Anatomical Variability and Functional Ability of Vascular Trees Modeled by Constrained Constructive Optimization

WOLFGANG SCHREINER,∗† FRIEDERIKE NEUMANN,† MARTIN NEUMANN,‡ ADELHEID END† AND SUSANNE M. ROEDLER§

* Department of Medical Computer Sciences, † Department of Cardiothoracic Surgery, Working Group for Biomedical Computer Simulation, ‡ Institute for Experimental Physics, Division of Computational Physics and the § Department of Cardiology, University of Vienna, Spitalgasse 23, A-1090 Vienna, Austria

(Received on 10 July 1996, Accepted in revised form on 24 January 1997)

1. Introduction

Realistic models of the coronary arterial tree can be generated by Constrained Constructive Optimization (CCO). CCO has been introduced as a new computational technique yielding complex dichotomously branching arterial tree models (Schreiner, 1993; Schreiner & Buxbaum, 1993) which were shown to reproduce key structural features of coronary arterial trees (Schreiner et al., 1994, 1995). The construction of a model tree is accomplished by the stepwise addition of individual segments, so as to mimic a kind of natural growth. At each step, this growth is guided by an optimization target (minimum intravasal volume) and by the necessity for the growing tree to fulfill invariant boundary conditions at every stage of its development.

In addition to these principles, which remain unchanged throughout the development of a particular tree, there is also a stochastic feature to the model: a pseudo random number sequence (PRNS) (Press et al., 1992; Kalos & Whitlock, 1986) determines the sites of new terminal segments to be added to the tree. Terminal segments emerging in the early stages of development become major branches of the fully developed tree, and hence the topography of these major branches depends to a large extent on the particular PRNS used.

This specific feature of CCO can be exploited to investigate a question which is both general and...
crucial for understanding the principles of vascular function: “do variations in the vascular pattern between individuals necessarily have functional consequences?”. In other words: are some arterial branching patterns more advantageous than others? In real patients the problem of standardization and evaluation in general precludes a specific answer to such a general question. Using the CCO model, however, we have the opportunity of:

(i) keeping the most important functional covariables constant by including them into the boundary conditions (i.e. the constraints) of the model;
(ii) controlling and evaluating the variations due to the remaining covariables by statistical descriptors.

All in all, this concept offers the chance to observe the “undisturbed net effect” of anatomical variability on vascular function.

Specifically, in the present work we investigate the variability induced in CCO model trees when using different PRNSs, each of which produces a particular “realization” of the model. Even though a maximum of parameters is kept constant (the same optimization target is applied under a unique set of boundary conditions), each of these realizations results in a topographically different tree.

In general, different realizations are recognized as such by mere visual inspection and may be interpreted as the correlate to the anatomical variations found in real vascular trees. Real coronary trees, for example, also exhibit well-known variations of the branching pattern, such as right vs left coronary dominancy and indifferent type, varying sizes of side branches, etc. (MclAlpine, 1975). In analogy, we call the differences in the branching patterns of CCO trees “anatomical variability” if they solely emerge from different PRNSs.

Since in a computer-model all geometrical data are known precisely, descriptive quantities and special graphs may be readily produced and evaluated in order to obtain a comprehensive morphometrical description of each model tree. These descriptors may be used to quantify the “anatomical variability”.

### 2. The Method of Constrained Constructive Optimization (CCO)

The method of “Constrained Constructive Optimization” (CCO) has been developed and described in detail in a previous technical paper (Schreiner & Buxbaum, 1993), so that in the present work we can restrict ourselves to an overview.

#### 2.1. Constraints Representing Physiologic Perfusion Conditions in CCO

We presume that blood should be carried and delivered to all parts of the tissue considered. In the present work this “perfusion area” is selected to be a circle with 5 cm radius, representing the vascular bed of a human left anterior descending (LAD) coronary artery. The arterial network is modeled as a binary (dichotomously) branching tree of straight cylindrical segments, in each of which the flow-resistance is governed by Poisseulle’s law (Fung, 1984).

The tree is supplied via a feeding vessel (root segment with a flow \( Q_{\text{perf}} = 500 \text{ ml min}^{-1} \)) at constant perfusion pressure \( p_{\text{perf}} = 100 \text{ mm Hg} \). Total perfusion flow was chosen to represent a fully vasodilated state and cardiac arrest for which we assume 5 times the normal flow \((5 \times 100 \text{ ml min}^{-1} 100 \text{ g}^{-1})\). All terminal segments are supposed to supply their corresponding microcirculatory areas at equal pressure \( p_{\text{term}} = 60 \text{ mm Hg} \) and flows. Note that the flow through each terminal segment is

\[
Q_{\text{term}} = \frac{Q_{\text{perf}}}{N_{\text{term}}}
\]

where \( N_{\text{term}} \) is the number of terminal segments. So far, these conventions are called “perfusion constraints”. Additionally, a “branching law” frequently observed in real arterial trees (Zamir & Chee, 1987; Zamir, 1988), is incorporated into the model to govern the relation between radii of parent \( r_{\text{parent}} \) and daughter segments:

\[
r_{\text{parent}} = r_{\text{left}} + r_{\text{right}}
\]

