Vessel Connectivity Using Murray’s Hypothesis

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Abstract. We describe a new method for vascular image analysis that incorporates a generic physiological principle to estimate vessel connectivity, which is a key issue in reconstructing complete vascular trees from image data. We follow Murray’s hypothesis of the *minimum work principle* to formulate the problem as an optimization problem. This principle reflects a global property of any vascular network, in contrast to various local geometric properties adopted as constraints previously. We demonstrate the effectiveness of our method using a set of microCT mouse coronary images. It is shown that the performance of our method has a statistically significant improvement over the widely adopted minimum spanning tree methods that rely on local geometric constraints.

1 Introduction

In modern vascular modeling research, a key issue is the lack of highly automated and reliable methods for *vessel connectivity*. Vascular research has been greatly facilitated by the advances of 3D imaging technologies such as MicroCT, but quantifying the images remains challenging, and constitutes a bottleneck in vascular research [1]. Although vascular image analysis has been extensively researched in the past decade [2], most previous research focuses on vessel enhancement, detection, and the segmentation and quantification of a few vessel segments or small vascular sub-trees, while vessel connectivity is seldom discussed. As a result, there are few methods capable of reconstructing complete vascular networks [3,4,5,6]. These methods are usually limited by the need for: (I.) the manual setting of numerous thresholds [3,4,5,6], (II.) the truncation of small vessels [5], (III.) manual correction [3,4]. The connectivity problem is a result of the imperfection of vessel detection. Like any feature detection results, there are missing parts and also outliers. The handling of the missing vessels (gaps) is found to be critical for connectivity. The failure of vessel detection is due to imaging artifacts/noise, missing contrast agents (*e.g.* by air bubbles), and morphology beyond detection models.

Previous work in vessel connectivity [2] largely depends on local image or vascular context. Many methods (*e.g.* [4,6]) connect vessels based on a set of intuitive rules using local vessel orientation and distances. A set of thresholds are

often employed to decide connectivity. Minimum spanning tree (MST) methods offer a more principled approach. Various distance metrics (thus cost functions), *e.g.* Euclidean distance [7], Mahalanobis distance [8], and a mixture of Euclidean distance and vessel orientation difference [3] has been developed for this approach. Although their cost functions are global, they have optimal substructure and still establish the connections based on local context. Some methods use “gap filling” techniques which more systematically explore the local image context. They adjust the distance between nodes [3,8], or estimate missing nodes by tensor voting and adaptive thresholding, *etc.* However, the use of local context fails as the gaps get larger. Furthermore, intuitively defined thresholds and distance metrics also have difficulty coping with spatially varying gap geometries.

Our method: In this paper, we leverage physiologically-based global properties of vasculature trees to guide the estimation of vessel connectivity. There has been little work in vascular image analysis that attempts to explore the wealth of knowledge accumulated in physiology research, such as (I.) the morphometric statistics of vasculature experimentally measured; (II.) measured fractal properties of the vascular trees; (III.) the minimum work principle [9]; (IV.) The scaling laws among perfusion, mass, and vascular morphology; (V.) The flow and pressure within the vascular system. In this paper, we start with *the minimum work principle* (MWP), Murray’s hypothesis, as introduced in Section 2.2, which is conceptually simple and also comparatively easy for mathematical formulation. A few previous methods on vessel image segmentation were also inspired by this principle [10,11], but the resulting formulations were ad-hoc and the results were not quantitatively evaluated. We present a formal derivation by strictly following this principle and quantitative validation on its utility for determining vessel connectivity.

2 Method

2.1 The Vessel Connectivity Problem

We consider the problem as: **given** vessel centerline points $\mathcal{V}$, and the vessel radii $\mathcal{R}$ at corresponding locations of $\mathcal{V}$, **find** the connections $\mathcal{E}$ among $\mathcal{V}$ so that the vascular tree $\mathcal{T} = (\mathcal{V}, \mathcal{E}, \mathcal{R})$ is reconstructed. In many cases, the vascular tree root v^r is also given. In this paper, we assume that the vascular network under consideration has a tree structure. We intend to design a cost function $\mathbf{F}(\cdot)$ which measures the truthfulness of the morphology and topology of a vascular tree. The connectivity problem can then be written as

$$\hat{\mathcal{E}} = \arg \min_{\mathcal{E}} \mathbf{F}(\mathcal{E}, \mathcal{V}, \mathcal{R}, v^r). \quad (1)$$

