A novel algorithm of the digital nervous tissue phantom creation based on 3D Voronoi diagram application

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Abstract. The essential part of mathematical modelling of nutrients convectional reaction-diffusion is creation of a digital phantom of considered biological object. This process becomes an especial problem which needs to be solved before numerical calculations of the concentration gradients will be done. There are two principal ways to get the solution in this case. The first approach is the reconstruction of a digital phantom on the base of the experimental data directly. The second one is the creation of a virtual object according to the experimental evidence and the known principals de novo. The main advantage of the created phantom is a high adaptability to modelling demands and a physical problem formulation. In the present study a new algorithm of a digital phantom creation has been established. The principles of the claimed procedures are demonstrated by the example of a nervous tissue. Initially, one needs to create N 3D objects according to Voronoi diagrams. Each object has 144 edges and 69 boundaries on average. Having chosen M rear objects, a long 3D structure mimicking neurons axons is created according to a loft procedure from the start boundaries to the end ones. Then, the set of Boolean operations has been applied to form continuous smooth objects. The remain \((N-(M+s))\) objects are combined into several whole bodies using the loft procedures between the closet neighbours. The final structure has a good conformity with a nervous tissue architecture. Furthermore, the obtained phantom is correct to the mesh application and further numerical calculations.

1. Introduction
Application of mathematical modelling is a well-known part of the scientific research in different areas of biology and medicine. For realistic models PDE problems are usually formulated. The initial stage of such kind a modeling is the creation of a validated space of coordinate where the considered equations will be solved. In fact, one needs to build up a virtual copy of the object of interest. Indeed, for a technical area this problem can be solved using different CAD software. Initial drawings of the objects make it possible to apply the solver procedures to the phantom \((\Omega)\) directly. However, if a biological object is considered for the modelling the evaluation of a digital calculation area becomes essentially complex. To avoid such an obstacle simplified geometrical samples are often used to fulfil a computation. The simulation can be performed using automatically generated primitives such as a tetrahedron, a sphere, a plane, etc. [1, 2].

However, to get more sophisticated results a complicated reconstruction of the biological geometry is necessary. It includes a spatial combination of heterogenous structures which have different
physicochemical properties. Therefore, the creation of a phantom must be based on an explicit incorporation of space irregularities and a periodic peculiarity repeat. Among many examples a nervous parenchyma has been chosen to consideration in the present study because the mammalian brain is more complicated than that of any other known biological tissue. Moreover, a great success in a volume fine structure reconstruction was achieved in this case [3]. Additionally, the neuronal spatial-time processes are attracted to be modelled using different numerical methods [4, 5]. Nevertheless, one tries to make the geometry of the system as simple as possible. For example, the computational domain of para-arterial to para-venous spaces in the brain extracellular space was taken as a triangular region in the hexagonal lattice [6]. Another problem is a necessity to get the geometry which is acceptable for further mesh application because the numerical calculations are evaluated in this case only. Thus, a common algorithm of a fine geometry generation is useful to different subject areas of models. In the present study, one of the possible ways to generate the heterogenic structure imitating a brain parenchyma is established.

2. Biological background for a virtual phantom creation for a nervous parenchyma
The recent generation of 3D reconstructions of brain neuropil together with representative extracellular space volume estimates have now finally opened the pathway for realistic simulations of solute transport in brain [7]. In the one of first studies a serial section transmission electron microscopy (EM) was automated to densely reconstruct four volumes, totaling 670 μm³, from the rat hippocampus as proving grounds to determine when axo-dendritic proximities predict synapses [8]. It was shown that the largest touch between an axonal bouton and spine indicated the site of actual synapses with about 80% precision but would miss about half of all synapses. Nevertheless, many essential geometrical parameters were measured and numerically estimated. Furthermore, Kinney et al. used manual and computational techniques to reconstruct the 3D geometry of 180 μm³ of rat CA1 hippocampal neuropil from serial EM and corrected for tissue shrinkage to reflect the in vivo state [9]. The reconstruction revealed an interconnected network of 40–80 nm diameter tunnels, formed at the junction of three or more cellular processes, spanned by sheets between pairs of cell surfaces with 10–40 nm width. It is remarkable, that the median sheet extracellular width distribution was 8 nm (N = 1,756,847), smaller than observed in EM images, suggesting a bias in contour placement toward the extracellular side.

Taking together, the data indicate that a nervous tissue is a very heterogenic media with a complex structure which usually depends on the brain area and substructures. Additionally, one needs to take into account the mean distance between the neurons to the closest microvessel is usual equal to 17.8 μm and the mean glial-capillary distance reaches 18.2 μm [10]. Moreover, it is commonly accepted that no brain cell is further than about 25 μm from a capillary [11]. These statements get the range for a pure nervous tissue phantom size. If the distance from any part of the considered area exceeds 25 μm, a blood capillary must be included into the created geometry.

