An Intelligent Parallel Method for Automatic Production of the Human Bronchial Tree Fulfilling Bronchopulmonary Segmental Isolation Based on Stochastic Parametric L-system

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An Intelligent Parallel Method for Automatic Production of the Human Bronchial Tree Fulfilling Bronchopulmonary Segmental Isolation Based on Stochastic Parametric L-system

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Abstract

In the human lung, air is transported from the environment to the respiratory zone by conducting airways containing ~60000 airways with different scales. An accurate model of this complicated structure is crucial for studying transport phenomena in the human lung. In the present study, the parametric Lindenmayer System (L-System) has been used to produce the human bronchial tree in the bronchopulmonary segments whose shapes have been obtained based on the medical image processing techniques. The airways propagate into the host segments simultaneously similar to what happens in real life using multi-threads parallelism method. Each module in rewriting rules of the formulated L-System plays the role of an airway with its characteristic properties that have been found almost independently based on an intelligent procedure. This feature enables the method to be less sensitive to change in the host shape and size of the lungs. In addition, the stochastic behavior of the proposed procedure generates slightly different structures with the same statistical properties. Furthermore, the dimensions of the terminal branches are functions of age, which make the proposed method capable of generating the tree structure for the subjects with various ages fulfilling almost all anatomical and physiological requirements. The morphometric characteristics of the generated structure are in good agreement with the corresponding experimental data reported in the literature. The results show that the proposed method outperforms the previously reported models. The accurate three-dimensional model proposed by this study can be used for simulation of fluid distribution, mass and heat transfer, drug delivery, and particle deposition in the human respiratory system.

Keywords: Lung; Bronchial tree; L-System; conducting airways.

1. Introduction

There are three and two lobes in the right and left lungs, respectively. Each lobe is also divided into sections called bronchopulmonary segments. Layers of connective tissue separate the segments from each other. Each segment is supplied by a segmental bronchus and bronchial artery and functions in a manner that does not depend on the other segments [1]. The right lung consists of 10 segments whereas the number of left lung segments varies from 8 to 10. The most common structure of the left lung comprises 8 segments. Air goes into trachea from nose or mouth during breathing. Then it passes through airways into the lungs and backs out again. The airways in the human lungs can be classified into two main parts: conducting airways and respiratory airways. Conducting airways start from the trachea and propagate into the lung as terminal bronchioles. They supply air from the trachea to respiratory units where gas exchange between respiratory airways and blood takes place. The airways have been confined in a limited space resulting in a complicated structure with multi-scales.

The conducting airways of the human lungs form a complex asymmetric tree. Mathematical models of the tracheobronchial tree have been widely used to study aerosol deposition[2], gas transport[3-6], ventilation distribution[7, 8], and heat transfer[9]. The accurate modeling of all aforementioned subjects requires appropriate and reliable modeling of the bronchial tree. For this reason, modeling of the bronchial structure has been attracted much attention. Since the problem does not have a unique answer, the previous research tried to present mathematical models with various simplifications in such a way that the statistical properties of the final structure satisfy the anatomical data. Weibel[10] and Yeh and Schum[11] respectively proposed one and five typical symmetric paths' models of the airways obtained based on cast measurement. Although this

approach has the lowest computational cost for studying the aforementioned applications it is not appropriate for studying the effect of anatomical asymmetry.

To study the properties of the bronchial tree, the branches should be classified. There are three methods of classification that are commonly used: generation, Horsfield and Strahler order. The first one was used by Weibel[10]. In this approach, counting starts at the trachea, considered as generation 0 or 1, and increases by one in each bifurcation. Strahler and Horsfield orders [12] are the most common classifying methods for asymmetric trees in which the branches are numbered upward from end branches instead of downward starting with the trachea. Horsfield et.al[13] used parameter delta, the difference between the order of the daughters' branches, to express the asymmetry at dichotomy. This method assumes a uniform degree of asymmetry throughout the tree but the branches with the same order have different diameters or lengths in reality. Koblinger and Hofmann[14] proposed a stochastic asymmetric model for human bronchial tree based on morphometric data of Raabe et.al. [15]. However, all mentioned simplified geometries do not take into account the spatial positions of airways.

Kitaoka et.al[16] used nine basic rules and four complementary rules to produce a three-dimensional tree (3-D) representing the bronchial tree of the lungs. They used a power-law relationship between the flow dividing ratio and diameter. To find the branching angle, the relation proposed by Murray[17] was employed, which has been derived based on the minimization of power dissipation and is a function of the flow dividing ratio. They assigned a value to the branch length that was three times its diameter. Their deterministic model was very sensitive to the initial value of model parameters and unable to generate various structures with identical structural properties. Tahwai et.al [18] proposed a model for the construction of a 3-D bronchial tree in each lobe based on Monte Carlo method. They distributed seed points on the host volume and space

was divided into two sub-volumes by a dividing plane. The branching angle was found based on a growing daughter branch toward the center of mass of the seed points in each subvolume. They assumed that the length of each branch to be a predefined fraction of the distance between the starting point of the branch and the center of the mass. The diameters were randomly assigned to all branches after the whole structure was constructed based on the Horsfield order with a coefficient of variation (defined as the ratio of standard deviation to the mean) of 0.1. Tahwai et.al [19] obtained the upper parts of the bronchial tree using Multi-Detector X-ray-row CT (MDCT) and used the model of [18] to complete the structure. They also improved the previous model by a change in the number of seed points, regrouping them throughout the generation process, and using Strahler order for the determination of branches diameters. Bordas et.al [20] used the same approach for the generation of the bronchial tree for healthy and asthmatic patients. For assignment of diameter to the branches, they used the terminal segmented branches as base branches instead of the trachea. The incorporation of features of diseases was not observed in their model parameters, and the difference between the structure of healthy subjects and patients only arises from the dissimilarity in the upper airways obtained by MDCT. Montesantos et.al [21] used Tawhai et.al[19] model along with HRCT data for producing deterministic three-dimensional branches into lobes. They assigned diameter to the branches by using a predefined value for length-to-diameter ratio instead of using Horsfield or Strahler order. The deterministic behavior, assigning diameter after construction, needing detailed knowledge before generating the structure, and assumption of one dimensional (1-D) branches during generation process are the main shortcomings of such models. Davoodi and Bozorgmehry[22] used a stochastic rule-based method to generate the structure of human conducting airways using Lindenmayer-system (L-system). They used a similar approach of Kitaoka et.al[16] for finding diameter and angle. Although the length was found independently in this method, the branching angle and diameter are correlated

100 causing the model to be sensitive to the model parameters and change in the host geometry. For
101 instance, if their model with the proposed parameters is used to obtain the conducting airways in
102 the bronchopulmonary segments, the structure will have too small terminal bronchioles. Another
103 shortcoming of their work is that they do not take into account the space occupied by other
104 branches in the procedure of finding the length of the growing branch.

105 The shape of the host volume significantly affects the structure of the generated tree. In this study,
106 we try to produce the tracheobronchial tree in the bronchopulmonary segments in contrast to the
107 previous models that generate the tree in the lungs or lobes. In the present work, we use parametric
108 L-System to generate the human bronchial tree because based on this approach it is possible to
109 define a branch as a function of its characteristic properties, i.e. diameter, length, and branch
110 orientation, and consider the growth of the tree over time. The major difference of the proposed
111 model with the previous ones is that the characteristic properties of the branches are found
112 independent of each other based on an intelligent procedure in such a way that the anatomical
113 constraints are satisfied. This approach makes the model so flexible to generate the bronchial tree
114 more realistically in quite various host volumes with the same rules and model parameters. In
115 addition, this approach makes model capable of producing the structure for other species with a
116 few prior information in contrast to that proposed by Tawhai et.al[19] that needs the diameter
117 reduction as a function of Strahler order. Another unique advantage of the proposed method is that
118 the branches do not grow in the bronchopulmonary segments independently and the branches of
119 all segments propagate in parallel which is what happens in reality. In other words, the positions
120 of branches near the segments' interfaces affect the orientation of growing branches. Furthermore,
121 the method is developed so that the airways grow 3-D quite similar to what happens in reality
122 while this is not the case the previous works in which the airways grow 1-D.

The remaining sections of this paper are organized as follows. Section 2 presents the methodology of finding bronchopulmonary segments and the mathematical formulation of the growing structure in the host volumes. In Section 3, the production rules and the proposed procedure for finding parameters of parametric L-system are discussed. In Section 4, the performance of the proposed model is evaluated by comparison of the model results with those reported in the previous studies. Finally, discussion and concluding remarks are given in Sections. 5 and 6, respectively.

2. Problem Statement

To construct the bronchopulmonary tree, the boundaries of each bronchopulmonary segment should be first determined. The next section goes through the procedure by which the bronchopulmonary segments are built. Sections. 2.2 and 2.3 elaborate the general mathematical formulation of the problem and growth based formulation of the problem using L-System.

