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# The Mechanics of Blood Vessel Growth

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## 1. Introduction

Blood vessel growth is pivotal in various processes in health and disease; examples are embryogenesis, inflammation, wound healing, cardiac ischemia, diabetic retinopathy, and tumor growth. The latter, in particular, has been the subject of extensive studies due to the high mortality rates associated with oncologic diseases. However, and despite the continuous efforts by the scientific community, both the genomic characterization of tumors (Maley et al., 2006; Wood et al., 2007) and the main physical mechanisms driving their development (Araújo & McElwain, 2004) are currently a matter of debate. These efforts have been greatly enriched through an interdisciplinary approach. Physics, Mathematics and computer simulation and modeling have currently a key role in the research of tumor growth in general and vessel development in particular. The approach of mathematicians and physicists provides remarkable new ways of looking into Biology: starting the modeling from basic principles, the fundamentals of the problem can be tested and understood.

The relevance of blood vessel growth for tumor development is well documented (Figg & Folkman, 2008). In the early stages of development, the growth of a solid tumor is limited in size due to cell apoptosis at its core by lack of nutrients. In simple terms, the acquisition of nutrients at the boundary is not able to meet the needs of the inner cells. This, in addition to a problem of confinement of the inner cells (the fast growth does not allow them to migrate) produces the so called core necrosis inside the tumor. When this stationary non-threatening stage is reached, malignant tumors adapt to the environment and undergo an active search for the nutrients they need to survive and proliferate. This can be achieved by releasing factors, such the Vascular Endothelial Growth Factor (VEGF), which drive nearby vessels to extend new branches in the direction of the tumor, through a process called angiogenesis, providing it with nutrients (Figg & Folkman, 2008). Hence, understanding angiogenesis is essential to the potential control of the blood delivered to a neoplasic tissue in order to prevent and contain its development and metastatic colonies. In fact, though hyper-vascularization is not a requirement for a tumor to metastasize (Mateus et al., 2009), the cells of a densely vascularized tumor have a much higher facility in entering the blood circulation.

During the last decade cancer therapies based on anti-angiogenic factors have been a focus of interest. However, this type of treatment has not given the expected results (Mayer, 2004) and recently, the concept of normalization of tumor vasculature has been proposed (Jain, 2005), where it is suggested that certain anti-angiogenic agents can transiently normalize

the abnormal tumor vasculature, to make more efficient the delivery of drugs (provided by chemotherapy) and the delivery of oxygen (thus enhancing the efficiency of radiation therapy). Therefore, a better understanding of vessel growth and remodeling will have an positive impact in the design of cancer treatments.

Pathological angiogenesis is central to various other diseases besides tumor growth. In fact, it is implicated in more than 70 disorders, and according to the Angiogenesis Foundation, the lives of at least 1 billion people worldwide could be improved with therapies targeting angiogenesis (Adair & Montani, 2010). Depending on the disorder type, angiogenesis might be either excessive or deficient, and therefore different pathologies will require different approaches to actively normalize the vasculature of the diseased tissue.

Processes related to vessel growth are extremely complex, typically involving hundreds of proteins and receptors in a well balanced cross-talk. Any modeling attempt of these systems involves forcefully a simplification by considering only some of the proteins and mechanisms present. There is a generalized agreement within the community with respect to which are the main biological mechanisms driving angiogenesis, nevertheless different teams of researchers opt for choosing different modeling strategies, and therefore the implementation of these mechanisms is far from being consensual.

To make matters worse, angiogenesis and vascular remodeling have an intrinsic multi-scale nature, and the final morphology of a vascular network depends on phenomena which occur at the cell level (e.g. the activation and subsequent sprouting of new branches) (Gerhardt et al., 2003) as well as on the large scale collective movements of the cells (which are a function of endothelial cell proliferation and the tissue mechanical properties) (Friedl, 2004; Friedl & Wolf, 2003; Painter, 2009). The majority of the computational works on this topic are devoted to sprouting angiogenesis, and in this case the multi-scale nature of this process led different research groups to address the topic through either the macroscopic or the microscopic perspective.

The first simulations were done 20 years ago using diffusion equations, and many others followed the same strategy (reviewed in Mantzaris et al. (2004)). These models describe the system macroscopically, through average endothelial cell densities. Some of these works are able to delimitate a capillary by considering the points where the concentration of endothelial cells is higher, but do not evidence branching and do not predict the resulting capillary network, or the areas where vessels are more fragile.

In the beginning of the nineties microscopic cell based models appeared in the context of angiogenesis (Bauer et al., 2007; Bentley et al., 2008; Chaplain et al., 2006; Markus et al., 1999; Owen et al., 2009). The large number of different cells in the tissue and the many processes in which they participate are a major stumbling block to cell based models. These models incorporate an extremely large number of rules and parameters, while being hard to control, because of their high sensitivity to small modifications. This is of importance, since many of the required parameters are a true challenge to measure experimentally, and have to be postulated.

Recently, hybrid models that integrate continuous and discrete descriptions of angiogenesis have come to light (Milde et al., 2008; Travasso et al., 2011a). In these models the capillary cells are described as a tissue, not as individual cells. This allows for a fast integration of the equations and a relatively low number of model parameters. Capillary tip cells, however, are modeled through an agent based component due to their distinct phenotype and relevance in the chemotactic migration mechanism of capillary sprouts (Gerhardt et al., 2003). Being multi-scale at their core, hybrid models are able to include processes occurring at the cellular and tissue levels, thus originating vascular patterns qualitatively similar to the ones observed *in vivo* (Travasso et al., 2011a).

In spite of important advances in the modeling field, the large majority of sprouting angiogenesis mathematical models do not yet include the mechanical properties of tissues and capillaries, and are not able to predict how these properties determine vessel growth (Waters et al., 2011). While far from trivial, the endothelial cells' response to mechanical signals is at the core of the dynamics of capillary growth. In fact in the biomedical engineering community it has been noticed that "because angiogenesis occurs in a mechanically dynamic environment, future investigations should aim at understanding how cells integrate chemical and mechanical signals so that a rational approach to controlling angiogenesis will become possible" (Shiu et al., 2005). Still in Shiu et al. (2005) the authors call for computational models that correctly integrate this mechanical aspect into angiogenesis simulations.

