***TITLE: Capturing complexity in respiratory system modelling***

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**Abstract**

Respiratory disease is a significant problem worldwide, and it is a problem with increasing prevalence. Pathology in the upper airways and lung is very difficult to diagnose and treat, as response to disease is often heterogeneous across patients. Computational models have long been used to help understand respiratory function, and these models have evolved alongside increases in the resolution of medical imaging and increased capability of functional imaging, advances in biological knowledge, mathematical techniques and computational power. The benefits of increasingly complex and realistic geometric and biophysical models of the respiratory system are that they are able to capture heterogeneity in patient response and predict emergent function across spatial scales from the delicate alveolar structures to the whole organ level. However, with increasing complexity, models become harder to solve and in some cases harder to validate, which can reduce their impact clinically. Here we review the evolution of complexity in computational models of the respiratory system, including successes in translation of models into the clinical arena. We also highlight major challenges in modelling the respiratory system, while making use of the evolving functional data that is available for model parameterisation and testing.

**Keywords:** computational modelling, respiratory system, clinical outcome prediction, mathematical modelling (medical), haemodynamics modelling

## 1. Introduction

Respiratory diseases account for about 14% of all deaths worldwide and are one of the few classes of disease whose prevalence is increasing (1). Despite the prominence of respiratory diseases, diagnostic and monitoring techniques remain relatively crude, and often are incapable of detecting pathology in the lung until a significant amount of lung tissue is damaged. For example, spirometry is a commonly used tool in the diagnosis and management of obstructive lung disease; this simple test measures the volume and flow of air into the lungs including the rate of expiration. However, spirometry has been shown to incompletely describe lung function and does not always correlate well with patient symptoms, quantitative estimates of lung tissue damage from imaging, or outcomes of disease (2, 3). The limitation in this type of measurement is that it provides an averaged assessment of lung function. Therefore, although regional pathology observed in computed tomography (CT) correlates with spirometry (4-6), the method typically cannot identify early stage disease for example due to changes in resistance of the small airways (5, 6), or multi-scale phenomena occurring at sub-organ level (for example changes at the gene, cell and tissue levels). Other techniques have and are emerging that can provide this additional information and computational modelling, in combination with medical imaging and clinical data, is one of these.

The primary function of the lungs is gas exchange. This is achieved by bringing air and blood into contact over an extremely large surface area, about 80 $m^2$, separated by only a very thin blood-gas barrier, less than 0.2 μm (7). Lung (volume) consists of more than 80% air and the remaining proportion is tissue and blood (8). Air is driven into the lung via an expansion of the chest cavity resulting in an increase in lung volume and a pressure differential driving air flow. The expansion of the cavity initiates expansion via tethering of the soft tissue network. Blood is circulated through the pulmonary circulation via the pressures induced by the heart. The structure and function of an individual's lungs is influenced by environmental factors such as pollutants as well as a unique genetic makeup that predisposes an individual to any particular lung disease. As such, when a patient presents to hospital with pulmonary disease, their condition and their response to therapy is unique. In addition to this individual heterogeneity, pathology can emerge across multiple spatial scales. This makes distinguishing between lung diseases, classifying severity and predicting disease progression in an individual difficult (9, 10).

The evolution of computational models of the respiratory system has paralleled developments in all scientific fields that feed into it, in particular imaging science, biology, physiology, mathematics and computation. Of particular note is the rapid advancement in the field of medical imaging with the first magnetic resonance imaging (MRI) and CT scans being obtained in the 1970s (11). CT images

in conjunction with computer software are now able to provide detailed information on lung structure, including lung volume and morphometry of the large airways and blood vessels. Adaptations of MR methods complement, as well as contribute to, this structural information by providing functional information, for example using hyperpolarised gases (12) and techniques such as arterial spin labelling and oxygen-enhanced proton MRI to measure ventilation and perfusion distributions (13). In addition, micro-CT and synchrotron imaging have been used to obtain realistic images of the lung microstructure (14, 15). This means that we can now classify organ-level structure alongside tissue-level characterisation, and assess how the lung structure and function varies regionally with disease in individuals (16).