3. A step-by-step algorithm of the digital nervous tissue phantom creation
The creation of a digital phantom can be shared in several sequence stages. First of all, a set of the bodies have to be generated. It will be used as a template for further structural modelling. The main aspect for such a set is a stochastic peculiarity of bodies placement combining with the ranged geometry. The next step is the forming of long-type structures which will be used for the geometric orientation of the system. The further step deals with the branched bodies leaning on the previous separated long-type objects.

The creation of the objects according to an algorithm has been fulfilled using COMSOL Multiphysics ver. 5.5. The standard set of a geometry transformation is applied to 3D Voronoi textures. It includes common Boolean operations and loft/split procedures. The final structures have been passed through the Form Union procedure and they are acceptable for further mech applications and modelling.
3.1. The initial set of bodies according to 3D Voronoi diagrams
The Voronoi diagram is one of the most useful geometrical constructions to study point patterns, since it provides all the information needed to study proximity relations between points [12]. A detailed review of Voronoi diagrams and their application one can find elsewhere [13]. Having omitted technical steps, let the set of the 3D bodies has been already created.

\[ \Omega_{\text{initial}} = \{ \xi_i \}_{i=1}^{N} \]  

where each \( \xi_i \) represented a 3D body having 69 faces, 144 edges and 77 points on average. Without loss of generality, the number of the considered objects is limited on 173 (N=173). The total volume of the initial set is equal to 11,982 \( \mu \text{m}^3 \) and the corresponding surface covering the objects is 15,404 \( \mu \text{m}^2 \). The generated set is represented in Fig.1. The essential property of \( \Omega_{\text{initial}} \) is the ranged limitation between the bodies surfaces distance:

\[ \forall i,k : (\partial \xi_i \subset \xi_k, \partial \xi_k \subset \xi_i) \Rightarrow |r_{ik}| \approx \delta \]  

The considered condition is required to form a structural model of nervous parenchyma as described above. According to experimental data the distance is distributed with median of 8 nm [9]. The value of \( \delta=7 \) nm is used in the present study.

Figure 1. The illustration of 3D Voronoi diagram set (N=173) used in the study. The general orientation is represented in an isometric projection (left). The examples of \( \xi_i \) are characterized by 75 faces, 159 edges and 86 points (right top); or 180 faces, 378 edges and 202 points (right centre); or 138 faces, 291 edges and 157 points (right bottom) respectively.

It should be noted that the structure of Voronoi texture was already used for modeling of convectional reaction-diffusion of hydrogen peroxide in a brain tissue [14]. It was shown that glutamate induced overproduction of hydrogen peroxide results in detectable increase of \( \text{H}_2\text{O}_2 \) in the model. This effect depends on the size of the considered area. However, if the modelling is fulfilled under the level of neuronal synapses a lengthy object structure is preferable. The following steps of an algorithm cause the generation of its examples.
3.2. The creation of a long-type structure in the initial set

A special feature of the nervous tissue is the existence of the long-type structures, which can cross the areas and be twisted. To form such a structure the rear bodies are chosen. Then the surfaces of the opposite objects are lofted to each other.

$$\omega_{j}^{\text{long}} = \bigcup_{j} \text{Loft}_{j} \left( \partial \omega_{i}^{\text{rear}} \rightarrow \partial \omega_{k}^{\text{rear}} \right), \quad j = 1, \ldots, M$$  

The resulted bodies are united into the uniform objects. Due to clarity of the presentation, $M$ is limited to 6. The example of the procedure (20) is shown in Fig.2. The final objects are uniform in the shape, but they have variation in approximately $\pm 20\%$ in their volume (Table 1). As an option the procedure fulfilled by (3) can be executed between the distant surfaces.

![Figure 2. The long-type structures of the phantom.](Image)

Table 1. The geometric characteristics of the long-type objects of the phantom.

| The structure | Volume   | Surface  | Faces | Edges | Points |
|--------------|----------|----------|-------|-------|--------|
| A            | 427.80 [μm$^3$] | 427.71 [μm$^2$] | 164   | 392   | 230    |
| B            | 396.61 [μm$^3$] | 424.87 [μm$^2$] | 151   | 334   | 185    |
| C            | 402.40 [μm$^3$] | 427.54 [μm$^2$] | 144   | 319   | 177    |
| D            | 256.74 [μm$^3$] | 377.51 [μm$^2$] | 173   | 357   | 186    |
| E            | 321.01 [μm$^3$] | 404.56 [μm$^2$] | 150   | 315   | 167    |
| F            | 266.47 [μm$^3$] | 350.43 [μm$^2$] | 176   | 361   | 187    |

The considered example demonstrates the objects formed by a lofting of face-to-face surfaces. If the procedure (3) is carried out between the surfaces of the distant sides, it has to be accompanied by Split/Unit procedure. The obtained objects will have reduced volume because the butt-end bodies are partially omitted. Moreover, the construction of the branched objects will be accomplished after the following operation:

$$\Omega^* = \Omega_{\text{initial}} \bigcup_{j} \omega_{j}^{\text{long}}$$  

The achieved set of bodies is appropriate to farther topological transformations.