The value of the parameter \( \gamma \) determines to what amount the cross sectional area of the vascular tree model expands from one bifurcation level to the next. Although \( \gamma \) plays an important role for the resulting pressure profile (Schreiner & Buxbaum, 1993) across the tree, preliminary CCO-runs have shown that \( \gamma \) has only a limited and indirect impact on the branching pattern of the generated vascular tree. Since the present work focuses only on “structural variability” we may (without loss of generality) conform to the widely accepted choice of \( \gamma = 3.0 \) (bifurcation constraint).

It is important to emphasize here (without proof) that every binary tree, regardless of its particular structure and geometry, can be forced to simultaneously meet the above perfusion- and bifurcation-constraints by choosing appropriate segment radii. Moreover, for \( N_{\text{term}} \) terminals, the total number of segments is always

\[
N_{\text{tot}} = 2 \cdot N_{\text{term}} - 1
\]
Details of the algorithm used to construct the model tree are described in the following sections and are schematically presented in a flow chart published previously [figure 1 in Schreiner et al. (1996)].

2.2. CONSTRUCTION BY ADDING BIFURCATIONS AND TERMINAL SEGMENTS

Assume that a small tree already exists, e.g. having 3 terminal segments and $3.2 - 1 = 5$ segments in total. For the next step of growth we draw another number from the PRNS to toss for the location of the distal end of the next terminal segment. This enters a stochastic feature to CCO, since the spatial arrangement of terminal sites becomes closely linked to the particular PRNS used. To provide optimum supply, terminals should not be located on a purely random basis but rather favour locations not yet supplied. Accordingly, after tossing we subject each prospective new location to a kind of “territorial claim & repulsion criterion”, disfavouring locations close to any already existing site of supply. Thus, terminal terminals should not be located on a purely random basis but rather favour locations not yet supplied. Having accepted a (new terminal) site, the new terminal segment is connected to “the most suitable” segment ($l_{\text{conn}}$) of the pre-existing tree (see below for how to find the most suitable segment).

2.3. UNIQUE OPTIMIZATION GOAL FOR TOPOLOGY AND GEOMETRY

Optimization is brought into CCO by selecting a target function, $T$, which globally quantifies the “optimality of the tree”. Based on physiological arguments, several possibilities for selecting $T$ have been proposed (Kamiya & Togawa, 1972; Lefevre, 1983). One of these is the total intravascular volume of a target function, $T$.

$$T = V = \pi \sum_{i=1}^{N_{\text{tot}}} l(i)r^2(i)$$  \hspace{1cm} (4)$$

where $l(i)$ are segment lengths. The optimization process itself has two components, a geometric one and a structural one. In CCO both are governed by the very same target function.

2.3.1. Geometric optimization

Suppose the already existing segment $l_{\text{conn}}$ has been selected to provide the connection site for a newly generated terminal. To these ends a new bifurcation is inserted at an arbitrary location along segment $l_{\text{conn}}$, thereby dividing the former segment $l_{\text{conn}}$ into its proximal part (i.e. new bifurcation segment) and its distal part (remainder of former segment $l_{\text{conn}}$). Segment radii are rescaled in order to re-implement the constraints including the new terminal. Then the “initial” value of the target function is computed for this arbitrary location of the new bifurcation. At this point it is important to note that the value of the target function [eqn (4)] in fact depends on the geometrical location [coordinates $x(i_{bif}), y(i_{bif})$] of the new bifurcation, even if the connective structure of the tree remains unchanged: If the position of the bifurcation is moved, generally all three adjacent segments change in lengths, and perfusion constraints have to be re-enforced by rescaling radii. Both actions jointly change $T$. Since this holds for any bifurcation (and in an analogous way even for terminal segments), $T$ is in general a continuous function of all segment coordinates:

$$T = T[x(i), y(i); D^1, D^2, y_{\text{tot}}].$$  \hspace{1cm} (5)$$

This feature can be exploited to move the new bifurcation [$x(i_{bif}), y(i_{bif})$] so as to optimize (reduce) the value of the target function step by step [gradient method (Fröberg, 1985; Press et al., 1992)], while all other segment coordinates and the tree structure remain unchanged. Upon convergence of this “geometrical optimization” of segment $i_{bif}$, one arrives at a minimum of $T$

$$T_{\text{conn}}^{\text{opt}} = \min_{D^1, D^2, y_{\text{tot}}} T[x(i), y(i); D^1, D^2, y_{\text{tot}}]$$  \hspace{1cm} (6)$$

which is only an optimum under the given structure which is encoded by indices $(D^1, D^2)$ pointing from each segment $i$ to the left and right daughter segments, respectively. Since this particular structure $(D^1, D^2, y_{\text{tot}})$ assumes that segment $l_{\text{conn}}$ was chosen as connection site for the new terminal, the corresponding minimum of $T$ represents only a “particular” (local) rather than a “global” optimum.

