VI International Conference on Computational Methods for Coupled Problems in Science and Engineering
COUPLED PROBLEMS 2015
B. Schrefler, E. Oñate and M. Papadrakakis (Eds)

COUPLING FLUID AND SOLID DOMAINS IN MODELING DRUG TRANSPORT WITHIN TUMOR

MILOS KOJIC*†, MILJAN MILOSEVIC*, VLADIMIR SIMIC*, ARTURAS ZIEMYS†, MAURO FERRARI†

* Bioengineering Research and Development Center BIOIRC
Prvoslava Stojanovica 6, 34000 Kragujevac, Serbia
e-mail: mkojic42@gmail.com

† Houston Methodist Research Institute
6670 Bertner Avenue
Houston, TX 77030, USA

Key words: Tumor model, Pipe Finite Element, Fictitious 1D Finite Element, Coupled Problems

Abstract. Development of a feasible model for transport within complex vasculature network and tissue remains a challenge. Such a model is particularly important when considering drug transport within tumor environment. A drug used to cure the cancer is first transported through blood vessels, then it attaches to the vessel endothelium and faces biological barriers in the vessel wall to reach cancerous cells.
We have developed a model for convective-diffusive drug transport which is simple and computationally efficient. One of the challenges was to couple fluid domain within blood vessels and solid domain of the tumor microenvironment. We have introduced fictitious 1D finite elements which appropriately take into account transport characteristics of the vessel walls. These characteristics include leakage and permeability of the walls. In evaluating wall permeability of a drug, we implemented our hierarchical multiscale methodology which couples molecular dynamics (MD) and continuum FE model. A numerical homogenization procedure was employed to obtain equivalent continuum transport parameters which account for interaction on molecular level between drug and solid components of the wall microstructure. Also, a possibility of using equivalent continuum transport models for capillary beds is investigated in order to further simplify and increase efficiency for the overall model of tumor.
As a numerical example, we calculate transport through a capillary bed to illustrate applicability of our methodology.

1 INTRODUCTION

We here study transport of particles/molecules dissolved within blood, and their subsequent transport through tumor tissue. The tumor vasculature consists of an arterial and venous system, including larger vessels (arterioles and venules) - with diameters on the order of hundred micrometers, and capillary vessels with diameters as small as a few micrometers. We consider that transport occurs from the arterial network into tissue, which is composed of

cells and intercellular space, and back - from tissue to the venous networks. There are two coupled transport domains: a fluid domain consisting of blood and a solid (tissue) domain. Transport within tumors is complex due to irregular blood vessel branching and variability of vessel diameters and lengths. Also, blood flow is affected by presence of cells within blood plasma, so that the fluid has a colloidal character. In our model we approximate the blood by a Newtonian fluid and neglect additional resistance at branchings.

Two references are cited here which are the closest to our study. The most commonly used is the "network" method [1], where the network is represented by blood vessel segments with common edges (nodes) within the network. Pressure change along segments is governed by the Hagen-Poiseuille law, while the pressure is equal for all segments at a common node, and the total flux at interior nodes is equal to zero. A system of linear equations with respect to nodal pressures is formed and solved with the given boundary conditions, pressures and/or fluxes. A generalization of this concept is given in [2].

In our transport model for large vascular systems [3], it was necessary to resolve the coupling of the fluid and solid domains, and to incorporate blood vessel wall properties with respect to hydraulic and diffusive transport. We here give details about the methodology for this coupling.

In the next section we outline the main features of our tumor computational model and in Section 3 introduce the concept of the fluid-solid coupling. One numerical example is given in Section 4, followed by concluding remarks in the last section.

2 COMPUTATIONAL MODEL FOR MASS TRANSPORT WITHIN LARGE BLOOD VESSEL NETWORK AND TISSUE

Here is summarized the formulation of our model for transport within large blood vessels systems and tissue, according to reference [3].

