Intraspecific scaling laws of vascular trees

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A fundamental physics-based derivation of intraspecific scaling laws of vascular trees has not been previously realized. Here, we provide such a theoretical derivation for the volume–diameter and flow–length scaling laws of intraspecific vascular trees. In conjunction with the minimum energy hypothesis, this formulation also results in diameter–length, flow–diameter and flow–volume scaling laws. The intraspecific scaling predicts the volume–diameter power relation with a theoretical exponent of 3, which is validated by the experimental measurements for the three major coronary arterial trees in swine (where a least-squares fit of these measurements has exponents of 2.96, 3 and 2.98 for the left anterior descending artery, left circumflex artery and right coronary artery trees, respectively). This scaling law as well as others agrees very well with the measured morphometric data of vascular trees in various other organs and species. This study is fundamental to the understanding of morphological and haemodynamic features in a biological vascular tree and has implications for vascular disease.

Keywords: scaling laws; cost function; minimum energy; intraspecific scaling

1. INTRODUCTION

The fractal dimension defined by Mandelbrot [1] has been shown to characterize natural phenomena with remarkable simplicity. The vascular [2–19], bronchial [20,21] and botanical trees [22–25] have been found to have fractal-like features. For interspecific scaling, based on three major assumptions in a fractal-like cardiovascular system (i) area-preservation for branching patterns of vessel diameter greater than 1 mm and cubed-law for smaller vessels as well as space-filling branching pattern; (ii) size-invariant capillaries; and (iii) minimum energy loss, West et al. [26] propose a mathematical model referred to as the WBE (West, Brown, and Enquist) model to support the allometric 3/4 scaling law of metabolism. In the process, they assumed that the fractal-like networks in life have a fourth spatial dimension [27], which served as the basis of the WBE model [26]. There is much debate on the WBE model, however, especially for the assumption of the space-filling branching pattern in the cardiovascular system (i.e. LR = BR^{1/3}, where BR and LR are the branching ratio and length ratio, respectively) [28,29].

For scaling laws within a species (intraspecific scaling), several power-law relations of vascular trees have been proposed with an empirical parameter determined experimentally in the exponent of equivalent tree resistance [30]. The objective of this study is to provide an alternative derivation that does not invoke an empirical parameter and to critically validate the model using detailed morphometric and haemodynamic measurements. In the process, we first derive volume–diameter and flow–length scaling laws from conservation of mass in a vascular tree without invoking the controversial space-filling assumption disputed in the WBE model. These two scaling laws, which agree well with the morphometric measurements of coronary and other vascular trees, lead to the diameter–length, flow–diameter and flow–volume scaling power-laws as a result of the minimum energy hypothesis. The physiological basis of these scaling laws is demonstrated and the implications on coronary heart disease (CHD) are discussed.

2. METHODS

2.1. Scaling laws in a vascular tree

A proximal vessel segment is defined as a stem and the tree distal to the stem (down to the smallest arterioles or venules) is defined as a crown, as shown in figure 1. An entire tree consists of many stem-crown units. The capillary network (vessel diameter less than 5 μm) is excluded from the present analysis because it is not tree-like in structure [31]. The vessel segment is assumed to be a cylindrical tube and other nonlinear effects (e.g. vessel compliance, turbulence, variation of viscosity in different vessel segments, etc.) are neglected because of their relatively small contribution to the haemodynamics of an entire integrated tree (millions of blood vessel segments) [26]. In an integrated system of stem-crown units, the crown volume (V_c[ml]) is defined as the sum of the intravascular volume of each vessel segment and the crown length (L_c[cm]) is defined as the sum of the lengths of each vessel segment in the entire crown from the stem to the most distal vessels.

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To determine scaling laws of a vascular tree, the branching ratio, diameter ratio and length ratio in a fractal-like tree structure are defined as:

\[ BR = \frac{n_i}{n_{i-1}} \]
\[ DR = \frac{D_i}{D_{i-1}} \]
\[ LR = \frac{L_i}{L_{i-1}} \]

where \( n_i \), \( D_i \) and \( L_i \) are the number, diameter and length of vessels in level \( i \), \( i = 1, \ldots, N_{\text{total}} \). Level 0 is the most proximal stem for an entire tree or a stem for the stem-crown unit, and level \( N_{\text{total}} \) refers to the smallest arterioles or venules.

Based on the assumptions of \( LR = BR^{-1/(3-\gamma)} \) and \( DR = BR^{-1/(2+\epsilon)} \) (where \( \gamma = 0 \) represents space-filling, \( \gamma = 1 \) area-filling and \( \gamma = 2 \) length-preservation; \( \epsilon = 0 \) represents area-preservation and \( \epsilon = 1 \) Murray’s law) for a tree structure, we provide a fundamental derivation of the volume–diameter and flow–length scaling laws for arbitrary \( \gamma \) and \( \epsilon \) (i.e. do not invoke the space-filling assumption) as shown in appendices A and B, respectively.

