Journal of the Serbian Society for Computational Mechanics / Vol. 19 / No. 1, 2025 / pp 416-425 / review paper
(10.24874/jsscm.2025.19.01.26)

NUMERICAL HOMOGENIZATION AS A METHOD FOR MODELING CONSTRAINED DIFFUSION

Milos Kojic[1,2*] [0000-0003-2199-5847], Miljan Milosevic[1,3,4] [0000-0003-3789-2404], Alessandro Grattoni[5] [0000-0001-7888-422X], Mauro Ferrari[5] [0000-0002-2218-1135]

[1]Bioengineering Research and Development Center BioIRC Kragujevac, Prvoslava Stojanovica 6, 3400 Kragujevac, Serbia.
[2]Serbian Academy of Sciences and Arts, Knez Mihailova 35, 11000 Belgrade, Serbia.
[3]Institute of Information Technologies, University of Kragujevac, Department of Technical-Technological Sciences, Jovana Cvijica bb, 34000 Kragujevac, Serbia.
[4]Belgrade Metropolitan University, Tadeusa Koscuska 63, 11000 Belgrade, Serbia.
[5]Houston Methodist Research Institute, The Department of Nanomedicine, 6670 Bertner Ave., R7-117, Houston, TX 77030, United States
**corresponding author*

Abstract

Material transport by diffusion is present in nature, as well as in living organisms as a vital process. The basic and generally used is a phenomenologically established law, named Fick's law, It states that the material flux is proportional to the concentration gradient and that the material flows from the higher to lower concentration. However, if the diffusion occurs in nano space, the interaction of the transported molecules produces deviation from Fick's law leading to a so-called restrained, or retarded diffusion. Using the Molecular Dynamics (MD) methodology, we have calculated the effects of the molecule-solid interaction by introducing the scale functions and used them in our finite element code PAK to find the equivalent bulk diffusivity and equivalent distance from the solid surface. This computational procedure is called numerical homogenization, where the equivalent diffusion parameters are evaluated from the mass release curves. Verification of our multiscale modeling of the retarded diffusion is demonstrated on glucose transport through a device with nanochannels (NDS). Our methodology is illustrated by two examples – one to show the effects of the molecular interaction within a space with solid spheres and several porosities, and another where the equivalent diffusion coefficients are computed using images of pancreatic tumor tissue.

Keywords: Constrained diffusion, Multiscale, Numerical homogenization, Composite media, Finite element method, Molecular dynamics

1. Introduction

In mass transport by diffusion within a fluid, Fick's law is generally used. This law is phenomenological and is defined by the following relation:

$$\mathbf{J} = -\mathbf{D}\bullet\nabla c, \quad J_i = -D_{ij}\frac{\partial c}{x_j} \tag{1}$$

where J is the mass (or volumetric) flux, c is concentration and D is diffusion tensor. In the case of an isotropic medium, the diffusion tensor is diagonal with values representing the diffusion coefficient D (Kojic et al. 2022). The physical law (1) corresponds to the so-called free diffusion. However, if the transported molecules flow within a nano space, as we have in the case, for example, of diffusion within the tissue, there is an interaction with the solid surfaces so that the proportionality between the flux and the concentration gradient is dependent on the concentration (Gladden and Dole, 1953, Grattoni et al. 2011, Ziemys et al. 2011), as given in Table 1.

c[M]	0.00	0.55	1.09	1.66	2.23	2.78	3.36
$D\cdot10^{-6}$ [cm^2/s]	6.75	5.80	4.86	3.96	3.02	2.20	1.33

Table 1. Experimental data of diffusivity used in the model (Gladden and Dole, 1953)**.**

Using Molecular Dynamics, it was shown that in the nano space, there is a significant effect of the interaction of the transported molecules with the solid surface, Fig. 1. We have introduced