3.3. A forming of a branched body structure and a short-cut structure

The next step is to choose the sets of the remain objects which will be proceeded into separate structures. The first operation is to select the closest to A-F objects. It will be done using the assumption:
\[ \omega^{(k)} = \left\{ \xi_j \right\}_{j=1}^{K}, \forall k : \xi_j \cap \bigcup_j \omega_{j}^{\text{long}} \neq \emptyset \]  \hspace{1cm} (5)

The second operation is to get the supposed objects on the base of the following operation:

\[ \omega_{j}^{\text{branched}} = \text{Union} \left( \text{Split} \left( \text{Loft} \left( \partial \xi_j^{\Omega^*} \rightarrow \partial \xi_j^{\Omega} \right) \right) \right) \]  \hspace{1cm} (6)

The procedure (6) will be repeated until the final object is assembled. A short-cut body is built by a single operation of (6). For a branched one the number of compilations can be as high as 10-12. The results of the step-by-step Boolean operations are shown in Fig.3. The obtained objects can be classified as the branched (OL, Ast-1, Ast-2) and the short-cut (D1-6). Indeed, the difference between the groups is essential (Table 2). However, medium objects, like Ast-1/2, have similar characteristics, and their outgrowths symmetrically cover the area of the phantom.

Figure 3. The branched/short-cut objects of the phantom.
The scrap bodies will be formed by connecting beans. The branched or long-type objects cannot be equal to zero. These objects are very essential for a fine turning of the created phantom. A small part can be attached to the branched or long-type objects forming a realistic spatial distribution of the geometry.

3.4. The rest part of the bodies set and a fine adjustment of the phantom
Despite a large volume of the objects generated using (1)-(6), the remain part of unattached $\xi_i$ is still vast (Table 2). Certainly, these values can be reduced by the additional forming of structures according to repeating loft/split/union procedures described above. However, the scrap bodies will be necessarily produced, and their number cannot be equal to zero. These objects are very essential for a fine turning of the created phantom. A small part can be attached to the branched or long-type objects forming a realistic spatial distribution of the geometry.

4. Discussion
The presented algorithm makes it possible to create a virtual imitation of a nervous parenchyma. The obtained examples of the objects have the general geometrical properties of the nervous cells. A part of them is lain with an axial orientation. Another one is placed with a multiply twisting network crossing the area. Indeed, the axon diameter was found to be reported as high as 200 μm [8]. However, the same study indicated 7 axons per μm². It means that the structures A-F can be associated with bunches of axons including additional structures. On the contrary, the long-type objects may be also identified with pyramidal neurons in layer 5 of the motor cortex where a scale bar is 10 μm [15]. OL and Ast-1/2 should be related to oligodendrocyte and astrocyte respectively. Certainly, each of them is assumed to be essentially branched with many processes. Similarly, astrocytes have a star-like structure with many body-connected beans. Their number and size depend on a biological species source of the cell. For instance, the increase in processes length and number lead to a remarkable enhancement of the domain of the protoplasmic astrocyte, which presents an average diameter of 142.6 μm against 56 μm in rodents [16].

The aim of the adjusted structure size can be reached if an additional condition is joined to the procedures (3)-(6). This suggestion will range the source surfaces and thereby a thinner structure is produced.

$$\forall i, k : \partial S_{\xi_i}^k < S_{\min}^I, \partial S_{\xi_i}^{Fv} < S_{\min}^H : S = \max \left\{S^I_{\min}, S^H_{\min}\right\}, S \leq S_{\text{measured}}$$

4.1. Conclusions
The represented algorithm converts a 3D Voronoi texture into a cross-sectioned heterogenous structure. Elements of the structure can be related to separate cells of a nervous parenchyma. A repeated procedure of the object transformations described in the study helps to improve the structure compliance with real measured objects. The final bodies are passed through the Form Union procedure, and they are acceptable for farther application of meshes and a numeric modelling. The suggested algorithm can be applied to creation of a virtual phantom of different other tissues such as liver, heart, kidney, muscles etc.

Table 2. The geometric characteristics of the branched/short-cut objects of the phantom.

| The structure | Volume [μm³] | Surface [μm²] | Faces | Edges | Points |
|---------------|-------------|---------------|-------|-------|--------|
| OL            | 2,429.30    | 3,865.20      | 3,048 | 7,397 | 4,334  |
| Ast-1         | 598.08      | 1,307.60      | 803   | 1,994 | 1,181  |
| Ast-2         | 508.37      | 1,153.60      | 777   | 1,971 | 1,185  |
| D1            | 25.66       | 75.39         | 33    | 73    | 42     |
| D2            | 93.22       | 136.90        | 65    | 200   | 137    |
| D3            | 57.73       | 107.10        | 36    | 108   | 74     |
| D4            | 63.08       | 95.14         | 39    | 97    | 60     |
| D5            | 32.86       | 87.26         | 35    | 86    | 53     |
| D6            | 44.31       | 96.84         | 36    | 112   | 78     |
| The rest part | 6,459.10    | 10,683.0      | 8,343 | 18,775| 10,579 |

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