As shown in appendix A, the crown volume is found to scale with the stem diameter in a stem-crown unit as:

\[ \frac{V_c}{(V_c)_{\text{max}}} = \left[ \frac{D_s}{(D_s)_{\text{max}}} \right]^3 \]  

(2.1)

where \( D_s \) is the stem diameter (cm) in a stem-crown unit. \( (V_c)_{\text{max}} \) and \( (D_s)_{\text{max}} \) refer to the cumulative vascular volume and the most proximal stem-crown unit in a vascular tree, respectively.

In appendix B, we derive a scaling relation between stem flow rate and crown length in a stem-crown unit expressed as:

\[ \frac{Q_s}{(Q_s)_{\text{max}}} = \left[ \frac{L_c}{(L_c)_{\text{max}}} \right]^\gamma \]  

(2.2)

where \( Q_s \) is the flow rate through the stem (ml s\(^{-1}\)), \( (Q_s)_{\text{max}} \) is the flow rate through the most proximal stem of the entire tree and \( (L_c)_{\text{max}} \) is the cumulative vascular length of the entire tree. The physical basis of this scaling law (equation (2.2)) is the conservation of mass in a fractal-like tree structure.

In appendix C, we derive the diameter–length scaling law from the minimum energy hypothesis and equations (2.1) and (2.2), which can be expressed as:

\[ \frac{D_s}{(D_s)_{\text{max}}} = \left[ \frac{L_c}{(L_c)_{\text{max}}} \right]^{3/7} \]  

(2.3)

A combination of equations (2.2) and (2.3) leads to the flow–diameter scaling law (similar to Murray’s
law but with a different exponent) as:

\[
\frac{Q_b}{(Q_b)_\text{max}} = \left( \frac{D_s}{(D_s)_\text{max}} \right)^{7/3}.
\]  (2.4)

If equation (2.4) is combined with equation (2.1), we obtain:

\[
\frac{Q_b}{(Q_b)_\text{max}} = \left( \frac{V_c}{(V_c)_\text{max}} \right)^{7/9}.
\]  (2.5)

Equations (2.1)–(2.5) refer to the volume–diameter, flow–length, diameter–length, flow–diameter and flow–volume scaling laws within a vascular tree, respectively.

### 2.2. Morphometric vascular trees

The scaling power-laws (equations (2.1)–(2.5)) are valid in the entire coronary arterial tree in pig hearts, based on the measured morphometric data [6]. Similarly, vascular trees of many organs down to the pre-capillary vessels were also used to verify the scaling power-laws, which are constructed in the Strahler system [30], based on the available literature [6–19]. The pulmonary arterial tree of rats was obtained from the study of Jiang et al. [7]; the pulmonary arterial/venous trees of cats from Yen et al. [8,9]; the pulmonary venous trees of dogs from Gan et al. [10]; the pulmonary arterial trees of humans from Singhal et al. [13]; the skin muscle arterial tree of hamsters from Bertuglia et al. [16]; the mesentery arterial tree of rats from Ley et al. [17]; the sartorius muscle arterial tree of cats from Koller et al. [18]; the bulbar conjunctiva arterial/venous trees of humans and the omentum arterial tree of rabbits from Fenton & Zweifach [19].

### 2.3. Data analysis

A least-squares fit of morphometric data was used to determine the exponents in the scaling power-laws of vascular trees. In particular, a least-squares fit of morphometric data \((D_i \text{ versus } n_i \text{ and } L_i \text{ versus } n_c, i = 0, \ldots, N_{\text{total}})\) was made to determine the parameters \(\varepsilon\) and \(\gamma\) in \(DR = BR^{\varepsilon/(2+\varepsilon)}\) and \(LR = BR^{\gamma/(3-\gamma)}\), respectively. The relative error was used to quantify the discrepancy of exponents fitted by a least-squares method and theoretical exponents. The relative error expressed as

\[
\left| \frac{(V_c)/((V_c)_\text{max}) - (D_i)/((D_i)_\text{max})^3}{(V_c)/((V_c)_\text{max})} \right|, \quad (i = 0, \cdots, N_{\text{total}})
\]

was also calculated in each generation of vascular trees. A two-sample \(t\)-test was used to compare the theoretical prediction with the anatomical data, where \(p < 0.05\) represented statistically significant differences.

### 3. RESULTS

#### 3.1. Volume–diameter scaling law

Figure 2 shows a log–log plot of normalized crown volume as a function of normalized stem diameter,
for the entire pig left anterior descending artery (LAD),
left circumflex artery (LCx) and right coronary artery
(RCA) trees. Using a least-squares fit, the log–log
plots have exponents of 2.96 ($r^2 = 0.999$), 3.00 ($r^2 = 0.999$) and 2.98 ($r^2 = 0.999$) for LAD, LCx and RCA
trees, respectively, which are in excellent agreement
with the model prediction.

