Branching design of the bronchial tree based on a diameter-flow relationship

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Kitaoka, Hiroko, and Béla Suki. Branching design of the bronchial tree based on a diameter-flow relationship. J. Appl. Physiol. 82(3): 968–976, 1997.—We propose a method for designing the bronchial tree where the branching process is stochastic and the diameter (d) of a branch is determined by its flow rate (Q). We use two principles: the continuum equation for flow division and a power-law relationship between d and Q, given by \( Q = d^n \), where \( n \) is the diameter exponent. The value of \( n \) has been suggested to be \( \sim 3 \). We assume that flow is divided iteratively with a random variable for the flow-division ratio, defined as the ratio of flow in the branch to that in its parent branch. We show that the cumulative probability distribution function of Q, \( P(Q) \), is proportional to \( d^{-n} \), which supports the validity of \( Q = d^n \) since \( P(Q) \propto Q^{-1} \). This allowed us to assign diameters to the segments of the flow-branching pattern. We modeled the bronchial trees of four mammals and found that their statistical features were in good accordance with the morphometric data. We conclude that our design method is appropriate for robust generation of bronchial tree models.

**Flow distribution**

The function of a ductal structure is to transport fluid to designated areas of an organ. In addition to efficient fluid transport, for large branching ductal systems such as the airway tree, one should also consider the optimal flow distribution at each terminal. What kind of a branching system is required from the point of view of flow distribution at the terminals where a given amount of fluid has to be delivered? The flow rate (Q) distribution is supposed to have a small deviation and be stable against perturbations. Statistical descriptions (19, 28) are necessary to evaluate this aspect of flow distribution. Previous morphometric airway models such as those proposed by Weibel (34) and Horsfield et al. (11, 12) are not adequate for studying the heterogeneity at the terminal ends.

In Weibel’s model (34), each terminal is completely identical. This simplification makes Weibel’s model attractive and easy to handle from the point of view of fluid mechanical computations along the airways. However, its usage is limited because there are no such ideal branching trees and under certain conditions (e.g., bronchoconstriction) the assumptions of symmetry and homogeneity cannot be maintained. The airway models proposed by Horsfield et al. (11, 12) are more realistic, because here each terminal has a different pathway, giving rise to a natural asymmetry of the tree. This feature has been exploited to predict the acoustic properties of the airways by Fredberg and Hoenig (3) and more recently has been further developed by Lutchen et al. (21) to investigate lung function (e.g., lung and airway resistances) during heterogeneous constrictions. Nevertheless, Horsfield’s models are self-similar in the sense that the branching patterns are completely determined by a rule of branching order, which, in turn, leads to identical diameters (d) of the terminals. In reality, according to the nomenclature of Boyden (2), we can name nearly a hundred proximal branches that may be genetically determined in the human airways. However, these airways constitute <0.5% of the total number of branches down to terminal bronchioles (TB), where no deterministic branching patterns have been found. We therefore realize that a stochastic description of the branching process is necessary, which leads to some heterogeneity of d and flow distribution at the terminal ends.

An optimal relationship between Q and d was proposed decades ago (7, 17, 23, 30) as follows

\[ Q = C d^n \]  

where \( n \) is the so-called diameter exponent (22) and C is a constant that depends on the organ in question and the fluid. Based on theoretical considerations, the value of \( n \) has been suggested to be \( \sim 3 \) (17, 23). Because the viscosity of the fluid is included in the constant C, the power law in Eq. 1 should be applicable for both vessels and airways containing blood and air, respectively. Thus the relationship in Eq. 1 appears to be quite useful for studying flow distribution in a given branching structure. Conversely, because flow division in a branching structure is easily solved, Eq. 1 may be used to design large branching structures.

Here we propose a method for designing branching ductal structures where the branching pattern is stochastic and the d of each branch is determined by its Q through Eq. 1. First, we will describe a stochastic process whereby Q is iteratively divided at each bifurcation. We then examine some general properties of this branching process that can be used to generate the branching pattern or the topology of the tree (see STOCHASTIC BRANCHING PROCESS IN A DUCTAL SYSTEM).

Next, we will present evidence of the applicability of the above diameter-flow relationship based on our analysis of Raabe’s morphometric data (25) (see DESIGNING THE DIAMETERS OF THE BRANCHES). Finally, combining the branching pattern of flow division with Eq. 1 will allow us to design the d of the bronchial tree, and we will present simulation trees for four mammals and compare the results with actual morphometric data.
STOCHASTIC BRANCHING PROCESS
IN A DUCTAL SYSTEM

Flow-Dividing Process Under Continuum Equation

First, we describe how fluid is divided at a bifurcation. We assume that mass is conserved at each bifurcation that is equivalent to the continuum equation for incompressible fluid. When the volume change of the duct during flow is negligible, the $Q$ before branching ($Q_0$) is equal to the sum of the $Q$ of the two daughter branches ($Q_1$ and $Q_2$; $Q_1 + Q_2$).

