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# Angiogenic Networks in Tumors–Insights via Mathematical Modeling

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**ABSTRACT** Angiogenesis, the formation of a network of blood vessels, is a vital process in the growth of solid tumors as it delivers required nutrients and oxygen. Prior medical studies assert that angiogenesis is influenced by a number of parameters such as endothelial cell migration and proliferation, existence of tumor angiogenesis factors, oxygen, extracellular matrix components, etc. Along with the early developments and findings in the area of tumor angiogenesis, a field of research that has emerged uses mathematical models to interpret and predict the time-course of the crucial factors, as well as new capillary vessel formation, loop formation, and vessel branching. However, most of these early mathematical approaches rely on a small number of parameters; and the characteristics of blood flow, which are significant factors in tumor vessel formation, are neglected. Relatively new integrated models based on the impact of multiple crucial factors and blood flow have seen some success in elucidating the behavior of angiogenesis. Here we review the contributions, opportunities, progress, and challenges of mathematical and computational models for understanding of the tumor-induced angiogenesis, and also consider studies that apply mathematical models to represent blood flow and opportunities for the investigation of therapies and treatments. At the same time, we identify a need for the inclusion of endothelial cell shape and dynamics in models of tumor-induced angiogenesis. Particularly, cell-matrix, cell shape, and cell-cell interaction is necessary for the explanation of blood vessel formation.

**INDEX TERMS** Angiogenesis, mathematical modeling, tumor angiogenesis factor (TAF), endothelial cells (ECs), extracellular matrix (ECM), matrix metalloproteinase MMPs), vascular endothelial growth factor (VEGF), blood flow, vascular adaptation, blood vessel formation, cancer.

## I. INTRODUCTION

Within the human body, tissue requires access to a blood supply for the provision of both oxygen and nutrients. This occurs via a connected network of blood vessels, which spans over 100,000 kilometers in each human adult. All inner walls of this vascular network are lined by an exceedingly thin single sheet of endothelial cells (ECs) that are structurally supported by connective tissue and stromal cells (e.g. pericytes and smooth muscle cells). The quantities of connective tissue and stromal cells that encase the vasculature vary according to the vessel diameter and function. Luminal ECs also have mechanoreceptors that allow them to sense the shear stress of the blood flowing over their surface to adapt their diameter and wall thickness to best support the blood flow. Because of the limited diffusion distance of oxygen in tissues, the vasculature establishes a network to ensure that almost every cell of the body is within 100–150 $\mu$m of the nearest capillary.

Angiogenesis is a physiological process through which new blood vessels develop out of an existing vascular network [1]–[3]. Angiogenesis is well documented to be vital in the normal processes of wound healing, embryonic development and the menstrual cycle; but it is also recognized as an essential step in growth of a solid tumor into a malignant mass [4]–[10]. In fact, solid tumors cannot grow beyond approximately one millimeter cubed before they require angiogenesis for access to oxygen and nutrients to survive [11]–[13]. *Sprouting angiogenesis* is often initiated via a drop in local oxygen levels that activates the hypoxia

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inducible factor (HIF1$\alpha$) in ECs, which in turn stimulates the transcription and production of angiogenic factors such as vascular endothelial growth factor (VEGF)-A as well as the expression of the cognate receptor VEGFR2 [14]. These pro-angiogenic factors activate ECs to form filapodia expressing tip cells that become the leading edge of a new sprouting vessel. A localized upregulation of matrix metalloproteinases (MMPs) enables these tip cells to become more invasive and motile as the surrounding basement membrane is degraded. Immediately following the tip cells are the ECs known as stalk cells that proliferate, elongate and establish a local basement membrane [15]. Upon meeting new or preexisting vasculature, anastomosis occurs resulting in the blood vasculature being extended and grown. Vessel maturation occurs with lumens forming in new vascular structures, together with pericytes and vascular smooth muscle cells being recruited and extracellular matrix (ECM) proteins (e.g. collagens and laminins) deposited.

Our increased knowledge of the processes that underpin angiogenesis are of particular interest as a means to combat cancer. Folkman first proposed that anti-angiogenics could be used to prevent tumor proliferate, elongate and establish growth [16]. The ongoing interest in blood vessel formation has revealed a number of factors that are pro-angiogenic and those that are anti-angiogenic. In particular, the role of VEGF family [17] and cytokines such as Interleukin-1, -6 and -8 have been described 'pro-angiogenic'. In contrast, a number of inhibitors are equally effective, including proteins such as angiostatin [18], endostatin [19], interferon, platelet factor 4, thrombospondin, prolactin (16 kd fragment), and tissue inhibitors metalloproteinase-1, -2, and -3 [20]. Taken together, it is clear that angiogenesis is controlled by the local equilibrium of 'activators' and 'inhibitors' [21], [22], the process is illustrated in Fig. 1.

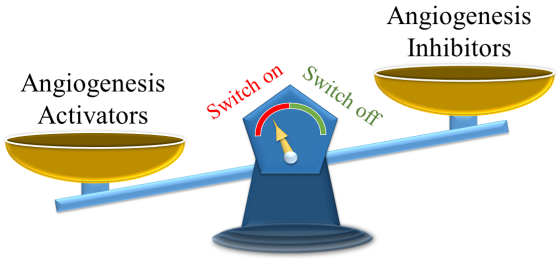


**FIGURE 1.** The regulation of angiogenesis under the impact of activators and inhibitors. The switch to the angiogenic phenotype involves a change in the local equilibrium between positive and negative regulators of angiogenesis.

These important biological interactions have inspired studies on the angiogenic process via mathematical and computational models to provide new insight on how ECs form vessels and thereby promising improved understanding of how tumors grow and cancer progresses. Mathematical models are generally a set of dynamical methods, statistical relations, differential equations, or game-theoretic approaches that describe how different entities in a system interact and change over time [23]–[27].

A well-defined model may assist in the description of a biological system for studying the effects of different agents, and for making predictions about future behavior. Typically, the use of mathematical models for biomedical problems can be divided into two classes. In one scenario, mathematical models are constructed with the aim of exploring the underlying patterns in existing clinical data. Notably, while these data-driven models have the benefit of allowing direct comparisons between the models and the real data, a drawback is that there is always the risk of over-fitting to a specific dataset, which means that the model is unable to generalize to different scenarios. Furthermore, some significant limitations in collecting clinical data such as low number of samples or uneven sampling may result in misleading outcomes [28].

In a second scenario, models can potentially be constructed from a mechanistic understanding of the biological phenomena in the absence of clinical data. Such a model may be employed to forecast the outcome of studies, experiments or clinical trials that have not yet been conducted [29]. Though such models are not necessary faithful over the entire parameter space, and can only be trusted through repeated validation with experiments [30]. In practice, mathematical models can be developed and refined by iterating between these two approaches. These mechanistic models can predict the future values of factors and provide useful information for clinical purposes [31], [32].

In this paper, we review some examples of how mathematical and computational models have improved our understanding of tumor-induced angiogenesis. The continuum and phase-field approaches are used widely to model tumor-induced angiogenesis, and they are the backbone of several combined models of angiogenesis. Therefore, we review some well-known continuum and phase-field approaches models of blood vessel formation in tumor-induced angiogenesis. In addition, the morphology of blood vessels formed into the extracellular matrix plays an essential role in tumor growth. We outline the studies explaining blood flow models that deal with morphology of blood vessels. Moreover, we illustrate the role of cell dynamics, branching and anastomosis. Finally, we discuss the association of tumor vascular structures and therapies.

## II. CRUCIAL AGENTS IN ANGIOGENESIS

More than a dozen different proteins have been identified as pro-angiogenic, including VEGF, basic fibroblast growth factor (bFGF), angiogenin, transforming growth factor (TGF)-$\alpha$, TGF-$\beta$, tumor necrosis factor (TNF)-$\alpha$, platelet-derived endothelial growth factor, granulocyte colony-stimulating factor, placental growth factor, interleukin-8, hepatocyte growth factor, and epidermal growth factor [13] (see Table 1). It is highlighted that these agents, collectively grouped here as 'tumor angiogenesis factors' (TAF), which are secreted from the cancerous cells or the tumor microenvironment of

**TABLE 1.** Endogenous regulators of angiogenesis.

| Activators | Inhibitors |
|---|---|
| ***Growth factors (GFs)*** | |
| Vascular endothelial GF family [40] | |
| Acidic and basic fibroblast GF [41] | |
| Angiogenin [42] | |
| Transforming GF [43] | |
| Placental GF [44] | |
| Hepatocyte GF [45] | |
| Granulocyto colony stimulating GF [46] | |
| ***Cytokines*** | |
| Interleukin-1 [47] | Interleukin-10 [38] |
| Interleukin-6 [48] | Interleukin-12 [49] |
| Interleukin-8 [37] | |
| Interleukin-3 [50] | |
| ***Trace elements*** | |
| Copper [51] | Zinc [52] |
| ***Proteases and protease inhibitors*** | |
| Stromelysin [53] | Tissue inhibitor metalloprotease [54] |
| Gelatinase A, B [55] | |
| Cathepsin [56] | |
| Urokinase-type plasminogen [57] | |
| ***Endogenous modulators*** | |
| Alpha v Beta 3 integrin [58] | Angiopoietin-2 [59] |
| Angiopoitin-1 [59] | Angiotensin II [60] |
| Endothelin [61] | Caveolin-1, -2 [62] |
| Erythropoietin [63] | Endostatin [19] |
| Hypoxia [64] | Interferon-alpha [65] |
| Nitric oxide synthase [66] | Isoflavones [67] |
| Prostaglandin E [68] | |
| ***Oncogenes*** | |
| c-Src [69] | p53/Rb [70] |
| v-Raf [71] | |
| Ras [72] | |
| c-Myc [73] | |
| c-Jun [74] | |

a solid tumor to create a chemical gradient [16]. There are many naturally occurring proteins that are anti-angiogenic, including angiostatin, endostatin, interferon, platelet factor 4, thrombospondin, prolactin, and tissue inhibitor of metalloproteinase-1, -2, and -3 (see Table 1).

Fibronectin, a glycoprotein of the extracellular matrix, plays a crucial role in cell adhesion, growth, migration, differentiation, and it has a key role in angiogenesis [33]. Endothelial cells that form the interior surface of blood vessels, employ fibronectin for attachment to the matrix [34]. Interleukin-1 induces angiogenesis indirectly through activation of VEGF expression in smooth muscle cells [35]. Interleukin-6 expression is also associated with the induction of angiogenesis during the development of ovarian cancer [36]. Interleukin-8 is found to function as a pro-angiogenic factor [37]. The role of interleukin-10 [38], and -12 [39] as an inhibitor is shown in previous studies.

## III. MODELING BLOOD VESSEL FORMATION

The morphology of blood vessels formed into the extracellular matrix plays an essential role in tumor growth—in recent decades a number of computational and mathematical models have been developed to explain the morphology. Many of these models have used a continuum deterministic framework, in only one dimension [75]–[80], which suggest there may be several limitations for the simulation of a realistic problem. The first one-dimensional study of tumor angiogenesis modeling was inspired by an analogy with fungal growth [81]—this is based on the formation of interconnected branches in response environmental factors and is the key point of commonality in this analogy.