Figure 3 shows a log–log plot of normalized crown
volume as a function of normalized stem diameter in
the vascular trees of various organs and species, where
the solid line represents the least-squares fit of all the
experimental measurements (exponent of 2.91, $r^2 = 0.966$). Accordingly, we identified the exponent by a
least-squares fit of morphometric measurements in
each vascular tree, as shown in table 1. The relative
errors as were calculated in each tree as

$$\text{least-squares fitted exponent} - 3$$

and

$$\frac{|(V_i^c/(V_{max}^c)) - (D_i^c/(D_{max}^c))^{3}|}{(V_i^c/(V_{max}^c))^{3}}$$

$$i = 0, \ldots, N_{total}$$ is the generation number.

Table 1 shows the mean value of relative errors where

$$\frac{|(V_i^c/(V_{max}^c)) - (D_i^c/(D_{max}^c))^{3}|}{(V_i^c/(V_{max}^c))^{3}}$$

was averaged over the total number of generations,
$N_{total} + 1$. The prediction of the present model agrees
very well with the measured morphometric data.

3.2. Scaling laws in a vascular tree

Table 2 shows the values of parameters $\varepsilon$ and $\gamma$ in
$DR = BR^{-1/(2+\varepsilon)}$ and $LR = BR^{-1/(3-\gamma)}$ for various
vascular trees corresponding to table 1, which have
mean $\pm$ s.d. of 0.64 $\pm$ 0.64 and 0.45 $\pm$ 0.49 over these
trees, respectively. Table 3 shows a comparison of
scaling laws (i.e. volume–diameter, flow–length,
diameter–length, flow–diameter and flow–volume
scaling power-laws) between the present theoretical
models and experimental measurements. The mean
$(\pm$ s.d.) of exponents was determined by a least-squares
fit of morphometric measurements in the vascular
trees of various organs and species in correspondence to table 1.

4. DISCUSSION

We derived a volume–diameter scaling power-law
(equation (2.1)), which agrees well with the measured
morphometric vascular trees. Moreover, based on
the conservation of mass, we theoretically derived the
flow–length scaling law (equation (2.2)) previously
confirmed by experimental observations [30,33]. A
combination of the two laws results in the diameter–length
($D_i \propto L_i^{7/3}$), flow–diameter ($Q_i \propto D_i^{2/3}$) and flow–
volume ($Q_i \propto V_i^{7/3}$) scaling power-laws in a fractal-like
vascular tree as a result of minimum energy hypothesis.
These laws provide a quantitative integration of

![Figure 3](http://rsif.royalsocietypublishing.org/)
support the area-preservation/cubed-law assumption in the WBE model to some extent. The exponents, however, vary greatly in different vascular trees of small orders in Table 2, which are close to $-1/4$ (e.g. rat MA, human BCA and cat SMA) or $-1/2$ (e.g. hamster SKMA, hamster RMA and human BCV) albeit the mean value is 3.1. Hence, a more general form of $DR = BR^{-1/(2 + \varepsilon)}$ was considered for various vascular trees regardless of the size of vessel segments. As shown in Table 2, there is a good least-squares fit ($r^2 > 0.93$) of $DR = BR^{-1/(2 + \varepsilon)}$ to the experimental measurements in vascular trees of various organs and species, which results in the value of $\varepsilon$ equal to 0.64 ± 0.64 (mean ± s.d.).

### 4.2. Volume–diameter scaling law

Although parameters $\varepsilon$ and $\gamma$ have large variation in different vascular trees, the volume–diameter scaling law has the exponent of 3 (equation (2.1)). Figure 3 shows good agreement between the present model of equation (2.1) and the least-squares fit of all the experimental measurements in various vascular trees (i.e. 3 versus 2.91). Since scaling laws are generalities, it is natural that estimates of the scaling properties should be somewhat noisy. In this context, the variation seen in Figure 3 is remarkably small ($r^2 = 0.966$), tending to validate the conclusions of the present study. Moreover, the exponents for all of vascular trees in Table 1 have a mean value ($\pm$ s.d.) of 3.38 ($\pm$ 0.63), which also supports the prediction of the volume–diameter scaling law in equation (2.1). The perfusion trees with a small number of orders of branching in rat MA, human BCA and cat SMA have a larger exponent of 4.45, 5.05 and 4.78, respectively, which is caused by

$$\frac{2 - \gamma}{3 - \gamma} - \frac{2}{2 + \varepsilon} > 0.$$ 

From equation (A 3) in appendix A,

$$\frac{2 - \gamma}{3 - \gamma} - \frac{2}{2 + \varepsilon} > 0$$

implies an increase in total blood volume of vessels in each generation from proximal to distal, which clearly does not occur over the entire organ level, but may exist in the smaller generations of microcirculation in some organs ($D_s < 15 \mu m$).

It should be noted that the WBE model is intended to express an allometric scaling law of metabolism between species of varying size. In future studies, the present scaling derivations need to be extended to encompass the metabolic scaling law at the organ–tissue level [36] and examined across species.

