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Correction function for accuracy improvement of the Composite Smeared Finite Element for diffusive transport in biological tissue systems

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Abstract

Modeling of drug transport within capillaries and tissue remains a challenge, especially in tumors and cancers where the capillary network exhibits extremely irregular geometry. Recently introduced Composite Smeared Finite Element (CSFE) provides a new methodology of modeling complex convective and diffusive transport in the capillary-tissue system. The basic idea in the formulation of CSFE is in dividing the FE into capillary and tissue domain, coupled by 1D connectivity elements at each node. Mass transport in capillaries is smeared into continuous fields of pressure and concentration by introducing the corresponding Darcy and diffusion tensors. Despite theoretically correct foundation, there are still differences in the overall mass transport to (and from) tissue when comparing smeared model and a true 3D model. The differences arise from the fact that the smeared model cannot take into account the detailed non-uniform pressure and concentration distribution in the vicinity of capillaries. We introduced a field of correction function for diffusivity through the capillary walls of smeared models, in order to have the same mass accumulation in tissue as in case of true 3D models. The parameters of the numerically determined correction function are: ratio of thickness and diameter of capillary wall, ratio of diffusion coefficient in capillary wall and surrounding tissue; and volume fraction of capillaries within tissue domain. Partitioning at the capillary wall – blood interface can also be included. It was shown that the correction function is applicable to complex configurations of capillary networks,

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providing improved accuracy of our robust smeared models in computer simulations of real transport problems, such as in tumors or human organs.

Keywords

diffusion; capillary-tissue system; smeared model; composite smeared finite element; correction function

1. Introduction

In investigating supply of nutrients or drugs to target cells, it is essential to achieve efficient transport through capillary walls as the biological barrier. In order to help in that goal it is desirable to have adequate simple, but accurate, computational models. Transport within capillaries and tissue has been the subject of study over past decades, especially molecular/particulate convective and diffusive transport within blood vessels and through the vessel walls, since it is the fundamental process in drug delivery. Capillaries are filled with plasma and cells, while tissue can be considered as a porous medium with very complex microstructure composed of extracellular fibrous matrix and cells. Interaction between particles/molecules and the capillary wall components can dominate the transport through the wall. This interaction on a molecular level may be incorporated into a continuum transport model [1,2], and appropriate multiscale model has been developed and applied to various bioengineering problems [3,4].

We here consider transport of matter by diffusion within biological systems, with a specific focus on solid tumors. Morphology of tumor vasculature has been intensively investigated, with experimental evaluation the role of capillary density within tissue, capillary lengths and diameters [5–9]. In most of the tissue, and especially in tumors, geometry of blood vessels is highly heterogeneous with irregular blood vessel branching and variability of diameters and lengths. Since the number of vessels is extremely large (total number of capillaries in the body ~ billions [10], modeling of each vessel within an organ or tumor would not at present be feasible. Also, tumor tissue is very heterogeneous and involves zones of significantly different permeability for fluid and particulate transport. Additionally, capillary networks are different for different tumor types; they vary from patient to patient, and are changing over the period of tumor growth.

Frequent mass exchange takes place in a heterogeneous environment among several phases, where mass partitioning (hydrophobicity) may occur at the interface of phases.

Hydrophobicity is usually present at the interface between solid and fluid phase [11], which has to be considered in computational models. Our numerical results [11], based on the analysis of diffusion kinetics in the parameter space of partitioning and diffusivity, showed that partitioning is an extremely important parameter which may control equilibrated mass distribution.

Flow through capillary branching is three-dimensional, which would require detailed 3D continuum models. However, 3D models of branching, in general, lead to significant effort in the 3D FE mesh generation and are computationally very demanding. Detailed models,

therefore, are not suitable for large pipe networks, as in case of capillary systems. Consequently, it is desirable to have a simpler, efficient model which can be used as a good approximation of the flow within large pipe networks. One of the options is to use 1D pipe capillary network for capillary vessels which are immersed in real tissue domain. In [12] a transport model was introduced which can be applied to large vascular systems [13]. The model is efficient since it uses 1D finite elements for larger vessels and equivalent continuum FEs for capillary beds. The introduced computational model relies on a number of approximations, summarized in these references, with respect to the real biological conditions within capillaries and tissue.

Furthermore, even with using 1D finite elements, there is still a problem of reconstructing complex geometries, so that FE meshes are with large number of nodes and large number of equations to be solved. All these facts have been a motivation to explore possibility of formulation of a smeared computational model. Generally, smeared procedures have been applied for crack distribution within materials in fracture mechanics studies, or for material properties of complex materials (e.g. [14, 15]). Our recently introduced smeared modeling concept [16] provides models for large domains which can effectively be employed for mass transport in the capillary system and tissue [12], [13]. This formulation is easy for implementation since it does not require numerical homogenization or 1D capillary modeling, and it can be used for modeling mass transport within entire body organs or tumors.

The basic requirement of the smeared concept is that the transport characteristics of the system should appropriately be preserved. This means that smeared model has to be as accurate as a true 3D model and needs to have approximately the same predictions regarding drug and nutrient transport to and from tissue, which is crucial in prediction for cancer and tumor treatment. Despite the appropriate theoretical considerations presented in [16], we found that there are still differences in the overall mass transport when comparing a true 3D model and smeared model. Following this findings, the main goal of this study is to introduce a numerical technic for improving accuracy of smeared model, especially in case of common drugs which are often hydrophobic.