Strikingly, mathematical models of the processes of intussusceptive angiogenesis and vessel remodeling have included mechanical forces from the start. In particular, some of the models describing these processes integrate directly the experimentally measured biological responses of capillaries to different stimuli, such as varying the capillary wall shear stress, through a rule-based model (Pries et al., 2005). This approach has recently been used to support the hypothesis of a new signaling mechanism present in capillary development (Pries et al., 2010).

In this chapter we will explore the mechanics of vessel growth and remodeling by focusing in the modeling strategies used in the community. We start by describing the influence of mechanical forces in endothelial cells and their relevance in angiogenesis and vascular remodeling. Next we focus on the modeling tools that have been used to describe the processes related to vessel growth and remodeling that are able to integrate the mechanical response of endothelial cells and of the vascular tissue. We finally conclude by calling for a collaborative effort between Material and Biomedical scientists to address the effect of these mechanisms in vessel growth, remodeling and maturation.

## 2. Mechanical influence in vessel growth and remodeling

### 2.1 Endothelial cells and the extracellular matrix

Cells have a cytoskeleton which can actively extend and alter, thus exerting forces in their surroundings (Alberts et al., 2002; Bray, 2001). In the various strategies cells adopt to move, they take advantage of their ability of changing shape and altering their micro-environment (Friedl, 2004; Friedl & Wolf, 2003). In the same way as they can exert forces in the extracellular matrix (ECM) and also produce proteins that are able to degrade and remodel the ECM (Painter, 2009), the forces exerted upon the cells are also able to influence their phenotype by changing their gene expression. Endothelial cells are no exception: their protein levels as well as the characteristics of the vessels they belong to strongly depend on forces exerted by the ECM and the blood flow.

Endothelial cells sense mechanical forces using membrane proteins such as integrins, which link the cells to the ECM, or E-cadherins, which link to other endothelial cells. The E-cadherins, for example, being directly attached to the cell's cytoskeleton, thus playing an active role in the regulation of the cell's size, trigger signaling pathways some of which regulate the proliferation rate of the cell (Nelson et al., 2004). In more detail, in regions of low cell density, the cell E-cadherins signaling through RhoA leads to a higher proliferation rate and lower adhesion to the ECM *in vitro*. The E-cadherin mediated proliferation control is influenced by the mechanical tension to which the cell is exposed (Nelson et al., 2004). A tension dependent proliferation rate should be present in mathematical models of angiogenesis and remodeling since it is shown theoretically and experimentally the relevance

of such process for the final vascular morphology (Gerhardt & Betsholtz, 2005; Travasso et al., 2011a). This dependence is straightforward to include in a discrete model which includes every endothelial cell (Merks et al., 2008), however, in continuous and hybrid models the inclusion of these effects has been proven to be challenging.

Measurement of the forces exerted on 2D and 3D environments by a single cell have showed a complex scenario of stresses depending on the cell type, matrix properties and previous matrix remodeling events (Kraning-Rush et al., 2011).

By exerting force in the ECM, endothelial cell are able to re-orient the ECM fibers thus altering the mechanical properties of their micro-environment. Endothelial cells migrate along these restructured fibers (Korff & Agustin, 1999). Through this mechanism two endothelial cells can interact mechanically via the forces they exert in the ECM without being in contact (Califano & Reinhart-King, 2009). These forces can be measured experimentally and are suggested as being the initiators of the movement of approximation between endothelial cells in a 2D matrix. The inclusion of these "long-range" mechanical interactions, which result from the cell's action upon the ECM, is an important ingredient of many models that describe the observed formation of a network structure when endothelial cells grow on a flat substrate (Murray, 2003).

Recently it has been found clear evidence of a signaling pathway triggered mechanically that is able to control the number of receptors of vascular endothelial growth factor, VEGFR2, at the cell membrane (Mammoto et al., 2009). VEGF, is the main factor driving sprouting angiogenesis *in vivo*, having a three-fold role at the cell scale: (i) to trigger the permeability of the capillaries and the subsequent activation of the tip cell phenotype, (ii) to promote migration of tip cells in the direction of its gradient, and (iii) to promote the proliferation and survival of the stalk endothelial cells. An alteration of the number of VEGFR2 in the endothelial cells has an large impact in the resulting vessel network.

Mechanical effects are therefore determinant for endothelial cell functioning, and in processes of vessel network growth such as vasculogenesis or sprouting angiogenesis, the mechanical interplay between the endothelial cells movement and the surrounding tissue is extremely relevant to the resulting network morphology. These effects have to be included in current models of angiogenesis, though a better quantitative understanding of the forces and motion of sprouts in 3D is needed.

### 2.2 Blood flow

A major player in exerting stresses in vessels is blood flow which has a pivotal role as a remodeling agent of vasculature. The process of intussusceptive angiogenesis, a fast branching process where the formation of new blood vessels results from the insertion and extension of transluminar pillars, can be triggered by alterations in blood flow (Djonov et al., 2002; Filipovic et al., 2009; Styp-Rekowska et al., 2011). Also the procedure of creating a hierarchical vasculature formed by vessels with different characteristics (arteries, arterioles, capillaries, venules, veins) results from an interplay of genetic and mechanical processes regulated to a large extent by blood flow.

Endothelial cells change their gene expression as a function of the flow pressure and shear stress, type of flow (laminar or turbulent) as well as the blood composition (hematocrit, oxygen pressure, etc). Also, the shear stress is able to align endothelial cells in the flow direction, thus influencing the vessel's mechanical properties (Allen et al., 2011; Styp-Rekowska et al., 2011). Due to the large importance of the influence of shear stress on gene expression there are currently a variety of assays with the aim of studying protein transcription for different types of flow (Nash & Egginton, 2006).

