Macroscopic Modeling of Vascular Systems

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Abstract. Angiogenesis, the growth of vascular structures, is an extremely complex biological process which has long puzzled scientists. Better physiological understanding of this phenomenon could result in many useful medical applications, from virtual surgery simulators for medical interventions, to cancer therapy, where e.g. influence of certain factors on the system could be simulated. Although there is a lot of research being done on blood circulatory systems and many models with high level of mathematical sophistication have already been proposed, most of them offer very modest visual quality for the resultant vascularities. This report is a proposition of a macroscopic model allowing for generation of various vascular systems with high graphical fidelity for simulation purposes.

Keywords: computer model, numerical simulation, angiogenesis, vascular system, capillary plexus, blood vessels, remodeling, hemodynamics.

1 Introduction

With the rapid progress on the field of computer technologies it is becoming now possible to build more and more realistic virtual simulators for medical training or surgery planning purposes. Modern graphic display devices offer new opportunities for medical visualization and constantly increasing computational power allows for heavy mathematical modeling needed by real-time simulations of human body. Virtual reality based surgical simulators require efficient biomechanical and physiological models of the organs as well as algorithms capable of providing convincing visualization of the anatomy. Realistic models of the vascularization is one of the most important requirements. Especially abdominal organs are highly perfused by blood vessels which become crucial for virtual simulations of any laparoscopic surgical interventions.

Vascular systems are not just strongly influencing organ appearance as part of their visible surface texture, but also behave like deformable organs with certain mechanical properties. They will also lead to bleeding when cut through. The final goal is therefore, to provide methods which, given an intuitive set of parameters, will generate vascular structures in an arbitrary abdominal organ. Such systems should not only carry geometrical information but also provide data on elasto-mechanical properties of the vascular system and the related blood flow.

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There has been a lot of activity in modeling of vascular systems. A group of models based on physiology has been proposed by A.Anderson and M.Chaplain [1]. Angiogenesis as formation of blood vessels is modeled there as a process where capillary sprouts are formed in response to externally supplied chemical stimuli. The sprouts then grow, develop and organize themselves into branching structures by means of endothelial cell proliferation and migration. The models take into account essential endothelial cell-extracellular matrix interactions via the inclusion of the macromolecule fibronectin. The models consist of a system of nonlinear partial differential equations describing the response of endothelial cells to growth factors and the fibronectin in the extracellular matrix. Although these models are very advanced from biological modeling point of view they still do not fully address all the biophysical issues like flow induced shear stress and its influence on the endothelial cells for example. Even if offering good qualitative understanding of the biological process, the models are not capable of producing any visually convincing results. The outcome is mostly in form of concentration contours or density maps and gives very poor, non-intuitive graphical output.

An interesting model has recently been proposed by R. Gödde and H. Kurz [2]. It covers all important biophysical properties of the flow and accounts for hemodynamic peculiarities like non-newtonian properties of blood. In the first phase an initial growth is performed by means of random assembly of vascular elements, starting from the predefined center and periphery. Then hemodynamic remodeling rules are applied to this pre-generated system of bifurcations which is subsequently grown or degenerated accordingly. Although the graphical output of this advanced model is a little more convincing, it still provides far too regular and too predictable structures not accounting for the variety of natural patterns due to the very simple topology defined by a two-dimensional isometric hexagonal grid.

A more visually oriented group of models have been used by the work of W. Schreiner and P. Buxbaum [3]. In so called *constrained constructive optimization* they were adding new terminal segments to an initial root of a tree according to a set of bifurcation rules. The simulation, performed on a two-dimensional domain, is a global optimization routine for a target function being typically the total vessel volume of the tree. Although the model leads to a homogeneous perfusion of the tissue and an optimal blood flow, it turns out to be too simple to generate complex and unpredictable structures encountered in natural vascular systems. The resulting patterns are too regular and visually not convincing enough.