The 1D continuity equation has the form

$$\frac{\partial v_x}{\partial x}+\frac{1}{r}\frac{\partial\left(rv_r\right)}{\partial r}=0 \tag{1}$$

where v_x and v_r are axial and radial velocity components, and x and r are axial and radial coordinates, respectively. Using boundary conditions at the (pipe) vessel internal wall R: v_x=0, $v_r=\partial R/\partial t$, this equation transforms into

$$\frac{\partial v}{\partial x}+2\frac{v}{R}\frac{\partial R}{\partial x}+\frac{2}{R}\frac{\partial R}{\partial t}=0 \tag{2}$$

where v is the mean velocity. We further assume that wall is incompressible and elastic with Young's modulus E, so that the radius change due to the change in pressure p (assuming cross-sectional uniformity), can be related by the equation:

$$\frac{\partial R}{\partial t}=k_E R^2\frac{\partial p}{\partial t} \tag{3}$$

where the elastic constant k_E is

$$k_E = \frac{3}{4\delta_0 E} \tag{4}$$

Here, we have neglected the change of the wall thickness δ_0 . The continuity equation (2) can be written in terms of the fluid flux Q ($Q=R^2\pi v$),

$$2R^3\pi k_E \frac{\partial p}{\partial t} + \frac{\partial Q}{\partial x} = 0 \tag{5}$$

The equation of the balance of linear momentum, the 1D Navier-Stokes equation, for a pipe cross-section with the radius *R*, is:

$$\frac{\partial v_x}{\partial t} + v_r \frac{\partial v_x}{\partial r} + v_x \frac{\partial v_x}{\partial x} + \frac{1}{\rho}\frac{\partial p}{\partial x} = \nu\left(\frac{\partial^2 v_x}{\partial r^2} + \frac{1}{r}\frac{\partial v_x}{\partial r} + \frac{\partial^2 v_x}{\partial x^2}\right) \tag{6}$$

where ν is kinematic viscosity, and ρ is fluid density. This equation can be written in terms of pipe flux Q as

$$\rho\frac{\partial Q}{\partial t} + 2\alpha\rho\frac{Q}{A}\frac{\partial Q}{\partial x} + \frac{1}{R}\left[-2\alpha\rho\frac{Q}{A}\frac{\partial R}{\partial x} + \frac{2\mu(\gamma+2)}{R}\right]\mathrm{Q} + A\frac{\partial p}{\partial x} = 0 \tag{7}$$

where A is the cross-sectional area, and μ is the fluid viscosity; α is a dimensionless parameter

$$\alpha = \frac{2}{R^2 v^2}\int_0^R r v_x^2 dr \tag{8}$$

which is a measure of variation of velocity with distance from the axis of symmetry (velocity profile); and γ is [4]:

$$v_x = \frac{\gamma+2}{\gamma}\left[1-\left(\frac{r}{R}\right)^{\gamma}\right]v \tag{9}$$

parameter which defines the profile shape, from parabolic to plug flow. The value γ=2 corresponds to a parabolic profile, while γ=9 can be used for oscillatory flow of one cardiac cycle. Parameters α and γ can be related as: $\alpha = (\gamma+2)/(\gamma+1)$. For a parabolic profile, which is commonly assumed, α=4/3.

Capillary wall is a multilayered composite structure with fenestrations (holes) allowing plasma leakage to the surrounding tissue [5]. Capillary walls can roughly be classified into non-fenestrated (continuous), fenestrated, and discontinuous (sinusoidal) [5]. The leakage can mathematically be described using the Starling hypothesis [6] (known also as Kedem-Katchalsky equation [7]):

$$Q = L_P A_w\left[(p_{ves} - p_{tis}) - \sigma(\pi_{ves} - \pi_{tis})\right] \tag{10}$$

where L_p is hydraulic conductivity [8], A_w is the surface area of the vessel-tissue interface, p_{ves} and p_{tis} are pressures within vessel and within tissue (interstitium pressure); π_{ves} and π_{tis} are osmotic pressures in vessel and tissue, and σ is the osmotic reflection coefficient. The leakage of fluid through vessel walls must be taken into account in the computational model.

Convective-diffusive transport within blood vessels can be simplified if blood is considered as a homogenous fluid, so that the governing equation of mass balance has the form [9]

$$-\frac{\partial c}{\partial t}-\frac{\partial c}{\partial x}v+\frac{\partial}{\partial x}\left(D\frac{\partial c}{\partial x}\right)+q=0 \tag{11}$$

where c is concentration, D is diffusion coefficient within fluid - which may depend on concentration, and q is a source term.

