Applying Graph Theory to Arterial Vascular Tree of the Kidney

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Abstract

The renal vascular development occurs through vasculogenesis and/or angiogenesis. Particularly, there are two types of vascular angiogenesis: sprouting and splitting. We show the graphs can generate binary tree structures by incorporating the physiological laws of the arterial branching of kidney. The graph prescribes a topology where each edge has the dynamics of the physiological phenomena of vascularization.

Key words: Graph, Renal Vasculature, Sprouting and Splitting Angiogenesis.

As introduction to our problem, we have to say the kidney is a highly vascularized organ [1–4] and consists of three vascular trees: arterial, venous, and ureter [5]. Vasculogenesis and angiogenesis are responsible of the formation of the renal vessels [2]. Angiogenesis is defined as the formation of new blood vessels from pre-existing vessels. Vascular endothelial growth factor (VEGF) plays an important role in renal vascularization [2]. Here, we are interested in arterial vascular tree of the kidney (AVTK), which develops by angiogenesis; *i.e.*, sprouting and splitting. In sprouting, endothelial cells activate branch out from a existing vessel to produce new vessels while in splitting new vessels are generated by dividing an existing blood vessel [6]. The AVTK is modeled using graph theory by including physiological information at edges. We also incorporate dynamics for development in renal arterial tree on the graph into edges.

The following definitions are required for completeness:

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Definition 1 *G_R is an ordered triple $(V(G_R), E(G_R), \psi_{G_R})$ that consist of a nonempty set $V(G_R)$ of vertices, a set $E(G_R)$ of edges which is disjoint from $V(G_R)$, and an incidence function $\psi_{G_R} : E(G_R) \to K_{\leq 2}^{V(G_R)}$, where $K_{\leq 2}^{V(G_R)}$ is the set of vertices ≤ 2, for each edge is met either of the following two conditions:*

(1) ψ_{G_R} associates each edge to a subset of $V(G_R)$ of size two; that is, $\psi_{G_R}(e) = \{u, v\}$.
(2) ψ_{G_R} associates to each edge, a subset of an element of $V(G_R)$; that is, $\psi_{G_R}(e) = \{u\}$.

Remark. (I) Let G_R be a tree, i.e., a connected acyclic graph. G_R has vertices with oriented edges in such form that of each vertex leave two edges and arrive an edge (the orientation symbolizes blood circulation flow in arteries). Thus, given any edges on a bifurcation in Fig. 1 (a), these are related as follows: $i = \frac{(m-1)}{2}$ if subscript m is odd or $i = \frac{(m-2)}{2}$ if subscript m is even. (II) The tree G_R has labeled edges, that is, each edge represents a blood vessel and its labeled $e_{i(j-1)}(s, C_{gf}, l, d, \theta)$ $(i, j \in \mathbb{N})$, i.e., a label in a tree G_R is a function $f : \mathbb{R}_+^{\pi} \cup \{0\} \to E(G_R)$, given by $\pi \mapsto e$, $\pi \in \mathbb{R}_+^{p}$ where p is a set of parameters. The edge has the physiological information: the parameter s has the dynamics (depends the process used in the development of the vessel, sprouting or splitting angiogenesis), concentration of VEGF (C_{gf}), length (l), diameter (d) and angle (θ), see Fig. 1 (b). We define mathematically the processes of sprouting and splitting angiogenesis.