The main idea of improving smeared model accuracy is to introduce correction function by which the diffusion coefficients of the wall are to be multiplied, in order that evolution of concentration in the tissue domain, obtained by the smeared model, is approximately the same as when using a true 3D model.

1.1. Fundamental equations

Here, we give the basic relations used in the formulation of the Composite Smeared Finite Element (CSFE) according to [16]. Formulation of the composite finite element has been present in the FE literature, as, for example in [17,18] where beam and continuum 3D are coupled. First, the diffusive transport in tissue can be described by a differential equation, based on Fick's law and mass balance equation, [19]:

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

where D_{ij} are diffusion tensor coefficients for the coordinate directions, c is concentration and q is a source term. Then, the corresponding FE balance equation, for the equilibrium iteration i is [12,19]

$$\left(\frac{1}{\Delta t} \mathbf{M} + \mathbf{K} \right)^{(i-1)} \Delta \mathbf{C}^{(i)} = \mathbf{Q}^{ext} + \mathbf{Q}^V - \frac{1}{\Delta t} \mathbf{M}^{(i-1)} (\mathbf{C}^{(i-1)} - \mathbf{C}^t) - \mathbf{K}^{(i-1)} \mathbf{C}^{(i-1)} \quad (2)$$

where $\mathbf{C}$ is the nodal concentration vector ($\mathbf{C}^t$ corresponds to start of time step t), $\mathbf{Q}_c^{ext}$ is the external flux; and “mass” matrix $\mathbf{M}$, diffusion matrix $\mathbf{K}$ and the source vector $\mathbf{Q}^V$ (evaluated at end of time step), are

$$\begin{aligned} M_{IJ} &= \int_V N_I N_J dV \\ K_{IJ} &= \int_V D_{ij} N_{I,i} N_{J,j} dV \\ Q_I^V &= \int_L N_I q dL \end{aligned} \quad (3)$$

1.2 Formulation of the Composite Smeared Finite Element (CSFE)

The CSFE contains two domains, capillary and tissue domain, Fig 1. Diffusive transport within capillary domain consists of (approximated) 1D diffusion in the capillary net, which can be transformed into a continuum form by formulating a diffusion tensor,

$$D_{ij} = \frac{1}{A_{tot}} \sum_K D_{capK} A_K \ell_{Ki} \ell_{Kj} \quad (4)$$

where D_{capK} is capillary diffusion coefficient, A_K is capillary internal cross-sectional area, A_{tot} is total cross-sectional area as sum of A_K , and ℓ_{Ki} , ℓ_{Kj} are directional cosines of the capillary axis with respect to the coordinate axes i and j . Then, diffusion within elementary capillary domain volume $dV_{cap} = r_v dV$ occurs according to equation (1), where r_v is the capillary volumetric fraction, or capillary density, and dV is the total elementary volume of continuum. Diffusion within tissue domain is governed by equation (1), with the corresponding tissue diffusion tensor, and within the volume $(1-r_v)dV$.

Diffusion through capillary wall can be considered as a 1D process. Graphical interpretation of capillary is shown in Fig. 2.

Elementary area of the internal surface of the wall dA_{cap} can be related to the elementary volume dV_{cap} ; further dV_{cap} can be related to the elementary total volume dV , so finally we have:

$$dA_{cap} = r_{AV}dV_{cap} = r_{AV}r_VdV \quad (5)$$

where r_{AV} is the surface ratio (capillary wall area-to-volume ratio, for a single straight capillary $r_{AV} = 4/d_{cap}$).

The mass concentration can be considered as linearly distributed through the wall thickness (acceptable for thin capillary walls). Then, the flux dQ_w , corresponding to the elementary surface dA_{cap} through the wall at point 2, can be expressed as

$$dQ_w = -K_{21}C_{sys} - \frac{1}{\Delta t}M_{21}(C - C^t)_{sys} - K_{22}C_{tissue} - \frac{1}{\Delta t}M_{22}(C - C^t)_{tissue} \quad (6)$$

where $C_{sys}, C_{sys}^t, C_{tissue}, C_{tissue}^t$ are the systemic (capillary) and tissue concentrations at the end and start of time step, respectively; both matrices M_{ij} and K_{ij} are specified in [16]. As a result, we have a tissue continuum within which capillaries are distributed and are producing the source of the mass according to (6). Therefore, the nodal fluxes of a continuum finite element are

$$Q_{wI} = \int_V N_I dQ_w = \int_V N_I(\dots)(1 - r_V)dV \quad (7)$$

where terms within the parenthesis (...) follow from (6), and N_I are the continuum interpolation functions of the element with the volume V . When evaluating the integral (7), concentration C_{tissue} is the current concentration within tissue at an integration point.

For hydrophobic drugs it is important to take partitioning effect into account. In case when partitioning phenomenon is present at the wall surfaces, the elementary mass flux can be expressed as [16]

$$dQ_w = r_{AV}r_V \left[D_{wall}(P_1C_{sys} - P_2C_{tissue}) - \frac{hP}{6\Delta t}(P_1C - C^t)_{sys} - \frac{h}{3\Delta t}(P_2C - C^t)_{tissue} \right] dV \quad (8)$$

where P_1 and P_2 are the partitioning coefficients at the internal and external capillary wall surfaces.

