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COMPUTER MODELLING OF VASCULAR SYSTEMS

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Abstract: A model of the vascular system perfusing an internal organ is presented in the paper. The system's development is driven by the increasing needs of growing tissue. The modelled network consists of 2 or 3 (in the case of the liver) vascular trees connected on the macro-cell level. Each appearance of a new macro-cell activates an angiogenic process. The geometry of newly formed vessels is determined as a result of local optimization of the bifurcation volume. The model can simulate modifications of the vascular network caused by pathological processes.

Keywords: computer modelling, vascular system, angiogenic process

1. Introduction

Substantial progress in computer science and especially the increased computational power of today's computers, enable performing more and more complex simulations. This is essentially important in biomedical applications, because thanks to computer modelling we are able to investigate many phenomena which are critical to the living organism in a non-invasive manner. Vascular systems considered in this paper are composed of hundreds of thousands of segments. Their growth and functioning are good examples of phenomena necessitating the use of the power of processors in their examination.

Individual parts of the whole vascular system are very diverse and their specificity should be taken into account during modelling. For example, the transportation function dominates in the main arteries delivering blood to the organs and the geometry of vessels is highly dependent on organism's anatomy. A different situation can be observed in the case of perfusion of abdominal organs like kidneys, where the most important task is filtration. In this case, the location of particular vessels is not crucial, but spatial vessel density is what matters for the organ to function properly.

There exist at least a dozen of vascular models and they differ considerably between each other. The models concern different organs and they have been designed with completely distinct aims and levels of details. One of the first proposals based on physiological mechanisms was described by Gottlieb [1]. As a result of an iterative algorithm inspired by the angiogenesis process, a fractal structure of a vascular tree was created. This model was then refined and formalized in [2]. Schreiner and Buxbaum proposed another method for arterial tree generation, which they called Constrained Constructive Optimization (CCO) [3]. The tree was developed by sequentially adding new bifurcations to the existing vascular structure. The optimal position of a bifurcation point was searched for to minimize the volume of the whole tree.

Recently, the aforementioned two-dimensional models have been replaced by much more realistic, three-dimensional models. The one proposed by Bézy-Wendling [4] enabled growth of an arterial tree inside a simple, analytically defined and gradually expanding volume. New simulated cells, which appear along with the growth of the organ, are perfused sequentially by the newly created vessels. In [5], the CCO method was extended in order to model arterial tree development inside a 3D volume imitating an organ. Improved CCO was applied to simulate the coronary artery.

The rest of the paper is organized as follows. In Section 2 the proposed vascular model is described. The proposed approach has been applied to simulate the growth and pathological modification of vascular systems in liver and kidney. The simulation results are presented in Section 3. The concluding section includes short conclusions and possible directions of future research.

2. Vascular system modelling

The model is designed to simulate the development (and/or pathological changes) of vascular systems in extensive abdominal organs, expanding by divisions of structural units (*hyperplasia*). Most of the model's features are not linked with any particular organ; however, when we deal with a given organ some specialization may be necessary to properly express its specificity. The liver is a good example of such a situation, because of its unique organization of the vascular network with three trees.

The vascular system develops in response to increasing metabolic needs of the organ. It means that at least rough tissue modeling is indispensable to model the growth of the vascular system. In the model the tissue is represented by a set of macro-cells distributed inside a 3D volume which defines the external shape of the organ. In the *growing phase*, the organ expands gradually until it reaches its maximum size. Then the *adult phase* begins, during which the size of the organ remains unchanged.

A macro-cell is a small, fixed size part of the tissue, the spatial position of which is given relatively to the shape and does not change with the organ's growth. Most of the functional and structural properties of a macro-cell is defined by its class (*e.g.* probability of mitosis/necrosis, metabolic needs,...). Several classes of macro-cells can be defined to differentiate various functional (or pathological) regions of the tissue.