2.3.2. Structural optimization

Selecting a different connection site $l_{\text{conn}} \neq l_{\text{conn}}$ means considering a “different structure” $(D^1, D^2, y_{\text{tot}})$ (topology) of the tree. Then, the geometric optimization of the new bifurcation usually yields a different value $T_{\text{conn}}^{\text{opt}}$, which is again a local minimum. The process of trying all “reasonable” segments to become the connection site is called “connection search”. As a result one obtains the “global” optimum

$$T_{\text{conn}}^{\text{glob}} = \min_{l_{\text{conn}}} \{T_{\text{conn}}^{\text{opt}}\}$$  \hspace{1cm} (7)$$


ANATOMICAL VARIABILITY AND FUNCTIONAL ABILITY OF VASCULAR TREES 149
Fig. 1. Anatomical variability of vascular patterns. A selection of six realizations of CCO generated model trees based on different random number seeds. All external parameters are equal for these trees: perfusion pressure, total flow, (as a consequence: total resistance), the number of segments (and terminal segments), and equal flows through all terminal segments. Every bifurcation in each tree fulfills the power law defined in eqn (2) and all trees are optimized according to minimum intravasal volume.
for adding the new segment to the pre-existing tree.* In summary:

(i) Geometric optimization is nested within structural optimization and
(ii) both types of optimization are based on the very same target function [eqn (4)].

The pre-existing structure is decisive for the outcome of geometrical optimization, which in turn determines the site of structural growth. Thus “new terminals are optimally added to an inherited structure”.

3. Anatomical Variability Represented in the Model

The precise locations and—even more important—the timewise sequence of newly generated terminal segments likewise depend on the particular PRNS used.

Any new connection (including the interconnecting segment) depends on both the location of the new terminal site and the shape of the pre-existing tree (e.g. which of the segments are close). The shape of the pre-existing tree, however, is nothing but the result of preceding steps of the above procedure and is therefore also strongly influenced by the PRNS used.

In summary:

(i) the PRNS directly influences each step of growth via the location of new terminals;
(ii) decisions in earlier steps of growth, having manifested themselves in tree structure, are “transmitted” to more advanced stages of the development where they become the substrate on which new decisions for growth are to be made.

In the present paper we quantify this two-fold impact of PRNS on vascular model trees generated by Constrained Constructive Optimization.

We used the pseudo random number generator supplied with the NAG* numerical library (The Numerical Algorithms Group, 1993) for a uniform distribution on the interval [0,1]. The seeds to initialize different PRNSs, which are usually many-digit numbers, are for convenience labeled 1, 2, 3, . . . in the following. Upon initialization, the generator produces deterministically a unique sequence of numbers which is statistically (almost!) undistinguishable from true random numbers that could be obtained from a stochastic physical process.

* Note that in each single step of adding, the tree grows by two new segments: (i) the “new terminal” and (ii) a new “bifurcation segment”, which becomes the mother of both the “new terminal” and the distal remainder of the segment found “most suitable” for connection (i.e.,

A total of ten trees with $N_{term} = 4000$ was produced by CCO, applying different PRNSs under identical boundary conditions and using total intravasal volume as target function of optimization. Figure 1 shows a subset of six trees (random seeds 1,2,3,4,7,8) which obviously differ in topology. In particular, with seed 2 all major branches emerge from more or less asymmetric bifurcations. Seed 1, distally of two asymmetric bifurcations, yields a nearly symmetric bifurcation into medium size branches close to the midpoint of the perfusion area. With seeds 3 and 4 almost symmetric bifurcations into large branches are situated slightly more proximal, but still remain distal of asymmetric side branches. Only with seeds 7 and 8 we find fairly symmetric bifurcations closer to the root, without any relevant proximal side branches.

4. Results: Statistical Morphometry to Characterize Anatomical Variability

Although each of the ten trees was generated on the same preset parameters and with the same optimization target function (total intravasal volume), the use of different PRNSs in CCO still includes a variability of model structure which is clearly evident to visual inspection (cf. Fig. 1) and may be quantified by two types of computed quantities:

(a) global quantities, characterizing an entire configuration (see Section 4.1) and
(b) quantities related to “classes of segments”.

In the present work we used two such classification systems, the “bifurcation level” (Section 4.2) and the “Strahler order” (Section 4.3).