A. Lindenmayer [4] proposed a mathematical model of cellular interaction known as L-systems. An L-system is an approach which can construct complex objects by subsequent replacements of parts of an initial object using a set of rewriting rules. The concept has been continuously developed over the years resulting in its many extensions, e.g. stochastic, context sensitive or parametric. The stochastic L-systems were used to generate vascular systems by V. Meier [5]. The algorithm he used consisted of two phases. First only a bifurcation pattern was generated from the root toward the leaves. Then, in the second

phase, geometric information of lengths and radii of individual segments was added. This recursive approach is able to produce reasonable vascular structures, they are, however, limited to tree topology and are still not very diverse in visual patterns compared with real cases. Another disadvantage is that the model incorporates no biophysics at all: there is no information on the distribution of pressures, flows and stresses in the system.

Another approach has been described by the same author in order to combine technical methods with some biological aspects. A vessel generation algorithm has been proposed based on simple physiological mechanisms. The metabolic activity of the tissue is represented by a scalar field which depicts oxygen consumption and carbon dioxide production of the tissue. In each simulation step the current O_2 and CO_2 concentrations are computed from perfusion of the tissue by the arterial and venous system. Based on their comparison to the metabolic activity, cells are producing certain biochemical transmitters that can either stimulate or inhibit the local growth of the system. The advantage of this approach is that the growth process is not only treated as insertion of new bifurcations but also allows for fusion of colliding vessels resulting in a network topology of the generated system. In real vascular structures this phenomenon is widely encountered and is known as anastomosis. The disadvantage of this model, however, is still the very little biophysical knowledge incorporated and the omission of capillary plexus formation, although this stage in the maturation of vessels has been experimentally proved to be crucial [6]. Moreover, the blood pressure and flow is not addressed at all and oxygen transport is simply a function of a segment's radius. While the generated visual patterns are of high quality, they are neither diverse nor complex enough to cover the whole range of real physiological cases.

There is therefore still a strong need for a more advanced procedure offering sufficient understanding of biophysical properties on one hand, and good visual quality on the other. The new extended model should include the formation of primitive capillary plexus prior to maturation of the vascular system and treat its later development as a dynamic growth controlled by biophysical factors. This way the dynamic remodeling of the vascular system can be applied, and full information on biophysical properties of the system can be provided at any time. The simulation should take into account existing experimental knowledge of the growing process, namely endothelial cell proliferation, migration and vessel retraction [7], non-newtonian properties of the blood and effects of flow induced shear stress.

2 Definition of the Model

In order to supply a tissue with oxygen and nutrients, and to take away its metabolic wastes, new blood vessels penetrating the growing tissue are formed. This process is called angiogenesis and is one of the most crucial processes taking place in living organisms. In the first stage, as a response to the tissue's oxygen demand, a primitive capillary plexus is created and a tissue becomes

covered/penetrated with a preliminary capillary bed. In the first approximation it is very reasonable to assume that the capillary plexus formation: *(a)* is directly controlled by so called Angiogenesis Growth Factors (AGF): the higher the oxygen demand, the higher AGF concentration, sprouting rate and thus the penetration, and *(b)* leads to effectively random connections between capillaries. Detailed issues like different AGF response from arterial or venous cells will not be considered here. In the next stage the network grows and remodels in order to assure the optimal blood supply and disposal of wastes, and that's where the main differentiation of vascularity's random shape comes into play. The third process contributing to the final pattern of the vascular system are external forces or forces resulting from the shape change of the growing tissue. It happens very often that the development is very rapid and actually all the three processes are either overlapping or even taking place at the same time.

The proposed model consists basically of two parts:*(i)* creation of a preliminary capillary plexus and *(ii)* vascular growth according to biophysical and hemodynamic rules. External forces and shape change of the tissue will not be addressed in this version of the model. The first part should be realized by a general purpose generator capable of producing random network structures with adjustable patterns. The input for the algorithm should contain information corresponding to a metabolic map of the tissue (oxygen demand and disposal of wastes). This way the pattern of the resultant vascular structure will depend on the tissue's function and its metabolic rate, which is much different in muscles or nerves (where oxygen demand is high) than in cornea (which plays mostly a structural role).

