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► **To cite this version:**

Raoul Sallé de Chou, Mohamed Ali Srir, Laurent Najman, Nicolas Passat, Hugues Talbot, et al.. Convex optimization for binary tree-based transport networks. International Conference on Discrete Geometry and Mathematical Morphology (DGMM), 2024, Florence, Italy. pp.217-228, 10.1007/978-3-031-57793-2_17 . hal-04359833

HAL Id: hal-04359833

<https://inria.hal.science/hal-04359833>

Submitted on 21 Dec 2023

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Convex Optimization for Binary Tree-Based Transport Networks^{*}

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Abstract. Optimizing transport networks is a well-known class of problems that have been extensively studied, with application in many domains. Here we are interested in a generalization of the Steiner problem, which entails finding a graph minimizing a cost function associated with connecting a given set of points. In this paper, we concentrate on a specific formulation of this problem which is applied to the generation of synthetic vascular trees. More precisely, we focus on the Constrained Constructive Optimization (CCO) tree algorithm, which constructs a vascular network iteratively, optimizing a blood transport energy efficiency. We show that the classical incremental construction method often leads to sub-optimal results, and that a better global solution can be reached.

Keywords: Constrained Constructive Optimization · Discrete optimal transport · Binary trees · Convex optimization · Numerical twin.

1 Introduction

Identifying an optimal transportation network is a topic of significant interest across a wide range of fields, including urban modeling, water supply, telecommunication, and the study of vascular system [1,10]. The problem consists of finding a path that minimizes a cost function while interconnecting points of interest and utilizing possible intermediate branching points. This paper specifically explores a formulation of the problem where the points of interest are the terminal leaves of a rooted binary tree. More specifically, we study the application of this approach to the generation of synthetic vascular trees.

With the emergence of patient-specific models as non-invasive diagnostic tools in medicine, it has become important to generate realistic vessel networks efficiently and effectively. An example is to construct numerical twins of various

^{*} Supported by an industrial grant from Heartflow, Inc.

organs, for example to study their associated vascular diseases [15], [13]. Most published methods construct these trees incrementally, branch by branch, with the underlying principle that blood vessels supply tissues by filling the tissue volume while minimizing transport costs.

A widely adopted method is the Constrained Constructive Optimization (CCO) tree algorithm, which locally optimizes the tree geometry after the addition of a new segment. This method aims to minimize total vascular volume and was initially developed by Schreiner *et al.* [16]. Several extensions of this method have been proposed for the generation of organ-specific vascular trees in 3D non-convex volumes [9,6,18,17] or the concurrent construction of multiple concurrent trees [3]. As stated by Keelman *et al.* [11], one of the main drawbacks of CCO is that it only performs local optimizations, leading to suboptimal results. In order to search for optimal global solutions, they devised a method based on simulated annealing (SA). This approach enabled them to explore multiple tree structures while trying to converge towards a global minimum with respect to a cost function. In a recent publication, Jessen *et al.* [7] combined the CCO algorithm with the SA method to address the local optimality issue. In order to reduce the search space of SA, and thus the high computational cost, they restrained the tree structure exploration to changes in the tree connectivity (or tree topology). The optimization of the branching node positions was computed thanks to a global non-linear solver inspired by CCO’s local optimization. While they successfully reduced the total vascular volume, there is currently no proof of convergence to a global minimum.

Another tree generation approach, known as Global Constructive Optimization (GCO) [4], also aims at building optimal tree structures. It starts from uniformly distributed random points in the volume, which remain fixed during the tree generation. The method is initialized by connecting all points to a root node. Subsequently, through a series of iterative split and merge operations, it reshapes the tree topology. During each iteration, the method optimizes the bifurcation positions with the objective of volume minimization. Notably, this optimization problem has been proven to be convex, guaranteeing the achievement of optimal node positions. In contrast to CCO, it is essential to note that a key limitation of this method lies in its inability to generate multiple trees within the same volume.

In our present work, we introduce a novel approach for the CCO algorithm. Instead of minimizing the total volume, our approach seeks to minimize an energy cost function. Notably, we demonstrate that our optimization framework exhibits convexity, leading to improved global results. Moreover, our approach significantly reduces computational costs in comparison to the volume-based CCO method.

