Published in final edited form as:

Comput Biol Med. 2018 August 01; 99: 7–23. doi:10.1016/j.combiomed.2018.05.022.

Multiscale smeared finite element model for mass transport in biological tissue: from blood vessels to cells and cellular organelles

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Abstract

One of the basic and vital processes in living organisms is mass exchange, which occurs on several levels: it goes from blood vessels to cells and organelles within cells. On that path, molecules, as oxygen, metabolic products, drugs, etc. traverse different macro and micro environments – blood, extracellular/intracellular space, and interior of organelles; and also biological barriers such as walls of blood vessels and membranes of cells and organelles. Many aspects of this mass transport remain unknown, particularly the biophysical mechanisms governing drug delivery. The main research approach relies on laboratory and clinical investigations. In parallel, considerable efforts have been directed to develop computational tools for additional insight into the intricate process of mass exchange and transport. Along these lines, we have recently formulated a composite smeared finite element (CSFE) which is composed of the smeared continuum pressure and concentration fields of the capillary and lymphatic system, and of these fields within tissue. The element offers an elegant and simple procedure which opens up new lines of inquiry and can be applied to large systems such as organs and tumors models. Here, we extend this concept to a multiscale scheme which concurrently couples domains that span from large blood vessels, capillaries and lymph, to cell cytosol and further to organelles of nanometer size. These spatial physical domains are coupled by the appropriate connectivity elements representing biological barriers. The composite finite element has “degrees of freedom” which include pressures and concentrations of all compartments of the vessels-tissue assemblage. The overall model uses the standard, measurable material properties of the continuum biological environments and biological barriers. It can be considered as a framework into which we can incorporate various additional effects (such as electrical or biochemical) for transport through membranes or within cells. This

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concept and the developed FE software within our package PAK offers a computational tool that can be applied to whole-organ systems, while also including specific domains such as tumors. The solved examples demonstrate the accuracy of this model and its applicability to large biological systems.

Keywords

diffusion; convection; partitioning; biological tissue; capillary system; cell interior; organelles; multiscale models; composite smeared finite element

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1. Introduction

In this study we consider convective and diffusive transport of molecules or particles (e.g. nanoparticles used in drug delivery) from the cardiovascular system to tissue, cells and eventually to organelles within cells [1],[2]. A transported molecule travels along its path through several physical domains: blood or lymph, extracellular space (micro-environment), intracellular space and interior of organelles; and thus through the corresponding biological barriers: vessel walls, cell and organelle membranes.

Nutrient, oxygen, or drug delivery to tissues from the blood circulation occurs as mass transport across blood vessel walls into tissues. Mass transport through systemic circulation, and its applicability to drug delivery and nanomedicine, is studied in the interdisciplinary field of transport called oncophysics [3–5]. It can be considered that, according to the physics point of view, mass transport is dominantly gradient driven – by a pressure gradient in convection and by a concentration gradient in diffusion. For a given gradient, the mass flux is affected by physical and chemical characteristics of the transported molecules or particles and the surrounding medium [6, 7]. Our focus in this study is to introduce a computational methodology which relies on the laws of physics and which is robust, accurate and applicable to general conditions of transport within large domains such as organs, and particularly to smaller domains such as tumors.

In the development of the computational models for problems related to mass transport in living organisms, outlined above, significant approximations have to be adopted. For example, blood is usually modeled as a homogenous fluid, although it represents a very complex multiphase fluid composed of plasma (which is also a complex fluid) and cells. In large vessels this approximation is made by using certain viscosity properties [8]. Also, it can be assumed that particle and molecule transport is governed by basic concepts of convection and diffusion within the fluid. In small vessels such as capillaries (human diameter size on the order of 10 micrometers [9]) the presence of cells, mainly red blood cells (RBCs), may affect transport [10]. However, in a simplified analysis, blood may still be considered as a homogenous fluid, where the effect of RBC is taken into account through viscosity [11, 12]. The dependence of the viscosity coefficient on the hematocrit (RBC volumetric content) and capillary diameter (known as the Fahraeus-Linquist effect) has been investigated numerically and in numerous experiments [13–15].

Further, considering tissue, we assume that tissue is composed of cells and extracellular space filled with fluid, hence it represents a complex medium. The approximation is made that tissue is a porous solid where molecules and particles are transported within extracellular space, and, additionally, they can bi-directionally pass through cell membranes. Transport through the extracellular space is governed by both convection and diffusion. This transport has also been the subject of extensive study over the past decades (e.g. within brain tissue [16]; or, according to experimental *in vitro* and *in vivo* data [17], where tissue glycosaminoglycan content and drug molecular weight are important parameters determining whether extravascular transport is governed by diffusion or convection). A review of models used for convection and diffusion, including also heat transfer, is presented in [18], while diffusivity of dextran molecules in tumor interstitium is experimentally evaluated in [19, 20].

Along the path from blood vessels to tissue and cells, and vice-versa, the overall transport is dependent on the blood vessel wall properties, as well as on properties of membranes of cells and organelles. Material parameters which specify these properties include hydraulic and diffusive components. On the other hand, it is important to emphasize that the amount of mass passing from one continuum domain to another (blood to extracellular space, extracellular space to cell cytosol, cytosol to organelles) depends on the size of the surface through which the transport occurs. This is illustrated by measurements of the volumes and cross-sectional areas of blood vessels of a dog [21] which show that the mass exchange in a body dominantly occurs at the capillary-tissue level. Hence, the capillary volumetric fraction (capillary density) is a very important parameter in the mass exchange process, as will be emphasized later in the text within the formulation of our computational models.

As described above, tissue is a composite medium with two distinct domains: extracellular and intracellular space. Further, extracellular space can be considered as a porous medium where the extracellular matrix represents the solid phase and the pores are filled with biological fluid. Fluid is constantly being renewed, in part by transport from capillary system to pores, and in reverse direction, through capillary walls (which have certain hydraulic permeability); and by the lymphatic system which serves as fluid drainage. On the other hand, molecules and other particulates are transported between the capillaries and extracellular space, but also to cells (and reverse) through cell membranes. It is usually adopted that the governing laws for transport within extracellular space are the Darcy velocity-pressure relationship for convection and Fick's law for diffusion [22]. There exists interaction between transported molecules and the surrounding media in the extracellular space so that these effects must be taken into account; details will be presented further when addressing computational modeling.

Considering transport within tumors, there are additional complexities due to irregular blood vessel branching and variability of vessel diameters and lengths [23, 24]. Experiments on flow within tumor vasculature showed that blood flow depends on parameters such as geometric resistance [25] (a measure of network irregularities), viscous resistance [26], and RBC mechanical properties [27]. Basic characteristics of blood flow within tumor vasculature are summarized in [28], while data about capillary wall transport parameters (vascular permeability, hydraulic conductivity, and reflection coefficient) are given in [29].

Mass exchange and transport within cells is one of the most fundamental processes in living organisms. It represents a separate branch of the overall biomedical and clinical investigations. The cell interior is composed of different compartments or entities. In the cell fluid – cytosol, are immersed organelles which include the cell nucleus, mitochondria, endosomes, vesicles, etc. with their own membranes and transport properties. Also, a fibrous network of cytoskeleton is spread within cytosol to support the cell membrane and contribute to cell's mechanical stiffness. There are various factors which affect mass exchange within cells. These factors range from biochemical to mechanical, to signaling pathways [30]. We here note several key papers in this field. In reference [31] a molecular background is introduced which offers insight into the process which leads to cell migration, while in [32] a theoretical basis of biochemical processes within different intracellular compartments is further formulated. In [33] a review of measurements and models of hepatocellular drug concentrations important for drug delivery in liver is given. A computational framework for modeling mass exchange within cells, formulated as a „virtual cell“, is presented in [34] and [35], which was further used in many applications, as, for example in [36].

Regarding computational methods, it is necessary to consider separately three domains: blood vessels, extracellular space and cell interior. First, for blood flow within networks of vessels, the most commonly used is the “network” method [37], where the network is represented by blood vessel segments with common edges (nodes). Pressure change along segments is governed by the Hagen-Poiseuille law [38], while pressure is equal for all segments at the common node, and the total flux at interior nodes is equal to zero. Particle diffusion is modeled according to Fick's law within moving fluid for pipe flow conditions [38]. In [39] motion of rigid elliptical particles in flow within small vessels was studied, while in [40] trajectories of different particle shapes within a net of small channels are investigated experimentally and numerically. In reference [41] modeling of deformable cell motion in fluid through a capillary narrowing is used to find a critical pressure-diameter of cell relationship for cancerous cells in metastatic processes.

