Grahp and Automata in Arterial Vascular Tree of the Kidney

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Abstract

The renal vascular development is not known and occurs through two mechanisms that sometimes overlap: vasculogenesis and angiogenesis. Here we only consider growth through angiogenesis, i.e., the arterial vascular tree of the kidney. There are two types of vascular angiogenesis in development: sprouting and splitting angiogenesis. We study these processes through mathematical tools. The graphs and automatas allow modeling the vascular growth, can generated tree structures by incorporating the physiological laws of the arterial branching. That is, the graph prescribes topology of the vascular tree and the automaton can include the rule of dynamics in the phenomena of vascularization.

Keywords: Renal Vasculature, Sprouting and Splitting Angiogenesis, Graph Theory, Automata.

1 Introduction

The kidney is a highly vascularized organ, the vascular tree of kidney has been the focus of a number of studies (Nordsletten, et. al., 2006; Sequeira and Gomez, 2000; Tomanek, 2001; Zamir, 2001; Zamir and Phipps, 1987). The kidney consists of three trees: arterial, venous, and ureter (Guyton and Hall, 2000). Vasculogenesis and angiogenesis have both been postulated as responsible for the formation of the renal vessels (Tomanek, 2001). The formation of new blood vessels is an important process in embryonic development, vasculogenesis is the formation of blood vessels from endothelial cells precursors.

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This process is predominant during early embryogenesis (Tomanek, 2001). Angiogenesis is defined as the formation of new blood vessels from preexisting vessels. The contribution of each process in the development of the kidney remains to be determined. It is likely, however, that small arterioles and capillaries are formed by vasculogenesis, whereas larger arteries may develop by angiogenesis. Vascular endothelial growth factor (VEGF) plays an important role in renal vascularization. VEGF is probably a crucial parameter in kidney vascularization. The growth of kidney vessels seems to depend on the regulation of VEGF by the tissue oxygen concentration. Both processes depend of VEGF (Tomanek, 2001).

Here, we only consider angiogenesis because we are interested in arterial vascular tree of the kidney. The renal arterial tree is structured as follows: the renal artery had divided into interlobar arteries, arcuate arteries, and interlobular arteries. Angiogenesis is divided in sprouting and splitting. Sprouting angiogenesis is a process in which endothelial cells activate branch out from a existing vessel to produce a new emerging vessel. This process involves degradation of the basement membrane surrounding the endothelial layer, migration of the endothelial cells towards the angiogenic stimulus, proliferation of the endothelial cells, lumen formation and fusion with the preexisting vessel (Patan, 2000). Splitting angiogenesis is a process in which new blood vessels are generated by dividing an existing blood vessel. Splitting may occur as the result of proliferation of endothelial cells inside the vessel lumen and the subsequent fusion and splitting of the vessels (Patan, 2000). In this work, we study the development of arterial vascular tree in the kidney by angiogenesis. The arterial vascular tree of the kidney is modeled using graph theory and automatas. A graph is used to visualize the topology of arterial vascular tree of the kidney providing physiological information into the edges. We can incorporate dynamics of the development in renal arterial tree on the graph and this information can go into edges also. That is, we found the rule of the automata for the dynamics. The paper is organized as follows: Section 2 includes definitions of graph, sprouting and splitting angiogenesis, and tree-automata. Section 3 our results are shown here and the manuscript is closed with some concluding remarks in section 4.

2 Definitions

We define a graph to visualize the topology of arterial vascular tree of the kidney with physiological and dynamical information in the edges.

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,* $\psi_{G_R}(e) = \{u\}$.

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 and). Thus, given any edges on a bifurcation, these are related as follows

$$i = \begin{cases} \frac{(m-1)}{2} & \text{if subscript } m \text{ is odd} \\ \frac{m-2}{2} & \text{if subscript } m \text{ is even} \end{cases}$$

on which i denotes the edge generating the other two in the bifurcation and, complementarily, in the tree G_R, the subscript j stands for depth of a vessel onto the tree (see Figure 1). Note that each edge includes information about the i-th pre-existent vessel from which the angiogenesis occurs via sprouting or splitting.