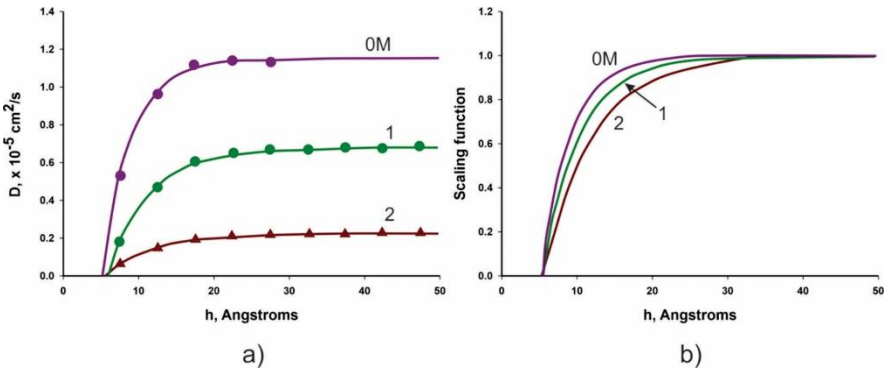

Fig. 1 Effects of the interaction of the transported molecules with the solid surface on diffusion. a) Diffusion coefficients of glucose through silica nanochannel in terms of the distance from the wall *h*, for three concentrations; MD solutions. b) Scaling functions - normalized diffusion coefficient by the bulk value in terms of the distance from the wall. (according to Ziemys, et al., 2011).

the functions $s(h,c)$, as the dependence of the normalized diffusion coefficient, with respect to the bulk diffusion coefficient D_{bulk} , on distance from the wall h and concentration c ,

$$s = \frac{D}{D_{bulk}} = s(h,c) \tag{2}$$

We have implemented this formulation of the constrained diffusion into our software PAK. The fundamental finite element balance equation of a finite element can be written as (Kojic et al. 2022),

$$\left(\frac{1}{\Delta t}\mathbf{M} + \mathbf{K} + \mathbf{K}_v\right)\Delta\mathbf{C} = \mathbf{Q}_{ext} + \mathbf{Q}_V - \left(\mathbf{K} + \mathbf{K}_v\right)\mathbf{C} - \frac{1}{\Delta t}\mathbf{M}\left(\mathbf{C} - \mathbf{C}^t\right) \tag{3}$$

where C and C^t are nodal concentrations at the end and the start of the time step of size Δt; Q_{ext} and Q_V are external and volumetric fluxes; and the matrices are

$$M_{IJ} = \int_V N_I N_J dV, \;\; K_{IJ} = \int_V D_{ij} N_{I,i} N_{J,j} dV, \; \mathrm{K}_{vIJ} = \int_V v_i N_I N_{J,i} dV = sum\ i,\ j = 1,2,3 \tag{4}$$

and N_I, N_J are the interpolation functions, D_{ij} is the diffusion tensor. and v_i are fluid velocities in the case of diffusion with convection. We modeled the nanodevice as a membrane composed of the microchannels and nanochannels for drug delivery (Ziemys et al. 2011), shown in Fig. 2a. Two-dimensional elements are used for microchannels,

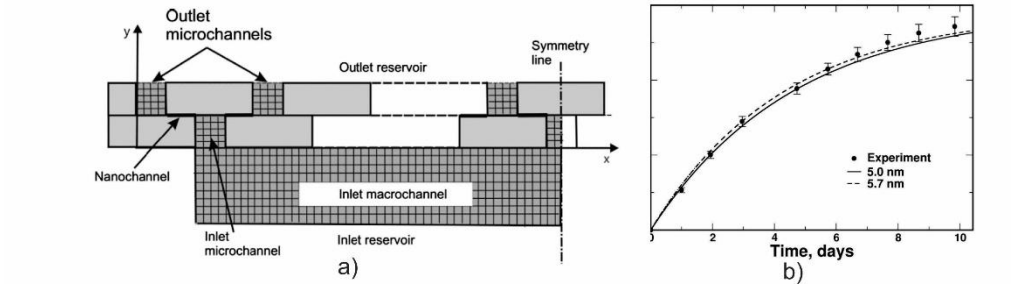

Fig. 2 a) Schematics of the nanodevice system (NDS) for drug delivery. b) Drug delivery through the NDS, computed and experimentally recorded.

while the nanochannels are modeled by 1D elements where the diffusion coefficient is numerically determined by a model of a nanochannel with the scaling functions (2) (computed by MD methodology). Agreement between computed and experimental results shows the correctness of our concept of the multiscale-hierarchical formulation. When the hydrophobicity is present at the interface between the fluid and solid phase, a factorization by 1/P (P is the partition coefficient) is performed on the corresponding terms in the diffusion matrix at the FE nodes on the interphase (Kojic et al. 2015).

