

Chapter 1

Functional modeling of idiopathic pulmonary fibrosis

In Chapter 4, HRCT based quantitative analysis and shape analysis methoda were developed to provide a consistent way of describing the features and progressions of IPF disease. However, it is not clear how - or whether - the spatial distribution of tissue abnormalities in IPF (including classifications of tissue type) correlate with lung function and their change over time, and currently, how to translate these imaging and shape biomarkers into functional biomarkers to directly help with the clinical diagnosis and treatment is still a challenging work. For the patient with IPF, V/Q mismatching and hypoxemia are frequent occurrences. Computational modeling provides a reliable way to simulate how these quantitative indexes contribute to the decline of lung function, therefore build a relationship between image-based biomarkers and functional presentations. This chapter outlines the functional modeling of IPF. The quantitative tissue-level and shape-level features combined with pulmonary functional test (PFT) were used to guide a patient-specific computational modeling of lung function of IPF. The lung function of

old normal people was modeled as well for comparison. This work aims to integrates data from volumetric imaging, PFTs, and computational models for lung function, to understand differences between IPF and normal older lungs.

1.1 Respiratory function in older people

The respiratory system of human keeps developing during the whole life, with the high-point of pulmonary function achieved before 30 years old (Janssens et al., 1999; Sprung et al., 2006). For most people, respiratory performance begins to gradually decline after reaching the maximal status. It is concluded by evidence that the ability of oxygen delivery to tissues decreases by four times from age 20 to age 70 in healthy people (Smith, 1986; Zaugg and Lucchinetti, 2000). Even in older athletes who experience vigorous endurance exercise and have better aerobic ability, the functional capability of lung will progressively deteriorate over time (Mittman et al., 1965; Pollock et al., 1997; McClaran et al., 1995).

The aging-related changes in respiratory physiology are usually associated with structural alterations in both lungs, dilatation of alveoli, enlargement of airspaces, decrease in exchange surface area, and increased residual volume (RV)and functional residual capacity (FRC) (Sprung et al., 2006; Lalley, 2013). There is a reduction in chest wall compliance and the static elastic recoil of the lung, which will lead to static air-trapping, decrease in vital capacity (VC), decrease in expiratory flows and increasing work of breathing compared with younger individuals (Sprung et al., 2006). The strength of respiratory muscles decreases in elders, and this is strongly correlated with nutritional status (lean body mass, body weight) and cardiac index (Janssens et al., 1999). The V/Q ratio heterogeneity tends to diminish results from a closing of de-

pendent airways, and carbon monoxide transfer capability also decreases which is associated with the reduced alveolar surface. Interestingly, despite of these changes, gas exchange almost maintains normal both at rest and during exertion, with only a slight reduction in arterial oxygen tension, but no significant change in arterial carbon dioxide tension (Janssens et al., 1999). These age-associated changes are summarized and described in detail in Table 1.1.

1.1.1 Aging-associated alterations in chest wall and respiratory muscle function

Several morphological changes occur in chest wall and diaphragm in older people that reduce the capability and efficiency of respiratory system. One of the most important changes is the progressive decline in chest wall compliance, which relates to the decrease of cross sectional areas of intercostal muscles, calcification of costal cartilage and rib-vertebral articulations, and narrowing of intervertebral disk spaces (Murray, 1986; Crapo, 1993). The structural changes in chest wall is found to be associated with the reduction in the curvature of diaphragm and maximal transdiaphragmatic pressure, however the thickness of the diaphragm seems not change too much in elders (Zaugg and Lucchinetti, 2000; Sprung et al., 2006). It is noted that the age-associated osteoporosis results in a shape change of the thorax geometry, that is an increase in dorsal kyphosis and anteroposterior chest diameter (Janssens et al., 1999; Sprung et al., 2006).

The reduction in respiratory muscle strength caused by the age-related decrease of maximal static inspiratory and expiratory pressures will lead to lower efficiency of respiratory muscle activity (Wijesinghe and Dow, 2005; Sprung et al., 2006; Lalley, 2013). It has been proved that the reduced respiratory muscle strength is associated with the

Table 1.1: Age-associated changes in respiratory function and their relationships to clinical presentations (Reproduced from (Sprung et al., 2006; Lalley, 2013))

Measurements	Changes, ≥ 60 yrs.	Clinical presentations
Static lung volumes		
- TLC	Unchanged	
- FRC	Increase	
- IRV	Modest increase	
- ERV	Increase	
- TV	Modest increase	
- VC	Decrease	
- IC	Increase	
- RV	Increase	Impaired gas exchange
Dynamic lung volumes		
- FVC	Decrease	
- FEV_1	Decrease	
- FEV_1/FVC	Decrease	
- Peak expiratory flow	Decrease	
Resistance and compliance		
- Respiratory system resistance	Increase	
- Small airways closure	Increase	Impaired gas exchange
- Chest wall compliance	Decrease	Increase in work of breathing
- Lung compliance	Increase	Decrease in ventilatory response to exercise
Respiratory (muscle) pressures		
- Mean pleural pressure	Unchanged	
- Respiratory muscle strength	Increase	
Gas transfer		
- Ventilation-perfusion mismatch	Increase	Impaired gas exchange
Altered control of breathing		
- Responsiveness to imposed respiratory loads	Decrease	Hypoventilation
- Responsiveness to hypoxemia and hypercarbia	Decrease	Hypoxemia and hypercarbia
- Sensitivity to anesthetic agents and opioids	Increase	Respiratory failure in early postoperative period

TLC: total lung capacity; FRC: functional residual capacity; IRV: inspiratory reserve volume; ERV: expiratory reserve volume; TV: tidal volume; VC: vital capacity; IC: inspiratory capacity; RV: Residual volume; FVC: forced vital capacity; FEV_1 : forced expiratory volume in 1 s; FEV_1/FVC : the ratio of the forced expiratory volume in the first one second to the forced vital capacity of the lungs.

deficient nutritional status in older people, and a strong relationship was found between maximal inspiratory/expiratory pressure and lean body mass (Arora and Rochester, 1982; Janssens et al., 1999). Meanwhile, some study has shown that the electromyographic signal produced by twitch stimulation decreases by around 50% in the 70-year-old people (average 73) compared with young subjects, and this reduction is attributed to the loss of type II fast-twitch muscle fibres (Larsson, 1983).

1.1.2 Aging-associated alterations in pulmonary mechanics and lung volumes

Although the chest wall becomes stiffer in elder people, their lung parenchyma actually become more compliant (Mittman et al., 1965; Turner et al., 1968; Zaugg and Lucchinetti, 2000). The elastic recoil pressure of lung tissue gradually reduces by aging, with a decrease rate around 0.1 to 0.2 cmH_2O averagely every year (Turner et al., 1968), and this reduction is attributed to the alterations in the spatial distribution of the elastic fibre network (Sprung et al., 2006). In elder people, it can be observed that the static pressure-volume curve of the lung was shifted to the left, in contrast, the pressure-volume curve of the thorax was shifted to the right (Zaugg and Lucchinetti, 2000; Sprung et al., 2006).

The tidal volume experiences a slight decrease by aging, whereas the respiratory rate gradually increases (Sprung et al., 2006). As mentioned in Section 1.1.1, the chest wall becomes stiffer by aging, while the lung tissues become more compliant. These changes will lead to an increase in RV and a decrease in VC (Lalley, 2013,?). Some research indicates that RV volume will increase by approximate 50% from 20-year-old to 70-year-old averagely, and VC will drop to around 75% of the peak value during this

period, with decreasing 20 to 30 ml per year (Janssens et al., 1999; Sprung et al., 2006). The TLC, which is the air volume in the lungs with a maximum respiratory effort, remains unchanged with age, as the effect of the decreased inward elastic recoil of the lung is offset by the reduction in the outward elastic recoil of the chest wall (Sprung et al., 2006). However, the FRC increases by 1 to 3% per decade, since the rate of decrease in lung recoil exceeds the rate of decrease in chest wall (Janssens et al., 1999; Lalley, 2013). Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) have been demonstrated to decrease progressively with aging in both men and women (Knudson et al., 1976), but the volume reduces more rapidly in males than in females (Crapo, 1993). FEV_1 decrease by 20 ml approximately per year in subjects aged 25 to 29 years, but for people more than 65 years old, the average annual rate of reduction is dramatically up to 38ml (Brandstetter and Kazemi, 1983).