### 4.3. Physiological basis of scaling laws in a vascular tree

Physiological trees provide flow transport to the capillary network to support tissue demands. Vascular development is generally guided by tissue’s metabolic needs and by the minimization of specific costs for growth and maintenance of the delivery of substrate
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Table 2. A least-squares fit of parameters \( e \) and \( \gamma \) in DR = BR\(^{1/2+s}\) and LR = BR\(^{-1/(3-s)}\) for vascular trees in various organs and species. A least-squares fit of morphometric data \( (D_i \text{ versus } n_i \text{ and } L_i \text{ versus } n_i, \ i = 1, \ldots, \ N_{\text{total}}) \) was made to determine the parameters \( e \) and \( \gamma \) in DR = BR\(^{1/2+s}\) and LR = BR\(^{-1/(3-s)}\), respectively.

<table>
<thead>
<tr>
<th>species ( (N_{\text{total}} + 1) )</th>
<th>( e )</th>
<th>( s^2 )</th>
<th>( \gamma )</th>
<th>( r^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>large number of orders</td>
<td>pig RCA (11)</td>
<td>0.11</td>
<td>0.096</td>
<td>1.08</td>
</tr>
<tr>
<td></td>
<td>pig LAD (11)</td>
<td>0.07</td>
<td>0.093</td>
<td>1.02</td>
</tr>
<tr>
<td></td>
<td>pig LCx (10)</td>
<td>0.04</td>
<td>0.094</td>
<td>1.20</td>
</tr>
<tr>
<td></td>
<td>rat PA (11)</td>
<td>0.22</td>
<td>0.098</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>cat PA (10)</td>
<td>0.37</td>
<td>0.097</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>cat PV (10)</td>
<td>0.30</td>
<td>0.093</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>dog PV (11)</td>
<td>0.5</td>
<td>0.098</td>
<td>0.995</td>
</tr>
<tr>
<td></td>
<td>human PA (17)</td>
<td>0.65</td>
<td>0.091</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>human PA (15)</td>
<td>0.73</td>
<td>0.094</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>human PA (17)</td>
<td>0.44</td>
<td>0.092</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>human PV (15)</td>
<td>0.65</td>
<td>0.098</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>human PV (15)</td>
<td>0.49</td>
<td>0.094</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>mean ( \pm s.d. )</td>
<td>0.38 ( \pm 0.24 )</td>
<td>0.48 ( \pm 0.51 )</td>
<td></td>
</tr>
<tr>
<td>small number of orders</td>
<td>hamster SKMA (4)</td>
<td>0.33</td>
<td>0.092</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>rat MA (4)</td>
<td>1.79</td>
<td>0.090</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>rabbit OV (4)</td>
<td>0.74</td>
<td>0.033</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>human BCA (5)</td>
<td>2.18</td>
<td>0.091</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>human BCV (4)</td>
<td>0.43</td>
<td>0.071</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>hamster</td>
<td>0.05</td>
<td>0.091</td>
<td>1.29</td>
</tr>
<tr>
<td></td>
<td>cat SMA (4)</td>
<td>1.98</td>
<td>0.038</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>mean ( \pm s.d. )</td>
<td>1.07 ( \pm 0.89 )</td>
<td>0.42 ( \pm 0.5 )</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. A comparison of scaling laws between anatomical data of various organs and theoretical model. \( V_{c} \propto D_{c}^{\delta} \), volume–diameter scaling law; \( Q_{c} \propto L_{c}^{\delta} \), flow–length scaling law; \( D_{c} \propto L_{c}^{\delta} \), diameter–length scaling law; \( Q_{c} \propto D_{c}^{\delta} \), flow–diameter scaling law (i.e. Murray’s law if \( X = 3.0 \)); and \( Q_{c} \propto V_{c}^{\delta} \), flow–volume scaling law. The exponents (mean \( \pm s.d. \)) for all trees in table 1 and 2.32 \( \pm 0.18 \) (mean \( \pm s.d. \)) for large-order trees in table 1. The present theoretical value of 2.33 agrees better with the measurements over many generations of vascular tree than Murray’s law. The structure–structure (equation (2.3)) and structure–function (equations (2.4) and (2.5)) scaling laws reflect the design of biological trees for flow transport under the principle of minimum energy.

<table>
<thead>
<tr>
<th>exponent ( X ) in power-law scaling relations</th>
<th>anatomical data</th>
<th>present model</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_{c} \propto D_{c}^{\delta} )</td>
<td>3.38 ( \pm 0.63 )</td>
<td>3</td>
</tr>
<tr>
<td>( Q_{c} \propto L_{c}^{\delta} )</td>
<td>0.94 ( \pm 0.28 )</td>
<td>1</td>
</tr>
<tr>
<td>( D_{c} \propto L_{c}^{\delta} )</td>
<td>0.37 ( \pm 0.08 )</td>
<td>0.43</td>
</tr>
<tr>
<td>( Q_{c} \propto D_{c}^{\delta} )</td>
<td>2.62 ( \pm 0.65 )</td>
<td>2.33</td>
</tr>
<tr>
<td>( Q_{c} \propto V_{c}^{\delta} )</td>
<td>0.70 ( \pm 0.055 )</td>
<td>0.78</td>
</tr>
</tbody>
</table>