Each vessel segment (a part of a vessel between two consecutive bifurcations) is represented by an ideal, rigid tube with fixed radius, wall thickness and position. It has

been assumed that wall thickness depends on a vessel's diameter and function (arteries have thicker walls than veins). In the model, all vessels above the level of capillaries are distinguishable. Only capillaries are not modelled directly and are "hidden" in the macro-cell. On the basis of morphometrical investigations of larger vessels (*e.g.* conducted by Zamir [6]), it has been assumed that a single vascular structure has the form of a binary tree. It means that anastomosis, which sometimes occurs, especially in pathological situations, cannot be modelled.

One of the most important assumptions concerns the blood flow. Blood is regarded as a Newtonian fluid of constant viscosity (μ), whose flow is governed by *Poiseuille's law*:

$$\Delta P = Q\frac{8\mu l}{\pi r^4}, \tag{1}$$

where P stands for blood pressure, l – vessel length, r – radius. It enables us to calculate the difference in blood pressure between the ends of a segment on the basis of blood flow and the geometry of the vessel. The physical law which has to obeyed at each bifurcation is the elementary law of *matter preservation*:

$$Q = Q_r + Q_l, \tag{2}$$

where Q_l (Q_r) denotes the blood flow in the left (right) descendant vessel, respectively. It means that the same quantity of blood that enters a bifurcation, has to leave it. Another constraint that has to be fulfilled in a bifurcation deals with radii of vessels. This relationship has been established empirically and is known as the *bifurcation law*:

$$r^\gamma = r_r^\gamma + r_l^\gamma, \tag{3}$$

where r_r (r_l) denotes the radius of right (left) descendant vessel, respectively, and γ varies between 2 and 3 [7, 6]. From this observation it is possible to estimate the radius of the ancestor vessels using radii of the descendant vessels.

Assuming that the positions of all vessels are fixed, it is necessary to assure consistency of the characteristics (*i.e.* blood flow and pressure,...) describing individual vessels. The vascular tree is consistent if: (i) it has the same blood pressure and fixed blood flow in all terminal vessels attached to macro-cells, (ii) the Poiseuille law is fulfilled in each vessel, while the matter preservation and bifurcation laws are fulfilled in each bifurcation. A computationally effective method to assure consistency in a vascular tree is described in [8].

Newly appeared macro-cells are initially ischemic, because they are not perfused by the existing vascular network. The macro-cell signals this by secreting angiogenic factors. In response to this biochemical stimulus, the closest vessels (called candidate vessels) sprout toward the source of stimulation. The stimulation ceases when the first vessel of each tree reaches the macro-cell and, consequently, the remaining new vessels retract. The geometry of a newly created bifurcation is controlled by local minimization of the additional blood volume needed for the macro-cell's perfusion. In order to find out the optimal configuration, each candidate vessel temporarily creates a bifurcation perfusing the macro-cell and volume of the vessels is calculated (Figure 1). Additionally, the problem of avoiding possible collisions between the perfusing vessels has to be taken into account. It concerns both intersection of vessels coming from the same tree and, more importantly, crossing of arteries (arterioles)

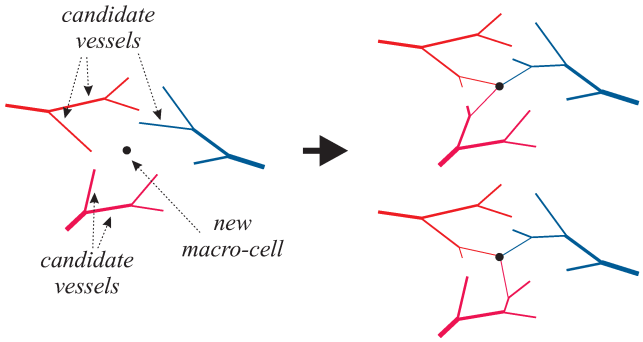

Figure 1. The perfusion process of a macro-cell newly created by a hepatic vascular network; the optimal configuration of vessels is chosen according to the minimal volume principle

and veins (venules). In the adapted simple approach, only non-crossing configurations are considered. Finally, the configuration of new bifurcations from all trees with the lowest sum of volumes permanently perfuses the macro-cell. The detailed description of the aforementioned process for two trees can be found in [9].

