A new model of tumor progression based on the concept of complex automata driven by particle dynamics

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Abstract

Angiogenesis, the growth of a network of blood vessels, is a crucial component of solid tumor progression, linking avascular and the potentially fatal vascular growth phases. Existing computational models assume that the interaction between tumor and vasculature takes place mainly via two concentration fields: the oxygen originating in the vessel network and the growth factor originating in the tumor cells. The dynamics of growing tumor involving mechanical remodeling of healthy tissue and vasculature are neglected in most of the models. This is due to the lack of efficient computational framework allowing for simulation of mechanical interactions. Meanwhile, just these interactions trigger global changes in tumor growth and are responsible for its volumetric and directional progression. We describe here a novel 3-D model of tumor growth, which combines particle dynamics with cellular automata concept. The particles represent both tissue cells (spherical particles) and fragments of vascular network (tube-like particles). They interact with their closest neighbors via semi-harmonic central forces simulating mechanical resistance of the cell walls. The particle dynamics is governed by both the Newtonian laws of motion and the cellular automata rules. These rules can represent cell life-cycle and other biological interactions involving smaller spatio-temporal scales. The particles (cells) can replicate by a simple mechanism of division, similar to that of a single cell reproduction and die due to apoptosis or necrosis. We introduce also diffusive substances (such as nutrients or signaling cues) which are described by means of continuum fields. We use Kirchoff’s laws to calculate the hydrodynamic quantities in each blood capillary. In this sense, our model represents extension of cellular automata paradigm (CA) to the complex automata (CxA), where the CxA nodes correspond to moving particles while their states evolve both accordingly to the regular CA rules and with dynamically changing continuous fields. We conclude that our concept can serve as a general framework for designing advanced multiscale models of tumor dynamics and is very competitive to the approaches presented before. The CxA particle based model can reproduce realistic 3-D dynamics of the entire system consisting of the tumor, normal tissue cells, blood vessels and blood flow. It can explain such the phenomena like: inward cell motion in avascular tumor, stabilization of its growth due to external pressure, trapping of healthy cells by invading tumor, remodeling of tumor vasculature due to the pressure inside the tumor, influence of external (boundary) conditions on the direction of tumor progression. We concluded that this computational framework can be used for developing computational models reproducing multi-scale dynamics of the particle ensembles in sub-scales ranging from diffusion of cytokines, blood flow up tumor growth and vascular network expansion.

Keywords: tumor progression, angiogenesis, computer simulation, complex automata, particle model

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1. Introduction

Despite the huge amount of resources that have been devoted to cancer research, according to National Center for Health Statistics (http://www.cdc.gov/nchs/FASTATS/lcod.htm), cancer is the second killer (after heart disease) in US. The set of diseases, which are categorized as cancer, are characterized by serious disruptions in the control mechanisms regulating growth and homeostasis in normal tissue. Up to now many aspects of cancer remain obscure for experimentalists and clinicians, and many of the currently used therapeutic strategies are not entirely effective.

A better understanding of the dynamics of tumor formation and its growth are expected from computer models and simulations. The modeling could improve the overall clinical outcome by predicting the results of specific forms of treatment administered at specific time points. Moreover, it might help to optimize the existing therapeutic procedures, design new ones, or even provide post-treatment predictions [5,21,34,43]. The degree of angiogenesis in human tumors varies widely and may be very low in some types of tumors. Therefore, tumors with a low level of angiogenesis may not be benefited when treated with antiangiogenic agents [16,21]. Computer modeling of tumor progression involving its both avascular and vascular phases, could allow for answering the question if the angiogenic therapy is justified or not in these uncertain cases.

Nevertheless, we should be aware of the computer modeling limitations from which the most important are as follows:

1. Tumor evolution is a complex process involving processes occurring over a variety of time and length scales: from the DNA level and intracellular processes, through tumor vascularization and metastasis, to the holistic, mental and environmental factors. Therefore, many aspects of tumor development can be investigated on a case-by-case basis. Meanwhile, the replication of living organism in silico is a computationally irreducible problem due to impassable barriers of the theory of computation, the theory of chaos and technological limits.

2. There is no well defined mathematical and computational methodology and adequately large computational resources for modeling truly multiscale phenomena. Till now, no significant progress is being made in this direction.

3. Even well known physical processes occurring in the real tissue, such as diffusion and blood flow, which can be described using partial differential equations (PDEs), become intrinsically complex to solve. This is due to the intricate boundary conditions imposed by inhomogeneous environment (e.g., extracellular matrix (ECM) structure, blood vessel structure, blood rheology etc.), incomplete parameter space and non-linear reaction terms.

Although global modeling of cancer development is impossible, more selective approach focusing on basic carcinogenic processes can allow for substantial reduction of both many methodological problems and computational resources. The approximate theories and numerical models can be used then to detect more precisely the cancer “points of failure” - the future targets of anticancer therapeutic strategies.

We focus our attention on the process of tumor growth from avascular phase to angiogenic phase, i.e., the process of the blood vessel formation from a pre-existing vasculature. Judah Folkman published in 1971 the theory [19] that angiogenesis is a principal process in tumor progression [17,20]. Vascularized tumor invades the surrounding tissue, blood and lymphatic vascular systems and the possibility of the cancer spreading (metastasis) increases dramatically. Antiangiogenic targeting of the neovasculature within tumors is currently considered as one of the most promising strategies in the search for novel antineoplastic therapies [3,19,21]. Because molecular phenotype of immature, angiogenic blood vessels is distinctly different from that of
resting blood vessels, tumor blood vessels can be selectively targeted without affecting the normal organ vasculature. The process of angiogenic signaling and formation of blood vessels can be disrupted or slowed down with small molecules. In addition to treatments directed to specific target, non specific agents can be used to eliminate endothelial cells thus inhibiting angiogenesis. This involves numerous expensive and demanding investigations both of hundreds of factors inhibiting angiogenesis and antiangiogenic chemical species which can be considered in drug design process. To cut expenses, the predictive power of mathematical modeling and computer simulation has to be employed. As shown in [6], in silico experiments can play the role of angiogenesis assays.

In this paper we present the concept of complex automata driven by particle dynamics as simulation framework, which is very competitive to existing paradigms used in modeling of tumor progression. We show its impact in: simulating mutual mechanical interactions between normal, tumor and vascular tissues, realistic three-dimensional visualization, and its inherent potential to be a framework of more advanced truly multi-scale models. To transfer the phenomenological observations into a computer model, we define the simplified metaphors of tumor progression in its avascular and vascular phases. In the following section we shortly present the main processes, phenomena and growth factors contributing cancerogenesis, which are included in various computational models of cancer proliferation. Then we present the most advanced concepts and models of tumor growth including continuum, cellular automata and hybrid models. We focus on such the modeling aspects as cell cycle, tumor growth factors, angiogenesis, blood flow and vessel remodeling. Next, we describe the model of complex automata driven by particle dynamics and we discuss its assumptions, limitations and simulation conditions. The following section collects the results from simulation of avascular and vascular phases of tumor growth. We scrutinize the role of mechanical interactions between swelling tumor, normal tissue and expanding vascular network on tumor dynamics. We explain the influence of mechanical interactions on compartmentalization of the avascular tumor into external shell of well oxygenated cells, deeper layer of cells in hypoxia and necrotic interior. We study the effect of mechanical remodeling on tumor progression in vascular phase and on differentiation of microvascular density in various regions of tumor. The role of processes involved in branching and vessels maturation, such as (Dll4) – Noch1 signaling [25,39], is analyzed. The results are confronted with experimental studies. For simplicity we do not discuss a parallel to blood vessel, lymph vessel network which assist normal tissue and tumor with lymph outflow and decrease in extracellular matrix pressures. This network is a critical component of tumor metastases pathway, however is only minimally involved in dynamics of tumor growth. In the last section we discuss the conclusions.

2 Simplistic model of tumor growth

Generally, we can recognize a few principal phases of tumor progression, representing various spatio-temporal scales [1,5,32,40].

1. Subcellular scale - involves genetic changes, distortion in the cell cycle and loss of apoptosis, absorption of vital nutrients.
2. Cellular scale – comprises interaction and competition at the cellular level with immune and environmental cells, activation and inhibition of the immune system. The cellular scale refers to the main activities of the cells: activation and proliferation of tumor cells and competition with immune cells.
3. Avascular tumor scale – includes condensation of tumor cells into cluster, macroscopic diffusion of TAF (tumor angiogenic factors) and oxygen.
4. Angiogenic phase – involves angiogenesis, sprouting, anastomosis, angiogenesis termination.
5. Vascular phase – includes blood flow, remodeling (vessel dilation and regression, mechanical reshaping of tumor and vessels), vessel maturation.
6. Detachment of metastases and invasion.

Fig.1. The scale separation map of the main processes considered in tumor-induced angiogenesis.

In Fig.1 we present the scale separation map (SSM) for this simplified model of tumor growth. The microscopic processes such as cell motility, cell cycle, and cell live cycle are discrete. The macroscopic scale refers to phenomena which are typical for continuum systems: diffusion (oxygen, TAF), overall tumor condensation, blood flow. In macroscopic models microscopic phases can be approximated by coarse grained, models as long as the methodology of multi-scale simulation or adequate computational resources are lacking. The arrows in Fig.1 show dependences between these processes. The particle model presented in the following sections refers only to the processes shaded in dark.

Four overlapping phases of growth are usually identified: the avascular phase, the angiogenic phase, the vascular phase and vessels and tumor remodeling. These phases go with such the physical processes like nutrients and TAF diffusion, blood flow and mechanical remodeling caused by interaction between growing tumor, vessels and the normal tissue.