2.1. Bronchopulmonary segments

Bronchopulmonary segments separate from each other by thin connective tissue, which is not visible in CT images. On the other hand, since the boundaries between lobes are visible in CT images; the lobes are segmented out using chest imaging platform module of 3DSlicer which is a free software for image analysis. After this lobe segmentation, bronchopulmonary segments fissures were segmented manually using their anatomical positions, lobe boundaries and considering the fact that each segment is fed by only one airway and artery. The process of segmentation of bronchopulmonary segments using predefined fissures was done by the segmentation module of 3DSlicer software. At the end of these steps, the surface of each bronchopulmonary segment is obtained as a set of triangular grids. It should be noted that the

boundaries of the bronchopulmonary segments are only manually found once. For other subjects, they can be estimated using the lobes' boundaries assuming that the relative position of the segments' boundaries in the corresponding lobes remain unchanged.

2.2. Mathematical formulation

Since the problem belongs to the category of inverse problems and there is no one to one mapping between the model parameters and the observations, the problem has no unique solution. In what follows, we present various models and show that the model with the least number of parameters is suitable because there is not enough data to determine many parameters.

The human bronchial tree can be described by a simple directed graph¹ whose edges are three-dimensional. All nodes and edges of the graph should be determined in such a way that the structure satisfies all anatomical and physiological constraints of a living organ. Therefore, the problem can be defined by:

$$\begin{aligned} & \text{minimize } f(G(N, E)): N \times E \rightarrow \mathbb{R}^+ \\ & \text{subject to: } \tilde{C}(G(N, E)) < \tilde{\epsilon} \end{aligned} \tag{2.1}$$

where $G(N, E)$ is a simple directed graph with a set of nodes N and a set of three dimensional directed edge E . f and $\tilde{C}$ are the norms of the vector of objective functions $\tilde{F}$, and vector of constraints whose elements are members of $\mathbb{R}^+$.

2.3. Growth based formulation

There are about 60000 conducting airways in the human bronchial tree[23] and thus the number of decision variables of the problem is 240000 calculated by considering four decision variables

¹ In mathematics, simple directed graph is a directed graph without loop.

(i.e. the diameter and the endpoint position) for each branch. It is difficult to find such a large number of variables in such a way that the proposed algorithm remains robust in the presence of small disturbances or deformations. Therefore, it is essential to reduce the number of decision variables in such a way that the model remains accurate and predictable. For this purpose, the graph G can be obtained using a rule-based method such as Lindenmayer system. This method and its application in the modeling of the structure are described in the rest of this section.

Lindenmayer system or L-system was introduced and developed by Aristid Lindenmayer[24, 25]. It is a type of formal grammar and a parallel rewriting system that uses production rules or a set of grammars to produce branching structures. L-systems have been used to describe the growth process of plants[26, 27], model morphology of organisms[22, 28], and the production of self-similar fractals. It can be defined as a triplet $L(V, \omega, P)$. L-System consists of four main parts:

- V : A set of symbols that are used to make string. It consists of both variables, elements that can be replaced, and terminal or constants, the elements that cannot be replaced. The set of all words and set of all nonempty words are denoted by V^* and V^+ , respectively.
- $\omega \in V^+$: An axiom that is an initial string from which the branching starts.
- $P \subset V \times V^*$: A set of production rules that are employed to make strings from each symbol. It consists of a predecessor and a successor and is written in the following format.

$$p: \text{predecessor} \rightarrow \text{successor} \quad (2.2)$$

The symbol “ $\rightarrow$ ” is used to separate the predecessor and successor.

- Turtle interpretation: a mechanism that interprets the strings into geometric shapes.

182 Lindenmayer used brackets “[“ and “]” to produce axial trees. These brackets are employed to
 183 enable L-system to produce branching structure. The brackets “[“ and “]” are not included in the
 184 set V , therefore the set V is extended to set $V_B = V \cup \{[,]\}$ for bracketed L-system.

185 If the graph representing the bronchial tree is obtained based on L-system, the formulation of the
 186 problem will be:

$$\begin{aligned} & \text{minimize} \quad f(L(V, \omega, P)) \\ & \text{subject to:} \quad \tilde{C}(L(V, \omega, P)) < \tilde{\varepsilon} \end{aligned} \quad (2.3)$$

187 To generate the structure of the human bronchial tree using the above approach, the number of
 188 production rules, i.e. decision variables, is numerous because the bronchial tree has a non-uniform
 189 structure. Therefore, it is of interest to reduce the number of production rules. For this purpose, the
 190 parametric L-system is used to generate the tree with a minimum number of decision variables that
 191 include both production rules and parameters.

192 In parametric L-system predecessors and successors are parametric strings with letters from set
 193 V and formal parameters, real-valued parameters appearing in words, from set Σ . Any module
 194 $F(a_1, a_2, \dots, a_n)$ with letter $F \in V$ and parameters $a_1, a_2, \dots, a_n \in \mathbb{R}$ belongs to set $V \times \mathbb{R}^*$.
 195 Parametric L-system is denoted by quadruplet $L(V, \Sigma, \omega, P)$ where:

196 $\omega \in (V \times \mathbb{R}^*)^+$ is axiom.

197 $P \subset (V \times \Sigma^*) \times \mathbb{C}(\Sigma) \times (V \times \mathcal{E}(\Sigma))^*$ is a set of production rules.

198 where $(V \times \mathbb{R}^*)^+$ and $\mathbb{C}(\Sigma)$ are a set of nonempty modules and a set of logical expressions,
 199 respectively. $\mathcal{E}(\Sigma)$ denotes the set of all procedures for finding parameters. Symbol “*” above any
 200 set B denotes the set of all finite combinations of members of B . The parametric production rule
 201 is written in the following format.

$$p: predecessor(parameters): condition \rightarrow successor(parameters) \quad (2.4)$$

Where the symbol “:” is used to separate the condition and predecessor. Any formal parameters may appear in the conditions. The reader is referred to the reference [24] for further details on different types of L-System. Using parametric L-system, Eq. (2.3) can be reduced to:

$$\begin{aligned} & \text{minimize} \quad f(L(V, \Sigma, \omega, P)) \\ & \text{subject to: } \tilde{C}(L(V, \Sigma, \omega, P)) < \tilde{\epsilon} \end{aligned} \quad (2.5)$$

All structures produced by the same deterministic L-system are identical. To generate the bronchial structure for various people, it is necessary to randomize parameters so that it considers case-to-case variations and preserves statistical properties of the structure. In the next section, the process of generating tracheobronchial structure using parametric L-system with random parameters is presented.

3. Application of Parametric L-System in the Modelling of Conducting Airways

Trachea branches into main bronchi which are then branching into lobar (secondary) bronchi. Lobar bronchi further divide into segmental (tertiary) bronchi which branch into smaller airways called bronchiole connected to terminal bronchiole feeding respiratory zone. Conducting airways can be divided into two main sections. The first section extends from the trachea to segmental bronchi. The second section comprises segmental bronchi to terminal bronchioles. All branches with identical segmental bronchus are generated into their corresponding bronchopulmonary segment and the generation of branches in each segment occurs in parallel. Parametric L-system is used to produce the branches of each mentioned section. Each airway can be determined using its parent, diameter, length, and orientation. Parameters of parametric L-system should be determined by an intelligent procedure to satisfy anatomic constraints for all cases. The decision variables of the proposed procedure should be determined in such a way that the objective function

of Eq. (2.5) is minimized. Each member of the vector $\tilde{F}$ corresponds to the difference between the statistical property of simulated structure and its reference value according to the following Eq. (3.1).

$$F_{i=1\dots n} = \begin{cases} \frac{|prop_{s,i}(L(V, \Sigma, \omega, P)) - prop_{desired,i}|}{prop_{max,i} - prop_{min,i}} & prop_{min} \leq prop_s(L(V, \Sigma, \omega, P)) \leq prop_{max} \\ 100 & otherwise \end{cases} \quad (3.1)$$

Where, $prop_{s,i}$ is a function that calculates the corresponding property of the simulated structure. The list of geometrical properties considered in Eq. (3.1) is given in Table 1. The other properties such as d_{min}/d_p (dimeter of minor daughter to diameter of parent), d_{min}/d_{maj} (dimeter of minor daughter to diameter of major daughter), HRb (Horsfield branching ratio), HRd (Horsfield diameter ratio), HRI (Horsfield length ratio), d_{TB} (diameter TB) and L_{TB} (length of TB) are used for validation of the obtained structure. The evaluation results are presented in Section 4. In addition, the proposed method fulfills the following requirements:

1. Each branch is three dimensional during the growth process.
2. Every parent branch is divided into two daughter branches.
3. The diameters of the daughter branches are less than that of their parent.
4. The branches intersect neither the host boundary nor each other.
5. The minimum angle between daughter branches is 10° .