For particulate transport within extracellular space, the molecular interaction can be taken into account by correction of the diffusivity within Fick's law [22]. With use of molecular dynamics (MD) the equivalent diffusivity is calculated [42–47] and incorporated within the FE computational models [47], hence the model has a multiscale character; while in reference [48] it was shown that mass release curves can be used as the constitutive curves for Fick's law. This multiscale hierarchical model was implemented in [49] to investigate the effects of collagen fiber density surrounding capillaries on tumor tissue; in [50] for modeling mass release from composite nanoparticles, and in [51] for transport within tumors, mouse brain and liver. It is important to emphasize that the connectivity elements are introduced in [51] as a fundamental concept in coupling transport between the blood and tissue domains.

Finally, a formulation of the composite smeared finite element (CSFE) is introduced in [52] which represents the foundation for this study.

We summarize the key equations in the next section which are further used as the basis in the development of the extension of the CSFE in Section 3. In Section 4 we first present

numerical examples which demonstrate accuracy of the extended CSFE, and then implement the multiscale smeared FE model to the entire pancreas. Finally, a summary and conclusions are given in Section 5.

2. Basic equations for modeling transport in blood vessels and tissue

Here, we summarize the methodology which will be further used as the basis for the development of the smeared models. This methodology relies mainly on our previous publications [38, 41–44, 46–48, 51–53].

2.1 Blood vessels

When considering blood as a homogenous, viscous, incompressible fluid, the flow in blood vessels can be described by the Navier-Stokes equations of balance of linear momentum, and by the incompressibility equation as the mass balance equation. Adopting that a vessel is an axisymmetric pipe, these equations can be reduced to the following differential equation in terms of the fluid pressure p [38],

$$-m_1^p \frac{\partial^2 p}{\partial t^2} - m_2^p \frac{\partial p}{\partial t} + k_p p_{,xx} = 0 \quad (1)$$

where coefficients m_1^p , m_2^p depend on the vessel internal diameter d , fluid viscosity and elasticity of the wall (details are given in [38]); and

$$k_p = \pi d^4 / 128 \mu \quad (2)$$

is the pipe conductance coefficient, and μ is viscosity. This equation can further be transformed into finite element form for the current time step t and iteration i as [22],

$$(\mathbf{M}^{p(i-1)} + \mathbf{K}^{p(i-1)}) \Delta \mathbf{P}^{(i)} = \mathbf{Q}^{(i-1)} - (\mathbf{M}^{p(i-1)} + \mathbf{K}^{p(i-1)}) \mathbf{P}^{(i-1)} + \mathbf{M}^{p(i-1)} \mathbf{P}^t \quad (3)$$

where $\mathbf{P}$ and $\mathbf{Q}$ are nodal pressure and flux vectors, and the matrix components are:

$$M_{IJ}^{p(i-1)} = \frac{1}{\Delta t} \int_L \left(\frac{m_1^{p(i-1)}}{\Delta t} + m_2^{p(i-1)} \right) N_I N_J dL \quad (4)$$

$$K_{IJ}^{p(i-1)} = \int_L k_p^{(i-1)} N_{I,x} N_{J,x} dL$$

Here, L is element length, and N_I are the FE interpolation functions. With the assumption that the deformation of the pipe does not affect flow, except thorough change of the radius

due to pressure, equation (3) can be used for a deformable pipe wall, but with the change of radius according to the relation [38]:

$$R = \frac{R_0}{1 - (1 - \nu^2) \frac{R_0 p}{\delta E}} \quad (5)$$

where R_0 is the initial radius of the cross-section, δ is the wall thickness (taken to be constant), E is Young's modulus and ν is Poisson's ratio. This relation is applicable when the wall thickness is small with respect to the radius (the wall can be considered as a cylindrical thin membrane), when axial deformation is negligible (physiologically verified condition for blood vessels) and the wall material is elastic. In case of rigid walls, equation (3) reduces to a linear incremental form,

$$\mathbf{K}^p \Delta \mathbf{P}^{(i)} = \mathbf{Q}^{(i-1)} - \mathbf{K}^p \mathbf{P}^{(i-1)} \quad (6)$$

where the matrix components are

$$K_{11}^p = K_{22}^p = -K_{12}^p = -K_{21}^p = \frac{k_p}{L} \quad (7)$$

Therefore, for given boundary conditions, the above equations provide solutions for nodal pressures (and consequently for fluxes and velocities). Equations (3) and (6) are applicable to a pipe network in 2D and 3D space, with any branching within the network, and are computationally efficient since the nodal unknowns are solely the pressures [38].

One-dimensional particle convective-diffusion transport is governed by the balance equation

$$-\frac{\partial c}{\partial t} - \frac{\partial c}{\partial x} v + \frac{\partial}{\partial x} \left(D_p \frac{\partial c}{\partial x} \right) + q = 0 \quad (8)$$

where c is concentration, v is fluid velocity, and q is a source term. Diffusion coefficient D_p may be constant or may be concentration-dependent. The corresponding FE balance equation is

$$\left(\frac{1}{\Delta t} \mathbf{M}^c + \mathbf{K}^c + \mathbf{K}^{cv} \right)^{(i-1)} \Delta \mathbf{C}^{(i)} = \mathbf{Q}_c^{ext} + \mathbf{Q}_c^V - \frac{1}{\Delta t} \mathbf{M}^{c(i-1)} (\mathbf{C}^{(i-1)} - \mathbf{C}^t) - (\mathbf{K}^c + \mathbf{K}^{cv})^{(i-1)} \mathbf{C}^{(i-1)} \quad (9)$$

where $\mathbf{C}$ is the nodal concentration vector, $\mathbf{Q}_c^{ext}$ is the external flux, and matrices and the source vector $\mathbf{Q}_c^V$ (evaluated at end of time step) are:

$$\begin{aligned}
M_{IJ}^c &= \int_L N_I N_J A dL \\
K_{IJ}^c &= \int_L D_p N_{I,x} N_{J,x} A dL \\
K_{IJ}^{cv} &= \int_L v N_I N_{J,x} A dL \\
Q_c^{IV} &= \int_L N_I q A dL
\end{aligned} \quad (10)$$

Note that the fluid velocity follows from solving fluid transport equations (3) or (6).

2.2 Models of tissue and intracellular space

We consider convective transport only within tissue, i.e. extracellular space, and neglect it within cells. Therefore the fluid flow goes from large vessels to capillaries and then to the extracellular space and the lymph. The lymphatic system is connected to the extracellular space with a drainage function. The extracellular space can be represented by a porous medium model and the flow can be described by Darcy's law. Hence, the FE equations have the form (6), with the convection matrix $\mathbf{K}^p$,

$$K_{IJ}^p = \int_V k_{Dij} N_{I,i} N_{J,j} dV, \quad \text{sum on } i: i = 1, 2, 3 \quad (11)$$

where k_{Dij} is the Darcy tensor. The components of the Darcy tensor can be obtained by a homogenization procedure for mass transport [47]. A reference domain can be selected and a detailed FE model generated (as in Fig. 1), with the imposed pressure boundary conditions. For example, if pressures P_{in} and P_{out} at surfaces with normal x are given, while on other surfaces are equal to zero, the equivalent coefficients of Darcy tensor $\bar{k}_{Dxx}$, $\bar{k}_{Dxy}$, $\bar{k}_{Dxz}$ in a direction x can be expressed as

$$\bar{k}_{Dxx} = \frac{Q_x}{A_x(P_{in} - P_{out})/L_x}, \bar{k}_{Dxy} = \frac{Q_y}{A_y/L_y}, \bar{k}_{Dxz} = \frac{Q_z}{A_z/L_z} \quad (12)$$

where A_x , A_y , A_z and L_x , L_y , L_z are surfaces and lengths of the model, respectively; and Q_x , Q_y and Q_z are fluxes through the model surfaces.

It is assumed here that extracellular space, together with cells, is rigid. In case of deformable tissue continuum, it would be necessary to include the field of Darcy velocities coupled with pressure, so that the element matrices will be extended by the terms corresponding to nodal Darcy velocities as additional variables [22]. In that case, velocities at deformable pipe elements also have to be included. Of course, this model with deformable continuum will be

more realistic and would provide results closer to the capillary-tissue biological system behavior.