From the technical point of view the capillary network is handled by a graph of connections and is represented by an adjacency matrix containing information on connections between the network's individual nodes. Each connecting vessel is ascribed a flow conductance dependent on the geometry of the vessel. The vessels are assumed to be straight elastic pipes of radius r and length L. In case of a laminar flow through a pipe, the ratio between the flow and the pressure difference inducing it is constant (so called Hagen-Poiseulle's law) and, based on analogy to electricity, called conductance $\mathcal{G}$:

$$\mathcal{G} = \frac{\mathcal{Q}}{\Delta p} = \frac{\pi r^4}{8\eta L} \ , \tag{1}$$

where $\mathcal{Q}$ is a flow induced by a pressure difference Δp, $\mathcal{G}$ is a vessel's conductance, η stands for blood viscosity and L for a vessel's length. Note, that in case of non-Newtonian fluid like blood, the viscosity is non-constant and becomes a function of a vessel's radius ($\eta = \eta(r)$), a phenomenon known as Fahraeus-Linquist effect. In the presented study a rough fit on experimental data has been used.

In order to calculate the hemodynamic variables needed to control the growth of such a capillary network, the nodal analysis from the theory of electrical circuits has been customized. In this method the network behavior is described by a matrix equation of the form:

$$\mathbf{Q} = \mathbf{G} \cdot \mathbf{p} \ , \tag{2}$$

where $\mathbf{Q}_i$ is a source flow entering ith node, $\mathbf{p}_i$ is a pressure at ith node and $\mathbf{G}$ is so called *Nodal-Admittance Matrix* derived directly from the network's adjacency matrix carrying the conductance information on the system's structure.

The problem of finding individual pressures is therefore equivalent to finding the inverse of the Nodal-Admittance Matrix allowing then to derive all further biophysical and hemodynamic quantities like flow, wall tension, shear stress, oxygen transport etc. This information can then be used for remodeling and the system can grow according to the following rules:

1. When a certain threshold is exceeded a vessel may increase its diameter in order to resist the stretching force,
2. A vessel can increase its diameter only when neighboring vessels have enough endothelial cells to support vessel formation and/or when cell proliferation rate is high enough to provide sufficient number of cells,
3. Endothelial cell recruitment (migration and proliferation) depends on the shear stress at the vessel wall and a local concentration of AGF:

$$\mathcal{S} = \frac{4\eta\mathcal{Q}}{\pi r^3} = \frac{\Delta p \cdot r}{2L} \ , \tag{3}$$

$$\mathcal{AGF} = const(O2_{demand} - O2_{delivery}) \ . \tag{4}$$

4. When the flow drops below a threshold the vessel can be deleted, and its cells can be contributed to the neighbors,
5. Oxygen transport through the vessel depends on the wall tension given by:

$$W_T = \frac{p_t \cdot r}{w} \ , \tag{5}$$

   where p_t is so called transmural pressure defined as the difference between the pressure inside and outside the vessel, and $w = w_0 e^{r/r_0}$ is the wall thickness fitted to experimental data. In order to calculate the total amount of oxygen transferred through a vessel integration over its surface must be performed. Note that this increases with the pressure and the diameter on one hand but quickly drops down with the wall thickness on the other hand. Therefore there should be an optimum in oxygen delivery for certain flow conditions.
6. When the tissue gets sufficient amount of oxygen (the system enters a dynamic equilibrium) no more AGF is being produced (no more cell recruitment) and the remodeling stops.