In more recent years, a number of studies containing 2D and 3D models have investigated the interaction of critical agents such as ECs (tip cells and stalk cells), tumor cells, tumor angiogenesis factors (TAFs), oxygen, fibronectin, etc. Also, several automated image analysis methods are proposed for quantification of *in vitro* angiogenesis [82]–[84].

### A. HOW CAN A CONTINUUM APPROACH CONSTRUCT A PRIMARY MODEL OF TUMOR ANGIOGENESIS?

The backbone of most mathematical modeling studies is a partial differential equation (PDE) describing the population of ECs and other factors. This PDE is originally an equation of conservation of matter [85], and is described as follows,

$$\frac{\partial u}{\partial t} = \nabla \cdot \mathbf{J} - f = 0. \tag{1}$$

The dependent parameter $u$ is typically the EC density, and $t$ is time. The function $f(x, t)$ is the sink and source density, which models the combined effects of cell proliferation and apoptosis. Finally, $\mathbf{J}$ is the EC flux that is influenced by net flow of cells and other terms such as chemotaxis, a response to chemical gradient [86], haptotaxis, the movement of a cell up an adhesive gradient, etc.,

$$\mathbf{J}_n = \mathbf{J}_{\text{random}} + \mathbf{J}_{\text{chemotaxis}} + \mathbf{J}_{\text{haptotaxis}} + \dots . \tag{2}$$

Building upon a simple 1D model [77], a two-dimensional model tracks motion of an EC population $n$, particularly at or near a capillary sprout tip [87]. In this 2D model, the TAF gradient is considered as the chemotactic flux, and the fibronectin gradients are used as the haptotaxis term in Equation 2.

Particularly, the sprouts use collagen fibers or fibrin strands to guide their growth. In essence this can be modeled as a biased random walk. The processes of angiogenic sprouting, anastomosis and cell proliferation are incorporated in this discrete biased random-walk model. The flux of the form $-D_n \nabla n$ can represent the random mobility where $D_n$ is a positive constant, the cell random-motility coefficient.

The chemotactic flux is considered to be $\chi(c)n\nabla c$, where $\chi(c)$ is a chemotactic function that is assumed to be constant in many previous models. The impact of fibronectin on the ECs is modeled by the haptotactic flux, $\rho_0 n \nabla f$, where $\nabla > 0$ is the haptotactic coefficient that is positive and constant.

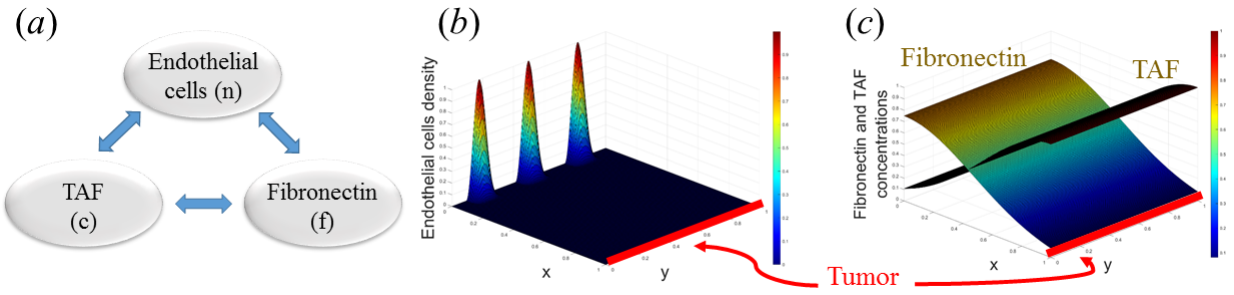


**FIGURE 2.** The basic dynamics model for tumor angiogenesis [87]. (a) Diagram for the variables and reactions tracked by the model, as described in the model. (b) Initial EC density for the two-dimensional simulations representing the three initial regions of capillary sprout outgrowth. (c) Initial fibronectin and TAF concentrations. The tumor is assumed a straight line at $x = 1$. The maximum value for TAF is near the tumor and for fibronectin is near the parent vessel at $x = 1$. The initial conditions can be modified for a circular tumor.

The framework of biased random walk developed by Othmer and Stevens [88] is a suitable tool for understanding of the link between continuum and discrete models [89], [90]. In these models, tip cells are represented as rigid shapes or points and their migration is considered as a reinforced random walk model, with directionality coming from chemotactic and/or haptotactic cues, and sometimes also from ECM topography [91]. A circular random walk model is suggested to the process of tumor angiogenesis. Despite the common approached that simulate the movement of tip cells on a regular lattice, the model allows the cells to move independently of a lattice [92]. Also, it is suggested that the reinforced random walk combined with models of tissue regeneration can be used to investigate the role of angiogenesis in regeneration [93].

Moreover, the model proposes an equation for TAF density. As ECs migrate through the tumor, there is some uptake of TAF concentration (c) by the cells [94], [95] at a constant rate $\lambda$. It is known that ECs themselves produce and secrete fibronectin [96]–[102]. There is also some uptake and binding of fibronectin ($f$) to the ECs as they migrate toward the tumor [103]. The constants $\omega$ and $\mu$ are used to specify the rates of production and uptake. These reactions indicated in Fig. 2.a can be described with the set of partial differential equations:

$$\begin{aligned}
\frac{\partial n}{\partial t} &= \underbrace{D_n \nabla^2 n}_{\text{random motility}} - \underbrace{\nabla \cdot \left(\chi(c) n \nabla c\right)}_{\text{chemotaxis}} - \underbrace{\nabla \cdot (\rho_0 n \nabla f))}_{\text{haptotaxis}}, \\
\frac{\partial f}{\partial t} &= \underbrace{\omega n}_{\text{production}} - \underbrace{\mu n f}_{\text{uptake}}, \\
\frac{\partial c}{\partial t} &= \underbrace{-\lambda n c}_{\text{uptake}}.
\end{aligned} \tag{3}$$

Cell proliferation is neglected in this model therefore the $f(x, t)$ term in Equation 1 is assumed to be zero. This model reproduces many of the qualitative features of angiogenesis.

The impact of MMPs that enhance the attachment of the cells to fibronectin contained in the extracellular matrix, is added to the equations in the other studies [104]. The initial and boundary conditions for this model can be assumed in a number of different ways. The initial condition assumptions in the study for ECs are shown in Fig. 2.b and the initial conditions for TAF and fibronectin are given in Fig. 2.c. These models assert that a sufficiently strong chemotactic response is necessary for the initial outgrowth of the capillary network. In addition, the models demonstrate the importance of interactions between ECs and the extracellular matrix.

Initially, the sprouts arising from the parent vessel grow essentially parallel to each other. It is observed that once the capillary sprouts have reached a certain distance from the parent vessel, they tend to incline toward each other [105], and the resulting fusions are known as anastomoses. The modeling of anastomoses is much more complicated in a 3D environment than in 2D. Moreover, the tumor is considered to be homogeneous. In reality, a tumor is highly heterogeneous, and there can be avascular and necrotic regions. A tumor can also have a variable growth rate and interstitial components. These can lead to variable transport properties throughout the tumor.

The interaction of tumor cell density, host tissue (extracellular matrix), MMPs and oxygen is described in a hybrid mathematical model [106]. In a recent study, the equation related to the concentration of TAF was added to the previous model showing the network of blood vessels develops gradually as the tumor grows [107].

Also, Spencer *et. al* proposed an ordinary differential equation model that describes how the balance of angiogenesis, genetic instability, cell death rates, and replication rates give rise to different kinetics in the growth of cancer [108].

### B. MODELING OF BLOOD VESSELS FORMATION VIA A PHASE-FIELD MODEL

When a particle moves with a velocity proportional to the gradient of field $u$, a class of non-equilibrium pattern formation problems appears, which itself obeys a bulk equation (diffusion and Laplace equations) and a Dirichlet boundary condition on the moving interface [109]. Traditionally, numerical approaches are used for explicit tracking of a sharp interface whose dynamics is linked to the bulk dynamics.

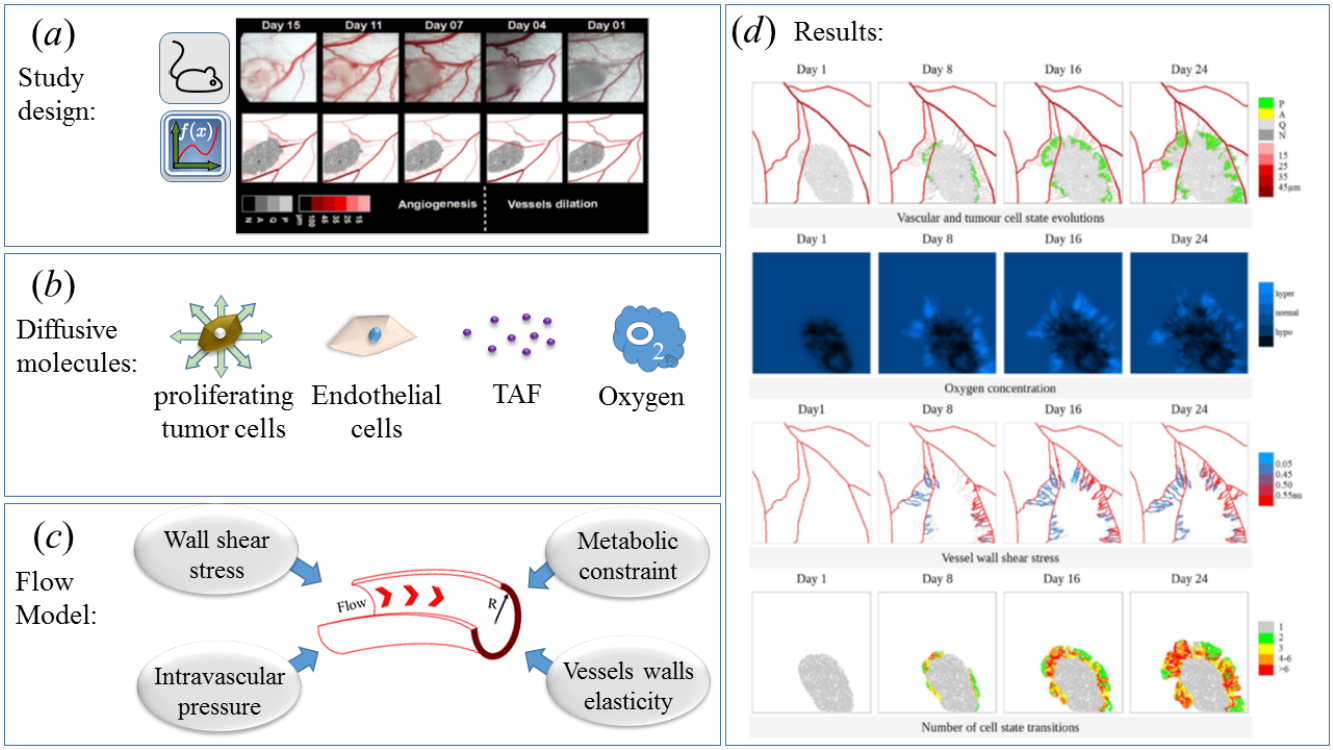


**FIGURE 3.** **Modeling blood vessel formation and flow in a recent angiogenesis mathematical framework. Adapted from [131]. (a) Design of a study in which the vascular structure of the host tissue was segmented from *in vivo* images and transposed into the computational framework. (b) The proposed model investigates the impact of diffusive molecules such as oxygen and TAF on interaction of tumor growth and vascular network. (c) The original model describing vascular adaptation is modified here with adding impact of elasticity of the vessel wall. (d) The growth of tumor and vascular network in 24 days. First row: vascular diameter changes and angiogenesis are exhibited, as well as tumor cell states with proliferative cells highlighted in green. Second row: oxygen concentrations from hypoxia (dark zones) to hyperoxia (bright zones). Third row: vessels wall shear stress in normalized units. As in row 1, unperfused vessels are displayed in grey. Last row: number of times that the cell state is changing from proliferative to quiescent and reciprocally.**

Alternatively, this can be achieved by corresponding moving boundary conditions or by projecting the whole dynamics into a single integrodifferential equation for the interface treating both dynamics together.