One approach to providing personalised respiratory medicine is to use statistical and mathematical techniques to assess correlations between an individual's responses to a pathology or treatment strategy, or to fit models to patient data. These approaches have proven potential in developing therapies for chronic obstructive pulmonary disease (COPD) patients (17), and for optimising ventilator settings in acute respiratory distress syndrome (ARDS) or acute lung injury (ALI) (18). However, they do not always provide new physiological understanding that can be used to guide treatment strategies. The second type of approach is a biophysically-based computational modelling approach that aims to provide an increased understanding of the complex multi-scale biology occurring within an organism in health and disease. This approach utilises the underlying physics of a system to predict behaviour. Models have typically focussed on a single aspect of lung function, and the most developed respiratory models relate to tissue mechanics (19-23), air flow (24-26), blood flow (27-31) and gas exchange (32-34). Each of these functions of the lung interacts to determine overall lung function, illustrated in Figure 1. Recent models have begun to couple functions with tissue mechanics models providing local elastic recoil pressure to parameterise perfusion and ventilation (24, 27), or poroelastic models of the lung parenchyma coupled to branching airway structures (35).

<INSERT FIGURE 1 HERE>

In this review we will describe the evolution of computational models, focussing on biophysically-based models, specifically in terms of the development of more realistic geometric models which exploit advancements in medical imaging, and models that aim to provide new clinical tools. We then discuss the major challenges standing between computational models of the lung and their clinical usability.

## 2. Functional models of the respiratory system

The earliest and simplest models for the lungs consist of a single compartment representing the whole lung, including the conducting and respiratory airways, and the blood circulation. They assume a constant flow of alveolar gas and blood, and no change in alveolar or blood volume, so the system is essentially static. This model is widely used in text books to describe lung physiology, but neglects critical spatial and temporal variation in lung function, which in many cases are drivers for disease response. In most cases, this simple description of the lung is considered *too simple* to adequately describe physiology (see (36) for a critical review of this approach) and so lung modellers have increasingly focussed on adding more physiological and geometric complexity. In this review, we do not aim to describe all models of respiratory function that exist, rather we will focus on examples which illustrate the evolution of modelling in the field, and which have moved or attempted to move towards increasing clinical applicability.

### 3.1 Models of air flow

Many models of the pulmonary airways rely on a 'balloon-on-a-straw" analogy (or more recently, "many-balloons-on-many-straws"). In its simplest form, the conducting airways of the lung are represented by a single tube (the straw) subtended by an expandable compartment representing the respiratory airways and parenchymal tissue (the balloon). The volume of the balloon, and pressure within it, changes over a breath, driven by a flow or pressure change at the mouth. The manner in which the elasticity of the respiratory airways is described varies between models, from a simple linear relationship between pressure and volume, to increasingly realistic representations of the non-linear elasticity of lung tissue (Figure 2). Single compartment "balloon-on-a-straw" models are simple to conceptualise and simple to solve, so they are often used in clinical studies. For example, a single compartment model of lung with linear elasticity has shown potential in providing patient-specific optimisation of ventilator settings (selection of positive end expiratory pressure, PEEP) through time, so that patients with lung injury or acute respiratory distress syndrome can be better managed in intensive care (18).

Ultimately, as the lung is not a single compartment, but a branching network of airways and blood vessels, embedded in an elastic tissue, single compartment models cannot always provide adequate descriptions of lung function. Often air and gas distribution in the lung is heterogeneous, and in pathological lungs respiratory airways can be regionally under- or over-expanded, with unaffected regions of the lung adjusting to account for this. As single-compartment models were shown not to predict function in certain pathologies, more and more elastic compartments were added to computational models to more adequately represent pathology (Figure 2). This addition of complexity

allowed models to predict airway recruitment and de-recruitment under PEEP (37), which has been applied clinically (37, 38). However, many multiple compartment models do not account for the conducting airway structure, which high resolution imaging studies have suggested are an important contributor to air flow (39).