Instead of using source terms at FE integration points, fictitious connectivity elements can be assigned at each continuum node (Fig. 2). Then, the balance equation for the connectivity element at continuum node I can be written as

$$\left(\frac{1}{\Delta t}M_{22} + K_{22}\right)P_2\Delta C_I = -\left(K_{21} + \frac{1}{\Delta t}M_{21}\right)P_1C_{sys} - \left(\frac{1}{\Delta t}M_{22} + K_{22}\right)P_2C_I \quad (9)$$

$$+ \frac{1}{\Delta t}M_{21}C_{sys}^t + \frac{1}{\Delta t}M_{22}C_I^t$$

where

$$M_{22} = \frac{1}{3}A_{capI}h_I, \quad M_{21} = \frac{1}{6}A_{capI}h_I \quad (10)$$

$$K_{22} = -K_{21} = A_{capI}D_{(wall)I}$$

and C_I are C_I^t concentrations at node I at end and start of time step, respectively. Also, P_1 and P_2 are partitioning coefficients as in (8); $D_{(wall)I}$ is the wall diffusion coefficient, h_I is the wall thickness at node I , and A_{capI} is the wall surface area belonging to the node I , which is

$$A_{capI} = (r_{AV}r_V)_I V_I \quad (11)$$

with $(r_V)_I$ and $(r_{AV})_I$ and V_I being the volumetric ratio, the area coefficient and the volume of the continuum which belongs to the node, respectively. The volume V_I can numerically be evaluated as

$$V_I = \sum_{elements} \int_V N_I dV \quad (12)$$

where summation includes all elements containing the node I . The parameters of the model, assigned to each continuum node I include geometrical data (the volumetric ratio of capillaries $(r_V)_I$, the surface ratio $(r_{AV})_I$, the wall thickness $(\delta)_I$; and material data of capillaries consisting of wall diffusion coefficient $(D_{wall})_I$ and partition coefficients P_{1I} and P_{2I} at the capillary surfaces (additional details given in [16]).

We note here that partitioning is usually present at the (blood plasma) – (internal wall surface) interface, while at the interface between the external wall surface and tissue can be discarded; hence in further presentation we take that $P_2=0$, and use parameter P for P_1 .

2. Accuracy of the smeared model

Before specifying our concept of improving accuracy of the smeared models, we present simple examples to gain insight into the concentration distribution in tissue around capillary and then consider mass accumulation within tissue according to detailed and smeared models.

2.1 Concentration gradient in tissue around capillary

First example is shown in Fig. 3a, as a 2D diffusion within tissue with a capillary in the middle of the square domain ($100 \times 100 \mu\text{m}$) and normal to the diffusion plane. It is assumed that concentration within capillary is constant and that there is no flux at the tissue boundary. Two models are considered: detailed model (FE mesh is shown in Fig. 3a and enlarged segment shown in Fig. 3b), and smeared model given in Fig. 3c. Note that the smeared model is represented by 1D connectivity elements with prescribed concentration c_0 at nodes 1 and concentration c of tissue at nodes 2 (Fig. 3c). Since concentration at nodes 1 is the same and the tissue domain is isolated, there is no lateral diffusion in tissue, and the resulting concentration field in tissue will be uniform (Fig. 4). Therefore, the smeared model can be represented by two 1D elements: connectivity element 1-2 with the cross-section A_{wall} of the capillary and diffusion coefficient D_{wall} ; and another 1D element 2-3, with cross-section of the entire tissue and diffusion coefficient D_{tissue} .

Parameters of the model which are varied are the wall thickness δ and diffusion coefficient in tissue D_{tissue} , while diffusion coefficient $D_{\text{wall}} = 10 \mu\text{m}^2/\text{s}$, capillary diameter $d_{\text{cap}} = 36 \mu\text{m}$ and model size $L=100 \mu\text{m}$ are kept constant. Hence, the volume fraction of the smeared model $r_V = 10.1\%$ is constant.

Concentration distributions along x-axis (Fig. 3) for wall thicknesses 0.9 and $3.6 \mu\text{m}$, hence for δ/d_{cap} ratios 0.025 and 0.10; and for four ratios of $D_{\text{tissue}}/D_{\text{wall}}$ and three times, are shown in Fig. 4. It can be seen that concentration profiles, as well as constant values predicted by smeared models, depend on the ratios δ/d_{cap} and $D_{\text{tissue}}/D_{\text{wall}}$.

By dashed line within Fig. 4 we denoted concentration in the corresponding smeared models. It can be seen that concentration field in smeared model is uniform and doesn't depend on diffusion coefficient change in tissue domain (smeared model produces same concentration change for any $D_{\text{tissue}}/D_{\text{wall}}$ ratio in range $[0.1, 1000]$).

In the second example, which is analogous with the previous one, we use two parallel capillaries in the square domain $100 \times 100 \mu\text{m}$ (Fig. 5). The following cases are considered:

- a. $r_V = 2.04\%$ ($D_{\text{tissue}}/D_{\text{wall}} = 1$, $D_{\text{cap}} = 18 \mu\text{m}$, $\delta = 0.9 \mu\text{m}$)
- b. $r_V = 8.18\%$ ($D_{\text{tissue}}/D_{\text{wall}} = 1$, $D_{\text{cap}} = 36 \mu\text{m}$, $\delta = 1.8 \mu\text{m}$)
- c. $r_V = 8.18\%$ ($D_{\text{tissue}}/D_{\text{wall}} = 10$, $D_{\text{cap}} = 36 \mu\text{m}$, $\delta = 1.8 \mu\text{m}$)

As expected, solutions obtained by smeared model are different when compared with the true model. The difference comes from the fact that the smeared model cannot capture the concentration gradients in the vicinity of the capillaries, which represents the foundation for explaining this difference. The difference depends on the model parameters which will be explored below.