**Avascular tumor:**
The cell cycle is the set of events which, eventually, leads to cell division. During the cell cycle a cell duplicates each of its components. The growth of tumor body is a consequence of the unique properties of cancerous cell cycle such as: almost unlimited ability of reproduction, escape from apoptosis, competitive advantage over normal cells and adaptation to hypoxic – low oxygen concentration – conditions [1]. The dynamics of the cell division cycle can be affected by the extracellular conditions, in particular by the level of oxygen [18,28,33,49]. In normal cells, hypoxia slows down the division process and may induce apoptosis, whereas in cancer cells and
cancer stem cells apoptotic signals are evaded and cells enter into quiescent phase, i.e., a latent state in which most of cell functions, including replication, are suspended. This ability provides the cancer cells with an amazing resistance to hypoxia [20,26].

The proliferating tumor cells start to condensate into a compact cluster and interact with the external environment. Solid tumor, which is smaller than 1-2 mm in diameter (about 10⁶-10⁷ cells [3]), removes wastes and acquires nutrients and oxygen through passive diffusion. The oxygen (and nutrients) is supplied to the tumor nucleus by the closest, mature blood vessels. It percolates through the surface of the solid tumor and diffuses inside its body. Due to differences in concentration of oxygen, the tumor cluster consists of the outer region with proliferating cells, an intermediate region of cells in hypoxia and the necrotic core of dead tumor cells. Most solid tumours, even those 1–3mm in diameter, exhibit hypoxic fractions that may range from 10 to 30% [3,30,41]. The avascular tumor is in dynamic equilibrium. Its critical mass has been reached, and diffusion based transport is no longer efficient for proliferation-dominated growth. Tumor size is regulated by proliferation speed, oxygen penetration depth and the external pressure [41].

The cells in hypoxia produce set of cytokines (TAF) such as growth inhibitory factors (GIF), and growth promoting factors (GPF) [26]. Just the GIF and GPF concentrations influence both the tumor and endothelial cells proliferation rate and boosts a new angiogenic phase of tumor growth. The tumor is ready to attract external blood supply from the adjacent parent vessels to acquire necessary oxygen and nutrients.

**Angiogenesis:**

The process of tumor-induced angiogenesis is initiated by tumor cells with the shortage of oxygen supply triggering the release of angiogenic growth factors [7,17,19,20,33]. Among many tumor angiogenic factors (TAF), Vascular Endothelial Growth Factor (VEGF) has been identified as one of the key components [7]. These cytokines, released from the tumor cells in hypoxia, diffuse through the extracellular matrix (ECM) – the biological material between tumor and existing vasculature - and produces a chemical gradient. Once VEGF has reached a vessel, it binds to the receptors located on endothelial cells lining blood vessel walls. This stimulates several enzymes (e.g. metalloproteinases) to degrade of basement membrane and sets off a cascade of events which triggers the outgrowth of new vessel sprouts [7,19,20]. Endothelial tip cells proliferate and migrate through the ECM. The tip cells follow along the VEGF gradient towards regions of higher concentration (chemotaxis) [45]. As shown in [7,45], in addition to the soluble isoform of VEGF, the presence of other VEGF isoforms significantly influence morphology of capillary network formation. Among other components involved in the process of angiogenesis is fibronectin - the high-molecular-weight glycoproteins distributed in the ECM and released by migrating tip cells [34, 35, 44]. Fibronectin establishes an adhesive gradient (haptotaxis) which serves as another migration force for the ECs. In addition to these two cues, the fibrous structures of ECM influence cell migration in fiber direction [2,35].

After initial sprouts have extended into the ECM for some distance, repeated branching of the tips can be observed. This causes numerous tip-to-sprout transitions. The newly formed vessels may form loops in a process called anastomosis. Along with anastomosis, the formation of lumen establishes a network that allows the blood circulation. The blood starts to circulate in the parts of network where the blood pressure gradient exists. There exist many factors which both promote and inhibit the process of angiogenesis (see overview in [7,17,20,32,45]). One of recently discovered factors, which is critical in process of angiogenesis, is delta-like 4 (Dll4)–Notch1 signaling [24,25,39]. It regulates the formation of appropriate numbers of tip cells to control vessel sprouting and branching. As shown in [24,25], inhibition of Notch signaling promotes increased numbers of tip cells. Conversely, activation of Notch leads to fewer tip cells and vessel branches. As reported in [39], tumor-derived VEGF induces Dll4 expression in angiogenic endothelial cells as a critical negative regulator of vascular growth. It acts to restrain
excessive vascular sprouting and branching, allowing angiogenesis to proceed at a productive rate.

**Fig.2.** Process of angiogenesis is initiated by stimulation of endothelial cells from neighboring blood vessel by tumor angiogenic factors released by tumor cells in avascular phase (top left panel). Endothelial cells in turn degrade extracellular matrix, form filopodia and start migrating towards TAF gradient along fibronectin, and collagen, fibers. Angiogenesis is initiated (right, upper panel). The endothelial cells form sprouts. In this phase lumen within sprouts starts to open at the site of parent vessel (left, bottom panel). Sprouts branch off and form anastomosis with neighboring sprouts. Lumen opens up and circulation of blood is initiated, which provides oxygen and nutrients to tumor. Blood vessels start to mature with growth of mural cells and help from recruited pericytes (right, bottom panel).

**Vascularization:**
Tumor vascularization is a complex process of vascular network development. It is initiated by the process of angiogenesis and begins with the formation of a primary capillary plexus. Once the sprouts approach the tumor, their branching dramatically increases until the tumor is eventually penetrated by vascular network. Due to better oxygenation, the concentration of TAF decreases also inside the tumor. However, the newly formed vessels are subsequently remodeled by the growing tumor and pushed away producing regions of lesser concentration of oxygen, which initiates TAF production. This causes simultaneous growth in size of both tumor and its vasculature [16, 21, 41].

Tumor vessels can be segregated into three categories [16].
1. Immature - with highly proliferative, nonperfused EC sprouts emanating from functional vessels.
2. Intermediate - with small, perfused vessels which, like the angiogenic sprouts, which lack support from mural, smooth muscle cells, and pericytes.
3. Mature - with larger vessels, which have recruited pericytes, and smooth muscle cells with quiescent ECs and few associated sprouts.
Tumor vessels develop through identifiable stages, beginning with treads of ECs sprouting from functional blood vessels. These proliferative endothelial sprouts evolve into small diameter tumor vessels. Deficiencies in inhibition of sprouts branching (e.g. from downregulation of Dll4-Notch signaling) may result in endothelial tube formation without luminal space, thus without blood flow [16,21,41]. This is observed in some tumors. The majority of intermediate size microvessels lack contact with pericytes. Pericyte recruitment from vascular smooth muscle progenitor cells residing in neighboring mature blood vessels or from circulating hematopoietic stem cells is associated with larger vessel caliber, fewer proliferating ECs, and termination of angiogenesis [9,38]. Tumors with a high fraction of pericyte-covered vessels have a greater proportion of mature vessels, fewer newly formed vessels, and may be less invasive. Anti-angiogenic agents may have less effect on these tumors because mature vessels have minimal angiogenesis.

Remodeling:
The process of tumor vascularization never becomes quiescent because the primitive vessels are continuously remodeled by dynamically evolving angiogenic factors, mechanical forces caused by growing tumor, blood flow, and intraluminal thrombosis. The last process is precipitated by invading into blood vessels tumor cells and exposure of tissue factor to factor VII and other coagulation factors. They involve decrease and arrest of blood flow within blood vessels due to tumoral invasion, a blood clotting, blood vessels reshaping, regression and dilation [7].

Local modifiers of vessel reshaping include growth factors, pericytes, extracellular matrix, and neighboring cells, such as smooth muscle cells, fibroblasts, macrophages. For example, inhibition of VEGF results in significant increase in EC apoptosis [9] contributing to fast regression of newly formed vessel. The inadequate pericyte coverage is also the reason of vessel decay [9,16,38].

As shown in [2,35], the ECM density and its structure modify the direction of growing vessels. The results shown in [35] confirm different degrees of tumor perfusion or vascularization, depending on the ECM heterogeneity. The vessel wall is not always formed by a homogenous layer of endothelial cells. Instead, it may be lined with neighboring cancer cells and endothelial cells [7] changing vessel functionality.

Global vessel modifiers are: the blood flow and mechanical remodeling involved by the interactions among growing tumor tissue, normal tissue and vasculature. High pressure and shear forces of blood exerted on vessel wall causes its perfusion and dilation. Both too dilated vessels and EC treads without circulating blood collapse. Vessel collapsing in the interior of the tumor initiates percolation process which is driven towards criticality - the percolation threshold - using a mechanism of vessel stabilization by increased blood flow in the remaining vessels [41]. Blood flow is also the source of both shear stress-dependent and pressure-dependent vessels reshaping [22]. The mechanical interaction between the tumor cells, normal tissue cells and vasculature is the most robust remodeling factor. The high pressure exerted on the vessel walls can make them collapsing. The mechanical forces may change also the location of vessels, destabilizing the tumor growth and changing its direction [41,43].

3 Computer models of tumor growth

Mathematical modeling of angiogenesis extends back a number of years [5,6,10,32,34,40,42,43,44]. The modeling concentrates on key events such as the response of endothelial cells to tumor angiogenic factors secreted by a solid tumor, endothelial cell proliferation, endothelial cell interactions with extracellular matrix macromolecules, capillary sprout branching, blood flow and vessel maturation. The substantial difference with respect to the physical models (such as molecular dynamics) is that the microscopic state of the cells is defined not only by mechanical
variables, such as position, velocity, pressure, but also by internal biological microscopic phenomena reflecting activities of the cells.

A large bibliography about mathematical models of tumor growth driven by the process of angiogenesis can be found in two books edited by Adam and Bellomo [5] and by Preziosi [40] and in more recent overview by Mantzaris et al. [32]. Three major categories of models of tumor-induced angiogenesis can be recognize: (a) continuum models that treat the EC and chemical species densities as continuous variables that evolve according to a reaction-diffusion system, (b) mechanochemical models that incorporate some of the mechanical effects of EC-ECM interactions (c) discrete, cellular automata or agent based models in which cells are treated as units which grow and divide according to prescribed rules (d) hybrid multiscale models involving processes from micro-to-macroscale.