2 Method

In this section, we first describe the general formulation of the optimal transport problem considered in this paper. Subsequently, we delve into the original CCO

method [16], and its model assumptions. Finally, we introduce our novel vision of the CCO framework. we emphasize that all the CCO implementations detailed in this paper are used for the generation of two-dimensional vascular trees, but that the construction generalizes to 3D trees without difficulty.

2.1 Optimal transport problem

The optimal transport problem explored in this paper can be formulated as follows: starting with a binary tree that originates from a root point, and connecting N terminal points through $N - 1$ branching points (bifurcation points), each defined by two-dimensional Euclidean coordinates, the objective is to determine the optimal positions for these bifurcation points while keeping the terminal and root nodes fixed. The cost function is expressed as follows:

$$S = \sum_{i=1}^{2N-1} w_i l_i \quad (1)$$

Here, the l_i values ($1 \leq i \leq 2N - 1$) denote the lengths of the segments between each pair of connected points, and the w_i values are positive weights assigned to each segment. Notably, since the Euclidean distance of a segment is convex with respect to its endpoints, the sum S itself is convex [4]. Consequently, optimal bifurcation positions, that minimize S , can be determined. However, it is essential to note that the solution may not be unique, as the Euclidean distance is not strictly convex [2].

2.2 Constrained Constructive Optimization

Model assumptions Vascular trees are represented as rooted binary trees composed of one root node and N terminal nodes. The edges constituting the tree are represented as cylindrical segments, interconnected through $N - 1$ branching—or bifurcation—nodes.

Blood flow is modeled in the vascular network as an incompressible, homogeneous Newtonian fluid, and is assumed unidirectional, axisymmetric, developed and stationary. Thus for each segment j , the resistance to flow R_j and subsequent pressure drop Δp_j are related to its flow rate q_j through Poiseuille's law:

$$\Delta p_j = R_j q_j \quad (2)$$

$$R_j = \frac{8\mu l_j}{\pi r_j^4} \quad (3)$$

with μ the blood viscosity, and l_j and r_j , q the segment length and radius respectively. At all terminal nodes, the flow rates q_{term} are set (here to be equal). Thanks to mass conservation, the sum of the q_{term} corresponds to the perfusion flow rate at the tree root q_{tot} .

At a bifurcation level, the parent and children segments radii obey the following power law:

$$r_{parent}^\gamma = r_{child1}^\gamma + r_{child2}^\gamma \quad (4)$$

with γ a parameter which has been shown empirically to vary between 2 and 3, depending on the size of the arteries or veins. In the next sections, this parameter is set to 3 to simulate small arteries. This relationship has been defined by Murray [14], and is derived from the assumptions that vascular networks should be constructed so that the cost to transport and maintain/generate blood is minimal. Indeed, for a vessel modeled as a tube with Poiseuille's law, Murray defines this cost as the sum of a term due to viscous work, and a second one due to the generation of the blood volume in the tube. This sum is homogeneous to an energy. Based on Poiseuille law, (3), this energy (or rather power) is defined as:

$$E_j = \frac{8\eta q_j^2 l}{\pi r_j^4} + b\pi l_j r_j^2 \quad (5)$$

with b the volumetric metabolic cost. Searching the minimum of this equation, with respect to the radius, leads to Murray's law:

$$q_j = k r_j^3 \quad (6)$$

with k a constant independent of j . At a bifurcation, with one parent and two children segments, mass conservation reads:

$$q_{parent} = q_{child1} + q_{child2} \quad (7)$$

which, combined with (6) leads to (4).

Current CCO algorithm The CCO method aims at generating a synthetic vascular tree incrementally, by adding segments one by one, until a desired number of terminal segments is reached. At each growth step, the new local structure is optimized: the total vascular volume is minimized, by considering the cylindrical segment:

$$V = \pi \sum_{i=1}^{N_{segments}} l_i r_i^2 \quad (8)$$

The addition of a new terminal segment can be described as follows: first, a new terminal node location is randomly sampled in the perfusion territory. Then, the connection between two points defining a neighboring segment and the new node, is tested. For that purpose, the latter segment is replaced by 3 new segments and a bifurcation node connecting the 3 points. Local optimization of the bifurcation structure is then performed. The bifurcation point position and the 3 newly added segments radii are optimized with respect to total volume, while ensuring Poiseuille's law (3) and Murray's bifurcation law (4). Since a new terminal node is added, the total flow in the tree is incremented by q_{term} . Segment resistances upstream to the new bifurcation, need to be adjusted by rescaling

recursively the segments radii. Finally, a fixed number of connections within the closest neighboring segments are tested and only the one inducing the lowest total volume is kept.