It is interesting to note, according to diagrams in Fig. 5b and 5c, that for two different values of D_{tissue} , concentration field in smeared model remains the same. But, the solutions obtained by true model are different, therefore, the difference between smeared and true model depends on the difference between D_{tissue} and D_{wall} , or the ratio $D_{\text{tissue}}/D_{\text{wall}}$.

2.2 Evolution of concentration in tissue surrounding a capillary

The main goal of introducing correction factors (resulting in formulation of a correction function) is to predict the same concentration evolution within tissue using true and smeared model. Following that goal, we determine mass accumulation (expressed by mean concentration) within tissue, in case of a model shown above in Fig. 5. Concentration in capillary is $C_{sys}=1.0$ M, the domain size is $1\text{ }\mu\text{m} \times 1\text{ }\mu\text{m}$, $d_{cap}=0.24\text{ }\mu\text{m}$, hence the capillary volumetric fraction is 18.3%; $D_{wall}=10\text{ }\mu\text{m}^2/\text{s}$. We selected the values of D_{tissue} : 10 and $1000\text{ }\mu\text{m}^2/\text{s}$; and values for δ : 0.012, 0.024 and $0.048\text{ }\mu\text{m}$. Time step of the simulation was 0.04s, and number of time steps was 20.

The evolution of the mean concentration in the tissue domain is shown in Fig. 6 (middle and bottom panels), for the true and smeared domain. It can be seen from Fig. 6, by comparing mean concentration change in smeared model for either $D_{tissue}=10$ (middle panel) and $1000\text{ }\mu\text{m}^2/\text{s}$ (bottom panel), that the evolution of the mean concentration in tissue is not affected by the diffusion coefficient D_{tissue} ; this is in accordance with the above statement related to Fig. 5. However, differences between the smeared and true model depend on the D_{tissue}/D_{wall} , hence this ratio can be taken as one of the parameters for corrections in the smeared model. Also, differences are dependent on the ratio δ/d_{cap} , hence this ratio will be taken as the other parameter for the correction function. The third parameter for correction is the capillary volume fraction r_V (results not shown here). The results show that when increasing volume fraction, differences between smeared and true model are linearly increasing.

3. Numerical determination of the correction function

According to the presented results (and others not shown here), there can be notable differences in mass release from capillaries to tissue when compared true and smeared models. We here introduce a numerical procedure in order to find a table of correction factors, or correction functions, by which we will multiply the capillary wall diffusion coefficient D_{wall} to obtain the same mass exchange between capillaries and tissue for true and smeared models. As a result, we generate a table (or field of correction factors) in terms of the following parameters:

- volume fraction r_V of the model,
- ratio of diffusion coefficients in wall and tissue D_{tissue}/D_{wall} , and
- ratio of capillary wall thickness and diameter δ/d_{cap} .

3.1 Model with local isotropy

We now introduce the conditions for the models to be used for numerical evaluation of correction function under general 3D diffusive transport in the capillary-tissue systems. Consider a common tumor capillary geometry (Fig. 7a) and also a reference volume of tumor tissue, Fig. 7b. Some of possible representative capillary configurations are shown in Figs. 7c–7e. We will investigate accuracy of the smeared model by computing mass transport from capillary system to tissue within reference volumes, using detailed 3D and smeared models. If the smeared model gives accurate results for any of those reference volumes, then the CSFE can be used for any tissue domain.

We assume general isotropic 3D conditions at a given spatial point, within a cubic reference volume (RV) as in Fig. 6d, with dimension of the cube L . This will be our basic model of local isotropy, with details shown in Fig. 8a. Then the following relation is applicable:

$$r_V = \frac{3d_{cap}^2 L \pi}{4L^3} = \frac{3}{4} \pi \frac{d_{cap}^2}{L^2} \quad (13)$$

This equation determines the size of the reference volume L in terms of capillary density (r_V) and diameter (d_{cap}). All other cases will be referred relative to this model, which therefore is considered as the reference model. We further assume local homogeneity, hence the capillary structure is the same within each reference volume surrounding the considered RV, Fig. 8b.

3.2 Numerical procedure for determination of correction function

In the numerical procedure, we changed diffusion coefficient in tissue and the ratio D_{tissue}/D_{wall} in range [0.1 ... 1000]. Four models are generated with different volume fraction of capillaries: 0.03, 1.1, 2.5, 4.5, and 10% (corresponds to vessels with 0.02, 0.12, 0.103, 0.138 and 0.206 μm in diameter), shown in Fig. 9. For each of these cases we used three ratios δ/d_{cap} : 0.025, 0.05 and 0.1.

In order to achieve that results of the smeared model are the same (the same evolution of the mean concentration in tissue) as for true 3D model, we explored the field of correction factors which depends on the three parameters listed above. Then, diffusion coefficient within the capillary wall, $D_{wall}^{smeared}$, used in 1D connectivity (fictitious) element of smeared model, is calculated as:

$$D_{wall}^{smeared} = c_f(\delta/d_{cap}, D_{tissue}/D_{wall}, r_V) \cdot D_{wall}^{true} \quad (14)$$

where: D_{wall}^{true} diffusion coefficient in capillary wall of true model, and c_f is the correction function. Correction function c_f is evaluated assuming that partitioning coefficient is $P=1$. Correction function in plane D_{tissue}/D_{wall} - c_f is given in Figs. 10a,b,c, while a 3D representation is shown in Fig. 10d.

