Using network descriptors for comparison of vascular systems created by tumour-induced angiogenesis

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Abstract: We check-out a set of statistical network descriptors for classification of various vascular networks generated by model of Tumour Induced Angiogenesis. In the model two spatio-temporal scales representing global behaviour of vascular network and local processes in surround tissue are clearly separated. The grid of cellular automata (CA) corresponds to both healthy and cancerous tissues as well as it is used as the environment for simulating the fast processes of nutrients ($O_2$) and TAF (tumour angiogenic factors) diffusion. Vascular network is modelled by using irregular graph of cellular automata placed on the top of CA grid. The model is controlled by a selected set of parameters reflecting influence of various factors such as: TAF and $O_2$ concentration and model parameters responsible for vessels sprouting and anastomosis. We discuss an application of single network descriptors against approach based on using a set of various descriptors subjected multidimensional analysis method.

Keywords: Cellular Automata, Tumour Induced Angiogenesis, Network descriptors

1. Introduction

Angiogenesis is the process of formation of blood vessels. Mainly, it occurs in embryogenesis when the new network of arteries, capillary vessels and veins is formed from endothelial precursors [1]. In adulthood it is very rigorously controlled by wide range of stimulators and inhibitors [2]. Their very precise balance make this process quiescent except tissue healing, placenta forming during pregnancy and in the cycling ovary. The angiogenic process can be activated by various metabolic or mechanical stresses (low $O_2$ (hypoxia), low $pH$, or local rapid proliferation of cells) [2].

Oxygen and nutrients penetrate the tissue only in a certain distance from the vessel. Distant cells, influenced by metabolic stress, synthesize angiogenesis stimulators such
as VEGF (Vascular Endothelial Growth Factor) and bFGF (Basic Fibroblast Growth Factor) [2], [7]. Stimulators migrate towards the nearest blood vessels. When they reach the vessel, the endothelial cells (ECs) that lines the wall of this vessel are activated. They start to proliferate and migrate towards the tumour cell attracted by VEGF and other stimulators. The wall of the parent blood vessel becomes degraded and it opens to a new capillary. Migrating and proliferating ECs form a hollow tube-like cavity (the lumen), which are stabilized later by smooth muscle cells and pericytes. Finally, a new capillary vessel becomes fully functional.

Cancer development can push the process of angiogenesis out of balance state. Solid tumours smaller than 2 mm in diameter remove waste and acquire nutrients and oxygen through passive diffusion. However, in order to advance beyond this quiescent size, tumours must induce the formation of a new vasculature. Although some neoplastic masses can crudely vascularize by developing internal channels or exploiting normal tissue vessels, in most cases an angiogenic switch [8] is triggered. Also mechanical stresses appear due to uncontrolled proliferation of tumour cells. In consequence “starving” and crowded tumour cells produce VEGF, bFGF and other stimulators of angiogenesis described in this case as Tumour Angiogenesis Factors (TAFs). Neighbouring vessels, activated by TAFs, start sprouting, and develop toward tumour tissue. Due to imbalance of angiogenic factors new vessels form a highly chaotic and disorganized network [9]. Moreover, their walls have a pathological form, i.e. they are thin and permeable, their diameter changes abruptly etc.

Inhibition of tumour-induced angiogenesis is the most promising strategy in anti-cancer therapy [1], [2], [5]. However, clinical tests show that none of the tested inhibitors did success in broad range types of cancers [1]. Monotherapies fail because angiogenesis is controlled by very complex balance of stimulators and inhibitors. Most of the currently tested therapies targeted preventing activity of endothelial cells. The inhibitors not only suppress ECs proliferation but also initiate their death what follows to vessels regression. On the other hand treatment directed toward normalizing chaotic structure and abnormal architecture of tumour induced vessels can improve drug delivery to tumour tissue.

