PARAMETER OPTIMIZATION OF TUMOR DRUG DELIVERY MODEL USING GENETIC ALGORITHMS

Vladimir Simić[1,3], Bogdan Milićević[2,3], Miljan Milošević[2,3,4], Arturas Ziemys[6], Nenad Filipović[2,3], Miloš Kojić[5,6]

[1] Institute of Information Technologies, University of Kragujevac, Jovana Cvijića bb, 34000 Kragujevac, Serbia, e-mail: vladimir.simic.991@gmail.com, miljan.m@kg.ac.rs
[2] Faculty of Engineering, University of Kragujevac, Sestre Janjić 6, 34000 Kragujevac, Serbia, e-mail: bogdan.milicevic@uni.kg.ac.rs, fica@kg.ac.rs
[3] Bioengineering Research and Development Center BioIRC Kragujevac, Prvoslava Stojanovica 6, 34000 Kragujevac, Serbia
[4] Belgrade Metropolitan University, Tadeuša Košćuška 63, 11000 Belgrade, Serbia
[5] Serbian Academy of Sciences and Arts, Knez Mihailova 35, 11000 Belgrade, Serbia
e-mail: mkojic42@gmail.com
[6] Houston Methodist Research Institute, Department of Nanomedicine, 6670 Bertner Ave., R7 117, Houston, TX 77030, e-mail: arturas.ziemys@gmail.com

Abstract:

Metastatic disease is, over the years, recognized as a major cause of mortality in patients diagnosed with cancer. Drug delivery properties of these types of tumors have not been sufficiently investigated, despite many drug delivery strategies for anticancer therapeutics, developed in preclinical studies. For that reason, there is a significant need for creating robust computational models which, combined with artificial intelligence tools (i.e. genetic algorithms), can establish a novel approach in the prediction of drug delivery inside the complex medium. Composite Smeared Finite Element (CSFE), introduced by a group of authors, provides a methodology for modeling diffusion transport of molecules and drugs in real tissue models consisting of capillaries and surrounding tissue. Here, the CSFE method is applied to a 3D drug delivery model comprised of a spherical tumor and surrounding liver, in order to evaluate parameters responsible for the mass accumulation differences between the tumor and surrounding liver. Patient-specific models are created, with given input systemic curves and experimental values for volume fraction. The main idea is to estimate the apparent diffusion coefficient inside the tumor, using data from tumor experimental concentration profiles (provided by Prof. Arturas Ziemys and Houston Methodist Lab). The genetic algorithms were used to find the diffusion and partitioning coefficients such that the CSFE simulation produces an experimental profile. Verification and applicability of the CSFE methodology for transport in this model is shown on a series of patients, where our numerical model matched experiments properly.

Keywords: composite smeared finite element, liver, tumors, genetic algorithm, optimization

1. Introduction

Current estimates regarding the global incidence of cancer predicted that, by the year 2020, the number of new cancer cases diagnosed will increase to 15 million annually and that cancer will be responsible for more than 12 million deaths [1]. Delivery of therapeutics and transport of mass inside complex has been a challenging subject to develop, throughout the last few decades. Most of the research in mass transport is done experimentally, rather than in a theoretical manner. The main reason was the complexity of mediums, especially tumors,

where irregularity of blood vessel branching, also its lengths and diameters can request almost impossible effort to model those kinds of problems. Despite all novel approaches, there is a significant need for the improvement of computational methods to develop appropriate methods and software as a tool for improving conventional drug therapies. Composite smeared finite element (CSFE), introduced in [2] and further generalized and applied in biomedical problems in [3-6], contains as many domains as there are physical domains in certain models: capillary, lymph, extracellular, domains of different types of cells, and organelles within cells, etc. In this paper we will apply this methodology to a 3D FE drug transport model that consists of a spherical tumor and surrounding cubic liver and using genetic algorithms, we will estimate a range of important parameters responsible for the mass transport. Applicability is shown on a random model, for random patient data, where we presented a field of concentration inside the whole model, as well as a comparison of concentration distribution for both experimental and computational model results.