The phase-field model (PFM) introduced by Fix [110] and Langer [111] is a key approach to the study of such problems. The method substitutes boundary conditions at the interface by a partial differential equation for the evolution of an auxiliary field (the phase field) that takes the role of an order parameter. This phase field takes two distinct values (for instance $+1$ and $-1$) in each of the phases, with a smooth change between both values in the zone around the interface, which is then diffuse with a finite width. A discrete location of the interface may be defined as the collection of all points where the phase field takes a certain value (e.g., 0) [112]–[115].

A multi-scale phase-field model has been proposed to combine the advantages of continuum equations and the capability of tracking individual cells [116]. The model describes the interaction among TAF, tip cells and stalk cells. The activation of the tip cell phenotype in ECs is the result of their response to the environment through internal gene regulatory processes.

The dynamics of an effective factor $T_i$ that represents the balance between activators and inhibitors of angiogenesis described in Fig.1 are analyzed using this model. Proliferative and non-activated cells are described by an order parameter $\Phi$ that is equal to -1 outside the capillary and $+1$ inside it. The activated tip EC moves chemotactically with velocity $v$ proportional to the gradient of angiogenic factor, $G \equiv |\nabla T|$. In order to merge tip and stalk cells the order parameter inside the tip cell $\phi_c$ is linked with the proliferation rate $\alpha_p(T)$ and chemotactic response $\chi$. These interactions can be described with the set of four PDEs,

$$\begin{aligned}
\underbrace{\frac{\partial T_i}{\partial t}}_{\text{variation of growth factor}} &= \underbrace{\nabla\cdot(D_i(r)\nabla T_i)}_{\text{migration by diffusion}} - \underbrace{\alpha_T T_i \phi \Theta(\phi)}_{\text{consumption by ECs}}, \\
\underbrace{\frac{\partial \phi}{\partial t}}_{\text{position of capillary}} &= \underbrace{M\nabla^2[-\phi+\phi^3-\epsilon\nabla^2\phi]}_{\text{interface dynamics}} \\
&\quad + \underbrace{\alpha_p(T)\phi\Theta(\phi)}_{\text{EC proliferation}}, \\
\mathbf{v} &= \chi\nabla T\left[1+\left(\frac{G_M}{G}-1\right)\Theta(G-G_M)\right], \\
\phi_c &= \frac{\alpha_p(T)\pi R_c}{2|\mathbf{v}|}, \qquad (4)
\end{aligned}$$

where $\Theta(\phi)$ is the Heaviside function, and all other parameters are constant. The results for this model show that with an increase in level of TAF in tissue, the branch density increases dramatically and the vessels begin merging making

the blood vessels thicker. The PFM is also used for modeling of tumor-induced angiogenesis growth, regression and regrowth based the interaction of capillaries and TAF [117]. The simple uptake term in the Equation 4 from previous model is modified in order to limit the concentration of TAF within a hypoxic cell.

## IV. MODELING BLOOD FLOW

It is well documented that shear stresses generated within the capillary network by the flowing blood play a significant role in structure of vessels [118]–[122]. In addition, haemodynamic stimuli (increase in endothelial wall shear stress and decreases in intravascular pressure), or metabolic stimuli, were assumed to initiate the vessel diameter increases [123] that is directly correlated with blood flow.

Investigating the impact of blood flow is a recent but ongoing field of study in tumor angiogenesis mathematical models. Generally, the consideration of blood flow in the models can be divided into two cases. In one scenario, models may be constructed with the aim of explaining the process of drug delivery to a tumor. Second, the formation of capillary networks can be influenced by the blood flow, which is neglected in many previous mathematical models. Blood is a complex fluid, and in several mathematical models its flow is ignored or assumed Newtonian of constant viscosity that is clearly a crude approximation.

As blood is not a simple fluid with constant viscosity, it is a limitation to model it as a Newtonian fluid. In an early mathematical model this problem is simplified with the assumption that blood is a suspension of red blood cells in a Newtonian fluid [124].

The above insights about the hydrodynamics of vascular beds and the fact that the vascular system continually adapts to the demands of the surrounding tissue can be explored in a mathematical formulation [123], [125]. The radius $R(t)$ of a vessel evolves over a time period $\Delta t$ as follows:

$$R(t+\Delta t) = R(t) + R(t)\Delta t\Bigg( \underbrace{\log\left(\frac{\tau_\omega}{\tau(\pi)}\right)}_{\text{haemodynamic stimulus}} + \underbrace{k_m(V)\log\left(\frac{\dot{Q}_{\text{ref}}}{\dot{Q}H}+1\right)}_{\text{metabolic stimulus}} - \underbrace{k_s}_{\text{shrinking tendency}}\Bigg), \tag{5}$$

where the flow rate is given by $\dot{Q}$, $H$ represents haematocrit (red blood cell volume), $\tau_\omega = R\Delta\pi/L$ is the wall shear stress acting on a vessel of length $L$ and $\pi$ is the transmural pressure. Here $\dot{Q}_{\text{ref}}$, $k_m$, and $k_s$ are constants. Note that $\tau(\pi)$ is set point value of the wall shear stress. It is assumed that the metabolic stimulus increases as the haematocrit decreases. The function $k_m(V)$ is assumed an increasing saturating function with

$$k_m(V) = k_m^0\left(1 + k_m^V\frac{V}{V_0+V}\right), \tag{6}$$

where $V$ denotes the VEGF concentrations and rest of parameters are constant. Finally, the last term indicates the shrinking nature of vessels. Therefore, in the absence of mechanical and metabolic stimuli, the vessels shrink. The results from this model illustrate that environmental inhomogeneity effectively restricts the ability of malignant colonies to grow and invade healthy tissue.

The above concept of blood flow modeling has been added to a prior angiogenesis model [87] containing EC, TAF, fibronectins and MMP interactions in a more recent study [126]. By using this mixed approach, it is possible to investigate the effects of simultaneous adaptation (vasodilation and vasoconstriction) of the vascular network. It is expected that ongoing achievements in this area can potentially provide considerable implications for clinical therapies.

Improvement has been achieved by considering the flow of a non-Newtonian fluid in a dynamic adaptive network, i.e. a network that evolves both spatially and temporally in response to its associated flow distribution [104]. Coupling with an improved continuum model of solid tumor invasion to produce a new multi-scale model of vascular solid tumor growth has been achieved [127].

In another study [128], the previous findings are combined with two fundamental mechanisms of vascular growth and homeostasis, (i) by explicitly accounting for the pruning of vessels that have insufficient flow for a sustained period of time, and (ii) via VEGF-dependent formation of angiogenic sprouts and the consequent creation of new vessel connections that establish blood flow. Adding these two mechanisms made the model capable of generating new vascular networks to supply regions with too low vascular density, and to remove vessels that do not sustain flow.

It is known that high levels of VEGF change the stability of the vessel wall by weakening and disrupting the bonds between ECs [129] and enhancing chronic hyperpermeability [130]. Therefore, the elastic stimulus is integrated in the mathematical model [131]. It is assumed that the elastic resistance of the vessel wall to the increase diameter depends on the local VEGF concentration. The study compares the obtained results from the computational model with images experimentally observing vascular changes induced by the introduction of a tumor on a mouse equipped with a dorsal skinfold chamber (Fig. 3). Figure 4 shows different parameters modeled in a number of well-known mathematical frameworks.

Also, a mathematical framework is proposed for both blood flow through a capillary network that is induced by a solid tumor, and fluid flow in a tumor's surrounding tissue [132]. The conservation laws for mass and momentum are employed for simulating interstitial and intravascular flows and Starling's law is used for closing this system of equations and coupling the intravascular and extravascular flows.

In addition to vessel thickness or caliber, vessels curvature may also play a major role in blood flow. A proposed approach attempts to quantify vessels curvature based on both curvature and thickness [133]. In addition, it is

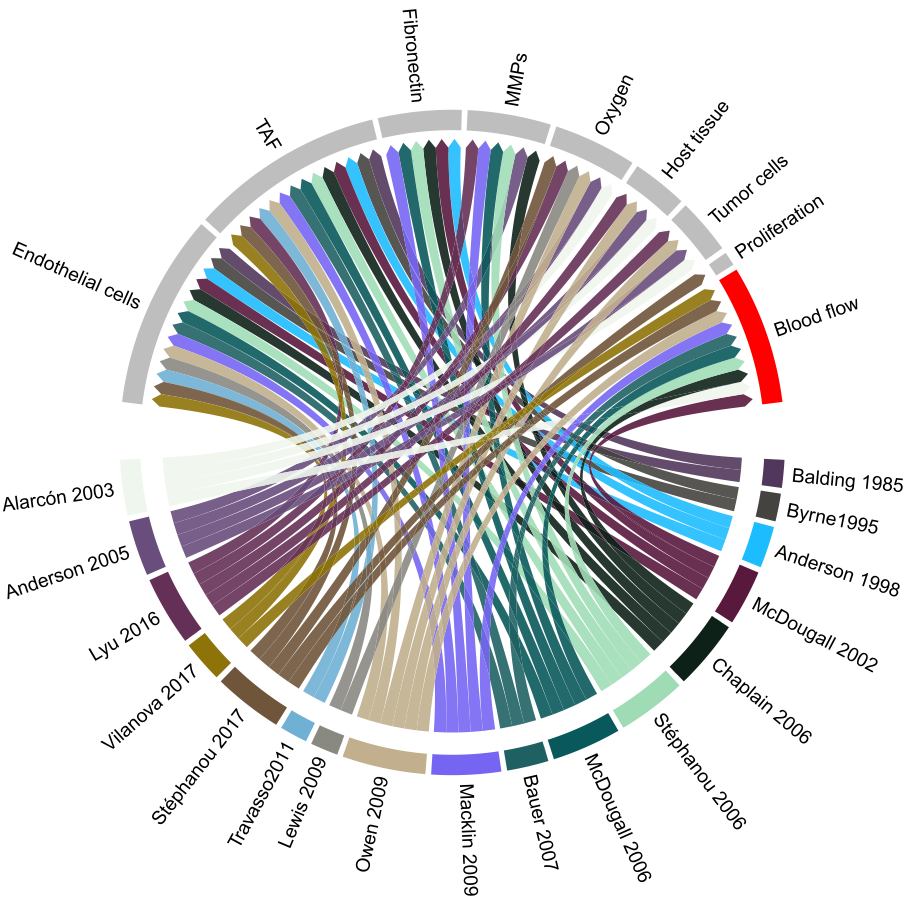


**FIGURE 4.** The circular diagram of previous mathematical models and their parameters. The following are shown in this figure: Balding 1985 [77], Byrne 1995 [79], Anderson 1998 [87], McDougall 2002 [161], Alarcón 2003 [124], Anderson 2005 [106], Chaplain 2006 [162], Stéphanou 2006 [126], McDougall 2006 [135], Bauer 2007 [135], Macklin 2009 [127], Owen 2009 [128], Lewis 2009 [125], Travasso 2011 [116], Lyu 2016 [107], Stéphanou 2017 [131], Vilanova 2017 [117]. The circular diagram is produced using the R package circlize [163]. The diagram illustrates which parameters each model considers and it can be noted that all these models use a limited number of parameters.

suggested that mechanical instability and remodeling can potentially be mechanisms for the initiation and development of tortuous vessels [134]. Another interesting development can be to study tumor-induced angiogenesis models considering vessels curvature as a factor of blood flow.