Diffusive transport in tissue can be described by using Fick's law for 1D and the mass balance equation. The balance equation (8) now is [22]

$$-\frac{\partial c}{\partial t} - \frac{\partial c}{\partial x_i} v_i + \frac{\partial}{\partial x_i} \left(D_{ij} \frac{\partial c}{\partial x_j} \right) + q = 0, \quad \text{sum on } i, i = 1, 2, 3 \quad (13)$$

where v_i are the velocity components and D_{ij} is the diffusion tensor. Components of the diffusion tensor can be determined by numerical homogenization, in a way analogous to that described for the Darcy tensor. Here, the mass release curves, representing the constitutive curves for diffusion [47, 54], need to be determined, from which the diffusivity tensor is calculated. Also, physico-chemical interaction between transported molecules and the surrounding solid phase within tissue can be taken into account. Scaling functions, shown in Fig. 1b, are evaluated using Molecular Dynamics to correct diffusivity (hence the model couples two scales hierarchically) [42]. The balance FE equations have the form (9), with the matrices:

$$\begin{aligned} M_{IJ}^c &= \int_V N_I N_J dV \\ K_{IJ}^c &= \int_V D_{ij} N_{I,i} N_{J,j} dV \\ K_{IJ}^{cv} &= \int_V v_i N_I N_{J,i} dV \end{aligned} \quad (14)$$

where v_i are the Darcy fluid velocities calculated from the fluid flow; and summation from 1 to 3 is implied for the repeated indices i and j .

2.3 Diffusion within the cell

The cell interior space is bounded by the cell membrane and is filled by a gel-like substance called cytosol. Different entities/compartments are submerged in the cytosol, called organelles, such as the nucleus, vesicles, mitochondria, etc. These entities are considered as continuous media occupying a part of the space within cell, with membranes separating them from the surrounding cytosol. Also, cytoskeleton, consisting of various fibers, is present within the cytosol as a supporting structure. Schematic of the cell model is shown in Fig. 2.

The governing process of molecule transport within a continuous medium may include diffusion, electrical and chemical components [56]. The molecular flux $\mathbf{J}$ of transporting molecules can be written according to the Nernst-Planck equation as

$$J_i = -D \frac{\partial c}{\partial x_j} - z \mu_m c \frac{\partial V}{\partial x_i} \quad (15)$$

where D is diffusion coefficient, z is ionic valence, V is electric potential, and

$$\mu_m = \frac{DF}{RT} \quad (16)$$

is the mobility; F is Faraday's constant, R is gas constant and T is absolute temperature. The balance equation (13) now has the form

$$-\frac{\partial c}{\partial t} + \frac{\partial J_i}{\partial x_i} + q = 0 \quad (17)$$

where q represents the source term due to chemical reactions. Electrical contribution to the mass transport occurs in case of charged molecules. In further analysis we will consider the diffusive transport only (although electrical effects can be included within the presented framework), without chemical reactions, and the governing equations reduce to those given for transport within tissue. Diffusion tensor for the cytosol space can be determined using the mass release curves for reference volumes schematically shown in Fig. 2. Also, each subcellular space has its own diffusion coefficient.

2.4 Transport through vessel walls and biological membranes

In the transport from fluid to solid domain, i.e. from blood vessels to tissue (and in the reverse direction), it is necessary to properly model transport through blood vessel walls. To achieve that, connectivity or fictitious elements were introduced in [51]. A schematic of the connectivity elements is shown in Fig. 3a. The vessel (i.e. pipe) is modeled by 1D, and continuum by 2D or 3D finite elements. The connectivity 1D element has two nodes at the same spatial position, 1 – pipe node, and 2 – continuum node, and the mass transport occurs along the direction x which is normal to blood vessel axis, shown at the enlarged element 1–2 in Fig. 3a. This element serves to represent mass transport through the vessel wall, for the segment of the vessel belonging to that node (length L in the figure).

The balance equation for convective (hydraulic-fluid) flow for the fictitious element has the form (6), with the flux $\mathbf{Q}^{(i-1)}=0$, and the matrix coefficients

$$K_{11}^p = K_{22}^p = -K_{12}^p = -K_{21}^p = k_h A_p \quad (18)$$

Here, k_h is the hydraulic permeability coefficient, and A_p is the surface area of the pipe internal surface belonging to the connectivity element node. In case of a straight pipe as

shown in Fig. 6, $A_p = L\pi d$ where L is the length of pipe element - assuming the same element lengths on both sides of the node, and d is the pipe internal diameter.

Considering the diffusive transport through the wall, a 1D approximation for radial diffusion can be used, since the vessel wall thickness is small with respect to the vessel radius. Then, we use equation (8) and obtain the FE balance equation of the form (9), where, with linear interpolation of concentration along the element, the matrices are:

$$\begin{aligned} M_{11}^c &= M_{22}^c = \frac{1}{3}A_p h, & M_{12}^c &= M_{21}^c = \frac{1}{6}A_p h \\ K_{11}^c &= K_{22}^c = -K_{12}^c = -K_{21}^c = D_{wall}A_p \\ K_{11}^v &= -K_{22}^v = -K_{21}^v = K_{12}^v = -\frac{1}{2}k_h A_p (P_1 - P_2) \end{aligned} \quad (19)$$

Here, D_{wall} is the wall diffusive transport coefficient, h is the wall thickness; and P_1 and P_2 are pressures in the pipe and tissue, respectively. Note that the D_{wall} represents the overall transport coefficient of the wall (with pores, fenestrations, etc.); it can be related to the diffusion coefficient of the wall porous material coefficient $D_{material}$ as $D_{wall} = h D_{material}$. Also, if the thickness is small with respect to the pipe diameter, as it is the case for capillaries, the transient terms can be neglected, and therefore the matrix $\mathbf{M}^c$ can be discarded.

The connectivity elements can be used for transport through lymph vessels, with the corresponding wall characteristics. Further, these elements are applicable for transport through biological membranes of cells or organelles (indicated in Fig. 2). As schematically shown in Fig. 6b, the connectivity elements have two nodes: 1 – belonging to extracellular space, and 2 – in the cytosol space. The above equations for the vessel wall are applicable, with the cross-sectional area equal to the membrane surface area belonging to the node at the membrane.

Partitioning, as a frequent measure of hydrophobicity in case of molecule redistribution between water and oil phases, can be included in the connectivity element, according to the FE formulation in [54, 57]. In general, partitioning is numerically expressed by the partitioning coefficient P as the ratio between particle/molecule concentrations C_1 and C_2 within two media at the common boundary surface, i.e. $P = C_1/C_2$. Then, the corresponding factorization of the matrices (19) by the partitioning coefficient has to be implemented, enabling simulations of mass distribution which deviates from the classical Fickian gradients; such situations are quite common in drug and cell transport. If the partitioning coefficients at the nodes 1 and 2 are P_1 and P_2 , respectively, then equation (9) becomes:

$$\begin{aligned} \bar{K}_{11}P_1\Delta C_1^{(i)} + \bar{K}_{12}P_2\Delta C_2^{(i)} &= -P_1\bar{K}_{11}C_1^{(i-1)} - \bar{K}_{12}P_2C_2^{(i-1)} \\ \bar{K}_{21}P_1\Delta C_1^{(i)} + \bar{K}_{22}P_2\Delta C_2^{(i)} &= -P_1\bar{K}_{21}C_1^{(i-1)} - \bar{K}_{22}P_2C_2^{(i-1)} \end{aligned} \quad (20)$$

where the matrix terms follow from equation (9).

2.5 A summary of the FE steps in the detailed model

We have presented above the equations which govern the mass transport starting from blood vessels and ending at the organelles within cells. Here we summarize the basic characteristics and the corresponding steps, needed in generating a FE model which includes all domains of mass transport. There are two types of finite elements – continuum and connectivity elements:

- Continuum elements – 1D for large blood vessels, capillary and lymph vessels; – 2D or 3D for extracellular space, cytosol domain within each cell, and organelle space for each cellular organelle.
- Connectivity elements – between: capillaries and tissue; lymph vessels and tissue; tissue and cytosol of each cell; and cytosol and organelles.

From this description of the detailed FE model, it is obvious that it is not feasible to generate this model for larger domains of tissue, or for organs and entire tumors. The difficulty in the practical applications also comes from the fact that the organs vary in shape, size and structure between samples of the same species, and particularly in case of tumors. Motivated by the indicated difficulties, we have introduced a smeared concept [57] which is here extended to include cells and cellular organelles. This generalized composite smeared finite element is formulated in the next section.

3. Formulation of the composite smeared finite element (CSFE) which includes cells and organelles

The recently developed composite smeared finite element (CSFE) [52], extended in [53] to include lymphatic system, is here further generalized to the cell interior and organelles, as schematically shown in Fig. 4. It is a composite continuum (2D or 3D) finite element which can be considered also as a multiscale element since it is used for modeling the length scales of different orders of magnitude (shown in the figure). This is a concurrent multiscale feature since the concentration fields are simultaneously evaluated for all element scales. The element also includes multiscale hierarchical modeling since diffusivity of the transported molecules through extracellular space and within cell cytosol may be determined using molecular dynamics (MD), as indicated in Fig. 4 (also discussed in Section 2.2). There are several steps in this development of the CSFE, as presented below.