Table 1. List of geometrical properties and their corresponding acceptable range considered in the objective function

$prop_i$	definition	Reported values	reference	$prop_{min,i}$	$prop_{max,i}$	$prop_{desired}$
l/d	length to diameter ratio	3.25-3.75	[29, 30]	2.9	4.1	3.5
d/d_p	Dimeter to diameter of parent	0.83-0.88	[29, 31, 32]	0.75	0.92	0.85
d_{maj}/d_p	Dimeter of major daughter to diameter of parent	0.86	[33]	0.81	0.95	0.89
l/l_p	length to length of parent	0.85	[29, 32]	0.76	0.94	0.9
θ	Branching angle	25-47	[31, 34]	35	50	43
SRb	Strahler branching ratio	2.51-2.81	[35]	2.45	2.95	2.8
SRd	Strahler diameter ratio	1.35-1.5	[35, 36]	1.3	1.6	1.41
SRI	Strahler length ratio	1.33-1.55	[35, 36]	1.3	1.6	1.41

3.1. Central airways

As mentioned before, the number of bronchopulmonary segments varies from 18 to 20. This causes the structure of central airways to vary among various people. To find the most common structure, 50 CT images of various people were studied[37, 38]. We found that the most common structure is a lung with 18 segmental bronchi as shown in Fig. 1. Table 2 shows the name of each segment fed by segmental bronchus indicated in Fig. 1.

Fig. 1 Central airways

Table 2. bronchopulmonary segments and corresponding segmental bronchus

Right Lung			Left Lung		
Branch number	Lobe	Segment	Branch number	Lobe	Segment
RS1	Upper Lobe	Apical	LS1,2	Upper Lobe	Apicoposterior
RS2		Posterior	LS3		Anterior
RS3		Anterior	LS4		Superior lingular
RS4	Middle Lobe	Medial	LS5		Inferior lingular
RS5		Lateral			
RS6	Lower Lobe	Superior	LS6	Lower Lobe	Superior
RS7		Medial	LS7		Anteromedial
RS8		Anterior	LS8		Lateral
RS9		Lateral	LS9		Posterior
RS10		Posterior			

249 Central airways shown in Fig. 1 can be generated using parametric L-system with seven rewriting
 250 rules. Because the central structure is slightly different from the one reported by Davoodi and
 251 Boozarjomehry [22], their production rules are modified to produce the central structure shown in
 252 Fig. 1. The modified production rules are shown in Eq. (3.2).

$$\begin{aligned}
 &\omega: T(l_0, d_0) \\
 &p_1: T(l_p, d_p) \rightarrow +(\delta) \setminus (\delta) E(\alpha l_p, \beta d_p) [+(\delta) \setminus (\delta) B(\alpha l, \beta d_p) + (\delta) \setminus \\
 &\quad (\delta) C(\alpha l_p, \beta d_p)] [+(\delta) \setminus (\delta) G(\alpha l_p, \beta d_p) + (\delta) \setminus (\delta) F(\alpha l_p, \beta d_p)] \\
 &p_2: B(l_p, d_p) \rightarrow E(\alpha l_p, \beta d_p) [+(\delta) \setminus (\delta) K(\alpha l_p, \beta d_p) + +(\delta) \setminus (\delta) M(\alpha l_p, \beta d_p)] \\
 &p_3: C(l_p, d_p) \rightarrow E(\alpha l_p, \beta d_p) [+(\delta) \setminus (\delta) M(\alpha l_p, \beta d_p)] [+(\delta) \setminus (\delta) K(\alpha l_p, \beta l_p) [+(\delta) \setminus \\
 &\quad (\delta) K(\alpha l_p, \beta d_p) [+(\delta) \setminus (\delta) K(\alpha l_p, \beta d_p) + (\delta) \setminus (\delta) M(\alpha l_p, \beta d_p)] \\
 &p_4: G(l_p, d_p) \rightarrow E(\alpha l_p, \beta d_p) [+(\delta) \setminus (\delta) K(\alpha l_p, \beta d_p) [+(\delta) \setminus (\delta) K(\alpha l_p, \beta d_p) + \\
 &\quad (\delta) \setminus (\delta) M(\alpha l_p, \beta d_p)] \\
 &p_5: F(l_p, d_p) \rightarrow E(\alpha l_p, \beta d_p) [+(\delta) \setminus (\delta) M(\alpha l_p, \beta d_p)] [+(\delta) \setminus (\delta) M(\alpha l_p, \beta d_p)] \\
 &p_6: M(l_p, d_p) \rightarrow E(\alpha l_p, \beta d_p) [+(\delta) \setminus (\delta) A(\alpha l_p, \beta d_p)] [+(\delta) \setminus (\delta) A(\alpha l_p, \beta d_p)] \\
 &p_7: K(l_p, d_p) \rightarrow E(\alpha l_p, \beta d_p) [+(\delta) \setminus (\delta) A(\alpha l_p, \beta d_p)]
 \end{aligned} \tag{3.2}$$

253 where l_p , d_p , δ , β , and α are branch length, diameter, orientation angle and ratio of diameter and
 254 length of daughter to its parent, respectively. $+(\delta)$ and $\setminus(\delta)$ denotes orientation in azimuthal and
 255 polar direction. If δ is positive (negative) the rotation will be counterclockwise (clockwise).
 256 $T(l_p, d_p)$ indicates a cylindrical airway with the length of l_p and the diameter of d_p . $T(l_0, d_0)$
 257 corresponds to the trachea. Actions of characters E, B, C, G, F, K, M, and N are similar to T.
 258 Character “A” represents an inactive branch, at which the growth is stopped. The current position
 259 and orientation are saved when turtle interpretation encounters the “[“, and they are restored when
 260 turtle interpretation encounters “]”. Rewriting the rules should continue until no active branch
 261 remains. Central airways are produced by three generations of growth based on the production
 262 rules.

All parameters are obtained by the analysis of CT images taken from Exact09 website [37]. This dataset contains 40 CT scan images. The datasets used in this study are case01 and case37 which belong to adult male subjects. The airway segmentation module of 3DSlicer software was used to extract central airways from CT images. The distance between two bifurcation points was considered for branch length and average diameter of branch used as diameter. Polar and azimuthal angles were estimated using the given branch orientation. All segmental bronchi (last branches of central airways) are used as the axiom of the second section.

3.2. Dichotomous structure

To generate the dichotomous tree, parametric L-System is used. Because the rules proposed by Davoodi and Boozarjomehry [22] are based on the bifurcating concept, we used their rules given in Eq. (3.1). In each generation, a parent airway divides into two daughter airways in a single branching plane. It should be noted that these rules are modified to include any rotation angle, which is the angle between two successive branching planes. In addition, the process of finding the parameters is different.

$$\begin{aligned}
\omega &: F(l_0, d_0, N_0, 0) \\
P_1 &: F(l_p, d_p, N_p, 0) \rightarrow E(l_p, d_p)[-(\theta_1)F(\Gamma(D, \gamma_1 d_p), \gamma_1 d_p, N(\varphi), c)][+(\theta_2)F(\Gamma(D, \gamma_2 d_p), \gamma_2 d_p, N(\varphi), c)] \\
P_2 &: F(l_p, d_p, N_p, 1) \rightarrow E(l_p, d_p)[-(\theta_1)A(\Gamma(D, \gamma_1 d_p), \gamma_1 d_p, N(\varphi))][+(\theta_2)F(\Gamma(D, \gamma_2 d_p), \gamma_2 d_p, N(\varphi), c)] \\
P_3 &: F(l_p, d_p, N_p, 2) \rightarrow E(l_p, d_p)[-(\theta_1)F(\Gamma(D, \gamma_1 d_p), \gamma_1 d_p, N(\varphi), c)][+(\theta_2)A(\Gamma(D, \gamma_2 d_p), \gamma_2 d_p, N(\varphi))] \\
P_4 &: F(l_p, d_p, N_p, 3) \rightarrow E(l_p, d_p)[-(\theta_1)A(\Gamma(D, \gamma_1 d_p), \gamma_1 d_p, N(\varphi))][+(\theta_2)A(\Gamma(D, \gamma_2 d_p), \gamma_2 d_p, N(\varphi))]
\end{aligned} \tag{3.3}$$

θ and φ are branching angle, the angle between the branch and its parent, and rotation angle, respectively. N_p and N are the normal vectors of the parents' plane and daughters' plane. The schematic of two successive branching planes is shown in Fig. 2. l_p and d_p are the length and diameter of the parent branch. γ is the ratio of branch diameter to that of its parent.