Increases in computational power have allowed asymmetric models representing the entire conducting airway tree to be generated. These include fractal representations of the lung, that have been used to predict ventilation-perfusion matching and 'patchiness' in ventilation with bronchoconstriction in asthma (40). Asymmetrically branching models of the conducting airways have evolved to be anatomically based with the geometry of several generations of airways defined explicitly from CT imaging and peripheral conducting airways generated algorithmically to match morphometric data (41-43), as shown in Figure 3. These models are in some cases freely available in open source software so that patient-specific conducting airway models can be produced and models for ventilation and lung impedance solved within them by interested users (42, 43). They typically represent airway segments by single elements (or vectors), which are assigned a radius representative of that airway. These conducting airway models are typically subtended by elastic respiratory airway units (~32,000 units, which each represent an acinus) to simulate ventilation (24). This type of model essentially fits with the "balloon-on-a straw" analogy, but incorporates biological realism both in structure and in function, by allowing for compliant conducting airways and non-linearly compliant respiratory airways. As this class of models is more geometrically accurate, and more physiologically accurate than the classical "balloon-on-a-straw" models, they are able to capture the subject-based nature of ventilation. This means, for example, that they can be used to relate the spatial location of ventilation defects seen in imaging to local changes in airway resistance (44). Anatomically-based models have also been loosely coupled to models of lung tissue mechanics meaning that local lung tissue deformation and elastic recoil due to gravitational influences are incorporated (24), allowing predictions of the relative influence of gravity and airway structure to ventilation distribution. The same concept has been employed to simulate an important clinical metric of lung function (the forced expiratory volume in one second, FEV1) (45), which allows estimation of normal variability in response to interventions, and could potentially aid clinicians to better interpret pulmonary function testing, which has been shown across several pathologies to be an indicator of structural lung damage only when this damage is severe.

<INSERT FIGURE 3 HERE>

The major advantage of anatomically based models is that they predict function in the whole lung and capture the inter- and intra-subject variability that is likely one of the key contributors to differences in clinical outcomes in patients with lung disease. However, despite a move to allow model generation in freely available software, these models are time consuming to generate and solve, and require anatomical and physiological knowledge to properly generate and interpret. This time expense means that in studies predicting subject-based function in anatomically based models, numbers of subjects for which the anatomy of the airways is described are low (often a single subject) (24, 44). As a recent study by Hedges et al. (46) showed, the applicability of a single subject to represent a cohort is limited, and accuracy of predictions depends on the pathology or function being assessed. Significant model testing and analysis is still needed to determine how representative these models are of a cohort. In some cases, anatomically based models are also considered *too complex*. For example, would a 40-50 compartment "balloon-on a-straw" model be sufficient to answer the physiological or clinical question? Conversely, they are often considered *not complex enough,* at least in capturing the dynamics of ventilation in the upper airways (where air flow is neither laminar nor fully developed), at airway bifurcations, and in the respiratory airways (which are not "balloons" but a complex network of alveoli with irregular structure).

More detailed simulations of air flow are beneficial for predicting drug deposition and biomarkers for lung health. In the largest and smallest airways, the most appropriate tool to model air flow dynamics is often computational fluid dynamics (CFD), and typical CFD geometries are shown in the middle panel of Figure 3. In the upper airways there have been extensive CFD studies of air flow and particle transport (representing drug delivery) in patient specific models of the upper airways derived mostly from CT. Normally five to six generations of conducting airways are incorporated into models to simulate quasi-steady or full breathing cycle flow distributions. CFD mainly suffers from difficulty in defining boundary conditions at the outlets represented in the model. Many registration-based and physics-based approaches (26, 47, 48) have been adopted to obtain realistic or patient-specific boundary conditions in these simulations. In one impedance-based approach, subject-based spirometry was used to obtain outflow pressure. Using regional ventilation from image registration and a 3D airway tree growing algorithm, a 1D-3D coupling was proposed to obtain subject-based boundary conditions at airway outlets. This algorithm was extended recently (26) to use imaging datasets acquired at three inflation pressures. At the sub millimetre scale of respiratory airways including respiratory bronchioles and acinus, flows are generally treated as independent of the conducting airways. Flow is laminar in these airways, though complexities may arise due to geometry and wall motion. Recent CFD studies have used imaging-based lung acinus geometry to

study micro and nano-particle transport (49). These studies have greatly improved our understanding of fate of inhaled drug particles in the acinus.

CFD studies have proved to have clinical application in drug administration for drug delivery in COPD patients, assessing disease progression and asthma treatment. Hence CFD combined with medical imaging serves as a potential biomarker for lung disease (50-52). CFD has also been a useful tool with potential clinical application for predicting aerosol bolus dispersion (53-55). Aerosol dispersion (which is different from gas dispersion) has shown promise in lung structure characterisation for healthy and diseased lungs. A cloud of inhaled aerosol bolus disperses through the lung and when exhaled, the bolus recombines and the resulting dispersion can be correlated with spatial locations within the airways. It provides a footprint for lung airway structure and has the potential to be a powerful non-invasive diagnostic tool (56) particularly for obstructive lung diseases.