Continuum models only incorporate the chemical interactions between the EC and the environment. Among the continuum models, Greenspan proposed some of the earliest mathematical description of tumor growth [23]. His models of avascular tumor growth were formulated as moving boundary problems, in which the solid tumor grows in suspension. The continuum models do not allow for cellular heterogeneity within the tumor mass, and the treatment of the mechanical properties of the tissue is rather simplistic. Moreover, they neglect mechanical interactions between vasculature and its environment. Some types of mechanical interactions were incorporated into mechanochemical models introduced in [23,31,46]. However, despite continuum models can provide significant insight into the relative role that different processes play in the formation of vascular network; they cannot predict its structure. Within these models, it is not possible to capture such the important events as repeated sprout branching and the overall dendritic structure of the network.

In contrast to these deterministic, continuum models, many types of discrete techniques, have been presented in the literature to explain and describe the branching morphology of the vascular networks. There are, for example, percolation models [8], Eden models [30,41], random walk and diffusion limited aggregation (DLA) models [2], cell based models [4], lattice models and cellular automata [11,36,48]. Unlike in the continuum models, discrete models can follow individual cells and can reveal more details about cell dynamics and its interaction with the tissue.

Discrete models are usually hybridized with continuum approaches in which molecular species are represented by their concentration while migrating EC tip cells are mimicked by particles [6,35,45]. The Stokes-Lauffenburger [45] model is one of the oldest hybrid models simulating two-dimensional spatial distribution of sprouts. It uses s classic Folkman simulation conditions [19]. The domain is a square (box) of surface S (volume V). The tumor is located at the top center of the domain and the capillary at the bottom (see Fig.3A). All of the boundaries have no flux conditions for cells and TAF. The evolution of molecular species is governed by reaction-diffusion equations that are discretized on grid. The particle, which dynamics on the TAF concentration field is described by a stochastic differential equation, simulates the migration of EC tip cells. This approach is the source of many other hybrid models (e.g., [1,2,6,11,35,30,48,51]) which differ in:

1. methodology of simulation of the process of vascularization and tumor growth (stochastic, deterministic, cellular automata, lattice-gas, DLA etc),
2. modeling accuracy and its depth - defined by the number of factors and subprocesses included in the model,
3. assumptions about geometrical properties of the simulation such as: dimensionality (2-D, 3-D), discretization of space and time (on-grid, gridless), structure of vascular network (rigid, structured, unstructured) etc.

One of the most popular paradigm used for modeling tumor growth are cellular automata (CA) (see the critical overview [36]). Cellular automata deal with the dynamics of discrete elements
populating the nodes of structural (mostly rectangular) grid. The elements take their state from a discrete (finite or infinite) space of states and evolve in discrete space and time. The dynamics of the elements is defined in terms of local, either deterministic or probabilistic, rules. Many models incorporate modifications to the classical definition of a CA hybridizing it, like in the Stokes-Lauffenburger model [45], with continuum fields of diffusive substances, such as nutrients or signaling substances. CA models, however, typically do not address the important mechanical interactions between the tumor and healthy tissue. Complex automata (CxA) are a generalization of cellular automata and represent a scalable hierarchical aggregation of CA and agent-based models [27]. The components represent a sub-system operating on its typical spatial and temporal scales. Globally, CxA can behave either as the classical CA nodes on a structural lattice or as interacting particles whose dynamics is described by the Newtonian laws of motion or stochastic laws. These CxA can be an interesting framework for the development of the multiple scale models.

The accuracy of the computational model is defined by its correspondence to the multiple processes and multiple scales involved in tumor growth (see Fig.1). Because of the complexity of the entire process, many models to date focus on single key subprocesses, disregarding their interactions with others. Many attempts assume either a static tumor and concentrate on dynamic vascularization in the absence of tumor growth [2,22,35,38,44] or a static network topology [11,46]. Some of them use dynamic network with blood flowing neglecting its interaction with concentration fields and tissue components (e.g. [22]).

Most popular models of angiogenesis, similar in spirit to the Stokes-Lauffenburger model [45], assume static tumor and dynamically growing vascular network. The hemodynamics is neglected or very simplified. Majority of them use various versions of hybrid CA [11,35,38] with CA rules based on discretized continuum models [6] or a set of phenomenologically derived rules. All this models produce brush-like type of vascular network shown in Fig.3A. They differ in modeling accuracy and the type or number of angiogenic factors simulated. For example in [2,35], the simulation results illustrate the influence of the extracellular matrix composition on endothelial cell migration and blood network formation and show different degrees of tumor perfusion or vascularization, depending on the ECM heterogeneity.

The most advanced models of vascular remodeling driven by the hemodynamics and angiogenesis and assuming static tumor are presented in [1,22,30,41,43,44]. In [22] the flow geometry was defined on a two-dimensional grid by using defined sources and sinks and elementary bifurcations that were able to proliferate or to regress under the influence of random and deterministic processes. Biophysics is defined by pressure, flow, and velocity distributions in the network. The nodal-admittance-matrix-method [22] is used with such detailed hemodynamic phenomena as Fahraeus-Lindqvist rheology and vessels interaction with surrounding tissue. The model predicts interdigitating arteriovenous patterning if shear stress-dependent but not pressure-dependent remodeling is applied.

Another interesting 2-D computer model, presented in [50] was implemented to provide the link between the microvasculature and interstitial space perfusion through a matrix describing the local vascular density, and accordingly couples the intravascular and interstitial flow by vascular leak. The results not only present the basic features and characteristics of tumor microcirculation, consisting with the corresponding experimental observations reported, but also predict a close relationship between the tumor intravascular and interstitial flow. It was shown that the vascular leakiness is one key factor to govern the systemic flowing pattern, influence the tumor internal environment and contribute to the metastasis of tumor cells.

Many models (e.g., [11,23,36,42]) focus only on avascular tumor simulation, which represent the earliest phase of tumor progression or represent tumors with low angiogenic response. For example, in [11] the authors present a typical two-dimensional hybrid cellular automaton model for the avascular growth phase simulated by means of lattice-gas approach. Cellular automata allow for the systematic analysis of cooperative effects in interacting cell
systems [11,36]. Contrary to differential equation models, it is possible to follow the fate of individual cells. All cells are subject to identical interaction rules. The model reproduces the processes, which are responsible for the growth of a layered and saturating tumor. In [11] the authors show that the layered pattern can be explained solely by the self-organized growth of initially small number of tumor cells.

An interesting 2-D model of avascular tumor involving mechanical interactions is presented in [46]. It represents the first attempt to create an in-silico model of a uterine leiomyoma, a typical example of a common benign tumor. The authors employ finite element method (FEM) to investigate the interaction between a chemically driven growth of the pathology and the mechanical response of the surrounding healthy tissue. The response of the tissue is that of a viscoelastic material. The stress exerted by expanding neoplasm is slowly dissipated. These partial models can be successful in describing various aspects of tumor growth and could be the ingredient of more detailed multiphysics and multiscale models.

Multiscale and multiphysic models represent the most advanced simulation methodologies. Very interesting 3-D model, integrating four aspects: a growing tumor, dynamically evolving vascular structure, blood flow and network remodeling simultaneously with very realistic visualization is described in [30,41]. The simulation results reveal emerging tumor morphology, characterized by the compartmentalization of the tumor into several regions. They differ in vessel density, vessel diameter, and extent of necrosis, what is in a good agreement with experimental data for human melanoma [30]. It was shown that the reduced blood flow and solid stress exerted by the tumor resulting in vessel collapse, stimulate a correlated percolation process that is driven towards criticality by the mechanism of hydrodynamic vessel stabilization.

Multiscale models extend the moving boundary approach to incorporate cellular heterogeneity, intercellular phenomena and the use of more complex mechanical laws to describe the response of the tissue to external forces. Advanced multiscale models of tumor progression are presented in papers by Bellamo et al. [5] and by Alacorn et al. [1]. The first paper provides rather a useful taxonomy of mathematical (continuous) models and methods of multiscale phenomena involved in tumor dynamics than is a truly multiscale model collecting all this processes in a single implementation. However, the second paper can be regarded as a fully multiscale model comprising many microscopic models on subcell and cell level (expressed in terms of ordinary differential equations), through diffusion-reaction models and hemodynamics described by partial differential equation and cellular automata rules as a coupling methodology. The weakness of these multiscale models are geometrical constrains and pure computational framework disabling realistic visualization and their further development.

Geometric constrains are one of the most important aspects of mathematical modeling and can be the sources of many artifacts. The most crude constrain is the reduction of one spatial dimension. The 2-D angiogenesis models can adequately approximate only tumors developing on a flat surface. However, even for these cases, 2-D approaches result in unrealistic and excessive tumor compartmentalization onto many regions separated by vessels. This compartmentalization may produce such the artifact as increase of the number of cells in hypoxia in these regions and, consequently, contributes to increase of microvascular density (MVD). This situation is shown in Fig.3, where growing, two-dimensional nucleus pushes the vascularization away from its interior, while in 3-D the tumor cells outgrow the vessels. Other constrains like assumptions about rigid structure of vascular network (such as in [1,30]), considerably limit the role of vessel remodeling in tumor progression. In [1], for example, the process of angiogenesis is replaced by artificial dilation of blood capillaries, without changes in vessel structure. Moreover, spatial anizotropy imposed by rectangular CA grid influences both the structural characteristic of vascular network and global behavior of growing tumor. As shown in Fig.4, all of these approximations result in a very poor, unrealistic visualization of the growing tumor. This is despite impressing effort in development of multiscale mathematical model, which combines processes from various spatio-temporal scales (see [1]).
Disregarding all microscopic and mesoscopic biological and biophysical processes, in macroscopic scales, tumor growth looks like a purely mechanical phenomenon. It involves dissipative interactions between the main actors: normal and cancerous tissues and vascular network. Any of existing computational paradigms is not able to reproduce this basic process, which influences the most tumor and vasculature remodeling, tumor shape and its directional progression. In our opinion, the lack of adequate computational framework is the main obstacle to produce truly multiscale model, which simultaneously allow for realistic visualization of tumor development.

