Validation of a spatial-time concentration gradients estimation by the superposition of sphere sources diffusion fields using the finite element method

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Abstract. A convectional reaction-diffusion is the main process causing a stable distribution of nutrients in biological objects. Indeed, the boundary problems for PDE are always used to describe this phenomenon. The spatial structure of biological objects is usually complex and non-uniform. Therefore, the creation of a digital phantom where gradients will be estimated becomes an especial procedure taking both a computational time and the resources. Recently, a simplified method of time dependent concentration gradient evaluation has been introduced. It represents the final spatial-time distribution as a superposition of the sphere sources diffusion fields. Using such an approximation, one can avoid preliminary reconstruction of digital mech-objects simulating a biological structure. In the present study the introduced approach is validated using the finite element method (FEM). It was shown that the exactness of coincidence is determined by the reciprocal distance of the sources and the scale of the considered area. The symmetry of a mutual boundary position plays an essential part in a validation conformity. A sphere sources formed field differs from the finite element method estimation on 7% under the most appropriate conditions. Other possible applications of the introduced approach to concentration gradient modelling in biological objects are discussed.

1. Introduction
A spatial-time distribution of different chemical compounds may be considered as an essential part of the fundamental background for living systems. The experimental evidence of a concentration gradients significance covers a wild range of a scientific research area from a bacterial chemotaxis to a fluid supply of neuromediators in a human brain. Moreover, diffusion analysis provides a unique window onto a domain that has been largely inaccessible experimentally [1]. The evaluation of concentration changes in time and space is usually made by computational calculations using PDE boundary problems. For this purpose, the finite elements method (FEM) is usually applied.

One the main problem which is used for a spatial-time concentration distribution modelling is the case of PDE with fixed concentration at the border. If the shape of the border is performed as a sphere, and the consumption rate is linear the summands in a diffusion equation can be simplified using a symmetry of the coordinates:
\[
\frac{\partial X(r,t)}{\partial t} = -k \cdot X(r,t) + D \left( \frac{\partial^2 X(r,t)}{\partial r^2} + \frac{2}{r} \frac{\partial X(r,t)}{\partial r} \right)
\]

(1)

\[
X(r,t) \big|_{r=0} = X_0; \quad \lim_{r \to +\infty} X(r,t) = 0; \quad X(r,0) = 0; \quad r_0 < r < +\infty; \quad 0 < t < +\infty;
\]

where \( D \) is a diffusion coefficient, \( k \) is a kinetic consumption constant. A spheric area forming the finite border in (1) can be considered as a source for the compound \( X \) in the medium. It means that the nutrient production place is indicated explicitly. A homogenous media surrounding the sphere only consumes \( X \). The production somewhere inside the sphere supplies the stable level of the nutrient on the boundary.

Another type of a special problem considers the conditions when the fluxes at the source’s borders are fixed. This description can be applied to the systems with a membrane transport with a stable steady-state activity of the carriers. Under assumptions described above, the problem is devised in the following

\[
\frac{\partial X(r,t)}{\partial t} = -k \cdot X(r,t) + D \left( \frac{\partial^2 X(r,t)}{\partial r^2} + \frac{2}{r} \frac{\partial X(r,t)}{\partial r} \right)
\]

\[
\frac{\partial X(r,t)}{\partial r} \bigg|_{r=r_0} = -Q; \quad \lim_{r \to +\infty} X(r,t) = 0; \quad X(r,0) = 0; \quad r_0 \leq r < +\infty; \quad 0 \leq t < +\infty;
\]

(2)

One should note that the flux may have both a positive and a negative sign. It means that an elemental source is able to produce and to consume the compound \( X \). The difference between the consumption at the source border and the summand in the diffusion equation is a diversification of reactions with \( X \). The area of spheres forming a definite location for the fluxes involving the nutrient. A combination of such sources makes it possible to examine a heterogeneity of a real biological object.

The advantage of the Problems (1-2) is an ability to get an analytical solution for \( X(\tilde{r},t) \). It evaluates the concentration in a distance from the center of the sphere. Furthermore, if there is a spatial distribution of spheres \( \{ \xi_i(\tilde{r}) \}_{i=1}^N \) with the fixed values of concentration( \( X_i^0 \)) or flux ( \( Q_i^0 \)) at the border, one is able to reconstruct the final gradient of \( X \) using the superposition of sphere sources diffusion fields (SSDF). For the case of the Problem (1) the design of a spatial-time concentration distribution was represented elsewhere [2]. The final \( X \) gradient for the Problem (2) is described by the expression in some point with the coordinate \( \tilde{r}_j \):

\[
X(\tilde{r}_j,t) = \sum_{i=1}^N \alpha_i(t) X_i(\tilde{r}_j - \tilde{r}_i,t)
\]

\[
\frac{\partial X_i(r,t)}{\partial r} \bigg|_{r=0} \alpha_i(t) + \sum_{s \neq i} \frac{\partial X_s(r,t)}{\partial r} \bigg|_{r=\tilde{r}_j} \alpha_s(t) = -Q_i^0
\]