1.1.3 Aging-associated alterations in gas exchange

The inhomogeneity or mismatch of ventilation-perfusion increases with age, especially in lower regions of the lung where intrapleural pressure becomes higher and the lung tissues become less elastic to keep small airways open (Holland et al., 1968; Paoletti et al., 1985; Lalley, 2013). The increased V/Q heterogeneity results in a reduction in P_aO_2 , with a progressive drop from approximate 95 mmHg at 20 years to about 75 mmHg at 70 years. However, $PaCO_2$ remains almost unchanged with increasing age, although PaO_2 declines (Wahba, 1983; Sprung et al., 2006). This can be probably explained by the decreased rate of basal metabolism and the higher diffusive capability of CO_2 across the alveolar-capillary membrane (Levitzky, 1984). Pulmonary perfusion can also reduce with age in some regions where are well ventilated but not fully perfused, and this al-

teration is associated with the reduced cardiac output (Levitzky, 1984; Lalley, 2013). The alveolar-arterial pressure difference for oxygen ($P_{A-a}O_2$) increases by aging due to the increased heterogeneity of V/Q, and is probably also related to the increase in closing volume during breathing (Janssens et al., 1999). It can be observed that the arterial oxygen tension reduces with approximately 5 mm Hg per decade from the age of 20 years, and the increasing alveolar-arterial oxygen gradient and the decreased arterial oxygen tension are expected to be the main reason of the impaired arterial oxygenation in elder people (Smith, 1986; Zaugg and Lucchinetti, 2000). Additionally, the diffusing capacity of the lungs for carbon monoxide (DLCO) decreases with aging (Guenard and Marthan, 1996), with about $0.3 \text{ mL}\cdot\text{min}^{-1}\text{mmHg}^{-1}$ and $0.2 \text{ mL}\cdot\text{min}^{-1}\text{mmHg}^{-1}$ for men and women, respectively (Murray, 1986). The reduction is more significant after 40 yrs of age, and the increased mismatch in V/Q, a decline in the alveolar surface area (Verbeken et al., 1992; Thurlbeck and Angus, 1975), the decreased density of lung capillaries (Butler and Kleinerman, 1970) and the reduction in pulmonary capillary blood volume (Guenard and Marthan, 1996) are all potential factors to cause the impaired diffusion capacity.

1.2 Patient-specific modeling of IPF lung function

In this section, a patient-specific computational modeling of lung function was proposed to explore the V/Q matching and the whole lung gas exchange for patient with IPF. In order to make a comparison of lung function between IPF patient and older normal people, for each patient, a subject-specific lung mesh that represents the statistical lung shape of old normal individual with the same age, BMI and pulmonary functional data was predicted using SSM. Anatomically based airway and blood vessel trees were generated

derived from HRCT images, respectively matched to IPF lung mesh and the corresponding old normal lung mesh. The ventilation, perfusion and gas exchange models were then constricted to simulate \dot{V} , \dot{Q} distribution and gas transport in normal and disease constricted condition, respectively. During this process, individual's lung parenchymal tissue classification and quantification data was mapped to model of IPF patient, with fibrosis reducing tissue compliance and narrowing vessels. Data from PFTs were used to parameterize the models and set the boundary conditions. The framework of modeling is illustrated in Figure 1.1.

1.2.1 Clinical data

6 patients diagnosed with IPF were selected from the clinical data used in Chapter 4 as representative subjects for functional modeling, among which one patients had two time points with 12 month interval, and 3 of them were female. The clinical data for each patient includes both HRCT images and PFT result, with less than 3 months between the scan date and the PFT date.

1.2.2 Construction of lung lobe geometry

In Chapter 4, Section ?? and ??, we compared the lung lobe shapes and volumes of IPF patients with old normal people. It can be observed that there is a significant difference of lung lobe geometry between IPF and old normal groups, and this alteration in lung shape mainly focuses on the basal part (lower lobe), strongly associated with the distribution of fibrosis in IPF. In order to involve the impact of shape change into the modeling of lung function, SSM of old normal people and patient's individual information were combined to predict an average lung lobe shape of old normal as a control

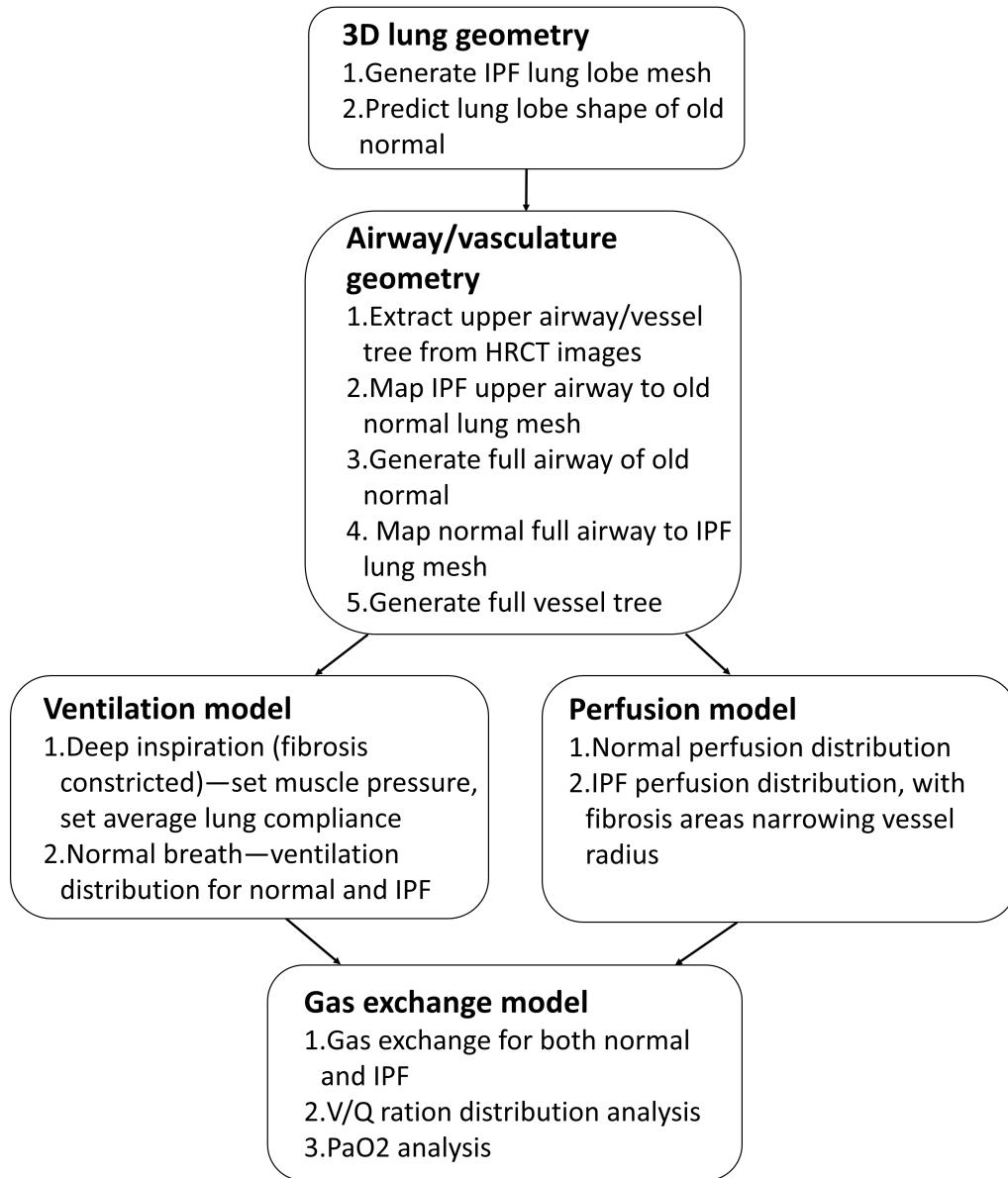


Figure 1.1: Computational modeling framework for IPF and older normal lung function.

group for each IPF patient. Meanwhile, the lung lobe mesh of each IPF patient was generated using the method introduced in Chapter 3, Section ??.