In an image analysis scenario, the vessel points actually detected, $\mathcal{V}^*$ (with corresponding radii $\mathcal{R}^*$), always contain a set of outlier points $\mathcal{V}^o = \mathcal{V}^* \setminus \mathcal{V}$ (false positive, with radii $\mathcal{R}^o$) and at the same time miss a set of points $\mathcal{V}^m = \mathcal{V} \setminus \mathcal{V}^*$ (false negative, with radii $\mathcal{R}^m$), due to various reasons including image noise,

artifacts, unrealistic modeling assumed in detection, *etc.* The vessel radius estimation will not be accurate either, but for simplicity, this is not discussed in this paper. Therefore the real vessel connectivity problem is a Steiner tree problem

$$(\hat{\mathcal{E}}, \hat{\mathcal{V}}^m, \hat{\mathcal{V}}^o) = \arg \min_{(\mathcal{E}, \mathcal{V}^m, \mathcal{V}^o)} \mathbf{F}(\mathcal{E}, \mathcal{V}^* \setminus \mathcal{V}^o \cup \mathcal{V}^m, \mathcal{R}^* \setminus \mathcal{R}^o \cup \mathcal{R}^m, v^r). \quad (2)$$

The topology of vasculature is often more important than the accurate locations of connection. In this paper, we focus on recovering the vascular topology without estimating $\mathcal{V}^m$, and also leave the estimation of $\mathcal{V}^o$ to future work.

2.2 Murray's Hypothesis

Nature pursues optimality in all her workings. Murray [9] was among the first to quantify this hypothesis for vascular systems. He proposed the Minimum Work Principle (MWP): the sum of the work overcoming flow resistance for perfusion and the metabolic consumption of the blood is naturally minimized. He defined the *work* [9] as

$$\mathbf{P} = \mathbf{P}^f + \mathbf{P}^b = p \cdot f + b \cdot \text{vol} \quad (3)$$

$$= (f^2 \cdot l \cdot 8\eta) / (\pi r^4) + b \cdot l \pi r^2, \quad (4)$$

where $\mathbf{P}^f$ denotes power dissipation caused by flow friction, and $\mathbf{P}^b$ represents the consumption of metabolism. Eqn. (3) applies to the whole vasculature, where p and f are pressure and flow at the entrance of vasculature, vol. is the volume of vessel, and b is the metabolic cost of blood in *ergs/sec./cm³*. Eqn. (4) calculates the work for one specific vessel segment, following Poisseuille's equation, where r is the vessel diameter, η is blood viscosity, and l is the length of the vessel segment. Using (4), it is straightforward to derive the optimal relationship between f and r for a vessel segment with fixed length l :

$$\partial \mathbf{P} / \partial r = 0 \Rightarrow f = r^3 \frac{\pi}{4} \sqrt{b/\eta}. \quad (5)$$

The above model has been justified in a number of ways [9]. The relation between branching angle and radii derived from this hypothesis, has been found to closely conform to the morphologies of various biological vascular systems including plants. Although the model does not conform to anastomoses in vasculature regions such as the Circle of Willis in cerebral vasculature, it is applicable to most of the vascular system.

2.3 Problem Formulation

If we assume Murray's $\mathbf{P}$ (3,4) measures the quality of an estimated vasculature, *i.e.* it can serve as the $\mathbf{F}(\cdot)$ in Eqn.(1), our vessel connectivity problem becomes

$$\mathcal{E} = \arg \min_{\mathcal{E}} \sum_{k=1}^N \underbrace{[(f^2(e_k, \mathcal{E}) \cdot l(e_k) \cdot 8\eta) / (\pi r^4(e_k))]}_{\mathbf{P}_k^f} + \underbrace{[b \cdot l(e_k) \pi r^2(e_k)]}_{\mathbf{P}_k^b}, \quad (6)$$

where $\mathbf{P}_k = \mathbf{P}_k^f + \mathbf{P}_k^b$ is the total work consumption for one vessel segment (Eqn.4), $e_k \in \mathcal{E}$, $e_k = (v_i, v_j)$, $v_i, v_j \in \mathcal{V}$, represents a vessel segment, starting at v_i and terminating at v_j , with $N = |\mathcal{E}|$ as the total number of segments, $f(\cdot)$ measures the flow through a vessel segment, $l(\cdot)$ calculates the segment length, and $r(\cdot)$ denotes the segment radius, which corresponds to the radius $r \in \mathcal{R}$ associated with the second point $v_j \in e_k$ or the mean of both points.