Particulate transport through the vessel wall is very complex due to various physical and biological effects, and can be expressed in the form [5]

$$Q_s = D_w A_w \left(c_{ves}-c_{tis}\right)+Q\left(1-\sigma\right)\Delta c_{lm} \tag{12}$$

where Q_s is the particulate flux, D_w is diffusion (or transport) coefficient of the wall (flux per unit area of the wall and unit concentration), c_{ves} and c_{tis} are concentrations within vessel and tissue; and Δc_{lm} is the mean logarithmic concentration,

$$\Delta c_{lm}=\frac{c_{ves}-c_{tis}}{\ln\left(c_{ves}/c_{tis}\right)} \tag{13}$$

which can also be taken as the arithmetic mean. Diffusion coefficient D_w can be determined experimentally or numerically.

Interaction between particles/molecules and the wall solid components (epithelium cells, fibers, etc.) can dominate the transport through the wall. This interaction on a molecular level may be incorporated into a continuum transport model by evaluation of the effective diffusion coefficients (or scaling functions) using MD procedures and a numerical homogenization (within a multiscale-hierarchical concept); such multiscale model has been developed and applied to various bioengineering problems [10-14].

We consider tissue as a porous medium where transport of fluid and particles/molecules (drugs, nutrients) occurs within intracellular space. The solid phase form a complex microstructure composed of cells, or cells and various types of fibers. The fundamental relations used for fluid flow and for diffusion are summarized in [15]. We cite here the basic Darcy's law (which can have additional terms [15]) and the continuity equation in case of neglecting deformations of the solid microstructure,

$$v_i=-k_{Di}\frac{\partial p}{\partial x_i},\ \text{no sum on } i; \qquad v_{i,i}+\mathrm{q}^v=0,\ \text{sum on } i\text{: } i=1,2,3 \tag{14}$$

where v_i are Darcy's velocities, k_{Di} are Darcy's coefficients, p is the interstitial pressure, and q^v is a source term; the second equation expresses the continuity equation. Diffusive transport equation has the form (11), now extended to three dimensions,

$$-\frac{\partial c}{\partial t}-v_i\frac{\partial c}{\partial x_i}+\frac{\partial}{\partial x_i}\left(D_i\frac{\partial c}{\partial x_i}\right)+q^V=0, \qquad \text{sum on } i\text{: } i=1,2,3 \tag{15}$$

and it also may be modified to account for specific biological effects [15]. Diffusion coefficients can also be calculated using the multiscale-hierarchical concept and numerical homogenization as for capillary wall: a reference volume is selected and equivalent diffusion parameters are evaluated from the mass release curves [14].

We next summarize the basic finite element equations for blood vessels and tissue, based on the above fundamental equations. First, the 2-node pipe 1D element for fluid flow is derived form (7) by a standard Galerkin procedure [9],

$$\left(\frac{1}{\Delta t}\mathbf{M}^{vv}+\mathbf{K}^{vv}\right)\mathbf{Q}+\mathbf{K}^{vp}\mathbf{P}=\mathbf{Q}^{ext}+\frac{1}{\Delta t}\mathbf{M}_{IJ}^{vv}\mathbf{Q}^t \tag{16}$$

where $\mathbf{Q}^{ext}$ is external nodal flux, and $\mathbf{Q}^t$ is the flux at start of time step of size Δt. The matrices are given in [3], with the matrix $\mathbf{K}^{\mathrm{vv}}$ being a function of the flux Q within the element. Further, we differentiate equation (7) with respect to axial coordinate x, and then write that equation in the weak form, as (for equilibrium iteration "i")

$$\left(\mathbf{M}^{p(i-1)}+\mathbf{K}^{p(i-1)}\right)\Delta\mathbf{P}^{(i)}=\mathbf{F}^{(i-1)}-\left(\mathbf{M}^{p(i-1)}+\mathbf{K}^{p(i-1)}\right)\mathbf{P}^{(i-1)}+\mathbf{M}^{p(i-1)}\mathbf{P}^t \tag{17}$$

where $\mathbf{P}^t$ is nodal pressure at start of time step. Details are given in [3].

The balance equation (17) represents the basic equation with pressures as the nodal variables in which the continuity equation (5) is incorporated. During solution process, equation (16) is used for updating fluxes in matrices of equation (17). The derived equations for 1D FE are applicable to deformable and rigid pipes. In case of a rigid pipe, equation (17) reduces to linear equation:

$$\mathbf{K}^p\mathbf{P}=\mathbf{F} \tag{18}$$

leading to a system of equations used in the "network" method [1], [2]. Details about the above derivations are given in [16].