Building model of any physical process requires their verification. We have to check whether the simulation results qualitatively and quantitatively follow the reality. In case of complex networked structure such the verification is not trivial. We need a parameter that will be able to display their structural properties. Unfortunately there is no such the universal descriptor. Instead, we use the feature vectors of statistical descriptors, hoping that these features, as an ensemble, will be able to discriminate the network having the structure we are looking for. Then we analyse the multidimensional space of feature vectors using pattern recognition tools.

In the following section we present foundations of our model. Next we present the application of single graph descriptors as well as the set of descriptors for vascular network classification. Finally, we discuss the conclusions.
2. The model

The model is founded upon the concept of transportation network and consuming (or producing) environment [10], [11], [12]. The network delivers certain resources to the system, where they are absorbed and changed into progress of the environment. Changes in the environment influence network structure. The system leads to the state of dynamic balance, when the whole environment is equally supplied. An anastomosing river [13] as well as a vascular system [12] are good examples of such the phenomenon.

The model [12] incorporates paradigm of continues cellular automata [14] with graph structure. Regular mesh of cellular automata represents consuming or producing environment. The distribution processes occurring in the environment are represented by cellular automata rules of local interactions. Moore neighbourhood is applied. The graph structure is constructed over the mesh of automata by selecting some cells and establishing additional relations of neighbourhood (see Fig. 1).

![Graph of Cellular Automata](Fig. 1. The idea of Graph of Cellular Automata)

The model of tumour induced angiogenesis we present in this paper use mesh of cellular automata for modelling extracellular matrix. Some cells are marked as “tumour cells” and acts as a source of TAF (Tumour Angiogenic Factors). Our tumour remain in stable state and it does not growth nor disappeared, only react for hypoxia. Tumour cells that are deprived oxygen produce TAFs. Diffusion of TAF and oxygen are modelled by using cellular automata rule of local interactions [3]. Network of capillary vessels is modelled by irregular structure of graph. It emerges from selected cells of the mesh connected with additional relation of neighbourhood. Such structure support flow calculations. In our model nodes of graph with blood flowing acts also as $O_2$ supplier in CA model. Summarizing our model is constructed as follows:

1. Cellular Automata model:
   - regular mesh in 2D or 3D space;
• Moore neighbourhood;
• cell states: “normal”, “tumour”, “hungry”, “$O_2$-supplier (“flow” in Graph);
• cellular automata rules: TAF distribution, $O_2$ distribution;

2. Graph structure:
• irregular structure represented by graph;
• neighbourhood defined by set of edges;
• cell state: “tip”, “immature” “mature”, “flow” ($O_2$-supplier in CA);
• rules: growth, branching, anastomosing, maturation;
• globally calculated flow;

The model of capillaries growth is constituted around the assumption that the motion of an individual endothelial cell located at the tip of a capillary sprout governs the motion of the whole sprout. The motion of an individual cell at the sprout-tip is therefore governed by its interactions with angiogenic factors and matrix macromolecules in its microenvironment. In addition we also explicitly incorporate the processes of branching, anastomosis and cell proliferation into our discrete model.

Summarizing, the assumptions laying behind our model [12] are as follows:

1. tumour cells neither migrate nor proliferate,
2. tumour cells in hypoxia produce TAFs at a constant rate,
3. TAFs diffusing through the tissue establish gradient of TAFs concentration,
4. TAFs concentration exceeding certain threshold activates endothelial cells in existing vessels,
5. only “mature” vessels are able to create sprouts,
6. sprouts grow is TAF gradient directed (chemotaxis),
7. a new vessel have to “mature” before it can be able to fulfil its function.

Most of these assumptions are based on real observations, however some of them are only hypothesis or they were included for the sake of clarity of the algorithms.