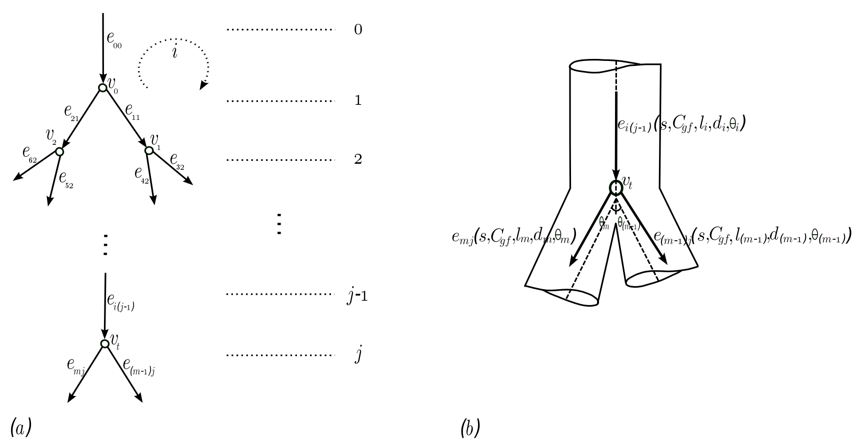

Fig. 1. (a) In G_R the subscript i indicate in order to know that edge generates what edge. G_R has depth j, each j is a segment of the tree. The subscript t ($t \in \mathbb{N}$) indicate the position of the vertex in G_R. (b) Representation of an arterial bifurcation in G_R with labeled and oriented edges

Definition 2 *Let a_b denote a sprouting angiogenesis. $s = a_b$ generates a new blood vessel in the edge $e_{i(j-1)}$, which is formed by k ($k \in \mathbb{N}$) endothelial cells (see Fig. 2 (1)).*

Definition 3 *Let a_p denote a splitting angiogenesis. $s = a_p$ generates two new blood vessels in the edge $e_{i(j-1)}$ (see Fig. 2 (2)).*

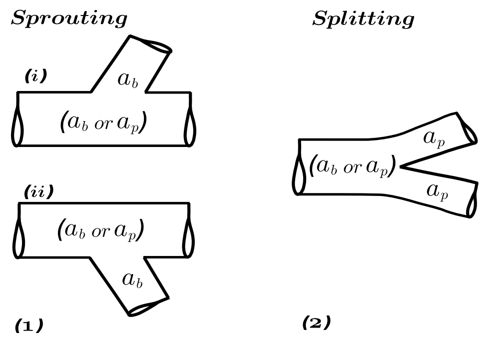

Fig. 2. (1) Sprouting: (i) If the new vessel in $e_{i(j-1)}$ is $e_{(m-1)j}$, formed by a_b, then $d_{m-1} < d_m$, $\theta_{m-1} > \theta_m$, and $d_m = d_i$ or, equivalently, (ii) if the new vessel in $e_{i(j-1)}$ is e_{mj}, formed by a_b, then $d_m < d_{m-1}$, $\theta_m > \theta_{m-1}$, and $d_{m-1} = d_i$ [7,6]. (2) Splitting: The vessel $e_{i(j-1)}$ bifurcates in $e_{(m-1)j}$ and e_{mj}. Diameters of new vessels are $d_{m-1} = d_m = \frac{d_i}{2}$ and $\theta_{m-1} + \theta_m = 75°$ [7,6].

We have for each $N_e = e_{i(j-1)} \in E(G_R)$ a local map $f_e : S^{N_e} \to S$ where $S = \{a_b, a_p\}$.

$$f_e(e_{i(j-1)}) = \begin{cases} a_b \text{ if } \exists \ ec \\ a_p \text{ if } \nexists \ ec \end{cases}$$

where ec is the migration of endothelial cells. f_e generates each bifurcation in the tree (see Fig. 1 (a)). Here we only consider $e_{i(j-1)}$, because we do not have experimental data of how it is the dependency with respect to its neighbors of the blood vessels.

We have three possible structures in the bifurcation when the pre-existing edge is a_b or a_p. All bifurcations have the same probability of $\frac{1}{3}$. As a matter of fact, if $e_{i(j-1)}$ is a_b, $\Rightarrow$ can be generated the bifurcations $= a_b a_b, a_b a_b$, or $a_p a_p$, or if $e_{i(j-1)}$ is a_p, $\Rightarrow$ can be generated the bifurcations $= a_b a_p, a_p a_b$, or $a_p a_p$.