2. Numerical homogenization

The above analysis and results of the hierarchical MD-FE coupling are further generalized to a numerical homogenization concept for modeling diffusion in complex media with strong

interaction between transported molecules and the surrounding solid phase (Kojic et al. 2011 and 2014),. An analogous numerical procedure was given in (Kojic et al. 2006 and 2012).We here give a brief review of this concept.

A generalization of the 1D formulation in Section 1 to the 3D diffusion is illustrated in Fig. 3. Here, we have a space with bulk diffusion and nanospace where diffusion is affected by solid surfaces. Following the definition of the scaling functions, we now have the restrained diffusion

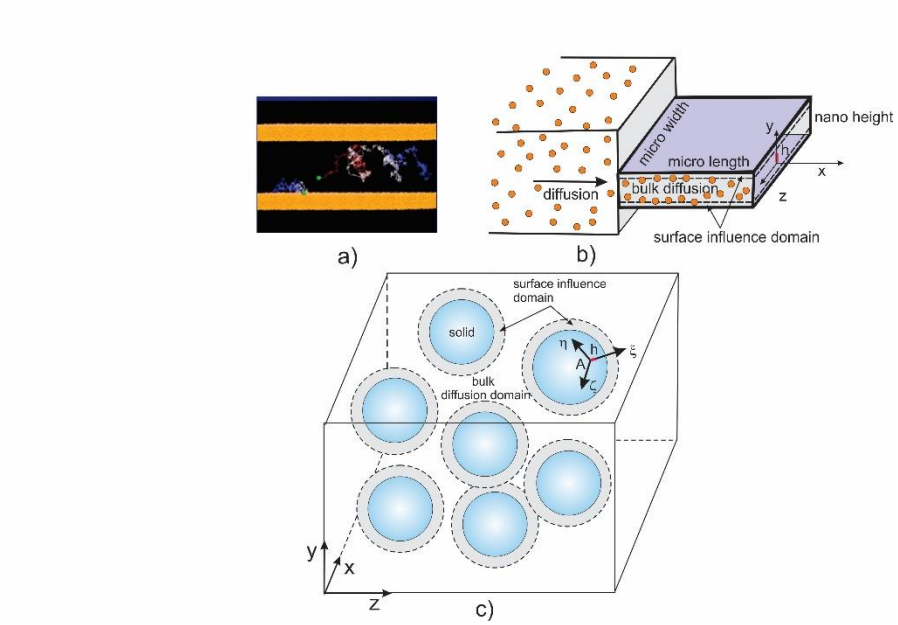

Fig. 3 Diffusion in nanospace. a) Nanochannel. b) Domain with free diffusion connected to a channel with nano-height. c) A 3D space with domains with bulk diffusion and those with the influence of solid surfaces. (according to Kojic et al. 2014 and 2022])

governed by the diffusion tensor with diagonal terms as,

$$D_{\xi\xi} = s_\xi D_{bulk}, \quad D_{\eta\eta} = s_\eta D_{bulk}, \quad D_{\varsigma\varsigma} = s_\varsigma D_{bulk} \tag{5}$$

where s_ξ, s_η, s_ς are the scaling functions in the local coordinate system at the solid surface (ξ and η are in the tangential plane, and ς is normal). Illustration of the FE procedure in modeling the retarded diffusion domain is illustrated in Fig. 4, where, for an integration point with the current concentration *c* we determine the bulk diffusion coefficient D_{bulk} , and the scaling functions – from the concentration and the distance *h* from the solid surface.