$$Q_0 = Q_1 + Q_2$$

We define the flow-dividing ratio ($r$) as the ratio of $Q$ of the parent branch to that of its daughter branch whose $Q$ is smaller, i.e., $r = Q_2/Q_0$ ($0 < r < 0.5$). Then, $Q_2/Q_0$ is always equal to $1 - r$. We will regard $r$ as a random variable. The value of $r$ determines the degree of asymmetry of the branching pattern. If, for example, $r$ is deterministic and fixed to 0.5, the branching pattern is completely symmetric. Because the $Q$ of all branches in a tree have not yet been measured, we do not know the actual distribution of $r$. Nevertheless, we can predict it from available morphometric data, as will be shown in STOCHASTIC MODELS OF MAMMALIAN BRONCHIAL TREES.

In a finite structure like a living organ, there are terminal branches where the flow-dividing process stops and the fluid is delivered into the terminal units of the organ. In the lung, the TB is defined as a terminal branch of the conductive airway tree (11, 34). Although there is further branching within an acinus, the acinus is defined as the functional unit for gas exchange because the respiratory bronchioles are no longer pure conductive ducts. Accordingly, it is reasonable to assume that there is a threshold flow ($Q_c$) below which there is no more conductive flow division. By definition, $Q_c$ provides the maximum $Q$ at the terminal branches. In the following, we will assume that the $Q$ is normalized to unity at the root. Thus, $Q_c$ represents the maximum fraction of the total flow that can be delivered to a TB.

The above three rules (continuum equation, flow-dividing ratio as a random variable, and the existence of a $Q_c$ as a parameter providing the maximum $Q$ at a terminal branch) enable us to create large branching systems simulating the actual branching pattern of the bronchial tree. Specification of $r$ and $Q_c$ that are appropriate for various mammals will be described in STOCHASTIC MODELS OF MAMMALIAN BRONCHIAL TREES.

Statistical Characteristics of Flow Distributions

Plotted on a log-log graph, Fig. 1 shows the cumulative distribution of $Q$, including every branch of a tree. $N(\geq Q)$ is the number of branches whose $Q$ is larger than a given value $Q$. The cumulative probability distribution function $P(\geq Q)$ is then given by $N(\geq Q)/N_T$, where $N_T$ is the total number of branches in the tree. As can be seen from Fig. 1, for $Q \geq Q_c$, $N(\geq Q)$ is proportional to $Q^{-1}$ so that

$$P(\geq Q) \sim Q^{-1}$$

We found that this result holds generally and independently from the distribution of $r$ and therefore independently from the branching pattern. In APPENDIX A, we also provide theoretical arguments supporting the validity of Eq. 3. The corresponding probability density distribution function $P(Q)$ is the derivative of $P(\geq Q)$, and hence it is proportional to $Q^{-2}$.

An interesting implication of Eq. 3 is that when a physical quantity is related to $Q$ according to a power law (e.g., the $d$ of the branch through Eq. 1), the probability-distribution function of that quantity will also be a power law, as will be discussed in the next section. Since Mandelbrot (22) proposed the concept of fractals, branching structures like the bronchial tree have often been categorized as fractal objects (1, 5, 6, 16, 18, 20, 33). Fractals are self-similar objects characterized by power-law distributions. Thus, since the results in Fig. 1 are quite independent of the particular distribution of $r$, the power-law distribution of flow demonstrates the general statistical self-similar property of branching structures.

DESIGNING THE DIAMETERS OF THE BRANCHES

Having generated branching patterns, we next propose a method to assign $d$ to the individual branches by using the diameter-exponent rule of Eq. 1. Combining Eqs. 1 and 2, we obtain the following relationship between the $d$ of a bifurcation

$$d_0^1 = d_1^n + d_2^2$$

where $d_0$ is a diameter of the parent branch and $d_1$ and $d_2$ are those of the daughters. Average values of $n$
calculated by using Eq. 4 at each bifurcation of various morphometric data have been reported as 2.6 for arteries by Groat (7), 2.7 for arteries by Suwa et al. (30), 2.4 for pulmonary artery by Horsfield et al. (14), and 2.4–2.9 for airways of four mammals by Horsfield et al. (13). Theoretical arguments to explain this relationship have also been offered. For example, Murray (23) proposed \( n = 3 \) based on minimum-cost principle for steadylaminar flow through a rigid duct. Kamiya et al. (17) also proposed \( n = 3 \), using a minimum-volume principle for steadylaminar flow through rigid branching ducts.

In this section, we first reanalyze the morphometric data of four mammalian airways published by Raabe et al. (25) and then examine the validity of Eq. 1 in two ways: by directly using Eq. 4 and by examining the probability-distribution function of the diameter exponent. The significance of this is that by establishing the validity of the \( d-Q \) rule (Eq. 1), we will be able to connect the \( d \) of a branch to its \( Q \). Thus, we can then simply transform the flow-branching pattern obtained in the previous section to diameter-branching pattern.