281 Turtle interpretation of the above rules is described in Table 3. $\Gamma(D, d)$ is a function for finding
 282 branch length based on parameter D and the branch diameter d . Branching procedure terminates
 283 at A which is terminal bronchiole (TB). The value of parameter c determines whether a branch
 284 terminates or not. The procedure of finding parameter c depends on the extent of our knowledge
 285 of the system, i.e. the tracheobronchial tree of humans or other species. If enough data are
 286 available about the length and diameter of terminal bronchioles, their values are used as
 287 termination criteria; otherwise, a reasonable distance to the corresponding boundary is considered
 288 for this purpose. Based on previous measurements on the human bronchial tree, the diameter and
 289 length of TB vary from $0.432 \pm 0.035 \text{mm}$ [39] to $0.66 \pm 0.04 \text{mm}$ [40], and from $0.8 \pm 0.35 \text{mm}$ [23]
 290 to 1.7mm [31] , respectively. A branch is considered TB if its diameter and length are both less
 291 than $d_{TB,max}$ and $L_{TB,max}$, respectively. Since maximum measured values for the parameters have
 292 not been reported in the previous studies, the values of $d_{TB,max}$ and $L_{TB,max}$ should be higher than
 293 $0.66 + 0.04$ and 1.7 , respectively. To prevent the production of very small TBs, these threshold
 294 values have been obtained through ad-hoc iterative method. The appropriate values of $d_{TB,max}$ and
 295 $L_{TB,max}$ are 0.8mm and 1.8mm , respectively.

296
 297 **Fig. 2** Schematic of two successive branching planes

298 **Table 3** symbols of commands in turtle interpretation for dichotomous rewriting rules

Command	Action
---------	--------

$F(l, d)_I$	move forward and draw a cylinder with length of l and diameter of d
$N(\varphi)$	Calculate the normal vector of daughters' plane and turn parent plane by angle φ
$-(\theta)$	Turn by angle θ in the clockwise direction
$+(\theta)$	Turn by angle θ in the counter-clockwise direction
C	Its value determines if the branching process continues from the daughter(s) branch or not

_I action of characters {A, E} is similar to F but the branching process terminates in A.

In the human bronchial tree, each branch divides into two branches with a reduction in diameter. Mauroy et.al [32] showed that the best structure minimizing total viscous dissipation is a fractal whose dimension is 3. In this ideal tree size ratio, the ratio of the daughters' dimensions to the corresponding dimensions of their parent, is $(1/2)^{1/3} \sim 0.79$. In addition, they demonstrated that a physically optimum tree does not have physiological robustness of the human bronchial tree. The human bronchial tree has an average size ratio of 0.85, which is larger than the physically optimum value, and with such a size ratio, the volume of the human bronchial tree is too large and its resistance is too small. Some previous research aimed to design a bronchial tree based on minimizing the volume and total resistance[41] or bifurcating resistance [16, 22]. However, physical optimization of the bronchial tree may be dangerous [32]. On the other hand, it is necessary to model the bronchial tree to satisfy the physiological constraints. In what follows, we suggest an intelligent procedure for finding the parameters of L-System to fulfill the physiological and anatomical requirements of dimensions and orientations.

Parameters γ_1 and γ_2 must be less than 1 since the daughters' diameters are always smaller than their parents. Murray[17] showed that $Q=Cd^3$ minimizes the power dissipation in an ideal tree assuming laminar flow. Uylings [42] extended the equation to $Q=Cd^n$ where 'n' is diameter exponent and depends on flow regime, $n=3$ for laminar and $n=2.34$ for the turbulent regime. Assuming a flow ratio 'r' the parameters γ_1 and γ_2 are:

$$\gamma_1 = r^{\frac{1}{n}} \quad \gamma_2 = (1 - r)^{\frac{1}{n}} \quad (3.4)$$

Kitaoka et.al [16] found that $n=2.8$ leading to the best structure. Flow is not turbulent in all parts of the dichotomous structure, so the value should be greater than 2.33. On the other hand, the viscous forces are only dominant in the periphery of conducting airways thus the value should be less than 3. 'r' is flow dividing ratio defined as the ratio of smaller flow in the daughters to that in the parent. In this study, it varies from 0.15 to 0.5 indicating the structural asymmetry. As this parameter gets closer to 0.5 the structure gets more symmetric. Since the human lung structure becomes more symmetric with the generation, the parameter approaches to 0.5 with increasing generation. Hence, this parameter is calculated by a normal distribution at each generation in such a way that it remains between r_{min} and r_{max} , where r_{min} and r_{max} are functions of generation and change after some generations to propel the structure toward symmetrizing.

To find the branch length an initial length ($L_m > d$) is considered. It is then examined whether this branch intersects the Segment boundary and other branches during its growth or not. In addition, this branch should be sufficiently far away from the Segment boundary so that there is enough space for the growth of other conducting airways and the acinar region. Therefore, the parameter D is defined as the minimum of the distance between the branch and other branches and a fraction (r_d) of its distance to the boundary. The latter was used to ensure the availability of enough space for growth of acinar region which was ignored in the model of Davoodi and Boozarjomehry[22] . Afterward, the branch length is adjusted in a value less than the minimum of D and L_m according to Eq. (3.5). Kiatoka[16] suggested that the length to distance ratio ranges from 0.17 to 0.34 by examining many computed tomography images. Because the length is reduced using Eq. (3.5), the value of r_d is set to 0.5.

$$\Gamma(D, d) = \min(L_m, D) \min(\exp(-\omega * D/d), 0.85) \quad (3.5)$$

where ω and is a measure of length reduction and is set at 0.04. Davoodi and Boozarjomehry[22] used a similar equation for length reduction. They decreased the length by a factor of $\exp(-\omega/D)$, where D was a minimum distance of the new branch to other branches and the boundary. However, this equation couldn't be used for different sizes of lungs originated from various ages because the parameter ω was not dimensionless. Therefore, the expression is age-dependent and results in more reduction in length for shorter branches. Hence, in their model, some parameters should be changed to make the model capable of the tracheobronchial tree construction for subjects with various ages successfully.

A mathematical model is required for the boundaries of all bronchopulmonary segments to calculate the distance of each branch to the corresponding boundary. Davoodi and Boozarjomehry[22] used the thin-plate smoothing spline method to describe the boundaries and subsequently calculated the distance between each branch and lobe boundaries. However, the method cannot accurately describe the non-convex characteristic of bronchopulmonary segments' boundaries. Therefore, each boundary is discretized by the triangular elements. The distance to the boundary is the minimum of the distance of the branch to all triangles. To find the distance, it is necessary to obtain the intersection of the branch with all triangular cells; accordingly, its calculation algorithm should be fast enough to avoid the computational time and demand. For this purpose, the ray-triangle intersection algorithm proposed by Moller and Trumbor [43] and Havel and Harout [44] were examined, which are the fastest algorithms. Finally, the algorithm suggested by Moller and Trumbor has been used. To further decrease the calculation time corresponding to the evaluation of branch distance to the boundary, the surface mesh became coarse as much as possible. For this purpose, the triangular cells of different sizes have been used to keep the shape of the segments unchanged as, for instance, indicated in Fig. 3. It should be noted that this

algorithm has been also used to obtain the distance between each branch with its surrounding branches. For this purpose, each branch is surrounded by a cuboid which can be described by 12 triangular cells. Therefore, the distance can be approximated by the minimum distance of the growing branch to the triangular cells of other branches. In addition, before the calculation of the intersection of the branch with the other ones, the probability of its collision with them is examined. In other words, for cases where the collision probability is not zero, the ray-triangle intersection algorithm has been used. The intersection probability will be zero if the distance between the centers of the branch and another branch is less than half of the sum of the length and diameter of both branches. This makes the algorithm 20 times faster.

Fig. 3 The structure obtained based on a coarse mesh (left) and extra fine (right) one for the apical segment of the right upper lobe

It is clear that the airway length depends on the branch orientation that is determined after finding the rotation angle of φ and the branching angle of θ . It should be noted that the parent and its daughters are on the same plane. The schematic of parents and daughters have been shown in Fig. 2. Accordingly, a normal vector to daughters' plane must satisfy the following equations.

$$\begin{aligned} N \cdot P &= 0 \\ N \cdot N_p &= |N| |N_p| \cos(\varphi) \\ |N| &= 1 \end{aligned} \tag{3.6}$$

378 where P , N , and N_p are branch orientation of parent, normal vector to daughters' plane, and a
 379 normal vector to the parents' plane, respectively. By solving the above equations, the elements of
 380 N are obtained by:

$$\begin{aligned}
 A &= (|N_p \times P|^2 - (|P||N_p|\cos(\varphi))^2)^{0.5} N \cdot N_p = |N||N_p|\cos(\varphi) \\
 N_x &= -A|N_p \times P|_x + (N_{px}(P_y^2 + P_z^2) - N_{py}P_xP_y - N_{pz}P_xP_z) |N_p|\cos(\varphi) \\
 N_y &= -A|N_p \times P|_y + (N_{py}(P_x^2 + P_z^2) - N_{px}P_xP_y - N_{pz}P_yP_z) |N_p|\cos(\varphi) \\
 N_z &= -A|N_p \times P|_z + (N_{pz}(P_x^2 + P_y^2) - N_{px}P_xP_z - N_{py}P_yP_z) |N_p|\cos(\varphi)
 \end{aligned} \tag{3.7}$$