3.1 Transformation of the 1D capillary and lymph vessels model to continuum

A capillary network in cancerous tissue according to [58], Fig. 5a, shows complexity of the capillary architecture. It would be very demanding to model that structure even with 1D finite elements, hence there is a need to transform this 1D transport within capillary network into the equivalent continuum description. It is achieved in the following way.

Consider a small volume V , shown in Fig. 5b, with mass fluxes along the capillary directions. Then, this 1D mass transport can be transformed into continuum representation with the same net flux within the volume occupied by the capillary interior. It is necessary to

determine the corresponding Darcy's and diffusion tensors. As shown in [59], these tensors can be expressed as follows. The Darcy tensor is

$$k_{Dij} = \frac{1}{A_{tot}} \sum_K k_{pK} \ell_{Ki} \ell_{Kj} = \frac{\pi}{128 \mu A_{tot}} \sum_K d_K^4 \ell_{Ki} \ell_{Kj} = \frac{1}{32 \mu A_{tot}} \sum_K A_K d_K^2 \ell_{Ki} \ell_{Kj} \quad (21)$$

and the diffusion tensor is

$$D_{ij} = \frac{1}{A_{tot}} \sum_K D_{pipeK} A_K \ell_{Ki} \ell_{Kj} \quad (22)$$

where summation goes over all 1D capillary (pipe) elements; d_K are internal diameters, μ is viscosity within pipes, D_{pipeK} are diffusivities, A_K cross-sectional areas, and ℓ_{Ki} are directional cosines. The total area A_{tot} is

$$A_{tot} = \sum_K A_K = \frac{\pi}{4} \sum_K d_K^2 \quad (23)$$

With these tensors, the governing equations for the continuum FE models are applicable for the capillary and lymphatic system.

3.2 Formulation of the composite smeared finite element (CSFE)

After the above transformations we can introduce a general smeared finite element (CSFE) which has the following continuum domains:

- Capillary
- Lymph
- Cytosol
- Organelles

For clarity, we first consider two layers of the CSFE: a) capillary-tissue, and b) cellular layer.

a) First layer, capillary-tissue—This layer represents part of the volume of the CSFE with the domains occupied by capillaries, lymph and extracellular space. In Fig. 6a we show schematics of this layer and Fig. 6b is a 2D representation of the CSFE. As given in the figure, the volume fractions of the domains, with respect to the total element volume V , are:

- for capillaries, $V_{cap}, r_V = V_{cap}/V$
- for lymph, $V_{ly}, r_{ly} = V_{ly}/V$
- for tissue, $V_{tis} = (1 - r_V - r_{ly})V, r_{tis} = 1 - r_V - r_{ly}$
- for extracellular space, $V_{ex} = r_{tis}(1 - r_{Vcell})V, r_{ex} = r_{tis}(1 - r_{Vcell})$

(24)

Here, $r_{Vcell} = V_{cell}/V_{tis}$ is the volumetric ratio of the total volume occupied by all cell types V_{cell} with respect to tissue volume V_{tis} which includes extracellular space and cells. Note that the connectivity elements couple the element physical fields between capillary and extracellular space and between extracellular space and lymph. A summary of the connectivity elements will be given in part c) of this section. Also, connectivity elements, which do not belong to the CSFE, are used to connect large vessels (arterioles and venules shown in Fig. 6a) and vessels in Fig. 4 – the first panel on the left) to the capillary nodal variables of the CSFE.

b) Second layer, cells—In this layer of the CSFE, cells of different types (with their organelles) are included. A schematic of the cell interior is given in Fig. 2, which serves as the basis for the second layer formulation. As shown in Fig. 7, a cell type ' i ' occupies volume V_{ci} of the element volume V and is specified by the volumetric ratio r_{ci} relative to the tissue volume, i.e.,

$$V_{ci} = r_{ci}(1 - r_V - r_{ly})V \quad (25)$$

while volumes of organelles are related to the cell volume. Hence, volume of the organelle j within cell type i is:

$$V_{org-ij} = r_{ci}r_{org-ij}(1 - r_V - r_{ly})V \quad (26)$$

where

$$r_{org-ij} = \frac{V_{org-ij}}{V_{ci}} \quad (27)$$

The cytosol volume is

$$V_{cyt-i} = (1 - r_{org-itot})r_{ci}(1 - r_V - r_{ly})V \quad (28)$$

where $r_{org-itot}$ is the volumetric ratio of all organelles, occupying volume V_{org-i} .

c) Connectivity elements—Connectivity elements are introduced in Section 2.4. They are used here to connect the physical fields within the CSFE, as indicated in Figs. 6 and 7. We introduce at each node of the CSFE connectivity elements between:

- capillary and extracellular space
- extracellular space and lymph
- extracellular space and cytosol of each of cell group
- cytosol and each of organelles within each cell group

The transport coefficients of a connectivity element depend on the material properties of the wall or membrane separating the corresponding domains. They include hydraulic coefficients, diffusivities and partition coefficients as material parameters. Cross-sectional areas depend on the value of the surface area which belongs to the CSFE node through which the mass transport occurs. In general, for a node J this area A_J can be expressed as

$$A_J = (r_{AV} r_V V)_J \quad (29)$$

where r_{AV} is the area-to-volume ratio, and r_V is the volumetric ratio – both for the node J , and V_J is the volume of the continuum belonging to the element node J . As schematically shown in Fig. 8, we calculate the volumes V_J as

$$V_J = \sum \int_V N_J dV \quad (30)$$

where summation includes all finite elements with the common node J . In case of capillaries with a circular cross-section, we have that $r_{AV} = 4/d_{cap}$, and for spherical cell $r_{AV} = 6/d_{cell}$.

We note that in a model with larger vessels represented by 1D finite elements and CSFEs for the continuum, the 1D elements are connected to the capillary domain for pressures and concentrations.

d) CSFE – summary—Here, we summarize the main features of the introduced generalized CSFE. For example, if we model a pancreas, we have large vessels as 1D elements and the 3D elements CSFE, as shown in Fig. 9. Therefore, we have CSFE which are simply 3 finite elements with the nodal variables DOFs as summarized in the figure. In general, the total number of DOF is

$$NDOF = 6 + (1 + N)K \quad (31)$$

where K is number of cell types and N is number of organelles in each cell-type (assuming that N is the same for each cell-type). It should be emphasized that, besides the CSFE simplicity for application – usual discretization by continuum finite elements, the material

parameters listed in Figs. 6 and 7 are based on the material properties of the tissue and transported particles (molecules), which are measurable in standard laboratory investigations.

This finite element has been built in our general-purpose FE package PAK [60] for 2D and 3D conditions.

Note that in case of single constituent within the CSFE, the smeared model reduces to the usual FE formulation (“unsmeared”) by using one domain active, with the volumetric fraction equal to unity and with the number of DOFs equal to that of the active constituent.

4. Examples

Here, we first present a group of examples which serve to show accuracy of the generalized CSFE, and then demonstrate applicability of the CSFE to large-scale model of pancreas.

We have studied accuracy of the basic CSFE in our previous publications. In [59] we introduced the concept of the smeared model and tested the model accuracy with respect to the “true” FE model consisting of 1D capillary network and surrounding tissue as homogenous continuum. Accuracy was further investigated in [61] with respect to the models where capillaries, as well as their walls, were discretized by continuum finite elements. There, a correction function for wall diffusivity was introduced to improve accuracy of the CSFE model. The parameters of the function are: capillary volumetric fraction, the ratio of the capillary wall thickness and diameter, and the ratio of diffusivities of tissue and capillary wall. In the examples below we will use this correction function, with the ratio of capillary volume with respect to the volume of the extracellular space. In [53] the basic smeared finite element is extended to include the lymphatic system, showing also accuracy of the CSFE model.