Relationship between lung function and lung shape

It is supported by evidence that the age-related changes in lung structures are strongly associated with a series of alterations in respiratory functions (introduced in Section ??). For example, the reduction in chest wall compliance of old people leads to a decrease in VC, while an increased RV in elders usually results in impaired capability of gas exchange which relates to a lower measured DLCO. In a previous study from our research group, the lung structure-function relationships were analyzed through quantifying the correlations of the first three PCA-based mode weights calculated from old normal SSM (introduced in Chapter 3, Section ??, and Chapter 4, Section ??) with age, BMI, lung volume and some pulmonary function measurements. For each training subject of SSM, the individual weight scores for each of the first three shape modes which captures most shape variation were examined. An ordinary least squares regression was applied to test the associations, and P value was used to quantify the strength of each association, with an alpha level of 0.05 considered statistically significant. Analysis result illustrates that Mode 1 has positive relationship with FEV_1 , FEV_1/FVC , Maximal mid-expiratory Flow (FEF25%-75%), BMI and DLCO, while has negative correlation with age, RV and RV/TLC. For Mode 2, only BMI is found a correlation with the shape variation, whereas quite a number of lung volume measurements, including FRC, TLC ,VC and RV show strong relationship with scores of Mode 3.

Shape prediction of old normal lungs

The lung shape prediction of old normal people was developed based on the previous analysis of lung structure-function relationship. Age, BMI, FVC, FEV_1 , FRC, TLC, VC, RV, RV/TLC and DLCO were selected as the individual functional measurements to train the lung shape predictive model, as these parameters show relatively strong correlations with the first three shape modes. The training process of lung shape predictive model is to find optimized equations that can best describe the relationship between the functional measures and the mode weights. For each shape mode, a multivariate regression model was constructed as follows:

$$w_i = \alpha_{0i} + \alpha_{1i}m_1 + \alpha_{2i}m_2 + \dots + \alpha_{ni}m_n + \varepsilon, \quad (1.1)$$

where w_i is the weight score of the i th shape mode, n is the number of functional measures, $\alpha_{0i}, \alpha_{1i} \dots \alpha_{ni}$ are the regression coefficients, in which α_{0i} is the intercept, m_i is the tested value of the i th functional measure, ε is a random error. Here, it is assumed that all the functional measures are independent variables.

Using Equation 1.1, a set of possible regression models can be developed for each shape mode (with different regression coefficients $\alpha_{0i}, \alpha_{1i} \dots \alpha_{ni}$). In order to find the best predictive model from all the possible models, two most common criterions for model selection, Akaike information criterion (AIC) and Bayesian information criterion (BIC), were used to deal with the trade-off between the goodness of fit of the model and the simplicity of the model. Both AIC and BIC are founded on information theory, with calculated by:

$$AIC = 2k - 2\ln L(\theta), \quad (1.2)$$

$$BIC = \ln(n)k - 2\ln L(\theta), \quad (1.3)$$

where k is the number of the estimated parameters (that is functional measures in this study) in the model, $L(\theta)$ is the maximized value of the likelihood function of the model and θ are the parameter values that maximize the likelihood function.

The multivariate regression models with the lowest value of AIC and BIC were selected as the best predictive models, then the models of the first three PCA modes were constructed in the form of Equation 1.1, shown as follows:

$$\begin{aligned} w_1 &= 1.38 + (-0.04 \times Age) + (0.38 \times FVC) + (-0.04 \times DLCO), \\ w_2 &= 3.49 + (-0.16 \times BMI) + 0.02 \times RV/TLC, \\ w_3 &= 4.90 + (-0.02 \times Age) + (-0.45 \times TLC) + (-0.05 \times DLCO), \end{aligned} \quad (1.4)$$

where w_1 , w_2 and w_3 are the weight scores of the first three shape modes. Through inputting the individual functional measures into the regression models, the weights of first three modes can be calculated. Then the subject-specific predicted shape of old normal lung can be reconstructed with adding linear combination of the first three modes into the average SSM:

$$S_{pred} = S_{mean} + \sum_{i=1}^3 \mathbf{u}_i w_i, \quad (1.5)$$

where S_{mean} is the mean shape of SSM for older normal people, S_{pred} is the subject-specific predicted lung shape. Table 1.2 lists the age, BMI and functional measures used for normal lung shape prediction of one patient with IPF. The values were from the

patient's individual information, among which FVC, TLC, RV/TLC and DLCO were the patient-specific normal reference values acquired from PFT results. Figure 1.2 presents the lung mesh of this IPF patient and the corresponding predicted lung mesh of older normal.

Table 1.2: Individual information used for normal lung prediction from one patient with IPF

Parameters	Age	BMI	FVC(L)	TLC(L)	RV/TLC	DLCO(mL/mmHg/min)
Values	82	32.77	3.87	7.22	46	25.1

FVC, TLC, RV/TLC and DLCO are the patient-specific normal reference values acquired from PFT results.

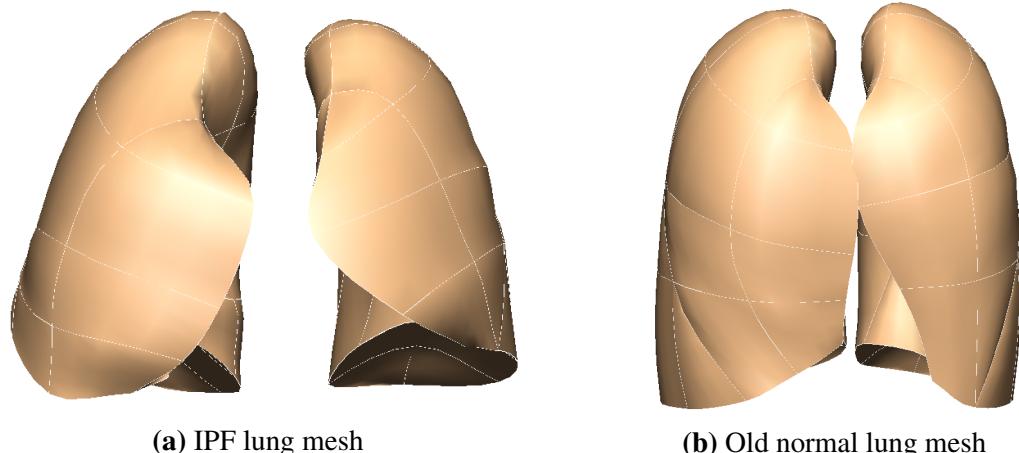


Figure 1.2: Lung mesh of IPF and the corresponding predicted lung mesh of old normal. (a) IPF lung mesh generated from CT imaging of a patient with IPF. (b) Old normal lung mesh predicted with the individual information of the same patient.

The average lobe volume proportion of each IPF lung mesh and each predicted old normal lung mesh were calculated, shown in Table 1.3.

As discussed in Chapter 4, Section ??, the shape change in IPF lung usually relates to a relatively larger anteroposterior diameter and smaller height of the lung. Meanwhile, IPF lung has a lower average volume proportion for left lower lobe and right lower lobe

Table 1.3: Average lobe volume proportion of IPF lung mesh and predicted old normal lung mesh.

Lobe	IPF	Predicted old normal
Left lower lobe	0.2314	0.2425
Left upper lobe	0.2474	0.2267
Right lower lobe	0.2213	0.2724
Right middle lobe	0.1260	0.0793
Right upper lobe	0.1739	0.1791

compared with old normal people. The results illustrated in Figure 1.2 and Table 1.3 are consistent with our previous findings, with predicted lung mesh of old normal showing a "thinner" and "higher" shape and lower average volume of left and right lower lobes compared with the IPF mesh generated from CT imaging.