The volume-based minimization method comes from Kanya [8]. The method seems similar to the energy-based approach, as it had the following objective: “*the lower the blood volume in the vascular tree becomes, the smaller the energy for blood maintenance is spent*”. Regarding (5), it seems that minimizing volume shares similarities with minimizing energy, but does not take into account the effect of viscous forces. One can note that this original CCO bifurcation optimization is not completely volume-based, as it integrates Murray’s bifurcation law (4). However, the use of the bifurcation relationship instead of (6) induces a loss of information, and the model is not mathematically well-posed. Consequently, the use of other equations such as Poiseuille’s law becomes necessary to solve the local optimization problem, which becomes more complex. Solving this problem is often done by iterative solvers, and no convergence toward a global minimum has been demonstrated.

2.3 New CCO approach

Local optimization algorithm We now describe a new method for optimizing a bifurcation in CCO that relies solely on energy considerations, and is mathematically well-posed. This approach should provide a more consistent and robust solution.

Because terminal flows q_{term} are fixed in CCO and mass is conserved at each bifurcation, one can compute from the terminal nodes to the tree root, the flow q_{parent} , q_{child1} and q_{child2} for every segment of a bifurcation. Additionally, the best radii r_0 , r_1 , r_2 and bifurcation coordinates (x, y) can be found by minimizing the energy defined in (5):

$$\left\{ \begin{array}{l} \frac{\partial E}{\partial x} = 0 \\ \frac{\partial E}{\partial y} = 0 \\ \frac{\partial E}{\partial r_i} = 0 \text{ for } i \in \{parent, child1, child2\} \end{array} \right. \quad (9)$$

As in Murray [14] for the case of a single bifurcation, with k a constant, the partial derivatives of E with regard to the radii, lead to:

$$q_i = kr_i^3$$

Since the flow rates q_i are known, this sets all the radii for a given k as:

$$r_i = \sqrt[3]{\frac{q_i}{k}} \quad (10)$$

Employing (10) in order to compute the total energy of a bifurcation, leads to:

$$E = \sum_i E_i = \left(\frac{8k^2\eta}{\pi} + b\pi \right) \sum_i l_i r_i^2 \quad (11)$$

This new form of the energy, when considering r_i as fixed values, can be expressed in a similar form as (1). As stated in Sect. 2.1, this objective function has been demonstrated to exhibit convexity with respect to the point coordinates defining the segment lengths l_i . Consequently, it becomes feasible to identify a global minimum solution for the new bifurcation point positions, ultimately leading to an optimal bifurcation geometry. This optimum can be reached under the condition that the constant k can be computed. In fact, it is easy to see by recursivity, that this constant is the same for the whole tree. In CCO, medical image data usually give the root radius. When such data is not available, an additional condition such as specifying a target pressure drop between the root and the leaves, needs to be given. This target pressure drop may, for instance, represent the average pressure drop occurring between arteries and arterioles. Based on this target value, and considering the overall tree resistance and total flow at growth step t , the root radius can be determined. Consequently, with the knowledge of the root radius, we can define at each growth step the constant k :

$$k^t = \frac{q_{tot}^t}{(r_{root})^3} \quad (12)$$

Global optimization algorithm When adding a new terminal node in the current CCO implementation, the entire tree is adjusted to be able to sustain the incremented total flow. These modifications specifically pertain to the radii, while the previous bifurcation points remain untouched. Nevertheless, the creation of a new bifurcation modifies the geometry of the tree, which leads to uncertainties regarding the optimality of the bifurcation positions previously found in the existing tree.