4.1 A 2D small domain of cancerous tissue – diffusion only, with prescribed concentrations at capillaries

We have selected a small 50×50 micron size 2D domain taken from images of cancerous tissue (E. J. Koay, MD Anderson Cancer Center, Houston) shown in Fig. 10a. It was assumed that there are two types of cells, with different cytosol properties, and with three organelles within each cell. Contours of cells and organelles are shown in Fig. 10b. It is assumed that there are 6 capillaries normal to the plane of the model, with prescribed concentration. Two FE models are generated, detailed model – in Fig. 10c, and smeared model – in Fig. 10d. It can be seen that there is large difference in the number of equations between the two models: 69457 for the detailed model and 1089 for the smeared model. Model geometrical data are as follows (lengths in microns):

Capillaries: 5, Diameter $d_{\text{mean}} = 3.97$, wall thickness = 0.62, vol fraction $r_V = 0.0247$ Tissue: 50×50 $A_{\text{total}} = 2500$, $A_{\text{tissue}} = (1 - 0.0247) * A_{\text{total}} = 2438$

Cell 1 (24): $r_V = 0.307$, $D_{\text{mean}} = 6.30$

Organelles: 1) $r_V = 0.334$, $D_{\text{mean}} = 3.64$; 2) $r_V = 0.034$, $D_{\text{mean}} = 1.16$; 3) $r_V = 0.03$, $D_{\text{mean}} = 1.10$

Cell 2 (21): $r_V = 0.257$, $D_{\text{mean}} = 6.16$

Organelles: 1) $r_V = 0.257$, $D_{\text{mean}} = 3.17$; 2) $r_V = 0.051$, $D_{\text{mean}} = 1.39$; 3) $r_V = 0.056$, $D_{\text{mean}} = 1.46$

In order to test accuracy of the smeared model, we chose a condition which is more severe with respect to anisotropy of the model (and hence more severe with respect to accuracy of the smeared model) – and it is assumed that the two cell types occupy separate domains; the boundaries of the two cell groups are shown by black and dark lines in Fig. 11b. Two concentration profiles are assumed within capillaries: constant and bolus-type. Also, different diffusivities and partitioning are considered, and here are given a few typical solutions. We compare mean concentration evolution within different compartments of the model. We presume that wall diffusivities are the same as for tissue and for the medium (for capillaries as in extracellular space, for cells as in cytosol, and for organelles as within organelles). All diffusivities are given in [μ^2/s] and concentrations in [M].

a) Constant concentration in capillaries, with partitioning—Since partitioning is a dominant factor in drug delivery, we here show results where diffusivities are the same in all domains and in walls, while there is partitioning at cell membrane and organelle membranes of cell group 2. Two cases are selected, with partitioning $P=10$ and $P=0.1$ for membranes of cell 2 and its organelles. Evolution of the mean concentration for four compartments is shown in Figs 11a and 12a, while the concentration field at time $t=0.5\text{s}$ and diagram of the ultimate concentration along the central axis x are shown in Figs 11b and 12b. It can be seen that concentration discontinuities occur at membranes with partitioning. Although there is a very heterogeneous field of concentration shown in the figure, there is quite good agreement between mass accumulation within compartments for the two models. There are some notable deviations between true and smeared model solutions for extracellular space and Cell 1, in case of partitioning equals to 0.1 and ultimate concentration equals to 1; while for Cell 2 and its organelle the agreement is excellent – where the ultimate concentrations are 10 and 100, respectively. This can be attributed to the large flux towards Cell 2 and its organelles produced by partitioning equal 0.1 (10 times large concentration within Cell 2 and 10 times further in organelles), particularly in the first part of the time period - when mass accumulation occurs within Cell 2 group. Also, concentration in extracellular space and Cell 1 group is orders of magnitude smaller. These effects cannot be captured by the smeared model. It can also be seen that the ultimate mean concentrations are appropriately scaled for the both models by the factor $P=10$ or $P=0.1$, for Cell 2 and further to its organelles. Concentration fields shown in the figures demonstrate very pronounced differences in the field within the domains occupied by the two cell groups.

b) Bolus-type concentration in capillaries, with partitioning—In this example we assume bolus-type concentration in capillaries, while using the same material parameters as in the example a), with partitioning $P=10$. The mean concentration change with time is shown in Fig. 13. As in the case of constant concentration in capillaries, there is even better

agreement between the true and smeared model. The scaling of the curves for domains with membrane partitioning has the P-factor scaling character.

c) Convective-diffusive model with lymphatic system—Here, we assume that the lymphatic system is present in the model, with 4 lymph vessels, as shown in Fig. 14, with mean diameters of $3.1\mu\text{m}$, and volumetric fraction of 1.26%. We assume that the pressure in capillaries is a constant $p=1$ Pa, while concentration is, as in previous cases, constant $C=1$ or bolus-type. Pressure and concentration within lymph is equal to zero. Diffusion material parameters are as in case a), including partitioning $P=10$. According to physiological facts and the above discussion of the model formulation in Section 3, fluid transport occurs within capillaries, extracellular space (called here tissue) and lymphatic system. The number of equations of the detailed model is $87943 = 18486 + 69457$ (pressures and concentrations, while in the smeared model is ~ 1200 .

Results in Fig. 14 show the effects of the lymphatic system. A non-uniform pressure field is generated within the extracellular space (Fig 14b); without the lymphatics, pressure will be constant and equal to the pressure in capillaries. The mean pressure in the extracellular space, according to the detailed model, is equal to 0.54 Pa, while the uniform pressure obtained by the smeared model is 0.57 Pa. Pressure gradients produce velocities which are shown in Fig 14c, and it can be seen that velocities are directed toward the lymphatic vessels. Evolution of the mean concentration for the detailed model and concentration of the smeared model, are shown in Fig. 14c,d for constant and bolus-type concentration in capillaries. It can be seen that these concentrations are much below those shown in Figs. 11 and 13 due to convection and the presence of lymphatic vessels. The solutions obtained by detailed and smeared models are in agreement, as in the case without the lymph system. Non-uniformity of the concentration field is shown in Fig. 14f, with obvious effects of the lymph (lower concentrations in the vicinity of the lymph vessels).

d) Model with prescribed concentrations and pressures in extracellular space at two opposite boundaries—The goal of this example is to investigate the agreement between the true and smeared model in the case when concentration and pressure gradients are present in extracellular space. These gradients are generated by prescribed pressure and concentration at two opposite boundaries: $p=1$, $C=1$ at the left and $p=0$ and $C=0$ at the right boundary, respectively. Cells are grouped, with partitioning $P=10$ as in case a).

Pressure distribution for detailed and smeared model are shown in Fig. 15a for the detailed model and Fig. 15b shows the pressure field within extracellular space for the smeared model. It can be seen that the continuous field of the smeared model follows the field displaced for the detailed model. The mean pressures calculated for the detailed and smeared model are 0.57 and 0.608 Pa, respectively – demonstrating very good agreement between the models.

The concentration field at time $t=100\text{s}$ is shown in Fig. 15d and within extracellular space and smeared model is given in Fig. 15e. As for pressures, the displaced fields are in agreement, although the true field is very non-homogenous, and very different between the

physical domains within the model. This non-homogeneity is illustrated in Fig. 15f, where concentration along the middle plane is given for all domains. Besides very pronounced differences between values in the physical domains, there is reasonably good agreement in the mean concentrations, demonstrated in Fig. 15g and Fig.15h for the constant and bolus-type concentration in capillaries.

4.2 Pancreas model

The model geometry, including large vessels and tissue, was generated at the Bioengineering R&D Center BIORC in Serbia, according to imaging data from: E. J. Koay, MD Anderson Cancer Center, Houston. The model is shown in Fig. 16, where we include the basic data about the model. Other data are as follows.

Large vessels: diameters 0.006–0.209mm, wall thickness 10% of diameter

diffusion coefficients: $1e+5$ [mm²/s] in vessel, 10 [mm /s] through the wall

viscosity: $1e-3$ Pa s, hydraulic coeff. of wall $1e-3$ mm / (Pa s)

Capillaries: volumetric fraction 2.47%

diameters 0.005 [mm], wall thickness 0.0005 [mm]

diffusion coefficients [mm²/s]: in capillaries =10, through the wall= 0.0001

Lymph: volumetric fraction 2.47%

diameters: 0.005 [mm]

hydraulic coefficient $1e-11$ mm / (Pa s)

Extracellular space: Darcy coefficient $1e-3$ mm²/(Pa s), diff coefficient =10 [mm² /s]

Cell 1: diameter = 0.00617, volumetric fraction =28.21%

diff coeff in cytoplasm and through cell membrane= $1.e-4$ [mm² /s]

organelle: diameter = 0. 0034, volumetric fraction = 30.30%

diff coeff and through organelle membrane= $1.e-4$ [mm² /s]

Partitioning: extracellular space / cell membrane $P=5$

cell cytoplasm / organelle membrane $P = 0.1$

Cell 2: diameter = 0.00630, volumetric fraction =28.17%

diff coeff in cytoplasm and through cell membrane= $1.e-4$ [mm² /s]

organelle: diameter = 0.00347, volumetric fraction = 30.30%,

diff coeff and through organelle membrane= $1.e-4$ [mm² /s]

Partitioning: extracellular space / cell membrane $P=10$

cell cytoplasm / organelle membrane $P = 0.1$

Since we use pressure and concentration as prescribed (equal to zero), the “degrees of freedom” of the lymph domain do not enter into the system of equations in this example. We selected data in a way that they fall in a realistic range, and assumed the only significant difference between the two group of cells was that for Cell 1 group partitioning is $P=5$, while for the Cell 2 group $P=10$ at the cell membranes. Since the partitioning coefficient is defined as the ratio between concentration in the extracellular space and within the membrane wall, it follows that, under the same other conditions (assumed here), concentration in the cell interior of Cell 2 will be half of the concentration within Cell 1 group (P of Cell 1 is 5, while P of Cell2 is 10). Also, the partitioning at the organelle membrane is defined as the ratio between concentration in the cytosol and within the membrane wall (for $P=0.1$ we will have that concentration in the organelle is 10 times larger than in cytosol). Further, we show some typical results.