In the following sections we present the advantages of the concept of complex automata driven by particle dynamics \[12,27,51\] as an interesting metaphor of the process of tumor progression stimulated by the angiogenesis. We advocate it as a potential framework for more advanced multiscale models. We describe the key components of our particle model and its implementation details. Finally we discuss possible extensions in our model.
snapshot generated from Alarcon et. al. [ ] multiscale model of tumor growth. In spite of the rich mathematical description of many multiscale processes covering scales from the cell level to the blood flow dynamics, the results of simulations are very unsatisfactory because of the 2-D geometry used, very simplified remodeling rules and unrealistic visualization. The red dots represent tumor, while green dots normal cells. The hexagonal grid of vasculature is assumed. The red edges represent vessels with hematocrit.

4 Complex automata model driven by particle dynamics

Our CxA model of angiogenesis follows the general principles of particle model described in [12,14,15]. The system, representing the fragment of tissue, is made of a set \( \Lambda_N = \{ O_i : O(x_i,v_i,a_i), i=1,...,N \} \) of particles (agents, in terms of CxA terminology), where \( i \) is the particle number and \( N \) is the number of particles. Each particle is defined by three vectors: position \( x_i \), velocity \( v_i \), and attributes \( a_i \). The attribute vector \( \mathbf{a} = (t_p, k_d, s_z, t_{cell}, c_{TAF}, c_{O_2}, c_{other}, p) \), where:

- \( t_p \) – is particle type: \( \in \{ \text{tumor cell (TC)}, \text{normal cell (NC)}, \text{endothelial cell (EC)} \} \),
- \( k_d \) – cell life cycle state: \( \in \{ \text{newborn, mature, in hypoxia, after hypoxia, apoptosis, necrosis} \} \),
- \( s_z \) – cell size,
- \( t_{cell} \) – cell age (life clock),
- \( t_{hp} \) – hypoxia time,
- \( c_k \) – concentrations of \( k=\text{TAF, O}_2 \) and other factors,
- \( p \) – total pressure exerted on particle \( i \) from its closest neighbors and the walls of the computational box.

In fine-grained models a particle mimics a single cell or components of ECM. Nevertheless, this assumption becomes very computationally demanding for modeling tumors of realistic sizes. The largest MD (molecular dynamics) simulation involved \( 2 \times 10^{10} \) particles [52]. However, the number of timestep of this simulation was not so impressive (only 50-100 timesteps). These computational restrictions impose current limits on spatio-temporal scales simulated by our particle model. Tumor of 1 mm in diameter consists at least of a million cells [3]. To simulate the proliferation of tumor of this size, located in a fragment of tissue of 8 mm\(^3\) in volume in 3-D, one needs at least \( 1.6 \times 10^7 \) particles simulated in \( 10^5 \) timesteps. This requires approximately the same computational resources as the largest MD simulations.

However, particle method can be also used in its coarse-grained form [15]. In particle models, such as DPD, FPM or SPH [12,14,15], the particle can represent the cluster of atoms or molecules. The clusters interact with each other via a pair potential such as in the pure MD method. This time, however, the interaction is different than for MD. It usually consists of conservative (repulsive), dissipative and Brownian parts [15]. In a similar way, we can assume that in our coarse-grained model a particle can represent a fragment of tissue with additional attributes, such as concentration of normal, tumor, EC cells and extracellular matrix ingredients. By defining cluster size (the model granulation), this approach allow for simulating tumor growth in various spatio-temporal resolutions.

Unlike in purely fine-grained particle model, where all cells and tissue ingredients are represented by particles, in our model a particle represents a single tumor or normal cell in ECM envelope. Thus, some ECM properties, such as density, can be reflected in parameters of cell-cell interaction model.

In the perspective of pure fine-grained model, vessel walls are made of small and thin endothelial cells. The process of sprouting and bifurcation of vessel tip is a very complex biological process involving tens of cells, many growth factors, chemical species and ECM structure [9,17,32,45]. For the sake of simplicity we assume here that the vessel is constructed of tube-like “particles”, each made of many EC cells. As shown in Fig.5, we define three types of interactions: sphere-sphere (A), sphere-tube (B), and tube-tube (C).
The spherical particles interact with each other via short-ranged forces, which mimic both mechanical repulsion from the cell walls and adhesive forces. We assume that the interaction potential $\Omega(d_{ij})$ (shown in Fig.5D) consists of repulsive core and attractive tail and is defined as follows:

$$
\Omega(d_{ij}) = \begin{cases} 
    a_1 d_{ij}^2, & \text{for } d_{ij} < d_{\text{cut}}, \\
    a_2 d_{\text{cut}}^2, & \text{for } d_{ij} \geq d_{\text{cut}}
\end{cases}
$$

where $a_1$ for $d_{ij} < 0$ and $a_1 << a_2$ (1)

and

$$
d_{ij} = |r_i - (r_i + r_j)|
$$

where $d_{ij}$ is the distance between cell walls. In more advanced models, tumor and normal cell interactions can be represented employing different interaction parameters $a_{1,2}$ (e.g. by defining different interaction potential) due to different mechanical properties: elasticity and adherence of normal and tumor cells [1,26,32]. The interactions between spherical cells and EC-tubes have similar character, and despite the elongated shape of the tube, are assumed to be central. The tube-tube interactions are also central. This approximation is justified because torque will not produce remarkable effects for slow and highly dissipative tumor dynamics. Moreover, by neglecting angular momentum, we can reduce computational load required for numerical integration of equations of motion. Only the tips of interacting tubes can fuse them together. Consequently, the chain of tubes forms blood vessels such as in Fig.5C and Fig.9.

**Fig.5.** The types of particles and interactions used in the particle based model

The particle dynamics is governed by the Newtonian laws:
where \( m_i, \mathbf{r}_i \) and \( \mathbf{V}_i \) are the mass, position and velocity of particle \( i \), respectively, while \( \lambda \) is a friction coefficient. This set of equations of motion is solved numerically by using direct leapfrog scheme (see overview [15]). The total forces acting on particles are calculated by using linked-cells method combined with the Verlet algorithm [15].

The particle system representing growing tumor is highly unstable. The number of cells increases and/or fluctuates because they can replicate or disappear. During the life-cycle, the normal and tumor cells change their states from new to apoptic (or necrotic) according to their individual clock and oxygen concentration. The cells of certain age and size and being well oxygenated undergo the process of “mitosis”. They split into two daughter cells. New born cell is in new state and its diameter is equal to \( d_{MIN} \). The diameter increases with time up to \( d_{MAX} \), proportionally to the oxygen concentration. The minimum and maximum particle diameters depend on the model granularity. Finally, after time \( T_N \), the particles undergo apoptosis, i.e., programmed cell death. Consequently, dead cells are removed from the system. For oxygen concentration smaller than a given threshold, the cell (which is not in the necrotic state) changes its state to hypoxia. Such the cells become the source of TAF. The cells, which are in hypoxia for a period of time longer than a given threshold, die and become necrotic. We assume that in the beginning, the diameter of necrotic cell decreases twice and, after some time, the cell is removed. This is contrary to apoptic cells, which are rapidly digested by their neighbors or by macrophages. The diagram of the cell cycle is shown below (Fig.6). As was mention before, the duration of phases of the cell cycle for normal and tumor cells differ considerably. Also the behavior of tumor and normal cell is different. For example, the proliferation rate of tumor cells, which were in hypoxia state, can change. As shown in Fig.7, the cells being a certain period of time in hypoxia proliferate faster than those evolving in normal conditions. In Fig.8 we present two snapshots from simulation of growing cell cluster.

![Fig.6. The simplified diagram of cell fate.](image-url)
Fig.7. The diagrams illustrating different proliferation rate of tumor before (control) and after hypoxia (0, 24 and 48 hours).

Fig.8. Two snapshots from simulation of increasing spherical particle cluster due to mitosis of cells.

The cell cycle for EC-tubes is different than for spherical cells. In fact, EC-tubes are clusters of EC cells. The tubes grow both in length and in diameter. The vessels collapse due to a combination of severely reduced blood flow, the lack of VEGF, dilation, perfusion and solid stress exerted by the tumor. However, because the tube is a cluster of EC cells, its division onto two adjoined tubes does not represent the process of mitosis but is a computational trick to make the vessels more flexible. Unlike, normal and tumor cells, the tubes can appear as tips of newly created capillaries sprouting from existing vessels. The new sprout is formed when the TAF concentration exceeds a given threshold. Then the “vessel particle” undergoes the process of “mitosis” directed to the local gradient of TAF concentration. The haptotaxis involving fibronectin [6,32] is not included yet in the model. In Fig.9 we show two snapshots from simulation of spontaneously growing tube cluster.

The cells interact with each other not only by means of mechanical forces. As shown in [1], under certain circumstances, cancer cells can modify their environment. Particularly, they are able to increase local acidity. Because tumor cells show greater resistance to acid concentration than the normal cells, they can eliminate normal cells from tumor cells neighborhood by increasing acidity. In our model, totalistic cellular automata rules are used to simulate competition between tissue and tumor cells. The decisions about survival or death of neighboring healthy cells will be taken comparing the intracellular concentration of acid to a critical threshold.