## V. CELL DYNAMICS MODELS

Cell shapes, movements, and dynamics play a vital role in process of vessel formation; however, they disregarded in various mathematical and computational angiogenesis models. Recently a number of models attempt to consider cell dynamics, but in a number of cases they ignore mechanical laws [91]. The cellular Potts model simulates the behavior of cells based on energy minimization and is widely used to model cell shape [135]–[140]. This is the first model where the extracellular space is modeled in an explicit way, rather than by means of a continuous field. Crucial agents such as ECs, matrix fibers, interstitial fluid and tissue specific cells all occupy grid cells, interact with each other and compete for space, as captured by appropriate energy terms [135]. The cellular Potts model is combined with a finite element approach to calculate cell traction force induced extracellular matrix (ECM) deformation [141].

A recent mathematical model of early stage angiogenesis explores the relative importance of mechanical, chemical and cellular cues. Endothelial cells proliferate and move over an extracellular matrix by following external gradients of VEGF, adhesion and stiffness, which are modeled using a cellular Potts model with a finite element description of elasticity [142]. As an early attempt, Bentley *et al.* proposed a hierarchical agent-based model simulating a suggested feedback loop that links VEGF-A tip cell induction with delta-like 4 (Dll4)/notch-mediated lateral inhibition [143]. The model is improved by combining membrane agents with Hookean springs to include actin cortical tension [144]. In fact, the Vilanova hybrid model integrates Bentley's approach [144] with Travasso's model [116], operating at different spatial scales [117]. This dynamic computational modeling, with mosaic sprouting assays *in vivo* and *in vitro*, particularly focuses on the dynamic competition between endothelial cells for the tip cell position [145].

Extracellular matrix fibers resist tension generated by cells and so generate an elastic restoring force. Additionally, the liquid component of the ECM also resists the pulling of the cells [146]. The elastic forces of ECs can be modeled using a spring system, and this has been a feature of several studies. The tip ECs are regarded as spring-dashpots [147], [148] with viscosity and friction included in the model. Also, the spring model is used in Bentley's model [144] where endothelial cells are represented by a number of nodes and springs.

## VI. WHAT CAN MATHEMATICAL MODELING TELL US ABOUT THE BRANCHING AND ANASTOMOSIS?

Vascular sprouts arising from the parent vessel begin to grow in parallel to each other [105], [149]. As the new sprout migrates through the tumor, branches develop when the sprout tip splits in two. In addition, under the influence of neighboring sprouts fusing together, closed loops can be formed— this is a process called anastomosis. Anastomosis can be formed tip to tip or tip to stalk. Anastomosis and branching is illustrated in Fig. 5. As can be intuitively seen, two lines will nearly always meet each other in 2D space while two lines in 3D will nearly always miss. The main drawback of one or two-dimensional mathematical models is that they are not able to interpret anastomosis in a clear way. The inclusion of branching and anastomosis to the mathematical framework assists with generating more realistic capillary simulations.

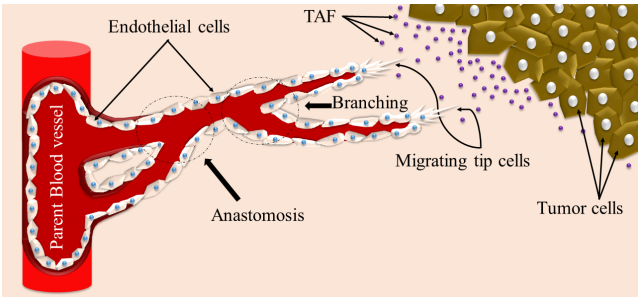


**FIGURE 5.** Early events in sprouting angiogenesis are given in this figure. The migration of ECs under the influence of TAFs has been demonstrated. The process of branching and anastomosis is a significant issue in angiogenesis and is illustrated here.

Several approaches are proposed to consider with branching and anastomosis in angiogenesis models. Earlier models [87] include extra rules for branching and anastomosis, while no rules are imposed in the latest mathematical models [135], and they are capable of simulating these issues naturally as a result of considered dynamics in the model.

The process of anastomosis is explained in a discrete model [150] in the most natural way when a sprout tip comes within the distance of a single cell from another sprout (either tip or main body), the sprout tip vanishes and its velocity is set to zero. Branching is accounted for using a specific probability. In the same way, the generation of new sprouts, branching is assumed [87] only from existing sprout tips, and branching is conditioned on a sufficient number of ECs around the tips. The formation of loops by capillary sprouts, anastomosis, is simply simulated by connecting one sprout to another neighboring vessel considering the finding that anastomosis starts to occur at some definite distance away from the parent vessel [105].

In a more recent study, tip ECs are modeled as circular, mesh-free, discrete agents that may potentially be activated and deactivated [151]. The result from defined branching and anastomosis rules leads to the activation and deactivation of cells in this model. Recent *in vivo* experiments show that anastomosis is driven by filopodia contact sensing rather than through chemotaxis [152]. This finding is used to model anastomosis in a mathematical framework based on the dependency of tumor-induced vascular networks on TAFs [117]. The model captures capillaries at full scale, the plastic dynamics of tumor-induced capillary networks at long time scales, and highlights the key role played by filopodia during angiogenesis.

In another study [135], it is assumed that the direction of sprout migration is predominantly determined by chemotaxis and EC adhesion to and movement along the matrix fibers. Because the tip cells encounter variable matrix densities and other stromal cells, the sprout changes direction to find a low resistance way through the stroma leading to branching and anastomosis. The numerical simulations show that no branching occurs in a homogeneous extracellular environment due to a loss of adhesive guidance cues.

## VII. WHAT CAN THE MATHEMATICAL MODELS OF ANGIOGENESIS TELL US ABOUT THERAPIES?

Drug delivery in tumors is associated with efficiency and structure of perfused vessels [153]–[155]. Experimental studies illustrate that the patients with low tumor perfusion show poorer response to chemotherapy and therefore shorter survival in comparison of patients with high perfusion [156]–[158].

Although anti-angiogenic treatments are proposed to avoid the formation of new capillary networks [16], the treatment can potentially regulate the tumor vasculature and enhance tumor perfusion for more efficient drug delivery [159], [160]. The incorporation of blood flow through the generated vascular networks has highlighted issues that not only may have major implications for the delivery of chemotherapeutic drugs to the tumor, but also there are implications for the delivery of anti-angiogenic drugs into the network itself.

Therefore, the interactions between the changing tumor vascular structure and blood flow have been evaluated by integrating an updated version of the multi-dimensional mathematical model explaining the drug delivery and efficiency of therapy.

As an early attempt towards taking advantage of mathematical modeling of blood flow for tracking chemotherapy drugs through tumor-induced vascular networks, one proposed approach was to chase concentration profiles of an injected tracer [161].

In order to examine the role of vascular changes in tumors, a simulation was carried out for two different cases with and without vascular changes [131]. As a consequence, tumor cells were subjected to less change in oxygen conditions and were mostly kept non-proliferative compared to the case without vascular changes. The computational model propose that tumor dormancy can potentially appear as one possible consequence of the intense vascular changes in the host tissue.

A 2D image-based approach is proposed to reconstruct the capillary network for extracting the various measures of fluid properties and drug concentration. A model based on convection-diffusion-reaction (CDR) equations is used to simulate the drug binding and uptake by tumor cells [164].

## VIII. DISCUSSION AND CONCLUSION

Mathematical models have been employed to understand tumor-induced angiogenesis. The models may be constructed in order to explore the hidden patterns in tumor-induced angiogenesis using real clinical data. The direct relationship between the models and real data is the benefit of these data-driven models. Alternatively, the models can be constructed from a mechanistic understanding of tumor angiogenesis in the absence of clinical data. In both scenarios, mathematical modeling cannot be firmly established in tumor-induced angiogenesis studies unless the approaches are rigorously validated with experimental data.

The fact that the density of endothelial cells and the formation of vessels are influenced by several factors such as TAF, oxygen, fibronectin, MMP, and tumor tissue, these are used as the backbone of mathematical and computational models. Partial differential equations are used to explain the behavior of different agents such as the population of ECs, growth of tumor cells, etc. Also, more recent angiogenic mathematical frameworks have included the role of blood flow into the vascular network. However, the blood flow parameter is simplified to depend only on the radius of blood vessels and may be an oversimplification of the true biology. The impact of anastomosis and branching are added to the models via considering a set of 'if-then' rules. Recent *in vivo* experiments revealed that anastomosis is driven by filopodia contact sensing rather than through chemotaxis. This finding is considered to model anastomosis in a mathematical framework based on the dependency of tumor-induced vascular networks on TAFs.

Moreover, significant progress in tumor angiogenesis can be made by developing combined models that aim at understanding the cell dynamics, shape and interactions. The cellular Potts model, which simulates the behavior of cells based on energy minimization, is widely used to model cell shape. The development of agent-based models has played a significant role in the description of cell interactions in tumor-induced angiogenesis.

Mathematical and computational models have provided useful insights into pathologies and have been used to characterize the response of anti-angiogenic therapies. Earlier attempts at characterization of cancer therapies using angiogenesis models is rooted in the fact that drug delivery in tumors is associated with efficiency and structure of perfused vessels. As a practical application, the mathematical modeling of blood flow may be used to better administer chemotherapy drugs that track through tumor-induced vascular networks.

## REFERENCES

[1] A. Birbrair, T. Zhang, Z.-M. Wang, M. L. Messi, J. D. Olson, A. Mintz, and O. Delbono, "Type-2 pericytes participate in normal and tumoral angiogenesis," *Amer. J. Physiol.-Cell Physiol.*, vol. 307, no. 1, pp. C25–C38, Jul. 2014.

[2] A. Birbrair, T. Zhang, Z.-M. Wang, M. L. Messi, A. Mintz, and O. Delbono, "Pericytes at the intersection between tissue regeneration and pathology: Figure 1," *Clin. Sci.*, vol. 128, no. 2, pp. 81–93, Jan. 2015, doi: 10.1042/CS20140278.

[3] J. S. Penn, *Retinal and Choroidal Angiogenesis*. Dordrecht, The Netherlands: Springer, 2008.

