A novel SPH algorithm to simulate tumour angiogenesis

Maria Inês A. Barbosa[1,3], Jorge Belinha[1], Renato M. Natal Jorge[3], Ana X. de Carvalho[4]

[1]*Institute of Mechanical Engineering and Industrial Management, University of Porto*
Rua Dr. Roberto Frias, S/N, 4200-465 Porto, Portugal
up201405732@edu.fe.up.pt
[2]*Dept. of Mechanical Engineering, School of Engineering Polytechnic of Porto*
Rua Dr. António Bernardino de Almeida, 431, 4200-072 Porto, Portugal
job@isep.ipp.pt
[3]*Dept. of Mechanical Engineering, Faculty of Engineering, University of Porto*
Rua Dr. Roberto Frias, S/N, 4200-465 Porto, Portugal
rnatal@fe.up.pt
[4]*Dept. of Cytoskeletal Dynamics, Institute for Research and Innovation in Health, University of Porto*
Rua Alfredo Allen, 208, 4200-135 Porto, Portugal
anacarvalho@ibmc.up.pt

Abstract. Nowadays, cancer is one of the foremost causes of death worldwide. As a tumor grows, it requires an increased supply of oxygen and nutrients to sustain its progression. However, once it reaches a critical size, the transportation of these molecules to the center of the tumor becomes challenging. In such circumstances, tumor cells initiate the process of angiogenesis to generate new blood vessels and so, a new nutrient source. Understanding the impact of angiogenesis on tumor progression is crucial for comprehending cancer. In recent decades, computational models have been extensively employed to investigate various biological problems, including tumor progression. The objective of this study was to develop a 3D algorithm to simulate the process of cell proliferation combined with angiogenesis. The algorithm utilizes the Smoothed Particle Hydrodynamics method and takes into account the concentration of Vascular Endothelial Growth Factor. To validate the algorithm, various high-concentration points were selected to observe whether the generated blood vessels followed appropriate paths. The proliferation process was assumed to follow an exponential pattern, and its reliance on the created blood vessels was analyzed. The results demonstrated that in all cases, the process of angiogenesis was successfully integrated with the process of cell proliferation.

Keywords: cell proliferation, angiogenesis, smooth particle hydrodynamics, meshless methods, numerical simulations.

1 Introduction

The blood vascular system initially develops during embryogenesis to supply nutrients throughout the body. Angiogenesis is the process responsible for forming blood vessels [1]. In angiogenesis, dormant endothelial cells are activated by pro-angiogenic factors like vascular endothelial growth factor (VEGF), causing them to migrate and grow towards the source of these factors [2, 3]. These factors attach to endothelial cells, triggering the breakdown of the basement membrane, cell migration, proliferation, and the creation of capillaries [4, 5].
In adults, angiogenesis remains under strict control, only becoming active during specific situations like wound healing. However, this process can be erroneously triggered by certain conditions, such as cancer, which exploits angiogenesis to further its progression [2].
Mathematical and computational models currently play a pivotal role in understanding biological processes and complement experimental studies [6, 7]. When considering angiogenesis, due to its dynamic, spatially varied, and nonlinear nature, making assumptions and simplifications is often necessary, leading to diverse models in existing literature [6].
Advancements in 3D modeling and computing have enriched computational and mathematical models, enabling the creation of more intricate and realistic representations, thereby contributing significantly to scientific research [8]. To solve such models, discrete numerical methods are frequently employed. Among these, notable examples

include the Finite Element, Cellular Automata, and Lattice-based models, capable of simulating various aspects of angiogenesis and tumor progression, encompassing cell movement, growth, division, extracellular matrix degradation, and cell migration [9-11].

Mesh-based methods, such as the Finite Element Method (FEM), are popular due to their simple discretization approach and ease of programming [12-14]. However, they encounter challenges with mesh distortion in cases of significant deformations. To address this issue, meshless methods have emerged [13]. These methods utilize a nodal mesh to discretize the problem domain, simplifying tasks like node introduction and removal [15, 16].

Within the realm of meshless methods, particle methods stand out. These methods approximate continuous field variables using particles, with the Smoothed Particle Hydrodynamics (SPH) being the most prominent example [17, 18, 19].