Following Fig. 10, correction function can be also expressed as function of δ/d_{cap} ratio and r_V . This is presented in Figs. 11 and 12.

3.3 Dependence of correction function on domain size

We also generated few models with different dimensions, in order to investigate effect of the domains size on field of correction functions. We generated four 2D square shape domains of: $a = 10, 20, 50$ and $100 \mu m$, while keeping constant volume fraction $r_V = 10\%$. For each domain we used capillaries of $d_{cap} = 3.6, 7.2, 18$ and $36 \mu m$.

When calculating mean concentration change in each of these domains, we found that the only difference between the cases with selected domain sizes is in total time T needed for the whole mass to fill the diffusion domain, which is proportional to length of domain: $T_{10} = t_0$, $T_{20} = 2^2 \times t_0$, $T_{50} = 5^2 \times t_0$, and $T_{100} = 10^2 \times t_0$. Therefore, we can conclude that the field of correction function is independent on domain size.

3.4 Correlation between correction functions of 3D and 2D reference domains

Here we investigate the relations between the correction functions for models given in Fig. 7c (2D model) and the basic model (3D isotropic conditions) – Fig. 7d. We compared the correction functions, and tracked deviations in the diagrams $c_f (D_{\text{tissue}}/D_{\text{wall}})$, for various values of r_V , by changing d_{cap} . Correction functions for $d_{\text{cap}} = 20.7 \mu\text{m}$ and $r_V = 10.1\%$, are shown in Fig. 13a, while for case with $r_V = 2.1\%$ results are shown at Fig. 13b.

Since the differences in correction functions between 2D and 3D models are small (less than 5% for usual physiological conditions) we can adopt that correction function of the basic model (3D model with local isotropy) can also be used for 2D models.

4. Effects of partitioning on correction functions

A phenomenon called hydrophobicity may be important in diffusion through biological system. Majority of drugs are hydrophobic substances, meaning that those chemical compounds prefer the organic phase over water [20]. The simplest way to express partitioning phenomena in molecular transport is to take that, within a time step, the ratio between numbers of molecules passing the boundary between two media [11],

$$\Delta N_s / \Delta N_f = P \quad (15)$$

where N_s and N_f are the numbers at solid and fluid side, respectively. We will further use, for a convenience of implementation, a reverse value

$$p = 1/P \quad (16)$$

Instead of the ratio of number of molecules we can relate increments of concentration (and concentrations) at the common point in solid and fluid, C_s and C_f as

$$\Delta C_f = p \Delta C_s, \quad C_f = p C_s \quad (17)$$

We have formulated a numerical concept within the FE method by the appropriate factorization of the nodal values of concentration increments and terms of diffusion FE matrices; details are given in [11].

For the purpose of investigating partitioning effect on correction function, we used the same examples as in Section 3 (Fig. 6), with volume fraction of 10.1% and with partitioning at the

lumen- (tissue wall) interface, Fig. 14a. Field of concentration for cases with $P = 0.01, 0.1, 1, 10$ and 100 are presented in Fig. 14b (lower panel), while evolution of the mean concentration (or mass release curves) in tissue is shown in Fig. 15a. The mass accumulation curves are the same when using the true and smeared model (with parameters $D_{\text{tissue}}/D_{\text{wall}} = 1, r_V = 0.1, \delta/d_{\text{cap}} = 0.05$) with the correction function according to the basic model.

The mass release curves are affected by the partitioning coefficient P . However, the normalized curve shown in Fig. 15b, obtained as c/c_{final} , where c_{final} is the ultimate mean concentration, is the same for all values of the partitioning coefficients.

It can be concluded that the correction function obtained for the basic model is applicable to diffusion in case of partitioning at the capillary wall – blood plasma interface.

5 Applicability of correction function to general conditions and practical aspects of application to smeared computational models of diffusion

In the previous section we introduced and evaluated correction function c_f in terms of three parameters ($\delta/d_{\text{cap}}, D_{\text{tissue}}/D_{\text{wall}}, r_V$) to be used for multiplying the wall diffusion coefficient according to the relation (14). Here, we present some practical aspects of use of the scaling functions and implement that concept to general cases, including complex branching, unsteady diffusion, tissue with a number of capillaries and cells; and, finally, a simplified model of pancreatic tumor.

5.1 Practical aspects of application of correction functions in smeared models

Table of the correction function values, in form of a 3D matrix graphically displayed in Fig. 16a, is implemented in our CAD software for pre-processing and used for various calculations. Table consists of discrete values of correction factors within certain ranges of the three parameters, which can be expressed in the form:

$$c_f^{ijk} = c_f((\delta/d_{\text{cap}})^i, (D_{\text{tissue}}/D_{\text{wall}})^j, r_V^k) \quad (18)$$

For example, we have determined the discrete values within the following ranges of parameters: $r_V = \{0.03, 1.1, 2.5, 4.5, 10.0\}$, $D_{\text{tissue}}/D_{\text{wall}} = \{0.1, 1, 2, 5, 10, 50, 100, 200, 500, 1000\}$ and $\delta/d_{\text{cap}} = \{0.025, 0.050, 0.10\}$. Then, for a given values of r_V , $D_{\text{tissue}}/D_{\text{wall}}$ and δ/d_{cap} we perform numerical interpolation to calculate the corresponding correction factor. For easier implementation, we normalize parameters by the maximum values, hence the ranges become $[0,1]$, and map the table (3D domain in Fig. 16a) to the unit cube (Fig. 16b).