In case of diffusion, there is additional system of equations, following from the balance equation (15),

$$\left(\frac{1}{\Delta t}\mathbf{M}^c+\mathbf{K}^c+\mathbf{K}^{cv}\right)^{(i-1)}\Delta\mathbf{C}^{(i)}=\mathbf{Q}_c^{ext}+\mathbf{Q}_c^V-\frac{1}{\Delta t}\mathbf{M}^{c(i-1)}\left(\mathbf{C}^{(i-1)}-\mathbf{C}^t\right)-\left(\mathbf{K}^c+\mathbf{K}^{cv}\right)^{(i-1)}\mathbf{C}^{(i-1)} \tag{19}$$

where the matrices and the source vector $\mathbf{Q}_c^V$ are evaluated at end of time step; $\mathbf{C}^{(i-1)}$ and $\mathbf{C}^t$ are nodal concentrations at the iteration (i-1) and start of time step, respectively; and $\mathbf{Q}_c^{ext}$ is

the external nodal flux vector. The matrix which couples convection and diffusion within the pipe is the matrix $\mathbf{K}^{cv}$. The matrices are given in [16].

The FE balance equation for fluid transport within tissue follows form continuity equation (14),

$$\mathbf{K}^t \Delta \mathbf{P}^{(i)} = \mathbf{Q}_t^{ext} + \mathbf{Q}_t^V - \mathbf{K}^t \mathbf{P}^{(i-1)} \tag{20}$$

while the convective-diffusive balance equation has the form (19); details are given in [3].

3 FINITE ELEMENT FOR COUPLING FLUID AND SOLID DOMAIN

We have above summarized the governing transport equations in differential and FE form. They differ for the fluid domain (within blood vessels) and tissue. The boundary between these two domains is represented by blood vessel walls, which have their own transport characteristics. Here, following [3] we introduce a 2-node 1D fictitious element to connect the two domains, with including the wall transport properties. The fictitious element AB (Fig. 1) have the node A connected to fluid, hence the node A is a node of 1D pipe element; and the node B is the node of the continuum (tissue) medium. Geometrically, the nodes A and B are at the same spatial position. There are gradients of pressure and concentration between nodes A and B. The characteristics of the AB element are such that they represent the particulate and fluid transport properties of the parts (L/2 in Figure 1) of pipe elements associated to the common node A.

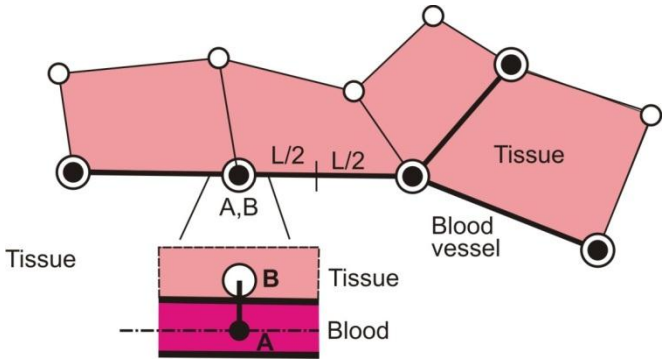

Figure 1: Fictitious 1D element for connection of blood vessel and tissue finite elements [3]. The node A belongs to a 1D vessel FE, while (at the same spatial position) the node B of the fictitious element belongs to a tissue continuum FE.

In order to formulate the fictitious FE, we express the fluid flux according to equation (10) as

$$Q_f = \bar{L}_p \bar{A}_p \left(P_A - P_B \right) \tag{21}$$

where $\bar{L}_p$ and $\bar{A}_p$ are the equivalent hydraulic conductivity and surface, respectively. We have neglected the osmotic part of the transport in this equation. The product $\bar{L}_p \bar{A}_p$ can be evaluated as

$$\bar{L}_p \bar{A}_p = \frac{1}{2}\sum_e L_p^e A^e \tag{22}$$

where summation is over elements *e* with the common nod A; the coefficient ½ indicates that half of the total element surface belongs to the common node A. Then, the incremental form of balance equation can be written as,

$$\bar{\mathbf{K}}^p \Delta \mathbf{P}^{(i)} = \mathbf{Q}^{ext(i-1)} - \bar{\mathbf{K}}^p \mathbf{P}^{(i-1)} \tag{23}$$

where

$$\bar{\mathbf{K}}^p = \bar{L}_p \bar{A}_p \begin{bmatrix} 1 & -1 \\ -1 & 1 \end{bmatrix} \tag{24}$$

$\mathbf{Q}^{ext(i-1)}$ are fluxes from the surrounding elements (for node A those are 1D blood vessel elements, and for node B are tissue elements); and the nodal pressure vector has the terms P_A and P_B.