### Resampling Raabe's Morphometric Data

The morphometric data of Raabe et al. (25) are based on two human lungs, two dog lungs, one rat lung, and one hamster lung. To every data set, they assigned a minimum \( d \) beyond which the measurement was complete. For branches in which \( d \) was smaller than the minimum \( d \), the tree was arbitrary. The precision of measurement was 0.1 mm; therefore, we did not use \( d < 0.5 \) mm because of the large relative measurement errors. We resampled Raabe’s data so as to include only those branches that formed a complete tree with their diameters larger than the minimum \( d \). The trunk of a tree was not limited to the trachea. As long as all branches beyond the minimum \( d \) belonging to one trunk were measured, the tree arising from this trunk was included in the statistical analysis. However, to obtain statistically meaningful results, we required that a tree contained at least 400 branches.

We generated nine trees from Raabe’s data (Table 1). Six of the trees were from bilateral lungs of six individuals, one tree was from a subsegmental bronchus of a human right upper lobe (HM-272), and two trees were obtained from the right apical lobe and the right intermediate lobe of a dog (DM-272).

### Calculation of the Diameter Exponent

Calculation of the \( d \) exponent was performed by solving Eq. 4 numerically at each bifurcation. For the human and dog airway trees, all bifurcations were selected where \( d_0 \) was larger than the minimum \( d \). For rat and hamster airway trees, only those bifurcations were selected where \( d_1 \) and \( d_2 \) were all \( > 0.5 \) mm. Bifurcations with \( d_1 \) (or \( d_2 \)) \( < d_0 \) were excluded from the analysis, since in this case there is no finite positive solution to Eq. 4.

The calculated values of \( n \) are summarized in Table 1. In all cases, the SD were large. Figure 2 shows a histogram of \( n \) obtained from the dataset HM-272. The distribution of \( n \) could be approximated with a log-normal distribution not only for HM-272 but also in all other cases, similar to previous reports (13, 30). As

### Table 1. Diameter exponents in Raabe’s data

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>Age, yr</th>
<th>Body mass, kg</th>
<th>Min. diameter, mm</th>
<th>Max. diameter, mm</th>
<th>No. of branches</th>
<th>No. of bifurcations calculated</th>
<th>AM ( \pm SD )</th>
<th>GM</th>
<th>Measured value</th>
<th>Correlation coefficient</th>
<th>Corrected value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HM-272</td>
<td>60</td>
<td>81.0</td>
<td>3.0</td>
<td>20.1</td>
<td>632</td>
<td>443</td>
<td>3.3 ( \pm 0.3 )</td>
<td>3.0</td>
<td>3.4</td>
<td>0.995</td>
<td>3.0</td>
</tr>
<tr>
<td>HM-373</td>
<td>50</td>
<td>81.0</td>
<td>3.0</td>
<td>23.5</td>
<td>479</td>
<td>350</td>
<td>3.1 ( \pm 1.8 )</td>
<td>2.9</td>
<td>3.3</td>
<td>0.993</td>
<td>2.9</td>
</tr>
<tr>
<td>DM-572</td>
<td>2.0</td>
<td>10.3</td>
<td>2.0</td>
<td>16.1</td>
<td>1,198</td>
<td>864</td>
<td>2.9 ( \pm 1.1 )</td>
<td>2.7</td>
<td>2.9</td>
<td>0.998</td>
<td>2.6</td>
</tr>
<tr>
<td>DM-272</td>
<td>1.4</td>
<td>11.6</td>
<td>2.0</td>
<td>18.0</td>
<td>1,507</td>
<td>937</td>
<td>2.7 ( \pm 0.9 )</td>
<td>2.6</td>
<td>3.0</td>
<td>0.997</td>
<td>2.7</td>
</tr>
<tr>
<td>Rat</td>
<td>0.9</td>
<td>0.33</td>
<td>0.5</td>
<td>3.5</td>
<td>842</td>
<td>85</td>
<td>2.5 ( \pm 0.9 )</td>
<td>2.4</td>
<td>2.5</td>
<td>0.984</td>
<td>2.3</td>
</tr>
<tr>
<td>Hamster</td>
<td>0.7</td>
<td>0.14</td>
<td>0.5</td>
<td>3.3</td>
<td>488</td>
<td>56</td>
<td>2.6 ( \pm 1.3 )</td>
<td>2.4</td>
<td>2.8</td>
<td>0.961</td>
<td>2.5</td>
</tr>
<tr>
<td>HM-272, subsegment of right upper lobe</td>
<td>0.8</td>
<td>6.0</td>
<td>6.0</td>
<td>521</td>
<td>343</td>
<td>2.9 ( \pm 1.3 )</td>
<td>2.7</td>
<td>3.1</td>
<td>0.969</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>DM-272, right apical lobe</td>
<td>0.8</td>
<td>10.5</td>
<td>10.5</td>
<td>2,328</td>
<td>1,079</td>
<td>2.6 ( \pm 1.3 )</td>
<td>2.5</td>
<td>2.8</td>
<td>0.997</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>DM-272, right intermediate lobe</td>
<td>0.8</td>
<td>6.4</td>
<td>6.4</td>
<td>1,015</td>
<td>505</td>
<td>2.6 ( \pm 0.9 )</td>
<td>2.5</td>
<td>3.0</td>
<td>0.983</td>
<td>2.7</td>
<td></td>
</tr>
</tbody>
</table>

Min, minimum; Max, maximum; AM, algebraic mean; SD, standard deviation; GM, geometric mean.