In this section, we describe a method to optimize all bifurcation positions and all segment radii at once in a tree. This method starts from given terminal nodes positions and connectivity of a tree, for example here given by a CCO tree. It is based on an energy-based system of equations. This system has been shown to deliver an optimal solution [5].

Similarly, as in (9), one can define, for a vascular tree with N terminal nodes, a system of $3N - 1$ equations with $3N - 1$ unknowns:

$$\left\{ \begin{array}{l} k = \frac{Q_{tot}}{(r_{root})^3} \\ \frac{\partial E}{\partial x_i} = 0 \\ \frac{\partial E}{\partial y_i} = 0 \\ \frac{\partial E}{\partial r_j} = 0 \end{array} \right. \quad (13)$$

with i iterating over the $N - 1$ bifurcation nodes, and j over the $2N - 1$ segments. Solving the partial derivatives of E with respect to the radii leads to:

$$r_j = \sqrt[3]{\frac{f_j}{k}} \quad (14)$$

After injecting (14) in the energy equation, we obtain:

$$E = \sum_{j=0}^{N_s-1} E_j = \sum_{j=0}^{N_s-1} \left(\frac{8k^2\eta}{\pi} + b\pi \right) l_j r_j^2 \quad (15)$$

We note that (15) has the same form as (8), thus a global solution minimizing this energy function with regard to the bifurcation nodes can be found. This time however, it is a minimum for all the bifurcations at once, so global to the whole tree.

2.4 Tree comparison metric

To be able to compare the trees in terms of morphometry, and more precisely to measure the asymmetry between branches, an asymmetry ratio is defined for every branches starting from a segment u as:

$$\mathcal{A}_u = \frac{|l_u - r_u|}{l_u + r_u - 2} \quad (16)$$

where l_u (resp. r_u) is the number of leaves node downstream to the left (resp. right) children segment of the parent segment u . An asymmetry ratio of 0 means the branch is completely symmetric, while a value of 1 exhibits an asymmetric branch.

3 Results

3.1 Comparison of volume vs. energy approaches

To facilitate a comparative analysis of the two distinct approaches, one based on volume optimization (section 2.2) and the other on energy optimization (local optimization algorithm, section 2.3), we generated synthetic trees with varying numbers of terminal nodes: 100, 200, 300, and 400. For each specific number of terminal nodes, we constructed a total of 10 different trees, with different random seeds for the generation of new random node locations within the tree generation. All trees were grown within the same circular domain, as depicted in Fig. 1.

Fig. 2 shows that the energy-based method yields significantly lower computational time than the volume-based approach. The time saved seems more or less constant as the relative time difference exhibits an average gain of 31.7%, 36.2%, 33.9% and 36.3% for trees with 100, 200, 300 and 400 terminal segments (or nodes), respectively.

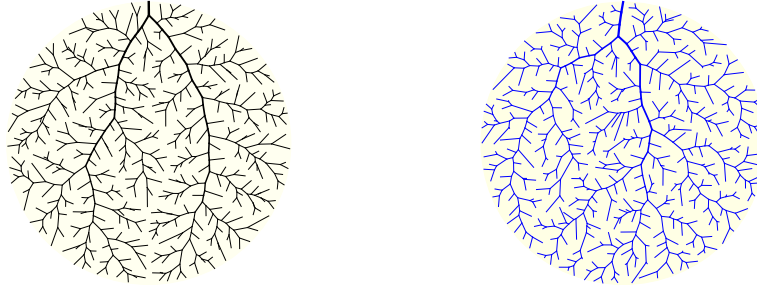


Fig. 1. Example of trees with 400 terminal segments simulated with the volume-based (left) and energy-based (right) methods.

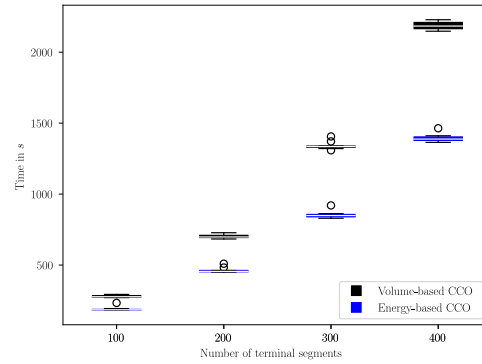


Fig. 2. Boxplot of the computational time vs the number of terminal segments for the volume and energy-based CCO (without global optimization) methods.