Main parameters that tune our model is as follows:

1. $t_g$ — TAFs gradient coefficient.
2. $o_g$ — Oxygen gradient coefficient.
3. $tt_{mat}$ — TAFs threshold that triggers branching for mature vessels.
4. $tt_{amat}$ — TAFs threshold that triggers branching for immature vessels.
5. $bp_{mat}$ — Branch probability for mature vessels.
6. $bp_{umat}$ — Branch probability for immature vessels.
7. $o_h$ — Oxygen threshold that triggers hypoxia.
8. $m_s$ — Maturity speed.
9. $m_a$ — Maturation age.

Other important aspects of angiogenesis such as blood flow through the capillary network, with potential application to drug delivery and optimization of chemotherapy are also included in this model.

![Sample 2-dimensional vascular network generated by using presented model](image)

**Fig. 2.** Sample 2-dimensional vascular network generated by using presented model

### 3. Network descriptors

Vessels encoded in graph structure provide quantitative measurement of the structure of the new vasculature (surface area, volume, vessel number, fractal dimension, extent of basement membrane etc.). However application of single descriptor does not display clear distinction between structures generated with different sets of parameters. As shown in Figure 4 diagrams may partially overlap or cross what makes classification hard or unable.

An application of several different descriptors can overcome this problem. Treated together as n-element feature vector and subjected multidimensional analysis can clearly separate resulted vascular network in parameter space. In our investigations we applied a selected collection of statistical graph descriptors (detailed description in literature i.e. [6]).
Fig. 3. Sample 3-dimensional vascular network. Tumour cells are located on the top side of the box.

Fig. 4. Sample classification of 3D vascular network by using Wiener Normalized Index. The network were generated with different values of $bp_{umax}$ parameter.
1. **Graph diameter** — is the maximum length of the distance between any two vertices: \( \text{diam}(G) = \max_{u,v \in V} d(v, w) \), where \( d(v, w) \) is the distance between vertices \( v \) and \( w \).

2. **The A/D index** — defined as \( A/D = \frac{2m}{\sum_{v \in V} \sum_{w \in V} d(v, w)} \), where \( m = |E| \).

3. **The B Index** — defined as \( B(G) = \sum_{v \in V} \frac{\deg(v)}{\deg(v)} \), where \( \deg(v) = \sum_{w \in V} d(v, w) \).

4. **The Wiener index and the normalized Wiener Index** — is calculated as the sum of lengths of shortest paths between every pair of vertices: \( W(G) = \frac{1}{2} \sum_{v \in V} \sum_{w \in V} d(v, w) \).

5. **The Randić Connectivity Index** — defined as \( \chi(G) = \frac{1}{2} \sum_{(v,w) \in E} (\deg(v) \cdot \deg(w))^{-1/2} \).

6. **M₁ Zagreb Index** — defined as \( M_1(G) = \sum_{v \in V} (\deg(v))^2 \).

7. **Connectivity** — is a ratio of number of edges to maximal possible number of edges: \( \text{Conn}(G) = \frac{2m}{m(m-1)} \), where \( n = |V| \) and \( m = |E| \). It can be interpreted as a density of edges in the graph.

8. **Total Adjacency Index** — defined as \( A(G) = \sum_{v \in V} \deg(v) \).

In the experiments presented here we have produced two sets of results (denoted as A and B), each consisting of three clusters of networks (0,1,2). All networks has similar size. Each set represents changes in different parameters (A — \( tt_{mat} \), B — \( tt_{umat} \)). The clusters were generated during simulations differing in only one (the same) parameter, while single cluster consists of networks obtained for the same set of simulation parameters. We generate 10 networks for each set of parameters. Because the simulations are stochastic, two different networks are generated in two different runs.