4.1. SMALL VARIABILITIES OF SURFACE, ROOT-RADIUS AND VOLUME

The different anatomical structures emerging from different PRNSs give rise to differences in key quantities such as total volume, total surface, and radius of the root segment (inlet to the tree), cf. Table 1. The relatively smallest variation was observed in total surface (0.015%), followed by the radius of the root segment (0.07%) and total volume (0.5%). Note that each coefficient of variation $[=100.(standard
deviation)/mean]$ was computed from a sample of 10 trees.

4.2. VARIABILITY OF FREQUENCIES RELATED TO “BIFURCATION” LEVELS

The bifurcation level $[A_{bif}(i)]$ of an arbitrary segment $i$ in a binary tree is defined (Zamir & Chee,
1987) as the number of proximal bifurcations (along the uniquely defined path towards the root segment, for which we set \( \Lambda_{\text{str}} = 0 \)). Note that, as one advances from the root to the leaves of a tree, \( \Lambda_{\text{str}} \) increases by 1 at each bifurcation. Parent and daughter segments can never belong to the same level, whereas both daughters of a bifurcation always have the same level, regardless of their radii.

First the ten model trees showed different numbers of bifurcation levels, varying between 113 and 134 (±17% variation).

Second, the frequency distributions of segments over bifurcation levels varied between trees. Generally, these frequency distributions are right skewed (−0.33 ≤ skewness ≤ −0.08), with modes* occurring between level 68 and 92. The “average frequency distribution” is shown in Fig. 2 (diamonds), which has a skewness of −0.249 and its mode at level 84.

In order to quantify the variability between distributions for different trees, we consider the standard deviations of segment frequencies observed at each level. For level zero each tree has exactly one (root) segment and hence the standard deviation is zero. For all other levels, the standard deviations are shown as upward bars and characterize the variability of these distributions between trees. This is equivalent to 10–25% in terms of coefficients of variation. Additionally, the distribution is shown for the subgroups of terminal segments (triangles, standard deviations as downward bars).

4.3. VARIABILITY OF QUANTITIES RELATED TO “STRAHLER” ORDERS

The concept of classification into Strahler orders \( (\Lambda_{\text{str}} = 0, 1, 2, \ldots) \) was originally invented for the geomorphological classification of rivers and their tributaries (Strahler, 1952, 1957; van Bavel & Spaan, 1992). First, \( \Lambda_{\text{str}} = 0 \) is assigned to all terminal segments. Then proceeding towards the root, \( \Lambda_{\text{str}} \), of the parent segment of each bifurcation is determined as follows: If both daughters have equal Strahler order, the order of the parent segment is increased by one. Otherwise, the parent segment retains the higher Strahler order of its two daughter segments. As opposed to bifurcation levels, Strahler orders are low near the terminals of the tree and highest for its root segment. Since the same Strahler order generally extends over several bifurcation levels along a path from distal to proximal (covering multiple generations of parent and descendant segments), a complete tree usually has a much lower number of Strahler orders than of bifurcation levels.

Using different PRNSs, the resulting number of Strahler orders in a tree with given \( N_{\text{term}} \) is a stochastic quantity. Out of the ten realizations investigated, eight had Strahler orders 0–6, and two realizations had Strahler orders 0–7.

By construction, there are always exactly 4000 (terminal) segments at order zero [frequency distribution of Strahler order \( F_s(0) = 4000 \)]. Towards the root of a tree, as Strahler orders increase, segment frequencies \( F_s(\Lambda_{\text{str}}) \) decrease, see Fig. 3. Note that several segments belong to the highest Strahler order (as opposed to only one root segment belonging to the lowest bifurcation level). It turned out that the frequency distribution of segments closely follows an exponential function, which can be parameterized as follows:

\[
F_s(\Lambda_{\text{str}}) = N_{\text{term}} \cdot \exp[-a \cdot \Lambda_{\text{str}}].
\]  

The factor \( N_{\text{term}} \) was preset rather than fitted in order to guarantee that eqn (8) reproduces the a priori known number of terminal segments for \( \Lambda_{\text{str}} = 0 \) correctly. Only the remaining parameter “\( a \)” was subjected to a least squares fit.

In a first step the fit was performed over the whole set of ten realizations, resulting in an estimate of \( a = 0.68021 \). The goodness of fit \( (R^2 = 0.999) \) as well as the low spread of the fitted parameter (68% confidence limit: 0.00282) confirms the obvious fact that trees with different PRNSs show almost identical distributions of segments over Strahler orders. We may use the spread of the fitted parameter \( (a) \) as an estimate of “anatomical variability” resulting from different PRNSs.