We formulate the convective-diffusive FE starting from the expression for flux,

$$Q_c = \bar{D}_w \bar{A}_c \left(C_A - C_B\right) + \bar{Q}\left(1-\sigma\right)\Delta C_{lm} \tag{25}$$

where $\bar{D}_w$ and $\bar{A}_c$ are the equivalent diffusive transport coefficient and equivalent diffusion surface, respectively; $\bar{Q}$ is the equivalent fluid flux, which can be determined from pipe flow equations; and ΔC_{lm} is the is the mean logarithmic concentration (according to (13)). The equation (25) can be transformed into the incremental form and then written into the FE format (23),

$$\bar{\mathbf{K}}^{c(i-1)} \Delta \mathbf{C}^{(i)} = \mathbf{Q}_c^{ext(i-1)} - \bar{\mathbf{K}}^{c(i-1)} \mathbf{C}^{(i-1)} \tag{26}$$

where $\bar{\mathbf{K}}^{c(i-1)}$ is the transport matrix, and $\mathbf{Q}_c^{ext(i-1)}$ are diffusion fluxes coming from connecting pipe and continuum elements. The matrix $\bar{\mathbf{K}}^{c(i-1)}$ is

$$\bar{\mathbf{K}}^{c(i-1)} = \left(\bar{D}_w \bar{A}_c + \frac{\bar{Q}^{(i-1)}}{\ln\left(C_A / C_B\right)^{(i-1)}}\left(1-\sigma\right) \right) \begin{bmatrix} 1 & -1 \\ -1 & 1 \end{bmatrix} \tag{27}$$

The flux $\bar{Q}^{(i-1)}$ can be determined from equation (21).

Finally, we present a concept of the tumor model where the role of the fictitious 1D finite element is emphasized. Figure 2 shows a tumor model where larger vessels are represented by 1D pipe elements, while capillary bed is modeled by the equivalent continuum elements [3]. The pipe elements are connected to tissue by the fictitious elements. Also, the fictitious elements are employed in the numerical homogenization to obtain equivalent transport parameters of the continuum. With this concept, the model of tumor becomes very efficient and can be used in research and further in medical practice.

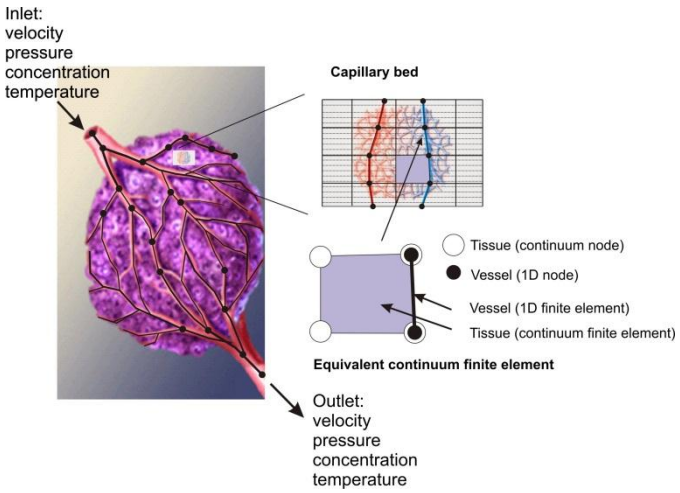

Figure 2: Concept of a tumor model with use of 1D fictitious elements for coupling fluid and solid domains

4 NUMERICAL EXAMPLE

Here we present application of our model on a capillary bed domain. The model consists of capillary network, located between the inlet artery (left) and outlet vein (right side of model). Blood vessels are modeled by 1D finite elements and surrounding tissue is modeled by 2D FEs. Boundary conditions include: inlet and outlet pressures and inlet and outlet concentration of a drug, with P_{IN} = 25mmHg, P_{OUT} = 10 mm Hg, C_{IN} = 25 M/l and C_{OUT} = 10 M/l.

