of FEV₁/FVC in both Chronic Obstructive Pulmonary Disease (COPD) and asthma (Braman & Abu-Hijleh, 2010; Ranu 2011). The American Thoracic Society (ATS)/European Respiratory Society (ERS) standards for diagnosis and management of respiratory disorders, have graded disease severity based on the ratio FEV₁/FVC (Celli et al. 2004).
Peak expiratory flow is the largest expiratory flow achieved with a maximally forced effort from fully inflated lungs. The peak expiratory flow relates better to tracheal cross-sectional area and is also dependent on the expiratory muscle strength. It detects narrowing of large and medium sized airways. Flow measurements derived from spirometry over middle half of vital capacity namely Forced Expiratory Flow (FEF) at 75% and \( \text{FEF}_{25\%-75\%} \) are more specific to small airway function (Ohwada & Kazuhisa Takahashi 2012).

The shape of the flow-volume curve reflects the underlying mechanics limiting the maximal flow. It also provides information about the physiologic basis for locating the site of airway obstruction (Arora & Raghu 1996). In healthy younger adults the shape of the flow-volume curve generally approximates a straight-sided triangle with maximum flows decreasing linearly with lung volume. But in individuals with lung impairment, the key physiological features are reduced expiratory flows proportion to disease severity (Johns et al. 2014).

The earliest change associated with airflow obstruction in small airways is thought to be reflected in the terminal portion of the spirogram. The slowing of expiratory flow in obstructive subjects is most noticeably revealed as a concave shape on the flow–volume curve. Quantitatively, it is expressed as a proportionally greater reduction in the instantaneous flow measured after 75% of the FVC (FEF\(_{75\%}\)) or in mean expiratory flow between 25% and 75% of FVC (Perez et al.1998).

Restrictive diseases are caused due to variations in structures surrounding the lung or abnormalities of the lung parenchyma. Since the airways are normal in restrictive disorder, the flow volume curve has a normal shape. The presence of a restrictive ventilatory defect is suspected when vital
capacity is reduced. FEV$_1$ is equally lowered with FVC and hence the ratio of FEV$_1$/FVC remains normal or is even increased. (Koegelenberg et al. 2013).

Spirometry is therefore understood to be a maximum expiratory maneuver that determines air volumes and respiratory flow rates. The test is effort-dependent necessitating patient co-operation and understanding to complete the test (Manoharan et al. 2009). A good learning capability and dexterity are prerequisites for high-quality spirometry. Sometimes, both these attributes are inadequate in the elderly subjects and in young children.

The cognitive and functional impairment in the elderly subjects may sometimes lead to sub maximal efforts (Pezzoli et al. 2003). Children with breathing difficulty, patient discomfort and stress are other causes of incomplete spirometric measurements. A remedy to these inconclusive tests and to provide improvement in the quality of treatment received by individuals, prediction of significant spirometric parameters from the available incomplete data set is required (Kavitha et al. 2011). A prediction model with computerized data utilization to predict pulmonary parameters may be useful in population-based efforts to improve disease diagnosis.

Predicting clinical outcome and diagnosing disease from available information is an important task for patient care and disease cure. The involvement of certain specific features is unknown and a significant inter-subject variability is expected. Effective handling of uncertainty is one of the central issues in medical decision making.

Consequently, a decision system allowing adaptation for subject and environment conditions has to be designed to evaluate biomedical signal classification. A variety of pattern recognition approaches are used to design models that can separate and classify subjects into different prognostic classes. These techniques ascertain and identify patterns, the relationships
between the features even in complex datasets. They are able to effectively predict future outcomes of unseen data.

Clinical decision support systems are modern development in healthcare that supports clinicians in identifying individuals early in the course of their disease. A significant improvement in 68% of trials has been achieved in clinical practice with the inclusion of the decision systems (Kawamoto et al. 2005). Hence, healthcare organisations are increasingly turning to clinical decision support systems, that can provide clinicians with patient-specific assessments or recommendations to aid clinical decision making.

Machine Learning (ML) relates to the ability of data-driven models to “learn” information about a system directly from observed data without predetermining mechanistic relationships that govern the system (Shikhina et al, 2017). They are capable to adaptively improve their performance with each new data sample and discover hidden patterns in complex, high dimensional data. In clinical and biomedical engineering domain ML offers predictive models, such as Artificial Neural Networks (ANNs), Decision Trees (DTs), Random Forests (RFs), and Support Vector Machines (SVMs), that are able to map highly non-linear heterogeneous input and output patterns even when physiological relationships between the features could not be determined due to complexity or pathologies, or lack of biological understanding.

