Numerical modeling of new 4,7-dihydroxycoumarin derivative diffusion within finite element liver model

Vladimir Simić[1*], Miljan Milošević[1,2,4], Žiko Milanović[1], Miloš Kojić[2,3,5]

[1] University of Kragujevac, Institute for Information Technologies, Department of Technical-Technological Sciences, Jovana Cvijica bb, 34000 Kragujevac, Serbia.; e-mail: vsimic@kg.ac.rs, miljan.m@kg.ac.rs, ziko.milanovic@uni.kg.ac.rs
[2] Bioengineering Research and Development Center (BioIRC), Prvoslava Stojanovića 6, 34000 Kragujevac, Serbia
[3] Houston Methodist Research Institute, The Department of Nanomedicine, 6670 Bertner Ave., R7 117, Houston, TX 77030, USA.; e-mail: mkojic42@gmail.com
[4] Belgrade Metropolitan University, Tadeuša Košćuška 63, 11158, Belgrade, Serbia
[5] Serbian Academy of Sciences and Arts, Kneza Mihaila 35, 11 000, Belgrade, Serbia

* *Corresponding author*

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Abstract: Blood coagulation, also known as blood clot formation, is an essential biochemical process which occurs when a blood vessel is damaged and requires repair [1]. Blood clot development, inevitable to exclude excessive bleeding and damaged area healing, can be detrimental if clots form in blood vessels improperly, leading to various problems- thrombosis, pulmonary embolism, etc. In order to prevent those scenarios, there is a certain need for the development of novel drugs. For that purpose, we have performed computational modeling of a diffusion process of a newly investigated and synthesized 4,7-dihydroxycoumarin derivative. Also, for the purpose of the diffusion modeling process, a smeared modeling concept for gradient-driven mass transport and formulation of a new composite smeared finite element (CSFE) is introduced in [2] and generalized in [3]. CSFE is composed of multiple domains: capillary, extracellular space, cells and organelles, with pressure and concentration for each domain. The domains are coupled by connectivity elements at each node. Here, we implemented this concept to a 3D liver model, which illustrates the applicability of the CSFE element and smeared concept to large biological systems. Special emphasis was placed on the distribution of the potential drug, which was monitored by the flow through the liver and blood vessel network via a purposely developed computational model of the liver. The main goal of the application of computational models is to reduce the financial costs of in vivo experiments, as well as to avoid the direct use of drugs on animals as well as humans.

Keywords: diffusion, smeared model, composite smeared finite element, liver model

1. Introduction

Transport of particles and molecules from the blood to tissue and from tissue back to blood is a complex process. Transport within tumors has additional complexities due to irregular blood vessel branching and variability of vessel diameters and lengths. It is not feasible to model each capillary, cell and organelles, even in small domains. Here, we implement a smeared modeling concept in order to provide models for large domains which can effectively be used for transport in the capillary system and tissue, with a focus on the diffusion process of the potential anticoagulation drug. Anticoagulants are drugs which extensively used to treat conditions in which a blood clot (thrombus) forms in the blood vessels. In addition, they are used to prevent the formation of new or growth of existing blood clots in patients who suffer from illnesses and disorders associated with an increased risk of clot formation.

2. Composite smeared finite element formulation

To introduce the smeared methodology, we consider a 'detailed model' of a composite medium. Fig. 1a shows a schematic of a medium composed of continuum domains- compartments and a network of fiber-like 1D domains. The continuum domains include extracellular space, cells and organelles. First, it is necessary to transform the 1D balance equations into the corresponding continuum format. Also, each domain has its own field within the corresponding volume of the CSFE. Finally, we include connectivity elements to couple the corresponding domains, at each node of the CSFE (equations are given in [2] and [3]).

There are the following physical fields within the element: pressure and concentration in capillaries, within extracellular space and cytosol of cells; and concentration within organelles. These fields are mutually dependent. Schematics of a finite element with elementary volumes and connectivity element are shown in Fig. 1c [3].

3. Computational finite element liver model

The geometry of the liver and blood vessel network, shown in Fig. 1d, is generated at R&D Center BIOIRC from micro-CT scan of a mouse liver. The computational model consists of three parts: one-dimensional finite elements for larger vessels (7216 elements), three-dimensional composite smeared finite elements (36 243 elements) representing surrounding tissue, and connectivity elements (689 elements) necessary to connect large vessels and continuum nodes of smeared finite elements. The complete procedure is explained in [4], where it is noted how micro-computed tomography (micro-CT) was used to scan the vascular structure.