Consequently, every vascular network is represented by the 8-dimensional feature vector. The features (network descriptors) are normalized. We use the algorithm of multidimensional scaling (MDS) to visualize original 8-dimensional feature vectors in 3-D target space [4]. Each of point from Figs 6 and 8 corresponds to single feature vector (network). As shown in Fig. 6 we can observe distinct clusters of points relating to the respective clusters of networks 0,1,2. The spread of these clusters shows the sensitivity of descriptors on statistical fluctuations in network shapes generated for the same parameters set, while their separation reflects structural changes in networks caused by the changes in one simulation parameter. Analysing visually in Fig. 5 the networks belonging to various clusters it seems to be obvious that the three clusters must be separated also in the feature space. However, the picture is not so clear for B set (Fig. 7) though we can also observe three separate clusters in the corresponding feature space (see Fig. 8). This shows that the network descriptors could be used as very structure-sensitive features, discriminating the networks generated using, e.g., different simulation parameters.
Fig. 5. Data set A: four samples for each cluster generated with three different values of $tt_{mat}$ parameter:
“0” - 0.08, “1”-0.16, “2”-0.32.
4. Conclusions

The analysis of graphs using statistical descriptors has recently gained interest as efficient and accurate method for characterization of complex networks, in particular those of biological origin. We propose to use it as a methodology for validation of the simulation accuracy.

So far we show preliminary results displaying that the statistical network descriptors can be used as a sensitive tool for discriminating structural changes in vascular networks caused by the changes in the parameters of the model of the process of angiogenesis. On the other hand, they are semi-invariant on particular realization of the simulation (initial conditions, randomness, geometry etc.) for the same set of model parameters. Nevertheless, our preliminary results show that the separation of clusters corresponding to different simulation parameters compared to they spread leaves room for improvement. The reason is that the set of descriptors we have used was selected arbitrary, without deeper analysis. More sophisticated approach involves additional expertise and deeper insight in both medical images of real tumour vasculature and the simulation results for broader set of parameters.

In the nearest future the development of our simulation model will be tightly coupled with data from in vivo experimental results. The rigorous approach based on pattern recognition methods and feature vectors representing vasculature will allow for direct comparison of medical images and the results produced by the computer model. Furthermore, the analysis variations in the values of the descriptors during tumour development and after admission of various treatments may lead to better understanding of structural changes in vasculature occurring during these processes. This could result in obtaining knowledge having direct impact on both planning and monitoring the antiangiogenic therapy.
Fig. 7. Data set B: four samples for each cluster generated with three different values of $t_{umat}$ parameter:

“0”-0.1, “1”-0.2, “2”-0.5.
Fig. 8. Feature space for clusters from data set B visualized with MDS

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References


Zastosowanie deskryptorów sieciowych do klasyfikacji sieci naczyń krwionośnych generowanych przy pomocy modelu angiogenezy stymulowanej rozwojem guza litego

Streszczenie

W artykule przedstawiono metodę klasyfikacji sieci naczyń krwionośnych generowanych z użyciem modelu angiogenezy stymulowanej rozwojem guza litego przy użyciu zespołu statystycznych deskryptorów sieciowych. W prezentowanym modelu angiogenezy dwie skale przestrzenno-czasowe skale reprezentujące odpowiednio globalne zachowanie sieci naczyń oraz lokalne procesy zachodzące w tkance zostały wyraźnie rozdzielone poprzez zastosowanie różnych paradygmatów modelowania. Regularna siatka Automatu Komórkowego obrazuje zdrową oraz zajętą przez nowotwór tkankę. Lokalne reguły przejścia automatu komórkowego modelują procesy dyfuzji tlenu, substancji odżywczych oraz czynników angiogenezy. Sieć naczyń krwionośnych przedstawiona jest przy pomocy nieregularnej struktury Grafu Automatu Komórkowego konstruowanego nad siatką klasycznego automatu komórkowego. Dla modelu zdefiniowano szereg parametrów odzwierciedlających wpływ czynników takich jak tempo dyfuzji czynników angiogenezy i tlenu, tworzenie rozgałęzień i anastomoz. W artykule przedstawiono wstępne wyniki symulacji oraz zademonstrowano wyniki badań zastosowania zespołu deskryptorów sieciowych do klasyfikacji otrzymanych wyników.