Spatially-Realistic and Reduced Models for Integrative Biomedical Computing

C. Bajaj[1], A. DiCarlo[2] and A. Paoluzzi[3]

[1] Dept of Computer Sciences & ICES, Center for Computational Visualization, 201 East 24th Street, Austin, TX 78712-0027, USA

[2] Dept of Studies on Structures, Modelling & Simulation Laboratory Via Corrado Segre 6, I-00146 Roma, Italy

[3] Dept of Informatics and Automation, Geometric Computation Laboratory Via della Vasca Navale 79, I-00146 Roma, Italy

Abstract— **Biomedical computing will greatly benefit from a progressive and adaptive approach to modelling, combined with novel adaptive methods for multiphysics and multiscale simulation. Both symbolic and hierarchical characterizations of the various components should be allowed for, as well as shape reconstruction from high-resolution imaging techniques [2]. Managing finer and finer details and transforming them into additional parameters for coarse-grain models is of the greatest importance. However, it is also essential to be able to analise complicated shapes and patterns, in order to identify their salient features, using computational topology methods based on Morse theory [7]. We apply such ideas to modelling of spatially realistic and reduced domains of structures and ultrastructures of the nervous tissues, where running numerical simulations of the functional behaviour of neurons. In particular, we generate spatially realistic reconstructions of dendrites, axons, glia, and extracellular space domains, using quality surface meshing algorithms to make these reconstructions ready for realistic modeling of dendritic signaling. Reconstruction and modeling tools are used to quantify the variation in surface area and volume of axons, den- drites, glia, extracellular space, synapses, and core subcellular organelles, that could impact electrical signaling. To bridge the gap to one-dimensional models that have been used for electrophysiological simulations, we develop appropriately reduced domain models. In this paper we introduce a novel method to compute a minimal fat skeleton, made by hexahedral elements, starting form a point sampling of shape boundary and from the one-dimensional and two-dimensional unstable manifolds of the the index 1 and index 2 saddle points of the Morse structure induced by the shape. The result is a cell decomposition with a minimal number of cells, that yet approximate well the shape. The output mesh can be used for simulation of physical behaviour of neural tissue with a minimal number of degrees of freedom.**

Keywords— **Geometry generation & processing, computational geometry and topology, computational physiology.**

I. Introduction

The biological and medical research must deal with problems of higher and higher complexity, for which the traditional approach—based on the subdivision of biological systems by dimensional scales, scientific disciplines or by anatomical sub-systems—is inadequate. It is therefore necessary to give computational support to an integrative approach aimed to combine observations, theories and predictions across temporal and dimensional scales, scientific disciplines and anatomical sub- systems. This intuition gave origin to a number of initiatives such as integrative biology, system biology, Physiome, VPH, etc. The physiome term hence refers to human modelling using mathematics and computational methods, accommodating cross-disciplinary science (chemistry, biology, physics, computer science) and several dimensional and temporal scale (sub-cellular to organs, sub-microsecond to tens-of-years).

The Physiome Project [8] is a worldwide effort to provide a computational framework for understanding human and other eukaryotic physiology. It aims to develop integrative models at all levels of biological organisation, from genes to the whole organism. The VPH (Virtual Physiological Human) is a European initiative intending to provide a unifying architecture for the integration and cooperation of multi-scale physiome models [6]. It is foreseen that maturing physiome activities will increasingly influence medicine and biomedical research. The novel computational framework proposed for Proto-PLASM [2] is a specialized and high-performance extension of the geometric language Plasm [9] strongly inspired by the functional language FL, designed after Backus' earlier FP programming language [1], providing specific support for what Backus termed function-level programming, and oriented to work on programs as mathematical objects.