Now our results are discussed in context of the development of vascular tree in the kidney by incorporating physiological information. The parameter s is defined in f_e and (C_{gf}, l, d, θ) belongs to a experimental range as follows:

(1) $C_{gf} \in [\underline{C_{gf}}, \overline{C_{gf}}] ng/mL$ where $C_{gf} \in \mathbb{R}^+ \cup \{0\}$.
(2) $l : [\underline{C_{gf}}, \overline{C_{gf}}] \to [\underline{l}, \overline{l}]$ where $l \in \mathbb{R}^+$. Function l assigns the value segment j in which it is as follows (see Fig. 1): $j \in [1, 2]$ $l \in [0.793, 10.306] mm$, $j \in [3, 4]$, $l \in [0.357, 4.569] mm$ and $j \in [5, 9]$, $l \in [0.014, 1.217] mm$.
(3) $d : [\underline{C_{gf}}, \overline{C_{gf}}] \to [\underline{d}, \overline{d}]$ where $d \in \mathbb{R}^+$. d also depends of $d_i^x = d_{m-1}^x + d_m^x$, the relationship is known as a Murray's law [7]. d satisfies the requirements laid down in Fig. 2.
(4) θ of the vessel formed by a_b is larger than θ of the other vessel, and the sum of these angles $\in [60°, 80°]$. When the new vessels are formed by a_p,

we have that $\theta_{m-1} + \theta_m = 75°$.

We have that C_{gf} is directly related with length and diameter of the new vessels, but we do not have enough information to make an approximation in order to define functions of l and d based on C_{gf}. Moreover, by definition of sprouting and splitting angiogenesis, we have that these processes are different and the most important different is that a_b has migration of endothelial cells whereas a_p does not have [6].

Axiom 1 $a_b \neq a_p$.

Remark. According to experimental data, the AVTK is structured as follows: renal artery, segment 0; interlobar arteries, segments 1-2; arcuate arteries, segments 3-4; interlobular arteries, segments 5-9. Hence, we have that the depth of G_R is $j = 9$. We have that a_b generates only one new vessel while a_p generates two vessels, we can associate on each branching point one vertex v_t, only two vessel are found after each vertex (see Fig. 1).

Theorem 1 *If the AVTK is developed through a_b and a_p, each segment has an even number of blood vessels (b_v).*

Proof AVTK development obeys the following steps indistinctly if a_b or a_p occur on each vertex: For the segment $j = 0$, the renal artery is the unique vessel on the vasculature. For $j = 1 \ \exists \ 2 \ b_v$. For $j = 2 \ \exists \ 4 \ b_v$, that is, we have $2 \cdot 2 = 2^2$. Then, inductively, we have that for $j = n, \ n \in \mathbb{N}, \ \exists \ 2^n \ b_v$. Hence, for the n-th segment, $2 \cdot 2^{n-1} = 2^n \ b_v$. Therefore, if the AVTK G_R is developed by means of a_b and a_p, each segment $0 < j \leq 9$ has an even number of b_v. $\square$

Corollary 1 *$\forall v \in V(G_R)$ has degree 3.*

Remark. For $j = 0$ in the G_R, there exists the initial configuration $c_0 = \{e_{00}\}$, which is the renal artery. For $j = n \ \exists$ the configuration c_n, on which we have exactly 2^n labeled edges by f_e. Thus, $c_{n+1} = \{f_e(c_n(e_{1n}), c_n(e_{2n}), ..., c_n(e_{2^n n}))\}$. All configuration c_j has 2^j edges with $2^j = r + k$ $(r, k \in \mathbb{N})$, where r and k is the number of labeled edges by a_b and a_p, respectively. For each $c_j \ \exists \ (3r)(3k)$ possible configurations for generate the next configuration c_{j+1}.

Proposition 1 *If in the configuration $c_j \ \exists$ labeled edges with a_b and a_p, it is possible generate the configuration c_{j+1} with all labeled edges by a_p.*

Proof $\exists$ labeled edges with a_b and a_p in c_n. Then, we have that the bifurcation of a_b can have labeled edges by a_p and the bifurcation of a_p can have labeled edges by a_p (see Figure 2). Consequently it is possible generate the configuration c_{j+1} will all labeled edges a_p. $\square$

Remark. As we have all labeled edges by a_b or a_p, then no it is impossible to generate the next configuration c_{j+1} with all labeled edges by a_b, due to the presence of a_p in c_j.