1.2.3 Construction of airway/vasculature geometry

Subject-specific conducting airway trees and pulmonary vasculature trees were constructed in both IPF and predicted old normal lung mesh. The geometry of pulmonary airway and vasculature are representative of the important structural features of the pulmonary circulation, therefore are the basis on which the following anatomically based functional models can develop. In this section, airway/vasculature trees were firstly generated with filling 1-D finite element branches in the predicted old normal lung mesh, then were deformed to the shape of IPF lung mesh which presents a compression effect in the lower lobes in our previous analysis. The airway/vasculature diameters were assigned to each branch as a postprocessing step specific to IPF and old normal geometry respectively. Using this way, the branches of IPF and old normal airway/vasculature will be kept in the same geometric connectivity and same lobar distribution, but with different radius and length.

Airway tree

In order to generate airway tree in the lung shape, the bi-cubic Hermite finite element mesh of lung surface was converted to a tri-cubic Hermite volumetric mesh which describes not only the lung surface but also the internal anatomy (Tawhai and Burrowes, 2003). The volumetric mesh has 40 nodes and 30 elements for left lung, and 56 nodes and 38 elements for right lung. For each node, it has 24 DOFs which store the global coordinates (x , y and z) and the first, second and third nodal derivatives ($\frac{\partial n}{\partial \xi_1}$, $\frac{\partial n}{\partial \xi_2}$, $\frac{\partial n}{\partial \xi_3}$, $\frac{\partial^2 n}{\partial \xi_1 \xi_2}$, $\frac{\partial^2 n}{\partial \xi_2 \xi_3}$, $\frac{\partial^2 n}{\partial \xi_1 \xi_3}$ and $\frac{\partial^3 n}{\partial \xi_1 \xi_2 \xi_3}$), where n is x , y and z , and ξ is the local element coordinate.

An anatomical based structure of the bronchial airways (from trachea to terminal bronchioles) was generated using the methods developed by Tawhai et al, as described in details in Tawhai et al. (2000, 2004). In brief, the centerlines of the largest airways (trachea, left and right pulmonary airway branches of the first 6 generations) were manually segmented from the subject's HRCT images, which provides an incomplete description of the airway tree. Then, the larger airways was used as initial condition to generate the branches down to the level of the terminal bronchioles (smaller airways) within the subject's lung mesh using a volume-filling branching algorithm. The steps to generate patient-specific airways in IPF and old normal lungs were summarized as follows:

1. 1-D finite element mesh of the centerlines of IPF larger airways were created manually from HRCT raw images of IPF patient (shown in Figure 1.3a).
2. The 1-D tree of central airways obtained above was mapped to the volumetric mesh of old normal lung. The nodal positions inside the mesh were mapped through calculating the local coordination ξ_i with respect to its element (details in Chapter 4, Section ??). The branches outside the mesh were then scaled to match the target lung

volume, followed by a manual adjustment. The element connectivity remains the same during mapping.

3. The mapped larger airway in step 2 was used as a starting geometry for generating a full airway tree by volume-filling branching algorithm (Tawhai et al., 2000, 2004), to fill the lung-shaped of old normal volumetric mesh. Briefly, uniformed spaced grid seed points were created within the 3D volumetric lung mesh. The number of seed points is around 32000 (45% for left lung and %55 for right lung) which equals to the number of pulmonary density of acinar units in the lung (Haefeli-Bleuer and Weibel, 1988). The branching algorithm was designed to generate a branching structure recursively towards the center of mass of seed point units, until each seed point was assigned a terminal bronchiole (shown in Figure 1.3b).

4. The generated linear mesh of full airway tree in step 3 was mapped back to the volumetric lung mesh of IPF patient using the same method in step 2.

In the next stage, the diameters of airway branches were calculated for both IPF and old normal geometry, the method proceeds as follows:

1. The trachea radius of IPF was measured from segmented HRCT images through averaging the values at the position of 1/4, 1/2 and 3/4 along the centerline of the trachea, with treating trachea as a circular cross-section.
2. Radius of the terminal branch of IPF was assumed to be constricted based on a found that 70% of the IPF patients occur narrowed airways (Crystal et al., 1976). The radius of narrowed terminal branch was calculated by:

$$RdT_{IPF} = RdT_{normal} \times \sqrt[3]{\frac{FRC_{IPF}}{FRC_{Normal}}}, \quad (1.6)$$

where FRC_{IPF} is the measured FRC volume of IPF patient and FRC_{Normal} is the

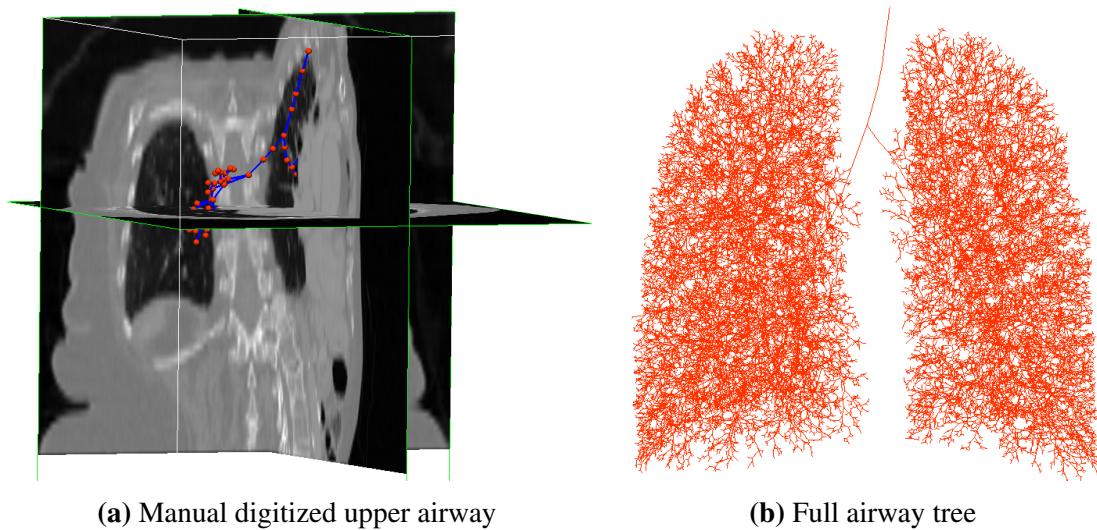


Figure 1.3: Generation of airway tree. (a) Manual digitized upper airway tree from HRCT images in 3D. Blue lines are the centerlines of upper airway tree, and red points represent airway nodes. (b) Geometry of full conducting airway tree generated using volume-filling algorithm. The model is shown from the anterior view, with the left lung on right, and right lung on left.

reference FRC volume of old normal people obtained from PFT report. RdT_{normal} is the terminal bronchiole radius of normal lung, estimated to be around 0.2mm (Horsfield et al., 1976). RdT_{IPF} is the constricted IPF terminal radius.

3. Radius of the other airway branches of IPF were calculated after initializing the trachea radius and Horsfield diameter ratios (R_dH). The R_dH was adjusted during each calculation until the terminal radius RdT_{IPF} can touch the value obtained from step 3. The conducting airway volume of IPF was then acquired by summing up the branch volume from distal to the trachea.

4. It has been proved by evidence that an increase in airway volume occurs in IPF lung, therefore, here the conducting airway volume of old normal lung was predicted using a statistically measured ratio R_{volume} , which represents the ratio of IPF conducting airway volume to the old normal conducting airway volume (Plantier et al., 2016). By

setting up the normal terminal radius with 0.2mm and the predicted conducting airway volume, the R_dH and the radius of other branches for old normal airway tree can be specially calculated. During this process, the normal range of trachea radius of the human lung (5mm to 11mm for women, 6.5mm to 12mm for man) was also taken into consideration (Breatnach et al., 1984) by adjusting the volume ratio R_{volume} until the predicted trachea radius can reach the normal range. R_{volume} was initialized as 34.2/45.3 (normal/IPF) which is the average volume ratio measured among a number of IPF patients and normal people.

Using the above steps, patient-specific pulmonary airway geometry for IPF and old normal lung were constructed. Figure 1.4 illustrates the generated airway trees of one IPF patient and its corresponding predicted airway tree of old normal.