Fig. 17 shows the concentration field at the surface of elements for five different time points and for all continuum domains calculated within CSFEs. As can be seen, there is a drastic difference between the values of the two cell groups, coming as a consequence of partitioning, discussed above. An insight into concentration distribution within the pancreas at time $t=20s$ is displayed in Fig. 18.

We have calculated the evolution of the mean concentration within each continuum domain. Change of mean concentrations with time are shown in Fig. 19. This figure graphically depicts the effect of partitioning at the cell membrane. It can be seen that concentration within the group Cell 2 (including its organelle) is two times smaller than within the Cell 1 group, as discussed above. Also, it is interesting to note that the maximum concentration in the extracellular space (and approximately within cells) is reached with a time-lag, which is a consequence of the diffusion nature. After the maximums are reached, a reverse (clearing) process takes place, and at some later time the concentration in the capillaries becomes even higher than in the connecting large vessels. Concentration changes are also affected by convection and the role of lymph, which is included in the model and has a drainage role.

Finally, we present some details regarding fluid transport. Fig. 20 shows the pressure distribution, where it can be seen that the pressure field in the capillary and extracellular space domain are similar, but differing in values. The vector velocity field within capillaries is displayed in Fig 21. It is interesting to note that velocities are large in the areas where there is a large change in the pancreas shape.

5. Summary and concluding remarks

We have generalized our previously introduced composite smeared finite element CSFE [52, 53] to include the cell interior and organelles. Now, we have the following continuum domains which occupy parts of the total element volume: capillary, lymph, extracellular space, cell cytosol of each of cell groups, and organelle space for each organelle within cells.

The nodal variables ('degrees of freedom', DOF) thus include pressures and concentrations of all compartments within the element.

The capillary and lymph are the fluid domains where the continuum (2D or 3D) representation is achieved by the corresponding transformation of 1D fluid flow or diffusion. The Darcy and diffusion tensors are derived in a consistent manner. It is further assumed that fluid transport occurs in the capillary, lymph and extracellular space, while diffusion includes also intracellular space with cytosol and organelles.

The volumetric fraction of each domain is specified in a way convenient for interpretation and practical use. For example, for capillaries and lymphatics we relate their volumes to the total volume; and for an organelles we relate the organelle volume to its cell volume.

The connectivity 1D fictitious finite elements are assigned to each node and they include all biological barriers present in the element: capillary wall, lymph vessel wall, cell membrane, and organelle membrane. Cross-sectional areas of each of these 1D FEs are evaluated according to size of the surface area of the barriers belonging to the node.

Material characteristics includes parameters related to convective and diffusive transport of particles (molecules) within each of the compartments and also transport through biological barriers. Physico-chemical specifics of the transport, such as molecule interaction with the surroundings, can be included in the model by use of molecular dynamics for correction of the effective diffusivity [42, 47] or hydrophobicity at the biological barriers – by an appropriate partitioning coefficient.

It can be considered that the formulated CSFE has a multiscale character – it includes in a hierarchical manner MD and the macro-scale continuum (the above mentioned correction of diffusion coefficient), but also it contemporary couples different length scales (schematics in Fig. 4).

The presented methodology is built into our FE code PAK [60], with the corresponding interface CAD for mesh and data generation.

A number of numerical solutions were presented for transport within a small domain of pancreatic tumor tissue. It was shown that, despite the very complex tissue composition and very non-uniform field of pressure (and consequently velocity) and concentration, a simple model using the CSFE provides accurate results for mass transport to all compartments: extracellular space, cell cytosol and organelles. Therefore, the CSFE can provide adequate and accurate solutions for transport taking into account local tissue composition and material properties.

Finally, the CSFE was used to model the entire pancreas. It was shown that it is possible to provide concentration fields for the various length scales, from the tissue macro-scale to the nanometer-scale of organelles.

The introduced multiscale composite smeared finite element (CSFE), due to its robustness and simplicity for applications, offers a new computational methodology to model complex

problems of mass transport, including drug delivery, ranging from small domains such as tumors to the whole-organ level.

Acknowledgements

Dr. Ferrari acknowledges the support from NCI U54 CA210181 and The Ernest Cockrell Jr. Presidential Distinguished Chair at Houston Methodist Research Institute.

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

References

- [1]. Hall JE, Guyton and Hall Textbook of Medical Physiology 13 ed., Elsevier, Philadelphia, 2016.
- [2]. Rushmer RF, Cardiovascular Dynamics, Fourth ed., W. B. Saunders Co., Philadelphia, 1976.
- [3]. Ferrari M, Frontiers in cancer nanomedicine: directing mass transport through biological barriers, Trends Biotechnol, 28 (2010) 181–188. [PubMed: 20079548]
- [4]. Koay EJ, Ferrari M, Transport Oncophysics in silico, in vitro, and in vivo. Preface, Phys Biol, 11 (2014) 060201. [PubMed: 25426742]
- [5]. Blanco E, Shen H, Ferrari M, Principles of nanoparticle design for overcoming biological barriers to drug delivery, Nat Biotechnol, 33 (2015) 941–951. [PubMed: 26348965]
- [6]. Reulen HJ, Graham R, Spatz M, Klatzo I, Role of pressure gradients and bulk flow in dynamics of vasogenic brain edema, J Neurosurg, 46 (1977) 24–35. [PubMed: 830812]
- [7]. Popel AS, Pittman RN, The microcirculation physiome, in: Bronzino J (Ed.) Handbook of Biomedical Engineering, CRC Press, Boca Raton, FL.
- [8]. Shi Y, Lawford P, Hose R, Review of zero-D and 1-D models of blood flow in the cardiovascular system, Biomed Eng Online, 10 (2011) 33. [PubMed: 21521508]
- [9]. Mathura KR, Vollebregt KC, Boer K, De Graaff JC, Ubbink DT, Ince C, Comparison of OPS imaging and conventional capillary microscopy to study the human microcirculation, J Appl Physiol (1985), 91 (2001) 74–78. [PubMed: 11408415]
- [10]. D'Apolito R, Tomaiuolo G, Taraballi F, Minardi S, Kirui D, Liu X, Cevenini A, Palomba R, Ferrari M, Salvatore F, Tasciotti E, Guido S, Red blood cells affect the margination of microparticles in synthetic microcapillaries and intravital microcirculation as a function of their size and shape, J Control Release, 217 (2015) 263–272. [PubMed: 26381900]
- [11]. Sevcik EM, Jain RK, Viscous resistance to blood flow in solid tumors: effect of hematocrit on intratumor blood viscosity, Cancer Res, 49 (1989) 3513–3519. [PubMed: 2731173]
- [12]. Cinar Y, Demir G, Pac M, Cinar AB, Effect of hematocrit on blood pressure via hyperviscosity, Am J Hypertens, 12 (1999) 739–743. [PubMed: 10411372]
- [13]. Pries AR, Secomb TW, Microvascular blood viscosity in vivo and the endothelial surface layer, Am. J. Physiol. Heart Circ. Physiol, 289 (2005) 2657–2664.
- [14]. Pries AR, Secomb TW, Gaehtgens P, Gross JF, Blood flow in microvascular networks. Experiments and simulation, Circulation Research, 67 (1990) 826–834. [PubMed: 2208609]
- [15]. Pries AR, Secomb TW, Microvascular blood viscosity and endothelial surface layer, Am. J. Physiol. Heart Circ. Physiol, 289 (2005) 2657–2664.
- [16]. Nicholson C, Diffusion and related transport mechanisms in brain tissue, Rep. Prog. Phys, 64 (2001) 815–884.
- [17]. Swabb EA, Wei J, Cullino PM, Diffusion and convection in normal and neoplastic tissues, Cancer Research, 34 (1974) 2814–2822. [PubMed: 4369924]
- [18]. Khaled A-RA, Vafai K, The role of porous media in modeling flow and heat transfer in biological tissues, Int. J. Heat and Mass Transfer, 46 (2003) 4989–5003.
- [19]. Nugent LJ, Jain RK, Extravascular diffusion in normal and neoplastic tissues, Cancer Research, 44 (1984) 238–244. [PubMed: 6197161]