Formulation (MST+) assuming optimal $f \sim r$: If the optimal relation between f and r (5) is assumed, it's straightforward to simplify (6) and yield an $r^2(e_k)$ weighted MST (we label it as **MST+**) formulation as:

$$\mathcal{E} = \arg \min_{\mathcal{E}} \sum_{k=1}^N l(e_k) r(e_k)^2. \quad (7)$$

This indicates that published MST variants [3,7,8] can also be derived from MWP with certain simplifying assumptions (*e.g.* $r = 1$), which was not previously demonstrated.

Formulation with flow conservation constraint: Eqn. (7) does not impose the flow conservation between parent and their daughter branches. In the original form (6) this constraint is embedded in the calculation of $f(e_k, \mathcal{E})$ which is unfortunately computationally intractable. In this paper, we impose this constraint by converting the resistive tree into a parallel network. As illustrated in Fig. 1, resistor R_0 in a tree network is split into R_0^1 and R_0^2 , which are determined by their flow, I_1 and I_2 respectively:

$$R_0^1 = I_0/I_1 \cdot R_0, \quad R_0^2 = I_0/I_2 \cdot R_0, \quad \text{where } I_0 = I_1 + I_2. \quad (8)$$

We apply this simple conversion repetitively starting from the branch ends of the vascular tree, $v_m^e, m = 1, 2 \dots M$, all the way to its root, v^r , which makes the vascular structure in between fully parallel. Then the total work dissipated on flow friction is simply the sum of the work through each path,

$$\mathbf{P}^f = \sum_{m=1}^M f_m^2 \sum_{e_k \in \mathcal{P}(v_m^e, v^r, \mathcal{E})} \frac{f(e_k, \mathcal{E})}{f_m} \cdot \frac{l(e_k) \cdot 8\eta}{\pi r^4(e_k)}, \quad (9)$$

where f_m is the flow at branch end v_m^e , and $\mathcal{P}(v_m^e, v^r, \mathcal{E})$ denotes the flow path from v_m^e to vascular root v^r . This formulation explicitly involves the connectivity of the vasculature by introducing $\mathcal{P}(v_m^e, v^r, \mathcal{E})$. Assuming the optimal $f \sim r$ (5), the cost function using (9) is simplified to be

$$\mathcal{E} = \arg \min_{\mathcal{E}} \underbrace{\sum_{m=1}^M \frac{r(e_m)^3}{2}}_{SPT} \sum_{e_k \in \mathcal{P}(v_m^e, v^r, \mathcal{E})} \frac{l(e_k)}{r(e_k)} + \underbrace{\sum_{k=1}^N l(e_k) r(e_k)^2}_{MST}, \quad (10)$$

which is a mixture of the shortest path like tree (SPT) and MST.

Fig. 1. Converting a tree-structure resistive circuit to a parallel one

Fig. 2. **Left:** The simplest tree with a gap (v_1, v_2) . **Right:** two possible solutions.

It is not difficult to show that the formulation with flow constraint (10) has advantages over the former MST formulation (7) on bridging the gaps between detected vessel segments. The simplest tree in Fig. 2 is used for illustration, with a root node v^r and two branches ending at v_1^e and v_2^e . The detected vessel points along both branches are assumed to be continuous except for the gap between v_1 and v_2 , where points are totally missing. Consider the effect of this gap on connecting v_2 to v_1 , as desired, or to some point v_3 along branch (v^r, v_1^e) by mistake. We assume that the radii $r(v_1^e) = r(v_2^e) = 1$ for simplicity which results in (7) becoming a pure MST formulation. In this case, the optimal angle between the branches $\alpha \approx 75^\circ$ and often smaller in real data [9]. The MST cost function (7) becomes $\sum_{k=1}^N l(e_k)$ and the proposed formulation (Eqn. 10) equals $\sum_{m=1}^M \frac{1}{2} \sum_{e_k \in \mathcal{P}(v_m^e, v^r, \mathcal{E})} l(e_k) + \sum_{k=1}^N l(e_k)$. In order to establish the right connection, connecting (v_1, v_2) must have a lower cost than connecting (v_3, v_2) . Using MST (7), we need