The transport of bloodborn oxygen and TAF into the tissue is modeled by means of reaction-diffusion equations. The distribution of heamatocrit is the source of oxygen, while the distribution of tumor cells in hypoxia is the source of TAF. On the other hand, the distribution of cells gives us the spatially distributed sink of both oxygen and TAF. We assume that the cells of
any type consume oxygen and the rate of oxygen consumption depends on both cell type and its current state [49]. We assume additionally that only EC-tubes absorb TAF. TAF is washed out from the system due to blood flow. Of course, one could employ more detailed models involving VEGFb absorption in ECM [35], however, at the expense of considerable increase of computational time.

Diffusion of oxygen and TAF is many orders of magnitude faster than the process of tumor growth. On the other hand, the blood circulation is slower than diffusion but still faster than mitosis cycle (see Fig.1). Therefore, we can assume that both the concentrations (of oxygen and TAF) and hydrodynamic quantities are in steady state in the time scale defined by the timestep used for numerical integration of equations of motion (Egs.3). This allows for employing fast approximation procedures for both calculation of blood flow rates in capillaries and solving reaction-diffusion equation.

We compute the blood flow rates employing Kirchoff’s laws (as in [1]). We assume that only vessels with circulating blood (anastomosing vessels) are the sources of oxygen. Moreover, both the oxygen and haematocrit concentrations in blood do not change along capillaries and the oxygen supply is proportional to the blood flow rate.

![Fig.9. The snapshots from simulation of growth of tube particle cluster due to mitosis.](image)

To calculate the concentrations of oxygen and TAF we solve the reaction-diffusion equations numerically by using approximation theory. One can estimate a function $f$ at position $\mathbf{r}$ by using smoothing kernels $W$ as follows:

$$f(\mathbf{r}) = \sum_{j=1}^{n} m_j \frac{f_j}{\rho_j} W(\mathbf{r} - \mathbf{r}_j, h)$$  \hspace{1cm} (4)
where $m_j$ is the mass, $r_j$ is the position, $\rho_j$ is the density and $f_j$ is the quantity $f$ for neighbor particle $j$, respectively. Here, $n$ is the number of neighbor particles within cut of radius $h$ ($|r - r_j| \leq h$). When $r = r_i$, $f(r)$ is denoted by $f_i$. The smoothing kernel approximates a local neighborhood $r$ within distance $h$. Thus, we can estimate the density $\rho_i$ for a particle $i$ at location $r_i$, by:

$$\rho_i = \sum_{j=1}^{n} m_j W(r_i - r_j, h)$$

(5)

where $j$ denotes the index of the neighbor particle. The kernel should be smooth, symmetric and satisfy the following equation:

$$\int_{\Omega} W(r, h) dr = 1$$

(6)

We used 3D poly6 kernel proposed by Muller et al. [37].

$$W_{\text{poly6}}(r, h) = \frac{315}{64 \pi h^9} \left\{ \begin{array}{ll} \left(\frac{h^2}{h^2 - |r|^2}\right)^3 & |r| \leq h \\ 0 & \text{otherwise} \end{array} \right.$$

(7)

The Laplacian can be approximated then:

$$\Delta f_i = \sum_{j=1}^{n} \frac{m_j}{\rho_j} f_j \Delta W(r_i - r_j, h)$$

(8)

As shown in [37], a better approximation can be used, however, more computationally demanding. Substituting Laplacian in the reaction-diffusion equation by Eq.(8) we got the following expression for concentrations $c_i^K$ of $K=\{\text{oxygen}, \text{TAF}\}$ in particle $i$ ($\chi^K$ – reaction factor). When $K=\text{oxygen}$, then $I=\text{TAF}$ and vice versa.

$$c_i^K = \frac{\chi_i^K c_i^K}{D} - \sum_{j=1, j \neq i}^{n} \frac{m_j}{\rho_j} c_i^K \Delta W(r_i - r_j, h)$$

(9)

By solving this equation iteratively for each time-step of Newtonian equation integration, we got approximate concentration of TAF and oxygen in each particle location.

The particles are confined in the cubical computational box of volume $V$. Because the average kinetic energy in the system is negligible small, from the virial theorem we obtain that:

$$P = \frac{1}{3V} \sum_{i<j}^{N} F_{ij} \cdot r_{ij}$$

(10)

The internal pressure increases due to increasing number of particles (cells). The increase of box volume $V$ compensates the pressure increase above a given threshold.
Unlike in models of angiogenesis in which either vascularization or tumor are static, the hybrid model presented in [30] introduces mutual interactions – chemical and mechanical - between growing tumor and dynamically evolving blood vessel network. Vessels can grow due to the process of angiogenesis or can collapse due to lack of TAF, severely reduced blood flow or solid stress exerted on weakly perfused capillaries. However, these phenomena reflect only the effects of local interactions between the tumor and its vasculature. The model cannot reproduce mechanical remodeling of vessels and tumor body caused by their both local and global dynamics.

In Figs.3,10-11 we display the effects of mechanical interaction between vessels and growing tumor simulated by using our particle based model. The figures clearly show how important role this process plays in tumor progression. In Fig.10 two vessels are pushed away by growing tumor opening the gap filled with cells in hypoxia. The cells, being in hypoxia during a period of time longer than a given threshold, die and are removed from the system. This produces an empty – necrotic - region in the middle of growing tumor. This effect has principal consequences on tumor dynamics in its both avascular (see Fig.3) and angiogenic phases. In avascular phase (see Fig.3) the existence of the necrotic region decreases the internal tumor pressure slowing down its growth.

**Fig.10.** The snapshots from 2-D simulation, which display the growth of tumor and remodeling of blood vessels supplying oxygen to TCs. The colors show the oxygenation of the cells (from blue – the highest, to green – the lowest). The cells die (disappear) when the O2 concentration falls below the threshold (the region pointed by the white arrow).
Fig. 11. The process of tumor growth from Fig. 9 but with angiogenesis module switched on. Due to better oxygenation of the cells, the tumor grows faster. The necrotic region (see Fig. C) is reborn (see Fig. D) because of oxygen supply by the newly formed vessels.

Fig. 12. The snapshots from 3-D simulation of angiogenesis and tumor progression. We display only the evolution of the vascular network. The angiogenesis starts from a single vessel (A). The sprouts of blood vessels, stimulated by TAF secreted by TCs, emerge (B). They are represented by black threads. Only those threads, which can conduct blood - i.e., the closed loops with pressure difference in the bifurcation points (anastomoses) - can survive, provided that the VEGF level is sufficiently high. They are marked in red. The unproductive vessels are removed from the system after some time.
---{1. Initialization}------------------------------------------------------------------------------------------------------------------------

define boundary_conditions();
define_initial_conditions();
assign_simulation_parameters();
divide_the_computational_box_onto_sub-boxes();

for each time step:

---{2. calculate O2 and TAF concentrations in cells and tubes locations}---------------------------------------------------------------------
calculate_diffusion_of_O2(); \{Eqs.5,7,9\}
calculate_diffusion_of_TAF(); \{Eqs.5,7,9\}

---{3. cell dynamics and life-cycle }----------------------------------------------------------------------------------------------------------
for each cell and tube:

\{3.1 mechanical interactions of cells and vessels\}........................................................................
assign_cells_to_sub-boxes;
\{calculate_cell_interactions_within_sub-boxes_and_their_closest_neighbors_for_all_kind_of_cells\}
calculate_forces_between_cells; \{both tumor and tissue cells\}
calculate_forces_between_tubes;
calculate_forces_between_tubes_and_cells;
calculate_new_positions_and_velocities_of_cells \{integrate the Newtonian laws of motion\}
calculate_new_positions_and_velocities_of_tubes
\{3.2 cell and vessel life cycle\}..............................................................................................
change_size(); \{the cell diameter is increasing for well oxygenated cells or collapses for cells in apoptosis\}
change_state(); \{based on age, cell densities, probability of mitosis, apoptosis and necrosis \}
update_time_counters;
if conditions are met:
proliferate(); \{replication, in case of tubes chemotaxis in direction of TAF gradient\}
if other conditions are met
quiescent();
else
apoptosis or necrosis(); \{rapid size reduction to complete removal in the next steps\}

\{3.3 sprouting\}................................................................................................................................
if conditions are met (e.g. TAF concentration>TAFMAX + other factors)
sprout_out_new_vessels();
endfor

---{4. remodeling}-------------------------------------------------------------------------------------------------------------------------
\{4.1 flow\}..................................................................................................................................
calculate_blood_flow_intensity_in_vessels();
calculate_pressure(); \{based on pressure in neighboring vessel pipes\}
calculate_flow(); \{based on pressure differences\}
if conditions are met (e.g.VEGF concentration<VEGFMIN || the intensity of flow in the vessel<INTMIN)
vessel_degradation(); \{for immature vessels only\}

\{4.2 maturation\}................................................................................................................................
if conditions are met (e.g. time counter>MAXTIME && the intensity of flow in vessel>INTMAX)
vessel_maturation();
endfor.

--- Fig.13. The main procedures of the model ---
As shown in Fig.11, where the tumor progression goes with vascular network evolution – the angiogenic phase – the evolving network is being continuously remodeled by mechanical forces exerted by growing tumor. On the other hand, the vessels reshape the tumor body and influence its compartmentalization. The separate regions of low oxygen concentration become the sources of TAF. Due to chemotaxis, these regions attract the growing vessels, which can be the sources of oxygen. Supply of oxygen down-regulates TAF production and can rebuild tumor tissue in the necrotic regions. This process occurs in various spatial scales resulting in the transformation of the regular vasculature in normal tissue into a highly inhomogeneous vasculature of the tumor.

The progression of tumor vasculature is shown in Fig.12. The straight initial vessel transporting blood is then remodeled due to tumor growth dynamics. Because of increasing TAF concentration we can observe newborn capillaries sprouting from the source vessel (black threads). The sprouts can bifurcate and merge creating anastomoses. The blood flow is stimulated by pressure difference in anastomosing vessels. Only productive vessels – marked in red - have a chance to survive if the TAF concentration is sufficiently high. Unproductive vessels undergo regression and disappear after some time.