Our goal is to obtain spatially realistic reconstructions of dendrites, axons, glia, and extracellular space domains within representative hippocampal and cortical mouse neuropil (see Figure 1). Modeling of electrical signals in dendrites has typically been done on simplified cases that treat the complex dendritic arbor and local variation in dendritic structure as a series of cylinders. Reconstruction from serial section transmission electron microscopy (ssTEM), however, reveals substantial deviation from these cylindrical

approximations. It is an open question how this local variation in dendritic structure affects the local electrical signals in dendrites. Previous modeling of dendritic function has also lacked sufficient data to explore the effects of variation in the physical relationships between dendrites, axons, glia, and extracellular space in the dense tangle of the local neuropil. Reconstruction and modeling tools is used [4] to quantify the variation in surface area and volume of axons, dendrites, glia, extracellular space, synapses, and core subcellular organelles (smooth endoplasmic reticulum, endosomal compartments, and mitochondria) that could impact electrical signaling in dendrites. To bridge the gap to one-dimensional models that have been used for electrophysiological simulations [5], we are developing a set of tools to construct appropriately reduced domain models from the spatially realistic quantifications, shown in Figure 1 for some portion of the neuropil reconstruction, from paper [4].

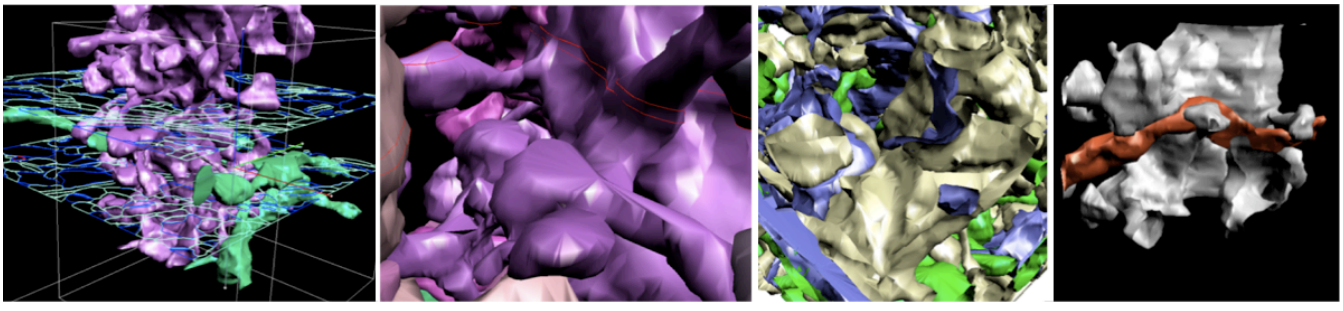

Fig. 1 (a) Portion of the neuropil reconstruction from [4]; (b) Zoom to portion of the CA1 apical dendrite process; (c) Axons (green), glial cells (blue) & dendrites; (d) An axon (orange) and dendrite (gray).

II. Generation of reduced models

The aim of the work described in this section [3] is to provide a minimal set of (convex) hexahedra covering the 1-skeleton of a two-dimensional discrete space embedded in 3D. In order to get a spatially-realistic partitioning, we may use a measured 1-complex $K = (K_0 , K_1)$, with a positive function mass $\mu : K_0 \rightarrow R_+$ supported by the vertices of K, to be interpreted as the minimum distance of vertices from the boundary of the space to be approximated by the hexahedral partition.

According to [7], where the flat and tubular regions of a three dimensional shape are identified from the point sample of its boundary, we start from the Morse structure induced by it on $\Re_3$ and by the unstable manifolds of the the index 1 and index 2 saddle points. Such submanifolds are respectively two-dimensional and one-dimensional, and are embedded in Euclidean 3-space.

Given a 2-complex M (see Figure 2a), a path-reduced complex $K(M)$ is obtained by substituting every maximal path with a 1-cell in the same homotopy class, i.e. with the same extreme vertices (see Figure 2b). In practice, a path in a complex is a 1-chain that is incident to other 1-cells at most in the extreme vertices. An alternative definition of path-reduced complex could be given as the quotient space M/H , where H is the homotopic path-equivalence.

