COMPARISON OF SEVERAL REACTION AND DIFFUSION MODELS OF GROWTH FACTORS IN ANGIOGENESIS

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Abstract. We compare three types of mathematical models of growth factor reaction and diffusion in angiogenesis: one describes the reaction on the blood capillary surface, one in the capillary volume, and one on the capillary centerline. Firstly, we explore the analytical properties of these models including solution regularity and positivity. We prove that the surface-reaction models have smooth and positive solutions, and the volume-reaction models have continuous and positive solutions. The line-reaction models utilize distributions on the capillary centerline to represent the reaction line source. The line-reaction model-I employs the Dirac delta function and the mean value of the growth factor around the centerline, which gives a valid model. The line-reaction model-II and -III use the local value of the growth factor, which either create singularity or decouple the reaction from diffusion, thus invalid. Secondly, we compare the programming complexity and computational cost of these models in numerical implementations: the surface-reaction model is the most complicated and suitable for small domains, while the volume-reaction and line-reaction models are simpler and suitable for large domains with a large number of blood capillaries. Finally, we quantitatively compare these models in the prediction of the growth factor dynamics. It turns out the volume-reaction and line-reaction model-I agree well with the surface-reaction model for most parameters used in literature, but may differ significantly when the diffusion constant is small.

Key words. Reaction, Diffusion, Angiogenesis, Growth Factors, Equations with Distribution Coefficients, Singular Solutions

AMS subject classifications. 35K57, 36K67, 92B99

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 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 radius ranges from 2 to $20\,\mu m$ [26], but the length can extend to the size of the tissue, for example, $2\,mm$ in diameter of a rat cornea [26] or a dormant tumor [7]. The reaction (binding kinetics) occurs only on the thin capillaries, while the diffusion happens in the tissue domain.

The purpose of this work is to compare the existing reaction and diffusion models of growth factors in angiogenesis. There exist mainly four types of models, depending on where the binding reaction is modeled. The first type describes the reaction on the capillary surface, such as [15, 17, 5, 13, 14]. We call these the surface-reaction models. The second type treats the reaction occurring in the whole capillary volume, such as [28, 6, 19, 16, 3, 10], which is called volume-reaction model in this paper. The third type models the reaction only on the capillary centerline, such as [33, 27, 29], which are called line reaction models. More details of these models will be discussed in § 2.

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