In a second step we discriminated between the eight trees with Strahler orders 0–6 and those two trees with Strahler orders 0–7. Separate fits to segment frequencies resulted in \( a = 0.677 \pm 0.000064 \) (68% confidence limit) and \( 0.684 \pm 0.00012 \), respectively. Calculating the upper 95% confidence limit of the

### Table 1

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Unit</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Coefficient of variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radius of root</td>
<td>cm</td>
<td>0.1314</td>
<td>9.189 × 10⁻¹</td>
<td>0.070</td>
</tr>
<tr>
<td>Total volume</td>
<td>cm³</td>
<td>0.946</td>
<td>0.005</td>
<td>0.533</td>
</tr>
<tr>
<td>Total surface</td>
<td>cm²</td>
<td>64.648</td>
<td>0.099</td>
<td>0.0153</td>
</tr>
</tbody>
</table>

Each of ten model trees having 4000 terminal segments was generated using a different pseudo random number sequence and was optimized for minimum intravascular volume. Mean values and standard deviations characterize the impact of anatomical variation.

---

* The mode is the most frequent value of a distribution.
first estimate \((0.677 + 1.96 \times 0.000064 = 0.677)\), this difference is significant on the 5%-level. However, we assume this statistical difference to arise from the method of segment classification into two different numbers of Strahler orders—and therefore the number of Strahler orders as such appears to be the primary and more direct parameter reflecting differences in tree structure.

4.4. VARIABILITY RELATED TO "VESSELS"

If a segment and its parent belong to the same Strahler order they may be combined into one "vessel" (van Bavel & Spaan, 1992), see Fig. 4. This may occur in succession, aggregating several consecutive segments (belonging to different bifurcation levels) into one vessel. Since all segments within a vessel (and the vessel itself) have the same Strahler order, we can consider the "vessel frequency" over Strahler orders. Terminal segments play a special role since they never share the same Strahler order with their parent, and each terminal constitutes a vessel of its own. The concept of vessels corresponds to the intuitive perception of large "connective" arterial branches apparent to visual inspection. Our ten trees comprised between 5309 and 5370 (median = 5343) vessels each.

Binning the vessels of one tree into classes by Strahler order, we always have (by definition) 4000 vessels in Strahler order \(A_{st} = 0\) and one single vessel in the maximum Strahler order \(\max\{A_{st}\}\) of the tree. This latter vessel also contains the root segment. Similar to segment frequencies, the frequencies of vessels also seem to decrease exponentially over Strahler order. However, a corresponding mathematical formula has to meet two boundary conditions:

\[
F_v(L_{str} = 0) = N_{term} \quad \text{and} \quad F_v(\max\{L_{str}\}) = 1. (9)
\]

If a single exponential curve has to pass through two predefined points, nothing remains to be fitted but we rather obtain an algebraic solution:

\[
F_v(A_{st}) = \exp \left( -\log\left(\frac{N_{term}}{\max\{A_{st}\}}\right) \frac{\left[A_{st} - \max\{A_{st}\}\right]}{\max\{A_{st}\}} \right). (10)
\]

In a semi-logarithmic plot, this curve appears as a straight line (see Fig. 5), being fully defined by its endpoints. Frequencies observed for intermediate Strahler orders may be compared with the values.
500
0
1000
1500
2000
2500
3000
3500
4000

STRAHLER order
Number of segments

0 1 2 3 4 5 6 7 8

Fig. 3. Number of segments by Strahler order. x-axis: Strahler order, starting at 0 (corresponding to terminal segments). y-axis: segment frequency. Error bars denote the standard deviations of segment frequencies within the respective Strahler order. The solid curve represents a least squares fit of an exponential function.

predicted by the straight line and, remarkable enough, the deviations found are very small. $R^2$, the goodness of fit parameter, may be calculated as usual even though no actual fit was performed, and $R^2 = 0.999$ (eight trees with Strahler orders 0–6) and $R^2 = 0.995$ (two trees with Strahler orders 0–7) qualify the fidelity of prediction as excellent.

In summary, we conclude that in any tree of the type considered here the frequency distribution of vessels per Strahler order is analytically predictable to a high precision [eqn (10)] from the boundary conditions [eqn (9)] alone, regardless of the particular PRNSs used.

5. Discussion

5.1. VARIABILITY OF THE (OPTIMIZED) TARGET FUNCTION

Variability was inspected for three global quantities (cf. Table 1), out of which the intravasal volume played a special part in that it also represented the optimization target. Nevertheless and surprisingly, the volume showed a larger coefficient of variation than did root-radius and total vascular surface. As yet, we do not have an explanation for this finding.

In summary, different PRNSs were found to induce only very small variabilities (<1%) in each of the global quantities. If volume were the actual target function in a “natural” phylogenetic selection process, an evolutionary advantage as small as approximately 0.5% is unlikely to lead to a unique branching pattern. Any “anatomically” different patterns, as obtained from different PRNSs in the present work, in fact differ very little in their abilities (in terms of target function), which is in agreement with findings on “the cost of deviation from optimality” (Zamir & Bigelow, 1984), reported in the literature.

