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# A conservative and variation preserving finite volume method for non-overlapping meshes of reaction and diffusion in angiogenesis

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## HIGHLIGHTS

- Reaction and diffusion of growth factors in angiogenesis.
- Reaction and the diffusion meshes are non-overlapping.
- Conservative and reaction-variation preserving finite volume method.
- Handle non-uniform discretization and arbitrary shaped reaction domains.

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## ABSTRACT

We propose a conservative and variation preserving finite volume method for reaction and diffusion in angiogenesis. The reaction domain keeps changing the morphology and length, and its mesh is non-uniform and does not overlap with the diffusion mesh. These facts make it very challenging to develop a numerical method that conserves the mass when transferring data between the reaction and diffusion domains. We prove the method developed in this work not only conserves the mass locally but also retains the variation in the reaction domain. In contrast, the direct interpolation may smear out the reaction data in the data transfer process. This method is applied to the growth factor reaction and diffusion problems in angiogenesis.



## 1. Introduction

Angiogenesis, the formation of new blood vessels, is crucial to many processes such as wound healing and cancer. It is controlled by growth factors such as Vascular Endothelial Growth Factor (VEGF). VEGF is released by injured tissue or hypoxic cancer cells and diffuses in the tissue. Once reaching blood vessels, VEGF binds to receptors such as VEGFR2 on endothelial cells (ECs) that line the blood vessel. The activation of VEGFR2 triggers a sequence of intracellular events resulting in cell proliferation and migration. These new blood vessels are called capillaries because they are very thin. Their diameter is at most 20 $\mu$m, but the length can extend to the size of the tissue, for example, 2 mm in diameter of a rat cornea [1] or a dormant tumor [2]. The reaction (binding kinetics) occurs only on thin capillaries, but the diffusion happens in the whole tissue domain.

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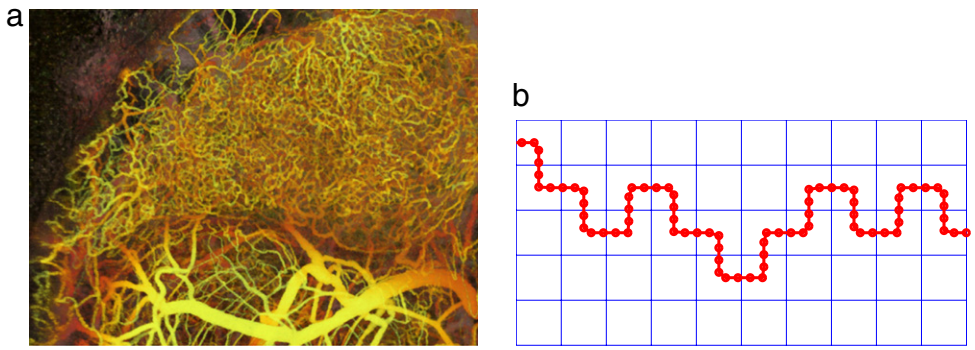


**Fig. 1.** (a) The highly irregular and tortuous blood vessel capillaries in a xenotransplanted U87 human glioblastoma multiforme tumor (upper part) in a mouse brain. The size of this tissue is 2.6 mm by 2 mm. This picture is taken from [12] with permissions. (b) multi-resolution of diffusion and reaction domains/meshes. The square meshlines are for the diffusion domain, and the irregular line represents a capillary centerline where the dots are the reaction mesh points.

The real problem is three-dimensional (3-D) but for simplicity we only consider a two-dimensional (2-D) tissue, denoted as $\Omega$. Note that the proposed numerical method and its properties can be straightforwardly extended to the 3-D case. We denote the capillary domain as $\Omega_C \subset \Omega$, which is the collection of all capillaries in $\Omega$. For simplicity, we assume the capillaries are of the uniform diameter $d_c$. Denote the centerline of the capillaries as $\Sigma$, its arc length parameter as $s$, and its spatial point as $\mathbf{x}(s)$.

Denote $u$ as the concentration of the free growth factor, and $[FR]$ and $[BR]$ as the concentrations of free receptors and growth factor/receptor complexes (or bound receptors), respectively. The mathematical model of our study can be written as (e.g. [3,4])

$$\frac{\partial u}{\partial t} + H_{\Omega_C}\vec{v}\cdot\nabla u = D\nabla^2 u + H_{\Omega_C} f(u) \quad \text{in } \Omega, \tag{1}$$

where $H_{\Omega_C}$ is the Heaviside function of the domain $\Omega_C$, $\vec{v}$ is the velocity of the capillary, and $D$ is the diffusion constant. The term $H_{\Omega_C}\vec{v}\cdot\nabla u$ models the convection of growth factor by the capillary. The reaction function "$f$" represents the reaction on the capillary. One often used example (e.g. [4]) considers the binding kinetics between the growth factor and its receptor:

$$\left\{\begin{array}{c} f(u) = -k_{\text{on}} u[FR] + k_{\text{off}}[BR], \\ \dfrac{\partial [FR]}{\partial t} + H_{\Omega_C}\vec{v}\cdot\nabla[FR] = -k_{\text{on}} u[FR] + k_{\text{off}}[BR] + k_p[BR], \\ \dfrac{\partial [BR]}{\partial t} + H_{\Omega_C}\vec{v}\cdot\nabla[BR] = k_{\text{on}} u[FR] - k_{\text{off}}[BR] - k_p[BR] \end{array}\right\} \quad \text{in } \Omega_C, \tag{2}$$

where $k_{\text{on}}$, $k_{\text{off}}$, and $k_p$ are rates of association, disassociation, and internalization, respectively. In this model, the sum of free receptors and bound receptors is constant, denoted as $R_T \triangleq [FR] + [BR]$.

The growth factor model (1) and (2) are usually combined with a capillary growth model. There are mainly two types of capillary growth models: lattice models and non-lattice models [5]. In lattice models such as [6,5], all the mesh points of a capillary is a subset of the diffusion mesh points. That is, the reaction sites and the diffusion sites are identical. In this case, there is no need to transfer data between the reaction and diffusion meshes. However, in many non-lattice models such as [7,8,5,9,10,3,4] and this work, the capillary mesh (reaction mesh) and the diffusion mesh do not overlap. In this case, the growth factor has two expressions: one on the reaction mesh and the other on the diffusion mesh. To connect the reaction and diffusion processes, a data transfer between the two meshes is required.

We have two criteria in developing the data transfer algorithm between the non-overlapping meshes: mass conservation and reaction data variation preserving. When a quantity is expressed on two different meshes, it is natural to expect that these two expressions are identical in some measure. The measure we use is the mass conservation that includes both the local conservation (Theorem 4) and the global conservation (Theorem 5). The accurate computation of growth factors on the capillary is very important because their concentrations and variations can directly determine the fate of ECs. For example, the viability and proliferation of ECs are directly controlled by the VEGF concentrations, and the variation of VEGF along the capillary determines the direction of EC migration [11,4]. Therefore, it is critical to conserve the mass locally and preserve the variation of data in the reaction domain when designing the data transfer algorithm.

To the best of our knowledge, this work is the first to address these two criteria among numerical methods for reaction and diffusion on non-overlapping meshes. In this study, the diffusion domain is discretized with a uniform Cartesian mesh and the reaction domain is discretized with a non-lattice method. In general, the reaction mesh points are not uniform along the capillary and they are not overlapping with the diffusion mesh points or center points (see Fig. 1(b)). Furthermore, the reaction mesh points keep changing positions during capillary growth. These facts pose a big challenge in developing a data