$$l(v_1, v_2) < \min_{v_3} l(v_3, v_2), \quad (11)$$

whereas using formulation (10), it is not difficult to derive the constraint:

$$l(v_1, v_2) < \min_{v_3} [l(v^r, v_3)/3 + l(v_3, v_2)]. \quad (12)$$

This means the upper bound of the allowed gap $l(v_1, v_2)$ is *always* greater when using the second cost function.

2.4 Optimization

The optimization for the proposed formulation (10), despite its simple form, turns out to be non-trivial. In this paper, we approximate it by assuming that radius r_m is given and remains the same for all branch ends $\{v_m^e\}$, which is the size of an image voxel r_{vox} . Note that not all points of radius r_{vox} belong to $\{v_m^e\}$. $\{v_m^e\}$ is still a result of the optimization. Then the first term in (10) is further approximated by a pure cost of shortest path tree (*i.e.* making every node a branching end) multiplied by an coefficient $\lambda \in (\frac{M}{|V|}, 1)$. The cost is then approximated by

Fig. 3. A visual comparison of reconstructed trees: (a) The original image; (b) Manually validated vascular tree; (c) The image contaminated by gaps; (d) The tree constructed by MST; and (e) The tree constructed using our cost function (10). The warmer colors indicate deeper branching levels of vessel segments.

Table 1. Significance

Gap	$P_{\lambda=0.1}$	$P_{\lambda=0.3}$	$P_{\lambda=0.5}$
6%	0.154	0.100	0.102
8%	0.064	0.061	0.062
10%	0.029*	0.028*	0.029*
12%	0.003*	0.003*	0.002*
14%	0.004*	0.003*	0.003*
16%	0.026*	0.021*	0.023*
18%	0.000*	0.000*	0.000*
20%	0.065*	0.031*	0.031*

Fig. 4. A quantitative comparison of reconstructed trees (Section 3). Each subfigure presents the error obtained from one vascular tree. **MST**: minimizing MST cost function; **MST+**: minimizing (7); The others: minimizing the proposed function (10)(approximated by (13) with different λ). P values from t tests comparing the proposed function (10) with MST are in Tab. 1. * marks significant results.

$$\mathbf{P}^* = \lambda \cdot \frac{r_{vox}^3}{2} \sum_{j=1}^N \sum_{e_i \in \mathcal{P}(v_j, v^r, \mathcal{E})} \frac{l(e_i)}{r(e_i)} + \sum_{k=1}^N l(e_k) r^2(e_k). \quad (13)$$

Note that as a tree, $N = |\mathcal{E}|$ is also the number of all vertices besides v^r . This expression is equivalent to the so-called cable-trench problem [12]. Although it

is still a difficult problem (NP-complete), we found that it can be effectively approximated by Prim's algorithm with distance between vertices defined in (13). As a greedy algorithm, when implemented in Matlab it can establish the connection for 10,000 vessel points within 10 seconds on a state-of-the-art PC. Although (10) can be better approximated by more sophisticated algorithms, this formulation is shown to be adequate in the results described below.

3 Experimental Results

We evaluate the algorithm performance by examining how well the connectivity of a set of real mouse coronary arterial trees can be recovered. These trees were manually validated and gaps at known locations with known sizes were inserted.

Vascular trees: Five healthy C57Bl/6 mouse coronary arterial trees were extracted from their ex-vivo microCT images with manual image processing by an expert. The image size is $512 \times 512 \times 742$ with voxel resolution of $16\mu m$. The data were first manually edited within the Volume Viewer of the GE Advantage Workstation to remove venous and other outlier structures. They were then down-sampled (to resolution of $32\mu m$) to reduce the computational demand of validation. The resulting images were skeletonized by image thinning with manual adjustment of the threshold.