381 Now, branch orientation can be determined by solving Eq. (3.8) and there are two possible
 382 solutions which are given in Eqs. (3.9-3.10) for both clockwise and counter-clockwise directions,
 383 respectively.

$$\begin{aligned}
 N \cdot d &= 0 \\
 P \cdot d &= |d||P|\cos(\theta) \\
 |d| &= 1
 \end{aligned} \tag{3.8}$$

$$\begin{aligned}
 A &= (|N \times P|^2 - (|P||N|\cos(\theta))^2)^{0.5} \\
 d_x &= A|N \times P|_x + (P_x(N_y^2 + N_z^2) - P_yN_xN_y - P_zN_xN_z) |P|\cos(\theta) \\
 d_y &= A|N \times P|_y + (P_y(N_x^2 + N_z^2) - P_xN_xN_y - P_zN_yN_z) |P|\cos(\theta) \\
 d_z &= A|N \times P|_z + (P_z(N_x^2 + N_y^2) - P_xN_xN_z - P_yN_yN_z) |P|\cos(\theta)
 \end{aligned} \tag{3.9}$$

$$\begin{aligned}
 A &= (|N \times P|^2 - (|P||N|\cos(\theta))^2)^{0.5} \\
 d_x &= -A|N \times P|_x + (P_x(N_y^2 + N_z^2) - P_yN_xN_y - P_zN_xN_z) |P|\cos(\theta) \\
 d_y &= -A|N \times P|_y + (P_y(N_x^2 + N_z^2) - P_xN_xN_y - P_zN_yN_z) |P|\cos(\theta) \\
 d_z &= -A|N \times P|_z + (P_z(N_x^2 + N_y^2) - P_xN_xN_z - P_yN_yN_z) |P|\cos(\theta)
 \end{aligned} \tag{3.10}$$

386 In this study, the rotation angle is fixed at 90° , which is consistent with the previous studies
 387 [16, 20, 22]. The branching angle (θ) has a significant effect on branch length.

388 If an inappropriate value for θ is selected, many airways with small lengths are produced and
 389 this prevents the growth of other airways and consequently, the development of conducting
 390 airways would be stopped before reaching the acinar region. Besides, this causes the terminal

bronchioles with an inappropriate length to be generated. For example, an improper branching pattern may lead to a bronchiole with a large diameter lies near the boundary, while its diameter is not in the reasonable range. Furthermore, since it is in the vicinity of the boundary it cannot be long enough and this causes too low length-to-diameter ratio. Such a scenario results in inappropriate short branches. In addition, this may similarly cause small diameters. Furthermore, the orientation of the branch affects the tree weight, fluid friction, and energy dissipation. Therefore, it is essential to determine this parameter properly. Kitaoka[16] considered a simple bifurcation and obtained Eq. (3.11) based on the minimization of power dissipation and the total volume of bifurcation. Davoodi and Boozarjomehry [22] used Eq. (3.11) for this purpose.

$$\begin{aligned} \cos(\theta_1) &= (1 + r^{4/n} - (1 - r)^{4/n})/2r^{2/n} \\ \cos(\theta_2) &= (1 + (1 - r)^{4/n} - (r)^{4/n})/2(1 - r)^{2/n} \end{aligned} \quad (3.11)$$

However, all these methods were solely based on ongoing bifurcation, and this does not guarantee the minimization of the objective function for the whole structure of the human lung. Although these mathematical relations decrease the resistance in the current bifurcation, it may result in lots of bifurcations leading to the severe increase of total resistance. On the other hand, the human lung is not physically optimized and such models are physiologically dangerous[32]. Therefore, an intelligent procedure is required to lead the branches to the corresponding boundary so that the anatomical constraints of the human lung are satisfied. Thus, instead of using any of the above relations(e.g., Eq. (3.11)), the growth of each branch is examined in the several angles to obtain enough information about the surrounding then the best angle is chosen based on some heuristic rules used to satisfy anatomical and physiological constraints. For this purpose, the angle changes by increment $\Delta\theta$ between θ_{min} and θ_{max} and an angle is randomly selected at each subinterval $([\theta_i, \theta_i + \Delta\theta])$ by a normal distribution with a mean of θ_i and a standard deviation of $\Delta\theta/2$. After that, branch orientation is calculated for each θ using Eq. (3.9) or (3.10). To find the best branch

413 orientation among these potential directions, the following rules are used. It should be noted that
414 each direction has its diameter, length, and distance to the corresponding boundary whose
415 calculation algorithm mentioned previously.

416 *Rule 1: if $d/d_{TB} \leq 1.2$ then the probability of being TB in the next few generations (i.e. up to*
417 *three generations) is high, thus a direction with the minimum length is chosen.* This rule
418 prevents the production of TB's with too small diameter because if the minimum length was not
419 chosen, then there would be numerous growth cycles (generations) from this branch and this would
420 lead to branches whose diameters are significantly lower than their corresponding anatomically
421 meaningful values.

422 *Rule 2: if $1.2 < d/d_{TB} \leq 1.5$ then the probability of being TB in the next few generations is*
423 *medium, hence a direction with the minimum distance to the corresponding boundary is chosen.*
424 This rule leads branches to the corresponding bronchopulmonary segment boundary and prevents
425 growing procedure stopped in the middle of the segment.

426 *Rule 3: if the length of the selected direction is too small ($L/d < 2$), this direction is replaced by*
427 *another one that satisfies this condition and has the least length.* This rule prevents the
428 production of branches with too small aspect ratio.

429 *Rule 4: if the probability of being TB in a few next generations is low (i.e., neither of the above*
430 *rules is fired), the best direction is the one with the highest score defined in Eq. (3.12).* This rule
431 leads branches to the less crowded regions with higher lengths and thus the congestion caused by
432 the physical presence of the surrounding branches is reduced and a structure with the minimum
433 number of bifurcations is well constructed.

$$S = \frac{L}{L_{\max}} + \max((\text{gen} - 15), 1) \frac{\rho}{\rho_{\max}} \quad (3.12)$$

434 where ρ is a measure of emptiness around a growing branch which is defined in Eq. (3.13).

$$\rho_i = \frac{\sum_{j=1}^N l_{ij}}{N} \quad (3.13)$$

435 where N is the number of branches with non-zero collision probability around the growing branch.

436 l_{ij} is the distance between the center of the i 'th branch and that of the j 'th branch. The second term

437 will be dominant in the last generations because of $\max((\text{gen} - 15), 1)$.

438 As mentioned above, these rules generally conduct branches to bronchopulmonary segments
 439 boundaries and less crowded regions. These rules primarily may cause few branches to be
 440 generated because they may direct the branches forward rather than distribute them. To solve this
 441 problem, the initial range of the branching angle ($\theta_{\min}$ and $\theta_{\max}$) should be determined based on
 442 its relative distance to the corresponding boundary in the axial and lateral directions to provide the
 443 branch with the necessary information about its vicinity. These parameters tell the branch that it
 444 is in a round space or a long thin region. In addition, to ensure that the lung surface and the
 445 segments' interfaces are fed at least by one branch, the adjacent bronchopulmonary segments are
 446 also considered in the determination of the angle range. Hence, conducting airways in all segments
 447 should be generated simultaneously. If a portion of the interface is not fed by branches in the
 448 neighbor segment, the angle is set in such a way that the chance of getting it fed through the
 449 growing branch increases. Accordingly, the ratio of the distance between a branch and its segment
 450 interface to the segment diameter along the direction of branch orientation (ld_{axial}), and the same
 451 for the lateral direction ($ld_{lateral}$), and the congestion difference on both sides of the interface ($\Delta\beta$)

452 are applied to obtain the range of the branching angle. $\Delta\beta$ is defined in Eq. (3.14) and calculated
453 for each cell of the interface.

$$\beta = \frac{\sum_{i=1}^N A_i}{A_{\text{cell}}} \quad (3.14)$$

$$\Delta\beta = \beta_{\text{neighbor}} - \beta_{\text{owner}} \quad (3.15)$$

454 where A_{cell} and A_i are cross-section area of a triangular boundary cell and its adjacent airways,
455 respectively.

456 Although we understand that the range of branching angle depends on the mentioned parameters,
457 the exact relation is unknown. However, we know qualitatively the effect of each parameter on the
458 branching angle. To find the branching angle based on non-numerical information, the fuzzy
459 inference system is employed. The fuzzy inference system is a type of inference systems in which
460 the reasoning is done based on the facts and concepts whose truths are subjective (and /or cannot
461 be validated firmly). The logic behind such reasoning differs from conventional logic. In Fuzzy
462 logic, a fact might be partly true or false, while this is also the case for a rule or logical expressions.
463 The truth values of rules, logical expressions, and facts vary from 0 to 1. The design of a fuzzy
464 inference systems includes three steps: 1) Specifying the Fuzzy sets comprising the universe of
465 discourse of each variable (either input or output) used in the inference system, 2) Development
466 of rule base which consists of all the rules (coming from intuition and/or results obtained from
467 qualitative or quantitative phenomenological studies) based on which the fuzzy inputs get mapped
468 to fuzzy outputs 3) Selection of defuzzification method by which the fuzzy values of each fuzzy
469 output variable transformed back to a crisp numeric value. There are various useful resources
470 (including books and articles) that the interested readers can refer to among which reference [45]
471 is very informative.