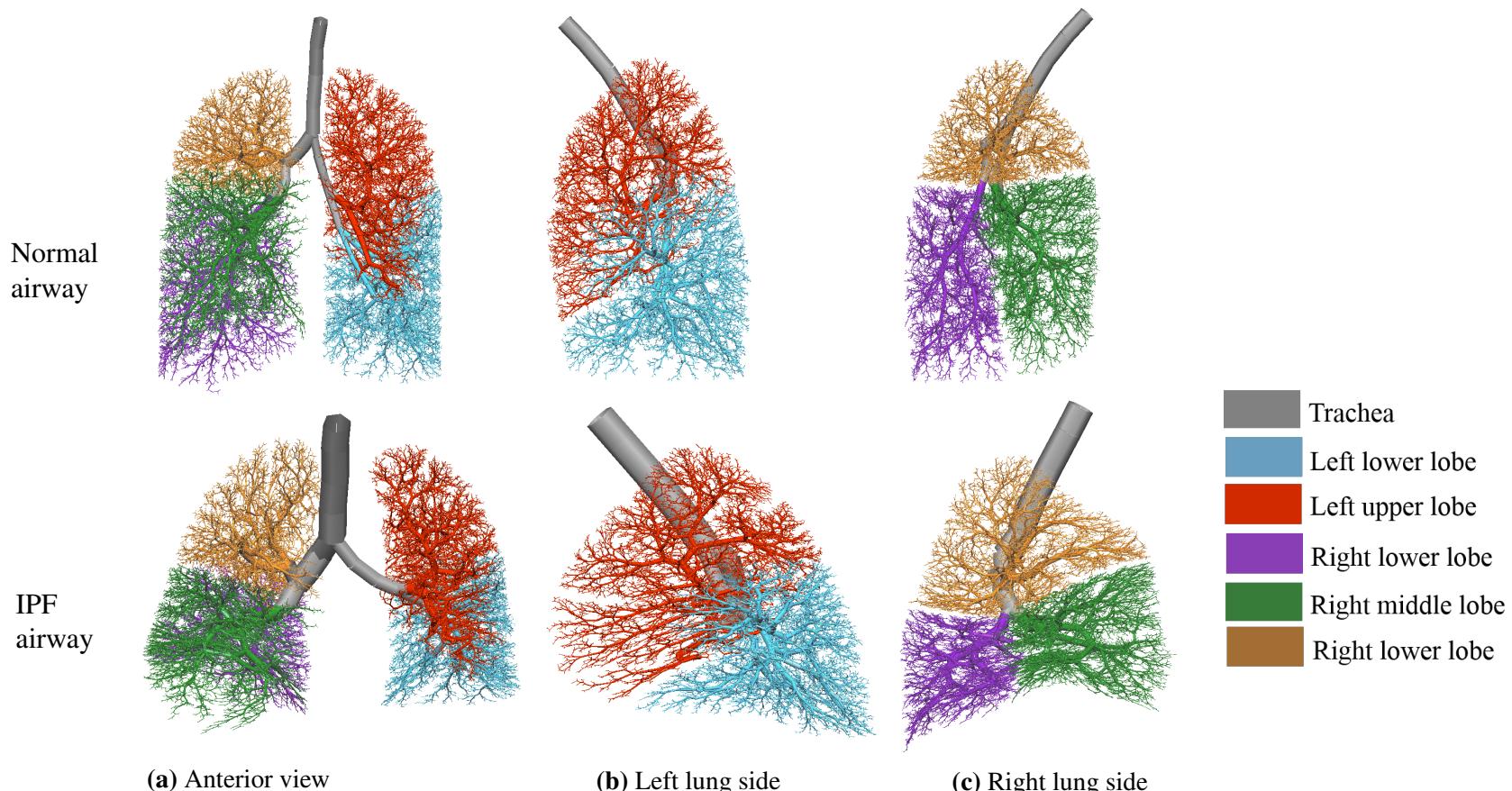


Figure 1.4: Generated normal airway tree (top row) and IPF airway tree (bottom row) for one patient diagnosed with IPF. (a) Anterior view. (b) Left lung side. (c) Right lung side.

From Figure 1.4, it can be seen that compared with old normal airway tree, IPF airway tree has a larger trachea radius (which is associated with the dilation of conducting airway in IPF lung), a relatively smaller lower lobe and a larger anteroposterior diameter. These features are consistent with the SSM based analysis result of lung lobe shape of IPF in Chapter 4, which means our method of generating old normal and IPF airway tree is reasonable and acceptable.

Vasculature tree

The centrelines of large vessel tree (the first two generations) were manually recognized from HRCT images, represented as 1-D finite element mesh. In this thesis, the pulmonary arterial and venous trees of other generations were assumed to be approximate replicas of the airway tree. Using the airway tree to construct vessel geometry is a reasonable assumption at this level, as the pulmonary arteries generate closely surrounding the airways trees, the airways and blood vessels have similar lengths and orientations, airway and vasculature bifurcate in union from larger branch to bronchiole level, and the veins divide at the midpoint between adjacent airway bifurcations (Weibel, 1984; Hsia et al., 2016). The manual branch of the main vessel plus the finite element of airway tree provided a full pulmonary blood vessel geometry of IPF patient. The vasculature structure of old normal was obtained using the same mapping procedure used for airway which has been described previously. Based on the vasculature model developed by Clark et al (Clark et al., 2010, 2011), intra-acinar arterioles and venules (microcirculatory system) were assumed to be connected at each generation through a "ladder-like" pattern that a capillary bed covers the alveoli at the acinar circulatory unit.

The unstrained (zero transmural pressure (P_{tm}))) radius of main pulmonary artery and vein were assigned based on the patient-specific trachea radius and the data from

morphometric studies (Horsfield, 1978; Horsfield and Gordon, 1981; Huang et al., 1996). The radius of all the other arteries and veins down to the distal level were calculated based on a defined rate of increase in diameter with vessel order, Strahler diameter ratio (R_dS). The value of R_dS for arterial tree and venous tree were specified according to the radius of main artery and vein, and the consistency compared with the values from raw human data (Horsfield, 1978; Horsfield and Gordon, 1981; Huang et al., 1996). The vessel radius for IPF and old normal lung were calculated respectively, and the generated IPF and old normal vessel trees are shown in Figure 1.5.

Table 1.4 parameters used for generating airway tree. Table 1.5 lists the parameters for generating vessel trees.

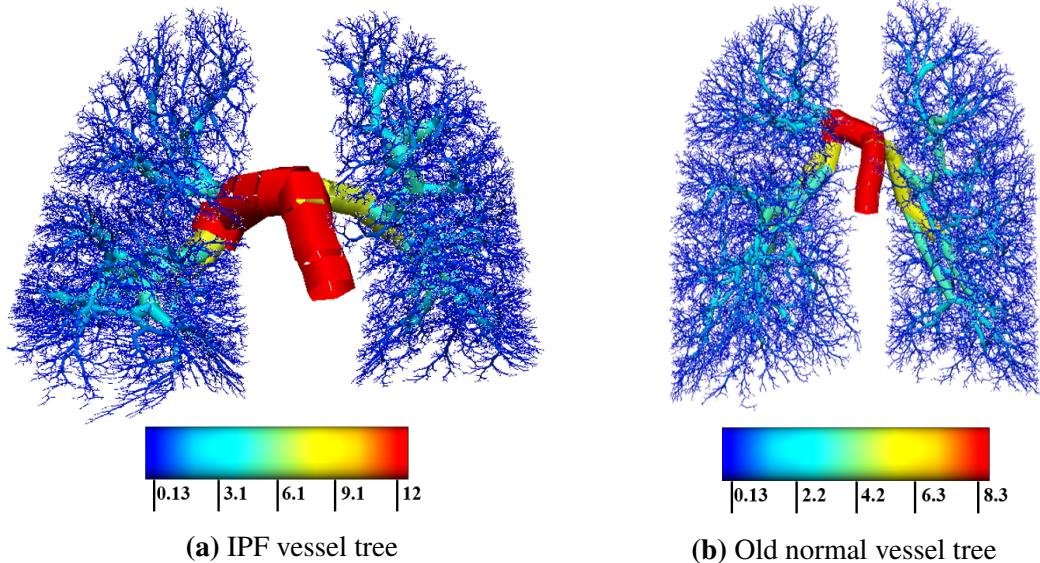


Figure 1.5: Generated geometry of vessel tree. (a) IPF vessel tree. (b) Old normal vessel tree. The radius of branches were visualized with different colors, and the colorbar shows the range of radius.