4.4. Comparison with Huo & Kassab’s model

Huo & Kassab [40] previously proposed a volume–diameter–length scaling relation \( (V_{c} \propto D_{c}^{\delta} L_{c}) \) based on experimental observation of \( V_{c} \propto M^{\delta} \) [41] and two assumptions of \( D_{c} \propto M^{\beta/3} \) and \( L_{c} \propto M^{\beta/3} \). Equations (2.1) and equations (2.3)–(2.5) of the present study were also obtained from the volume–diameter–length scaling relation coupled with the hypotheses of minimum energy loss and flow–length scaling law (see appendix in [40]). Equations (2.1) and (2.3) resulting from the volume–diameter–length scaling relation, however, suggest that \( D_{c} \propto M^{\beta/3} \) and \( L_{c} \propto M^{\beta/3} \), respectively, which slightly differ from previous exponents (i.e. \( D_{c} \propto M^{1/3} \) versus \( \beta/3 \) and \( L_{c} \propto M^{1/3} \) versus \( \beta/3 \)). I.e. 0.33 versus 0.37 and 0.78 versus 0.75, respectively. It is experimentally difficult to discriminate between such similar exponents based on the least-squares fit. In conclusion, this formulation provides the same volume–diameter–length scaling relation \( (V_{c} \propto D_{c}^{\delta} L_{c}) \) [40].
In the present study, we provide a more fundamental derivation of the volume–diameter scaling law (equation (2.1)) and the flow–length scaling law (equation (2.2)) from conservation of mass in a fractal-like tree structure (see appendices A and B), which results in the volume–diameter–length scaling relation without invoking the previous assumptions of $D_i \propto M_i^{3/8}$ and $L_i \propto M_i^{1/4}$. Therefore, the present study substantiates the previous conclusion [40] and confirms the scaling power-laws of vascular tree (equations (2.1)–(2.5)). In Table 3, the mean values ($\pm$ 1 s.d.) of exponents for various morphometric vascular trees agree well with the scaling power-laws of vascular tree.

### 4.5. Implications for coronary heart disease

The coronary blood volume and flow rate are important parameters for the assessment of CHD. The volume–diameter (equation (2.1)) and flow–diameter (equation (2.4)) scaling power-laws can provide estimates of blood volume and flow rate from medical imaging (e.g. digital subtraction angiography, computed tomography, magnetic resonance imaging, etc.). Moreover, regional values of myocardial blood volume (MBV) and blood flow (MBF) can also be quantified by using fast mapping techniques of MRI [42]. A comparison of MBV and MBF between normal and CHD populations can provide a severity index for the extent of myocardial ischaemia. The validation of this rationale requires future studies.

### 5. SUMMARY AND CONCLUSION

The power-law scaling relation has been assumed to be ubiquitous in biology and is relevant to medicine, nutrition and ecology. For the intraspecific scaling laws within an organ of a given species, we derived and validated the volume–diameter and flow–length scaling laws (equations (2.1) and (2.2), respectively) using conservation of mass in a fractal-like and the minimum energy hypothesis. The fundamentally derived scaling laws are in very good agreement with the available morphometric and haemodynamic data in various vascular trees. These scaling laws have significant merit in basic studies and ultimately in clinical diagnosis and therapy.

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### APPENDIX A

An idealized symmetric tree is used to obtain the relationship between crown volume and stem diameter. The crown distal to a stem is composed of $N_i$ levels (or generations) from the stem (level zero of a crown) to each terminal (the smallest arterioles or venules, level $N_i$ of each crown). The volume of a crown, $V_c$, can be written as:

$$V_c = V_s + \sum_{i=1}^{N_i} n_i V_i = \frac{\pi}{4} D_i^2 L_i;$$

$$\text{A1}$$

where

$$V_c = \frac{\pi}{4} D_i^2 L_i$$

$V_c, L_s$ and $D_i$ are the volume, length and diameter of the stem, respectively. Similarly, $V_i, L_i$ and $D_i$ are the volume, length and diameter of a vessel in level $i$, respectively, and $n_i$ is the total number of vessels in level $i$. Equation (A1) can be written as:

$$V_c = \frac{\pi}{4} D_i^2 L_i \left(1 + \sum_{i=1}^{N_i} n_i \left(\frac{D_i}{D_{i-1}}\right)^2 \left(\frac{L_i}{L_{i-1}}\right)\right)$$

(A2)

In the following derivation, we introduce three definitions:

#### A.1. Branching ratio

The branching ratios ($BR_i = n_i/n_{i-1}$) are relatively constant in each level from the stem (level 0) to the smallest arterioles or venules (level $N_i$), such that $n_i = BR_i$ in a crown.