It is suggested that an important regulatory function of blood flow is the stabilization of the vasculature. In fact shear stress has been shown *in vitro* to up-regulate anti-angiogenic factors such as the proteinase ADAMTS1 (Hohberg, et al.) and down-regulate pro-angiogenic factors such as the Forkhead box protein O1A, Foxo-1 (Chlench et al., 2007). Alterations in blood flow have consequences to vessel stability, and for example, a localized low shear stress region at bifurcations may lead to intussusceptive angiogenesis, while a generalized low shear stress leads to vessel destabilization and regression (Styp-Rekowska et al., 2011). Sprouting angiogenesis has also been suggested to be modulated by blood flow shear stress, with sprouting in 3D collagen matrices being observed for increasing flow above the endothelial cell culture (Kang et al., 2008).
In vessel remodeling is also relevant the role of pericytes and smooth muscle cells in controlling lumen size and vessel wall thickness (Jacobsen et al., 2009; Pries et al., 2005; 2009). In fact, these cells can alter their (and the vessel's) mechanical properties depending on their activation state and on the chemical and mechanical stimuli in their micro-environment, through the process of tone-driven remodeling (VanBavel et al., 2006).
The mechanical mechanisms driving vascular remodeling, intussusceptive angiogenesis and sprouting angiogenesis are different. In the next section we will explore how the current mathematical modeling approaches in the literature of these three topics describe the influence of the mechanical forces in each process. We start, however, by analyzing the modeling strategies used to address the mechanics of vascular stability.

## 3. Modeling mechanical processes in vessels development

### 3.1 Vascular stability: stresses in blood vessels

Blood vessels in physiological conditions are under varied types of mechanical stresses. The interior layer of the vessel constituted by endothelial cells is in direct contact with the blood flow and is exposed to the blood pressure and to the flow produced wall shear stress (see Figure 1). The wall shear stress is the main remodeling agent in vascular systems (Jacobsen et al., 2009). Blood vessels also exhibit a stretch in the longitudinal direction which ranges between 1.4 and 1.6 (Learoyd & Taylor, 1966). This stretch is the result of a longitudinal stress imposed by the tissue and its absence may lead to vessel malformations (Goriely & Vandiver, 2010). On the other hand, the circumferential stress is related to the vascular pressure but also to the structure and properties of the vascular wall, which provides blood vessels with high residual stresses. These residual stresses are closely related to vascular remodeling (Fung, 1991).
Due to the large axial stretch and residual stresses in arteries, a study of the mechanical properties of vessels cannot be done using elementary mechanics, since these large displacements require the use of non-linear continuum mechanics. Models of this type of vessel mechanical properties have to consider the different layers of arteries, since their layered structure is responsible for the large residual stresses (Holzapfel et al., 2000). These models do not take in consideration the genetic response of the vessel cells and do not describe vascular remodeling, however, the use non-linear continuum mechanics can provide important insights about the stability of single vessels and vessel networks.
The area of non-linear elastic modeling of vessels is very active (Fung, 1991; Holzapfel et al., 2000; Holzapfel & Weizsäcker, 1998; Ogden, 2003; Rachev & Hayashi, 1999), and to exemplify the methods used by this community, we will look into detail to the work of Goriely & Vandiver (2010). These authors have extended the model in Holzapfel et al. (2000) to consider vessel growth. In the formalism used, the deformation gradient tensor $\mathbf{F}(\mathbf{X}, t)$ relating the transformation from an initial unstressed reference state $\mathcal{B}_0$ (with a material point

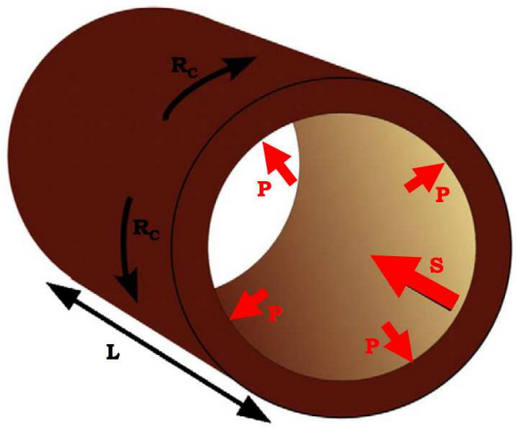



Fig. 1. Forces related to the vessel wall. Arrows in red represent forces exerted by the blood flow on the endothelial layer: pressure forces normal to the interior of the vessel (**P**) and the shear stress of the flow, in the flow direction (**S**). Arrows in black represent forces that, though influenced by the blood flow, may have a different origin: longitudinal forces (**L**) and circumferential stresses ($\mathbf{R_C}$). Figure based on Jacobsen et al. (2009) with permission of Elsevier B. V.

given by a position vector **X**) to the current state $\mathcal{B}_f$ (at time $t$) is the result of a local growth step defined by the tensor **G** and an elastic process **A**. The local growth transformation originates conceptually a virtual discontinuous stress-free configuration $\mathcal{V}$, which, through the elastic process **A**, leads finally to the stressed continuous current configuration $\mathcal{B}_f$ (see Figure 2):

$$\mathbf{F}(\mathbf{X},t) = \mathbf{A}(\mathbf{X},t) \cdot \mathbf{G}(\mathbf{X},t)\,. \tag{1}$$

In the final step, the interior blood pressure **P** is included as a boundary condition in order to obtain the correct stresses in the vessel as a function of the flow pressure. The wall shear stress is not considered.

The experiments of cutting an artery and measuring the opening angle (see conformation $\mathcal{B}_1$ in Figure 2) allow the quantification of the residual stresses in the current conformation $\mathcal{B}_f$. In Goriely & Vandiver (2010) this analysis is done using the parameters measured experimentally for a rabbit carotid artery. Having obtained the residual stresses, the authors calculate the value of the stresses in the system as a function of the pressure. The total stress is much lower in the system with residual stress than in a hypothetic vessel without residual stresses. This is the traditional function associated with residual stresses in Biology and Engineering: to decrease the stress the system undergoes when subjected to pressure forces (Fung, 1991).