- [20]. Gerlowski LE, Jain RK, Microvascular permeability of normal and neoplastic tissues, *Microvascular Research*, 31 (1986) 288–305. [PubMed: 2423854]
- [21]. Rushmer RF, Cardiovascular Dynamics, 4th Edition ed., W. B. Saunders, Philadelphia, 1976.
- [22]. Kojic M, Filipovic N, Stojanovic B, Kojic N, Computer Modeling in Bioengineering - Theoretical Background, Examples and Software, John Wiley and Sons, Chichester, England, 2008.
- [23]. Less JR, Skalak TC, Sevick EM, Jain RK, Microvascular architecture in a mammary carcinoma: branching patterns and vessel dimensions, *Cancer Res*, 51 (1991) 265–273. [PubMed: 1988088]
- [24]. Roberts WG, Palade GE, Neovasculature induced by vascular endothelial growth factor is fenestrated, *Cancer Res*, 57 (1997) 765–772. [PubMed: 9044858]
- [25]. Sevick EM, Jain RK, Geometric resistance to blood flow in solid tumors perfused ex vivo: Effects of tumor size and perfusion pressure, *Cancer Research*, 49 (1989) 3506–3512. [PubMed: 2731172]
- [26]. Sevick EM, Jain RK, Viscous resistance to blood flow in solid tumors: Effect of hematocrit on intratumor blood viscosity, *Cancer Research*, 49 (1989) 3513–3519. [PubMed: 2731173]
- [27]. Sevick EM, Jain RK, Effect of red blood cell rigidity on tumor blood flow: Increase in viscous resistance during hyperglycemia, *Cancer Research* 51, 51 (1991) 2727–2730. [PubMed: 2021951]
- [28]. Jain R, Determinants of tumor blood flow: A review, *Cancer research*, 48 (1988) 2641–2658. [PubMed: 3282647]
- [29]. Jain R, Transport of molecules across tumor vasculature, *Cancer and Metastasis Reviews* 6(1987) 559–593. [PubMed: 3327633]
- [30]. Rangamani P, Iyengar R, Modelling spatio-temporal interactions within the cell, *J. Biosci*, 32 (2007) 157–167. [PubMed: 17426388]
- [31]. Lauffenburger DA, Horwitz AF, Cell Migration: Review A Physically Integrated Molecular Process, *Cell*, 84 (1996) 359–369. [PubMed: 8608589]
- [32]. Sun H, Pang KS, Permeability, Transport, and Metabolism of Solutes in Caco-2 Cell Monolayers: A Theoretical Study, *Drug Metabolism and Disposition*, 36 (2008) 102–123. [PubMed: 17932224]
- [33]. Chu X, Korzekwa K, Elsby R, Fenner K, Galetin A, Lai Y, Matsson P, Moss A, Nagar S, Rosania GR, Bai JPF, Polli JW, Sugiyama Y, Brouwer KLR, Intracellular Drug Concentrations and Transporters: Measurement, Modeling, and Implications for the Liver, *Clinical Pharmacology & Therapeutics* 94 (2013) 126–141. [PubMed: 23588320]
- [34]. Schaff J, Fink CC, Slepchenko B, Carson JH, Loew LM, A General Computational Framework for Modeling Cellular Structure and Function, *Biophysical Journal*, 73 (1997) 1135–1146. [PubMed: 9284281]
- [35]. Moraru II, Schaff JC, Slepchenko BM, Blinov ML, Morgan F, Lakshminarayana A, Gao F, Li Y, Loew LM, Virtual Cell modelling and simulation software environment, *IET Syst. Biol*, 2 (2008) 352–362. [PubMed: 19045830]
- [36]. Slepchenko BM, Schaff JC, Macara I, Loew LM, Quantitative cell biology with the Virtual Cell, *TRENDS in Cell Biology*, 13 (2003) 570–576. [PubMed: 14573350]
- [37]. Lipowsky HH, Zweifach BW, Network analysis of microcirculation of cat mesentery, *Microvascular Research*, 7 (1974) 73–83. [PubMed: 4821172]
- [38]. Kojic M, Milosevic M, Simic V, Ferrari M, A 1D pipe finite element with rigid and deformable walls, *J. Serbian Soc. Comp. Mechanics*, 8 (2014) 38–53.
- [39]. Isailovic V, Kojic M, Milosevic M, Filipovic N, Kojic N, Ziemys A, Ferrari M, A computational study of trajectories of micro- and nano-particles with different shapes in flow through small channels, *J. Serb. Soc. Comp. Mech*, 8 (2014) 14–28.
- [40]. Kiseliovas V, Milosevic M, Kojic M, Mazutis L, Kai M, Liu YT, Yokoi K, Ferrari M, Ziemys A, Tumor progression effects on drug vector access to tumor-associated capillary bed, *J. Controlled Release*, (2017).
- [41]. Koji N, Milošević M, Petrović D, Isailović V, Sarioglu AF, Haber DA, Koji M, Toner M, A computational study of circulating large tumor cells traversing microvessels, *Computers Biology Medicine*, 63 (2015) 187–195.

- [42]. Ziemys A, Kojic M, Milosevic M, Kojic N, Hussain F, Ferrari M, Grattoni A, Hierarchical modeling of diffusive transport through nanochannels by coupling molecular dynamics with finite element method, *J. Comp. Physics*, 230 (2011) 5722–5731.
- [43]. Ziemys A, Kojic M, Milosevic M, Ferrari M, Interfacial effects on nanoconfined diffusive mass transport regimes, *Phys. Review Letters*, 108 (2012).
- [44]. Kojic M, Milosevic M, Kojic N, Ferrari M, Ziemys A, On diffusion in nanospace, *J. Serbian Soc. Comp. Mechanics*, 5 (2011) 84–109.
- [45]. Kojic M, Milosevic M, Kojic N, Isailovic V, Petrovic D, Filipovic N, Ferrari M, Ziemys A, Transport phenomena: Computational models for convective and diffusive transport in capillaries and tissue, in: De S, Hwang W, Kuhl E (Eds.) *Multiscale Modeling in Biomechanics and Mechanobiology*, Springer, London, 2015, pp. 131–156.
- [46]. Kojic M, Ziemys A, Milosevic M, Isailovic V, Kojic N, Rosic M, Filipovic N, Ferrari M, Transport in biological systems, *J. Serbian Soc. Comp. Mechanics*, 5 (2011) 101–128.
- [47]. Kojic M, Milosevic M, Kojic N, Kim K, Ferrari M, Ziemys A, 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 (2014) 123–138.
- [48]. Kojic M, Milosevic M, Kojic N, Koay EJ, Fleming JB, Ferrari M, Ziemys A, Mass release curves as the constitutive curves for modeling diffusive transport within biological tissue, *Computers in Biology and Medicine*, 92 (2018) 156–167. [PubMed: 29182964]
- [49]. Yokoi K, Kojic M, Milosevic M, Tanei T, Ferrari M, Ziemys A, Capillary-wall collagen as a biophysical marker of nanotherapeutic permeability into the tumor microenvironment, *Cancer Research*, 74 (2014) 4239–4246. [PubMed: 24853545]
- [50]. Ruiz-Esparza GU, Wu S, Segura-Ibarra V, Cara FE, Evans KW, Milosevic M, Ziemys A, Kojic M, Meric-Bernstam F, Ferrari M, Blanco E, Polymer Nanoparticles Encased in a Cyclodextrin Complex Shell for Potential Site- and Sequence-Specific Drug Release, *Adv. Funct. Mater.*, (2014) 10.1002/adfm.201400011, 201402014.
- [51]. Kojic M, Milosevic M, Kojic N, Starosolski Z, Ghaghada K, Serda R, Annapragada A, Ferrari M, Ziemys A, A multi-scale FE model for convective-diffusive drug transport within tumor and large vascular networks, *Comput. Methods Appl. Mech. Engrg*, 294 (2015) 100–122.
- [52]. Kojic M, Milosevic M, Simic V, Koay EJ, Fleming JB, Nizzero S, Kojic N, Ziemys A, Ferrari M, A composite smeared finite element for mass transport in capillary systems and biological tissue, *Comp. Meth. Appl. Mech. Engrg*, (2017).
- [53]. Kojic M, Milosevic M, Kojic N, Koay EJ, Fleming JB, Ferrari M, Ziemys A, 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*, 11 (2017) 108–120.
- [54]. Kojic M, Milosevic M, Kojic N, Koay EJ, Fleming JB, Ferrari M, Ziemys A, Mass release curves as the constitutive curves for modeling diffusive transport within biological tissue, *Computers in Biology and Medicine* 92 (2018) 156–167. [PubMed: 29182964]
- [55]. Ma PX, Zhang R, Synthetic nano-scale fibrous extracellular matrix, *J. Biomed. Mater. Res*, 46 (1998) 60–72.
- [56]. Schaff J, Fink CC, Slepohenko B, Carson JH, Loew LM, A General Computational Framework for Modeling Cellular Structure and Function, *Biophysical Journal*, 73 (1997) 1135–1146. [PubMed: 9284281]
- [57]. Kojic M, Milosevic M, Wu S, Blanco E, Ferrari M, Ziemys A, Mass partitioning effects in diffusion transport, *Physical Chemistry Chemical Physics*, (2015).
- [58]. Skinner SA, Tutton PJM, O'Brien PE, Microvascular architecture of experimental colon tumors in the rat, *Cancer Research*, 50 (1990) 2411–2417. [PubMed: 2317825]
- [59]. Kojic M, Milosevic M, Simic V, Koay EJ, Fleming JB, Nizzero S, Kojic N, Ziemys A, Ferrari M, A composite smeared finite element for mass transport in capillary systems and biological tissue, *Comp. Meth. Appl. Mech. Engrg*, 324 (2017) 413–437.
- [60]. Kojic M, Slavkovic R, Zivkovic M, Grujovic N, Filipovic N, Milosevic M, PAK - Finite Element Program for Linear and Nonlinear Analysis, Univ Kragujevac and R&D Center for Bioengineering, Kragujevac, Serbia, 2010.