Fig. 2. Distribution of calculated values of diameter exponent (n) at each bifurcation in a human airway tree (HM-272). No. of bifurcations included in the calculations was 443.
explained in Appendix B, the wide distribution of \( n \) could primarily be due to the high sensitivity of the calculation of \( n \) from the measured values of \( d \) using Eq. 4. Although airways are not ideally cylindrical, Eq. 4 is based on the assumption of cylindrical configurations; therefore, slight changes in the measured values of \( d \) can cause a wide distribution of \( n \).

There was a significant correlation between geometric mean (GM) of \( n \) and the minimum \( d \) (correlation coefficient = 0.86, \( P < 0.01 \)), which is in accord with Horsfield’s report (13). This correlation, however, is a result of the influence of measurement error in \( d \) (see Appendix B). Also, there was a significant correlation between GM of \( n \) and body mass (correlation coefficient = 0.83, \( P < 0.01 \)). However, one should not conclude that there are species-related differences in \( n \), because this correlation is also influenced by the correlation between GM of \( n \) and the minimum \( d \). This analysis thus indicates that the diameter exponent rule (Eq. 1) may be acceptable in large trees.

Probability-Distribution Function of Diameters

The cumulative distributions of diameters, \( N(\geq d) \), were examined by counting the number of branches whose \( d \) was larger than a given diameter \( d \). When the total number of branches in the tree is \( N_T \), the corresponding probability-distribution function, \( P(\geq d) \), is given by \( N(\geq d)/N_T \). Before the calculation of \( P(\geq d) \), the measured \( d \) were first corrected for measurement error by subtracting the absolute error, 0.05 mm, from the values of the \( d \). The reason is that the number of branches with \( d \) larger than the measured value \( D \) should also include the number of branches whose diameters are between \( D - 0.05 \) and \( D \). The cumulative distribution of \( d \) showed an apparent inverse power law for all species, i.e., \( N(\geq d) \sim d^{-m} \). Figure 3 shows examples of \( N(\geq d) \) in the two human bronchial trees. The values of \( m \) were obtained from the slope of the regression line (Table 1). However, since the total number of branches, \( N_T \), was not large enough in all trees to establish reliable statistics of the slope \( m \), the data was further corrected according to the procedure detailed in Appendix C. This correction procedure resulted in values of \( m \) that were quite close to the GM of \( n \) (Table 1). Indeed, it is easy to show that \( m \) and \( n \) should be the same. From Eqs. 1 and 3, the probability distribution of \( d \), \( P(\geq d) \), is derived as

\[
P(\geq d) \sim d^{-n}
\]

where the value of exponent \( n \) is exactly identical to that in Eq. 1. Thus, the probability-distribution function of \( d \) is a consequence of the power-law relationship between \( d \) and \( Q \) and the scaling property of the flow distribution given by Eq. 3. Finally, there was also a significant correlation between \( m \) and the minimum \( d \) (correlation coefficient = 0.86, \( P < 0.01 \)). This can be explained with the effects of measurement errors in \( d \) (Appendix B). Therefore, one should not conclude that there are species-related differences in \( m \).

Besides Raabe’s actual morphometric data, Fig. 4 demonstrates that the cumulative distribution of \( d \) both in Weibel’s (34) and Horsfield’s human model (11) complies with Eq. 5. Because Weibel used Eq. 4 with \( n = 3 \) for generations between 2 and 10, the slope on a log-log plot in this range is 3.0, with a correlation coefficient of 0.995. Although Horsfield did not use this relationship, the cumulative distribution of \( d \) in his model also showed a good accordance with an inverse power function. The regression lines from the trachea to preterminal bronchioles showed a slope of 3.2 with a correlation coefficient of 0.981 in Weibel’s model, and a slope of 3.1 with a correlation coefficient of 0.988 in Horsfield’s model. In summary, these together provide evidence that the slope \( m \) of the distribution of \( d \) is statistically equivalent to the slope \( n \) obtained from Eq. 3, further supporting the applicability of the diameter-flow relationship given by Eq. 1.