### 3.2 Models of blood flow

An equivalent evolution of structural and functional models has followed in the pulmonary circulation, with a large range of structural and functional representations applied to probe pulmonary blood flow. Like air flow models, simple models of the whole pulmonary circulation represented as a single unit (57, 58), or as a symmetric or fractal (self-similar) arterial and/or venous tree (59) have been employed to predict blood flow distributions and the response of the pulmonary vasculature to hypoxia.

Patient-based geometric representations of the vasculature, have also emerged following similar geometric models of the airways (28, 29, 60, 61). Increases in geometric detail require decreased levels of complexity in the flow equations for predictions of perfusion to the entire pulmonary vasculature. Thus, CFD studies are generally restricted to the largest blood vessels but can represent turbulent, non-Newtonian and three-dimensional flow (28, 29, 62-65). Conversely 1D spatially distributed models of the pulmonary vasculature use basic flow equations, representing fluid flow in each vessel as one-dimensional, steady-state, laminar, and Newtonian (Poiseuille flow) (27, 66-68). 1D pulsatile flow has been predicted in models that represent the entire arterial tree (69), and in each extra-acinar vessel of the lung (30), but the additional complexity of pulsatile flow means that simplifying assumptions regarding the acinar vessels and/or the influence of gravity on perfusion need to be made. The type of model required depends on the underlying question or problem being investigated.

<INSERT FIGURE 4 HERE>

1D models of the pulmonary circulation are able to represent the vasculature of the entire pulmonary circulation including arteries, capillaries and veins (27, 30). This means that boundary conditions can be applied at the exit and entry to the heart; here values of pressure and/or flow are reasonably well defined. 1D spatially distributed models have also been coupled to models of micro-vessel structure that incorporate known features of capillary recruitment and collapse in response to perfusion pressure and gravitational influences (27). Clark et al. (70) predicted blood flow and gas exchange in 12 patient-based models of pulmonary embolism (PE). While this model used 1D flow equations to predict steady-state blood flow (i.e. a relatively simple representation), novel insights into the impact of clot distribution on functional outcomes could be made due to a detailed structural model, and incorporation of gravitational influence on lung function. Current clinical scores for PE severity assess only the structural volume of tissue occluded but do not include the impact of heterogeneous regional blood flow. The model predicted that large central clots have a greater impact on lung function than smaller distributed clots occluding the same amount of tissue. An example simulation outcome comparing two patients with similar tissue occlusion but significantly different functional outcomes is shown in Figure 4. This study proposed that a modified index which incorporates functional information as well as tissue occlusion better predicts the impact of PE than current scoring systems.

<INSERT FIGURE 5 HERE>

3D CFD simulation studies of blood flow have predominantly focussed on the estimation of wall shear stress (WSS) and how it changes in disease, particularly in pulmonary hypertension (PH). 3D flow simulation describes flow properties throughout the cross-section of each vessel so intuitively will enable a more accurate prediction of WSS than 1D flow models. Like in CFD models of airways, it is problematic to set outflow boundary conditions and approaches have been used to define these including application of pressure or flow boundary conditions, zero traction, constant resistance at all outlets or the use of a resistance structured tree outflow boundary conditions (29). The resistance structured tree outflow boundary condition calculates the distal vasculature resistance as a function of the outflow vessel radius, and is considered a realistic model that can allow, for example, investigation of the change in peripheral resistance on flow-derived predictions. Figure 5 shows a typical methodology used to create the geometric meshes for 3D CFD simulations and illustrates the typical level to which pulmonary vasculature is simulated in CFD. Patient specific CFD models have been used to predict flow-induced stress acting on the vascular endothelium in pulmonary hypertension (PH) (29). They showed that WSS, and other CFD simulation metrics, correlated with

clinical measures indicative of disease and right ventricular afterload, showing promise for this type of model as an indicator of disease progression in PH.