Afterwards the authors study the behavior of the pressure in function of the axial stretch observed for different external loads. They observe that for higher external loads, the stretch becomes approximately independent of the interior pressure, thus providing a biological function for the high stretches in arteries.

Finally the authors preform a stability analysis where they observe that a increase in pressure or a decrease in the external load leads to a buckling instability. They suggest that the remodeling of the artery after the instability may lead to permanent tortuosity, though this step is out of the scope of this modeling approach. Permanent vessel tortuosity is a hallmark

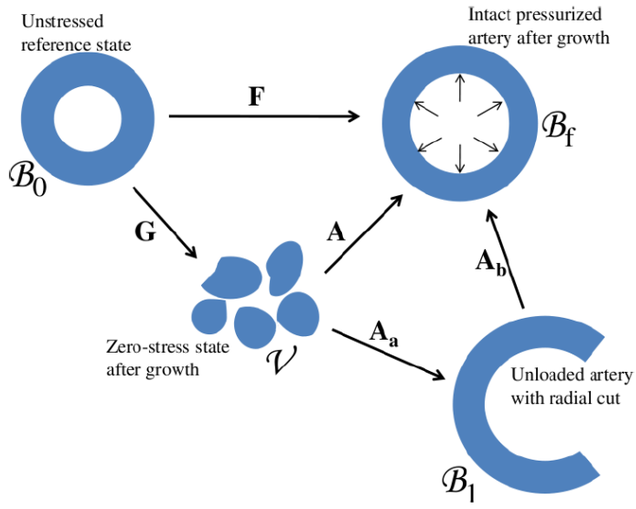



Fig. 2. Schematic representation of the decomposition of the deformation tensor **F** into growth tensor **G** and elastic deformation tensor **A**. In the presence of a radial cut, the boundary conditions are different and the elastic deformation tensor $\mathbf{A_a}$ will also be different. In both conformations $\mathcal{B}_f$ and $\mathcal{B}_1$ residual stresses are present. Figure from Goriely & Vandiver (2010) with permission of Oxford University Press.

of various pathological scenarios such as proliferative diabetic retinopathy and also may lead to stroke, vertigo or permanent tinnitus.
Models using non-linear elasticity such as the one presented above provide a detailed analysis of the mechanical forces in vessels. These models are rather complex and though do not include the biological driven alteration of the mechanical properties of the tissues, they are still extremely useful in laying down the conditions needed for vessel stability. These models could be used to tackle important questions such as: how would the vessel stability be influenced as a function of the tissue mechanical properties?, how is the external load applied *in vivo*?, what are the required geometries of bifurcations and the corresponding vessel lengths in order for a network in a particular tissue to be stable?

### 3.2 Vessel remodeling

Using the previously discussed models, the stresses could in principle be calculated and used to predict how the cells respond to alterations in the mechanical cues of the environment. Hence, mathematical models have been developed that are able to calculate the mechanical adaptation of the system and draw important conclusions related to relevant biological mechanisms regulating this process. These models are based in experimental observations, for example on the data of how does a vessel diameter changes in response to an increase in the wall shear stress, and aim at describing the progressive change in vessel morphology and the consequent development of a hierarchical structure in a vessel network.
Vessels can alter independently their lumen diameter (by a process called *remodeling*) and their wall area (*trophic* response, see Figure 3) by responding to mechanical and physiological cues in their micro-environment. These alterations may be the result of cell rearrangement (smooth muscle cells may rearrange themselves, leading to a change in lumen diameter while keeping the same wall area, i.e. leading to eutrophic remodeling), or smooth muscle cells or endothelial cells may undergo extension, contraction, proliferation or apoptosis, leading to

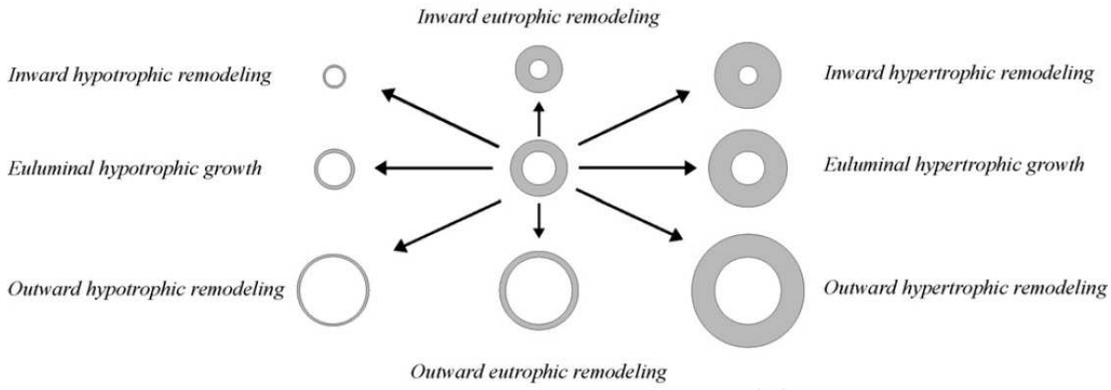



Fig. 3. Possible models of remodeling (lumen diameter change) and trophic response (change of vessel wall area). Figure based on Mulvany (1999) with permission of Oxford University Press.

alterations both in lumen size and wall area. Essentially, the micro-environmental cues are transduced at cell level leading to complex signaling pathways and a consequent alteration of the cell's properties and/or gene expression. These signaling pathways are theme of intense investigation nowadays, and most of their mechanisms are not yet known. The solution adopted by many models of vessel remodeling is either using dependences obtained from *in vitro* and *in vivo* experiments or using educated guesses about these dependences (Jacobsen et al., 2009).