Interpolation for correction factors (values of the correction function) is performed as follows. We first find at most 8 points from table of correction factors, which are closest to point A, denoted as B_i in Fig. 16b. Distances between point A and points $B_1, B_2, B_3, \dots, B_n$ are denoted as $L_1, L_2, L_3, \dots, L_n$. We first calculate coefficients $\bar{c}_i$ as:

$$\bar{c}_1 = \frac{L_1}{L}, \bar{c}_2 = \frac{L_2}{L}, \bar{c}_3 = \frac{L_3}{L}, \dots, \bar{c}_n = \frac{L_n}{L} \quad (19)$$

where

$$L = L_1 + L_2 + \dots + L_n, \quad (20)$$

further calculate coefficient $\bar{a}$,

$$\bar{a} = \frac{1}{\bar{c}_1} + \frac{1}{\bar{c}_2} + \frac{1}{\bar{c}_3} \dots + \frac{1}{\bar{c}_n} \quad (21)$$

and finally determine the interpolation coefficients:

$$c_1 = \frac{1}{\bar{c}_1 \bar{a}}, c_2 = \frac{1}{\bar{c}_2 \bar{a}}, c_3 = \frac{1}{\bar{c}_3 \bar{a}}, \dots, c_n = \frac{1}{\bar{c}_n \bar{a}} \quad (22)$$

Note that the following relation is fulfilled:

$$c_1 + c_2 + c_3 + \dots + c_n = 1 \quad (23)$$

Using this interpolation coefficients $c_1, c_2, c_3, \dots, c_n$ we can calculate the resulting correction factor in the point A as

$$c_f^A = \sum_K c_K c_f^K \quad (24)$$

where c_K is the interpolation coefficient for a point B_K and c_f^K is the correction function at point B_K of the table. It can be noted that the interpolation coefficients (22) provide interpolation where contribution of a given value c_f^K to the c_f^A is inversely proportional to the “distance” L_K between points A and B_K . Calculated value is then used in the form of equation (14) to determine the corresponding value of the wall diffusion coefficient for the smeared model. In the examples below we will show that this corrected wall diffusion coefficient provides adequate accuracy of the smeared model.

5.2 Applicability of correction function to general case of capillary network

In reality, capillary-tissue system in any tissue, and particularly in tumors, has very irregular and complex capillary network with large number of branching. Models with complex capillary branching are schematically shown in Fig. 17.

Here, we used a model shown in Fig. 17a – the first case from the left, and calculated mean concentration within the tissue by employing the true model (Fig. 17b) and smeared model with the above described correction function values. Mean concentration evolution within tissue is shown in Fig. 17c. It can be seen that the smeared model, with use of the CSFE finite element and the established correction function, is applicable to general case of capillary branching.

5.3 Application to unsteady conditions

For this purpose we used the basic model shown in Fig. 8, with concentration C_{sys} in the capillary varying with time. The following data are used:

- $\delta/d_{cap} = 0.05$, $\delta = 1.8 \mu\text{m}$, $d_{cap} = 36 \mu\text{m}$
- Domain $100 \times 100 \mu\text{m}$, volume fraction 10%.
- $D_{tissue}/D_{wall} = 1$, $D_{wall} = D_{tissue} = 10 \mu\text{m}^2/\text{s}$

Three different cases $C_{sys}(t)$ were investigated: linearly increasing (Fig. 18a), linearly decreasing (Fig. 18b), and a bolus-type (Fig. 18c).

As can be seen from the diagrams, use of the correction function provides accurate results in all three cases of $C_{sys}(t)$. It can be also seen that when using smeared model without correction function (Smeared – No CF) results obtained by smeared model are quite different from those obtained using the true model.

5.4 Diffusion transport in 2D tissue with cells and capillaries

Here we have a 2D tissue model, reconstructed from images, which consists of 8 capillaries (denoted as $C_1 \dots C_8$), 352 cells, and extracellular space (Fig. 19). Assumption is that diffusion coefficient of drug is different within cells and extracellular space, and partitioning is not present at (extracellular space)/(cell membrane) interface. It is assumed that concentration inside capillaries is constant over time.

Based on number of capillaries and their geometric properties of the true model, we calculated volumetric fraction of capillaries, average diameter and average capillary wall thickness – which are inputs to our smeared model. Smeared model is represented as a homogenous continuum with isolated boundaries, with prescribed concentration in capillaries, and with appropriate diffusion coefficients for the capillary and tissue domain.

The following data are used:

Data used for true and smeared model:

Systemic concentration in capillaries:	$C_{sys} = 0.02 \text{ M}$:
Diffusion coefficient in capillary and cell wall:	$D_{wall} = 100 \mu\text{m}^2/\text{s}$
Diffusion coefficient in tissue:	$D_{tissue} = 100$, and $10000 \mu\text{m}^2/\text{s}$
Diffusion coefficient in cells:	$D_{cell} = 0.1 \times D_{tissue}$
Time interval:	$20 \times 0.5\text{s}$ and $20 \times 0.1 \text{ s}$

Data for Smeared Model:

Total area:	$6087.68 \mu\text{m}^2$
Capillary domain area:	$112.65 \mu\text{m}^2$

Volume fraction of capillary domain:	0.0185
Thickness of capillary wall:	0.6 μm
Mean diameter of capillary:	3.87 μm

Since diffusion coefficients in cells and extracellular space are different, we calculated equivalent diffusion coefficient in tissue domain by using numerical homogenization procedure [21]. We found that equivalent diffusion coefficient in tissue domain is $D_{\text{eqv}} = 0.418 \times D_{\text{tissue}}$. Correction function for smeared model is evaluated according to the $D_{\text{eqv}}/D_{\text{wall}}$ ratio.