(3)

\[
\alpha_i(t) = 1 - \delta(t); \quad \forall t \geq 0: \quad 0 < \delta(t) \ll 1; \quad i = 1,..,N
\]

An essential convenience of SSDF is a reduced way to get the calculated gradient after the experimental measurements (Fig.1). Having applied an Imaging Technology to the sample, one obtains the sets of coordinates with an indication of the color. After then, a digital structure must be reconstructed and imported into the solver software. The final geometry has to meet the requirements of meshes applications. Indeed, all these steps take a time and the computational resources, and they
may be unsuccessful at any operation. Due to a simplified technique of the solution reconstruction SSDF makes it possible to avoid the most 3D design steps which are usual to FEM. Nevertheless, SSDF give FEM up essentially in calculation abilities. Moreover, the second infinity condition in Problems (1-2) is a weak point. In the present study SSDF is validated by FEM, and the spatial design recommendations has been proposed to get the best coincidence between the methods.

Figure 1. A scheme of procedures to obtain a calculated spatial distribution of a chemical compound concentration based on experimental measurements.

2. The geometry of the validation area
A validation geometry area is chosen based on a minimal requirement of 3D symmetry. The radius of each source is fixed \( r_0 \). The set of spheres is limited by \( N=8 \). They are placed in the vertexes of a cube with an edge length which is equal to \( a \). The space area for SSDF calculations \( \Omega \) is determined as a cube with a side length calculated as the following:

\[
L_{\Omega} = a + (2 \cdot r_0) + (2 \cdot \delta a)
\]  

(4)

where \( \delta a \) is a geometrical parameter of the sources shifting. As it is noted above, the second assumption defining the solution of (1-2) according to SSDF is the limitation of \( X (\vec{r}, t) \) at infinity. Under such a condition one assumes that there is a physical area with a long distance from the considered phantom where the level of \( X \) is equal to zero. The position of a physical infinity for SSDF is determined by the size of an outer cube \( \Omega \) which includes \( \Omega \). The edge length is defined as the following relation in this case:

\[
L_{\infty} = \alpha_{\infty} \cdot L_{\Omega}
\]  

(5)

where \( \alpha_{\infty} \) is a scale coefficient. The example of a described system is shown in Fig.2. A validation processes is fulfilled on the set of cut-planes \( Z = \{ Z_i \}_{i=1}^{16} \) which have the fixed coordinates under the fixed \( a \). The set of physical parameters used in the modelling is shown in Table 1.
Table 1 The parameters of the models.

| Parameters | Description                | Value                                    |
|------------|----------------------------|------------------------------------------|
| D          | Diffusion coefficient      | $8.7 \cdot 10^{-10}$ [m$^2$/s]           |
| k          | Kinetic consumption constant | 0.3 [s$^{-1}$]                           |
| $X_0$      | Fixed boundary concentration | 1 [mM]                                  |
| $J_0$      | Fixed boundary flux        | $1 \cdot 10^{-6}$ [mol/(m$^2$·s)]       |
| $\delta a$ | Sources shifting           | 0.1                                      |

Figure 2. A scheme of a validation geometry area. It consists of two cubes and eight spheres. The spheres ($\xi_i$) are placed in the vertexes of the inner cube ($\Omega$), and they are symmetrically shifted inside on a value of $\delta a$ (left). The size of the outer cube ($\Omega_\infty$) depends on the inner cube edge length ($L_\Omega$). The represented drawing corresponds to $a=10$ μm; $\alpha_\infty=2$. The validation comparison is fulfilled on the set of 16 cut-planes which carve the inner cube in the perpendicular to Z-axis (right).

3. A mutual comparison of the final concentration gradients

A validation of SSDF is carried out on the base of the analysis of numerical difference between the average values of $X(\bar{r},t)$ in $Z_i$. The calculations for FEM were made using COMSOL Multiphysics version 5.5 and an original self-made software (SSDF). FEM gradients have been obtained using Extra Fine Physics-Controlled Mesh. The equations were solved for on average 89,056 (plus 543686 internal DOFs) number of degrees of freedom. The temperature is considered as a global model parameter, and it is equal to 310.15[K]. The diffusion coefficient corresponds to the same one for glucose in astrocytes and neurons at 37°C [3].

The Problems (1-2) are re-formulated according to Cartesian coordinates and the limited outer border of $\Omega_\infty$:

$$\frac{\partial X(\bar{r},t)}{\partial t} = \nabla \cdot \left( D \cdot \nabla X(\bar{r},t) \right) - k \cdot X(\bar{r},t);$$

$$X(\bar{r},t)|_{\tau=0} = 0; \quad X(\bar{r},t)|_{\bar{r} \in \Omega_\infty} = 0;$$

for (1): $X(\bar{r},t)|_{\bar{r} \in \xi_i} = X_0$, $i = 1,..,8$;

for (2): $-\vec{n} \cdot \vec{J}|_{\bar{r} \in \xi_i} = J_0$, $i = 1,..,8$;
3.1. A validation of the first boundary problem of SSDF by FEM

The results of the concentration simulations are represented in Fig.3. The solutions according to SSDF coincide with FEM qualitatively. However, if $a = r_0$, the difference between the method results is essential and it reaches the value of 25% (Fig.4). On the contrary, the case of $a \gg r_0$ yields a good accordance with numerical estimations. The difference is not higher than $\pm 8\%$ and it is really in the range of 2-4%.