The Value of Diameter Exponent

What is the appropriate value for \( n \)? Arguments have been offered by several groups (29, 32, 35, 36) to explain the discrepancy between empirical values of \( n \) and the theoretical value 3 for laminar flow. Considering the results of other studies (13, 30) and our analysis of measurement errors in this study (see Appendix B), we adopted a single value of \( n = 2.8 \) for modeling the mammalian airways. The case of HM-272 in Raabe’s data, a 60-yr-old human man with unknown smoking history was described as “Tissue section showed emphysematous change, typical of aging.” The GM of \( n \) in this case was slightly higher (3.0 vs. 2.8) than that of the other human, HM-283, whose tissue section showed no apparent change. This slight increase of \( n \) appears to be consistent with aging (31).
In the previous section, we established a method for determining the flow of the branches where the Q is known. Combining this with the stochastic method of flow division introduced in STOCHASTIC BRANCHING PROCESS IN A DUCTAL SYSTEM now allows us to design the bronchial tree. There is one deterministic parameter, Qc, and one random variable, r, in our model. We will first discuss how Qc and the probability-density-distribution function of r should be assigned, and then we will present simulation trees for four mammals based on the actual morphometric data obtained by Raabe et al. (25).

The value of Qc and the distribution of r should be assigned based on actual morphometric data. Qc can be approximately determined from the number of TB. If, for example, \( r = 0.5 \), the branching is symmetric and all TB have the same flow. Recall that the flow at the trunk was assumed to be unity. The total flow at the terminals is the sum of the individual flows at the TB, and hence the product of the number of terminals and the mean Q at TB is equal to 1. Accordingly, Qc is the reciprocal of the number of terminals. If now \( r \) is a random variable with a given mean and SD, Qc will be the maximum flow at TB, and the number of terminal branches will be \( >1/Q_c \). Nevertheless, as a first approximation, this argument can still be used to determine the value of Qc. The expected value of r is related to the distributions of the generation numbers and Q of TB. As the expected value of r is closer to 0.5, these distributions become narrower. In the present work, we only used a uniform distribution of r. For example, when we assign \( Q_c = 0.00006 \) and r is distributed uniformly between 0.2 and 0.5, the distribution of generation numbers of terminal branches is approximately normal, with a mean of 15.9 and SD of 2.0, as shown in Fig. 5. This result agrees well with those derived from morphometric data of human airways reported in the literature (10, 34).

We generated 10 trees with the same Qc and the same range of r. There were no identical trees; however, the statistical features of these trees were identical. The mean ± SD of the number of terminal branches was 26,431 ± 19. The means and the SD of the generation numbers at the terminal branches were distributed between 15.8 and 16.3 and between 1.9 and 2.2, respectively. The mean Q at the terminal branches were identical, and the coefficient of variation (CV) of the Q ranged from 31 to 34%.

Comparison with Morphometric Data

In Raabe's data, TBs were reported in one of the humans (HM-272), one of the dogs (DM-272), and in the rat and the hamster lungs. The terminated branches exactly recognized as TB were assigned a T, and other terminated branches were assigned an F. We only analyzed those which were exactly recognized, and the results are given in Table 2. Because the measurement of the inner diameter in rat and hamster was completed down to TB as closely as possible, we estimated the total number of TB to be between \((T + F)\) and \((T + 1.5 \times F)\), where T and F denote the number of branches marked with a T and an

![Fig. 4. Cumulative distribution of diameters in Weibel's (33) and Horsfield's (10) human airway models show on log-log plots. In Weibel's model, for generations between 2 and 10, the slope of the regression line is 3.0, with a correlation coefficient of 0.995. In Horsfield's model, the slope of the regression line over the full range of diameters is 3.1, with a correlation coefficient of 0.988.](image)

![Fig. 5. Distribution of generation nos. of terminal branches in simulated tree whose flow distribution is shown in Fig. 1; no. of terminal branches is 26,419.](image)
In that case, as pointed out in DESIGNING THE DIAMETERS by 27%. This is consistent with aging actually observed OF THE BRANCHES. Therefore, the value of Q to all terminal branches in his human model (11); models (11, 12) as follows. Horsfield assigned identical bifurcation by using histogram of Q in his dog model (12), we can calculate the value of the flow-dividing ratio and distribution of the flow-dividing ratio earlier (11, 12, 34). Although we used a uniform distribution of the generation numbers of TB, and subsequently we used them to create model trees of the four mammalian bronchial trees. The diameter distributions in these model trees showed good accordance with the morphometric data summarized in Table 2. Additionally, when we changed the value of the d exponent from 2.8 to 3.0 in humans, which corresponded to the case of HM-272 in Table 2, the mean d of TB increased by 27%. This is consistent with aging actually observed in that case, as pointed out in DESIGNING THE DIAMETERS OF THE BRANCHES.