We analyzed two cases: without partitioning ($P=1$) and with partitioning ($P=10$) at lumen/wall border. The field of concentration for true models with ($D_{\text{tissue}} = 100$, $D_{\text{cell}} = 10 \mu\text{m}^2/\text{s}$) and ($D_{\text{tissue}} = 10000$, $D_{\text{cell}} = 1000 \mu\text{m}^2/\text{s}$) are given in Figs. 19a and Fig. 19b, respectively. For given time interval, we calculated accumulated mass in tissue (both cell and extracellular space), represented by mean concentration vs. time diagram. It can be seen from Figs. 19c,d that mean concentration change using smeared model, with implementation of the correction function, is approximately the same as for the corresponding true model.

5.5 Iodine transport in human pancreatic tumor based on clinical

One of the main goals in modeling of drug transport in medicine is to understand how transport properties of tissues and drugs affect the delivery of therapeutics deep into tissues to reach pathological cells, e.g. tumors, in order to make clinical decisions. Here we used human data and model a realistic transport problem of iodine molecules which are employed in clinical imaging studies to differentiate tumors from normal tissues based on their respective transport properties [22]. We created a CSFE simplified model of tumor as a sphere embedded in pancreatic tissue, and calculated biodistribution kinetics of iodine within pancreas and tumor (Fig. 20a). The smeared model was executed with and without using the developed correction functions. The model consists of tumor (a sphere of 200 μm in diameter) embedded into tissue (cube of 400 μm); due to its symmetry, only 1/8 of the entire space is shown and used in the model. The nominal parameters for tissue and tumor are: capillary internal diameter is 10 μm , capillary wall thickness is 1 μm , and diffusion coefficient of capillary wall is 400 $\mu\text{m}^2/\text{s}$ in both tumor and tissue. As measured from biopsies, volume fraction of capillaries in tumor is $r_V = 0.099$, and in surrounding tissue r_V is 0.025.

Diffusion coefficient in tumor and surrounding tissue domain, and partitioning coefficient at lumen/wall interface are selected as variable parameters which have to be estimated in order to match experimental data. Experimental data of iodine signal from Computer Tomography (CT) imaging is shown in Figs. 20b,c by the curve $C_{\text{sys}}(t)$ (systemic concentration, used through input data for the model), as given iodine concentration in capillaries in both surrounding tissue and tumor domain of the computational model. Experimental results to be matched by the FE simulation are given in Table 1.

Using the CSFE model with partitioning included at lumen/wall border, we estimated that the numerical curve will approximately have the same values as measured at two time points (Table 1), if we use parameters given in Table 2.

It can be seen that there are differences in results for tissue concentration profile when correction function is used with respect to the case without this function, for both tissue and tumor domain.

6. Conclusions

The goal of this study was to investigate accuracy of our recently introduced smeared finite element modeling concept [16]. The capillary network is replaced by a smeared continuum representation which mainly cannot capture detailed non-uniform pressure and concentration field within tissue, in the vicinity of capillaries. Although the corresponding Darcy's and diffusion tensors are correctly derived, due to the mentioned characteristic of the smeared model, there is a difference between the true (3D continuum FE models of capillaries and tissue) and smeared model results. Here, we introduced correction function for multiplying the wall diffusion coefficient in order to have that results of the smeared model agree with those of the true model.

The correction function is determined numerically in terms of three parameters, which were found to be relevant: capillary volumetric ratio, ratio between wall thickness and capillary diameter, and ratio of diffusion coefficients of tissue and wall. The correction function of these three parameters is evaluated on the reference 3D model assuming local isotropy. Validity of the established correction function is further tested on 2D examples, 3D complex branching, unsteady conditions and simplified model of tissue with capillaries and cells. Also, applicability of the correction function to a case with partitioning (at capillary wall – blood interface) is demonstrated, which is common for various hydrophobic drugs that are recently highly used in cancer treatment. Finally, an example of simplified pancreatic tumor is modeled to match clinical human data.

This computational methodology is implemented into our FE code PAK [23] - research code developed over decades, which has been verified and also used in research and in industrial applications.

The presented procedure for calculation of the correction function of the wall diffusion coefficient improves accuracy of the smeared model and offers a possibility of reliable modeling of heterogeneous properties of the capillary-tissue domain, as they are in real biological systems.

The smeared concept offers a robust methodology which is suitable for numerous laboratory and clinical applications, since experimental and imaging data can be directly connected to the model generators. These generators could further be adapted to parametric generations of “virtual” representations of large domains such as organs or tumors. With a sufficient number of simulations it would be possible to validate the model and to establish a patient-specific database for practical use.

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Fig. 1. Composite smeared finite element (CSFE). Capillary and tissue domain and connectivity element at node I . Elementary volumes are dV_{cap} and dV_{tissue} within each domain.

Fig. 2. Diffusion from capillary to tissue through elementary capillary wall surface dA_{cap} which corresponds to the capillary volume dV_{cap} and total volume dV .

Fig. 3.

Detailed and smeared 2D model with no flux at the boundary. a) Capillary with concentration C_0 and surrounding tissue discretized by continuum FEs; b) Enlarged area of detailed model; c) Smeared model representation of 1D diffusion between points 1 and 2 through the wall area A_{eff} belonging to the connectivity element.

Fig. 4.