#### A.2. Diameter ratio

The diameter ratio is defined as:

$$DR_i = \frac{D_i}{D_{i-1}}, i = 1, \ldots, N_i$$

It can be shown that $n_i \pi D_i^{1+\varepsilon} = n_{i-1} \pi D_{i-1}^{1+\varepsilon}$, where $\varepsilon = 0$ represents Murray’s law; $i.e.$ $n_i \pi D_i^3 = n_{i-1} \pi D_{i-1}^3$ area-preservation from one level to the next. Conversely, $\varepsilon = 1$ represents Murray’s law; i.e. $n_i \pi D_i^1 = n_{i-1} \pi D_{i-1}^1$. This provides the relation:

$$\left(\frac{D_i}{D_{i-1}}\right) = \left(\frac{n_i}{n_{i-1}}\right)^{-1/(2+\varepsilon)}$$

In the following derivation, we introduce three definitions:

#### A.1. Branching ratio

The branching ratios ($BR_i = n_i/n_{i-1}$) are relatively constant in each level from the stem (level 0) to the smallest arterioles or venules (level $N_i$), such that $n_i = BR_i$ in a crown.

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The diameter ratio is defined as:

$$DR_i = \frac{D_i}{D_{i-1}}, i = 1, \ldots, N_i$$

It can be shown that $n_i \pi D_i^{1+\varepsilon} = n_{i-1} \pi D_{i-1}^{1+\varepsilon}$, where $\varepsilon = 0$ represents Murray’s law; $i.e.$ $n_i \pi D_i^3 = n_{i-1} \pi D_{i-1}^3$ area-preservation from one level to the next. Conversely, $\varepsilon = 1$ represents Murray’s law; i.e. $n_i \pi D_i^1 = n_{i-1} \pi D_{i-1}^1$. This provides the relation:

$$\left(\frac{D_i}{D_{i-1}}\right) = \left(\frac{n_i}{n_{i-1}}\right)^{-1/(2+\varepsilon)}$$

Therefore, the diameter ratio relates to the branching ratio as: $BR_i = DR_i^{-1/(2+\varepsilon)}$ or $D_i = BR_i^{-1/(2+\varepsilon)} D_{i-1}$ in a crown.

#### A.3. Length ratio

The length ratio is defined as:

$$LR_i = \frac{L_i}{L_{i-1}}, i = 1, \ldots, N_i$$

West et al. [26] proposed that the perfused volume from one level to the next was constant, so that

$$\frac{4}{3} \pi \left(\frac{L_i}{2}\right)^3 n_i = \frac{4}{3} \pi \left(\frac{L_{i-1}}{2}\right)^3 n_{i-1},$$

which has been highly disputed and for which there are no supporting experimental data [28,29]. Here, we assume a more general relation that has an experimental basis; namely:

$$\left(\frac{L_i}{2}\right)^{3-\gamma} n_i = \left(\frac{L_{i-1}}{2}\right)^{3-\gamma} n_{i-1},$$

where $\gamma = 0$ represent space-filling, $\gamma = 1$ represent area-filling and $\gamma = 2$ represent length-preservation. This leads to

$$\left(\frac{L_i}{L_{i-1}}\right)^{3-\gamma} = \left(\frac{n_i}{n_{i-1}}\right)^{-1/(3-\gamma)}$$

The length ratio relates to the branching ratio as $LR_i = BR_i^{-1/(3-\gamma)}$ or $L_i = BR_i^{-1/(3-\gamma)} L_{i-1}$ in a crown.
A.4. Parameters $\epsilon$ and $\gamma$ in vascular trees

Table 2 shows the relation between the branching and diameter ratios and the length ratio in vascular trees for various organs and species. It is found that $\text{DR} = \text{BR}^{-1/(2.64 \pm 0.64)}$ and $\text{LR} = \text{BR}^{-1/(2.55 \pm 0.49)}$. Parameters $\epsilon$ and $\gamma$ are equal to $0.64 \pm 0.64$ and $0.45 \pm 0.49$, respectively, which are significantly different from zero ($p < 0.05$).

A.5. Volume–diameter scaling law

From $n_i = \text{BR}^4$, $D_i = \text{BR}^{-(2+\epsilon)}/D_0$, $L_i = \text{BR}^{-(3-\gamma)}L_0$, and equation (A 2), we obtain the following equation:

$$V_c = \frac{\pi}{4} D_i^2 L_i \left(1 + \sum_{i=1}^N BR^{-(2+\epsilon)/2}(BR^{-1/(2+\epsilon)})^2 \right)$$

or

$$V_c = \frac{\pi}{4} D_i^2 L_i \left(1 + \sum_{i=1}^N BR^{(2-\gamma)/(3-\gamma)-2/(2+\epsilon)} \right)$$

Equation (A 3) relates the crown volume to the branching ratio of the vascular tree. Since $2-\gamma)/(3-\gamma)-2/(2+\epsilon) < 0$ for most vascular trees (mean of approx. $-0.15$ for vascular trees of various organs), the last term in Equation (A 3) has $0 < \text{BR}^{(2-\gamma)/(3-\gamma)-2/(2+\epsilon)} < 1$. This implies a decrease in total blood volume of vessels in each level from the stem (level zero) to the terminal (level $N$) as supported by the experimental data [6]. Equation (A 3) is written as:

$$V_c = \frac{\pi}{4} D_i^2 L_i \left(1 - \text{BR}^{(2-\gamma)/(3-\gamma)-2/(2+\epsilon)} \right)$$

for $2 - \gamma - 2/2+\epsilon < 0$.  