### 3.3 Models of tissue mechanics

When we breathe, the lung undergoes large deformations inside the pleural cavity and so there is significant potential for spatial and temporal changes in lung tissue mechanical behaviours. Figure 6 illustrates regional differences in lung mechanical behaviour which emerge due to the deformation of lung tissue under gravity and heterogeneities in lung structure. Lung tissue behaves like a 'slinky' under gravity (71), Tissue elastic recoil is higher and lung tissue density lower in non-dependent compared to dependent lung regions. There may also be locally regions of higher tissue density for example in the hilum region where large blood vessels enter the lungs. The gravitational influence on lung tissue is a key contributor for known postural differences in lung function, including the potential benefits of prone posture for gas exchange function in patients with acute lung injury or acute respiratory distress disorder (19, 72, 73). On average elastic recoil pressure varies from ~5 $cmH_2O$ at functional residual capacity (FRC) to ~30 $cmH_2O$ at total lung capacity (TLC), and at FRC there is approximately a 10 $cmH_2O$ variation in elastic recoil through the lungs. This directly influences ventilation and perfusion as local tissue expansion and tethering forces determine the patency of airways and blood vessels. There is a mechanical coupling between airways, blood vessels and surrounding lung tissue (parenchyma) at different spatial scales, and changes in tissue composition or alveolar size and shape in pathology potentially have significant impact on gas exchange function.

<INSERT FIGURE 6 HERE>

At the organ level, researchers have chosen to simulate the mechanics of the lung from the ventilation side or tissue side. From the ventilation side, one-dimensional, three-dimensional or 1D-3D coupled approaches are adopted. In these models, lung tissue provides a boundary displacement. From the tissue side, it is harder to incorporate fluid pressure; the mechanical properties of the tissue are not fully known and experimental measurements are often local (74). Fluid pressure during lung inflation causes the tissue to become stiffer at higher inflation – as found in many vascularised tissues. Additionally, the presence of surfactant layer brings in an additional level of complexity to the mechanics. Often the question posed of the model determines the choice of computational model and the level of complexity required. For example, when computing static lung tissue elasticity, lumped tissue models considering lung tissue as a compressible and hyperelastic material are used (19). More recently, coupled approaches which combine ventilation and tissue elasticity using a combination of tools such as image registration, poroelasticity (75) and airway tree generation have been employed.

However, these models have not been widely used to date to provide answers to clinical questions. This is partly due to large number of modelling parameters and assumptions that are needed to completely describe the biophysics of the problem.

Parenchymal tissue stress and elastic recoil at the macro-scale can be predicted using finite element models. These models have ranged from predicting strains at static inflation pressures (76) utilising CT images to dynamic tumour tracking utilizing 4DCT imaging . At the micro-scale functional units of the lung are compliant structures, with irregular structure. Thin alveolar walls are subjected to strain and stress and microscopic changes in alveolar structure are related to changes in nature and efficiency of lung inflation. Imaging has helped evaluate micro-level mechanics both directly and indirectly (14, 76). However, while this imaging has revealed a lot about microstructural complexity of lung acinus and alveolar mechanics, application to clinical diagnosis and treatment for lung diseases has been limited.

Long-term the clinical usefulness of models of lung tissue mechanics, particularly micro-mechanics, will likely require translation of predictions of mechanical models to predictions of observable lung function such as gas exchange efficiency, imaged structure/function, or use in image registration algorithms to allow tracking of diseased regions for surgical planning, radiation treatment, and patient monitoring. Models of tissue deformation coupled to models of gas exchange may help to answer open questions regarding how changes in posture during mechanical ventilation appear to improve lung function in some subjects, and perhaps help to indicate which subjects may benefit from prone posture. Models of stress distribution in emphysema (77), aim to provide predictions regarding potential sites of and mechanisms of disease progression, which may allow earlier detection or help to manage treatment strategies. Also, models of tissue mechanics under mechanical ventilation combined with electrical impedance tomography (EIT), a rapid functional imaging modality that provides regional air content, may allow for improved feedback in determining ventilator settings for mechanically ventilated patients that maximise gas exchange and minimise chances of lung injury.

**4. Challenges of bringing computational models of the respiratory system into clinical practice**

Computational models, derived and parameterised from medical imaging, are being continually developed to study the complex biophysics of the respiratory system. Often, application to the clinical setting, is challenging, but examples described here show that translation is possible, and the prospects for the future are bright. To improve clinical translation in this area, and to decide what level of complexity and/or subject specificity is required of a model several questions must be

addressed, which relate both to the model employed to answer a specific clinical question, and how to best develop multi-scale and multi-physics representations of lung function.