DISCUSSION

To design the bronchial tree in this study, we introduced a stochastic flow-dividing process instead of using deterministic branching patterns as proposed earlier (11, 12, 34). Although we used a uniform distribution of the flow-dividing ratio r, there are no direct data to support this assumption. Nevertheless, we can estimate the range of r in Horsfield’s human and dog models (11, 12) as follows. Horsfield assigned identical Q to all terminal branches in his human model (11); therefore, the value of r can be calculated at each bifurcation by using Eq. 1. Although Horsfield did not use Q in his dog model (12), we can calculate the value of r in the same way as in his human model. The histogram of r for Horsfield’s human and dog models is shown in Fig. 6. In the human model, the branching pattern between the lobular bronchi and TB is completely symmetric. However, there have been several reports demonstrating that the branching pattern within the secondary lobule is not symmetric (4, 26). When we exclude this part of his model, the mean value of r was 0.36, almost equal to the mean value of r in our simulation, 0.35. In his dog model, r has a wider distribution than in his human model with a mean of 0.25. We need to point out that this value is exactly the same that we used in our simulation, although we determined r from Raabe’s data. The distributions of r in Fig. 6 are not smooth, most likely due to the rigid branching pattern of the Horsfield model, and hence they appear to be less realistic than the uniform distribution we used.

It seems feasible that the distribution of r also depends on the Q in the parent branch. We examined the correlation between r and the Q of the parent branch in both Horsfield’s models and found no systematic correlation except in the central airways. We also examined the influence of a nonuniform probability-density distribution function of r on the statistical features of the tree model. For example, we replaced the uniform distribution of r with a normal distribution truncated at 0 and 0.5. We found that the distributions of generation numbers and Q at the terminal branches were almost completely determined by the expected value of r, rather than the type of the probability distribution. Therefore, we suggest that, for simplicity, the uniform distribution of r is sufficient to generate large tree models. If a more realistic branching pattern is required in the proximal part of the tree, one can assign deterministic rules to r for the first several generations. This alteration, however, will not change the overall statistical features of the tree because of the small number of such proximal bifurcations.

Several studies have pointed out that the diameters in a branching structure are distributed according to a power law (15, 24). However, to our knowledge, no study has proposed how this distribution could be related to the distribution of Q. Horsfield et al. (13) also analyzed the Raabe data and obtained the value of n in two different ways. One way was to calculate it based on his own ordering method, and the other way was by using Eq. 4. One can show that his former method is

**Table 2. Generation numbers and diameters of terminal bronchioles in Raabe’s data**

<table>
<thead>
<tr>
<th>Sample</th>
<th>No. of TB Exactly Recognized in Casts</th>
<th>Generation No.</th>
<th>Relative Diameter Against Trachea</th>
<th>Estimated Total No. of TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>515</td>
<td>15.5±2.2</td>
<td>0.030±0.005</td>
<td>20,000–30,000</td>
</tr>
<tr>
<td>Dog(DM-272)</td>
<td>489</td>
<td>18.2±5.0</td>
<td>0.028±0.006</td>
<td>20,000–30,000</td>
</tr>
<tr>
<td>Rat</td>
<td>1,041</td>
<td>16.2±4.9</td>
<td>0.056±0.015</td>
<td>2,396–3,077</td>
</tr>
<tr>
<td>Hamster</td>
<td>894</td>
<td>14.4±4.6</td>
<td>0.079±0.015</td>
<td>1,113–1,283</td>
</tr>
</tbody>
</table>

Values of generation no. and relative diameter are means ± SD. TB, terminal bronchioles.

**Table 3. Simulation bronchial trees of 4 mammals**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Threshold Flow Rate Qc</th>
<th>Flow Dividing Ratio</th>
<th>Diameter Exponent n</th>
<th>Generation Nos. of Terminal Branches</th>
<th>Diameters of Terminal Branches Against the Trunk</th>
<th>Total No. of Terminal Branches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>0.00006</td>
<td>0.2–0.5</td>
<td>2.8</td>
<td>15.9±2.0</td>
<td>0.026±0.003</td>
<td>26,419</td>
</tr>
<tr>
<td>Dog</td>
<td>0.00008</td>
<td>0.1–0.4</td>
<td>2.8</td>
<td>18.2±3.8</td>
<td>0.027±0.005</td>
<td>23,136</td>
</tr>
<tr>
<td>Rat</td>
<td>0.00007</td>
<td>0.1–0.3</td>
<td>2.8</td>
<td>16.1±4.4</td>
<td>0.056±0.012</td>
<td>2,923</td>
</tr>
<tr>
<td>Hamster</td>
<td>0.0018</td>
<td>0.1–0.3</td>
<td>2.8</td>
<td>14.4±4.1</td>
<td>0.078±0.016</td>
<td>1,151</td>
</tr>
</tbody>
</table>

Values for generation nos. and diameters of terminal branches are means ± SD.
approximately equal to the method of obtaining a distribution function of \( d \). Values of \( n \) he obtained with this method were similar to our results.