In Fig.13 we show basic procedures of our CxA particle model, which include the model initialization phase, i.e., definition of initial and boundary conditions, and its evolution driven by the following phenomena:

1. Newtonian dynamics of interacting cells,
2. diffusion of oxygen and TAF,
3. cellular life cycle modeled by CxA rules,
4. vessels sprouting and growth,
5. vessels remodeling due to flow and maturation.

In the following section, we describe modeling results of the tumor proliferation in both avascular and vascular phases by using the particle model described above.

5 Results of modeling

5.1 Assumptions and simulation parameters

In this paper we do not investigate a behavior of specific cancer. We focus our attention on the functionality and correctness of our model as a metaphor of tumor growth. Below we discuss the parameters and shortcomings we employ in our model.

The spatial scales we used in the particle model are defined by the cell diameter, the size of computational box and microvascular density (MVD). We have assumed that the tumor cell (TC) diameter is 30 µm. It is larger than in typical models (e.g. in [1,30]) (10 µm) but it is smaller than V-79 cell described in [53]. This is rather technical shortcoming to decrease the computational load. The tumor of about 1 mm in diameter would consists then of 5x10^4 cells instead of millions. The particles (cells) are confined in the computational box of size 1.5mmx1.5mmx1.5 mm (or 2mmx2mmx2mm for the largest simulations). Total number of cells in the box is 10^5 of order. We have assumed that if the total pressure exceeds a given threshold, the stress is dissipated and the pressure in the box stabilizes. In order to keep it constant, those cells which are close to the box walls and which are the most suppressed are removed from the system. The initial state of the particle system at t=0 represents a regularly vascularized region of a given micro-vascular density MVD with a small tumor in the center (see Fig.3). Vessels are arranged in a regular grid with a lattice constant a=100µm. This yields MVD=100 vessels per...
mm² in 3 dimensions. As shown in Fig.14, this structure ensures well oxygenation of modeled tissue fragment.

We have chosen the timestep of simulation assuming typical time scales of cell life cycle and tumor progression rates such as division time, average cell life time in hypoxia, doubling time of tumor volume (see Table.1). In Eden model described in [30] Δt is set to 1h. Due to dynamics of cells caused by cell proliferation and their death, in our particle model the timestep for integration of Eqs. (3) has to be smaller. On the other hand, because of high dissipation rate in the equations of motion (sufficiently large friction λ in Eq.(3)) the time-step has not to be so rigorously defined as for other particle methods, e.g., such as in molecular dynamics. We have assumed that in our simulations Δt=0.25 h.

Functional vessels, i.e., the vessels with flowing blood, are sources of oxygen while the distribution of cells defines the spatially distributed sinks of oxygen. For computational tractability we assume a fixed O2 secretion rate along the vessel with a given flow intensity. This assumption overestimates the O2 concentration in regions with high MVD, but this does not alter the model outcome significantly [30]. We solve diffusion equation assuming that the diffusion coefficient is D_{O2}=1.75x10⁵ cm²/s [49,54]. The resulting O2 concentration profile is fit to experimental data from Fig.14. Given this initial configurations, we use Kirchoff’s laws to calculate the flow intensities in newly formed anastomoses and remodeled vessels. This then provides us with initial conditions for updating the O2 concentration profiles in the following simulation steps. As shown in Table 1, maximal survival time in hypoxia are considerably lower for normal than for tumor cells, moreover, tumor cells can survive in much lower O2 concentration [26,33]. Diffusion coefficient for TAF is assumed to be 10⁻⁶ cm²/s [30]. The concentration profiles for TAF and oxygen are updated simultaneously according to Eqs.(9).

Fig.14 Oxygen penetration depth for mouse according to [18]. The O2 pressure (Po2), dropped exponentially and reached plateau values of 3 mmHg at around 200 µm away from the blood vessel. Assuming that critical Po2 for healthy tissue is about 8-10 mmHg while about 2-4 mmHg for tumor cells [ ], the average distance to the hypoxic TCs should be about 150 µm. The red curve is the exponential fit of experimental data.
At the beginning of simulation, apart from the grid of vessels, the box is filled with only normal cells. Tumor growth always starts from a small number of tumor cells located in the box centre. We assumed that the normal cells do not proliferate and their life-time is very long. However, they can die due to necrotic factors like hypoxia or high local acidity caused by tumor cells [1]. The growing tumor pushes away the vessels, opening the gap of poorly oxygenated cells. When hypoxic region in avascular tumor is sufficiently large to secrete enough quantity of TAF, the angiogenic phase is initiated [33].

The newly formed blood vessels become functional when they form anastomoses allowing for blood flow due to pressure difference on its ends. Otherwise, we assume that the capillaries dissolve during 70 h. Moreover, nonfunctional and immature vessels are removed from the system after 10 h from the moment the VEGF concentration falls below a given threshold.

The vessel maturation is controlled by the density of pericytes [9,16,32,38]. The varying degrees of pericyte recruit indicate differences in the functional status of the tumor vasculature. In our simulations we assume very simplistic model of vessel maturation. The regression time depends on the local density of EC tubes. If the density is too high regression time is shorter. Dll4 regulates the sprouting rate. The lack of Dll4 results in excessive sprouting of newborn vessels. As shown in Table 1, some simulation parameters such as those defining particle-particle interactions are specific for our particle model and cannot be measured experimentally. The others, like pressure limits and energy dissipation rates were set heuristically on the base of observation of the model behavior. The majority of measurable biological parameter is typical for similar type of computer modeling presented in [1,6,30,32]. The main parameters are collected in Table 1.

<table>
<thead>
<tr>
<th>Table.1</th>
<th>Main simulation parameters (p.u. – program units)</th>
</tr>
</thead>
</table>

1. **global physical and numerical parameters**

<table>
<thead>
<tr>
<th>name</th>
<th>description</th>
<th>values</th>
<th>units</th>
</tr>
</thead>
<tbody>
<tr>
<td>time_step</td>
<td>The length of timestep</td>
<td>0.25 h</td>
<td>h</td>
</tr>
<tr>
<td>no_timesteps</td>
<td>Typical number of timesteps</td>
<td>$10^4$ - $10^5$</td>
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<tr>
<td>box_size</td>
<td>The size of computational box</td>
<td>1 - 2 mm</td>
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</tr>
<tr>
<td>no_cells</td>
<td>Typical total number of cells</td>
<td>up to $3\times10^5$</td>
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<td>diffusion_coef_TAF</td>
<td>Diffusion coefficient of TAF</td>
<td>0.002</td>
<td>p.u.</td>
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<tr>
<td>diffusion_coef_O2</td>
<td>Diffusion coefficient of O2</td>
<td>0.035</td>
<td>p.u.</td>
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<tr>
<td>force_cut_off</td>
<td>Cut-off radius in forces calculations</td>
<td>30 µm</td>
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</table>

2. **biological and local physical parameters**

   a. **tumor cells**

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<thead>
<tr>
<th>name</th>
<th>description</th>
<th>values</th>
<th>units</th>
</tr>
</thead>
<tbody>
<tr>
<td>tc_mass</td>
<td>Mass of cell</td>
<td>0.5 - 1 p.u.</td>
<td></td>
</tr>
<tr>
<td>tc_diameter</td>
<td>Diameter of mature cell</td>
<td>30 µm</td>
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</tr>
<tr>
<td>tc_mitosis_rate</td>
<td>Doubling time for tumor</td>
<td>200 h</td>
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<tr>
<td>tc_nutrient_consumption</td>
<td>O2 consumption speed in cell</td>
<td>0.12 p.u./h</td>
<td></td>
</tr>
<tr>
<td>tc_nutrient_mitosis</td>
<td>Minimal concentration of O2 for mitosis</td>
<td>6 mmHg</td>
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<tr>
<td>tc_nutrient_hypoxia</td>
<td>Min-Max concentration of O2 in hypoxia</td>
<td>2.5 - 5 mmHg</td>
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</tr>
<tr>
<td>tc_max_hypoxia_time</td>
<td>Maximal life time in hypoxia</td>
<td>50 h</td>
<td></td>
</tr>
<tr>
<td>tc_grow_speed</td>
<td>Cell growth rate</td>
<td>0.2 µm/h</td>
<td></td>
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<tr>
<td>tc_min_mitosis_size</td>
<td>Minimal cell size for mitosis</td>
<td>90 %</td>
<td></td>
</tr>
<tr>
<td>tc_taf_generation</td>
<td>TAF generation</td>
<td>0.1 p.u./h</td>
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<tr>
<td>tc_force_in(out)</td>
<td>Coefficient of cell-cell interactions</td>
<td>0.001 p.u.</td>
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<td>tc_mitosis_pressure_limit</td>
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<td>0.3 p.u.</td>
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<tr>
<td>tc_grow_pressure_limit</td>
<td>Pressure inhibiting cell growth</td>
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<tr>
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<td>Speed of necrotic cell shrinking</td>
<td>10 µm/h</td>
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<tr>
<td>tc_dead_age</td>
<td>Maximal time rate of dead cell removal</td>
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<tr>
<td>tc_dead_reduction</td>
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### b. healthy cells