3 Results

A configurable generator to create random network structures has been developed in C++. The code is based on random walk algorithm and is capable of generating a wide range of different structures - from regular homogeneous grids and loops to very irregular and unpredictable patterns. The generator offers many parameters influencing the geometry of the network and an unlimited number of starting points or vessels with given initial properties. The vessels' mean

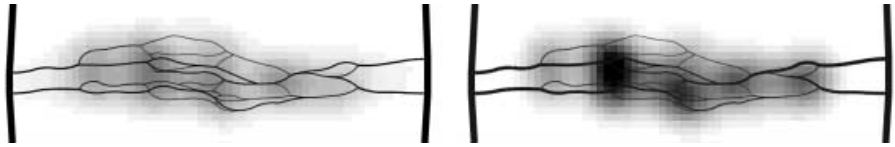


Fig. 1. Result from a simulation of a small test capillary system: an initial *(left)* and optimal *(right)* stage against the corresponding oxygen concentrations.

lengths and diameters, preferred global and local angles, bifurcation parameters and curvature are generated according to predefined probability distributions (uniform, normal, logarithmic normal). Any arbitrary probability distribution is also allowed facilitating future relation of growth probabilities to the metabolic map of the tissue. All the parameters can be interdependent and can also be an arbitrary function of vessel age. A collision detection of line segments has been implemented which is used for simulating fusion with certain segments (anastomosis) and/or avoiding selected vessels (e.g. to prevent so called arterio-venous malformation or to test if there is enough space to create a vessel). The program has been written in standard C++ and outputs a list of segments carrying information on a particular segment's geometry (2D or 3D), age, and branching generation. These geometrical structures can then be visualized, studied or remodeled by a separate C++ codes using appropriate libraries. If blood vessels and capillaries are modeled as a network of very many small tubes it is possible to use this code to generate preliminary capillary beds forming bases for further growth. This approach may seem somewhat random, but firstly, by its randomness it offers a big diversity of network patterns, and secondly, the distribution of parameters can be actually related to physiology. For example, growth angles can be related to the concentration of angiogenic factors and metabolic activity of the tissue, lengths can depend on external physical forces or deformations etc. This option will be implemented in the later, refined version of the program.

A code to calculate the pressure, flow and stress distributions in a flow network has been separately developed in C++. The output data of the capillary plexus generator is converted into an adjacency matrix of network connections, which can then be used to solve the biophysics of the whole system using the Nodal-Admittance Method described before. The previously described random walk algorithm was used to generate a sample vascular structure and the *vnl_sparse_matrix_linear_system* and *vnl_lsqr* classes from the VXL package ([9]) were used to solve the linear problem. Figure 1 shows a preliminary result from a simulation of such a small test capillary system. The thickest vertical lines are pre-existing mother vessels. In-between there was a tissue with a simple metabolic map. First all mother vessels sprouted towards the tissue creating a capillary bed having more or less equal diameters. This corresponds to the first part of the simulation, where random connections between capillaries are established. In the second part hemodynamics driven remodeling was carried out and oxygen transfer was calculated for every iteration step. An optimum between oxygen delivery and complexity of the system has been found, like in