Artificial Neural Network’s (ANN) are mathematical computational model that mimics in its structure, the functional aspects of biological neurons. It is a structure with interconnected group of artificial neurons and processes information using a connectionist approach. ANN possesses an inherent structure that suits mapping of complex characteristics, learning and optimization. Due to their notable properties of parallelism,
distributed storage and adaptive self-learning capability, they have also been utilized to solve biomedical problems, especially in the areas of classification and prediction.

In the past two decades, Support vector machines (SVM) and their variants have been extensively used in the task of classification due to their surprising classification ability. These models are based on the theory of risk minimization and are able to find an optimal separation hyper plane in a multi-dimensional space to perform classification.

However, the primary challenges in applying SVM modelling method to a given domain lies in the choice of its parameters as well as the magnitude of the soft margin. In addition, different variants of support vector machines are required to suit various practical applications. Alternatively, the kernel function based Extreme Learning Machine (ELM) avoids such trivial and tedious situations faced by SVM.

ELM as emergent technology, overcomes some challenges such as slow learning speed, trivial human intervene faced by other techniques and had attracted the attention from more researchers. ELM provides better generalization performance at a much faster learning speed and can obtain global optimal solution when compared with other techniques. A variant of ELM, the multiclass kernel ELM machine naturally unifies the concepts of network generalization, linear system stability and maximal separating margin. The machine uses a wider type of feature mapping and has shown to yield higher scalability with less computational complexity.

Decision Trees (DT) are one of the earliest and most prominent machine learning methods that have been widely applied in biomedical applications for they are easy to interpret. It follows a tree-structured classification scheme where the nodes represent the input variables and the
leaves correspond to decision outcomes. But they are less robust and yield suboptimal performance.

The shortcomings of conventional decision trees are overcome in Random forest. Diversifications of the input with randomized feature selection have enhanced the performance of ensemble of decision trees. The forest is able to combine heterogeneous data types into a single model, whilst also performing an automatic principal feature selection. Averaging over a large collection of trees with low correlation yields a high predictive performance. The foremost benefit of the tree based strategy lies in its flexibility to adapt to several types of learning ranging from regression to multi-label classification. (Al-Maathidi & Li 2016; Chen et al. 2014; Girshick et al. 2011).

A variety of competing approaches utilizing artificial neural networks (Veezhinathan et al (2007); Manoharan et al (2008)), support vector regressor (Kavitha et al. 2010) and fuzzy logic (Myithili et al 2012) applied for analysis, prediction and classification of pulmonary parameters have been reported erstwhile. However, the methods have demonstrated with difficulties in finding a good generalization performance, optimization of the upper bound on the regularization parameter and determination of optimal functional parameters (Umit Uncu 2010).

As well, it was observed that the performance assessment of these computational models with binary categorization were dominant. Conversely, in actual medical diagnosis of pulmonary disorder such labelling does not depict the reality that owns diverse categories. Subsequently, in a quest to enhance such diagnosis, the parametric and non-parametric methods are applied and analyzed in the applicability as a decision support system to assist clinicians.
1.3 OBJECTIVE OF THE THESIS

The objectives of the thesis are:

- Acquisition of respiratory function data in Normal, Obstructive and Restrictive lung conditions using flow-volume spirometry

- Predict the significant flow volume parameter Forced Expiratory Volume in one second (FEV1), Forced vital capacity (FVC) regression techniques

- Characterization of the multiclass lung function conditions using classifier models with the predicted FEV₁ and FVC flow volumes

1.4 ORGANISATION OF THE THESIS

The work reported in the thesis is organized into 5 Chapters:

Chapter 1 deals with brief introduction, objectives and organization of the thesis.

Chapter 2 discusses a brief review of the literature on pulmonary function test, spirometry, prediction and classification

Chapter 3 describes the protocols and methods, explains the theoretical evaluation of data obtained from spirometry and analysis of data from flow volume curve.

Chapter 4 focuses on the results obtained through the analysis.

Chapter 5 summarizes the work carried out in this thesis and suggests directions for future work.