- [61]. Milosevic M, Simic V, Milicevic B, Koay EJ, Ferrari M, Ziemys A, Kojic M, Correction function for accuracy improvement of the Composite Smeared Finite Element for diffusive transport in biological tissue systems, *Comp. Meth. Appl. Mech. Engrg*, under review (2018).

Fig. 1. Evaluation of equivalent Darcy's tensor and diffusion tensor for tissue by numerical homogenization. a) Extracellular fibrous space of skin [55] and simplified model of reference volume (RV) used for computational model; b) Scaling function for doxorubicin molecule interacting with tissue.

Fig. 2.
Schematics of the cell interior

Fig. 3. Schematics of the connectivity (fictitious) elements. a) Between pipe (blood vessel) and continuum extracellular space; b) Between extracellular space and cell. Nodes 1 and 2 are placed at the same spatial position but belong to different domains.

Fig. 4.

Mass transport from organ level (first panel from the left) to the microenvironment, to cellular and organelle domains (scales from 10^{-1} to 10^{-6} m). FE model includes large blood vessel and tissue discretized by CSFE elements (first panel on the left). Enlarged domains of microenvironment and further of cell interior, show the composition of the CSFE (abbreviations: ECM – extracellular matrix, MT-mitochondrion, ES-endosome, CP-cytoplasm, N-nucleus). MD+FE-panel indicate hierarchical FE-MD modeling of molecule interaction.

Fig. 5. Capillary network. a) Cancerous tissue with complex capillary architecture [58]; b) Capillary representation within small continuum volume V around spatial point P . Volume occupied by capillaries is $r_V V$, where r_V is capillary volumetric fraction. Fluxes within capillaries are Q_i , and total surface area of all capillary cross-sectional areas is A_{total} .

Fig. 6.

Composite Smeared Finite Element (CSFE)-Layer 1. a) Schematic of tissue connected to large vessels (according to C. Molnar and J. Gair, Concepts of Biology – 1st Canadian Edition, BC Open Textbooks); b) First layer (2D element) which includes domains of capillaries, lymph vessels and extracellular space. Nodal variables, material data and connectivity elements are displaced in the figure. Notation: C-concentration, P-pressure, D-diffusivity, Visc-viscosity, Darcy-Darcy's coefficient, Part-partitioning coefficient, Hydr Coeff – hydraulic coefficient.

Fig. 7.

Layer 2 of the CSFE. Elementary volumes, nodal variables, connectivity elements and material data. Cells (cytosol domains) are connected to the extracellular space, while organelles are within cytosol. Notation: C-concentration, D-diffusivity, Part-partitioning coefficient.

Fig. 8.
Evaluation of the cross-sectional area of connectivity elements from the volume of the continuum belonging to a FE node

Fig. 9.
Composite smeared finite element – a summary (applied to a model of the pancreas), with nodal variables and connectivity elements

Fig. 10.

Diffusion 2D model of tissue. a) Image of pancreatic cancer tissue; b) Contours of capillaries, cells and organelles; c) Detailed model with 2D elements; d) Smeared model with nodal concentrations to be calculated (concentrations in capillary domain are prescribed)

Fig. 11.

Grouped cells, constant concentration in capillaries is $C=1$. Diffusivities are the same in all compartments $D=100$, while partitioning for membranes is: $P=1$ for Cell 1 and its organelles, and $P=10$ for Cell 2 and its organelles. a) Mean concentration evolution in four compartments. b) Concentration field at time $t=0.5s$ and diagram of ultimate concentration along the axis x .

Fig. 12.

Grouped cells, constant concentration in capillaries is $C=1$. Diffusivities are the same in all compartments $D=100$, while partitioning for membranes is: $P=1$ for Cell 1 and its organelles, and $P=0.1$ for Cell 2 and its organelles. a) Mean concentration evolution in four compartments. b) Concentration field at time $t=0.5s$ and diagram of ultimate concentration (logarithmic scale) along the axis x .

Fig. 13.

Mean concentration evolution of concentration in compartments for the case when concentration in capillaries is a bolus shown in the left upper panel. Diffusivities are the same as in capillaries within all compartments with $P=1$, while the curves are scaled by 10 for cytosols of Cells 2, and by 100 for their organelles.

Fig. 14.

Model with lymphatic system. a) Model with cells (organelles shown in each cell), capillaries C1,...C4, and lymph vessels L1,...L4; b) Pressure field in extracellular space, capillaries and lymph (prescribed pressures are equal to 1 and 0 in capillaries and in lymph, respectively). c) Vectors of velocities in the extracellular space. Velocities are directed from capillaries toward lymph vessels which represent drainage system (enlarged around capillary C3 and lymph L3); d, e – mean concentration evolution within extracellular space for constant ($C=1$) and bolus-type concentration in capillaries. The ultimate concentration in extracellular space is around 0.60 due to lymph effects (comparing to 1, when there is no lymph); f) Concentration field at time $t=10s$ in case of constant concentration in capillaries.

Fig. 15.

Pressure and concentration in the case of prescribed pressure and concentration in the extracellular space at the boundary. Pressure field for the detailed a) and smeared model b); c) Velocity field in the extracellular space (enlarged around capillary C3 and lymph L3); Concentration field at Time $t=100$ s, for: detailed d) and e) for smeared model; f) Concentration distribution along the middle plane; Mean concentration evolution within organelle in Cell 2, for: g) constant concentration and h) bolus concentration in capillaries. Partitioning is $P=10$ for Cell 2 and organelle in Cell 2.

Model data

Number of FE nodes 127,783

Number of pipe nodes 1,602

Domains in tissue :

capillary, lymph, extracellular space

cell 1 - cytosol and 1 organelle

cell 2 - cytosol and 1 organelle

Number of variables per node of CSFE:

3 pressures+7concentrations = 10

Additional for pipe nodes: 1 press+1 conc

Number of system equations: 1,025,502

Boundary condtions:

Large vessels: Intet pressure 30mmHg=4000Pa

Intet pressure 20mmHg=2666Pa

Inlet concentration - bolus $c(t)$

Outlet concentration - eq. 0

Lymph: pressure eq.0, conc. eq.0

Fig. 16.

Model of pancreas, with large vessels and finite elements on the surface. Color in blood vessels corresponds to pressures. Model data include basic characteristics of the FE model.

Fig. 17.

Concentration field within elements CSFE at the pancreas surface, for five selected time points. Maximum concentration, among the shown five time points, at each domain at $t=20s$ when concentration C_{in} reaches maximum

Fig. 18. Concentration fields within the pancreas at time $t=20s$. Concentration for the Cell 2 group (portioning $P=10$ at cell membrane) is significantly smaller than for Cell 1 ($P=5$) due to partitioning.

Fig 19. Evolution of the mean concentration within the continuum domains: capillary, extracellular space, cell groups Cell 1 and Cell 2 with their organelles. Input concentration at large vessels $c(t)$.

Fig. 20.
Pressure field within capillary and extracellular domains.

Fig. 21. Vector velocity field in the capillary domain. The domain of maximum velocities (seen in the left panel) is enlarged in the right panel.