The influence of the ECM is not explored in the current models of vessel remodeling (Jacobsen et al., 2009; Waters et al., 2011): the ECM has been interpreted as serving as support for the vessels, while the major mechanical role is played by the blood flow, the stresses acting upon the vessels, and the tissue nutrient requirement. Moreover, most models use a rather simplified description of both flow and vessel elasticity (typically using the Kirchhoff laws and the Poiseuille flow profile, with some models considering the Fåhræus-Lindqvist effect, to obtain blood flow, pressure and shear stresses; and being still far from the non-linear elastic description introduced previously), and because of the lack of knowledge about the cell response to the mechanical stimuli *in vivo*, a careful calculation of the stresses in the system would not bring an increase in the precision of the results of the code.

Nevertheless, in spite of this lack of biochemical knowledge, mathematical models have been very important in providing evidence for new mechanisms relative to cell-cell communication (Pries et al., 2009; 2010; Pries & Secomb, 2008). The model described in Pries & Secomb (2008), and also used in complex multi-scale simulations of vascular dynamics (Owen et al., 2009; Perfahl et al., 2011), takes into account both mechanical and metabolical stimuli relevant to vessel dynamics. It focuses on lumen dynamics, not considering alterations in the vessel wall area. Essentially, the diameter $D$ of a particular vessel is given by

$$\frac{1}{D}\frac{\partial D}{\partial t} = k_h(S_t + k_p S_p) + k_m(S_m + k_c S_c) - k_s \,, \tag{2}$$

where $k_h$, $k_p$, $k_m$, and $k_c$ are constants, $S_t$, $S_p$, $S_m$, and $S_c$ are the different stimuli for the vessel to grow and $k_s$ represents the tendency of the vessel to shrink if no stimuli are present. The first two stimuli represent the tendency for the vessel to become wider with increasing pressure and wall shear stress. The stimulus $S_m$ represents the response to the concentration of a metabolite present in the blood flow which is included in the current at a rate proportional

to the lack of oxygenation of the tissue at that particular point. When entering the blood stream, the metabolite flows with the current triggering the response of increasing vessel thickness if there is little oxygenation. Pries & Secomb (2008) show that the model is only able to provide reasonable results, if there is a counter-flow signaling mechanism, through a chemokine conducted upstream along the endothelial cells of the vessel. The last stimulus, $S_c$, represents the response of the diameter to this last signaling mechanism.
With this model, Pries et al. (2010) address the situation of the existence of shunts connecting arterial to venous flow in tumor vasculature. Pries et al. (2010) show that the presence of $S_c$ is sufficient for the shunt formation to be controlled. In the presence of this signaling mechanism when the shunt is formed, there is a lowering of the irrigation downwards in the vascular tree, and the signal for a vessel remodeling is sent upstream. This will lead to a thicker equilibrium artery diameter, but not to a thick shunt. Besides, since the shunt is not providing oxygenation to the tissue it may regress due to the $k_s$ term of the model. The authors suggest that in a tumor this mechanism is altered giving rise to a non functional vessel network with a higher density of vascular shunts.
The same model is used in Pries et al. (2009) to show that a network with vascular shunts and whose vessels do not organize hierarchically is obtained after running the model on a normal vasculature but using the parameters that stabilize a tumor vasculature. On the other hand, a tumor vasculature may be "normalized", i.e. present a hierarchical structure, by carrying out remodeling with the parameters of a healthy tissue.
Hence the authors suggest that malformations in the tumor vasculature might be the result of deficient remodeling. Therefore the biochemical mechanisms involved in vascular remodeling may be a valid target for anti-angiogenic therapy.
While most of the recently published work in vascular network remodeling *in silico* is based on models which compute the different stimuli and simulate lumen dynamics, there are other models in the literature that go further, by focusing as well on the description of the vessel wall dynamics (Jacobsen et al., 2003). On the other hand, other researchers adopt a rather different strategy and use rule-based cellular automata (Peirce et al., 2004) to predict the evolution of the network.
Modeling vessel remodeling, even under the simplified setting up discussed in this section, can suggest mechanisms that can be pivotal in vessel remodeling in pathological scenarios and that are worthwhile to investigate. However, integrating more precise descriptions of the mechanics in these models would require more experimental work leading to the understanding of how the different cells respond to the different mechanical factors.

### 3.3 Intussusceptive angiogenesis

Angiogenesis occurs when new vessels have to be created in order to vascularize a growing tissue. In tissues with a little number of vessels, through the process of sprouting angiogenesis new capillaries sprout from existing vessels. Sprouting angiogenesis is a slow process that is dependent on the migration of endothelial cells and also on their proliferation, and occurs extensively in embryo growth and in retinas of new-born mice, for example.
On the other hand, in situations where a vasculature already exists, intussusceptive angiogenesis occurs with the aim of increasing local vessel density. In this process vessels divide in two through the insertion and extension of a transluminar pillar (see Figure 4). This type of angiogenesis occurs in inflammation and in tumor growth. It is fast and does not depend on proliferation. The resulting thinner vasculature is afterwards target of remodeling in a maturation process (as described previously).
Mechanical forces are at the onset of intussusceptive angiogenesis, which is enhanced with an increase of the flow velocity (Djonov et al., 2002). Blood flow simulations in the geometries

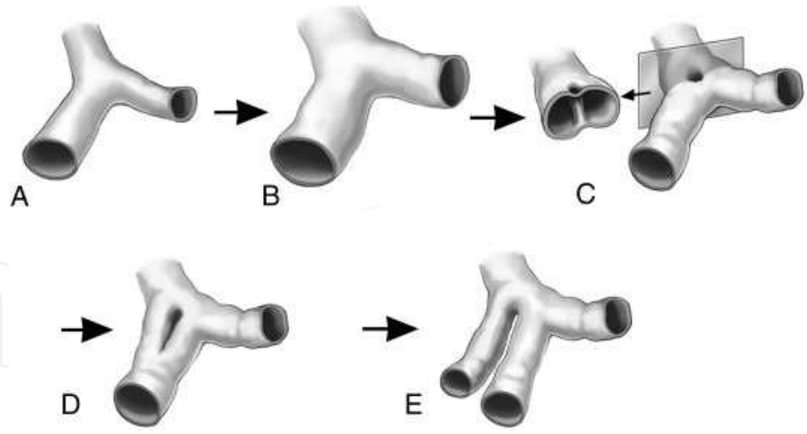



Fig. 4. Intussusceptive angiogenesis: from formation of pillar until the branching of a new vessel. Figure from Filipovic et al. (2009) with permission of Elsevier B. V.