Although Eq. 1 predicts that the value of \( n \) is constant in a branching system, the calculated values of \( n \) using Eq. 4 showed a wide distribution (see Fig. 2). We therefore examined the sensitivity of \( P(\geq d) \) to fluctuation in \( n \). First, we generated a tree where \( Q \) of all branches were assigned. Then, starting from the trunk, we iteratively calculated the diameters at each bifurcation by applying the following equations

\[
\begin{align*}
d_1 &= d_0(Q_2/Q_0)^{1/n} \\
d_2 &= d_0(Q_3/Q_0)^{1/n}
\end{align*}
\]

where \( n \) becomes a random variable \( > 0 \). The results showed that the corresponding \( P(\geq d) \) still maintained an inverse power-law form but with an exponent identical to the GM of \( n \) and not the algebraic mean of \( n \). The highest correlation coefficient of the regression on the log-log plot was obtained when the probability-density distribution of \( n \) had a log-normal distribution. This result appears to be complementary to the high sensitivity of \( n \) to variations in \( d \) as mentioned in Appendix B. Moreover, it also supports our choice of using GM instead of algebraic means.

We also examined the distribution of airway lengths in Raabe's data. However, there were no significant power-law distributions. Although we tried to extract relationships among \( d \), lengths, and angles, we did not find any significant correlation that would have allowed us to build deterministic relationships among these quantities. There are two types of angles in Raabe's reports. The first is the angle of the branch relative to the direction of gravity, and the other is relative to the parent branch. These two angles are not sufficient to reconstruct the three-dimensional structure of the trees from Raabe's data. If the angles had been measured so as to determine the location in the three-dimensional space, some significant correlation might have been detected. These are further problems to be investigated for modeling a three-dimensional branching structure.

Our model lends itself to immediate investigation of the distribution of \( d \) of TB that can then be compared with those derived from morphometric data. Although the model is based on the relationship between \( d \) and \( Q \) (Eq. 1), in its current form, it may not be used to predict \( Q \) at TB, because the model does not incorporate the effect of local compliance which determines the regional \( Q \) (27). However, from the point of view of designing the bronchial tree, this does not seem to be a serious limitation, because the predictions of the model were in excellent agreement with morphometric data. To predict more precisely the distribution of \( Q \) at TB, one would have to know the distribution of the local compliances. There is evidence that parenchymal expansion is quite heterogeneous (27), indicating a wider distribution of local compliances. Presumably, the spatial arrangement of the peripheral airway tree and the spatial distribution of local compliances are closely related. Thus, to take local compliance into account, one would also have to know the relationship between local compliance and the terminal airway structure, which is beyond the scope of the present study. Nevertheless, we note that the model presented here may be directly applicable to designing vascular trees where tissue compliance is less of an issue.

Despite the simplicity of the model, our method of designing the bronchial tree offers two advantages over previous airway tree models. Because there are no assumptions of any kinds of unity at the terminals, we are able to investigate heterogeneity at the terminals. More importantly, our model also enables us a diameter-based analysis. Most methods investigating branching ductal structures have been based on various branching orders (1, 5, 16, 22). When we use a branching order, starting either from the top or the bottom of the tree, we have to transform this quantity into a physical quantity such as the \( d \) of the branch. The anatomic structure of the airway wall is, however, more correlated with the diameter than with the branching order, and the most effective regulation of local flow is achieved by changing the diameter of the airway. We may use our model in a statistical sense to relate diameter to various quantities in lung, such as flow or airway resistance, independently from branching order.

In summary, we have presented a stochastic design of the bronchial tree based on the \( d \) exponent law. We find that the design is robust against perturbations in its parameters and provides trees that are statistically equivalent to morphometric data. The design principle is simple and will enable us to predict distributions of various quantities related to lung function.
APPENDIX A

Distribution of Flow in a Branching Tree

There is a simple relationship (which can be symmetric or asymmetric) between the total number (N_T) of branches in the tree and the number of terminal branches (E) as follows

\[ N_T = 2E - 1 \]  (A1)

When the number of branches is large enough to neglect the term \(-1\), Eq. A1 can be approximated as

\[ N_T = 2E \]  (A2)

Consider, now, a part of the original tree, where we keep only those branches which have \( Q > Q_a \), where \( Q_a \) is an arbitrary value, but larger than \( Q_c \). The total number of branches in this partial tree is \( N(\geq Q_a) \) which we would like to express explicitly with \( Q_a \). The terminal branches in this partial tree have \( Q \) near \( Q_a \). However, there will be bifurcations where only one of the two daughter branches has a flow \( > Q_a \), and hence the other branch is not considered as part of the partial tree. When the branching pattern is almost symmetric, the number of such bifurcations is negligible. By using Eq. A2, the number of terminals in the partial tree \( E' \) is given by \( N_T'/2 \) where \( N_T' \) is the total number of branches in the partial tree which is exactly \( N(\geq Q_a)/2 \). However, since the flow at the terminals of the partial tree is approximately equal to \( Q_a \), the product of \( E' \) and \( Q_a \) should give the total flow at the trunk, i.e., unity. Therefore

\[ N(\geq Q_a)/2 = 1/Q_a \]  (A3)

After normalizing by \( N_T \), we obtain

\[ P(\geq Q) \sim Q^{-1} \]  (A4)

which describes the straight line of \( P(\geq Q) \) on a log-log graph in Fig. 1.