The development of a pathological process (*e.g.* a tumour) is usually connected with changes in the functional and structural properties of the tissue region, which often entail modifications of vascular structures. In the framework of the proposed model, distinct tissue regions can be studied by defining different classes of macro-cells. Under normal conditions, the class of a macro-cell generally remains unchanged throughout its life, but this is not the case in pathological situations. A mechanism of conversions has been introduced into the model to enable initialization of a distinct region by substitution in the macro-cell's class. Each conversion represents the period when the current class of macro-cells inside the defined volume (*e.g.* a sphere) can be changed (with a given probability) to another class. Conversions can be arranged in sequences or operate in a parallel way. A sequence of conversions enables us to simulate, for example, various stages of lesion development, when the characteristics of the infected region evolve gradually in time. Parallel conversions operating in various parts of an organ allow us to model multiple lesions (*e.g.* the spread of a tumour in the form of metastasis). After the initialization of a pathological region using the conversion mechanism, a disease develops leading to changes in the vascular system of the organ.

3. Experimental results

The computer program implementing the presented model was developed in the C++ language. It allows us to perform various simulations including the growth of the vascular network in a given organ and modifications of the vascular system induced by pathological processes. In this section, selected results of simulations concerning two very essential organs, *viz.* the liver and kidneys are presented.

All experiments were performed on a standard PC (Pentium IV 2GHz, 512 MB RAM). The main parameters of the model used in the simulations are presented in Table 1 (kidney) and Table 2 (liver). Physiological parameters were initialized by average, typical values corresponding to normal conditions. The external envelope of the kidney and acceptable positions of macro-cells were defined analytically. In the

Table 1. Main parameters used for simulation of vascular network growth in the kidney

Model parameter	Arterial tree	Venous tree
Blood pressure at the input (mm Hg)	95	10
Blood pressure at the output (mm Hg)	15	5
Blood flow (ml/min)	500	
Number of macro-cells in the adult organ	∼3200	
Change of the liver's size (initial→adult) (cm^3)	10→400	

Table 2. Main parameters used in the simulation of the hepatic vascular system growth

Model parameter	Hepatic artery	Portal vein	Hepatic vein
Blood pressure at the input (mm Hg)	95	25	12
Blood pressure at the output (mm Hg)	20	15	5
Wall thickness ratio (fraction of radius)	0.2	0.1	0.1
Blood flow (ml/min)	400	1100	1500
Number of macro-cells in the adult organ	∼12000		
Change of the liver's size (initial→adult) (cm^3)	75→1500		

case of the liver, the shape was reconstructed from a set of CT-images after interactive delineation. The main branches of each tree were initialized according to standard atlas positions inside the corresponding organ (7 segments – liver, 3 – kidney).

The growth of the vascular structure in the kidney is presented in Figure 2. In the left panel the initial structures are depicted, in the center – the intermediate phase and on the right – the adult vascular trees. In this figure, the trees are represented separately for better visualization, but both trees are physically connected on the macro-cell level. In Figure 3 the complete vascular structures of the kidney and the liver are shown.

The possibilities of the proposed model in simulation of vascular modifications induced by pathological processes are illustrated on the example of hepatic tumours.

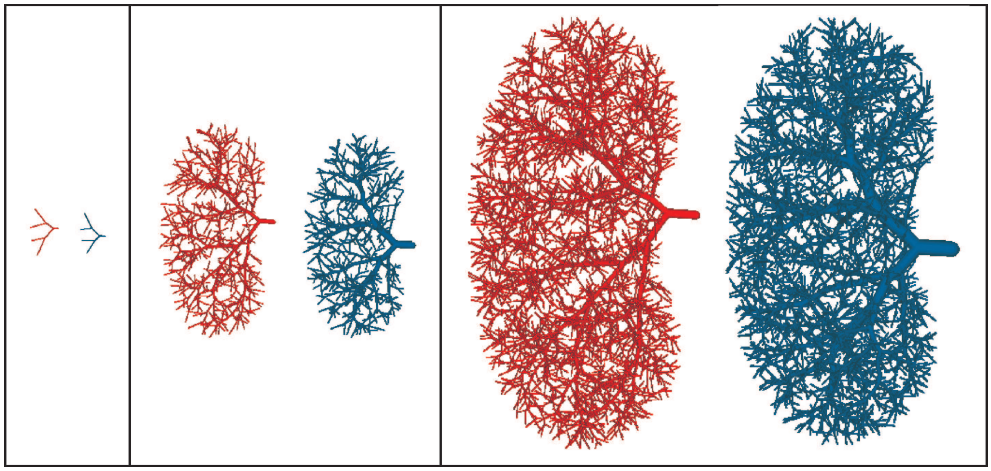

Figure 2. Simulation of a kidney vascular system (an arterial tree on the left and a venous tree on the right of each panel)

