Journal of Theoretical Biology 437 (2018) 187–201

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/jtbi

Topological graph description of multicellular dynamics based on vertex model

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ARTICLE INFO

Article history:
Received 7 February 2017
Revised 16 October 2017
Accepted 20 October 2017

Keywords:
Multicellular dynamics
2D/3D vertex model
Graph theory
Operational soundness and completeness

ABSTRACT

Vertex models are generally powerful tools for exploring biological insights into multicellular dynamics. In these models, a multicellular structure is represented by a network, which is dynamically rearranged using topological operations. Remarkably, the topological dynamics of the network are important in guaranteeing the results from the models and their biological implications. However, it remains unclear whether the entire pattern of multicellular topological dynamics can be accurately expressed by a set of operators in the models. Surprisingly, vertex models have been empirically used for several decades without any mathematical verification. In this study, we propose a rigorous two-/three-dimensional (2D/3D) vertex model to describe multicellular topological dynamics. To do this, we classify several types of vertex models from a graph-theoretic perspective. Based on the classification, mathematical analyses reveal several conditions that enable us to apply the operators accurately without topological errors. Under these conditions, the operators can completely express the entire pattern of multicellular topological dynamics. From these results, we newly propose rigorous 2D/3D vertex models that can be applied to general multicellular dynamics, and we clarify several points to verify the results obtained from previous models.

1. Introduction

Multicellular dynamics are fundamental to the construction and maintenance of tissue and organ structures in multicellular organisms. In most tissues, individual cells adhere to each other within a three-dimensional (3D) geometry with a slight boundary gap. Because the gap is negligible, the geometry of such tissues can be approximated by the cell packing geometry, where the gap width can be zero. Under this geometry, cell–cell boundaries are tensile because of cytoplasmic and cytoskeletal activities. Hence, individual cell shapes tend to be angulated, especially on the apical area of the epithelium. Moreover, under their geometric constraints, cells show active behavior such as deformation, migration, division, and apoptosis. Therefore, multicellular dynamics are accompanied by changes in cellular shape, position, and number under the packing geometry.

To deal with such multicellular dynamics, vertex models have frequently been used over recent decades (Bielmeier et al., 2016; Farhadifar et al., 2007; Fletcher et al., 2014; Honda and Nagai, 2015; Honda et al., 1982, 2004; Misra et al., 2016). Various extensions of these models can express aspects of cellular dynamics such as cellular rearrangement (Honda et al., 1982; Nagai et al., 1990; Okuda et al., 2013c), division (Farhadifar et al., 2007; Okuda et al., 2013b), and apoptosis (Monier et al., 2015; Okuda et al., 2016). These expressions are directly described in 3D space, or are approximated to two-dimensional (2D) space. This versatile description has made it possible to apply the models to various simplified and realistic phenomena (Honda et al., 2008). In particular, over the past few years, several studies have focused on the importance and applicability of vertex models in enabling a greater understanding of multicellular systems (Fletcher et al., 2013, 2014; Honda and Nagai, 2015; Okuda et al., 2015a). Therefore, vertex models are powerful tools for expressing 2D/3D multicellular dynamics.

Vertex models express multicellular dynamics from both topological and physical perspectives. From a topological perspective, 2D models represent individual cell shapes as a single polygon whose vertices and edges are shared by neighboring cells. We re-

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https://doi.org/10.1016/j.jtbi.2017.10.023

fer to this topological representation as a cell packing graph (CPG). Importantly, the network topology changes dynamically under several topological operators, such as those expressing cell rearrangements, divisions, and apoptosis (Farhadifar et al., 2007; Honda et al., 1982; Nagai et al., 1990; Okuda et al., 2016, 2013b, 2013c). In addition, from a physical perspective, the spatial quantities of edges, surfaces, and volumes are calculated from the vertex positions and network topology. Based on these spatial quantities, physical parameters such as the gradients of the effective energy and molecular density can be calculated (Fujita et al., 2011; Honda et al., 1982, 2004; Okuda et al., 2015c). Namely, in vertex models, the network topology is a hyperparameter of the physical parameters.