[4] P. Carmeliet and R. K. Jain, "Molecular mechanisms and clinical applications of angiogenesis," *Nature*, vol. 473, no. 7347, 2011, pp. 298–307, doi: 10.1038/nature10144.

[5] T. Roque, L. Risser, V. Kersemans, S. Smart, D. Allen, P. Kinchesh, S. Gilchrist, A. L. Gomes, J. A. Schnabel, and M. A. Chappell, "A DCE-MRI driven 3-D reaction-diffusion model of solid tumor growth," *IEEE Trans. Med. Imag.*, vol. 37, no. 3, pp. 724–732, Mar. 2018.

[6] M. Langer, R. Prisby, Z. Peter, A. Guignandon, M.-H. Lafage-Proust, and F. Peyrin, "Simultaneous 3D imaging of bone and vessel microstructure in a rat model," *IEEE Trans. Nucl. Sci.*, vol. 58, no. 1, pp. 139–145, Feb. 2011.

[7] C. Patsch *et al.*, "Generation of vascular endothelial and smooth muscle cells from human pluripotent stem cells," *Nature Cell Biol.*, vol. 17, no. 8, pp. 994–1003, Jul. 2015, doi: 10.1038/ncb3205.

[8] Z. Z. Wang, P. Au, T. Chen, Y. Shao, L. M. Daheron, H. Bai, M. Arzigian, D. Fukumura, R. K. Jain, and D. T. Scadden, "Endothelial cells derived from human embryonic stem cells form durable blood vessels *in vivo*," *Nature Biotechnol.*, vol. 25, no. 3, pp. 317–318, Feb. 2007, doi: 10.1038/nbt1287.

[9] K. J. Bayless and G. E. Davis, "The Cdc42 and Rac1 GTPases are required for capillary lumen formation in three-dimensional extracellular matrices," *J. Cell. Sci.*, vol. 115, no. 6, pp. 1123–1136, 2002.

[10] T. L. Jackson, *Modeling Tumor Vasculature: Molecular, Cellular, and Tissue Level Aspects and Implications*. New York, NY, USA: Springer, 2011.

[11] L. Holmgren, M. S. O'Reilly, and J. Folkman, "Dormancy of micrometastases: Balanced proliferation and apoptosis in the presence of angiogenesis suppression," *Nature Med.*, vol. 1, no. 2, pp. 149–153, Feb. 1995.

[12] S. Parangi, M. O'Reilly, G. Christofori, L. Holmgren, J. Grosfeld, J. Folkman, and D. Hanahan, "Antiangiogenic therapy of transgenic mice impairs de novo tumor growth.," *Proc. Nat. Acad. Sci. USA*, vol. 93, no. 5, pp. 2002–2007, Mar. 1996.

[13] N. Nishida, H. Yano, T. Nishida, T. Kamura, and M. Kojiro, "Angiogenesis in cancer," *Vascular Health Risk*, vol. 2, no. 3, pp. 213–219, 2006.

[14] N. Tang, L. Wang, J. Esko, F. J. Giordano, Y. Huang, H.-P. Gerber, N. Ferrara, and R. S. Johnson, "Loss of HIF-1$\alpha$ in endothelial cells disrupts a hypoxia-driven VEGF autocrine loop necessary for tumorigenesis," *Cancer Cell*, vol. 6, no. 5, pp. 485–495, Nov. 2004, doi: 10.1016/j.ccr.2004.09.026.

[15] C. Y. Lee and V. L. Bautch, "Ups and downs of guided vessel sprouting: The role of polarity," *Physiology*, vol. 26, no. 5, pp. 326–333, Oct. 2011, doi: 10.1152/physiol.00018.2011.

[16] J. Folkman, "Tumor angiogenesis: Therapeutic implications," *New England J. Med.*, vol. 285, no. 21, pp. 1182–1186, 1971.

[17] P. Salven, A. Lymboussaki, and P. Heikkila, "Vascular endothelial, growth factors VEGF-B and VEGF-C are expressed in human tumors," *Am. J. Pathol*, vol. 153, pp. 103–108, Jul. 1998.

[18] M. S. Stack, S. Gately, L. M. Bafetti, J. J. Enghild, and G. A. Soff, "Angiostatin inhibits endothelial and melanoma cellular invasion by blocking matrix-enhanced plasminogen activation," *Biochem. J.*, vol. 340, no. 1, pp. 77–84, May 1999.

[19] M. S. O'Reilly, T. Boehm, and Y. Shing, "Endostatin: An endogenous, inhibitor of angiogenesis and tumor growth," *Cell*, vol. 88, pp. 277–284, Jan. 1997.

[20] F. Winkler, S. V. Kozin, and R. T. Tong, "Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: Role of oxygenation, angiopoietin-1, and matrix metalloproteinases," *Cancer Cell*, vol. 6, pp. 553–563, Dec. 2004.
[21] M. Majima, I. Hayashi, and M. Muramatsu, "Cyclo-oxygenase-2 enhances basic fibroblast growth factor-induced angiogenesis through induction of vascular endothelial growth factor in rat sponge implants," *Brit. J. Pharmacol*, vol. 268, pp. 641–649, Jun. 2000.
[22] G. L. Semenza, "Signal transduction to hypoxia-inducible factor 1," *Biochem. Pharmacol.*, vol. 64, nos. 5–6, pp. 993–998, Sep. 2002.
[23] N. V. de Mendizábal, J. Carneiro, R. V. Solé, J. Goñi, J. Bragard, I. M. Forero, S. M. Pasamar, J. Sepulcre, J. Torrealdea, F. Bagnato, J. Garcia-Ojalvo, and P. Villoslada, "Modeling the effector-regulatory T cell cross-regulation reveals the intrinsic character of relapses in multiple sclerosis," *BMC. Syst. Biol.*, vol. 5, no. 114, p. 114, Dec. 2011, doi: 10.1186/1752-0509-5-114.
[24] R. Martinez-Corral and J. Garcia-Ojalvo, "Modeling cellular regulation by pulsatile inputs," *Current Opinion Syst. Biol.*, vol. 3, pp. 23–29, Jun. 2017.
[25] S. L. Spencer and P. K. Sorger, "Measuring and modeling apoptosis in single cells," *Cell*, vol. 144, no. 6, pp. 926–939, Mar. 2011.
[26] P. C. Davies, L. Demetrius, and J. A. Tuszynski, "Cancer as a dynamical phase transition," *Theor. Biol. Med. Model.*, vol. 8, no. 1, p. 30, 2011, doi: 10.1186/1742-4682-8-30.
[27] C. Li and G. Balazsi, "A landscape view on the interplay between EMT and cancer metastasis," *npj Syst. Biol. Appl.*, vol. 4, no. 1, pp. 1–9, Aug. 2018, doi: 10.1038/s41540-018-0068-x.
[28] M. Dorraki, A. Fouladzadeh, S. J. Salamon, A. Allison, B. J. Coventry, and D. Abbott, "On detection of periodicity in C-reactive protein (CRP) levels," *Sci. Rep.*, vol. 8, no. 1, Aug. 2018, Art. no. 11979.
[29] A. L. Hill, D. I. S. Rosenbloom, M. A. Nowak, and R. F. Siliciano, "Insight into treatment of HIV infection from viral dynamics models," *Immunol. Rev.*, vol. 285, no. 1, pp. 9–25, Aug. 2018.
[30] D. Abbott, "The reasonable ineffectiveness of mathematics," *Proc. IEEE*, vol. 101, no. 10, 2013, pp. 2147–2153.
[31] M. Dorraki, A. Fouladzadeh, S. J. Salamon, A. Allison, B. J. Coventry, and D. Abbott, "Can C-reactive protein (CRP) time series forecasting be achieved via deep learning?" *IEEE Access*, vol. 7, pp. 59311–59320, 2019.
[32] M. Dorraki, A. Fouladzadeh, A. Allison, B. Coventry, and D. Abbott, "Deep learning for C-Reactive protein prediction," in *Proc. 2nd Eur. Conf. Electr. Eng. Comput. Sci. (EECS)*, Dec. 2018, pp. 160–164, doi: 10.1109/EECS.2018.00037.
[33] R. Pankov, "Fibronectin at a glance," *J. Cell Sci.*, vol. 115, no. 20, pp. 3861–3863, Oct. 2002.
[34] B. Alberts, D. Bray, J. Lewis, M. Raff, K. Roberts, and J. D. Watson, *Molecular Biology of the Cell*, 3rd ed. New York, NY, USA: Garland, 1994.
[35] P. Salven, K. Hattori, B. Heissig, and S. Rafii, "Interleukin-1$\alpha$ promotes angiogenesis *in vivo* via VEGFR-2 pathway by inducing inflammatory cell VEGF synthesis and secretion," *FASEB J.*, vol. 16, no. 11, pp. 1471–1473, Jul. 2002.
[36] B. Motro, A. Itin, L. Sachs, and E. Keshet, "Pattern of interleukin 6 gene expression *in vivo* suggests a role for this cytokine in angiogenesis.," *Proc. Nat. Acad. Sci. USA*, vol. 87, no. 8, pp. 3092–3096, Apr. 1990.
[37] A. Koch, P. Polverini, S. Kunkel, L. Harlow, L. DiPietro, V. Elner, S. Elner, and R. Strieter, "Interleukin-8 as a macrophage-derived mediator of angiogenesis," *Science*, vol. 258, no. 5089, pp. 1798–1801, Dec. 1992.
[38] S. Huang, K. Xie, C. D. Bucana, S. E. Ullrich, and M. Bar-Eli, "Interleukin 10 suppresses tumor growth and metastasis of human melanoma cells: Potential inhibition of angiogenesis," *Clin. Cancer Res.*, vol. 2, pp. 1969–1979, Dec. 1996.
[39] C. Sgadari, A. Angiolillo, and G. Tosato, "Inhibition of angiogenesis by interleukin-12 is mediated by the interferon-inducible protein 10," *Blood*, vol. 87, no. 9, pp. 3877–3882, May 1996.
[40] N. Ferrara, K. Houck, L. Jakeman, and D. W. Leung, "Molecular and biological properties of the vascular endothelial growth factor family of proteins," *Endocrine Rev.*, vol. 13, no. 1, pp. 18–32, Feb. 1992.
[41] J. Slavin, "Fibroblast growth factors: At the heart of angiogenesis," *Cell Biol. Int.*, vol. 19, pp. 431–444, May 1995.
[42] K. Kishimoto, S. Liu, T. Tsuji, K. A. Olson, and G.-F. Hu, "Endogenous angiogenin in endothelial cells is a general requirement for cell proliferation and angiogenesis," *Oncogene*, vol. 24, no. 3, pp. 445–456, Nov. 2005.
[43] A. B. Roberts, M. B. Sporn, R. K. Assoian, J. M. Smith, N. S. Roche, L. M. Wakefield, U. I. Heine, L. A. Liotta, V. Falanga, and J. H. Kehrl, "Transforming growth factor type beta: Rapid induction of fibrosis and angiogenesis *in vivo* and stimulation of collagen formation *in vitro*," *Proc. Nat. Acad. Sci. USA*, vol. 83, no. 12, pp. 4167–4171, Jun. 1986.
[44] A. Luttun, M. Tjwa, and P. Carmeliet, "Placental growth factor (PlGF) and its receptor Flt-1 (VEGFR-1): Novel therapeutic targets for angiogenic disorders," *Ann. New York Acad. Sci.*, vol. 979, pp. 80–93, Dec. 2002.
[45] F. Bussolino, M. F. Di Renzo, M. Ziche, E. Bocchietto, M. Olivero, L. Naldini, G. Gaudino, L. Tamagnone, A. Coffer, and P. M. Comoglio, "Hepatocyte growth factor is a potent angiogenic factor which stimulates endothelial cell motility and growth.," *J. Cell Biol.*, vol. 119, no. 3, pp. 629–641, Nov. 1992.
[46] T. Natori, M. Sata, M. Washida, Y. Hirata, R. Nagai, and M. Makuuchi, "G-CSF stimulates angiogenesis and promotes tumor growth: Potential contribution of bone marrow-derived endothelial progenitor cells," *Biochem. Biophys. Res. Commun.*, vol. 297, no. 4, pp. 1058–1061, Oct. 2002.
[47] E. Voronov, D. S. Shouval, Y. Krelin, E. Cagnano, D. Benharroch, Y. Iwakura, C. A. Dinarello, and R. N. Apte, "IL-1 is required for tumor invasiveness and angiogenesis," *Proc. Nat. Acad. Sci. USA*, vol. 100, no. 5, pp. 2645–2650, Feb. 2003.
[48] T. Cohen, D. Nahari, L. W. Cerem, G. Neufeld, and B.-Z. Levi, "Interleukin 6 induces the expression of vascular endothelial growth factor," *J. Biol. Chem.*, vol. 271, no. 2, pp. 736–741, Jan. 1996.
[49] E. E. Voest, B. M. Kenyon, M. S. O'Reilly, G. Truitt, R. J. D'Amato, and J. Folkman, "Inhibition of angiogenesis *in vivo* by interleukin 12," *J. Nat. Cancer Inst.*, vol. 87, pp. 581–586, Apr. 1995.
[50] P. Dentelli, L. Del Sorbo, A. Rosso, A. Molinar, G. Garbarino, G. Camussi, L. Pegoraro, and M. F. Brizzi, "Human IL-3 stimulates endothelial cell motility and promotes *in vivo* new vessel formation," *J. Immunol.*, vol. 163, no. 4, 1999, pp. 2151–2159.
[51] K. S. Raju, G. Alessandri, M. Ziche, and P. M. Gullino, "Ceruloplasmin, copper ions, and angiogenesis," *J. Nat. Cancer Inst.*, vol. 69, pp. 1183–1188, Nov. 1982.
[52] S.-G. Shian, Y.-R. Kao, F. Y.-H. Wu, and C.-W. Wu, "Inhibition of invasion and angiogenesis by zinc-chelating agent disulfiram," *Mol. Pharmacol.*, vol. 64, no. 5, pp. 1076–1084, Oct. 2003.
[53] X. Jin, M. Yagi, N. Akiyama, T. Hirosaki, S. Higashi, C.-Y. Lin, R. B. Dickson, H. Kitamura, and K. Miyazaki, "Matriptase activates stromelysin (MMP-3) and promotes tumor growth and angiogenesis," *Cancer Sci.*, vol. 97, no. 12, pp. 1327–1334, Dec. 2006.
[54] R. E. Galardy, D. Grobelny, H. G. Foellmer, and L. A. Fernandez, "Inhibition of angiogenesis by the matrix metalloprotease inhibitor N-[2R-2-(hydroxamidocarbonymethyl)-4-methylpentanoyl)]-L-tryptophan methylamide," *Cancer Res.*, vol. 54, pp. 4715–4718, Sep. 1994.
[55] T. H. Vu, J. M. Shipley, G. Bergers, J. E. Berger, J. A. Helms, D. Hanahan, S. D. Shapiro, R. M. Senior, and Z. Werb, "MMP-9/Gelatinase b is a key regulator of growth plate angiogenesis and apoptosis of hypertrophic chondrocytes," *Cell*, vol. 93, no. 3, pp. 411–422, May 1998.
[56] D. Keppler, M. Sameni, K. Moin, B. F. Sloane, T. Mikkelsen, and C. A. Diglio, "Tumor progression and angiogenesis: Cathepsin b &Co.," *Biochemistry Cell Biol.*, vol. 74, no. 6, pp. 799–810, Dec. 1996, doi: 10.1139/o96-086.
[57] C. Iwasaka, K. Tanaka, M. Abe, and Y. Sato, "Ets-1 regulates angiogenesis by inducing the expression of urokinase-type plasminogen activator and matrix metalloproteinase-1 and the migration of vascular endothelial cells," *J. Cellular Physiol.*, vol. 169, no. 3, pp. 522–531, Dec. 1996.
[58] P. Brooks, R. Clark, and D. Cheresh, "Requirement of vascular integrin alpha v beta 3 for angiogenesis," *Science*, vol. 264, no. 5158, pp. 569–571, Apr. 1994, doi: 10.1126/science.7512751.
[59] P. C. Maisonpierre, C. Suri, P. F. Jones, S. Bartunkova, S. J. Wiegand, C. Radziejewski, D. Compton, J. McClain, T. H. Aldrich, N. Papadopoulos, T. J. Daly, S. Davis, T. N. Sato, and G. D. Yancopoulos, "Angiopoietin-2, a natural antagonist for Tie2 that disrupts *in vivo* angiogenesis," *Science*, vol. 277, no. 5322, pp. 55–60, Jul. 1997, doi: 10.1126/science.277.5322.55.
[60] S. L. Amaral, P. E. Papanek, and A. S. Greene, "Angiotensin II and VEGF are involved in angiogenesis induced by short-term exercise training," *Amer. J. Physiol.-Heart Circulatory Physiol.*, vol. 281, no. 3, pp. H1163–H1169, Sep. 2001.