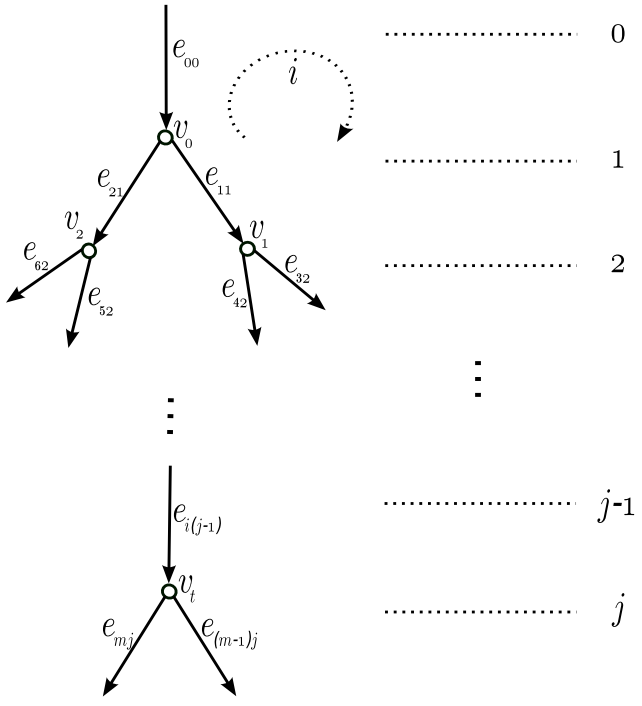

Fig. 1. In G_R the subscript i indicate in order to know that edge generates what edge. G_R has depth j, each j is a segment of the tree. The subscript t ($t \in \mathbb{N}$) indicate the position of the vertex in G_R.

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., the edge has the physiological information: the parameter s has the dynamics (depends the process used in the development of the vessel, i.e., a_b or a_p), concentration of VEGF (C_{gf}), length (l), diameter (d) and angle (θ), see Fig. 2.

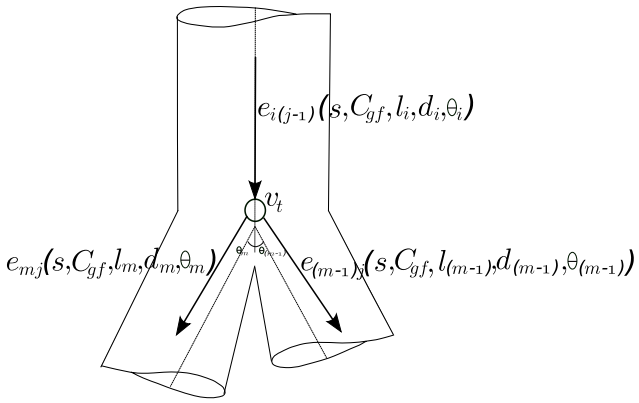

Fig. 2. Representation of an arterial bifurcation in G_R with labeled and oriented edges.

All parameters are important, but C_{gf} is an essential regulatory factor for both processes of angiogenesis. While C_{gf} promotes endothelial cell migration, proliferation and tube formation, its effect on splitting angiogenesis has still to be investigated. We define mathematically the processes of sprouting and splitting angiogenesis:

Definition 2 *Let a_b be a sprouting angiogenesis, 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.*

Definition 3 *Let a_p be a splitting angiogenesis, a_p generates two new blood vessels in the edge $e_{i(j-1)}$.*

We can to define a cellular automata in the tree G_R, now the set of configurationes is $C = S^{E(G_R)}$ (maps of edges of $E(G_R)$ to S), for every $e \in E(G_R)$ we denote $N_e \subseteq E(G_R)$ (finite subset) and is called the set of neighbors of the edge e, which contains e and its neighboring. Finally we have for each $e \in E(G_R)$ a local map f_e from S^{N_e} to S (where S^{N_e} is the set of maps from N_e to S).