The cascade fuzzy inference system is used to find the range of branching angles based on previously mentioned affecting parameters. Figure 4 shows a schematic of the fuzzy system. Figures 4-7 indicate the fuzzy sets for the input and output variables and the rule table of the fuzzy inference system, respectively. The rule table has been prepared based on our knowledge of the structure. $ld_{lateral}$, ld_{axial} , and $\Delta\beta$ are divided into 3 fuzzy sets, and θ_i , θ_{min} , and θ_{max} are divided into 5 fuzzy sets. Symbols VL, L, M, H, VH, N, Z, P denote Very Low, Low, Medium, High, Very High, Negative, Zero, and Positive, respectively. It should be noted that the first input of the second fuzzy system will be θ_{min}^i (θ_{max}^i) if its output is θ_{min}^i (θ_{max}^i).

Fig. 4 Fuzzy logic system to find the range of branching angle

Fig. 5 Fuzzy sets for $ld_{lateral}$ and ld_{axial}

Fig. 6 Fuzzy sets for $\theta_{\min}$ and $\theta_{\min}^i$

Fig. 7 Fuzzy sets for $\theta_{\max}$ and $\theta_{\max}^i$

Fig. 8 Fuzzy sets for $\Delta\beta$

491

Table 4. Rules for the first fuzzy system

$ld_{lateral}$		L	M	H
ld_{axial}	L	L	H	VH
	M	L	M	H
	H	VL	L	H

492

493

Table 5. Rules for the second fuzzy system

θ_i		VL	L	M	H	VH
$\Delta\beta$	N	L	M	H	VH	VH
	Z	VL	L	M	H	VH
	P	VL	VL	L	M	H

494

495 In the human bronchial tree, there are some branches called “links” whose orientations are in
 496 the direction of their parent orientation. In order to include the links in the structure, the best
 497 direction of each daughter is compared with the link and replaced via the following procedure. It
 498 should be noted that only one daughter can be replaced and the procedure determines which one
 499 is compared with the link. It worth noting that the “links” have been ignored in model of Davoodi
 500 and Bozorgmehry[22].

501 i) If $\theta_1(\theta_2) = \hat{\theta}_{min}$ and $\theta_2(\theta_1) > \hat{\theta}_{min}$, the daughter 1(2) is compared with the link to prevent
 502 a very small angle between daughters.

503 ii) If $\theta_1 \& \theta_2 > \theta_{min}$, the daughter with smaller l/d is compared with the link based on previous
 504 rules. To ensure that the branches are well distributed, the generation of more than three subsequent
 505 links are avoided.

506 According to the production rules, each branch is divided into two daughter branches provided
 507 that the parameters of the daughters are determined. The orientation and dimensions of the
 508 daughters are found via the following steps:

1. A random value is chosen for 'r' from a random number generator with a uniform distribution.
2. The diameter of each branch is calculated using the diameter ratio given in Eq. (3.4).
3. Using a predefined value for rotation angle, φ , the normal vector of daughters' plan calculated by Eq. (3.7).
4. The lateral and axial distances of each branch to the host boundary are calculated.
5. The value of parameter $\Delta\beta$ is obtained using Eq. (3.14).
6. The range of branching angle ($\theta_{\min}$ and $\theta_{\max}$) are determined through the proposed fuzzy scheme.
7. Several branching angles are selected in the range of ($\theta_{\min}$ and $\theta_{\max}$), and the branch orientation corresponding to each branching angle is calculated using Eq. (3.9) and Eq. (3.10).
8. The distance to the boundary and parameter D is calculated for each potential branch orientation. Then the corresponding branch length is calculated by Eq. (3.5).
9. The best orientation of each branch is selected among the potential orientations through the proposed predictive rules.
10. At most one daughter branch is compared with the link and the best direction is chosen using the same predictive rules.
11. The daughters are compared and if the branch with a larger diameter does not have a greater length, the procedure is repeated from step 1. Because the branch with greater length has a greater distance to the boundary and is located in the less crowded region, it should be thicker to deliver air to the larger volume.

12. Although the predictive rules are designed to find the best direction, there may be few terminal bronchioles with too small length. To remove such branches in the structure, the algorithm goes back and reduces the diameter ratio in order for the paths to reach to terminal bronchioles earlier and stop their growths in this direction before too short branches are produced.

All parameters of the proposed procedure except $d_{TB,max}$ and $L_{TB,max}$ are dimensionless and independent of the size of the human lungs. Therefore, these parameters should be estimated for the children. Menache et.al [46] proposed an equation for the diameter of terminal bronchioles of subjects aged 0.75 yrs to 30yrs. To find $d_{TB,max}$, we improved the equation by multiplying it in a correction factor so that it gives $d_{TB,max}$ of 0.8mm for adults. The equation is given in Eq. (3.16). The value of $L_{TB,max}$ is assumed to be equal to $2.25d_{TB,max}$.

$$d_{TB,max} = 0.9236 - 0.7547e^{-0.0603 \text{ age}(yrs)} \quad (3.16)$$

4. Results

In this section, the segmentation results of bronchopulmonary segments are presented. Then the generated bronchial tree using the proposed method is evaluated through comparison of geometrical properties with morphological measurements and the other alternate methods. The analyses are performed for both central airways and the whole structure. In what follows, the daughter branches with the smaller and larger diameters are called the minor and major branches, respectively. The subscripts ‘min’, ‘maj’, and ‘p’ denote minor, major, and parent branches, respectively. The results correspond to a total lung capacity of 5500ml.

The central airways have been generated via three generations of applying production rules. The mean diameter of segmental bronchi, lobar bronchi, and total airways are 4.32mm, 7.8mm, and 6.59mm which is comparable with the value of 4.61, 6.73, and 6.29 measured by Horsfield et.al [13]. The insignificant difference between the values may originate from the difference in the method of measurement and size of the lung. The geometric properties of central airways are summarized in Table 6. The mean values of l/d , d/d_p and d_{min}/d_{maj} are consistent with the previously reported values. The value of l/l_p has large standard deviation because in upper airways there are some branches with short parent length. The difference between the reported values originates from the fact that they are based on various number of extracted airways and the variations that exist in the structure of central airways among various people. Peripheral airways are classified as Strahler order and Horsfield order of 1. The mean value of diameter for Strahler order of 1, 2 and 3 are 4.32mm, 7.00mm, and 12.19mm, respectively. The results show the increase of diameter with the Strahler order. The variation of number, diameter, and length against the Horsfield order are shown in Fig. 9. This figure indicates that the length doesn't decrease as uniformly as diameter. The trend reveals that the length reduction has almost a linear trend for small Horsfield orders.

Table 6. Geometric properties of central airways

	The present method	Published values		
		[13]	[19]	[22]
l/d	2.74 ± 1.39	2.15 ± 1.16	3.04 ± 2.2	3.42 ± 1.61
d/d_p	0.70 ± 0.14	0.75 ± 0.16	0.71 ± 0.14	0.63 ± 0.16
l/l_p	0.98 ± 0.61	1.10 ± 1.30	1.18 ± 1.1	
d_{min}/d_p	0.60 ± 0.1	0.67 ± 0.08	0.66 ± 0.12	
d_{maj}/d_p	0.79 ± 0.09	0.83 ± 0.17	0.79 ± 0.12	
d_{min}/d_{maj}	0.78 ± 0.17	0.83 ± 0.13	0.85 ± 0.14	0.69 ± 0.17
θ	$41.6^\circ \pm 17.5^\circ$		$36.11^\circ \pm 20.85^\circ$	$37.38^\circ \pm 15.75^\circ$

Fig. 9 Variation of the number of branches, mean diameter and mean length of central airways against Horsfield order

The bronchopulmonary segments were obtained using 3DSlicer software. The segmentation results for both right and left lungs are shown in Figs. 10-11. The eighteen dichotomous structures are merged with the central airways to generate the whole structure of the tracheobronchial tree as shown in Fig. 12. Each bronchopulmonary segment and central airway are shown with different colors: central airways are gray and the color of each segment is similar to its corresponding ones in Figs. 10-11. In addition, bronchial airway tree produced by parametric L-system for the smallest segment (RL_medial), and two of the largest segments (RL_posterior and LU_anterior) are indicated in Figs. 13-15. These figures indicate that the bronchial tree has grown properly up to the host boundaries.