[61] D. Salani, G. Taraboletti, L. Rosanó, V. Di Castro, P. Borsotti, R. Giavazzi, and A. Bagnato, "Endothelin-1 induces an angiogenic phenotype in cultured endothelial cells and stimulates neovascularization *in vivo*," *Amer. J. Pathol.*, vol. 157, no. 5, pp. 1703–1711, Nov. 2000.

[62] P. M. Bauer, J. Yu, Y. Chen, R. Hickey, P. N. Bernatchez, R. Looft-Wilson, Y. Huang, F. Giordano, R. V. Stan, and W. C. Sessa, "Endothelial-specific expression of caveolin-1 impairs microvascular permeability and angiogenesis," *Proc. Nat. Acad. Sci. USA*, vol. 102, no. 1, pp. 204–209, Dec. 2004, doi: 10.1073/pnas.0406092102.

[63] K. Jaquet, K. Krause, M. Tawakol-Khodai, S. Geidel, and K.-H. Kuck, "Erythropoietin and VEGF exhibit equal angiogenic potential," *Microvascular Res.*, vol. 64, no. 2, pp. 326–333, Sep. 2002.

[64] C. Paternostro, "Hypoxia, angiogenesis and liver fibrogenesis in the progression of chronic liver diseases," *World J. Gastroenterol.*, vol. 16, no. 3, pp. 281–288, 2010.

[65] Z. von Marschall, A. Scholz, T. Cramer, G. Schafer, M. Schirner, K. Oberg, B. Wiedenmann, M. Hocker, and S. Rosewicz, "Effects of interferon alpha on vascular endothelial growth factor gene transcription and tumor angiogenesis," *J. Nat. Cancer Inst.*, vol. 95, no. 6, pp. 437–448, Mar. 2003.

[66] M. Ziche and L. Morbidelli, "Nitric oxide and angiogenesis," *J. Neurooncol.*, vol. 50, pp. 139–148, Oct. 2000.

[67] T. Miura, L. Yuan, B. Sun, H. Fujii, M. Yoshida, K. Wakame, and K.-I. Kosuna, "Isoflavone aglycon produced by culture of soybean extracts with basidiomycetes and its anti-angiogenic activity," *Biosci., Biotechnol., Biochemistry*, vol. 66, no. 12, pp. 2626–2631, 2002.

[68] P. Ben-Av, L. J. Crofford, R. L. Wilder, and T. Hla, "Induction of vascular endothelial growth factor expression in synovial fibroblasts by prostaglandin e and interleukin-1: A potential mechanism for inflammatory angiogenesis," *FEBS Lett.*, vol. 372, no. 1, pp. 83–87, 1995.

[69] D. Mukhopadhyay, L. Tsiokas, X.-M. Zhou, D. Foster, J. S. Brugge, and V. P. Sukhatme, "Hypoxic induction of human vascular endothelial growth factor expression through c-Src activation," *Nature*, vol. 375, no. 6532, pp. 577–581, Jun. 1995.

[70] Y. Ling, Y. Chen, P. Chen, H. Hui, X. Song, Z. Lu, C. Li, N. Lu, and Q. Guo, "Baicalein potently suppresses angiogenesis induced by vascular endothelial growth factor through the P53/Rb signaling pathway leading to G1/S cell cycle arrest," *Experim. Biol. Med.*, vol. 236, no. 7, pp. 851–858, Jul. 2011.

[71] S. Grugel, G. Finkenzeller, K. Weindel, B. Barleon, and D. Marme, "Both v-Ha-Ras and v-Raf stimulate expression of the vascular endothelial growth factor in NIH 3T3 cells," *J. Biol. Chem.*, vol. 270, no. 43, pp. 25915–25919, Oct. 1995.

[72] N. J. Ball, J. J. Yohn, J. G. Morelli, D. A. Norris, L. E. Golitz, and J. P. Hoeffler, "RAS mutations in human melanoma: A marker of malignant progression," *J. Investigative Dermatol.*, vol. 102, no. 3, pp. 285–290, Mar. 1994.

[73] T. A. Baudino, "C-MYC is essential for vasculogenesis and angiogenesis during development and tumor progression," *Genes Develop.*, vol. 16, no. 19, pp. 2530–2543, Oct. 2002.

[74] M. M. Vleugel, A. E. Greijer, R. Bos, E. van der Wall, and P. J. van Diest, "C-jun activation is associated with proliferation and angiogenesis in invasive breast cancer," *Hum. Pathol.*, vol. 37, no. 6, pp. 668–674, Jun. 2006.

[75] L. A. Liotta, G. M. Saidel, and J. Kleinerman, "Diffusion model of tumor vascularization," *Bull. Math. Biol.*, vol. 39, pp. 117–128, Jan. 1977.

[76] D. F. Zawicki, R. K. Jain, G. W. Schmid-Schoenbein, and S. Chien, "Dynamics of neovascularization in normal tissue," *Microvascular Res.*, vol. 21, no. 1, pp. 27–47, Jan. 1981.

[77] D. Balding and D. L. S. McElwain, "A mathematical model of tumour-induced capillary growth," *J. Theor. Biol.*, vol. 114, no. 1, pp. 53–73, May 1985.

[78] M. A. J. Chaplain and A. M. Stuart, "A model mechanism for the chemotactic response of endothelial cells to tumour angiogenesis factor," *Math. Med. Biol.*, vol. 10, no. 3, pp. 149–168, 1993.

[79] H. Byrne and M. Chaplain, "Mathematical models for tumour angiogenesis: Numerical simulations and nonlinear wave solutions," *Bull. Math. Biol.*, vol. 57, no. 3, pp. 461–486, 1995.