*Are models accurate physiologically?* To be clinically useful a computational model must be able to capture the key features of pathology and/or treatment that define patient outcome. The greatest and most obvious challenge here is whether or not models are accurate and realistic. To prove this rigorous validation of modelling is required. A problem with validating increasingly complex models is that high-resolution data to match the output of the model is not always available, or is not available in the subject for which the geometric model is available. Along with increases in the resolution of structural imaging of the lung, recent years have seen improvements in the quality and resolution of functional imaging, which aims to provide 3D data on ventilation, perfusion and gas/oxygen distributions and flow profiles in the lungs. Validation of CFD models is typically achieved by testing model predictions against high-resolution *in-vivo* imaging (e.g. SPECT (25), MRI (78)). Anatomically based models that cover the whole lung have been tested for consistency with existing functional imaging data describing the distribution of ventilation and perfusion in the lung (24, 27) and whole organ measures in the same patient (45, 70). But assessment of regional function in the individual whose lung is modelled is lacking. In the normal lung, which provides the baseline for most modelling studies, high resolution imaging of structure and function simultaneously are hard to obtain as many high resolution imaging techniques use high amounts of radiation and/or contrast. In pathology, acquiring functional imaging can be time-consuming and is difficult to justify. However, functional imaging techniques that do not require contrast are emerging, particularly from magnetic resonance imaging (79, 80), so acquiring both structural and functional imaging in the same patients for validation of models is becoming more easily accessible. This will provide increasingly rigorous tests for model predictions in the coming years.

*How much complexity is too much?* A key aspect of any modelling study is making appropriate choices regarding the level of complexity required to solve a given problem. Access to high resolution imaging data has driven a rapid increase in complexity of models of the lung. However, complexity means high computational cost, and often slow model run times. This does not tie in well with clinical need, as in most clinical situations decisions must be made rapidly. Maintaining the balance between accuracy and simplicity is critical for modern developers of computational models. Ideally a model would run in real time so that clinicians can respond to dynamic changes in patient condition. But, sometimes the amount of geometric or functional detail to adequately predict behaviour is too great for this to be possible. This does not necessarily mean that a model is not worthwhile. Potentially, if a model is too complex to use clinically, but this complexity is required to adequately describe the

physiology, modellers can consider whether the physiological knowledge provided by the model could be used to guide clinical scoring (based on simple clinical measures). An example of this type of approach is given by Clark et al. (70), who used detailed model predictions to propose a flow-weighted 'clot load' score in PE. This score accounts for the concept that not all segments of the lung are equal, but does not require clinicians to develop or run computational models to assess patient state.

*Do models need to be personalised?* Computational models are becoming increasingly personalised, and personalised medicine is becoming a widely attempted and increasingly complex phenomenon. However, is the drive for subject specificity in models necessary, or is it sufficient to model function in a small number of subjects that capture population variability? Researchers have begun the process of building up databases of subject-based models to represent a particular pathology and studies are moving away from using one geometric model to represent all subjects (29, 45, 70). Capturing the important structural contributors to function in small number of "generic" models would be beneficial to providing clinical usefulness both in CFD studies, and 1D spatially distributed models. One possible way to do this is via development of a model of statistically average lung (and models representing extremes of normal variability). There are studies that aim to classify subjects based on the statistical properties of their airway geometries (81), and studies have attempted to define normal lobar structure (82, 83). However, cohort modelling has shown that some aspects of lung function may not be captured in a generic model (29, 46), and classifying when it is and is not necessary to develop subject-specific models requires more analysis in the future.

*How to integrate multi-scale and multi-physics functions?* Most modelling studies to date have incorporated a single aspect of pulmonary function: air flow, blood flow, tissue mechanics, or gas transfer. Multi-scale function has been predicted in asthma from cell to organ levels (84), and similarly structured models of other pulmonary functions are likely to follow from this example. Multi-physics models are typically loosely coupled, such as ventilation and perfusion driven by tissue mechanics, but without feedback. In reality, airways effect blood flow (timing of breathing is potentially important as local tissue inflation influences blood vessel patency), the distribution of blood and air may influence tissue mechanics (a higher volume of blood/air may alter tissue distribution profiles and local airway constriction may stiffen tissue locally). Increasing computing power means that more tightly coupled models are likely in the future but in developing these models it is critically important to remember that validation of each model component, together and separately, will be required.