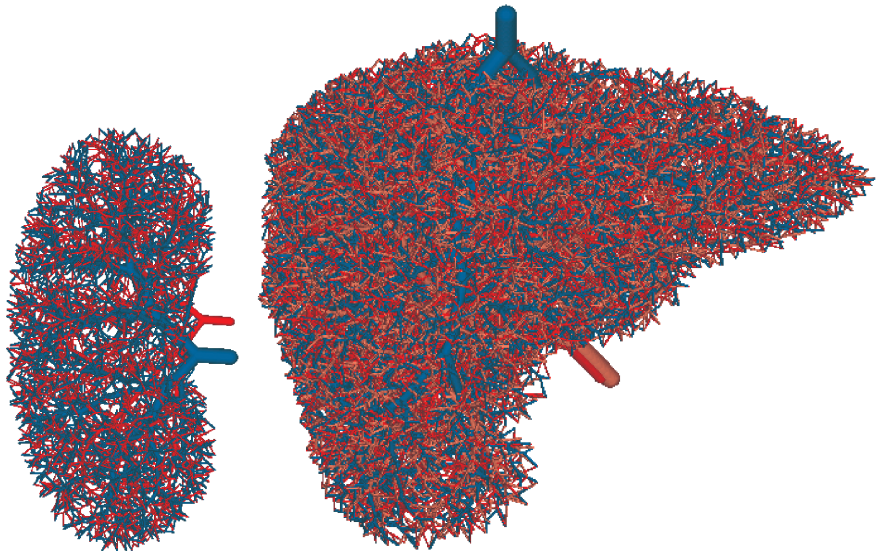

Figure 3. The complete vascular structures of the kidney (on the left) and the liver (on the right)

Two opposite situations are possible: hyper- and hypovascularization. In both cases, the pathological process is simulated in the same area by applying a single conversion with appropriately defined macro-cell classes. In Figure 4 the same part of the hepatic vein tree is presented in three situations: in the normal condition and after modifications induced by tumours: hypervascularization (on the left) and hypovascularization (on the right).

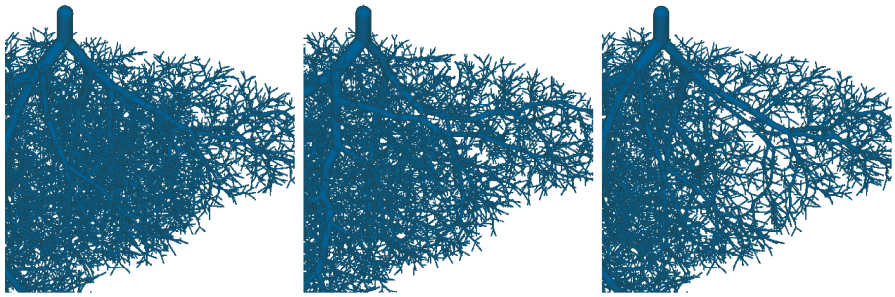

Figure 4. Simulation of pathological modification of vascular structures in the liver; only the hepatic vein tree is presented

4. Conclusions

The model presented in the paper is capable of simulating the growth of vascular systems of extensive abdominal organs both in normal and pathological conditions. According to this model, a simulation method of contrast product propagation in CT imaging was introduced [10] that makes it possible to examine the influence of acquisition protocols on tomographic images.

It should be emphasized that the described model continues to be improved. We are currently investigating the use of compartment models in macro-cells. Further-

more, we plan to incorporate more elastic vessel representation and pulsating blood flow in arteries.

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