Table 1.4: Parameters of old normal and IPF airway tree

Sub. No.	Trachea radius (mm)		Horsfield diameter ratios(R_dH)		Terminal radius (mm)		Conducting airway volume (ml)	
	Normal	IPF	Normal	IPF	Normal	IPF	Normal	IPF
IPF203	5.000	7.690	1.121	1.145	0.200	0.174	55.024	66.779
IPF405	6.500	9.471	1.143	1.170	0.200	1.598	92.001	109.683
IPF511	6.000	8.806	1.139	1.161	0.200	0.182	76.141	99.800
IPF501	6.000	9.821	1.139	1.166	0.200	0.184	75.530	123.871
IPF703	9.100	11.564	1.158	1.171	0.2	0.191	142.066	187.954
IPF801	6.500	9.083	1.137	1.160	0.200	0.173	77.966	83.434
IPF924	5.000	5.705	1.127	1.138	0.200	0.179	58.601	51.496

IPF511 and IPF501 are two time points from one patient.

Table 1.5: Parameters of old normal and IPF vessel tree

Sub. No.	Main artery radius (mm)		Artery R_dS		Main vein radius (mm)		Vein R_dS	
	Normal	IPF	Normal	IPF	Normal	IPF	Normal	IPF
IPF203	6.41	9.85	1.43	1.49	7.34	12.42	1.45	1.52
IPF405	8.33	12.13	1.52	1.58	11.18	17.89	1.57	1.64
IPF511	7.69	11.28	1.45	1.51	9.17	14.66	1.48	1.54
IPF501	7.69	12.58	1.45	1.52	9.17	16.75	1.48	1.56
IPF703	11.66	14.81	1.57	1.61	17.02	22.96	1.63	1.68
IPF801	8.33	11.64	1.52	1.57	11.18	16.98	1.57	1.63
IPF924	6.41	7.31	1.43	1.45	7.34	8.62	1.45	1.47

IPF511 and IPF501 are two time points from one patient.

1.2.4 Construction of computational models

In this thesis, the computational modeling of lung function integrates previously published models of ventilation (Swan et al., 2012), perfusion (Clark et al., 2010, 2011) and gas exchange (Swan and Tawhai, 2010) to simulate \dot{V} , \dot{Q} distribution and oxygen and carbon dioxide exchange during tidal breathing in the upright posture. The patient-specific geometry of airways and vessels were used as input for these models. A brief introduction of the model components is summarized below, details can be found in the reference papers.

Ventilation model

The ventilation model developed by Swan et al. (2012) was used to predict the time-averaged topological distribution of inhaled air in the upright human lung, governed by local tissue deformation, elastic recoil pressure, airway resistance and acinar compliance. Approximate 32000 acinar units were generated subtending each terminal bronchiole, and worked as an individual compliant compartment. The acinar volume and compliance were initialized at FRC state using the tissue mechanics model developed by Tawhai et al. (2009). The anatomical geometry of airways were embedded in the model, and its relationship to air flow resistance was included in the model construction. The movement of air into each acinar unit was determined by expansion of the alveolar tissue and airway resistance through a temporally changing pleural pressure.

In this model, the flow through conducting airways was assumed to be Poiseuille flow, which was fully developed and laminar with a correction factor to account for additional energy losses occurred according to the work of Pedley et al. (1970). Additional energy losses caused by flow disturbances were created at the airway bifurcations and

involved in the calculation of pressure drop across the junction. A correction term, Z_{Pe} , was used to define the ratio of actual energy dissipation to Poiseuille flow dissipation, then the ratio of actual airway resistance (R_{aw}) to its Poiseuille flow equivalent (R_P) can be calculated by (ignoring kinetic energy changes):

$$Z_{Pe} = \frac{R_{aw}}{R_P} = \frac{K_{Pe}}{4\sqrt{2}} \left(R_e \times \frac{2r}{l} \right)^{0.5}, \quad (1.7)$$

where R_e is the Reynolds number, r and l are the radius and length of the airway, respectively. $R_e = \frac{2Q\rho}{\pi r \mu}$, where ρ and μ are the density ($1.51 \times 10^{-6} g.mm^{-3}$) and viscosity ($1.92 \times 10^{-5} P_a.s$) of air, respectively. K_{Pe} is a constant, set to 1.85. Then, the resistance of each airway branch was calculated as the Poiseuille resistance (R_{aw}) multiplied by the term Z_{Pe} , and the Poiseuille flow through conducting airway can be acquired by the following equation:

$$P_{aw_2} - P_{aw_1} = R_{aw} R_P = Z_{Pe} R_P Q = Z_{Pe} \frac{8l\mu}{\pi r^4} Q, \quad (1.8)$$

where P_{aw_1} , P_{aw_2} are the air pressures at the start and end of airway branch, Q is the air flow through the airway. The air flow into the acinar unit (modeled as a compliant unit subtending terminal bronchiole) was derived by an equation of motion that relates airway resistance, air flow, tissue compliance and the rate of change of internal and external pressures:

$$P_{aw} = \frac{V_A}{C_A} + R_{aw} Q + I \frac{dQ}{dt} - P_l, \quad (1.9)$$

where P_{aw} , R_{aw} and Q are the pressure, Poiseuille resistance and flow in the terminal bronchiole, V_A and C_A are the volume and compliance of the acinar unit, I is inertance

of the unit, and P_l is the local pleural pressure (varied sinusoidally) working to expand the unit and drive air flow through conducting airway to terminal acinus.

Here, we assumed that the rate of change of airflow Q is small enough, therefore the item $I \frac{dQ}{dt}$ in Equation 1.9 can be neglected. A suitable small time interval, $\Delta t = t_n - t_{n-1}$, was defined, and the flow at the end of the time period $Q_n = Q(t_n)$ (Q respect to t) can be calculated as:

$$Q_n = C_A(\nu - \beta) + Q_{n-1} - C_A(\nu - \beta)\exp\left(\frac{-\Delta t}{R_{aw}C_A}\right), \quad (1.10)$$

where $Q_{n-1} = Q(t_{n-1})$ is the flow at the end of the previous time period. $\nu = dP_{aw}/DT$, $\beta = dP_l/dt$ are the change of bronchiole pressure and pleural pressure with respect t . This equation is derived from Equation 1.9, the detailed description can be found in Swan et al. (2012).

Perfusion model

The multi-scale pulmonary perfusion model developed by Clark et al. (2011) was used to simulate a time-averaged distribution of blood flow, capillary blood volume and average red blood cell (RBC) transit time for each acinar unit. The full vasculature structure (including arteries, veins, intra-acinar arterioles and venules, capillaries) generated in Section 1.2.3 was embedded in this model. Distension of blood vessels and hydrostatic effects were also involved in the model, with arterial and venous diameter and the thickness of the capillary sheet assumed proportional to the transmural pressure (P_{tm}). The intra-acinar (extra-capillary) blood flow was modeled in a symmetric ladder structure which relates the vessel diameter, length and the thickness of capillary sheet.

Similarly to air flow, the flow through pulmonary arteries and veins was predicted

using a Poiseuille equation with a term of gravitational effects acting on the vessels, and can be described by:

$$\Delta P = P_{b2} - P_{b1} = \frac{128\mu_b L \dot{Q}}{\pi D^4} + \rho_b L g \cos\theta, \quad (1.11)$$

where P_{b1} and P_{b2} are the blood pressures at the beginning and end of the vessel element, μ_b and ρ_b are the viscosity and density of the blood in the vessel, L and D are the vessel length and radius, \dot{Q} is the volumetric flow rate in the vessel, g is the gravitational acceleration ($9.81 m/s^2$), and θ is the angle between the vessel and the direction of gravity.