Fig. 10 Bronchopulmonary segments of the right lung

Fig. 11 Bronchopulmonary segments of the left lung.

Fig. 12 Anterior view of conducting airway produced by the proposed method

Fig. 13 Conducting airways in RL_medial produced by the proposed method

Fig. 14 Conducting airways in RL_Posterior produced by the proposed method

Fig. 15 Conducting airways in LU_anterior produced by the proposed method

The generation number is a measure of the distance of a branch and the trachea. The greater the generation number reflects that the branches are further from trachea. Table 7 indicates the mean, minimum and maximum generation number of terminal bronchioles in the lungs and each lobe. The acini are appeared in the mean generation of 16.7, with a minimum of 8 and maximum of 25. The number of TB's in the structure obtained by the proposed method is 30201 and is comparable with those reported in the literature as shown in Table 7. The number of TB's obtained by Haefeli-Bleuer and Weibel [23] lies in the range of 26000 to 32000. Generation number of TB's is a measure of the number of bifurcations from trachea at which an acinus may appear. Lobes that are further away from trachea have a larger mean generation number of TB's as shown in Table 7. For instance, the right lower lobe has the largest generation number because it has the furthest distance from the trachea and is the largest lobe.

Table 7. Number of terminal bronchioles and corresponding generation number

	NO of Acini	Generation distance of acini from the trachea						Min	max
		RU	RM	RL	LU	LL	Lungs		
The present method	30201	15.9	16.2	18.3	16.5	16.6	16.7	8	25
[21]	27763	15.3	15.2	17.2	15.9	16.3	16.2±1.7	8	25
[10]							15	8	25
[16]	28313						17.6±3.4	8	32
[47]		15	15	17	15	16	15.6		
[18]	29445	16.4	16	17.4	16.3	16.2	16	10	26

Although using generation number is useful for locating the branches in relation to the trachea, it is not appropriate for asymmetric trees because this classification locates very dissimilar branches in one generation. Therefore, the branches should be classified by order instead of generation. Strahler and Horsfield orders are the most common classifying methods for asymmetric trees. The number of branches is decreased with the increase in Strahler and Horsfield

orders and hence trachea has the highest Strahler and Horsfield orders. The relative increase in each order is called branching ratio, R_b , and is defined as the antilog of the slope of the line representing the number of branches versus the branching order in a logarithmic plot. The diameter ratio (R_d) and length ratio (R_l) are calculated similarly and are measures of the reductions in diameter and length, respectively. Figures 16-17 show the logarithmic plot of the number of branches, diameter, and length against Horsfield and Strahler orders. Table 8 compares R_b , R_d , and R_l obtained by the proposed method and their corresponding published values. The value in parenthesis is R squared (coefficient of determination) of the corresponding variable. Prefixes “S” and “H” indicate the parameters calculated from Strahler and Horsfield ordering, respectively. HR_b and SR_b are equal to 2 for symmetric trees. SR_b becomes greater than 2 and HR_b approaches to 1 with an increase in asymmetry. SR_b of 2.76 obtained in this study is higher than those given by [18, 21, 47] and less than those predicted by [19, 22]. HR_b of 1.52 is consistent with the published values. The difference in the reported values may be originated from the degree of asymmetry of the methods and the shape of the lungs. Round lungs have a lower R_b than long thin ones. Figure 15 shows a more linear trend comparing to those that exist in Fig. 16 and hence SR_b is more consistent throughout the lungs. However, every branch is not separately ordered in Strahler ordering method. This makes a simpler description with loss of details compared to the Horsfield ordering method in which each branch is separately ordered. To minimize resistance or entropy production, the value of R_d is expected to be almost equal to $R_b^{1/3}$ [48]. The predicted values for R_b and R_d well follow this relation (1.12% relative deviation for Strahler ordering and 0.25% for Horsfield ordering).

Fig. 16 Number, length, and diameter of airways against Horsfield order

Fig. 17 Number, length, and diameter of airways against Strahler order

Table 8. Structural properties of the human bronchial tree obtained by the proposed method and previous studies

	The proposed method	Published									
		[21]	[22]	[18]	[19]	[20]	[48]	[47]	[10]	[31]	[30]
l/d	3.49 ± 1.09	3.25 ± 0.52	4.05 ± 0.41		2.92 ± 0.92	4.51 ± 0.25			3.25	3.35	3.75 ± 0.21
d/d_p	0.856 ± 0.091	0.789 ± 0.194	0.76 ± 0.14		0.79 ± 0.15	0.82 ± 0.00			0.88		
d_{min}/d_{maj}	0.796 ± 0.091	0.663 ± 0.184	0.64 ± 0.15		0.69 ± 0.06	0.81 ± 0.00					
d_{maj}/d_p	0.914 ± 0.036	0.914 ± 0.087	0.88 ± 0.09		0.88 ± 0.14	0.85 ± 0.00					
d_{min}/d_{maj}	0.87 ± 0.092		0.75 ± 0.19		0.81 ± 0.17	0.97 ± 0.00		0.86			
l/l_p	0.86 ± 0.267		0.78 ± 0.7		0.81 ± 0.30	0.89 ± 0.00			0.85		
θ	41.4 ± 22.5	42.1 ± 21.4	36.1 ± 4.88		50.31 ± 28.92	42.89 ± 0.10				47	20-25
SRb	2.76 (0.996)	2.49	2.81	2.358	2.8		2.805	2.508			

SRd	1.42 (0.99)	1.397	1.51	1.323	1.41	1.427	1.351
SRI	1.40 (0.95)	1.392	1.47	1.344	1.39	1.402	1.33
HRb	1.51 (0.99)	1.56	1.44	1.39	1.47		
HRd	1.15 (0.97)	1.166	1.14	1.109			
HRI	1.12 (0.89)	1.13	1.11	1.11	1.13		

637

638 Table 8 compares the geometrical properties of the tracheobronchial tree generated in this study
639 with those reported in the previous studies.

640 Because the diameters of three branches involving in a bifurcation are different, it is of interest
641 to observe the relation between them. In this study, the diameter decreased based on Eq. (3.4)
642 reflecting the relationship between flow rate and branch diameter in a living organ to make it
643 capable of overcoming the energy lost due to fluid friction in an optimal manner. For typical human
644 bronchial tree the diameter exponent, ‘n’, is approximately 2.9₂ [48], which is closer to that in the
645 laminar flow. We examined several values for ‘n’ in the range of 2.4 to 3.5 and found that the best
646 structure could be obtained with a value of 2.8 as proposed by Kitaoka et al[16] and used by
647 Davoodi and Bozorgmehry[22]. Weibel [29] showed that D/D_p is higher for generations >10 with
648 a minimum average value of 0.84. Therefore, the minimum value of 0.7 was considered for D/D_p
649 in generations>10. The stochastic behavior of the proposed procedure originates from the random
650 flow-dividing ratio (r) building slightly different structures with the same structural properties. It
651 is randomly set for each branch in such a way that the larger host volume is fed by the major
652 daughter r. D/D_p, D_{min}/D_p, D_{maj}/D_p, D_{min}/D_{maj} are consistent with those reported in the previous
653 studies. The obtained value of D/D_p is 0.856 which is higher than that predicted by the previous
654 methods[19-22] and slightly less than that measured by Weibel [29]. In an ideal fractal tree, this
655 ratio is 0.79 (2^{1/3}). However, Mauroy et al [32]showed that the human bronchial tree is not

² It is approximated as $\log(\text{SRb}=2.805)/\log(\text{SRd}=1.427)=2.9$

656 physically optimal and the ratio in the real tree is about 0.85 which is approximately equal to that
 657 obtained in this study. Diameter reduction in the human bronchial tree is greater than that predicted
 658 by the previous models and that is due to the fact that the physiological robustness of human lung
 659 is obtained at the expense of its deviation from the physically optimum structure. This
 660 physiological robustness makes the lungs functional in the case of slight damage in its structure.
 661 That is, the diameter ratio in the proposed method is greater than that in the previous models.
 662 Furthermore, D/D_p predicted by the proposed method has been compared with those measured by
 663 Weibel[29] and Yeh and Schum[11] in Fig. 18. This figure confirms the ability of the proposed
 664 procedure in the prediction of real data. d_{min}/d_{maj} calculated by the present model is much smaller
 665 than those reported by Bordas et.al [20] because the present method is more asymmetric comparing
 666 to their obtained structure[20]. It is greater than those reported in [22] and [19] and is comparable
 667 to [47]. Weibel [29] measured d_{min}/d_{maj} of 0.86 ± 0.01 , which is almost the same as the value
 668 predicted in our work.

669
 670 **Fig. 18** Diameter ratio against generation number

672 The predicted mean value of the length-to-diameter ratio is inline with those calculated in the
673 previous studies as indicated in Table 8. The higher standard deviation (SD) may be originated
674 from considering bronchopulmonary segments as host volume while the tree was grown in the
675 lungs or lobes in the previous studies. For instance, the inferior lingular is a long thin segment.
676 Therefore, airways along axial direction should have a large length, whereas those in lateral
677 direction have smaller length, this results in greater standard deviation compared to the previous
678 models. However, the coefficient of variation is comparable to what estimated by Tawhai et.al
679 [19].