The objective of this study is to introduce an innovative 3D model employing SPH to simulate angiogenesis triggered by VEGF concentration, combined with a cell proliferation algorithm. The algorithm directs blood vessel growth towards VEGF gradients through iterative steps, tested using various VEGF focal points and initial vessel positions. Additionally, the proliferation process was considered, assessing the effectiveness of the dual-process combination within a tumor growth context.

2 Methods

2.1 Smooth Particle Hydrodynamics

As previously discussed, the method used to solve the proposed algorithm is the SPH method [20]. The SPH uses disconnected particles to discretize the domain where the cells, extracellular matrix and blood vessel are described. Moreover, this method uses an integral representation to create approximation functions that estimate the desired field function, which are then applied to the Navier-Stokes equations. After that, particle approximation step is performed and the results are obtained taking into account the positions of the particle set [17, 19, 20].

In this work, to calculate the physical forces acting on the particles the Navier-Stokes equations are used [20]. The equations governing the momentum and mass conservation are:

$$\rho \frac{D\boldsymbol{v}}{Dt} = -\nabla p + \rho \boldsymbol{g} + \mu \nabla^2 \boldsymbol{v} \tag{1}$$

$$\frac{D\rho}{Dt} = -\rho \nabla \cdot \boldsymbol{v} \tag{2}$$

Here, $\boldsymbol{v}$ represents the velocity, p the pressure, μ the viscosity, $\boldsymbol{g}$ the gravity acceleration and ρ represents the density [20].

If the second law of Newton is considered, then the acceleration $\boldsymbol{a}_i$ of a particle $\boldsymbol{x}_i$ can calculated using the following expression:

$$\boldsymbol{a}_i = \frac{D\boldsymbol{v}_i}{Dt} = \frac{\boldsymbol{F}_i}{m_i} \tag{3}$$

where, $\boldsymbol{F}_i$ is the sum of all forces that are applied on particle $\boldsymbol{x}_i$ [20].

To perform the summation over the particles in order to make the discretization within each support domain, the particle approximation step of the method is done resorting to a continuous integral representations [17]. Thus, considering an integral equation represented as $f(\boldsymbol{x})$, it can be expressed in the form of discretized particle approximation using the next equation [17, 21]:

$$f(\boldsymbol{x}) = \int_{\Omega} f(\boldsymbol{x}') W(\boldsymbol{x} - \boldsymbol{x}', h)\, d\boldsymbol{x}' = \sum_{j=1}^{n} f(\boldsymbol{x}_j) W_{ij} \frac{m_j}{\rho_j} \tag{4}$$

where $W(\boldsymbol{x} - \boldsymbol{x}', h)$ corresponds to the smoothing kernel function, h to the smoothing length, n to the number of particles inside of the support domain of the particle j, m_j corresponds to the mass of particles $j = \{1, 2, \ldots, n\}$ and ρ_j to their density [17].

With this equation, it is possible to estimate the value of a function at a certain particle $\boldsymbol{x}_i$ and, through it, the spatial derivative of the function can obtained:

$$\langle \nabla \cdot f(\boldsymbol{x}_i) \rangle = -\sum_{j=1}^{n} f(\boldsymbol{x}_j) \nabla W_{ij} \frac{m_j}{\rho_j} \tag{5}$$

where, r_{ij} is the distance between the particles i and j.

Assuming the previous equation, the gradient of smoothing function ∇W adjusts the value of the gradient of a function at particle $\boldsymbol{x}_i$, allowing us to estimate this value [17].

In the present work, three different kernel functions were used.

For the majority of the variables, a polynomial equation was used to describe them. This equation is given by the next expression:

$$W_{poly6}(\boldsymbol{x}_{ij}, h) = \frac{315}{64\pi h^9} \begin{cases} \left(h^2 - \boldsymbol{x}_{ij}^2\right)^3 & 0 \leq \boldsymbol{x}_{ij} \leq h \\ 0 & otherwise \end{cases} \tag{6}$$

A spiky kernel function is used to calculate the pressure force of the particles and it is defined as:

$$W_{spiky}(\boldsymbol{x}_{ij}, h) = \frac{15}{\pi h^6} \begin{cases} \left(h - \boldsymbol{x}_{ij}\right)^3 & 0 \leq \boldsymbol{x}_{ij} \leq h \\ 0 & otherwise \end{cases} \tag{7}$$