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<th>Description</th>
<th>Value</th>
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<td>Mass of cell</td>
<td>0.5-1 p.u.</td>
</tr>
<tr>
<td>hc_diameter</td>
<td>Diameter of cell</td>
<td>30 µm</td>
</tr>
<tr>
<td>hc_max_live_age</td>
<td>Maximal life time of cell</td>
<td>5000 h</td>
</tr>
<tr>
<td>hc_nutrient_consumption</td>
<td>O2 consumption speed in cell</td>
<td>0.12 p.u.h⁻¹</td>
</tr>
<tr>
<td>hc_nutrient_mitosis</td>
<td>Minimal concentration of O2 for mitosis</td>
<td>10 mmHg</td>
</tr>
<tr>
<td>hc_nutrient_hypoxia</td>
<td>Min-Max concentration of O2 in hypoxia</td>
<td>5-7 mmHg</td>
</tr>
<tr>
<td>hc_max_hypoxia_time</td>
<td>Maximal life time in hypoxia</td>
<td>5 h</td>
</tr>
<tr>
<td>hc_force_in(out)</td>
<td>Coefficients of cell-cell interactions</td>
<td>0.001 p.u.</td>
</tr>
<tr>
<td>hc_shrink_speed</td>
<td>Speed of necrotic cell shrinking</td>
<td>10 µm/h</td>
</tr>
<tr>
<td>hc_dead_age</td>
<td>Maximal time rate of dead cell removal</td>
<td>20 h</td>
</tr>
<tr>
<td>hc_dead_reduction</td>
<td>Radius reduction rate for dead cell</td>
<td>1 µm/h</td>
</tr>
</tbody>
</table>

### c. vessel tubes

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>vc_mass</td>
<td>Mass of EC tube</td>
<td>2.3-5 p.u.</td>
</tr>
<tr>
<td>vc_diameter</td>
<td>Diameter of EC tube</td>
<td>10-50 µm</td>
</tr>
<tr>
<td>vc_length</td>
<td>The length of the EC tube</td>
<td>70-150 µm</td>
</tr>
<tr>
<td>vc_tip_mitosis_rate</td>
<td>Doubling time for vessel tip tubes</td>
<td>200 h</td>
</tr>
<tr>
<td>vc_grow_speed</td>
<td>Growth speed</td>
<td>0.2 µm/h</td>
</tr>
<tr>
<td>vc_thicken_speed</td>
<td>Thickening speed</td>
<td>0.002 µm/h</td>
</tr>
<tr>
<td>vc_min_mitosis_size</td>
<td>Minimal tube diameter for division</td>
<td>95 %</td>
</tr>
<tr>
<td>vc_branch_taf_trigger</td>
<td>TAF concentration allowing for sprouting</td>
<td>0.00005 p.u.</td>
</tr>
<tr>
<td>vc_force_in(out)</td>
<td>Coefficient of tube-tube interactions</td>
<td>0.001 p.u.</td>
</tr>
<tr>
<td>vc_glue_force</td>
<td>Coefficient of forces gluing tubes in vessels</td>
<td>0.005 p.u.</td>
</tr>
<tr>
<td>vc_mitosis_pressure_limit</td>
<td>Pressure inhibiting cell mitosis</td>
<td>100 p.u.</td>
</tr>
<tr>
<td>vc_grow_pressure_limit</td>
<td>Pressure inhibiting cell growth</td>
<td>100 p.u.</td>
</tr>
<tr>
<td>vc_max_flowless_time</td>
<td>Regression time allowed for non-functional vessels</td>
<td>40 h</td>
</tr>
</tbody>
</table>

### 5.2 Modeling of avascular phase of tumor growth

Because the size of computational box is about 1.5-2 mm, we assume that the diameter of avascular tumor does not exceed 0.5 mm. It means that the thresholds on vessels sprouting must be kept on such the level that TAF secretion from hypoxic part of tumor is not sufficient to initiate the process of angiogenesis. The other factor, which controls the tumor growth rate, is the pressure computed from Eq.(10). As shown in Figs.3,15, swelling tumor pushes away the capillaries increasing the space of poorly oxygenated cells in its interior. The nodule after being exposed to the critical stress, gradually relaxes its stress allowing the pathology to continue expanding. At the beginning the pressure weakly constrains tumor progression. However, as shown in Fig.17, after an initial exponential growth phase leading to tumor expansion, growth saturation is observed even in the presence of a periodically applied nutrient supply. This observation is in a good correspondence with experimental results [Folkman and Hochberg, 1973]. A section of the tumor spheroid, shown in Fig.15, displays a layered structure: A core zone composed mainly of necrotic material is surrounded by a thin layer of quiescent tumor cells and an outer ring of proliferating tumor cells. It is crucial to understand the processes, which are responsible for the growth of a layered and saturating tumor.

With increasing size and cell number, the spheroid requires more oxygen (more energy). Since the nutrient concentration is the lowest in the center of the avascular tumor, cells will starve here at first and may eventually die (necrosis). Under necrosis cells swell and burst, forming a necrotic site. The necrotic center collects the necrotic remains, and is much ‘softer’ than living cell layers [11]. The external pressure stimulates the mixing phenomenon similar in spirit to Rayleigh-Taylor instability boosted additionally by spherical geometry of the particle system (see [13]). As shown in Fig.16, the cells from the outer shell are pushed towards the necrotic center.
Initially, the inward flow is slow since the necrotic core is not existing or small. Consequently, the outmoving cell population dominates, i.e. the tumor expands. Later on, if the necrotic core has reached a critical size, the inward motion takes over which limits further growth.

The experimental work by Dorie et al. [55] confirms this observation. They showed that there are not only cells moving towards the periphery. This is a significant number of proliferative and quiescent tumor cells moving from the periphery towards the core area. This inward cell motion is a necessary condition for growth saturation of avascular tumor. If there would be no cell flowing towards the center but only stationary cells and cells moving in the direction of the outer shell, constant oxygen delivery would imply unbounded tumor growth.

This "antagonistic growth direction" was explained in [11] by the chemotaxic migration of tumor cells into the direction of the maximum necrotic signal gradient. Accordingly, the authors [11] assumed in the model that a diffusible signal emitted by bursting tumor cells is attracting living tumor cells. Such the destructive biological mechanism is suspicious and rather ill-founded. We showed that this inward cell motion is poorly mechanistic and necrotic chemotactic mechanism is superfluous.

As shown in Fig.17, higher external pressure produces tumors of smaller volume. However, this effect is not spectacular. Considerable increase of the external pressure (two times) results in rather small (10%-15%) decrease of tumor volume and causes that also the volume fraction occupied by quiescent cells decreases (by 20% in Fig.17). Most solid tumors, even those 1–3mm in diameter, exhibit hypoxic fractions that may range from 10 to 30% [56]. On the other hand, the size of necrotic center cannot shrink to be too small to stop the inward motion of cells. Its size should be adequate to guarantee the stabilization of the tumor proliferation. We can conclude that high external pressure can decrease the hypoxic fraction of avascular tumor below a threshold required to initiate the angiogenic processes. Such the quiescent tumor can survive years to the moment of the internal pressure drop caused, e.g., by osteoporosis in bones, or muscle flaccidity. It can also develop along blood vessels (see Fig.21).

Fig.15. The snapshots from 3-D simulation of avascular tumor. The tumor from Fig. B is stable and its size does not increase any longer. Figs C and D shows the cross-sections through the tumor from Fig. B. The tumor diameter is about 0.35 mm. The initial distance between the vessels is 0.15 mm. Only tumor cells are
shown. Blue particles are well oxygenated cells; green represents hypoxic cells, and black necrotic center. The tissue cells are invisible and we assume that they are well oxygenated.

**Fig.16.** The snapshots from similar simulation as this shown in Fig.15. The figures illustrate the inward motion of tumor cells from the tumor surface to its necrotic interior. The three arrows of various colors show the cells which disappear, one by one, in the necrotic tumor center.
**Fig.17.** The plots representing the number of TCs – the total number of tumor cells, cells in hypoxia, and dead cells - with time in growing tumor (see Fig.13) under different external pressure exerted by the tissue on the tumor body. The filled symbols denote the plots representing the tumor growing in 10% softer tissue than the tumor evolution represented by the plots with open symbols.

![A B C](image)

**Fig.18.** The cross-sections of avascular tumors (A,B) and tumor with vascularization (C). The tumor diameters are about 0.45 mm (A) and 0.55 mm (B,C). Unlike the tumor from Fig.A, the tumor from Fig.B has a few necrotic centers. The tissue cells are invisible and only tumor cells are shown. Blue particles represent well oxygenated cells while green and black cells are hypoxic and necrotic, respectively.

![No. of EC tubes](image)

**Fig.19.** The histogram of vascularization around the pre-angiogenic tumor. Blue bars show the microvascular density in the absence of tumor.

When avascular tumor is getting larger, non-uniform remodeling of capillaries caused by mechanical forces (see Fig.3B and Fig.18) may result in hypoxia not only in the central but also in many peripheral parts of the spheroid (see Fig.18B). Deployment of additional sources of TAF
can accelerate the process of angiogenesis. The angiogenesis in the peripheral part of the tumor is even more feasible, because of high density of blood vessels on its border (see Fig.3 and Fig.19).

As shown in Fig.18C, the process of angiogenesis eliminates the hypoxic spots. All the tumor cells are almost uniformly oxygenated. The angiogenic tumor growth phase commences. In the following section we show how the process of vascularization changes the way of tumor proliferation.

5.3 Modeling of tumor vascularization and remodeling

Because of high computational load required for 3-D simulations, i.e., small size of computational box, we assumed that angiogenesis initiates in a very early stage of tumor growth (its diameter is about 100 µm instead more realistic 1 mm). This assumption does not change too much the scenario of tumor progression at the start of vascularization process. As shown in Fig.20, increasing vascularization leads to increasing acceleration growth rate. The tumor evolution starts from power law growth with increasing power order. At this stage however, we cannot estimate which kind of growth is expected for larger tumor. Because of limited size of computational box, the growth is restrained due to increasing pressure.

![Fig.20](image.png) The acceleration of tumor progression due to angiogenesis for two VEGF thresholds.

The tumor evolution in bone cavity is shown in Fig.21. During unrestricted growth (no pressure exerted from healthy tissue) avascular tumor expands fast along the capillary. In angiogenic phase, tumor cells fill the whole cavity as long as the high pressure stops tumor proliferation. The
high acidity of tumor cells allows for local destruction of the porous bone structure. The vessels percolate throughout the bone body due to high pressure exerted by the tumor on the bone walls (see Fig.21B).