Evaluation: We created gaps by masking out part of $\mathcal{V}$ using 500 spherical balls from any original phantom tree $\mathcal{T} = (\mathcal{V}, \mathcal{E}, \mathcal{R}, v^r)$. The simulated gaps are similar to those common ones in real images (*e.g.* caused by air bubbles or weak vessel detection). The ball diameters ranged from 2% to 20% of the width of the bounding box of the whole vasculature. The resulting gaps had maximum lengths around 0.06–0.6 mm in physical space, or 2–20 voxel widths in the image space. For each ball size, 100 random configurations of the ball locations are used for evaluation. The ground truth connectivity $\mathcal{E}^-$ for the remaining vessel points and associated radii $(\mathcal{V}^-, \mathcal{R}^-, v^r)$ can be obtained from $\mathcal{E}$. $(\mathcal{V}^-, \mathcal{R}^-, v^r)$ were input into different algorithms to find $\hat{\mathcal{E}}^-$. Directly comparing $\mathcal{E}^-$ and $\hat{\mathcal{E}}^-$ to counting the number of wrong connections is inadequate to reflect the significance of error in terms of the function of a vascular tree. We consider the path lengths from tree root v^r to each vessel point as better error measures, because they are associated with the tree function, and will also be altered by erroneous connections. We define the error as $\mathbf{E} = \frac{1}{|\mathcal{V}^-|} \sum_{v_i \in \mathcal{V}^-} |l(\mathcal{P}(v_i, v^r, \hat{\mathcal{E}}^-)) - l(\mathcal{P}(v_i, v^r, \mathcal{E}^-))|$, where $\mathcal{P}(\cdot)$ finds the shortest path between two nodes within a tree, and $l(\cdot)$ measures its length. For each ball size, $\mathbf{E}$ is further averaged over random configurations of ball locations.

Results: The experimental results are plotted in Fig. 4. The error $\mathbf{E}$ generally increases when the maximum gap length increases. It is observed that when the maximum gap length is greater than 8% of the vasculature width, the errors resulting from minimizing our proposed cost function (10) are significantly lower

than those from minimizing the pure MST cost function, with λ in a comparatively wide range, (0.1, 0.5). It is also observed that MST+ formulation (7) leads to a similar level of error to the pure MST. This is not surprising as discussed earlier in Section 2.3. In Fig.3 we also plot a sample result of both MST and our algorithm for a visual comparison. To create large gaps but keep the majority of the vasculature, only 100 balls of random diameters from 2 to 20 voxel width were used. It is obvious that at the places where significant gaps exist, our cost function recovers far more better connectivity than MST.

4 Conclusions and Future Work

We hypothesized that global vascular properties would provide better guidance for vessel connectivity than those local ones. In this paper, we follow Murray's hypothesis of the MWP [9] to formulate the vessel connectivity as an optimization problem. A cost function (10) that naturally imposes flow conservation is derived, and a greedy algorithm is also proposed for optimization. We evaluate the performance of our algorithm quantitatively using real vascular image data and demonstrate that it can achieve significant improvements in comparison with the results of MST, whose variants were widely adopted [3,7,8].

Others have attempted to apply similar principles. Bruyninckx *et al.* [10] employed Murray's law for extracting vascular trees from images. As briefly mentioned in Section 2.2, Murray's law is derived from the MWP, describing a local vascular property. For the global constraints they minimized the total vascular volume, which is half of MWP (the second term in (3)). Previously we also tried to employ the MWP to connect vessels [11]. The major difference is that a pseudo vascular resistance was used to formulate the cost function, instead of deriving it directly from the MWP. The algorithms developed in [10,11] are far more computationally demanding than the greedy one proposed in this paper and there were no quantitative evaluations conducted for vessel connectivity.

We conceptually validated the idea of using Murray's hypothesis for vessel connectivity. Future work will include refining the optimization process and developing other formulations of the vessel connectivity problem using MWP, including using perfusion volume constraint for outlier detection (estimation of $\mathcal{V}^o$), and the extraction of multiple vascular trees (e.g. arterial and venous trees).

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