The kernel function that describes the viscosity of the particles is given by the following expression:

$$W_{viscous}(\boldsymbol{x}_{ij}, h) = \frac{15}{2\pi h^3} \begin{cases} -\frac{\boldsymbol{x}_{ij}^3}{2h^3} + \frac{\boldsymbol{x}_{ij}^2}{h^2} + \frac{h}{2\boldsymbol{x}_{ij}} - 1 & 0 \leq \boldsymbol{x}_{ij} \leq h \\ 0 & otherwise \end{cases} \tag{8}$$

2.2 Numerical Algorithm

The presented algorithm aims to simulate angiogenesis by simulating the growth of blood vessels towards a VEGF source and integrating it with cell proliferation in a tumor growth scenario. The process begins by introducing input parameters that define domain characteristics such as initial volume, pressure, material properties, dimensions, and time step. Subsequently, the domain is discretized, initially assuming all particles represent the extracellular matrix. A boundary is established as a static reference at the domain's bottom, and the initial blood vessel particle is positioned at this boundary. Material properties are adjusted to correspond to the designated type of material. Additionally, when considering cell proliferation, an initial cell is defined at the domain's center. Once all particles are defined, their initial velocity, pressure, and acceleration are computed.

To initiate blood vessel growth, a VEGF gradient is applied. In the first iteration, a constant finite element mesh is generated based on the particle setup, and a VEGF concentration is assigned to each element. Subsequently, the blood vessel begins to grow along the gradient, with new particles incorporated into the domain after a predetermined number of iterations.

Concerning cell proliferation, the process encompasses cell growth and division, leading to the introduction of a new particle within the domain. Angiogenesis commences once a specific number of cells are reached.

Throughout the entire simulation, influence domains and kernel functions are defined for all particles in each iteration, enabling the calculation of the total force applied to each particle. Consequently, the particles' positions, accelerations, and velocities are updated.

3 Results and Discussion

Angiogenesis, triggered by VEGF concentration, was simulated using different blood vessel starting points and VEGF concentrations. In each instance, the resulting blood vessels grew as intended, with variations primarily in time to reach the VEGF source and vessel shape.

When combining cell proliferation and angiogenesis, the results matched expectations. This scenario simulated hypoxic tumor cells releasing VEGF to prompt endothelial growth towards their direction. Uniform blood vessel growth patterns emerged in all cases. Furthermore, when simulating the two processes simultaneously, the performance of the algorithm remained consistent and aligned with its defined parameters and with what was designed.

In conclusion, the algorithm proficiently simulated angiogenesis, maintaining consistent growth patterns across various conditions. The introduction of cell proliferation did not disrupt the results, suggesting potential for the algorithm to effectively simulate both processes.

4 Conclusions

Angiogenesis, the process of forming new blood vessels, holds paramount importance in both physiological and pathological contexts, encompassing embryonic development, wound healing, and tumor progression. Grasping its mechanisms is indispensable for devising enhanced therapeutic strategies against diseases like cancer. In this process, VEGF plays a pivotal role, triggered by factors such as hypoxia, inflammation, or growth signals.

While experimental studies have historically constituted the majority of angiogenesis research, mathematical and computational models have increasingly become essential complements. Numerical methods, including meshless techniques, are employed to solve these models. Among these techniques, the SPH method stands out, discretizing domains using particles.

This study aimed to develop an algorithm utilizing SPH to simulate the combined process of angiogenesis and cell proliferation, influenced by VEGF concentration and considering a tumor growth scenario. The algorithm's efficacy was analyzed in terms of blood vessel growth in response to varying VEGF concentrations and different initial blood vessel positions. Ultimately, all blood vessels grew towards the VEGF sources. The combination of angiogenesis and cell proliferation yielded favorable outcomes, aligning with expectations. Furthermore, the SPH method demonstrated efficiency in simulating both processes.

While the results were satisfactory, the algorithm is still in its preliminary stages, warranting several improvements.

Acknowledgements. The authors truly acknowledge the funding provided by Ministério da Ciência, Tecnologia e Ensino Superior - Fundação para a Ciência e a Tecnologia (Portugal), under the grant SFRH/BD/146272/2019. Additionally, the authors acknowledge the funding provided by LAETA, under the project UIDB/50022/2020.

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