When the branching pattern is asymmetric, the number of bifurcations where one of the two daughters does not belong to the partial tree cannot be neglected. The total flow coming out of the terminals of the partial tree, \( Q' \), is <1 because of the missing branches. The number of terminal branches which is \( \sim Q'/Q_a \) which is also <\( N(\geq Q_a)/2 \). However, the total flow coming out of the partial tree is also smaller than unity by an amount \( Q' = 1 - Q' \). The number of missing daughter branches can then be approximated as the ratio of \( Q' \) to the mean flow through the missing branches. The \( Q \) of the missing branches are ranged from 0 to \( Q_a \) with an average of \( \sim Q_a/2 \). Thus, the number of missing branches is estimated to be \( 2Q'/Q_a \). If we now add the missing daughters to the partial tree, this new tree has a complete set of bifurcations, and so Eq. A1 would again be applicable. Accordingly, for this new tree, the total number of branches is \( N(\geq Q_a) + 2Q'/Q_a \). Therefore, Eq. A1 can now be written as

\[ N(\geq Q_a) + 2Q'/Q_a \equiv 2(Q'/Q_a + 2Q'/Q_a) \]

which can be rearranged into a similar form as Eq. A3. Thus Eq. A4 is valid for both symmetric and asymmetric branching processes.

APPENDIX B

Influence of Measurement Errors on the Calculation of Diameter Exponent

When calculating the \( d \) exponent with the use of Eq. 4, the influence of measurement errors in \( d \) is extremely important. In Raabe's data, the precision of measurement was 0.1 mm. If it were 0.01 mm, there would be 1,000 possible combinations of the measured \( d \) of the three branches at a bifurcation. We examined how \( n \) is distributed corresponding to all possible combinations. In the following, we define \( d_i \) (i = 0, 1, or 2, with 0 denoting the parent, and 1 and 2 the daughters) as a measured value of \( d \) and \( D_i \) as its true value. For example, let us examine the combination of measured values of \( d_0 = 0.8 \) mm, \( d_1 = 0.7 \) mm, and \( d_2 = 0.5 \) mm. The calculated value of \( n \) at this bifurcation is 2.61. If \( D_0 = 0.75 \) mm, \( D_1 = 0.74 \) mm, and \( D_2 = 0.54 \) mm, the \( n \) is 7.90. If \( D_0 = 0.84 \) mm, \( D_1 = 0.65 \) mm, and \( D_2 = 0.45 \) mm, the \( n \) is 1.83. We calculated \( n \) for all possible combinations, and obtained the distribution of \( n \) as shown in Fig. 7. The distribution of \( n \) is approximately log-normal, having a higher mean value than the original value. When the diameters are larger, the distribution of \( n \) is narrower and the mean value of \( n \) is closer to the original value, because the relative measurement error is smaller for larger diameters. This is one reason for the significant correlation between the minimum diameter and the mean value of \( n \) in the analysis of Raabe's data. Another reason is as follows. When \( D_1 \) and/or \( D_2 \) is close to \( D_0 \), the value of \( n \) is high. However, such a bifurcation is often excluded when the relative measurement error is large (e.g., a combination of \( D_0 = 0.74 \) and \( D_1 = 0.73 \), both of which would be measured at 0.7 mm when the precision is 0.1 mm). Therefore, at a smaller diameter, there are less bifurcations with higher values of \( n \), resulting in smaller mean of \( n \) in the analyses of Raabe's data.

APPENDIX C

Correcting the Slope \( m \) for Smaller Trees

In practice, when the \( N_T \) of branches in a tree is not large enough to neglect the \(-1\) in Eq. A1, the estimated value of \( m \) should be corrected for it. When \( N_T \) is smaller, the influence of \(-1\) is bigger and the slope obtained from the log-log plot of flow distribution becomes slightly >1, as shown in Fig. 1. The slope of \( P(\geq Q) \) on a log-log plot (a) can then be calculated as

\[ a = \log N_T / (\log N_T - \log 2) \]

Algebraic mean = 2.78
(\text{SD} = 0.77)

Geometric mean = 2.69

Fig. 7. Distribution of calculated values of \( d \) exponents corresponding to 1,000 possible combinations of the values of the 3 \( d \) when \( d_0 = 0.8 \) mm, \( d_1 = 0.7 \) mm, and \( d_2 = 0.5 \) mm (see text for details).
where we have utilized Eq. A1 instead of Eq. A2. The exponent in the probability distribution function of another quantity \( x \), which is related to flow, \( Q \), through a power law such as \( Q \sim x^\alpha \), also alters from \( b \) to \( a \). As shown in Table 1, the total number of branches was not always enough to neglect the influence of \(-1\). There is another condition under which Eq. A3 breaks down, namely, when \( Q \) is below \( Q_c \). In this analysis, we did not include small diameters near \( T_B \), and hence it was not necessary to correct for the effect of \( Q \) being smaller than \( Q_c \).

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