The term $\rho_b L g \cos\theta$ in Equation 1.11 represents the gravity effects acting on the vessels. In this model, an arteriole and an venule were joined at each generation by a capillary bed, forming a "ladder-like" structure, to construct the intra-acinar circulation. Therefore, the item $\rho_b L g \cos\theta$ can be negligible if the length of acinar arterioles and venules was assumed to be small enough:

$$\Delta P = \frac{128\mu_b L \dot{Q}}{\pi D^4}, \quad (1.12)$$

The deformation of vessels in the axial and radial directions due to the surrounding lung parenchyma and the tethering force of lung tissues was included in the model through calculating the axial stretch from tissue deformation. The strained diameter D in Equation 1.12 was assumed a linear relationship with the transmural pressure P_{tm} as:

$$\frac{D}{D_0} = \alpha P_{tm} + 1, \quad (1.13)$$

where D_0 is the unstrained vessel diameter, α is the vessel compliance constant. The

tethering pressure acting on the blood vessel in the radial direction was assumed to be equal and opposite to the local tissue elastic recoil pressure (P_e), therefore $P_{tm} \approx P_b - P_e$, where P_b is the average blood pressure across the vessel. Then, the blood flow through a capillary sheet (\dot{Q}) was modelled using the classic sheet flow theory developed by Fung and Sabin (1969):

$$\dot{Q} = \frac{SA}{\mu_c f l_C^2} \int H^3 dP_{tm}, \quad (1.14)$$

where A is the alveolar surface area, S is the proportion of alveolar surface area (A) composed of capillaries, μ_c is the apparent viscosity of blood in the capillaries, f is the numerical friction factor, l_C is the average path length through the capillary network between arteriole and venule. H is the thickness of the capillary sheet which was assumed to be approximately linearly dependent on P_{tm} similar to Equation 1.13:

$$\frac{H}{H_0} = \alpha_C P_{tm} + 1, \quad (1.15)$$

where H_0 is the unstrained sheet thickness. In both Equation 1.13 and Equation 1.15, maximum P_{tm} was assumed up to $32\text{cmH}_2\text{O}(3.1\text{kPa})$. α_C is the compliance of the capillary sheet, which was assumed to reduce linearly with the increasing of transpulmonary pressure (P_{tp}):

$$\alpha_C(P_{tp}) = a + bP_{tp}, \quad (1.16)$$

where a and b are constants, P_{tp} is assumed to be equal and opposite to P_e . The values of a and b were firstly measured for dogs by Glazier et al. (1969), then scaled for human as $a = 0.165\mu\text{m}/\text{cmH}_2\text{O}$, $b = -2.58\mu\text{m}/(\text{cmH}_2\text{O})^2$.

Gas exchange model

The ventilation and perfusion distribution predicted by the ventilation and perfusion model described in the previous section were used as inputs in the whole lung model of gas transport and exchange. The ventilation model provided the volume change in each acinar unit during inspiration and expiration. The perfusion model determined the acinar capillary blood volume and average RBC transit time. The modeling was based on the assumption that the acinus was well-mixed whin in a gas exchange unit, and the ventilation and perfusion distribution were time-invariant. Then the rate of O_2 removal from the alveolar air and the rate of CO_2 transferred to the well-mixed alveolar compartment of acinus were determined. The steady-state gas transfer model developed by Kapitan and Happleman (1986); Swan (2010) was used to predict the partial pressure of oxygen in alveolar (P_AO_2) and in arterial blood (P_aO_2).

An 1-D advection-diffusion equation was applied to model the gas transport through the conducting airway. The secondary flows in radial and circumferential directions were neglected here, thus the gas transport was solved in the axial direction along the airway branch at each time step:

$$\frac{\partial c}{\partial t} + u_x \frac{\partial c}{\partial x} = D \frac{\partial^2 c}{\partial x^2}, \quad (1.17)$$

where c is the gas concentration (O_2 or CO_2), x is the axial coordinate along the airway, $0 \leq x \leq L$ (L is the length of airway), u_x is the axial velocity predicted by the ventilation model through conducting airway, D is the binary gas diffusion coefficient of gas. The advection-diffusion equation 1.17 was solved for each 1-D finite element of airway tree.

The flow at the trachea ($Q(0,t)$) was set as a constant square waveform during a

respiratory cycle:

$$Q(0, t) = \begin{cases} 0.16 L s^{-1} & \text{during inspiration} \\ -0.16 L s^{-1} & \text{during expiration} \end{cases} \quad (1.18)$$

During inspiration, a zero flux was applied to the end of each terminal bronchiole as boundary condition. During expiration, the terminal bronchiole concentration ($c(L, t)$) was set to be equal to the mixed acinar concentration (c_A):

$$\begin{aligned} \frac{dc(L, t)}{dx} &= 0 && \text{during inspiration,} \\ c(L, t) &= c_A && \text{during expiration,} \end{aligned} \quad (1.19)$$

where $x = 0$ and $x = L$ represent the location of trachea and terminal bronchioles. The volume change of acinar unit during each time step (dV_A) during respiratory cycle was acquired by:

$$dV_A = Q(0, t) \dot{V}_A \Delta t, \quad (1.20)$$

where \dot{V}_A is the proportional ventilation received for that acinar unit to the total lung ventilation, Δt is the time step. Therefore, the updated acinar volume at the n^{th} time step can be represented as: $V_{A(n)} = V_{A(n-1)} + dV_A$.

Acinar concentration ($c_{A(n)}$) was updated with the inspired air into the acinar unit during inspiration, and with the gas exchange flux during expiration:

$$C_{A(n)} = \begin{cases} \frac{(c_{A(n-1)}V_{A(n-1)} + n_{insp}) + n_{exch}}{V_{A(n)}} & \text{during inspiration} \\ \frac{(c_{A(n-1)}V_{A(n-1)} + n_{exch})}{V_{A(n)}} & \text{during expiration} \end{cases} \quad (1.21)$$

where $n_{insp} = dV_{Ac}(L, t)$ is the mass of inspired O_2 or CO_2 . $n_{exch} = q_A \Delta t$ is the mass of O_2 or CO_2 exchanged with the capillary blood, where q_A is the gas exchange flux for O_2 or CO_2 .

The exchange of O_2 in an acinar unit was predicted at each time step using the model developed by Ben-Tal (2006); Swan and Tawhai (2010); Swan (2010):

$$\frac{dP_aO_2}{dt} = \frac{T_{tO_2}}{\sigma_{O_2} V_b} \left(1 + \frac{4[Hb]_b}{\sigma_{O_2}} \frac{dS_{O_2}}{dP_aO_2}\right)^{-1} \times (P_AO_2 - P_aO_2), \quad (1.22)$$

where P_aO_2 and P_AO_2 are oxygen partial pressure in alveolar and in arterial blood, respectively. σ_{O_2} is the O_2 diffusion coefficient, V_b is the capillary blood volume, $[Hb]_b$ is the concentration of haemoglobin in blood, S_{O_2} is the slope of the oxyhaemoglobin dissociation curve. T_{tO_2} is the oxygen transfer factor which represents the ability of transferring O_2 from lungs into capillary blood by:

$$T_{tO_2} = \left(\left(\frac{\eta\phi S_A}{\tau_h}\right)^{-1} + (V_b\theta_{O_2})^{-1}\right)^{-1}, \quad (1.23)$$

where S_A is the alveolar air surface area in an acinus available for exchange and is assumed to be equal for all acinus. τ_h is the total membrane thickness, η and ϕ are constants. θ_{O_2} is the rate of O_2 uptake by the whole blood which is determined by:

$$\theta_{O_2} = \dot{k}_c \sigma_{O_2} (1 - S_{O_2}) k [Hb]_b, \quad (1.24)$$

where \dot{k}_c is the forward reaction velocity for O_2 binding to haemoglobin, k is the capacity of O_2 carrying haemoglobin, S_{O_2} is the oxyhaemoglobin saturation. The details of the calculation of S_{O_2} can be found in Swan and Tawhai (2010); Swan (2010).