Proposition 2 *If all edges are a_b in the configuration c_n, the configuration c_{j+1} is generated with all labeled edges by a_b or a_p.*

Proof The bifurcation of a_b can have labeled edges by a_b or a_p, and the bifurcation of a_p can have labeled edges by a_b or a_p as well. Then, it is possible generate the configuration c_{n+1} will all labeled edges by a_b or a_p. □

The degree of diametral asymmetry on a bifurcation is expressed by the index: $\alpha = \frac{d_{m-1}}{d_m}$, where $0 < \alpha \leq 1$ and diameters d_{m-1} and d_m are related to discussion on the Figure 1. As $\alpha = 1$, i.e., $d_{m-1} = d_m$ and, oppositely, $d_{m-1} < d_m$ as $\alpha < 1$.

Theorem 2 *If there exist a_b and a_p in the developed of AVTK, tree is assymmetric.*

Proof Suposse $\exists$ a_b and a_p in G_R. If a new vessel is formed by a_b, $d_{m-1} < d_m$ which implies $\alpha < 1$. If the two new vessels are formed by a_p, $d_{m-1} = d_m$ which implies $\alpha = 1$. Hence, α is not constant in developing the AVTK. □

Example 1 *Our algorithm was programmed at Mathematica to generate an AVTK. Items (1) to (4) were included in program with the following parameters: $s =$ 0.5, $C_g f \in [0, 35]$ ng/mL. Function l is fitted from experimental data [8] to have $l = 0.00878C_{gf}^3 - 0.513C_{gf}^2 + 8.521C_{gf} + 81.12$. Figure 3 shows the AVTK, which agrees with experimental studies [9] and other models (see Table 5 in [1]). For this example we have: average walk 12.7898 ± 0.725 mm.*

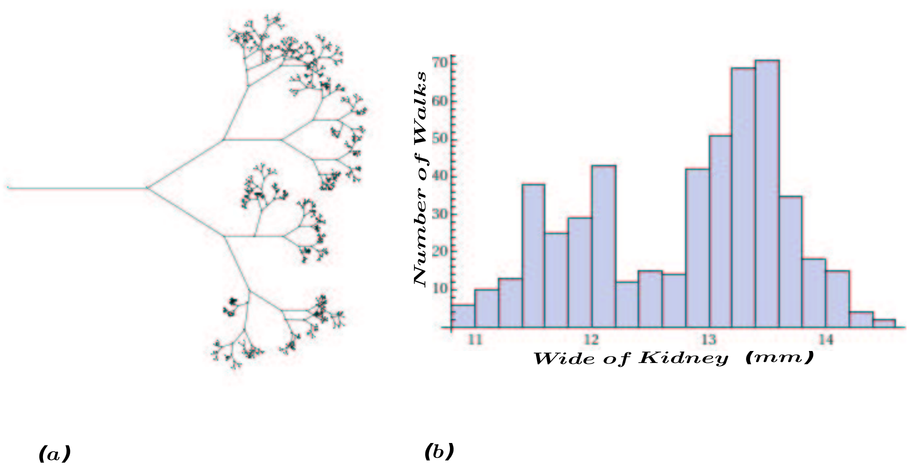

Fig. 3. (a) AVTK in G_R where a_b and a_p have 50% of probability in the development. (b) Histogram with wide of kidney for all walks in G_R, i.e., the length of the root until the leaves.

As a summary, we show a function f_e in G_R for AVTK. The physiological parameters C_{gf}, l, d and θ were found within the ranks studies experimentally. We also show there exists six possible bifurcations from sprouting and splitting in the AVTK. The AVTK has a depth until the interlobular arteries, i.e., the depth of G_R is $0 < j \leq 9$ and each segment has an even number of blood vessels $\forall v \in V(G_R)\ deg_{G_R}(v) = 3$. For each configuration $c_j\ \exists\ 2^j = (3r)(3k)$ possible configurations for generate the next configuration c_{j+1}. If all edges are a_b in c_j, it is possible generate the configuration c_{j+1} with all edges labeled by a_b or a_p, whereas if all edges are a_b and a_p in c_j, it is possible generate the configuration c_{j+1} with all labeled edges by a_p. We conclude that the tree G_R is assymmetric when the AVTK develops by a_b and a_p, which is consistent with experimental data.

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