**Fig.21.** The cross-section of tumor evolution in a bone cavity. The white motionless cells represent the bone. The tumor fills the cavity exerting pressure on the bone walls.

Since MVD is used as a diagnostic tool in cancer therapy [16], a quantitative understanding of the mechanism that cause compartmentalization of the tumor vasculature into various regions differing substantially in vessel density appears very important. The mechanism leading to increasing vascularization on the peripheral of the tumor was explained in the previous section (see Figs.3, 19). We showed that a high fraction of vessels on the tumor shell come from normal tissue. These vessels are stable and dense enough to stabilize neovasculature. Whereas vasculature of tumor interior is in many respects different from the regular vasculature in normal tissues. Tumor vessels are less stable than their normal counterparts and when encapsulated by the growing cancerous tissue they undergo a dematuration process. As a consequence, these newly formed vessels collapse very easily, and the whole process starts all over again. Vessel collapsing in the interior of the tumor stimulates percolation process. Percolation is driven towards criticality - the percolation threshold - via a mechanism of vessel stabilization by increased blood flow in the remaining vessels [11].

The functional status of the neovasculature depends on many factors. The most unstable are open vessels without blood flowing that dissolve quickly. Only vessels creating anastomizes and pass up blood have a chance to survive. Nevertheless, inhibition of VEGF, e.g. in cocultures, lead to a 75% increase in EC apoptosis [9] what cases vessel regression and blood leaks. All of these factors cause that in the most cases the MVD decreases in direction from peripherals to the tumor interior [16, 21, 30, 41].

As shown in Fig.22, our particle model reproduces well this highly inhomogeneous tumor specific capillary network. The resulting network is very heterogeneous, composed of dense and void regions, and has distinctly different structure from normal arteriovenous or normal capillary networks [21]. Moreover, the emerging tumor morphology is characterized by the compartmentalization of the tumor into several regions differing in vessel density, and extent of
hypoxia [16]. This situation is clearly displayed in Fig. 22, which presents the snapshots from 2-D simulation of tumor growth in well oxidized normal tissue.

![Fig. 22. Two-dimensional simulation of vascularized tumor evolution. The gray cells correspond to normal (healthy) tissue while colored cells represent tumor. The color denotes the extent of cells oxygenation (from blue - highly oxygenated cells, to green – cells in hypoxia). The arrows shows the tissue cells absorbed inside the tumor body due to mechanical remodeling.](image)

Two corresponding factors regulating vessels stability are considered in our model. First, we can mimic the activation (inhibition) of delta-like 4 (Dll4)–Notch1 signaling [25,39]. It regulates the formation of appropriate numbers of tip cells to control vessel sprouting and branching. Inhibition of Notch signaling promotes increased number of tip cells. Conversely, activation of Notch leads to fewer tip cells and vessel branches. Pericytes are the second factor has been suggested to play a role in regulation of vessel stability [9,32,38]. Pericytes secrete an inhibitor that controls endothelial growth at certain cell densities. The varying degrees of pericyte recruitment indicate differences in the functional status of the tumor vasculature and may reflect varying degrees of maturation of the tumor vascular bed.

![Fig. 23. The snapshot from 2-D model of angiogenesis, showing pericyte uptake by growing vessels.](image)
High inhibition of Dll4, resulting in excessive number of vessels, causes that pericytes concentration may appear too low and immature vessels dissolve fast. Otherwise, for high activation of Dll4, as in situation shown in Fig.23, pericyte covered vessels stabilize and become functional. The maturation of vessels due to pericytes for high activation of (Dll4)–Notch1 signaling were simulated using our 2-D particle model. The snapshots from this simulation are presented in Fig.24.

![Fig.24. The snapshots of 2-D simulation of vascularization in tumor. The green vessels represent mature, pericyte covered vessels.](image)

6 Concluding remarks

The concept of Complex Automata and interacting particles represent a novel framework for constructing multi-scale models of tumor progression. We show that this approach is competitive to existing paradigms based on continuum models, classical - on grid - cellular automata and heterogeneous sub-models. The greatest advantage of our model is the possibility of tumor dynamics simulation, which involves mechanical forces for simultaneous remodeling of the blood vessel system. Moreover, realistic 3-D dynamics of the entire system consisting of the tumor and other tissue cells, blood vessels and blood flow can be reproduced by using the same homogeneous particle model.

Our simulation results indicated that not only redistribution and uptake of angiogenic factors during angiogenesis had significant effects on the structure and functionality of vascular networks. The results of mechanical remodeling can suggest as follows.

1. The layered structure of tumor can be explained solely by the self-organized growth of an initially small number of tumor cells.
2. The inward motion of peripheral tumor cells to its necrotic interior can be explained on purely mechanical ground, without somehow suspicious necrotic chemotaxis suggested in [11].

3. Larger value of MVD on the tumor peripheral is initiated due to mechanical interaction of expanding tumor borders on existing vasculature.

4. External pressure decelerate tumor growth rate and transfer a growing tumor into a saturated (non-growing and quiescent) regime.

5. Our modeling support controversy surrounding Folkman’s model for tumor therapy that disrupting angiogenesis yields a starving tumor, which eventually dies. In our model due to mechanical remodeling of healthy tissue many disparate fragments of tumor become very well oxidized. Expanding tumor can push out healthy cells and use regular vasculature to support its growth without the need of excessive angiogenesis.

6. The functionality of neovasculature depends on the balance between pericyte and Dll4 concentrations.

To check if the vascular networks generated in numerical simulations are really similar to the realistic ones we plan to validate our model. This validation will be conducted on the basis of the comparison between realistic images of tumor vascular networks from confocal microscopy and computer experiments. The comparisons will be made employing structural properties of tumor vascularization. The vascular networks can be described by the feature vectors with statistical and/or algebraic descriptors of complex networks [57] as the feature vector components. Finally, pattern recognition methods such as clustering and feature extraction will be used for the vector classification.

The computational complexity and geometrical constrains are the main disadvantages of our model. The first problem result in shortcomings we used in our simulations. We applied our particle model to a more developed stage of tumor growth, where the tumor is likely to comprise millions of cells rather than thousands of cells. To solve this problem we need to define multi-scale model and resort to parallel computing techniques. Although this certainly implies some degree of complication from the computational point of view, the particle model is not too difficult to implement in parallel [15]. The most serious geometrical constrains and simplifications used in our model are as follows:

1. Due to limited size of computational box and growing number of cells the pressure in the box increases. Computationally expensive procedures have to be used to maintain constant pressure inside the box.

2. The cells interaction is radial, what suggests that they are of spherical shape. Implementation of more realistic anisotropic interactions is very demanding computationally.

3. We use for simplicity rigid EC-tubes instead of EC cells, what influences the shape of vessels and may introduce structural artifacts (see Fig.9).

Our model of tumor-induced angiogenesis addresses a limited number of the involved biological processes. For example, blood hydrodynamics have received much less attention than in other models (e.g., [1,30,34,41,43,44]). We did it intentionally to reduce the computational load. However, we definitely agree that in larger tumors, vascular remodeling due to blood circulation cannot be neglected. The existing flow models (e.g. as in [30,41]) can be easily adapted in the scope of our particle model. For simplicity we neglect other phenomena. In particular, our model has not addressed the effect of perfusion and different concentration of oxygen along the vessel. Moreover, we consider only oxygen as the nutrient while tumor cells often do not require much oxygen for growth, but glucose, fat, and amino acids. Another area in which our model could be improved is introduction of microscopic sub-models representing important intra
cellular phenomena such as cell proliferation in hypoxic conditions. This challenge, however, can be undertaken provided that the efficient parallel version of the model will be implemented.

In our CxA framework it is easy both to develop principal mechanisms of tumor dynamics such as cell proliferation, vascularization, vessels remodeling and incorporate sub-models of other important processes like: microscopic intracellular phenomena, blood circulation and extracellular matrix models. The particle model can be supplemented by more precise models of reproduction mechanism, cell-life cycle, lumen growth dynamics, haptotaxis mechanism and others. Some models of intracellular phenomena can be copied directly from the work of Alancorn at al. [1]. Moreover, more angiogenic factors can be considered, such as various TAF activators and inhibitors. Instead of simplistic model of blood circulation used in our model, advanced blood flow algorithms from Chaplain [6] and Stephanou et al., [43,44] can be implemented in a straightforward way.

For simplicity, our model does not reflect the influence of the extracellular matrix composition on endothelial cell migration and network formation [32]. These very important processes can be simulated easily employing more complicated (e.g., anisotropic) interaction forces between cells. One can assume, for example, that the particle represent the cell with a fragment of extracellular matrix. We can use then interaction forces depending on both the range and the angle of interactions. More realistic though more computationally demanding way for simulating processes occurring in ECM involves additional type of particles representing various ECM components.

Most of these possible improvements will require supercomputing power to simulate realistic tumor sizes. This is mainly due to assumption we made that one particle corresponds to a single cell. This puts the upper limit on the size of simulated 3-D system to a few millimeters or at most centimeters when employing nowadays high performance multiprocessor systems. However, as shown in [14,15], particle models can be used for simulating fluid flows in various spatio-temporal scales by using a coarse graining procedure. We postulate that the similar procedure can be defined for modeling the tissue. Depending on the spatio-temporal scale of simulation, the particle can represent a cell, a cell with a fragment of ECM matrix, cluster of cells and fragments of ECM matrix, or a cloud made of mixture of cells, fragments of ECM matrix and microscopic blood capillaries. If such the scalability of the particle model is possible, this would allow for simulating tumors in various spatio-temporal scales from small avascular clusters to large masses.

Summarizing, we showed that the CxA particle model developed in this study can be used as a robust modeling framework for developing more advanced tumor growth models. Consequently, these models can be used to evaluate effects of individual factors on angiogenesis, understand mechanisms of interactions among them, and generate experimentally testable hypotheses.

Acknowledgments

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References