Definition 4 *A G_R-automata is an ordered pair (G_R, A) where G_R is a tree defined by $(V(G_R), E(G_R), \psi_{G_R})$ as described above and A is an triple (S, N_e, f_e), we have for each element $e_{i(j-1)} \in E(G_R)$ a finite subset N_e of $E(G_R)$ that contains $e_{i(j-1)}$ (and its neighboring) and is called the set of neighbors of the edge $e_{i(j-1)}$. We have a set of values $S = \{a_b, a_p\}$. Finally we have for each*

Sprouting

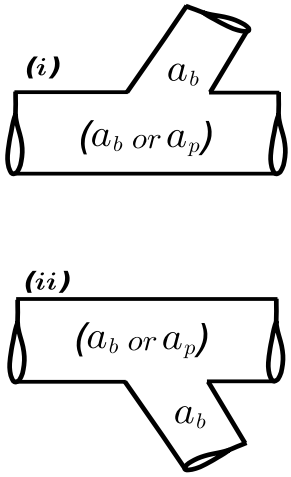

Fig. 3. (i) If the new vessel in $e_{i(j-1)}$ is $e_{(m-1)j}$, formed by a_b, then $d_{m-1} < d_m$, $\theta_{m-1} > \theta_m$, and $d_m = d_i$ or, equivalently, (ii) if the new vessel in $e_{i(j-1)}$ is e_{mj}, formed by a_b, then $d_m < d_{m-1}$, $\theta_m > \theta_{m-1}$, and $d_{m-1} = d_i$ (Gabryś, et. al., 2005; Patan, 2000).

Splitting

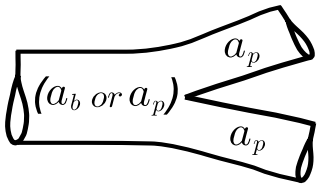

Fig. 4. The vessel $e_{i(j-1)}$ bifurcates in $e_{(m-1)j}$ and e_{mj}. Diameters of new vessels are $d_{m-1} = d_m = \frac{d_i}{2}$ and $\theta_{m-1} + \theta_m = 75°$ (Gabryś, et. al., 2005; Patan, 2000).

$e_{i(j-1)} \in E(G_R)$ *a local map* $f_e : S^{N_e} \to S$.

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

where ec is the migration of endothelial cells. f_e *generates each bifuration in the tree (see Fig. 2).*

Here, we only consider $N_e = e_{i(j-1)}$, 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, and three possible structures in the bifurcation when the pre-existing edge is 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 $= \begin{cases} a_b a_b, \\ a_b a_b, \text{or} \\ a_p a_p \end{cases}$

or

If $e_{i(j-1)}$ is a_p, $\Rightarrow$ can be generated the bifurcations $= \begin{cases} a_b a_p, \\ a_p a_b, \text{or} \\ a_p a_p \end{cases}$

The local maps f_e induce a global map F from the set of configurations to itself as follows. Let c be a configuration, we define the configuration $F(c)$ by:

$$\forall e_{i(j-1)} \in E(G_R) \;\; F(c)(e_{i(j-1)}) := f_e(c_{|N_e}),$$

where $c_{|N_e}$ is the restrition of c to the set N_e.

3 Results

Our results are discussed in context of the development of vascular tree in the kidney from the angiogenesis. 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.

Axiom 1 $a_b \neq a_p$.

According to experimental studies in the vascular tree of the kidney, we conclude that the renal arterial tree reaches the depth of the interlobular arteries (Guyton and Hall, 2000).

Proposition 1 *Let G_R-automata be an arterial vascular tree of the kidney formed by a_b and a_p, depth of the tree G_R is $0 \leq j \leq 9$.*

Proof Let G_R-automata be an arterial vascular tree of the kidney, which is formed by a_b and a_p. The arterial vascular tree of the kidney is structured: the renal artery is branched in interlobar arteries, arcuate arteries, interlobular arteries which are formed by bifurcation (Guyton and Hall, 2000). In fact, a vascular tree of the kidney until the interlobular arteries can 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 $0 \leq j \leq 9$.

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).

Teorem 1 *If the arterial vascular tree of the kidney is developed through a_b and a_p, each segment has an even number of blood vessels (b_v).*

Proof The arterial vascular tree of the kidney is developed obeying 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 branch on the vasculature. As vascular development occurs, for the segment $j = 1$ $\exists$ 2 b_v. For the segment $j = 2$ $\exists$ 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, we have $2 \cdot 2^{n-1} = 2^n$ b_v.

Therefore, if the arterial vascular tree of the kidney G_R-automata is developed by means of a_b and a_p, each segment $0 < j \leq 9$ (by proposition 1) has an even number of b_v.