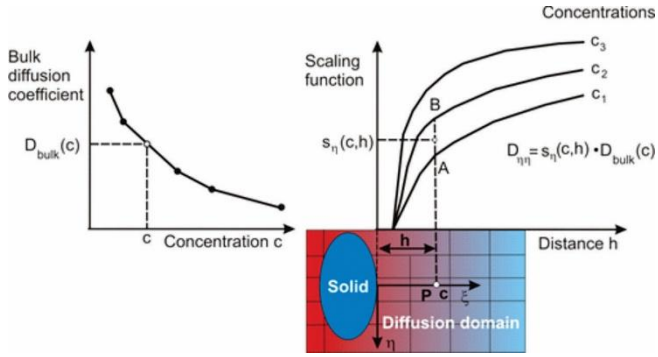

Fig. 4 Illustration of the FE computational procedure for modeling diffusion while taking into account the interaction between transported molecules and solid surface. (according to Kojic, et al. 2014 and 2022),

Using this computational procedure we have introduced the concept of numerical homogenization. Namely, we consider that the effects of the constrained diffusion within composite media as tissue can be properly taken into account by evaluation of mass release curves. If we take a small sample, as schematically shown in Fig. 5, we can perform experiments or compute the mass release curves in the three orthogonal directions by separately enforcing diffusion in these directions. Then, from these curves, we can evaluate the equivalent bulk diffusion coefficients $\bar{D}_i$ and equivalent distance for the solid surface $\bar{h}_i$. Details are given in our references (Kojic et. al. 2011, 2014, 2015 and 2022). We have shown that the equivalent diffusion parameters do not depend on the size of the sample and the boundary conditions (difference between inlet and outlet concentrations). It can be seen from Fig. 6 and Table 2 that different mass release curves give the same equivalent parameters. Hence, the mass release curves can be considered constitutive curves (analogous to constitutive curves in mechanics), as discussed in detail in our reference (Kojic et. al. 2018 and 2022).

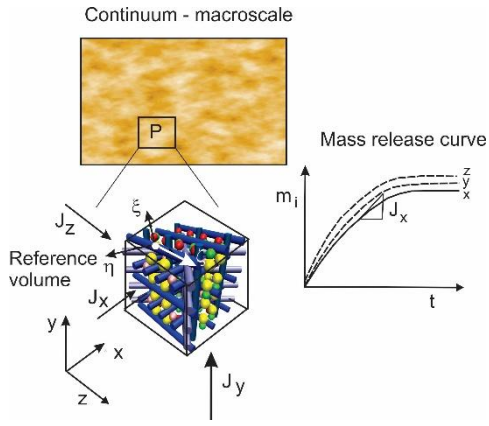

Fig. 5 Numerical homogenization by evaluation of mass release curves (according to Kojic et al. 2014 and 2022).

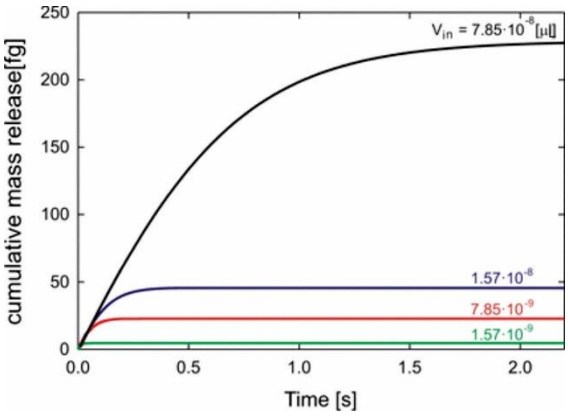

Fig. 6 Mass release curves for volumes of the inlet reservoir: 7.85 ·10^{-8}, 1.57 ·10^{-8}, 7.85 ·10^{-9} and 1.57 ·10^{-9} μL. Porosity is 64%. (according to Kojic et al. 2018 and 2022)

	V_{in} [μL]	$\bar{D}$ [μm^2/s]	$\bar{h}$ [nm]
1	$7.850\cdot10^{-8}$	381.010	0.89676
2	$1.570\cdot10^{-8}$	381.010	0.89676
3	$7.850\cdot10^{-9}$	381.010	0.90579
4	$1.570\cdot10^{-9}$	381.010	0.89676

Table 2. Material parameters $\bar{D}$ and $\bar{h}$ for four reservoir volumes V_{in}, porosity 64%, with the same initial concentration $c_0 = 2.75M$

3. Examples

Here are given two examples as illustrations of the accuracy and application of our homogenization methodology to large models.

