**Summary**

{clark2011interdependent}

The model geometry presented here is anatomically based, in that it captures aspects of the branching asymmetry of the extra-acinar pulmonary blood vessels and the spatial relationship between blood vessels and lung parenchymal tissue. It is subject specific to the extent that it describes the lung shape, the distribution of the largest blood vessels, and the regional tissue density ($\rho\_t$) measured from multirow detector computed tomography (MDCT) data in an individual. Where subject-specific data are not available from MDCT data, the modeling methodology aims to capture a structure that corresponds as closely as possible to published data in human subjects.

{swan2012computational}

The ventilation model presented here combines the results of previously published models of the structure of the lungs and conducting airways \citep{tawhai2003developing, tawhai2004ct} and lung tissue mechanics \citep{tawhai2009supine} with a model of airflow. The airflow model couples flow in the conducting airways (based on measurements made by \citep{pedley1970energy}) and an equation of motion which drives flow into the acinus via a temporally changing pleural pressure. The model of the acinus is similar in its translation of physical processes to the classic single compartment model \citep{ben2006simplified}; however, each acinus is now represented by an individual compartment, resulting in ~32;000 individual expanding and contracting compartments plus ~ 64;000 airways that comprise the conducting airway tree.

**Airway/Vessel tree**

{kang2017gravity}

An anatomically structured model of the bronchial airways (from trachea to terminal bronchioles) was generated using the methods of Tawhai et al (). The lung surface and centerlines of central airways were segmented using custom-written software PASS. Finite element models of the lung shape and airways (from trachea to approximatedly generation 6) were geometry-fitted to the imaging segmentations. Airways down to the level of the terminal bronchioles were generated using a volume-filling branching algorithm () that recursively branches toward the center of mass of sets of seed points that represent the distribution of pulmonary acini.

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Airways additional to the segmented central airways were generated using a volume-filling branching algorithm, to fill the lung-shaped volumetric mesh. The algorithm uses the central airways as initial conditions and the lung shape as a boundary condition for ‘‘growth’’ of a space-filling tree geometry.

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The geometry of the lung surface, central airways, and the largest pulmonary arteries and veins were derived from MDCT data.

Each extra-acinar blood vessel was defined using a one-dimensional (1D) finite element, representing its centerline plus a numeric value for its unstrained [zero transmural pressure (Ptm)] radius. Therefore, a blood vessel (or vessel segment) is described by a vector (its centerline), which places it spatially within the lung structure, and its radius. The vector representing the vessel centerline is defined to be in the direction of flow and so begins at the inlet to each vessel and ends at the vessel outlet. This 1D approach assumes vessels to be approximately cylindrical when unstrained, which differs from a three-dimensional (3D) approach, which explicitly describes the volume of each vessel. Although 3D models provide an accurate description of fluid transport, they are not considered here, as they are computationally intensive and are currently not able to describe perfusion in a whole lung structure.

The geometries of the large arteries and veins were modeled using a combination of MDCT data and computational algorithms, as described in detailed in Refs. \citep{burrowes2005anatomically, tawhai2004ct, tawhai2009supine}. The centerlines of the largest blood vessels (main, left, and right pulmonary arteries) were manually segmented from the subject’s MDCT data. Each of these blood vessels was represented in the model by multiple 1D finite elements, which reflect the spatial distribution and curvature of the large blood vessels.

Automated image segmentation methods are not yet capable of reliable separation of, and differentiation between, the pulmonary arteries and veins. Because of this constraint, the (subject-specific) centerlines of the central airways obtained from MDCT data were used to construct approximately four generations of the arterial and venous trees distal to the left and right pulmonary arteries and veins. Using the airway tree to construct the blood vessel geometry at this

level is a reasonable approximation, as the airways and blood vessels have very similar lengths and orientations: the pulmonary arteries closely follow the airways, and the veins divide at the midpoint between neighboring airway bifurcations \citep{weibel1984pathway}. This airway centerline data plus the centerline data of the main, left, and right pulmonary vessels provided a 1D finite-element description of the pulmonary blood vessels down to generations \citep{bshouty1990distensibility, burrowes2009species, burrowes2005anatomically, burrowes2006evaluation}.

Finally, the 1D finite-element tree obtained from MDCT data, as described above, was used as an initial condition for generating a tree structure within the subject’s lung volume. The methodology for obtaining volumetric meshes from MDCT data, as well as the detail of the volume-filling algorithm used to create the vessel tree structure, are given in previous studies \citep{burrowes2005anatomically, tawhai2004ct}. The branching algorithm is deterministic and designed to generate a branching structure that matches as closely as possible morphometric data on vessel lengths and branching angles (see Refs \citep{burrowes2005anatomically, tawhai2004ct} for details). The imaged lung volume (including tissue and air) and the seed point density of acinar units [~30,000 acini \citep{haefeli1988morphometry}] in the lung are input parameters. The blood vessel models were generated to represent all accompanying (non-supernumerary) arteries and veins, down to the level of the vessels that accompany the terminal bronchiole in the airway tree (that is, each terminal vessel supplies a single acinus) with each artery and vein represented by a single 1D finite element.