Corollary 1 *All vertices in the arterial vascular tree of the kidney G_R has degree 3, i.e., $\forall v \in V(G_R)$ $deg_{G_R}(v) = 3$.*

Initially for $j = 0$ in the G_R-automata, there exists the initial configuration $c_0 = \{e_{00}\}$, which is the initial condition (the renal artery). In general, for the segment $j = n$ $\exists$ the configuration c_n, which have exactly 2^n labeled edges by f_e. Then, we have

$$c_{n+1} = \{f_e(c_n(e_{1n}), c_n(e_{2n}), ..., c_n(e_{2^n n}))\}$$

where $f_e(c_n(e_{2^n n}))$ generates each bifurcation.

All configuration c_j has 2^j edges with $2^j = l + k$ vessels, where l is the number of labeled edges by a_b and k is the number of labeled edges by a_p:

- If l and $k \neq 0$, $\exists$ $(2l)(3k)$ possible configurations for generate the next configuration c_{j+1}.
- If $l = 0$ or $k = 0$, $\exists$ $3k$ or $2l$ possible configurations for generate the next configuration c_{j+1}. $l = 0$ and $k \neq 0$ is greater in number of possible configurations (c_{n+1}) that when $l \neq 0$ and $k = 0$.
- When $l = k$, we have the number maximum of possible configurations for the next configuration c_{j+1}.

For each c_j $\exists$ $(2l)(3k)$ possible configurations for generate the next configuration c_{j+1}.

Proposition 2 *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 (pre-existing vessel) can have labeled edges by a_p and the bifurcation of a_p (pre-existing vessel) can have labeled edges by a_p (see Figure XX). Consequently it is possible generate the configuration c_{j+1} will all labeled edges a_p.

When we have all labeled edges by a_b or a_p, then 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 3 *If in the configuration c_n all edges are a_b, it is possible generate the next configuration c_{j+1} with all labeled edges by a_b or a_p.*

Proof In the configuration c_n all edges are a_b, we have that the bifurcation of a_b (pre-existing vessel) can have labeled edges by a_b or a_p, and the bifurcation of a_p (pre-existing vessel) can have labeled edges by a_b or a_p too. 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 XX. The index is a measure of the asymmetry of the two diameters at an arterial bifurcation. As $\alpha = 1$, both diameters are equal (i.e., $d_{m-1} = d_m$), and, oppositely, one of the two diameters is larger than the other (i.e., $d_{m-1} < d_m$) as $\alpha < 1$.

Teorem 2 *If there exist a_b and a_p in the developed of arterial vascular tree of the kidney, tree is asymmetric.*

Proof $\exists$ a_b and a_p in G_R, we have that if a new vessel is formed in the bifurcation by a_b, which implies that $d_{m-1} < d_m$, the index of diametral asymmetry is $\alpha < 1$. If the two new vessels are formed in the bifurcation by a_p, which implies $d_{m-1} = d_m$, the index of diametral asymmetry is $\alpha = 1$. Hence, α is not constant in developing the arterial vascular tree of the kidney.

We observe that the sprouting angiogenesis contributes to an increase of complexity in arterial vascular tree of the kidney.

4 Conclusions

We studied the development of arterial vascular tree of the kidney using the graph theory and automatas. We define a G_R-automata to represent the development of arterial vascular tree of the kidney, which is generated through angiogenesis. Since there exist two types of angiogenesis: sprouting and splitting, we analyzed the renal arterial vasculature development through of these

processes. The development dynamics in the arterial vascular tree of the kidney on G_R and the physiological information can go into edges. That is, we found the rule of the automata for the dynamics.

There exists six possible bifurcations from sprouting and splitting in the arterial vascular tree. By definition sprouting and splitting are two different processes in the development of the G_R-automata. Then, we have that a_b generates one whereas a_p generates two blood vessels, we conclude that the angiogenesis generates only bifurcations in the G_R-automata. Consequently, each segment $j > 0$ has an even number of blood vessels ($j = 0$ has the renal artery), i.e., $\forall v \in V(G_R)\ deg_{G_R}(v) = 3$. The arterial vascular tree of kidney has a depth until the interlobular arteries, and we determine the depth of the G_R-automata is $0 < j \leq 9$. For each configuration c_j there exists $2^j = (2l)(3k)$ (where l is the number of labeled edges by a_b and k is the number of labeled edges by a_p) 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. Additionally, we conclude that the tree G_R is asymmetric when the arterial vascular tree of the kidney is developed by a_b and a_p, which is consistent with experimental data.

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