3.1. Diffusion in the space with spheres with several values of porosity

We consider diffusion within a space with spheres according to Fig. 7. The goal of this example is to demonstrate the accuracy of the model using the equivalent diffusion parameters obtained by numerical homogenization, and the detailed models following the description related to Fig. 3. It is shown that surface interaction plays an important role in diffusion and that solutions obtained using the equivalent parameters agree with the detailed model solutions.

The porosity of the space is changed by changes in distances between spheres and includes the case with even intersecting spheres. The mass release curves obtained by estimated parameters in the first step are also shown in the figure.

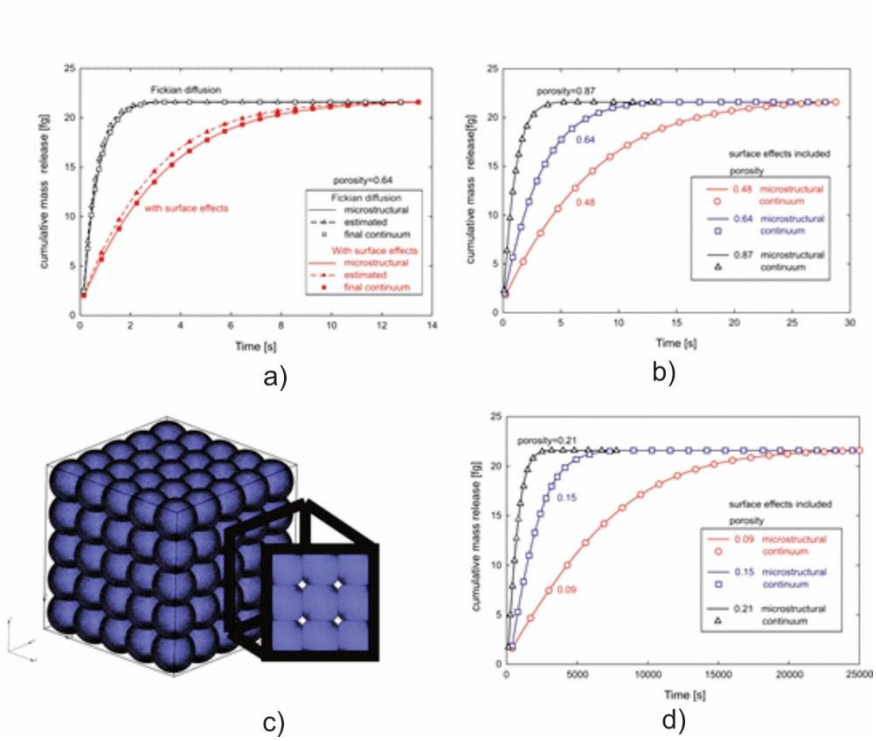

Fig. 7 Mass release curves for microstructural and continuum (MC) models, porous medium with spheres. a) Fickian and surface-affected diffusion, initial and final curves. b) Microstructural and final continuum mass release curves, with surface effects for three porosities; c) Microstructure consisting of intersecting silica nanospheres, porosity 9%; d) Mass release curves for the model with intersecting spheres and for three small porosities (9, 15, 21%); the time scale is three orders-of-magnitude greater than in b). (according to Kojic et al. 2018 and 2022)

3.2. Diffusion in pancreatic tumor

We used images from pancreatic tumor samples (Kojic et al. 2018) shown in Fig. 8. We have performed numerical homogenization for reference volumes (RVs) and the calculated equivalent diffusion parameters; details are given in (Kojic et al. 2018 and 2022).