*Is imaged function relevant?* High resolution imaging is almost exclusively obtained supine (occasionally prone). However, normal function is predominantly upright. Geometric models are thus almost exclusively developed in a posture that does not match with normal function and little is known about how changes in lung morphometry between postures influence function. The assumption is typically made that upright function can be simulated in supine geometries. Recent studies have shown that upper airway structure is significantly different upright compared with supine (85), and preliminary attempts have been made to understand how lung shape changes between supine and upright may influence tissue mechanics (86). However, significant further investigation is required to assess the applicability of anatomically based models between postures.

In the last two decades, researchers have moved away from the concept of the lung as a simple "balloon-on-a straw" and are addressing the known complexity of lung function in their models. This progress has been supplemented by advances in medical imaging. This has potential in translation of models to the clinic, as there is significant heterogeneity in patient response to many common lung diseases which must be captured to determine appropriate management strategies for individuals. However, practically, large-scale models of lung function that require super-computers or long timescales to solve, are unlikely to be of clinical benefit. The challenge to modellers that must then be met is to use improved knowledge of complexity in lung structure-function relationships to guide clinical decision-making. This challenge is increasingly being addressed by modellers and will likely bring improved healthcare solutions in the future.

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**Figure 1:** The multiple interacting factors that define lung function. Pathology in the upper airways can influence air flow to the conducting airways that lie distal to the trachea. Regional air and blood flow is determined by the size, structure and distribution of the branching airways and pulmonary blood vessels, as well as the size and structure of the respiratory structures (the acinar airways and blood vessels). These small airways and blood vessels are sensitive to environmental factors, but also to dynamic changes in local oxygen and carbon dioxide levels. Finally, lung airways and blood vessels are embedded in lung tissue which deforms under gravity and whose mechanical properties are sensitive to pathological changes in airways and blood vessels (for example due to tissue destruction, stiffening or oedema).

**Figure 2:** The evolution of anatomical and physiological complexity in compartmental models of air flow in the lung. *From left:* Early models of the lung, and those used frequently in clinical textbooks assume that the lung can be represented by a single compartment, which expands and contracts linearly with changes in pressure. These simple models have been found to be inaccurate in representing many aspects of pulmonary function so have evolved to incorporate a notion of the non-linear nature of parenchymal mechanics, and to incorporate multiple 'compartments' with potentially different flow and mechanical properties.

**Figure 3:** Advances in imaging technologies have allowed increasingly complete models of the pulmonary airways to be developed. *From left*: The first class of anatomically based model represents conducting airways as 1D elements, of known radius, distributed in 3D space to the level of the acinus. Each acinus is then represented as a non-linearly elastic "balloon-on-a-straw". At the same time realistic anatomical models of the upper and respiratory airways have been developed, within which 3D air flow and particle deposition can be simulated using CFD. More recently, to address limitations in each of the 1D spatially distributed and full 3D approach, the two types of model have been coupled.

**Figure 4:** Pulmonary blood flow predictions from two patient-based models of pulmonary embolism. Each patient has the same organ-level score of tissue occluded by emboli (using the Qanadli index, QOI of 45%) but showed different functional responses to the embolisation. The top panel depicts model predictions for pulmonary blood flow pre (baseline, $Q_{BL}$) and post-embolus occlusion ($Q_E$). Pulmonary arterial pressure, PAP, is higher and arterial oxygen partial pressure ($P_aO_2$) is lower in subject 2. The bottom panel presents the end-capillary oxygen distribution for the two subjects, illustrating an increased physiological deadspace in subject 2. Figure used with permission from Clark et al. (70).

**Figure 5:** The typical methodology employed in constructing computational fluid dynamics (CFD) meshes of the central pulmonary arteries. Typically, several generations of blood vessels can be included in CFD models, and beyond this level appropriate boundary conditions must be determined to accurately predict blood flow. Figure used with permission from Kheyfets et al. (87).

**Figure 6:** A schematic of regionally varying recoil pressure ($P_E$), lung tissue density ($\rho$) and ventilation (V) in the lung in the supine posture. Ventilation and tissue deformation are coupled between the micro- and macro-scales, and small-scale changes in pulmonary tissue affect the global lung deformation.