Concentration along x -axis in true model for different D_{tissue}/D_{wall} ratios. Case with $r_V = 10.1\%$, and $\delta/D = 0.025$ (a) and 0.10 (b). D is D_{wall} , $D_{tissue} = c_f D_{wall}$, and c_f is in range $[0.1, 1000]$ is D_{tissue} . Results for three time steps of simulation ($t = 20, 40$ and $60s$).

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Fig. 6.

2D capillary model with volume fraction $r_V = 18\%$ ($d_{cap} = 0.24 \mu m$). Mean concentration vs. time in the 2D tissue domain obtained by true and the corresponding smeared model, for two diffusion coefficients in tissue: 10 (middle panel) and $1000 \mu m^2/s$ (bottom panel), and for three wall thicknesses: a) $\delta=0.012\mu m$, b) $\delta=0.024\mu m$ and c) $\delta=0.048\mu m$.

Fig. 7. Capillary bed geometry of cancerous tissue, (a) and (b), according to [6] and [7]. Simplified configurations of reference volume, (c), (d) and (e), to approximate complex capillary networks within tissue.

Fig. 8.

a) Isotropic 3D conditions for capillary network. b) Local isotropic and homogeneity conditions

Fig. 9.
3D capillary/tissue models with local isotropy, with different volume fractions in (%): 0.03, 1.1, 2.5, 4.5 and 10.

Fig. 10.

Correction function (c_f) for diffusion coefficient in capillary wall of smeared model – dependence on $D_{\text{tissue}}/D_{\text{wall}}$ ratio, for models with different volume fractions (r_v) of capillaries: 0.03, 1.1, 2.5, 4.5, and 10%, for: a) $\delta/d_{\text{cap}} = 0.1$, b) $\delta/d_{\text{cap}} = 0.05$, c) $\delta/d_{\text{cap}} = 0.025$; d) 3D representation of correction function

Fig. 11.

Dependence of correction function on the δ/d_{cap} ratio for different δ/d_{cap} and D_{tissue}/D_{wall} ratio, for $rV=10, 4.5$ and 0.03%

Fig. 12.

Dependence of correction function on the volume fraction r_v for different δ/d_{cap} and $D_{\text{tissue}}/D_{\text{wall}}$ ratio

Fig. 13.

Correction function (c_f) vs. $D_{\text{tissue}}/D_{\text{wall}}$ diagram for 2D and 3D models, for three values of δ/d_{cap} . Model with $d = 20 \mu\text{m}$, $r_v = 10.1\%$ (upper panel) and 2.1% (lower panel),

Fig. 14.

Concentration field at $t = 0.4s$ (end of first time step) in case of capillary with partitioning at the internal capillary wall surface. a) Enlarged zone around capillary; case with $P = 100$ at lumen/wall interface; b) Concentration field for different values of partitioning at lumen/wall border ($P = 0.01, 0.1, 1, 10, 100$)

Fig. 15.

a) Concentration vs. Time for 5 different values of partitioning at Lumen/Wall boundary ($P = 0.01, 0.1, 1, 10, 100$); b) Normalized $[c/c_{\text{final}}]$ vs. Time curve.

Fig. 16.

Evaluation of correction factor from table of discrete values, a) Geometrical interpretation in the 3D parametric space (r_v , $D_{\text{tissue}}/D_{\text{wall}}$, δ/d_{cap}) of the table of correction factors calculated using the basic 3D model (Fig. 8a); b) Reference domain used in the interpolation procedure for calculation of the correction factor.

Fig. 17.

Model with complex capillary branching; $r_V = 6.767\%$, diameter $d_{\text{cap}} = 10 \mu\text{m}$, and $r_{AV} = 37.072$. a) Schematics of complex capillary network in a reference volume (RV); b) Field of concentration at $t = 10$ s, 3D (true) model; c) Concentration vs. time diagrams for true and smeared model of the complex capillary branching. Dashed line corresponds to solution without use of correction function (No CF).

Fig. 18.

Mean concentration vs. Time for a) linearly increasing $C_{sys}(t)$ in capillary, b) linearly decreasing $C_{sys}(t)$ and c) real nonlinear $C_{sys}(t)$ in capillary. Cases with $D_{tissue}/D_{wall} = 10$ ($D = D_{tissue} = 100$), 1 ($D = 10$), and 0.1 ($D = 1$)

Fig. 19.

Field of concentration for true model with $P = 1$ and $P = 10$, and with a) $D_{tissue} = 100$, $D_{cell} = 10$, and b) $D_{tissue} = 10000$, $D_{cell} = 1000$, after $t = 0.1s$. Concentration vs. time diagram for smeared and true model, for $D_{eqv} = 41.8$ (c) and 418 (d); Diffusion coefficients are in $[\mu m^2/s]$.

Fig. 20.

Spherical tumor within pancreatic tissue. a) Domain used in the FE model ; b) and c) Iodine mean concentration profiles within tumor and surrounding tissue obtained by fitting model parameters to match experimental data of a patient; solutions for case with no partitioning ($P=1$) and for the fitted value $P=0.453$. Concentration profiles within tissue obtained with and without correction function (CF) are shown to emphasize the effect of CF.

Table 1

Experimental values of concentration in pancreas and tumor for two time moments

Time[s]	C _{pancreas} [M]	C _{tumor} [M]
9	117	85
38	26	32

Table 2

Evaluated parameters for diffusion and partitioning coefficients in pancreas and tumor domains

	Pancreas tissue	Tumor
D_{tiss} [$\mu\text{m}^2/\text{s}$]	20	60
P	0.453	0.05