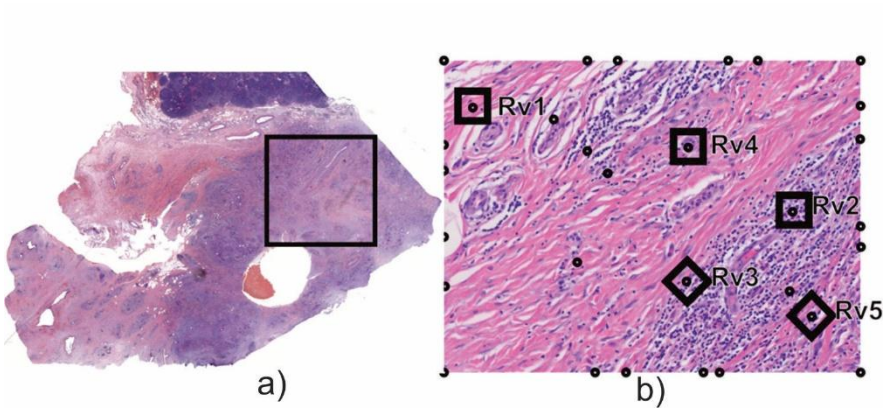

Fig. 8 a) Image of a cross-section of pancreatic cancer (Koay, et al. 2014). b) Five reference volumes (RVs) are used to compute equivalent diffusion coefficients by applying numerical homogenization. (according to (Kojic, et al. 2018 and 2022) .

Concentration fields and concentration profiles for two RVs are shown in Fig. 9. The profiles are displayed for the case of detailed models (microstructural) and using equivalent diffusion coefficients.

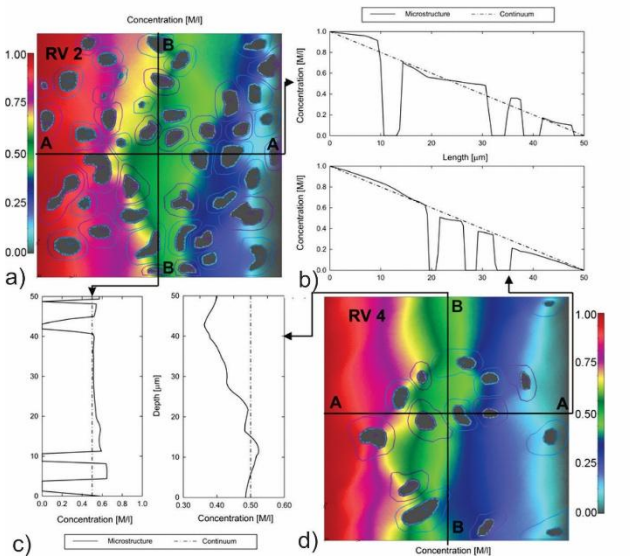

Fig. 9 Concentration fields and concentration profiles at time 1s for RV2 and RV4. Concentrations on the left side and the right side are prescribed: 1M and 0M; while bottom and top boundaries are impermeable. a) and d) – Concentration fields. b) and c) Concentration profiles along the two orthogonal lines; full lines – detailed model, dashed lines – use of equivalent diffusion coefficients. (according to (Kojic, et al. 2018 and 2022).

Computed equivalent diffusion coefficients for the RVs are interpolated; interpolation points are shown in Fig. 8 by black points. Fig. 10 shows distributions of the equivalent diffusion coefficients to demonstrate the anisotropy of the tumor tissue.

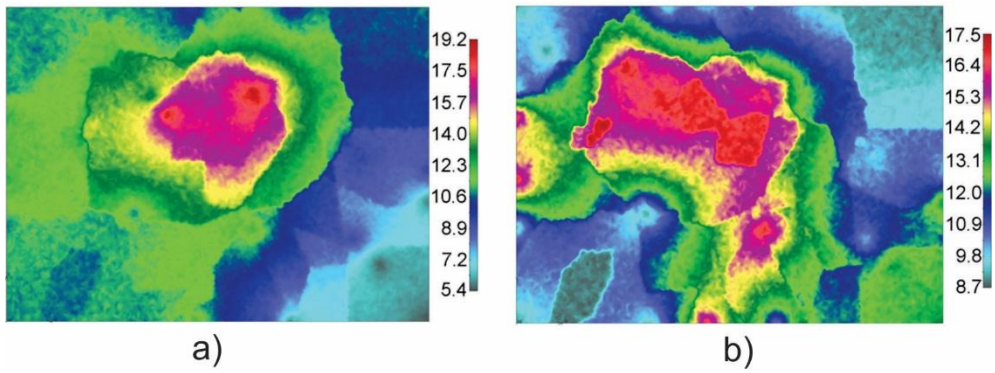

Fig 10 Distribution of the equivalent diffusion coefficient (in [$\mu m^2 / s$]) for the entire domain. a) x-direction, b) y-direction. (according to (Kojic, et al. 2018 and 2022).