5.2. REVIEW OF CONCEPTS AND RATIONALS FOR SEGMENT CLASSIFICATION

In morphometric analysis basically two different concepts exist to define classes of arterial segments:

(i) classes are separated according to (several) cutpoints adopted for a continuous variable, e.g. segment radius;
(ii) purely topological classes are constructed, such as bifurcation levels or Strahler orders, which depend only on structure rather than on measurements related to (absolute) size.

Concept (i) has the advantage that it can be applied even to arbitrary portions of corrosion casts. However, the need to define class boundaries more or less arbitrarily is certainly a drawback.

In summary, we conclude that in any tree of the type considered here the frequency distribution of vessels per Strahler order is analytically predictable to a high precision [eqn (10)] from the boundary conditions [eqn (9)] alone, regardless of the particular PRNSs used.

5. Discussion

5.1. VARIABILITY OF THE (OPTIMIZED) TARGET FUNCTION

Variability was inspected for three global quantities (cf. Table 1), out of which the intravasal volume played a special part in that it also represented the optimization target. Nevertheless and surprisingly, the volume showed a larger coefficient of variation than did root-radius and total vascular surface. As yet, we do not have an explanation for this finding.

In summary, different PRNSs were found to induce only very small variabilities (<1%) in each of the global quantities. If volume were the actual target function in a “natural” phylogenetic selection process, an evolutionary advantage as small as approximately 0.5% is unlikely to lead to a unique branching pattern. Any “anatomically” different patterns, as obtained from different PRNSs in the present work, in fact differ very little in their abilities (in terms of target function), which is in agreement with findings on “the cost of deviation from optimality” (Zamir & Bigelow, 1984), reported in the literature.

5.2. REVIEW OF CONCEPTS AND RATIONALS FOR SEGMENT CLASSIFICATION

In morphometric analysis basically two different concepts exist to define classes of arterial segments:

(i) classes are separated according to (several) cutpoints adopted for a continuous variable, e.g. segment radius;
(ii) purely topological classes are constructed, such as bifurcation levels or Strahler orders, which depend only on structure rather than on measurements related to (absolute) size.

Concept (i) has the advantage that it can be applied even to arbitrary portions of corrosion casts. However, the need to define class boundaries more or less arbitrarily is certainly a drawback.

In summary, we conclude that in any tree of the type considered here the frequency distribution of vessels per Strahler order is analytically predictable to a high precision [eqn (10)] from the boundary conditions [eqn (9)] alone, regardless of the particular PRNSs used.
Figure 5. Number of vessels per Strahler order. x-axis: Strahler order, starting at 0 (corresponding to terminal segments). y-axis: vessel frequencies. Error bars denote the standard deviations of vessel frequencies within the respective Strahler order. Results are displayed separately for the set of eight trees with Strahler orders 0–6 and for the two trees with Strahler orders 0–7. The solid line simply joints the a priori known frequencies for \( L_{str} = 0 \) and \( \max\{L_{str}\} \) for the set of eight trees (diamonds). The dashed line applies to the set of two trees (plus signs).

On the contrary, the classification of arterial segments according to “topological” (i.e. structural) concepts, such as “bifurcation level” (Zamir & Chee, 1987) and “Strahler order” (Ellsworth et al., 1987; van Bavel & Spaan, 1992), renders the disputable choice of cutpoints unnecessary and thus offers a higher degree of “uniqueness” in the definition of classes. For this reason we rather adhere to structural classification concepts in the present work.

Most experimental morphometric data (Zamir & Chee, 1987) are presented in terms of bifurcation levels, since the root segment of a corrosion cast is always clearly defined, and incrementing levels distally is straightforward. Hence, in our previous work (Schreiner & Buxbaum, 1993) we utilized bifurcation levels in order to validate our model by comparison with experimental data. A drawback is certainly that each bifurcation level usually holds a very heterogeneous population of segments, as indicated by large spreads of quantities (Zamir & Chee, 1987).

The concept of Strahler orders is sometimes difficult to apply to experimental data when many distal segments of corrosion casts are missing or damaged, the more so if this occurs to a varying degree in different parts of the cast. (Where should \( L_{str} = 0 \) be located in such a case?). As a consequence, computer generated data are sometimes represented with alternative offsets (van Bavel & Spaan, 1992) in order to facilitate the comparison with measurements. As opposed to bifurcation levels, Strahler orders usually assemble fairly homogeneous populations of segments within each class. This is surprising since most trees have much fewer Strahler orders than bifurcation levels. Anyhow, the low spread within Strahler orders justifies our expectation of maximum sensitivity to structural differences between trees. Since the quantification of such differences between trees is the main goal of the present work, we mainly resorted to Strahler classification when displaying our results.