A comparison of morphometric features is conducted between the two methods, as illustrated in Fig. 3. These features encompass the mean diameters and mean lengths at each bifurcation level (the number of segments in the path from the current segment to the root segment), along with the radius-weighted average asymmetry ratio (see (16)). On average, it appears that both methods yield similar tree structures in terms of radii and length distributions. Notably, the energy-based method tends to generate deeper trees, evidenced by a maximum of 46 bifurcation levels, in contrast to 43 levels achieved through volume optimization. Additionally, the distribution of branch lengths exhibits a slightly broader variation. However, the asymmetry ratio reveals no significant differences between the two methods. It is worth noting that both approaches produce somewhat asymmetric trees, with smaller branches exhibiting greater symmetry.

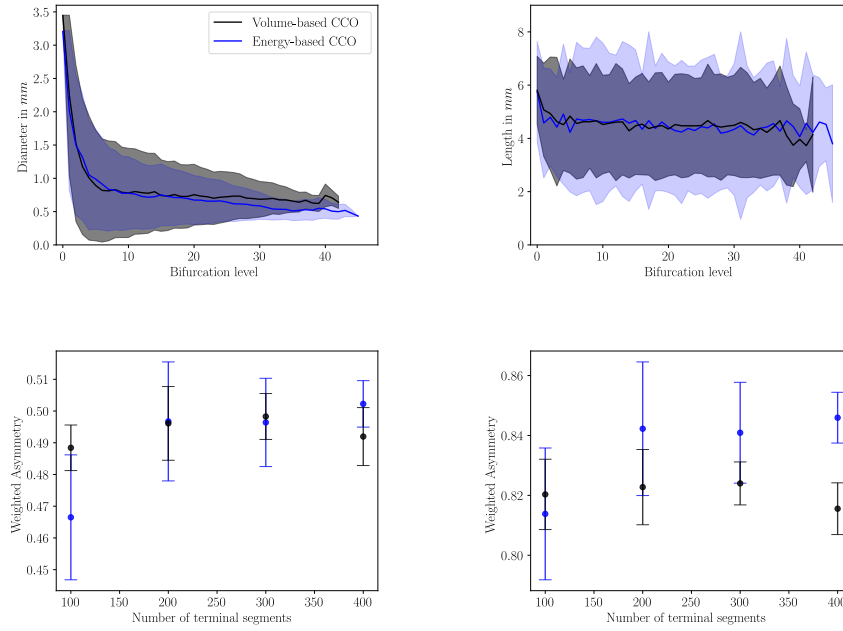


Fig. 3. Morphometric analysis along bifurcation levels: average diameter (top left), and average length (top right) along standard deviation envelope at each bifurcation level, on 10 simulated trees with 400 terminal segments. Weighted average asymmetry ratio, for both methods, for all segments (bottom left), and by taking into account only segments with at least 3 downstream children (bottom right). The average is weighted by the segment radius in both cases

3.2 Global optimization results

We applied our global optimization framework (section 2.3) to the previously generated synthetic trees that were initially constructed with the energy-based approach. Consistently with the energy formulation outlined in (15), an energy reduction achieved through our global framework should be approximately equivalent to a volume reduction, up to a constant factor. Consequently, for the purpose of comparing the energy-based approaches (with and without global optimization) to the volume-based method, we have plotted the total vascular volume in Fig. 5. The results show that even prior to global optimization, the energy-based method already yields lower volumes compared to the volume-based method. The mean relative volume differences are 21.3%, 36.7%, 36.1%, and 37.2% for trees with 100, 200, 300, and 400 terminal segments, respectively. In addition, our global optimization method successfully leads to a reduction in the total vascular volume (and energy) across all cases when compared to

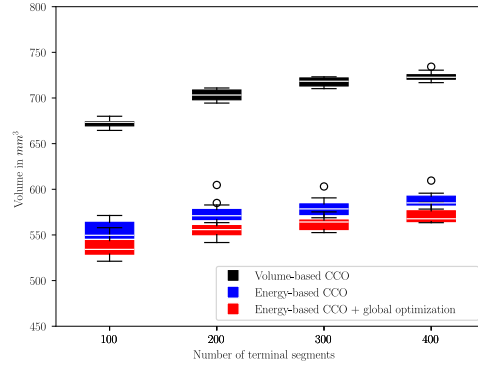


Fig. 4. Boxplot of the vascular volume vs the number of terminal segments for the volume and energy-based CCO (with and without global optimization) methods.