680 l/l_p has a higher standard deviation than d/d_p because the length doesn't decrease as uniformly
681 as diameter. Figures 16-17 also confirm the result where the trend of diameter reduction is more
682 linear than that of length.

683 The present method predicts TB's diameters (D_{TB}) of 0.49 ± 0.065 mm. The previous clinical
684 studies measured D_{TB} of 0.432 ± 0.035 mm [39] and 0.5 ± 0.054 mm [23] using direct cast analysis,
685 and 0.66 ± 0.04 mm [49] using synchrotron CT in a limited number of images. Previous models
686 predicted D_{TB} using some particular stopping conditions. D_{TB} of 0.48 ± 0.06 mm, 0.375mm, 0.6mm,
687 and 0.418 ± 0.114 mm reported by [16], [18], [19], and [20], respectively. Although Davoodi and
688 Bozorgemhry [22] did not report the value of D_{TB} , we obtained too small TB's using their method.
689 This is a major shortcoming because the small dimensions of TB's consequently affect the size of
690 the acini fed by them and subsequently underestimate the lung volume and gas exchange area too
691 much.

692 The TB length (L_{TB}) of 0.87 ± 0.40 mm has been predicted by the proposed method. The L_{TB} of
693 0.819 ± 0.14 mm, 0.8 ± 0.354 mm, and 0.93 ± 0.43 mm reported by [39], [23], and [40] using the

direct measurements on TB's. However, the values of $1.34 \pm 0.44 \text{ mm}$ and $\sim 1.8 \text{ mm}$ predicted by [20] and most of the previous models [19, 31, 50]. The L_{TB} predicted by the present method is less than those reported by the previous models and is more consistent with the experimental data. This is because, in the present method, the airways grow inside the bronchopulmonary segments which restrict the growth and length of TB's more than what lobes or lungs do.

The mean branching angle in our model is 41.4° . The mean branching angle is about 47° based on the data of 20 lung casts [31] and 41.26° reported by [41] which is close to that calculated by the proposed method. The calculated SD based on the data of [41] is 23.26° , which is almost the same as what obtained in this study. Due to the asymmetric behavior of the tracheobronchial tree, all proposed models experience relatively large standard deviations except the model of [20] with almost no SD. Although the model of [20] has an asymmetric manner, it seems that the asymmetric pattern is almost identical in all bifurcations as obvious from reported SD for other properties.

The calculated volume of the tracheobronchial tree is 133ml. The volume of 145ml was measured by Weibel et.al [29]. Kitaoka et.al [16] and Ismail et.al [51] estimated the volume of 175ml and 132.9ml, respectively. The difference between the reported values may correspond to the fact that they are obtained based on the lungs of different subjects. The anatomical dead space measured by the Fowler method is $156 \pm 28 \text{ ml}$. excluding the mouth volume of 40ml (estimated as 70% of the maximum volume of mouth[52]), the volume of conducting airways is expected to be $116 \pm 28 \text{ ml}$. Therefore, the value obtained by the proposed method is reasonable. The percentage volume of airways in each lobe is shown in Table 9. This table indicates that the volume of conducting airways is related to the volume of the corresponding lobe.

Table 9. The percentage volume of conducting airways in each lobe

	RU	RM	RL	LU	LL
Present Model	18.0	8.7	25.7	22.7	24.9
[18]	22.8	10.2	22.5	23.7	20.8
[12]	21	9	25	20	25
[51]	16.0	9.2	27.4	24.9	22.5

5. Discussion

In this study, to generate the human tracheobronchial tree, we tried to provide a robust rule-based method whose parameters were determined using an intelligent procedure. The bronchial tree was produced such that its various parts fit into bronchopulmonary segments obtained by analysis of CT images and anatomical slices. Various parts of the tree obtained by the proposed algorithm are completely contained by their corresponding host volumes in a homogenous manner while fulfilling various statistical indices reported by anatomical and physiological research articles.

The spatial hindrance during growth of an airway due to the presence of surrounding airways have been included in three-dimensional manner in this study, whereas its corresponding counterpart was handled in one-dimensional in the previous works. Furthermore, the proposed method predicted the more accurate dimensions of TBs and D/D_p ratio than their counterparts obtained by previous asymmetric models.

In the current study, the TB's are distributed near the bronchopulmonary segments, which is what happens in reality. Longitudinal pathways, the distances along the airways from the trachea to TB's, have a great contribution to the resistance against the fluid flow and subsequently on the ventilation and concentration distribution. Because TB's have been located near the boundaries of lungs or lobes in the previous studies, the values of Longitudinal pathways should have a significant deviation from reality but the values have not been reported.

To construct the conducting airways in host volume, it is usually required to describe the surface of the host volume, no matter whether the host volume is the whole lung, its constituting lobes, or bronchopulmonary segments. Therefore, several methods have been used in the previous studies for surface reconstruction: 1) thin-plate spline method, 2) surface fitting using hermit basis function, 3) combination of some convex geometrical shapes. The latter has the least accuracy among the others. On the other hand, the other two methods suffer from the fact that they are not capable of representing all concave surfaces very accurately. The mathematical description of the surface has not been used in the seed points-based methods, and it has been assumed that the new branch is inside if the end position of the branch lies close enough to the grid points. Thus, although the end of the branch lies inside the corresponding closed surface, it may intersect the boundaries in at least two points due to the concaveness of the surface. Therefore, we used neither mathematical relations for modeling of the surface nor grid points inside the host volume; instead, the closed surfaces were described using a set of triangular cells and the ray-triangle intersection algorithm was employed to find the distance to the boundary. This procedure overcomes the mentioned limitations and can accurately describe various shapes of the closed surfaces.

In the proposed method, the rules of finding branching angle implicitly restrict branches to reach back near one of their ancestors. In other words, the branches only go back if the desired region is not fed by another branch that has a shorter pathway from the trachea. None of the alternative methods has been addressing such an issue. This shortcoming may cause a more heterogeneous flow distribution in the models than in the real lungs.

The major advantages of the proposed method are the following features that make the method flexible according to the change in the shape of host volumes due to different ages and/or aspect

ratios of the human lungs. It should be noted the previous models cannot be applied for generation of bronchial tree of children.

- Finding the characteristic properties (i.e. the diameter, length, and direction) of the branches independently
- Choosing the best direction among the various potential directions based on the proposed rules
- Using dimensionless parameters and age-dependent terminating criteria
- Generation of the airways in parallel

It has been shown that if part(s) of lungs are surgically removed, the remaining parts gradually grow in directions that the obstacles have been taken out [53]. Another unique advantage of our method is that the airways do not grow in the host volumes independently to ensure that all interfaces are fed by at least one branch. It also enables the proposed method to simulate the growth of bronchial tree due to surgical removal of the neighbor segment(s) as soon as the growth rate is determined, which requires the clinical studies of the human lungs over the years. It should be noted that the previous models cannot be used for the generation of the structure in which some segments have been surgically removed. Furthermore, the generation of the airways in parallel decreases the computational cost 18 times.

6. Conclusion

A 3-D structural model of the human conducting airways has been proposed by a stochastic rule-based method that fulfills the anatomical constraints of the human lungs. The airways have propagated into the bronchopulmonary segments whose surfaces have been obtained from the CT

data. The parametric L-system (containing 11 rewriting rules) has been used to generate the structure, in a manner that each module in the rewriting rules represents an airway with its characteristic properties. The diameter, length, and orientation of the airways have been found independently based on an intelligent procedure in contrast to the previous studies that at least two properties were correlated. The morphometric characteristics of the obtained structure have been thoroughly compared against their corresponding experimental data. The results showed that the proposed method outperforms the previous models where it predicted the more accurate dimensions of TBs and D/D_p ratio than the previous asymmetric models. Furthermore, it is more robust and realistic than the previous models. Although the proposed algorithm has been developed based on the healthy subjects, it is capable of generating the abnormal structures if sufficient data is provided for adjustment of the parameters of the proposed method. The realistic structure obtained by the present method can be used in modeling of airflow distribution, aerosol deposition, gas and heat transport. It can be also used to determine the regions of the lung that are damaged by toxic gases or obstructed.

Availability of data and materials

The CT images used by this study are available in <http://image.diku.dk/exact/>. All data generated during this study are included in this published article and the additional material “Conducting airways.xlsx” which contains the geometric characteristics of all conducting airways generated by the proposed method.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZA and RB participated in ideas, development and design of the study, and evolution of the research goals. ZA implemented the computer codes using C++, validated the model results with experimental data, wrote the initial draft, and participated in the editing and revision of final version of the manuscript. RB supervised the research, edited, and revised the manuscript.

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