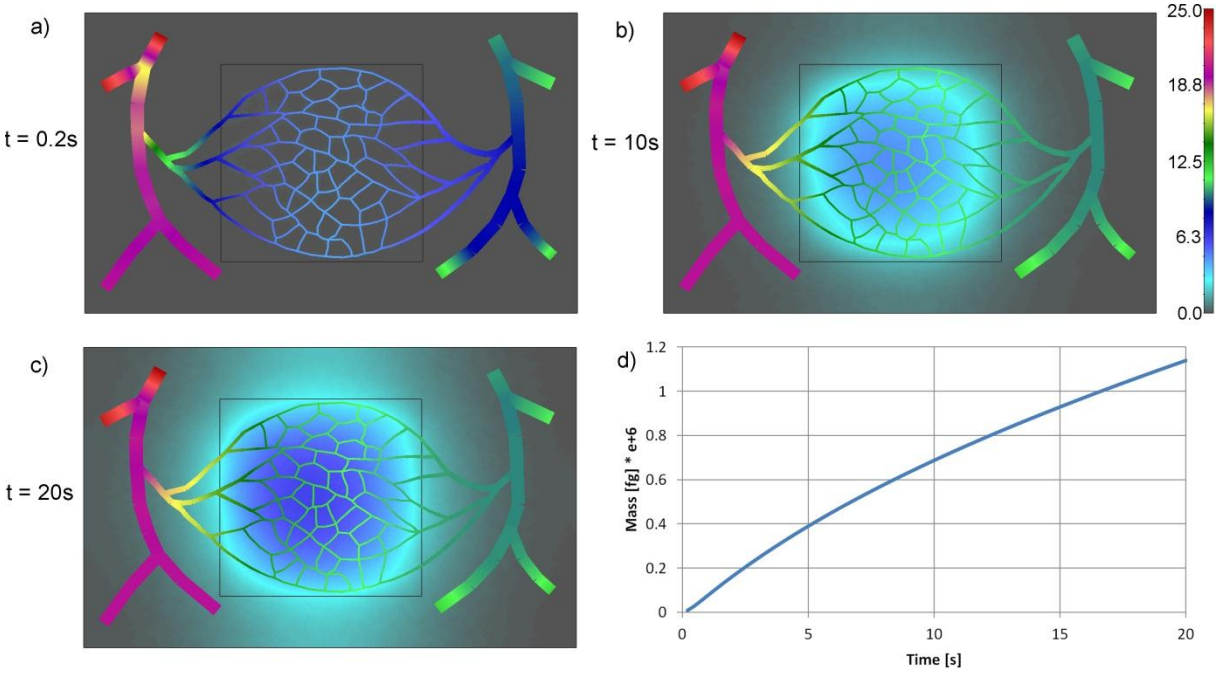

Figure 3: Concentration field within capillary bed domain for different times: a) t = 0.2s b) t = 10s and c) t = 20s; d) Mass change over time in the 2D surrounding tissue

It is taken that the tissue boundary, within the indicated square, is impermeable. Fluid viscosity is 7.5 x E-6 mmHgs, while diameters of vessels are in the range of 30 mm for artery and vain down to 4 mm for capillary network. Leakage coefficient of the wall is 1 x E-3 mm /s, permeability of capillary wall is 0.05 Mole / mm^2 s, diffusion coefficient in capillary is 5 x E+5 mm^2/s, diffusion coefficient in tissue is 1000 mm^2/s, and the Darcy coefficient in tissue is 1.0 x E-4 [mm^2 / mmHg s]. Concentration distributions of the drug within the capillary bed and surrounding tissue at times: t=0.2s, 10s and 20s is shown on Figures 3a,b,c respectively. Mass change during time in 2D surrounding tissue is shown on Fig 3d.

4 CONCLUSIONS

A 1D finite element is formulated for coupling fluid and solid domains in modeling transport within tumor. The element captures complex transport characteristics of capillary walls and provides an efficient way to simulate transport of drugs from blood vessels to tissue.

ACKNOWLEDGEMENTS

This study has been supported from funds of State of Texas Emerging Technology Fund, Alliance of NanoHealth (ANH), and the Ernest Cockrell Jr. Presidential Distinguished Chair (M.F.)

The authors acknowledge support from Ministry of Education and Science of Serbia, grants OI 174028 and III 41007, and City of Kragujevac.

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