Since $D_i = \text{BR}^{-(2+\epsilon)}D_0$ and $L_i = \text{BR}^{-(3-\gamma)}L_0$, equation (A 4) can be written as:

$$V_c = \frac{\pi}{4} D_i^2 L_i \left(1 - \text{BR}^{(2-\gamma)/(3-\gamma)-2/(2+\epsilon)} \right)$$

for $2 - \gamma - 2/2+\epsilon < 0$.

There is

$$1 \leq \frac{\text{BR}^{(1/(3-\gamma)-1/(2+\epsilon))(N+1)} - \text{BR}^{(e-1)/(2+\epsilon)(N+1)}}{\text{BR}^{(1/(3-\gamma)-1/(2+\epsilon))} - \text{BR}^{(e-1)/(2+\epsilon)}} < 10$$

for different crowns in various vascular trees (negligible variation given the range of variables is very large, 10 decades on the $y$-axis in figure 3).

To be exhaustive, we consider two alternate scenarios: (i) it may be that $(2-\gamma)/(3-\gamma)-2/(2+\epsilon) = 0$ (unchanged total blood volume of vessels in each level) or (ii) $(2-\gamma)/(3-\gamma)-2/(2+\epsilon) > 0$ (increase in total blood volume of vessels in each level from the stem to the terminal), which leads to:

$$V_c = \frac{\pi}{4} D_i^2 \left(\frac{L_i}{D_i}\right)_N \left(N+1\right)\text{BR}^{(1/(3-\gamma)-1/(2+\epsilon))(N+1)}$$

for $2 - \gamma - 2/2+\epsilon = 0$.

and

$$V_c = \frac{\pi}{4} D_i^2 \left(\frac{L_i}{D_i}\right)_N \left(N+1\right)\text{BR}^{(1/(3-\gamma)-1/(2+\epsilon))(N+1)}$$

for $2 - \gamma - 2/2+\epsilon > 0$.

For a symmetric tree, the ratio of vessel length to diameter, $(L_i)/D_i$ is constant in pre-capillary vessels. If we define that

$$K_s = \frac{\text{BR}^{(1/(3-\gamma)-1/(2+\epsilon))(N+1)} - \text{BR}^{(e-1)/(2+\epsilon)(N+1)}}{\text{BR}^{(1/(3-\gamma)-1/(2+\epsilon))} - \text{BR}^{(e-1)/(2+\epsilon)}}$$

and

$$K_s = (N+1)\text{BR}^{(1/(3-\gamma)-1/(2+\epsilon))}$$

where $(L_i)/D_i$ are the length and diameter of a pre-capillary vessel segment (i.e. the smallest arterioles or venules). Given that

$$\frac{1}{3-\gamma - 2/2+\epsilon} = \frac{1}{2.55 \pm 0.49} - \frac{1}{2.64 \pm 0.64} \approx 0.01,$$

$(e-1)/(2+\epsilon) \approx -0.14$, 0 $\leq N_i \leq 16$, and 2 $\leq BR \leq 4$, there is

$$V_c = \frac{\pi}{4} K_s D_i^2 = K_s D_0^2$$

and $K_d = \frac{\pi}{4} K_s$.  

When $V_c = (V_c)_{\text{max}}$ and $D_i = (D_i)_{\text{max}}$, where $(V_c)_{\text{max}}$ and $(D_i)_{\text{max}}$ refer to the cumulative vascular volume and the most proximal stem diameter in the entire tree, respectively, equation (A 8) is written as:

$$(V_c)_{\text{max}} = K_d (D_i)_{\text{max}}^3,$$

where $K_d = (V_c)_{\text{max}}/(D_i)_{\text{max}}^3$ depends on the branching ratio, diameter ratio and total number of tree generations in an entire tree, and the ratio of vessel length to diameter in the pre-capillary vessel segment. From equations (A 8) and (A 9), we obtain:

$$\left[\frac{V_c}{(V_c)_{\text{max}}} \right] = \left[\frac{D_i}{(D_i)_{\text{max}}}\right]^3.$$
Equations (A 8) and (A 10) are the volume–diameter scaling relation in a vascular tree.

**APPENDIX B**

The crown length, $L_c$, can be written as:

$$L_c = L_a + \sum_{i=1}^{N_i} n_i L_i; \quad i = 1, \ldots, N_i,$$

(B 1)

where $N_i$ is the same as defined in appendix A. From $n_i = BR^i$, $L_i = BR^{-i(3-\gamma)}L_a$ and equation (B 1), we obtain the following equation:

$$L_c = L_a + \sum_{i=1}^{N_i} n_i L_i = L_a \left(1 + \sum_{i=1}^{N_i} BR^i \cdot BR^{-i(3-\gamma)}\right)$$

(B 2)