The exchange of CO_2 was predicted using a simplified model by describing the bicarbonate (HCO_3^-) hydration-dehydration reaction to produce CO_2 and H_2O . The change rate of arterial partial pressure of CO_2 (P_aCO_2) was determined by the amount of CO_2 for exchanging between capillary blood and alveolar air. The CO_2 formed from hydration-dehydration reaction:

$$\frac{dP_aCO_2}{dt} = \frac{T_{tCO_2}}{\sigma_{CO_2} V_b} (P_aCO_2 - P_aCO_2) - \delta k_u P_b CO_2 + \delta \frac{k_v}{\sigma_{CO_2} K} [H]^+ [HCO_3^-], \quad (1.25)$$

where P_aCO_2 is the alveolar partial pressure of CO_2 , k_u is CO_2 hydration constant, k_v is constant of HCO_3^- dehydration velocity constant, and δ is a fitted constant of CO_2 hydration reaction acceleration rate. The CO_2 solubility coefficient σ_{CO_2} describes the capacity of carrying CO_2 , $[HCO_3^-]$ and $[H]^+$ are the bicarbonate and hydrogen ion concentrations respectively. T_{tCO_2} is CO_2 transfer factor which measures the capability to transfer CO_2 from capillary blood to the lungs:

$$T_{tCO_2} = ((20 \times T_{MO_2})^{-1} + (\frac{\ln(2)\sigma_{CO_2}}{t_{\frac{1}{2}RBC}(1/V_p + 1/V_r)})^{-1}), \quad (1.26)$$

where $T_{MO_2} = (\frac{\mu\phi S_A}{\tau_h})^{-1}$ is the membrane transfer factor for O_2 which equals to the first term of Equation 1.23. V_p and V_r are the volumes occupied by RBC and plasma respectively, which determines the RBC transfer factor component. $t_{\frac{1}{2}RBC}$ is the half time of equilibration of CO_2 across the erythrocyte membrane measured from experiment.

Some parameter values used in the ventilation, perfusion and gas exchange models are listed in Table 1.6. More details of the models are introduced in Swan and Tawhai (2010); Swan (2010); Clark et al. (2011); Swan et al. (2012).

Table 1.6: Parameter values and their source used in computational models

Parameter	Description	Value	Source
K_{Pe}	Pedley correction factor	1.85	Pedley et al. (1970)
p	Air density	$1.15 \times 10^{-6} g.mm^3$	Ideal gas law (37C)
μ	Air viscosity	1.92×10^{-6}	Sutherland's formula (37C)
α	Vessel compliance	$1.49 \times 10^{-4} Pa^{-1}$	Krenz and Dawson (2003)
μ_b	Blood viscosity	$3.36 \times 10^{-3} Pa/s$	Pries et al. (1996)
ρ_b	Blood density	$1.05 \times 10^{-6} kg/mm^3$	Pries et al. (1996)
μ_c	Apparent viscosity of blood in capillary bed	$1.92 \times 10^{-3} Pa/s$	Fung (2013)
f	Numerical friction factor	21.6	Fung (2013)
α_c	Compliance of capillary sheet	$1.30 \times 10^{-9} Pa/s$	Fung and Sabin (1969)
l_c	Pathlength from arteriole to venule	$11.86 \times 10^{-6} m$	Clark et al. (2010)
$[Hb]_b$	Haemoglobin concentration in blood	2.33 mM	Hall (2015)
S_A	Alveolar surface area of the lung	$130 \times 10^4 cm^2$	Weibel et al. (2005)
η	Krogh's permeation coefficient for O_2	$5.5 \times 10^{-10} cm^2 s^{-1} mmHg^{-1}$	Weibel et al. (1993)
ϕ	Correction factor for surface folds	0.8	Weibel et al. (1993)
τ_h	Harmonic mean thickness of the air-blood barrier	$1.11 \times 10^{-4} cm$	Weibel et al. (1993)
\acute{k}_c	Forward reaction velocity $O_2 - Hb$ binding	$4.4 \times 10^2 mM^{-1}s^{-1}$	Weibel (1997)
σ_{O_2}	O_2 solubility coefficient	$1.4 \times 10^{-3} mM mmHg^{-1}$	Keener and Sneyd (1998)
σ_{CO_2}	CO_2 solubility coefficient	$3.5 \times 10^{-2} mM mmHg^{-1}$	Keener and Sneyd (1998)
$t_{\frac{1}{2}RBC}$	Half-time of equilibration for CO_2 diffusion	0.0001 s	Hill et al. (1973)
k_u	CO_2 hydration velocity constant	$0.12 s^{-1}$	Hill et al. (1973)
k_v	HCO_3^- dehydration velocity constant	$89 s^{-1}$	Hill et al. (1973)
δ	CO_2 hydration reaction acceleration rate	$10^{1.9}$	Ben-Tal (2006)

1.2.5 Model solutions

Ventilation, perfusion and gas exchange models were solved in normal condition (using lung and airway geometry of older normal people) and diseased condition (using lung and airway geometry of IPF patient), respectively. Individual quantified fibrosis from CALIPER data was projected to its IPF airway/vessel trees as labeled disease regions to drive the patient-specific functional modeling of IPF, with fibrosis reducing tissue compliance and narrowing vessel radius. The subject-specific tidal volume, cardiac output, oxygen consumption (VO_2) and carbon dioxide consumption (VCO_2) were estimated based on patient's individual information. Data from PFT result were used as boundary conditions to control the simulation.

Disease region labeling

The different tissue patterns classified by CALIPER were mapped to the individual airway/vessel trees of each subject. For each airway/vessel node, the corresponding tissue pattern it belonged to (surrounded by) was extracted (through finding its closest tissue pattern), so that each terminal node can be labeled as different tissue patterns with an index number. In the meantime, the percentage distribution of each tissue pattern against gravitational height (dorsoventral axis) was also kept the same as the analysis result in Chapter 4, Section ???. That means if the initial labeled number of disease nodes can't reach the dorsoventral percentage, additional disease regions would be added in until the dorsoventral distribution of disease can match the CALIPER classified data. Figure (need to be added later) shows the disease labeled airway tree of one patient diagnosed with IPF.

Deep inspiration model

Deep inspiration model was constructed based on the ventilation model introduced in Section 1.2.4 to simulate the deep inspiration from FRC to TLC. For the simulation of old normal people, the reference FRC volume from PFT result (that is the patient-specific normal volume as reference) was used as an initial volume to start inspiration, and the subject-specific muscle pressure was adjusted to drive the lung expand to the target reference TLC volume (acquired from PFT result). For the simulation of IPF patient, the inspiration started from the measured FRC volume (acquired from PFT) and the muscle pressure set up in the normal condition was used to guide the lung expansion. Here, we assumed that the inspiratory muscle pressure is normal in IPF patient, as some research indicates that the inspiratory muscle force remains almost the same in IPF lungs compared with normal (De Troyer and Yernault, 1980). The simulation for IPF patient was divided into two separate stages:

1. The compliance of labeled fibrosis (sum of honeycomb, reticular and ground-glass) acinar unit (connected to its labeled terminal airway node) was reduced to a very low value (less than $0.001 \text{ L/cmH}_2\text{O}$) to make sure the fibrosis region was stiff enough. Then, inspiration volume was ...
2. The deep inspiration volume acquired in Step 1 was used as the target volume, and the tissue compliance of each acinar unit was scaled down until the simulated inspiration volume can hit the target. The scale factor ..

Passive ventilation model

Time-averaged passive ventilation distribution to each acinus within four breath cycles was predicted using the previously described ventilation model. Acinar volumes were

initialized at FRC volume, using reference value for normal condition and measured value for disease condition. The scale factor of acinar tissue compliance set in the above Step 2 was applied to the simulation of IPF patient. Patient-specific tidal volume was estimated based on patient's weight, gender and height [ref].

Perfusion model

The perfusion model introduced in Section 1.2.4 was used to estimate the distribution of blood. The individual age, weight, height and gender were integrated to predict the cardiac output for each patient [ref], and the inlet and outlet pressure were adjusted in order to match the estimated cardiac output. The blood vessel radius in the fibrosis labeled region was narrowed down for the modeling of IPF, so that the blood flow will be constricted in the lesion area.

Gas exchange model

1.3 Discussion

SSM based shape prediction provides a way to make a comparison with the patient-specific normal lung.

There is a dilation in trachea, but a constriction in small airway.

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