4. Concluding remarks

We have shown in this brief overview a concept of numerical homogenization for the evaluation of the equivalent diffusion parameters in the case when the interaction between transported molecules and the solid surfaces has significant effects. These effects are pronounced when diffusion occurs within the nanospace, as we have for diffusion within biological tissue. The numerical homogenization is based on the mass release curves which can be determined experimentally or computed. It was illustrated that these curves represent in essence the constitutive curves for a given transported molecule and the medium where the diffusion takes place. Two characteristic examples are selected to illustrate our diffusion models with the molecule-solid surface interaction effects.

Acknowledgments. This research was funded by the Ministry of Education, Science and Technological Development of the Republic of Serbia, contract numbers [451-03-68/2022-14/200107 (Faculty of Engineering, University of Kragujevac), 451-03-68/2022-14/200378 (Institute for Information Technologies Kragujevac, University of Kragujevac); grant number F-134 (Serbian Academy of Sciences and Arts). The authors are thankful to the Houston Methodist Research Institute (Department of Nanomedicine) and the City of Kragujevac, Serbia.

References

Gladden J, Dole M (1953). Diffusion in supersaturated solutions. II. Glucose solutions, J. Am. Chem. Soc., 75(16), 3900-3904.

Grattoni A, Shen H, Fine D, Ziemys A, Gill JS, Hudson L, Hosali S, Goodall R, Liu X, Ferrari M (2011). Nanochannel technology for constant delivery of chemotherapeutics: beyond metronomic administration, Pharm. Res., 28(2), 292-300.

Koay EJ, Truty MJ, Cristini V, Thomas RM, Chen R, Chatterjee D, Kang YA, Bhosale PR, Tamm EP, Crane CH (2014). Transport properties of pancreatic cancer describe gemcitabine delivery and response, J. Clin. Invest., 124(4).

Kojic M, Milosevic M, Ziemys A (2022). Computational Models in Biomedical Engineering - Finite Element Models Based on Smeared Physical Fields: Theory, Solutions, and Software, Elsevier.

Kojic M, Milosevic M, Kojic N, Kim K, Ferrari M, Ziemys A (2014). A multiscale MD–FE model of diffusion in composite media with internal surface interaction based on numerical homogenization procedure, Comput. Methods Appl. Mech. Engrg., 269, 123–138.

Kojic M, Milosevic M, Kojic N, Koay EJ, Fleming JB, Ferrari M, Ziemys A (2018). Mass release curves as the constitutive curves for modeling diffusive transport within biological tissue, Comput. Biol. Med., 92, 156–167. DOI: 10.1016/j.compbiomed.2016.06.026.

Kojic M, Milosevic M, Wu S, Blanco E, Ferrari M, Ziemys A (2015). Mass partitioning effects in diffusion transport, Phys. Chem. Chem. Phys., 17, 20630-20635.

Kojic M, Milosevic M, Kojic N, Ferrari M, Ziemys A (2011). On diffusion in nanospace, J. Serbian Soc. Comp. Mechanics, 5(1), 84-109.

Kojic M, Ziemys A, Milosevic M, Isailovic V, Kojic N, Rosic M, Filipovic N, Ferrari M (2011). Transport in biological systems, J. Serbian Soc. Comp. Mechanics, 5(2), 101-128.

Kojic N, Kojic A, Kojic M (2006). Numerical determination of the solvent diffusion coefficient in a concentrated polymer solution, Comm. Num. Meth. Eng., 22, 1003-1013.

Kojic N, Panzer MJ, Leisk GG, Raja WK, Kojic M, Kaplan DL (2012). Ion electrodiffusion governs silk electrogelation, Soft Matter, 8, 6897-6905.

Ziemys A, Kojic M, Milosevic M, Kojic N, Hussain F, Ferrari M, Grattoni A (2011). Hierarchical modeling of diffusive transport through nanochannels by coupling molecular dynamics with finite element method, J. Comput. Phys., 230, 5722–5731.