of a bifurcation have identified the location of the new pillars with the regions of low shear stress (Styp-Rekowska et al., 2011). In Figure 5A the wall shear stress is plotted in a bifurcation of two vessels (Filipovic et al., 2009). It is clearly visible a ring of low stress just before the bifurcation apex. It is in this region where the pillar will be formed.
In Figure 5B it is observed that when the pillar is formed, the high stresses are located on the sides of the pillar, closer to the lateral vessel walls, while there is a "dead zone" of very low stress between the pillar and the bifurcation apex. The growing of the pillar comes from this anisotropic distribution of stresses around it, and can extend in different directions depending on the relative flow of the two out vessels (Filipovic et al., 2009).
The main mechanisms responsible for the formation of the pillar are still unknown. It is suggested that there is a softening of the capillary wall allowing it to bend inwards in the region of low shear stress, until the two walls merge and form the pillar (Djonov et al., 2002). This softening is blamed on the regression of the fibers that provide rigidity to the vessel. However more mathematical and experimental studies should be done to unravel the mechanics of pillar formation.
Simulations of the process of pillar evolution are very challenging because of the interplay between continuum mechanics, flow and biological mechanisms, many of which are not yet known. Recently Szczerba et al. (2009) have implemented a level-set model of pillar evolution. Their model integrates the blood flow, simulated through Navier-Stokes equation together with the incompressibility condition and a shear dependent viscosity $\eta = m\dot{\gamma}^{n-1}$, where $m$ and $n$ are system parameters and $\dot{\gamma}$ is the shear rate. The concentration of various proteins in the blood can also be tracked through a diffusion-convection-reaction equation:

$$\partial_t c + \mathbf{u} \cdot \nabla c = D\nabla^2 c + R_c \,, \tag{3}$$

where $c$ is the concentration of the protein advected in the blood flow with velocity $\mathbf{u}$ and diffusion constant $D$. $R_c$ is a reaction term describing the reactions in which the protein participates.
The remodeling agents considered are the measured shear stress on the capillary wall, the concentration of pro- and anti-angiogenic factors (modeled by equation (3)) and the wall surface tension (giving rise to a velocity proportional to the local curvature in the direction of straightening up the vessel locally). The velocity of the wall is a function of the value of

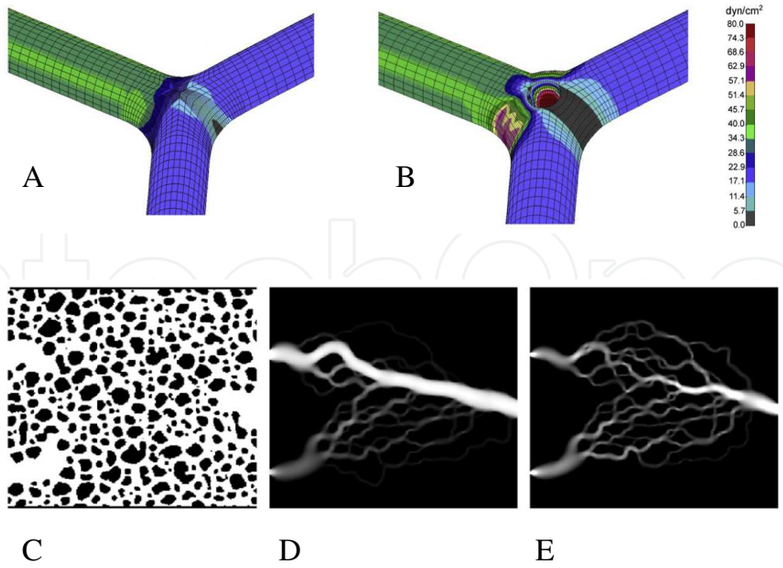



Fig. 5. Wall shear stress for a flow simulation of a Newtonian fluid in the geometry of a bifurcation (A) without pillar and (B) with a 10 $\mu$m diameter pillar. Figure from Filipovic et al. (2009) with permission of Elsevier B. V. Remodeling of an initial set of pillars (C) into a differentiated network. Flow pattern in the absence of any additional control: a large arterio-venous shunt forms (D). If, on the other hand, a steadily increasing concentration of strengthening fibers is considered, the arterio-venous anastomosis is avoided and numerous capillary vessels remain (E). Figure from Szczerba et al. (2009) with permission of Elsevier B. V.

these agents. However since the real dependence of the velocity on each one of these agents is not known experimentally, the authors consider the following simple form:

$$\mathbf{v} \sim (K - K_0)\frac{c_+}{c_+ + c_0}\mathbf{n}\,, \tag{4}$$

where $K$ is the wall shear stress, $K_0$ the target shear stress, $c_+$ and $c_-$ are respectively the concentration of pro- and anti-angiogenic factors, $c_0$ corresponds to the concentration of strengthening fibers and $\mathbf{n}$ is the normal vector pointing outwards.
First the authors simulate the model in three dimensions for the creation of a single pillar in the center of a vessel and its remodeling. They observe that the existence of the pillar increases the shear stresses in the walls near the pillar, leading to a force exerted on the pillar which leads to its elongation in the direction of the flow. This effect is verified experimentally (Hsiai et al., 2002). However the simulation in 3D is not feasible for a large system, and the authors opt for simulating a vascular network in 2D.
In Figure 5C the starting vascular network used in Szczerba et al. (2009) is presented. In this figure the black domains correspond to the spaces between vessels: the blood goes from left to right connecting the two arteries to the vein. When the system is remodeled with constant values of the factor concentrations, the authors observe non-functional network with a shunt connecting directly the artery and the vein (see Figure 5D). However when the concentration of strengthening fibrils or the concentration of anti-angiogenic factor increases progressively, the authors observe the creation of a hierarchical remodeled network (Figure 5E).