5.3. IMITATING THE PHYSICIAN’S VIEW: COMBINING SEGMENTS INTO VESSELS

Both bifurcation levels and Strahler orders draw on “segments” as the smallest units to be classified. However, a segment is rarely a suitable and useful unit for clinical practice, since every large vessel is multiply split into segments by even very small side branches. Length and volume of segments are hence subjected to a highly stochastic factor. However, the “natural” way of looking at a vessel ignores such small side branches and intuitively regards any two successive segments (mother and larger daughter) as an entity which has only formally been split by a “negligible” offspring (i.e. the smaller daughter). This intuitive process is imitated by the formal definition of “vessels”, see above and ref. van Bavel & Spaan, 1992). Since the Strahler order of the negligible offspring is relatively low, it normally does not affect the (constant) Strahler order of the mainstream segments which constitute one vessel.

The frequency distribution of vessels proved to be remarkably stable among different trees. Since there are fewer vessels than segments per Strahler order, one should expect that the relative variability of frequencies should be larger than it is for segments. Surprisingly, the opposite is true, as can be seen from the coefficients of variation in Table 2. In conclusion, we consider the concept of vessels, which imitates intuition, to be a classification criterion which perfectly aggregates segments into reasonably large vascular sections, which then can be grouped into fairly homogenous classes.

5.4. LACK OF CORRESPONDING EXPERIMENTAL DATA FOR COMPARISON

Numerous publications deal with morphometric measurements performed on corrosion casts of coronary arteries (Zamir & Chee, 1986, 1987; Zamir & Sinclair, 1988; van Bavel & Spaan, 1992; Kassab et al., 1993). Among the quantities described are segment radii, lengths and angles. However, to our knowledge, no data have been published about the total intravascular volume between the feeding artery
and arterioles of a given radius, e.g. 100 µm. This would be exactly the kind of information necessary to compare our results with.

However, even without having measurements at hand, it is likely that real coronary trees will show variabilities in intravascular volume much larger than seen in the model. Granted that this is true, we can interpret the difference in variability as follows:

(i) with full optimization (in a computer model) a very small variability between “different anatomical types” can be achieved (the model thus proves the feasibility of small variability);
(ii) in real coronary trees (showing larger variability than the model) optimization is certainly important but cannot be the only determinant of vessel growth.

5.5. OTHER SOURCES OF DIFFERENT ANATOMICAL STRUCTURES

In the present work only PRNS-induced anatomical variability was investigated between CCO trees generated under the very same boundary conditions and target functions. The rationale for this approach was the idea that bifurcation laws and optimization targets are more underlying concepts than topographic differences between individual patients: Even if arteries should run in different patterns, we would expect that structures (including bifurcations) are optimized according to the same principles for different patients.

Changes in bifurcation laws and/or the optimization target have a much more pronounced impact on structure and function of CCO trees than do different PRNSs. For example, changing the bifurcation exponent to γ = 2 leads to slightly different results of each geometrical optimization, already for a tree with only two terminal segments. The reason is that the total volume is distributed in a different way between parent and daughter segments of each bifurcation. While these geometrical differences usually do not affect topology during the very early stages (five to ten terminal segments), lines of development diverge after the first topologic difference has occurred due to a different result of a connection search.

Changing γ means to attempt to model a different physiological system for which, say due to different properties of tissue or blood, γ = 2 may be the optimum choice. Likewise, adopting a different optimization target function would mean to model a different system. Differences in generated structures would then represent differences between systems rather than differences between individuals of the same system (addressed as “anatomical variability”).

6. Conclusion

“Anatomical variability” was induced in a series of vascular tree models, which were optimized to fulfill the same perfusion task under equal boundary conditions of pressures and flows. In previous reports (Schreiner, 1993; Schreiner & Buxbaum, 1993; Schreiner et al., 1994) CCO models were shown to adequately reproduce experimental data regarding structure and function. Anatomical variability, being introduced into the model by different PRNSs, is evident to visual inspection, cf. Fig. 1. Obviously different patterns, such as for instance the structures resulting from seeds 2 and 7 in Fig. 1, suggest that these might substantially differ in their functional abilities.

To investigate this presumption on a quantitative basis we started with a statistical characterization of the model trees, using global quantities such as total volume and total surface area. In our previous work (Schreiner et al., 1995) both quantities were shown to react sensibly on the structural differences induced by changing the optimization target function (Schreiner et al., 1995): Total volume varied by 240%, total

---

**Table 2**

Variability of vessel frequencies compared to segment frequencies by Strahler order