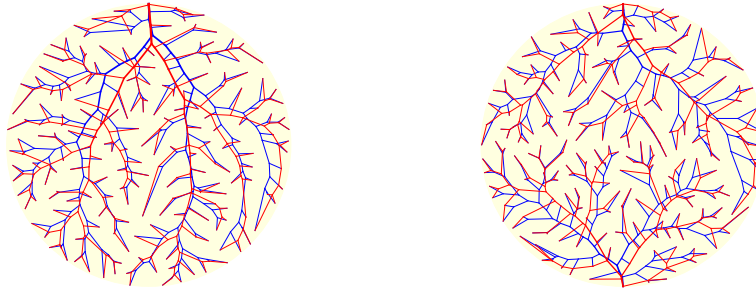


Fig. 5. Example of a tree generated with the energy-based CCO method (in blue), which is then optimized globally (in red). In the right image, two trees starting from two different root positions are constructed with the forest growth algorithm developed in [6].

the CCO energy-based trees. On average, the volumes are decreased by 3.0%, 7.9%, 7.8% and 7.7% for trees with 100, 200, 300 and 400 terminal segments, respectively.

4 Discussion

Most synthetic vascular tree generative models are built on the foundational principle, first proposed by Murray [14], that vascular structures aim for optimally minimizing transport costs. The CCO method aims to minimize vascular volume. However, relying solely on a volume-based objective could lead to an

incomplete transport cost. We introduce a term related to viscous work, consistently with the original Murray’s derivation for a single bifurcation. Incorporating this new objective function leads to a well-posed and convex problem. Related objective functions have been mentioned in previous publications on tree generation methods, but never in the context of CCO. For instance, Kim *et al.* [12] developed a tissue-growth-based tree generation method, which shares similarities with CCO in its incremental tree construction approach, involving local optimization at each new bifurcation. Although they aim at minimizing the same energy function, it remains unclear if they also utilize this energy function to scale the radii. In contrast to our findings, they report achieving similar volumes between their method and CCO, with differences below 5%. Our approach results in a significant reduction in tree energy (or volume, see Sect. 2.3), approximately by 36% compared to the volume-based CCO. This reduction can be attributed to the optimality of our solution and by our more consistent way to compute the radii.

Concerning tree morphometry, our analysis tends to indicate that the energy-based method produces similar trees as the volume-based method. In order to fully capture the impact of the new method, we plan to extend our local and global optimization frameworks to generate 3D organ-specific trees in the future. This will enable comparisons with real data.

A major consideration in CCO is the reduction of computational costs: our approach notably achieves an average cost reduction of approximately 35%. This improvement is facilitated by the convex nature of our problem, which enhances convergence efficiency.

As highlighted by previous publications [11,7], one limitation of CCO lies in its focus on optimizations of one bifurcation at a time only. In that sense it provides a local tree optimization. Based on our energy-based CCO method, we developed a global optimization framework. We showed that a global optimum solution can be reached, and we succeeded to obtain an energy reduction up to 8%. In comparison, the branching node positions optimization developed by Jessen *et al.* achieved a volume reduction of 4% from a volume-based CCO tree. Unlike our approach, their system of equations relies on a CCO volume-based local optimization, yielding non-optimal solutions.

In contrast to the aforementioned works [11,7], our approach does not attempt to modify the tree topology: we maintain the connectivity from CCO. However, we have seen that our tree generation problem can be linked to the well-studied field of optimal transport (section 2.1). Specifically, the task of finding optimal trees could be related to the Steiner tree problem [2]. Further research, potentially incorporating methods for solving this problem, could be addressed to identify an optimal tree topology.