This model suggests new hypothesis about the mechanisms controlling intussusceptive angiogenesis and the creation of hierarchical vessel networks. In particular, it suggests that implementing mechanics is not enough to obtain a functional network. For the hierarchical network to be formed, something has to change progressively (concentrations of fibers or of angiogenic factors in this case), i.e. the system has to be driven.
As with vascular remodeling, many mechanisms present in intussusceptive angiogenesis are still unknown. Mathematical and computational modeling can definitely play an important role in understanding this process helping to determine what are the possible mechanisms present and what is the role of each one of them; how can the forces exerted by one cell on its neighbor be described; or what is the effect of the layering structure of the vessels in this process.

### 3.4 Sprouting angiogenesis

The process of sprouting angiogenesis is strikingly different form intussusceptive angiogenesis. It starts when endothelial cells of existing capillaries acquire the tip cell phenotype by the action of a protein cocktail produced typically by tissue cells in a hypoxic micro-environment. Tip cells lead the growth of new capillary sprouts formed by other endothelial cells which acquire the stalk cell phenotype. The migration of endothelial tip cells is directed towards increasing concentrations of relevant growth factors. The angiogenic role of VEGF is opposed by different anti-angiogenic factors in the tissue (Figg & Folkman, 2008). After the sprouting, further processes such as anastomosis (linkage of different branches on the network), and vessel remodeling by the blood flow and the intrinsic mechanical properties of the tissue, contribute to the formation of the new vessel network and are finely tuned to determine the final vascular patterning (Jones et al., 2006).
The tip cell migration is regulated in part by the production of extracellular MMPs (Matrix MetalloProteinases) that are responsible for the remodeling of nearby ECM. The movement of the sprout through the ECM is only possible through an accurate positioning of the regions where its cells exert traction forces on the matrix, and the zones where the ECM fibers are degraded by the action of MMPs (Ilina & Friedl, 2009). Forces and MMPs work as remodeling agents of the ECM: traction forces align the fibers in the ECM, while MMPs cleave the fibers and thus alter the mechanical properties of the ECM. Endothelial cells' traction forces are improved in stiffer gels (Discher et al, 2005; Pelham & Wang, 1997), and mobility and sprout development is improved in more compliant tissues (see review Shiu et al. (2005)). These complex mechanisms in sprout growing, result in a nontrivial dependence on the mechanical properties of the ECM (modeled in Painter (2009), for example).
In spite of the mathematical modeling of sprouting angiogenesis literature being very vast (Alarcón, 2009; Mantzaris et al., 2004; Peirce, 2008), most models, do not focus on the mechanical mechanisms of this process, except for modeling haptotaxis (Cai et al., 2009; Chaplain et al., 2006; Holmes & Sleeman, 2000), i.e. the influence of a non-uniform distribution of fibers in the migration of the sprouts. The hypothesis behind haptotaxis modeling is that an increase in fibronectin, or other similar protein, implies an increase in cellular traction forces, and so, the endothelial cells move along the gradient of fibronectin. Fibronectin in these models is produced and consumed by endothelial cells.
The choice for using a simplified description of mechanical processes, such as the one mentioned above, in most models of sprouting angiogenesis is understandable since the two main mechanisms driving sprouting angiogenesis are endothelial cell chemotaxis and proliferation. Nevertheless, there is nowadays an increasing need for models to provide quantitative predictions about vessel growth, and therefore the complex relations between the

mechanical properties of the tissue and endothelial cell motility cannot keep being overlooked in this context.

Recently Bauer et al. (2009) implemented a two-dimensional cellular-Potts model of sprouting angiogenesis with the aim of investigating computationally the influence of matrix remodeling and fiber density orientation in vessel dynamics. In a cellular-Potts model each individual cell is a domain associated with an individual Potts ground-state (Graner & Glazier, 1992). The hamiltonian differs from the Potts hamiltonian since there are targets domain area and perimeter length, and an energy cost is associated to deviations from those targets. In other words, 2D cellular-Potts models create a tapestry of domains that during their dynamics maintain approximately their areas and perimeter lengths, akin to many real living cells.

In Bauer et al. (2009) the authors adapt the cellular-Potts model to sprouting angiogenesis, by including terms in the hamiltonian describing the chemotaxis and the adhesion to the matrix fibers (endothelial cells may grow filopodia and thus extend their perimeter, and so the perimeter constraint is not included in the model). The model also considers the different adhesions between an endothelial cell and the matrix fibers, the interstitial fluid and another endothelial cell. The authors explore carefully the parameter range of the model, comparing to experimental data, and thus obtaining its range of validity.

The authors observe a complex dependence of the sprout dynamics as a function of the matrix fiber fraction. At low fiber fractions the sprouts are thin, and ramified (since the matrix is sparse and in-homogeneous enough for some of the sprout cells to extend along directions not collinear with the leading VEGF gradient). As the fiber fraction increases it forms a scaffolding for the chemotaxis, and thus the number of branches decreases and the maximum sprout velocity is attained. For higher fiber density adhesion starts to dominate, the sprouting velocity becomes lower and the vessels thicker. Finally at very high fiber density, the sprouts are not able to form; though sprouting in these conditions is recovered by including in the model matrix degradation by the MMPs. These regimes have been recently observed in *in vitro* experiments (Shamloo & Heilshorn, 2010).

The model also predicts that matrix realignment does not influence in an appreciable manner the sprout velocity at low fiber densities, while at average densities variations in the fiber alignment can double the growth velocity. With respect to matrix degradation, it leads to an increase of sprout velocity (except for low matrix densities), and to more branching events.

While the cellular-Potts model is not a model suitable to study the effect of the elasticity or viscoelasticity of tissues in angiogenesis, since it does not include an unstressed reference frame, or a viscoelastic relaxation time, it is able to describe the adhesion properties of cells to the matrix fibers, thus putting forward relevant hypothesis about the complex dynamics of sprout formation that go well beyond the traditional haptotaxis formulation.