Since the goal of this work is to generate a space decomposition with hexahedra, there are some geometrical constraints to take into account, namely the coplanarity of the four edges and vertices bounding each 2-face. While three distinct points are always coplanar, four points in space are usually not coplanar. We compute a total ordering of the set that contains two instances of each 1-cell $\sigma_1 \in K_1$, and for each consecutive pair of 1-cells (say, mapped from even and odd indices), we consider their affine hull, i.e. the unique plane they determine, and there we generate two coplanar quadrilaterals that account for two 2-cells of the output 3-complex made by hexahedra.

Of course we show that such total ordering always exists (see Figure 2), so that the 2-chain of pairwise 1-adjacent quads exists and is continuous. Finally, we map bijectively such quadrilateral 2-cells σ_2 to hexahedra, by first generating the two (planar) quads associated to each input 1-cell σ_1, and finally by producing the last three boundary 2-cells, by an algebraic construction aiming at assuring their planarity. A special care is given to the subset of 2-cells incident on the same vertex σ_0 , in order to guarantee that no two hexahedra intersect around the vertex.

The result algorithm is a cell decomposition with a minimal number of hexahedral cells, that yet approximate pretty well the given shape. The output mesh can be used for simulation of physical behaviour with a minimal number of degrees of freedom.

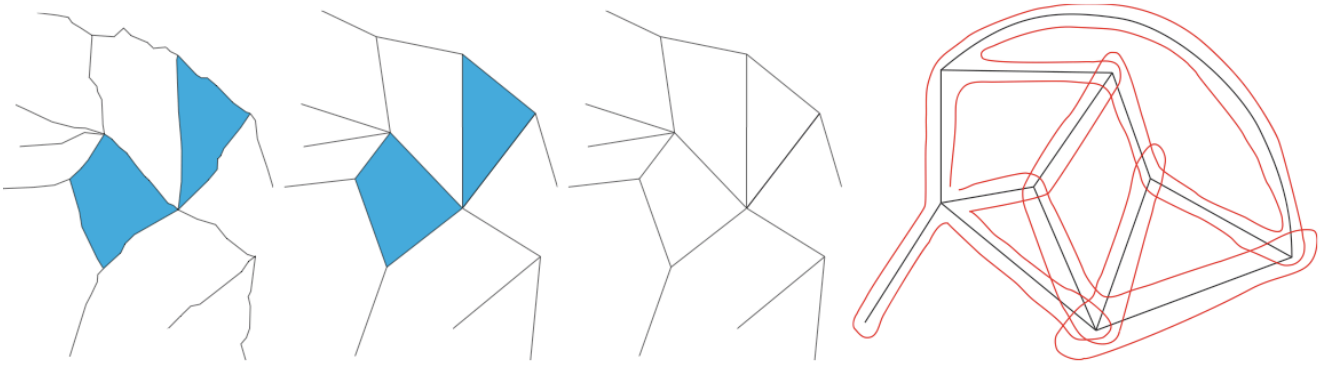

Fig. 1 (a) 2-complex M of unstable manifolds of the Morse structure induced by a shape; (b) reduced cell complex *K(M) = (K0 , K1 , K2)*; (c) 1-skeleton *K1* ; (d) the Euler cycle that traverses twice each edge always exists for a connected graph.

III. Conclusions

We are currently implementing the algorithmic scheme introduced in this paper, using constant local distances from the boundary. Next step will be the shape approximation with variable local distances, i.e.~with balls of variable radius centered at the 0-cells of the complex, and with the same number of hexahedra.

Of course, to such reduced-domain model, any amount of detail may be added everywhere needed, and even hierarchically and progressively. It is well kown that a structured mesh with hexahedral cells may be locally detailed at will, without leaving such a decomposition scheme.

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Use macro [author address] to enter the address of the corresponding author:

Author: Alberto Paoluzzi
Institute: Dip. Informatica e Automazione, Università Roma Tre
Street: Via della Vasca Navale, 79
City: 00146 Rome
Country: Italy
Email: paoluzzi@dia.uniroma3.it