To conclude, we have proposed a novel optimization framework for CCO, relying on an energy-based transport cost, which leads to a well-posed system of equations. While simulating similar 2D vascular trees as CCO in terms of morphometry, this new method succeeded to produce better optimal solutions, and more efficiently.

References

1. Bohn, S., Magnasco, M.O.: Structure, scaling, and phase transition in the optimal transport network. *Physical Review Letters* **98**(8), 088702 (2007)
2. Brazil, M., Zachariassen, M.: *Optimal Interconnection Trees in the Plane*, vol. 29. Springer (2015)
3. Cury, L., Maso Talou, G., Younes-Ibrahim, M., Blanco, P.: Parallel generation of extensive vascular networks with application to an archetypal human kidney model. *Royal Society Open Science* **8**(12), 210973 (2021)
4. Georg, M., Preusser, T., Hahn, H.K.: Global constructive optimization of vascular systems. Tech. Rep. WUCSE-2010-11, Washington University in St. Louis (2010)
5. Hahn, H.K., Georg, M., Peitgen, H.O.: Fractal aspects of three-dimensional vascular constructive optimization. In: *Fractals in Biology and Medicine*, pp. 55–66. Springer (2005)
6. Jaquet, C., Najman, L., Talbot, H., Grady, L., Schaap, M., Spain, B., Kim, H.J., Vignon-Clementel, I., Taylor, C.A.: Generation of patient-specific cardiac vascular networks: A hybrid image-based and synthetic geometric model. *IEEE Transactions on Biomedical Engineering* **66**(4), 946–955 (2018)
7. Jessen, E., Steinbach, M.C., Debbaut, C., Schillinger, D.: Rigorous mathematical optimization of synthetic hepatic vascular trees. *Journal of the Royal Society Interface* **19**(191), 20220087 (2022)
8. Kamiya, A., Togawa, T.: Optimal branching structure of the vascular tree. *The Bulletin of Mathematical Biophysics* **34**, 431–438 (1972)
9. Karch, R., Neumann, F., Neumann, M., Schreiner, W.: A three-dimensional model for arterial tree representation, generated by constrained constructive optimization. *Computers in Biology and Medicine* **29**(1), 19–38 (1999)
10. Katifori, E., Szöllösi, G.J., Magnasco, M.O.: Damage and fluctuations induce loops in optimal transport networks. *Physical Review Letters* **104**(4), 048704 (2010)
11. Keelan, J., Chung, E.M., Hague, J.P.: Simulated annealing approach to vascular structure with application to the coronary arteries. *Royal Society Open Science* **3**(2), 150431 (2016)
12. Kim, H.J., Rundfeldt, H.C., Lee, I., Lee, S.: Tissue-growth-based synthetic tree generation and perfusion simulation. *Biomechanics and Modeling in Mechanobiology* **22**(3), 1095–1112 (2023)
13. Menon, K., Khan, M.O., Sexton, Z.A., Richter, J., Nieman, K., Marsden, A.L.: Personalized coronary and myocardial blood flow models incorporating CT perfusion imaging and synthetic vascular trees. medRxiv pp. 2023–08 (2023)
14. Murray, C.D.: The physiological principle of minimum work: I. The vascular system and the cost of blood volume. *Proceedings of the National Academy of Sciences* **12**(3), 207–214 (1926)
15. Papamanolis, L., Kim, H.J., Jaquet, C., Sinclair, M., Schaap, M., Danad, I., van Diemen, P., Knaapen, P., Najman, L., Talbot, H., Taylor, C.A., Vignon-Clementel, I.: Myocardial perfusion simulation for coronary artery disease: A coupled patient-specific multiscale model. *Annals of Biomedical Engineering* **49**, 1432–1447 (2021)
16. Schreiner, W., Buxbaum, P.F.: Computer-optimization of vascular trees. *IEEE Transactions on Biomedical Engineering* **40**(5), 482–491 (1993)
17. Schwen, L.O., Preusser, T.: Analysis and algorithmic generation of hepatic vascular systems. *International Journal of Hepatology* **2012**, 357687 (2012)
18. Talou, G.D.M., Safaei, S., Hunter, P.J., Blanco, P.J.: Adaptive constrained constructive optimisation for complex vascularisation processes. *Scientific Reports* **11**(1), 6180 (2021)