However, viscoelastic effects of the ECM in sprouting angiogenesis modeling have been included by some authors through coupling the endothelial cell movement to a spring-dashpot viscoelastic model of the ECM (Cai et al., 2009; Holmes & Sleeman, 2000) by incorporating a description used in vasculogenesis modeling (Murray & Oster, 1984) and in other models of cell locomotion (Moreo et al., 2010). The same spring-dashpot viscoelastic model has been used to model the elasticity of the endothelial cells themselves (Jackson & Zheng, 2010). Before concluding about the influence of the mechanical properties in angiogenesis, this type of modeling should be extended to other kinds of viscoelastic descriptions of the ECM, explored the coupling mechanisms of the ECM with the endothelial cells and compared to experimental results.

## 4. Conclusion

In this chapter we explored some of the most relevant mechanisms related to the mechanics of vessel growth and described the strategies used by several groups to model these mechanisms. Forces and the tissue mechanical properties are central to the different processes of vessel growth, nevertheless many of the details are not yet understood. While using non-linear elasticity to describe vessels and tissues permits the analysis of the stresses and strains in the system with great detail, the difficulty of implementing such models in a large system together with the lack of knowledge of how the different cells respond to the forces and interact with each other, lead to very different strategies in describing intussusceptive angiogenesis and vascular remodeling. Also, sprouting angiogenesis is controlled to great measure by the mechanical properties of endothelial cells and of the ECM, however very few models explore these features.

One of the possible strategies for the task of including mechanics in the sprouting angiogenesis modeling, is the use of the phase-field model. Originally developed by the physics community in the context of non-equilibrium systems, it achieved great success over the past decades in describing a whole range of Materials Science phenomena related to nucleation and growth. The phase-field permits an elegant and multifaceted numerical description of complex nonlinear problems with moving boundaries, being a tailorable method that can be easily adapted to describe quantitatively an extremely vast range of mechanical and dynamical properties of interfaces as a function of the bulk properties (Emmerich, 2008). In Materials Science, the various phase-field applications developed so far have matured sufficiently to allow their use in realistic applications with a high degree of accuracy. In tumor and angiogenesis modeling the use of phase-field simulations is currently in its early stages of development with promising results (Oden et al., 2010; Travasso et al., 2011a;b). Phase-field models are able to describe systems with different mechanical properties and are a great promise for exploring the influence of the tissue mechanics on vessel development.

We are left with the feeling that we are still starting to unveil the complexity of phenomena and interactions between the different cells, tissues and proteins related with vessel development. New mechanisms are being discovered that require to be understood in a quantitative way. For example, complete networks have been found to migrate *in vitro* in the presence stresses in the ECM (see Figure 6) (Kilarski et al., 2009). It is suggested that this mechanism could occur in cicatrization, explaining the fast growth of the vascularization in these emergencies. What are the forces that play an important role here? Can a vasculature be so easily affected by the action of stresses? How can we take advantage of this fact to help in the treatment of tumor growth, diabetic retinopathy, or heart ischemia? Mathematical modeling can obviously help in answering these questions, by providing testable hypothesis. Modeling can also determine

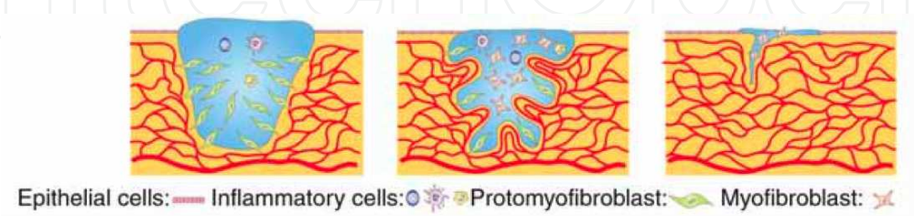



Fig. 6. Proposed model for dermal wound healing following the experiments on chick chorioallantoic membrane from Kilarski et al. (2009). Mechanical stresses provided by the fibroblasts pull the vasculature in the direction of closing the wound. Figure from Kilarski et al. (2009) with permission of Nature Publishing Group.

the mechanisms driving the process since it permits to test individually the effect of each one of them.
Much can be gained by following the research in the mechanical properties of vessel growth since it is pivotal in diverse pathological contexts, and this research can lead to definitive progresses in the therapeutics. However a stronger collaborative effort between Mathematics, Physics, computational simulations, together with advances in the understanding of the underlying biological processes has to be undertaken.

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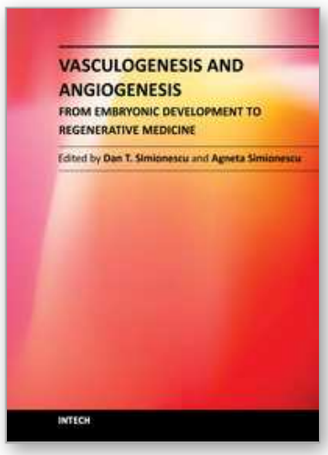
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**Vasculogenesis and Angiogenesis - from Embryonic Development to Regenerative Medicine**

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Vasculogenesis is the process of new blood vessel formation during embryonic development of the cardiovascular system. This is followed by formation of a vascular tree and finally the cardiovascular system with the myriad of blood vessels that nourish all tissues and organs. Angiogenesis, on the other hand is the process by which new blood vessels take shape from existing blood vessels by "sprouting" of endothelial cells thus expanding the vascular tree. Both scenarios are based on activation, migration, proliferation and maturation of unique precursor cells. The study of blood vessel formation is an essential component of embryonic development, congenital malformations, degenerative diseases, inflammation and cancer and thus has widespread appeal to the biomedical field. Moreover, scientists are now harnessing this information for the purpose of building living blood vessel substitutes for replacement of diseased arteries and veins. This book highlights novel advances in the field of vasculogenesis and angiogenesis, including embryogenesis and development, regulation of progenitor cells, cancer and blood vessel regeneration. We consider this book a good initial source of information for graduate students, medical students and scientists interested in the intricacies of blood vessel formation, maturation, disease and replacement.

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