**Vessel**

{kang2017gravity}

The similar geometries of the airway and vascular trees have been hypothesized to play in a

role in passive V/Q ˙ matching (16). To test this hypothesis, an almost exact matching of the vascular trees to the airway model geometry was adopted to ensure a “best case” scenario that represented the maximum theoretical contribution of structure to V/Q ˙ for trees with normal geometry. That is, for the purposes of this study the pulmonary arterial and venous trees were assumed to be exact replicas of the airway tree except for the primary feeding artery/vein. The trachea geometry was bent to a near 90 degree angle to represent the orientation of the pulmonary artery trunk, and the same geometry was adopted for the largest veins, as the predicted perfusion distribution in this one-dimensional (1D) network model is largely unaffected by central arterial/venous structure. The pulmonary veins were connected to the arteries at the terminal vessels through a ladder-like model for the pulmonary microcirculation.

**Small (intra-acinar) blood vessels**

{clark2011interdependent}

Each acinar circulatory “unit” is subtended by a single artery and a single vein that accompany a unique terminal bronchiole. Within each unit, the intra-acinar arterioles and venules were explicitly represented, with nine symmetric bifurcations of each type of vessel included in the model \citep{haefeli1988morphometry}. These intra-acinar vessels were assumed to be joined at each generation by a capillary bed that covers the alveoli present at that generation, forming a “ladder-like” structure, as previously described by Clark et al. \citep{clark2010contribution}.

The capillary bed was represented using the lumped parameter “sheet-flow” model, developed by Fung and Sobin \citep{fung1969theory}. The blood pressure at the midpoint of each arteriole and venule generation was assumed to be a good approximation to the average pressures into and out of pre- and postcapillary vessels arising from this generation. The midpoint of each arteriolar branch was joined to its corresponding venule branch by a capillary sheet, where each connection represents the capillary bed over multiple alveoli (with ?10–15 alveoli per sheet) and may have several feeding precapillary vessels; the small precapillary vessels that do not follow the branching structure of the larger arterioles and venules and have diameters approaching those of the capillary vessels were incorporated into the capillary sheet for modeling purposes. Detail of this intra-acinar model is given by Clark et al. (14).

**Airway/Vessel diameter**

{kang2017gravity}

Measurements from segmented CT for the subject were used to initialize diameters of the upper airway, arterial and venous trunk. Diameters of the lower order branches were calculated using Horsfield diameter ratios (R D H) weighted against the respective ratio of child to parent branch diameter for the tree type (airway, artery, or vein), such that the average diameter characteristics for each tree structure were consistent with data from morphometric studies (35). The values for R D H were 1.14, 1.54, and 1.55 for airways, arteries, and veins, respectively.

{swan2012computational}

To construct models of airway function, the proportion of the measured lung volume that resides in the conducting airways and the respiratory airways must be calculated. Conducting airway radii were assigned using the subject’s FRC tracheal radius (7.26 mm, calculated from the mean tracheal cross-sectional area from FRC imaging and assuming a circular cross-section) and a Horsfield diameter ratio ðR d HÞ of 1.152. The Horsfield diameter ratio was selected such that the model’s mean length to diameter ratio was close to 2.8 \citep{horsfield1976diameter}. Using this conducting airway geometry the volume of the conducting airways including and distal to the trachea was 102 mL. An additional 80 mL was included to account for the volume of the upper airways (proximal to the trachea), based on the predictive equation from\citep{hart1963relation} for total anatomical dead space as a function of body height. Alveolar volume at FRC was then 4.29 L (the PFT measured volume minus the volume of all conducting airways). To obtain the volume of a single acinus this value was divided by the number of acinar units in the model (31,800) resulting in a mean acinar volume, defined as V FRC , of 135 mm 3 . Fig. 1 shows the model geometry: the right lung is shown with spheres representing acinar units and the left lung is shown with the conducting airways only.

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The diameters of the left pulmonary artery (14.80 mm) and right pulmonary vein (12.97 mm) were assigned based on measurements made by Huang et al. (39) at zero Ptm and close to TLC. These diameters compare well to those given for the same order of vessel in other morphometric studies (36, 50). All other arteries and veins down to the level of the acinus were assigned diameters based on a constant rate of increase in diameter with vessel order (the Strahler diameter ratio R D S). Conventional Strahler ordering was used to classify vessels in the model (36, 50), with each peripheral vessel (distal-most arteriole or venule) defined as order 1, and a parent vessel being the same order as the child branch of the highest order, or else one order higher than two child branches of the same order.

As a range of values for R D S exist in the literature, R D S for the arteries and the veins were treated as fit parameters, such that the model gave physiologically realistic predictions for pulmonary vascular resistance (PVR) in the supine posture at FRC. The fitted R D S were 1.53 in the arterial tree and 1.54 in the venous tree. This compares with 1.56 $\pm$ 0.02 (arteries) and 1.58 $\pm$ 0.06 (veins) calculated from the raw human data of Ref. 39 (where diameter- defined Strahler ordering was used), and 1.56 $\pm$ 0.09 (arteries) and 1.61 $\pm$ 0.13 (veins) calculated from the raw human data of Refs. 36 and 50 (where conventional Strahler ordering was used).

In the absence of data providing diameter information per generation within the acinus, the diameters of intra-acinar arterioles and venules were assumed to decrease linearly with generation from the diameter value at the level of the terminal bronchiole to the level of Strahler order 1 arterioles and venules, as measured by Huang et al. (39) (0.020 and 0.018 mm, respectively). Similarly, the lengths of intra-acinar vessels were assumed to decrease linearly with generation from the length value in the generated large vessel tree to the level of Strahler order 1 arterioles and venules, as measured by Huang et al. (0.22 and 0.13 mm, respectively).