[80] M. Orme, "A mathematical model of the first steps of tumour-related angiogenesis: Capillary sprout formation and secondary branching," *Math. Med. Biol.*, vol. 13, no. 2, pp. 73–98, Jun. 1996.

[81] L. Edelstein, "The propagation of fungal colonies: A model for tissue growth," *J. Theor. Biol.*, vol. 98, no. 4, pp. 679–701, Oct. 1982.

[82] A. Niemisto, V. Dunmire, O. Yli-Harja, W. Zhang, and I. Shmulevich, "Robust quantification of *in vitro* angiogenesis through image analysis," *IEEE Trans. Med. Imag.*, vol. 24, no. 4, pp. 549–553, Apr. 2005.

[83] C. N. Doukas, I. Maglogiannis, and A. A. Chatziioannou, "Computer-supported angiogenesis quantification using image analysis and statistical averaging," *IEEE Trans. Inf. Technol. Biomed.*, vol. 12, no. 5, pp. 650–657, Sep. 2008.

[84] M. J. Gounis, B. B. Lieber, K. A. Webster, and A. K. Wakhloo, "A novel angiographic methodology for the quantification of angiogenesis," *IEEE Trans. Biomed. Eng.*, vol. 55, no. 3, pp. 996–1003, Mar. 2008.

[85] N. F. Britton, *Essential Mathematical Biology*. London, U.K.: Springer, 2003.

[86] D. Irimia, "Adaptive-control model for neutrophil ORIENTATION in the direction of chemical gradients," *Biophys. J.*, vol. 96, no. 3, pp. 629a–630a, Feb. 2009.

[87] A. Anderson, "Continuous and discrete mathematical models of tumor-induced angiogenesis," *Bull. Math. Biol.*, vol. 60, no. 5, pp. 857–899, Sep. 1998.

[88] A. Stevens and H. G. Othmer, "Aggregation, blowup, and collapse: The ABC's of taxis in reinforced random walks," *SIAM J. Appl. Math.*, vol. 57, no. 4, pp. 1044–1081, Aug. 1997.

[89] M. J. Plank, "A reinforced random walk model of tumour angiogenesis and anti-angiogenic strategies," *Math. Med. Biol.*, vol. 20, no. 2, pp. 135–181, Jun. 2003.

[90] N. V. Mantzaris, S. Webb, and H. G. Othmer, "Mathematical modeling of tumor-induced angiogenesis," *J. Math. Biol.*, vol. 49, pp. 111–187, Aug. 2004.

[91] T. A. M. Heck, M. M. Vaeyens, and H. Van Oosterwyck, "Computational models of sprouting angiogenesis and cell migration: Towards multiscale mechanochemical models of angiogenesis," *Math. Model. Natural Phenomena*, vol. 10, no. 1, pp. 108–141, Feb. 2015.

[92] M. Plank and B. Sleeman, "Lattice and non-lattice models of tumour angiogenesis," *Bull. Math. Biol.*, vol. 66, no. 6, pp. 1785–1819, Nov. 2004.

[93] G. Lemon, D. Howard, F. R. A. J. Rose, and J. R. King, "Individual-based modelling of angiogenesis inside three-dimensional porous biomaterials," *Biosystems*, vol. 103, no. 3, pp. 372–383, Mar. 2011.

[94] D. H. Ausprunk and J. Folkman, "Migration and proliferation of endothelial cells in preformed and newly formed blood vessels during tumor angiogenesis," *Microvascular Res.*, vol. 14, no. 1, pp. 53–65, Jul. 1977.

[95] D. Hanahan, "Signaling vascular morphogenesis and maintenance," *Science*, vol. 277, no. 5322, pp. 48–50, Jul. 1997.

[96] C. R. Birdwell, D. Gospodarowicz, and G. L. Nicolson, "Identification, localisation and role of fibronectin in cultured endothelial cells," *Proc. Nat. Acad. Sci. USA*, vol. 75, pp. 3273–3277, Jul. 1978.

[97] C. R. Birdwell, A. R. Brasier, and L. A. Taylor, "Two-dimensional peptide mapping of fibronectins from bovine aortic endothelial cells and bovine plasma," *Biochem. Biophy. Res. Commun.*, vol. 97, no. 2, pp. 574–581, Nov. 1980.

[98] E. A. Jaffee and D. F. Mosher, "Synthesis of fibronectin by cultured endothelial cells," *J. Exp. Med.*, vol. 147, 1978, pp. 1779–1791.

[99] E. J. Macarak, E. Kirby, T. Kirk, and N. A. Kefalides, "Synthesis of cold-insoluble globulin by cultured calf endothelial cells," *Proc. Nat. Acad. Sci. USA*, vol. 75, no. 6, pp. 2621–2625, Jun. 1978.

[100] P. Monaghan, M. J. Warburton, N. Perusinghe, and P. S. Rudland, "Topographical arrangement of basement membrane proteins in lactating rat mammary gland: Comparison of the distribution of type IV collagen, laminin, fibronectin, and Thy-1 at the ultrastructural level.," *Proc. Nat. Acad. Sci. USA*, vol. 80, no. 11, pp. 3344–3348, Jun. 1983.

[101] H. Rieder, G. Ramadori, H.-P. Dienes, and K.-H.-M. Z. Büschenfelde, "Sinusoidal endothelial cells from guinea pig liver synthesize and secrete cellular fibronectin *in vitro*," *Hepatology*, vol. 7, no. 5, pp. 856–864, Sep. 1987.

[102] H. Sawada, H. Furthmayr, H. Konomi, and Y. Nagai, "Immunoelectron-microscopic localization of extracellular matrix components produced by bovine corneal endothelial cells *in vitro*," *Experim. Cell Res.*, vol. 171, no. 1, pp. 94–109, Jul. 1987.

[103] R. O. Hynes, *Fibronectins*. New York, NY, USA: Springer-Verlag, 1990.

[104] S. R. McDougall, A. R. A. Anderson, and M. A. J. Chaplain, "Mathematical modelling of dynamic adaptive tumour-induced angiogenesis: Clinical implications and therapeutic targeting strategies," *J. Theor. Biol.*, vol. 241, no. 3, pp. 564–589, Aug. 2006.

[105] N. Paweletz and M. Knierim, "Tumor-related angiogenesis," *Crit. Rev. Oncol./Hematol.*, vol. 9, pp. 197–242, Jan. 1989.

[106] A. R. A. Anderson, "A hybrid mathematical model of solid tumour invasion: The importance of cell adhesion," *Math. Med. Biol. A, J. IMA*, vol. 22, no. 2, pp. 163–186, Jun. 2005, doi: 10.1093/imammb/dqi005.

[107] J. Lyu, J. Cao, P. Zhang, Y. Liu, and H. Cheng, "Coupled hybrid continuum-discrete model of tumor angiogenesis and growth," *PLoS ONE*, vol. 11, no. 10, Oct. 2016, Art. no. e0163173.

[108] S. L. Spencer, M. J. Berryman, J. A. García, and D. Abbott, "An ordinary differential equation model for the multistep transformation to cancer," *J. Theor. Biol.*, vol. 231, no. 4, pp. 515–524, Dec. 2004.

[109] R. Gonzalez-Cinca, R. Folch, R. Benitez, L. Ramirez-Piscina, and J. Casademunt, *Phase-Field Models in Interfacial Pattern Formation out of Equilibrium*, E. Korutcheva and R. Cuerno, Eds. New York, NY, USA: Nova, 2004, pp. 203–236.

[110] G. J. Fix, *Free Boundary Problems: Theory and Applications*, A. Fasano and M. Primicerio, Eds. New York, NY, USA: Pitman, 1983.

[111] J. S. Langer, *Models of Pattern Formation in First-Order Phase Transitions* (Series on Directions in Condensed Matter Physics). Singapore: World Scientific, 1986, pp. 165–186.

[112] W. J. Boettinger, J. A. Warren, C. Beckermann, and A. Karma, "Phase-field simulation of solidification," *Annu. Rev. Mater. Res.*, vol. 32, no. 1, pp. 163–194, Aug. 2002, doi: 10.1146/annurev.matsci.32.101901.155803.

[113] R. Folch, J. Casademunt, A. Hernández-Machado, and L. Ramírez-Piscina, "Phase-field model for hele-shaw flows with arbitrary viscosity contrast. II. numerical study," *Phys. Rev. E, Stat. Phys. Plasmas Fluids Relat. Interdiscip. Top.*, vol. 60, no. 2, pp. 1734–1740, Aug. 1999.

[114] A. Karma, D. A. Kessler, and H. Levine, "Phase-field model of mode III dynamic fracture," *Phys. Rev. Lett.*, vol. 87, no. 4, Jul. 2001, Art. no. 045501.

[115] E. Martínez-Pañeda, A. Golahmar, and C. F. Niordson, "A phase field formulation for hydrogen assisted cracking," *Comput. Methods Appl. Mech. Eng.*, vol. 342, pp. 742–761, Dec. 2018.

[116] R. D. M. Travasso, E. Corvera Poiré, M. Castro, J. C. Rodrguez-Manzaneque, and A. Hernández-Machado, "Tumor angiogenesis and vascular patterning: A mathematical model," *PLoS ONE*, vol. 6, no. 5, May 2011, Art. no. e19989.

[117] G. Vilanova, I. Colominas, and H. Gomez, "A mathematical model of tumour angiogenesis: Growth, regression and regrowth," *J. Roy. Soc. Interface*, vol. 14, no. 126, Jan. 2017, Art. no. 20160918, doi: 10.1098/rsif.2016.0918.

[118] S. Lehoux and A. Tedgui, "Signal transduction of mechanical stresses in the vascular wall," *Hypertension*, vol. 32, no. 2, pp. 338–345, Aug. 1998.

[119] L. A. Taber, "An optimization principle for vascular radius including the effects of smooth muscle tone," *Biophys. J.*, vol. 74, no. 1, pp. 109–114, Jan. 1998.

[120] C. M. Quick, W. L. Young, E. F. Leonard, S. Joshi, E. Gao, and T. Hashimoto, "Model of structural and functional adaptation of small conductance vessels to arterial hypotension," *Amer. J. Physiol.-Heart Circulatory Physiol.*, vol. 279, no. 4, pp. H1645–H1653, Oct. 2007.

[121] R. Gödde and H. Kurz, "Structural and biophysical simulation of angiogenesis and vascular remodeling," *Develop. Dyn.*, vol. 220, no. 4, pp. 387–401, Mar. 2001.

[122] A. B. Fisher, S. Chien, A. I. Barakat, and R. M. Nerem, "Endothelial cellular response to altered shear stress," *Amer. J. Physiol.-Lung Cellular Mol. Physiol.*, vol. 281, no. 3, pp. L529–L533, Sep. 2001.

[123] A. R. Pries, T. W. Secomb, and P. Gaehtgens, "Structural adaptation and stability of microvascular networks: Theory and simulations," *Amer. J. Physiol.-Heart Circulatory Physiol.*, vol. 275, no. 2, pp. H349–H360, Aug. 1998.

[124] T. Alarcón, H. M. Byrne, and P. K. Maini, "A cellular automaton model for tumour growth in inhomogeneous environment," *J. Theor. Biol.*, vol. 225, no. 2, pp. 257–274, Nov. 2003.