2. Methods

A schematic representation of the CSFE (details about derivations and steps necessary to formulate this element given in [2,6]) is shown in Fig. 1a. Each of the listed subdomains K corresponds to the volume V_K of the entire element volume V, as $V^K = r_V^K V$ where r_V^K is the volumetric fraction of each constituent. At each node J there are specified connectivity elements for coupling two domains and simulating transport conditions between separate domains. Also, each of the domains has its own concentration field C^K, with the nodal values C_J^K. Regarding the computational model, Fig 1b displays geometry of our model, consisted from 3D FE mesh for 1/8 spherical tumor (diameter 160um) surrounded by a cubic tissue (liver) domain (twice larger that tumor). We have simulated the diffusion process inside tumor domain, using experimental data for diffusion coefficients, volumetric fractions (no capillaries in the tumor, in the surrounding liver- capillary volume set to 20%.) and partitioning coefficients inside surrounding tissue. Field of concentration for a random patient inside both domains are shown in Fig. 1c as well as comparison of concentration distribution profiles (Fig. 1d).

The genetic algorithms were used to determine the partitioning and diffusion coefficients such that the simulation produces a similar concentration curve to the experimental one, inside tumor domain. Each individual within the initial population of the genetic algorithm represents one set of parameters. For each set of parameters, we automatically run the simulation and evaluate the individual by calculating the root mean squared error between simulation-produced and experimental concentration. This is our fitness or objective function, which the genetic algorithm is minimizing. Based on the evaluation of the individuals, within the genetic algorithm population, they are selected for cross-over and mutation operators thus producing a new generation that possibly contains a better solution to the problem. If the simulation failed to execute with a set of parameters of an individual, because of a finite element divergence or similar reasons, we introduced an additional penalty to the individual, lowering its chances of passing the parameters values to the next generation. The process is continued until we find a solution that leads to a satisfying similarity between experimental and simulation-produced concentrations or until the maximum number of generations is achieved.

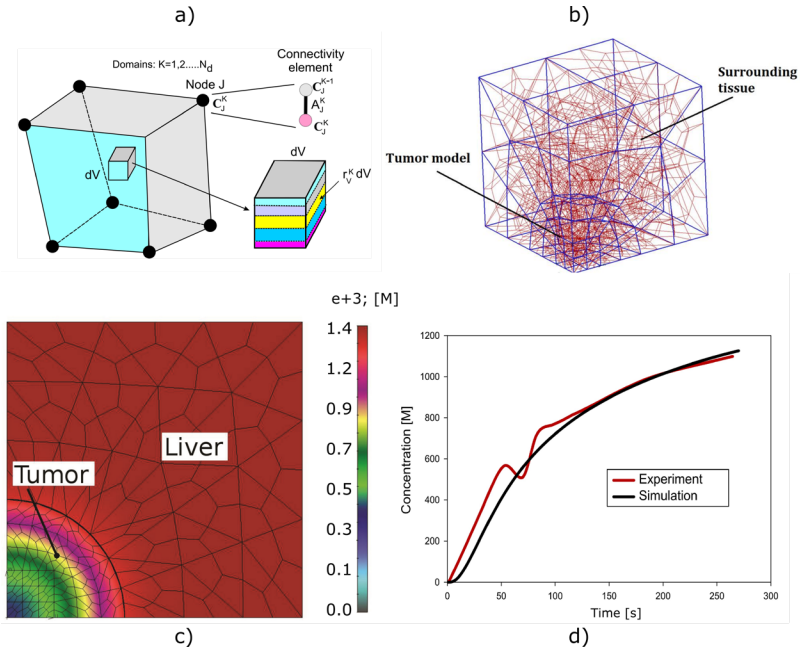

Fig. 1. a) CSFE formulation; b) Drug delivery model in our in-house software CAD; c) Field of concentration for a random patient inside Tumor and surrounding liver; d) Comparison of experiment and results obtained using our computational model for concentration distribution inside tumor domain (from Fig 1.c)

Table 1 shows results for concentration compared for experimental and numerical model (obtained using our computational procedure) for some random time steps, displayed also on Fig 1.b.