<table>
<thead>
<tr>
<th>Strahler order</th>
<th>Segments Average frequency</th>
<th>Coefficient of variation (%)</th>
<th>Vessels Average frequency</th>
<th>Coefficient of variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Eight trees with Strahler orders 0–6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4000</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2027.6</td>
<td>1.16</td>
<td>1040.8</td>
<td>1.44</td>
</tr>
<tr>
<td>2</td>
<td>1044.8</td>
<td>2.43</td>
<td>235.3</td>
<td>2.16</td>
</tr>
<tr>
<td>3</td>
<td>510</td>
<td>7.17</td>
<td>53.9</td>
<td>6.31</td>
</tr>
<tr>
<td>4</td>
<td>278.0</td>
<td>15.96</td>
<td>11.1</td>
<td>5.76</td>
</tr>
<tr>
<td>5</td>
<td>105.7</td>
<td>19.77</td>
<td>2.6</td>
<td>28.34</td>
</tr>
<tr>
<td>6</td>
<td>32.0</td>
<td>44.51</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>(b) Two trees with Strahler orders 0–7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4000</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2046.0</td>
<td>3.25</td>
<td>1029.0</td>
<td>0.14</td>
</tr>
<tr>
<td>2</td>
<td>1013.5</td>
<td>3.98</td>
<td>229.0</td>
<td>4.94</td>
</tr>
<tr>
<td>3</td>
<td>522.0</td>
<td>8.40</td>
<td>55.0</td>
<td>0.0</td>
</tr>
<tr>
<td>4</td>
<td>232.0</td>
<td>10.97</td>
<td>25.7</td>
<td>5.66</td>
</tr>
<tr>
<td>5</td>
<td>110</td>
<td>15.27</td>
<td>5.0</td>
<td>0.0</td>
</tr>
<tr>
<td>6</td>
<td>47.0</td>
<td>9.03</td>
<td>2.0</td>
<td>0.0</td>
</tr>
<tr>
<td>7</td>
<td>28.5</td>
<td>2.48</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

By definition Strahler order 0 comprises all terminal segments, each of which is also a vessel of its own. Hence, neither for segments nor for vessels is there a variability in frequencies between trees. In each tree the highest Strahler order holds several segments which form exactly one single vessel (which includes the root segment). Hence, segment frequencies for the highest Strahler order show variation, whereas vessel frequencies do not. Trees with different numbers of Strahler orders are shown in parts (a) and (b), respectively.
Trees quantitatively. The result was surprising: neither order to evaluate structural differences between the investigated the resulting frequency distributions in classification systems for arterial segments and slightly, cf. Table 1. Likewise the radius of the root segment varied only e.g. the choice of the optimization target function. anatomic variability has a much lower impact than quantities found for different anatomies in the present work proved to be surprisingly small, indicating that anatomical variability has a much lower impact than e.g. the choice of the optimization target function. Likewise the radius of the root segment varied only slightly, cf. Table 1.

In a second step we applied three different classification systems for arterial segments and investigated the resulting frequency distributions in order to evaluate structural differences between the trees quantitatively. The result was surprising: neither (i) segment classification into bifurcation levels nor (ii) segment classification into Strahler orders, nor (iii) vessel classification into Strahler orders showed remarkable differences between the ten trees (appearing so very different to the naked eye).

One could argue that frequency distributions are not an adequate criterion for functional ability, and the anatomic differences might only be reflected in parameters directly related to blood transport. Therefore, we additionally evaluated such a key quantity, namely the total cross-sectional area in each Strahler order. The result however, showing very small variability between trees (see Fig. 6), once more confirms that the differences striking to the eye need not find a quantitative correlate—not even in a parameter most directly related to vascular function.

Thus, the present investigation has exemplified that anatomical variability need not necessarily induce functional differences, as long as the model is optimized according to the same target and boundary conditions. In our CCO model all parameters were kept constant and the total variability thus restricted to “anatomy” only. What has been shown for the model does not imply that anatomical differences in real arterial trees never relate to functional differences, rather the opposite is likely to be true.

However, real perfusion areas vary in size and shape between individuals, and the corresponding impact on functional ability virtually cannot be separated from the effects of “anatomical variability”. In the frame of CCO models we have previously investigated this issue by growing model trees into perfusion areas of different (elliptical) shapes and additionally varying the site of perfusion inlet (Schreiner et al., 1996), while leaving all other parameters unchanged (and equal to those in the present work). As a result, the achieved optimization target (intravascular volume) increased by 230% when comparing a “medium ellipse” perfused via its minor vertex and a “stretched ellipse” perfused via its major vertex, respectively. We have to bear in mind, however, that any change in the shape of the perfusion area necessarily entails different locations of the terminal sites and thus changes “anatomy” similar to a different PRNS. Any observed changes therefore incorporate both the “shape-induced”—and the “anatomical” variability. Yet, by comparing the “shape plus anatomy”-effect (230%) with that of “pure anatomical” variability (<1%) found in the present work, there is no doubt that—at least within the frame of CCO models—anatomical variability plays a surprisingly small role with regard to functional consequences.

The unexpected conclusion of the present work is therefore that anatomical variability alone is not necessarily a source of severe functional differences.

This work was sponsored by the Austrian Ministry of Science and Research, grant nr. 49/820/4-24/92 and the Ludwig Boltzmann Institut für Herzchirurgische Forschung. The authors thank Mrs. S. Sumetzberger for preparing the manuscript.

REFERENCES