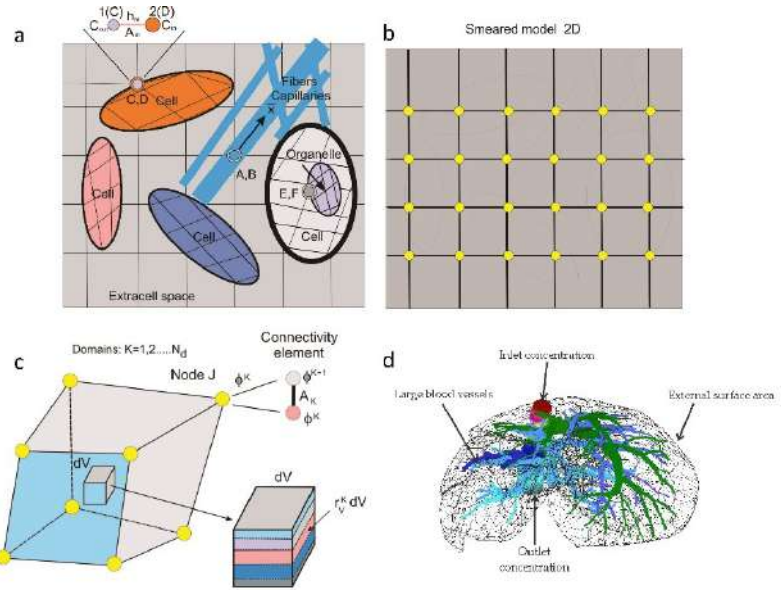

Fig.1. Schematic of detailed, smeared and liver model. a) Detailed model of tissue as composite medium, 2D representation, with 1D and connectivity elements; b) Smeared FE representation of the detailed model; c) Composite smeared finite element (CSFE) with subdomains and connectivity element at a FE node J; d) Geometry and boundary conditions of the liver model.

Material data applied in this computational model are used as in [5] with the addition of different diffusion coefficients for two different compounds (WF and L), used for representing the concentration field. The diffusion coefficient of the first compound, WF, is D_{WF} = 4.52 x 10^{-4} mm^2 s^{-1} while for L, the diffusion coefficient used is D_L = 4.34 x 10^{-4} mm^2 s^{-1}. Both values were estimated using the Stokes-Einstein equation. The simulation lasts for 400 s, divided into 40 equal time steps. The concentration field for three different time steps, in the vertical plane, within the capillary domain for both WF and L compounds is shown in Figure 2.

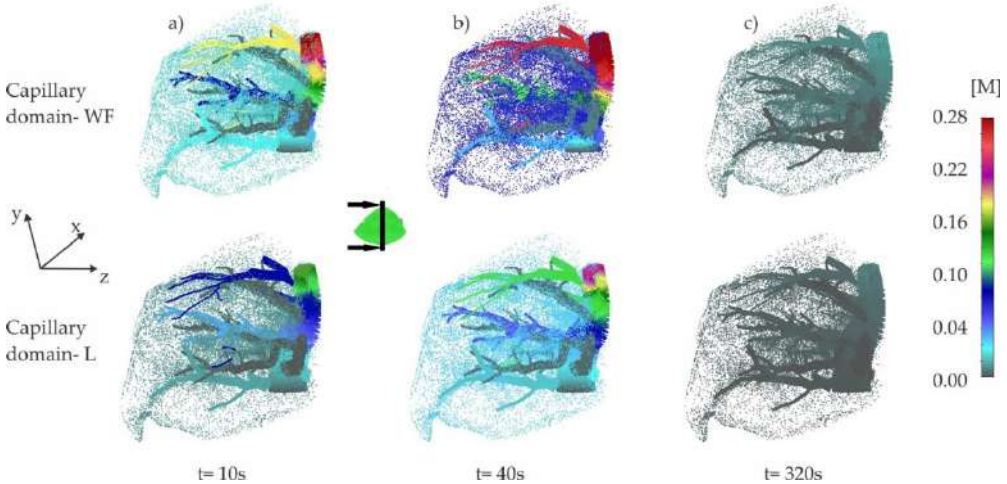

Fig.2. Mean concentration evolution inside the capillary and tissue domain within the liver, represented for both **WF** and **L** compound, for a) t= 10s, b) t= 40s and c) t= 320s.

4. Conclusions

In this study we summarized smeared methodology for field problems as a general concept for modeling gradient-driven field problems in complex biological media. The smeared model for transport offers a possibility to simulate in silico transport of small molecules and particles used in biomedical applications to improve drug delivery and therapeutics. Therefore, this computational model can serve as a basis for potential patient-specific drug delivery models, which can contribute to a better understanding of pharmacokinetic characteristics and the potential of novel anticoagulant compounds.

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