Patient 51- Tumor domain		
Time [s]	C(t)- experimental results [M]	C(t)- numerical results [M]
5.9	52	5.9
53.6	568	469.3
81.8	706	661.4
115.6	813	797.8
181.6	983	978.3
226.4	1051	1060.4
264.6	1098	1112.6

Table 1. Compared values at characteristic time points in experimental and simulated case.

We run a genetic algorithm with a population of 50 individuals, a mutation probability of 10%, and a maximum of 100 generations. After 70 generations, the process terminated finding the parameters which produced satisfying similarities between the experimental and acquired concentration curve (Fig.1 d). The values of parameters found by the genetic algorithm are: diffusion coefficient inside tissue (liver domain) - D_{tiss} = 10 um^2/s, diffusion coefficient through the wall- D_{wall} = 10 um^2/s and Partitioning coeffieient inside tissue domain- $P_{boundary}$ = 0.7.

3. Conclusions

Presented composite smeared finite element combined with usage of genetic algorithms proved its applicability and accuracy on a simple 3D drug delivery model. It may be concluded that the CSFE based on the smeared concept for mass transport, offers a reasonable computational tool for practical applications in biomedical investigations. This methodology is also applicable to a larger study, for example estimation of parameters required for modeling muscle mechanics, as published in [7].

Acknowledgement: This research is supported by the European Union's Horizon 2020 research and innovation programme under grant agreement No 952603 (http://sgabu.eu/). This article reflects only the author's view. The Commission is not responsible for any use that may be made of the information it contains.Research is also supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, contract number 451-03-68/2022-14/ 200378 (Institute of Information Technologies, University of Kragujevac).

References

[1] World Health Organization Press Release WHO/27/IARC/145, The World Cancer Report – The Major Findings, Available from: http://www.who.int/cancer/en/.

[2] M. Kojic, M. Milosevic, V. Simic, E.J. Koay, J.B. Fleming, S. Nizzero, N. Kojic, A. Ziemys , M. Ferrari , A composite smeared finite element for mass transport in capillary systems and biological tissue, Comp. Meth. Appl. Mech. Engrg., 324, 413–437, https://doi.org/10.1016/j.cma.2017.06.019, 2017.

[3] M. Kojic, M. Milosevic, V. Simic, E. J. Koay, N. Kojic, A. Ziemys, M. Ferrari, Extension of the Composite Smeared Finite Element (CSFE) to Include Lymphatic System in Modeling Mass Transport in Capillary Systems and Biological Tissue, J. Serb. Soc. Comp. Mech., Vol 11, No.2, 108-120, 2017.

[4] Milosevic M, Simic V, Milicevic B, Koay E.J, Ferrari M, , Ziemys A, Kojic M, Correction func-tion for accuracy improvement of the Composite Smeared Finite Element for diffusive transport in biological tissue systems. Comput. Methods Appl. Mech. Engrg, Vol 338, August 2018, pp 97-116, doi.org/10.1016/j.cma.2018.04.012 , ISSN : 0045-7825.

[5] M. Kojic, M. Milosevic, V. Simic, E.J. Koay, N. Kojic, A. Ziemys , M. Ferrari, Multiscale smeared finite element model for mass transport in biological tissue: from blood vessels to cells and cellular organelles, Computers in Biology and Medicine, vol. 99, pp. 7-23, 2018. https://doi.org/10.1016/j.compbiomed.2018.05.022.

[6] M. Kojic, M. Milosevic, V. Simic, A. Ziemys, N. Filipovic, M. Ferrari, Smeared multiscale finite element model for electrophysiology and ionic transport in biological tissue, Computers in Biology and Medicine, Volume 108, pp. 288-304, 2019.

[7] Milos Kojic, Miljan Milosevic, Vladimir Simic, Bogdan Milicevic, Vladimir Geroski, Sara Nizzero, Arturas Ziemys, Nenad Filipovic, Mauro Ferrari, Smeared Multiscale Finite Element Models for Mass Transport and Electrophysiology Coupled to Muscle Mechanics, Frontiers in Bioengineering and Biotechnology, ISSN 2296-4185, Vol. 7, No. 381, pp. 1-16, doi.org/10.3389/fbioe.2019.00381, 2019.