[125] A. M. Lewis, M. A. J. Chaplain, J. P. Keener, and P. K. Maini, *Mathematical Biology*. Providence, RI, USA: AMS, 2009.

[126] A. Stéphanou, S. R. McDougall, A. R. A. Anderson, and M. A. J. Chaplain, "Mathematical modelling of the influence of blood rheological properties upon adaptative tumour-induced angiogenesis," *Math. Comput. Model.*, vol. 44, nos. 1–2, pp. 96–123, Jul. 2006.

[127] P. Macklin, S. McDougall, A. R. A. Anderson, M. A. J. Chaplain, V. Cristini, and J. Lowengrub, "Multiscale modelling and nonlinear simulation of vascular tumour growth," *J. Math. Biol.*, vol. 58, nos. 4–5, pp. 765–798, Sep. 2008.

[128] M. R. Owen, T. Alarcón, P. K. Maini, and H. M. Byrne, "Angiogenesis and vascular remodelling in normal and cancerous tissues," *J. Math. Biol.*, vol. 58, nos. 4–5, pp. 689–721, Oct. 2008.

[129] S. Suarez and K. Ballmer-Hofer, "VEGF transiently disrupts gap junctional communication in endothelial cells," *J. Cell Sci.*, vol. 114, pp. 1229–1235, Mar. 2001.

[130] J. A. Nagy, A. M. Dvorak, and H. F. Dvorak, "Vascular hyperpermeability, angiogenesis, and stroma generation," *Cold Spring Harbor Perspect. Med.*, vol. 2, no. 2, Oct. 2011, Art. no. a006544.

[131] A. Stéphanou, A. C. Lesart, J. Deverchére, A. Juhem, A. Popov, and F. Estéve, "How tumour-induced vascular changes alter angiogenesis: Insights from a computational model," *J. Theor. Biol.*, vol. 419, pp. 211–226, Apr. 2017.

[132] M. Soltani and P. Chen, "Numerical modeling of interstitial fluid flow coupled with blood flow through a remodeled solid tumor microvascular network," *PLoS ONE*, vol. 8, no. 6, Jun. 2013, Art. no. e67025.

[133] E. Trucco, H. Azegrouz, and B. Dhillon, "Modeling the tortuosity of retinal vessels: Does caliber play a role?" *IEEE Trans. Biomed. Eng.*, vol. 57, no. 9, pp. 2239–2247, Sep. 2010.

[134] H.-C. Han, "Twisted blood vessels: Symptoms, etiology and biomechanical mechanisms," *J. Vascular Res.*, vol. 49, no. 3, pp. 185–197, 2012.

[135] A. L. Bauer, T. L. Jackson, and Y. Jiang, "A cell-based model exhibiting branching and anastomosis during tumor-induced angiogenesis," *BioPhys. J.*, vol. 92, no. 9, pp. 3105–3121, May 2007.

[136] J. T. Daub and R. M. H. Merks, "A cell-based model of Extracellular-Matrix-Guided endothelial cell migration during angiogenesis," *Bull. Math. Biol.*, vol. 75, no. 8, pp. 1377–1399, Mar. 2013.

[137] A. W. Mahoney, B. G. Smith, N. S. Flann, and G. J. Podgorski, "Discovering novel cancer therapies: A computational modeling and search approach," in *Proc. IEEE Symp. Comput. Intell. Bioinf. Comput. Biol.*, Sep. 2008, pp. 233–240.

[138] R. M. H. Merks, S. V. Brodsky, M. S. Goligorksy, S. A. Newman, and J. A. Glazier, "Cell elongation is key to in silico replication of *in vitro* vasculogenesis and subsequent remodeling," *Develop. Biol.*, vol. 289, no. 1, pp. 44–54, Jan. 2006.

[139] A. Shirinifard, J. S. Gens, B. L. Zaitlen, N. J. Popławski, M. Swat, and J. A. Glazier, "3D multi-cell simulation of tumor growth and angiogenesis," *PLoS ONE*, vol. 4, no. 10, p. e7190, Oct. 2009.

[140] A. Szabó and A. Czirók, "The role of cell-cell adhesion in the formation of multicellular sprouts," *Math. Model. Natural Phenomena*, vol. 5, no. 1, pp. 106–122, Feb. 2010.

[141] R. F. M. van Oers, E. G. Rens, D. J. LaValley, C. A. Reinhart-King, and R. M. H. Merks, "Mechanical cell-matrix feedback explains pairwise and collective endothelial cell behavior *in vitro*," *PLoS Comput. Biol.*, vol. 10, no. 8, Aug. 2014, Art. no. e1003774.

[142] R. Vega, M. Carretero, R. D. M. Travasso, and L. L. Bonilla, "Notch signaling and taxis mechanism regulate early stage angiogenesis: A mathematical and computational model," *PLoS Comput. Biol.*, vol. 16, no. 1, 2020, Art. no. e1006919.

[143] K. Bentley, H. Gerhardt, and P. A. Bates, "Agent-based simulation of notch-mediated tip cell selection in angiogenic sprout initialisation," *J. Theor. Biol.*, vol. 250, no. 1, pp. 25–36, Jan. 2008.

[144] K. Bentley, G. Mariggi, H. Gerhardt, and P. A. Bates, "Tipping the balance: Robustness of tip cell selection, migration and fusion in angiogenesis," *PLoS Comput. Biol.*, vol. 5, no. 10, Oct. 2009, Art. no. e1000549.

[145] L. Jakobsson, C. A. Franco, K. Bentley, R. T. Collins, B. Ponsioen, I. M. Aspalter, I. Rosewell, M. Busse, G. Thurston, A. Medvinsky, S. Schulte-Merker, and H. Gerhardt, "Endothelial cells dynamically compete for the tip cell position during angiogenic sprouting," *Nature Cell Biol.*, vol. 12, no. 10, pp. 943–953, Sep. 2010.

[146] M. J. Holmes and B. D. Sleeman, "A mathematical model of tumour angiogenesis incorporating cellular traction and viscoelastic effects," *J. Theor. Biol.*, vol. 202, no. 2, pp. 95–112, Jan. 2000.

[147] K. Larripa and A. Mogilner, "Transport of a 1D viscoelastic actin-myosin strip of gel as a model of a crawling cell," *Phys. A, Stat. Mech. Appl.*, vol. 372, no. 1, pp. 113–123, Dec. 2006.

[148] M. Gracheva, "A continuum model of motility in ameboid cells," *Bull. Math. Biol.*, vol. 66, no. 1, pp. 167–193, Jan. 2004.

[149] J. Ahn, Y. J. Sei, N. L. Jeon, and Y. Kim, "Probing the effect of bioinspired nanomaterials on angiogenic sprouting with a microengineered vascular system," *IEEE Trans. Nanotechnol.*, vol. 17, no. 3, pp. 393–397, Mar. 2018.

[150] C. L. Stokes and D. A. Lauffenburger, "Analysis of the roles of microvessel endothelial cell random motility and chemotaxis in angiogenesis," *J. Theor. Biol.*, vol. 152, no. 3, pp. 377–403, Oct. 1991.
[151] J. Xu, G. Vilanova, and H. Gomez, "A mathematical model coupling tumor growth and angiogenesis," *PLoS ONE*, vol. 11, no. 2, Feb. 2016, Art. no. e0149422, doi: 10.1371/journal.pone.0149422.
[152] L. K. Phng, F. Stanchi, and H. Gerhardt, "Filopodia are dispensable for endothelial tip cell guidance," *Development*, vol. 140, pp. 4031–4040, Oct. 2013, doi: 10.1242/ dev.097352.
[153] V. P. Chauhan, T. Stylianopoulos, Y. Boucher, and R. K. Jain, "Delivery of molecular and nanoscale medicine to tumors: Transport barriers and strategies," *Annu. Rev. Chem. Biomolecular Eng.*, vol. 2, no. 1, pp. 281–298, Jul. 2011.
[154] A. G. Tsai, P. C. Johnson, and M. Intaglietta, "Oxygen gradients in the microcirculation," *Physiol. Rev.*, vol. 83, pp. 933–963, Jul. 2003.
[155] R. K. Jain, "Normalizing tumor microenvironment to treat cancer: Bench to bedside to biomarkers," *J. Clin. Oncol.*, vol. 31, no. 17, pp. 2205–2218, Jun. 2013.
[156] M.-S. Park, E. Klotz, M.-J. Kim, S. Y. Song, S. W. Park, S.-W. Cha, J. S. Lim, J. Seong, J. B. Chung, and K. W. Kim, "Perfusion CT: Noninvasive surrogate marker for stratification of pancreatic cancer response to concurrent Chemo- and radiation therapy," *Radiology*, vol. 250, no. 1, pp. 110–117, Jan. 2009.
[157] A. G. Sorensen, K. E. Emblem, P. Polaskova, D. Jennings, H. Kim, M. Ancukiewicz, M. Wang, P. Y. Wen, P. Ivy, T. T. Batchelor, and R. K. Jain, "Increased survival of glioblastoma patients who respond to antiangiogenic therapy with elevated blood perfusion," *Cancer Res.*, vol. 72, no. 2, pp. 402–407, Nov. 2011.
[158] V. P. Chauhan, J. D. Martin, H. Liu, D. A. Lacorre, S. R. Jain, S. V. Kozin, T. Stylianopoulos, A. S. Mousa, X. Han, P. Adstamongkonkul, Z. Popović, P. Huang, M. G. Bawendi, Y. Boucher, and R. K. Jain, "Angiotensin inhibition enhances drug delivery and potentiates chemotherapy by decompressing tumour blood vessels," *Nature Commun.*, vol. 4, no. 1, p. 2516, Oct. 2013.
[159] R. K. Jain, "Normalization of tumor vasculature: An emerging concept in antiangiogenic therapy," *Science*, vol. 307, no. 5706, pp. 58–62, Jan. 2005.
[160] B. Sitohy, J. A. Nagy, and H. F. Dvorak, "Anti-VEGF/VEGFR therapy for cancer: Reassessing the target," *Cancer Res.*, vol. 72, no. 8, pp. 1909–1914, Apr. 2012.
[161] S. McDougall, "Mathematical modelling of flow through vascular networks: Implications for tumour-induced angiogenesis and chemotherapy strategies," *Bull. Math. Biol.*, vol. 64, no. 4, pp. 673–702, Jul. 2002.
[162] M. A. J. Chaplain, S. R. McDougall, and A. R. A. Anderson, "Mathematical modeling of tumor-induced angiogenesis," *Annu. Rev. Biomed. Eng.*, vol. 8, pp. 57–233, Aug. 2006.
[163] Z. Gu, L. Gu, R. Eils, M. Schlesner, and B. Brors, "Circlize implements and enhances circular visualization in r," *Bioinformatics*, vol. 30, no. 19, pp. 2811–2812, Jun. 2014.
[164] F. M. Kashkooli, M. Soltani, M. Rezaeian, E. Taatizadeh, and M.-H. Hamedi, "Image-based spatio-temporal model of drug delivery in a heterogeneous vasculature of a solid tumor—Computational approach," *Microvascular Res.*, vol. 123, pp. 111–124, May 2019.

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