Since $L_c = (L_a)_{N_i} \cdot BR^{N_i(3-\gamma)}$, where $(L_a)_{N_i}$ is the length of pre-capillary vessel segment, the crown length can be expressed as:

$$L_c = (L_a)_{N_i} \cdot BR^{N_i(3-\gamma)} \times \frac{BR^{-2(3-\gamma)(N_i+1)} - 1}{BR^{-2(3-\gamma)(3-\gamma)} - 1}.$$  

(B 3)

From conservation of mass, the flow rate at a stem vessel of a crown, $Q_s$, can be expressed by the flow rate at the pre-capillary vessel segment, $(Q_s)_{N_i}$ as:

$$Q_s = (Q_s)_{N_i} \cdot BR^{N_i}.$$  

(Equation (B 4))

**APPENDIX C**

Similar to Murray’s law, a cost function for an integrated system of stem-crown units is proposed [30], which consists of two terms: viscous and metabolic power dissipation. The cost function, $F_c$ (erg), is written as:

$$F_c = Q_c \cdot \Delta P_c + K_m V_c,$$  

(C 1)

where $Q_c$, $\Delta P_c$, and $V_c$ are the flow rate through the stem (ml s$^{-1}$), pressure drop in the distal crown (dynes cm$^{-2}$) and crown volume (ml) (defined as the sum of the intravascular volume of each vessel segment in the entire crown from the stem to the most distal vessels), respectively. $K_m$ is a metabolic constant of blood in a crown (dynes cm$^{-2}$ s$^{-1}$). Two important structure–structure scaling laws are needed to implement the minimum energy analysis in the cost function (equation (C 1)). First, we have shown that the resistance of a crown (dynes s cm$^{-5}$) has the following form:

$$R_c = K_c \cdot L_c \cdot \frac{D_c^{-4}}{D_s^{-4}}.$$  

(C 2)

or

$$\left[\frac{R_c}{(R_c)_0}\right] = \left[\frac{L_c}{(L_c)_{max}}\right] \left[\frac{D_c}{(D_c)_{max}}\right]^{-4},$$

where $L_c$ is the crown length (cm) (defined as the sum of the lengths of each vessel segment in the entire crown) and $D_c$ is the stem diameter (cm) [40]. $(D_c)_{max}$ and $(R_c)_0$ correspond to the most proximal stem diameter of the entire tree, the cumulative vascular length of the entire tree and the total resistance of the entire tree, respectively. $K_c = (R_c)_0 \cdot (D_c)_{max}^{-4} / (L_c)_{max}$ is a flow-resistance constant in a crown (dynes $s$ cm$^{-5}$), which depends on the branching ratio and the total number of tree generation in a crown [40]. Second, the crown volume is found to scale with the stem diameter (equation (A 11)).

When resistance (equation (C 2)) and volume–diameter (equation (A 11)) scaling laws are substituted into the energy cost function, equation (C 1) can be written as:

$$F_c = Q_c^2 \cdot R_c + K_m K_d D_s^3 = K_c Q_c^2 \cdot L_c \cdot D_s^3 + K_m K_d D_s^3.$$  

(C 3)

Equation (C 3) can be normalized by the metabolic power requirements of the entire tree of interest, $K_m V_c (L_c)_{max} = K_m K_d (D_s)_{max}^3$, to obtain the non-dimensional cost function ($f_c$). When the flow–length scaling law (equation (B 7)) is applied to the non-dimensional equation (C 3), the dimensionless cost function can be written as:

$$f_c = \frac{(Q_s)_{max}^3 (R_c)_0 \left[\frac{L_c}{(L_c)_{max}}\right]^3 + \left[\frac{D_c}{(D_c)_{max}}\right]^3}{K_m K_d (D_s)_{max}^3}.$$  

(C 4)
Similar to Murray’s approach, we minimize the cost function with respect to diameter at a fixed crown length to obtain the following:

$$\frac{\partial k}{\partial D_c/(D_c)_{\text{max}}} = 0 \Rightarrow \frac{(-4)(Q_{c})^2_{\text{max}} (R_c)_0}{K_m K_d (D_c)_{\text{max}}^3} \times \left[ \frac{L_c/(L_c)_{\text{max}}^3}{(D_c)_{\text{max}}^3} \right] = -3 \left[ \frac{D_c}{(D_c)_{\text{max}}} \right]^2.$$  \hspace{1cm} (C5)

Equation (C5) applies to any stem-crown unit. When

$$\left[ \frac{L_c}{(L_c)_{\text{max}}} \right] = 1 \quad \text{and} \quad \left[ \frac{D_c}{(D_c)_{\text{max}}} \right] = 1$$

in equation (C5), we find that

$$\frac{4(Q_{c})^2_{\text{max}} (R_c)_0}{3K_m K_d (D_c)_{\text{max}}} = 1$$

such that equation (C5) can be written as:

$$\left[ \frac{D_c}{(D_c)_{\text{max}}} \right] = \left[ \frac{L_c}{(L_c)_{\text{max}}} \right]^3.$$  \hspace{1cm} (C6)

This equation provides the diameter–length scaling law, which forms the basis for the formulation presented in this study.

**REFERENCES**