![Figure 3. A spatial-time distribution of a chemical compound concentration in $\Omega$. The different cases of an initial geometry are represented. The same gradients are calculated by using SSDF (left) and FEM (right) methods. The data are represented as the average value of $X(\tilde{r}, t)$ in $\tilde{r} \in \mathbb{Z}$.](image)

The considered cases clearly show that a mutual position of the sources get a great influence on the numerical results of modelling. At the same time a general type of spatial-time concentration distribution remains identical.
Figure 4. A spatial-time distributions of SSDF/FEM difference for the first boundary problem. The represented data are calculated using the set of results which are shown in Fig.3. The difference is determined as $100 \cdot \frac{\text{SSDF} - \text{FEM}}{\text{FEM}}$.

Figure 5. A diagram of SSDF/FEM concentration difference % according to the cut-planes. The abscissa indicates the distance between the spheres ($a$, [$\mu$m]), and the ordinate corresponds to the scale coefficient $\alpha$. The data are represented for the case $X(\tilde{r}, t = 1)$. According to the symmetry of $\Omega$ the rest part of the cut-plane ($Z_{i=9...16}$) surfaces will have an identical distribution of concentration differences.

The influence of a relative $\xi_j$ position on $X(\tilde{r}, t)$ appears strongly near the sources area under an asymmetric relative location to the point of view ($Z_i$) and the short mutual positions of the centers (Fig. 5). The physical infinity length value ($L_\infty$) is insufficient in this case. However, a shifting of the viewpoint to the symmetric position causes coincidence of SSDF and FEM. Having analyzed the distributions, one can conclude that SSDF will be more correct in the points $\tilde{r}_j$ where
\[ \forall i : |\tilde{r}_j - \tilde{r}_i| = \text{const} \]. If such a condition is violated, the assumption \( L_c \gg a \) helps to improve the situation.

3.2. A validation of the second boundary problem of SSDF by FEM

A comparison of the final gradients for Problem (2) can be made in the same way. The cut-planes are the area for the averaging of X concentration gradients. The spatial-time gradients are qualitatively the same for SSDF and FIM (data not shown). The result of this validation is represented in Fig. 6.

![Figure 6. A spatial-time distributions of SSDF/FEM difference for the second boundary problem. The difference is determined by the same relation as it was done in Fig.4.](image-url)

It is remarkable that the spatial-time distribution of the concentration difference calculated by the methods is essentially various as compared to the first boundary problem. For a narrow phantom (\( a=2 \)) a variation of the concentrations near the sources does not exceed \( \pm 5\% \). It is decreased down to \(-15\%\) deeply inside \( \Omega \). However, the distribution is stable. Moreover, one can conclude that the influence of a viewpoint symmetry is opposite in comparison with the Problem (1) case. The closest to \( \xi \) points have a nearly zero variation between methods. On the contrary, the central cut-plane exhibits the most pronounce variation. If the phantom is relatively large (\( a=10 \)) the SSDF/FIM discordance is time dependent. Having passed initial fluctuations, the difference aspires to the level of 7\%. Thus, the application of Problem (2) of SSDF seems to be more uniform and stable.

4. Discussion

FEM is very successful to apply for different biophysical modeling. It firmly covers a wide range of physical problem including cancer cells adhesion in a blood vessel [4], mesenchymal stromal cell growth in a packed bed bioreactor [5], and convectional reaction-diffusion in a nervous parenchyma [6, 7]. However, the creation of an appropriate digital phantom for further modelling is still a great problem. The evaluation of a shape and the size of biological structures sometimes takes significant computational resources [8]. It causes an increased time for a model preparing, and, in fact, adaptation of a numerical modeling to a routine biomedical practice becomes inaccessible. SSDF particularly opens a new ability. Using such a method, one is possible to incorporate a numerical algorithm to Image Technology software directly.

Considering the most influent options described in this study, the algorithm of sphere sources field may be used for routine clinical analysis. Indeed, the development of SSDF is necessary. The main ways are to include the correction terms in the final gradient and to improve a geometrical fitting of the sources' localization.
4.1. Conclusions
Validation of SSDF is done using FEM. The most appropriate area in the considered phantom yields the level of 93% coincidence between the methods. The most influential parameter is a reciprocal position of a nutrient source relative to the validation area. The position of the outstanding face with a zero condition plays essential part under relatively high mutual distances of sources only.

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