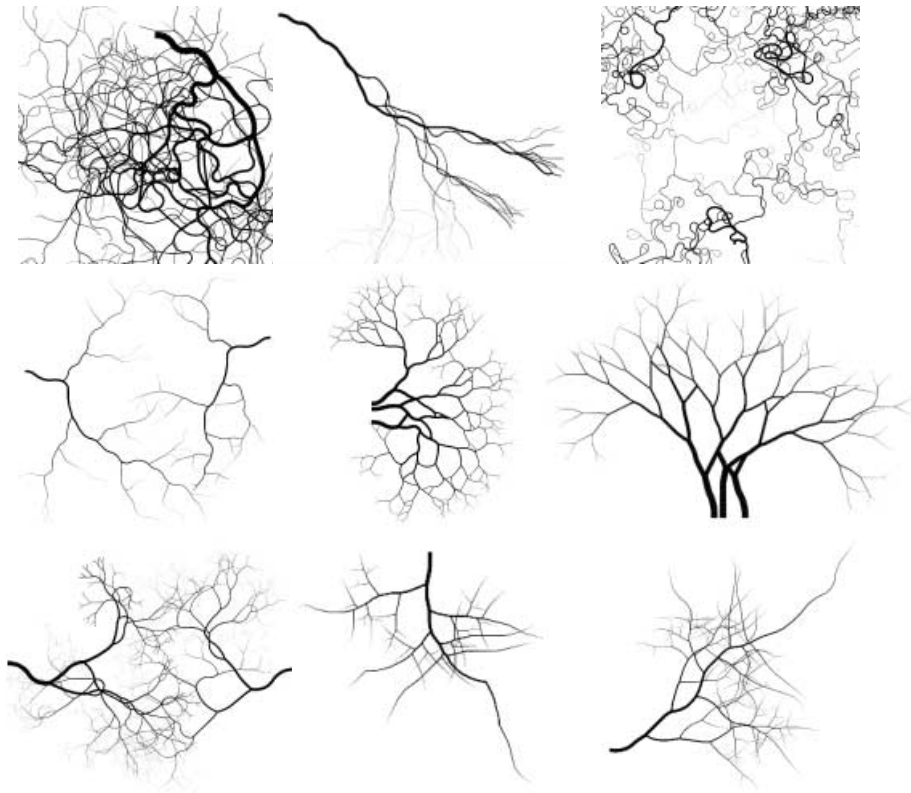
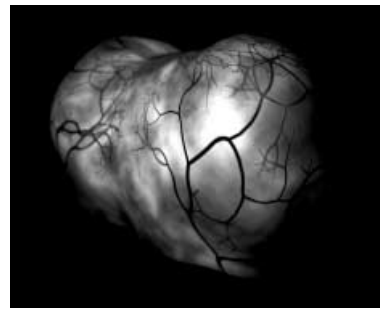


Fig. 2. Some structures generated by the code discussed in the text. Pictures in the second row show structures generated using collision detection. Full resolution images are available at `http://www.vision.ee.ethz.ch/~domi/angi/`

normal living tissues. First, when only a capillary bed is present, the oxygen delivery is insufficient. Although the oxygen perfusion probability is high (because the walls are thinnest), there is not enough flow through the system, so not enough oxygen particles are delivered to the tissue. Growing vessels are increasing their diameters (thus increasing the flow), but as their walls become thicker the perfusion probability drops and the oxygen delivery is not any more sufficient. Figure 1 shows an initial and optimal stage of the system against the corresponding oxygen concentrations.

Because of low speed of the remodeling part of the algorithm a simplified version has also been implemented. Instead of correct hemodynamic remodeling the diameters of the segments were simply related to the vessel's age. As can be seen from resulting structures (Figure 2), even such a naive "remodeling" rule produces convincing visual results. This is biologically incorrect in general, but is very fast and can be a choice when the speed has a higher priority than physiological correctness.

Figure 3 shows one of the resulting vascular structures mapped onto an artificial myoma generated for surgical simulation purposes [8].



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4 Outlook

It is still necessary to improve the robustness of the program. Reducing the number of parameters or possibly representing them in the form of some distribution maps would also make the algorithm more convenient to use. Tests with other algorithms to solve the linear problem are underway while first approaches to implementation of the third dimension as well as retraction and merging of neighboring vessels are planned for simulation in the future. At present, the metabolic activity of the tissue is represented by a static concentration map and arterial and venous parts of the system are coupled. It would be very interesting to see how a dynamically evolving metabolic map influences the growth of the capillary system and how the system changes if the arteries and veins are decoupled. It would also be interesting to perform tests with switching some of the remodeling factors on/off. This could allow for some simple studies on abnormal development of vascular systems. In parallel, experimental data is being gathered to compare real distributions of biophysical quantities to the ones obtained with the simulation.

Acknowledgments

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