The dynamic transition process of CPG is important for providing results that are physically consistent. First, if the operators are irregular (i.e., the network topology is irreversible before and after applying an operator), the inherent irreversibility would generate some artificial drift in the physical states (Okuda et al., 2013c). Second, for computational simulations, if topological operators are unsound (i.e., they cannot always be applied to the network), the computational algorithm may fail, or a part of the network may be locked (Okuda et al., 2013c). Third, if operators are incomplete (i.e., they have inexpressible patterns of CPG dynamics), the phenomena applicable to the models would be limited. Therefore, to ensure that we obtain physically consistent results, the operators of vertex models should satisfy the following topological properties:

Reversibility: operators have inverse functions.
Soundness: operators can be sequentially applied to the network.
Completeness: operators can express the entire pattern of CPG dynamics.

Although vertex models have been used in the past and will continue to be used in the future, there are currently no topological operators that satisfy the reversibility, soundness, and completeness requirements. Therefore, in this study, we mathematically explore the topological dynamics of vertex models from a graph-theoretic viewpoint, and propose a set of regular operations that maintains the soundness and whose sequential application ensures completeness. First, we classify several types of vertex models with respect to the graph property and operators. Second, we mathematically explore the applicable conditions of individual operators, and clarify whether individual operators satisfy the criteria for reversibility, soundness, and completeness.

2. Graph-theoretic description of multicellular topological dynamics

2.1. Description of multicellular topological structures

From a graph-theoretic viewpoint, the physical state of cells whose topology is within the CPG can be described as a graph $G(V, E, A)$. Here, the symbols V and E are topological parameters, i.e., sets of vertices and edges, respectively. The symbol A is a set of attribute physical parameters, such as spatial coordinates, mass, momentum, and energy.

From a physical viewpoint, cell movements can be regarded as a quasi-static process in the Newtonian mechanics, where the mechanical states of cells can be determined by spatial coordinates: cellular shape and configuration. Because the coordinates are represented by a set of V, E, and vertex coordinates, both V and E are hyperparameters of A. Therefore, to focus on the topological aspect of multicellular dynamics, we focus on V and E by describing the graph, without loss of generality, as $G(V, E)$ or G rather than $G(V, E, A)$.

G can be classified using a specific condition that is satisfied by each graph, as in Table 1. Let the graph class $\mathcal{G}$ be a set of graphs that satisfies a specific condition. In Table 1, graph classes are categorized by three points, namely the spatial dimension, regular number of edges connected to individual vertices, and presence or absence of a change in the number of cells.

First, the graph class can be categorized using spatial dimensions. From a physical viewpoint, cells have 3D structures that are directly analyzed in 3D space, or approximately analyzed in 2D space. Hence, there are two types of graph classes in vertex models, i.e., 2D and 3D. The graph class in the 2D and 3D cases are denoted by $\mathcal{G}$ and $\mathcal{Q}$, respectively.

Depending on the spatial dimensions, the correspondence between topological and physical objects differs. In 2D space, an edge e represents a boundary between two neighboring cells, and a vertex $v \in V$ represents a meeting point of cell boundaries (Fig. 1). The 2D region closed by a set of edges is called a "face," and corresponds to an individual cell. In 3D space, a face f represents a boundary between two neighboring cells. Then, the edge e represents an intercept of several faces, and the vertex $v \in V$ represents a meeting point of intercepts. The 3D region enclosed by faces is called "a polyhedral graph," and corresponds to an individual cell. A face can be represented by $f_1 = \{e_1, \dots, e_m\}$. Because the edge e is a set of two vertices, $e_1 = \{v_1, v_2\}$, the face can be rewritten as a set of vertices $f_1 = (v_1, \dots, v_m)$.

Second, the graph class can be categorized by the number of edges connected to individual vertices, which is referred to as the degree of vertex. From a topological viewpoint, in the 2D graph class, individual vertices must be connected to at least three edges. Similarly, in the 3D graph class, individual vertices must be connected to at least four edges. Hence, the graph classes have the minimum number of connected edges (three in 2D and four in 3D). In real biological systems, the degree of vertex is generally the minimum connected number, but this is not always the case, such as in the rosette formation (Blankenship et al., 2006). In physical uses of vertex models, the rosette structure is sometimes dealt with as an irreversible topological graph with more than the minimum connected number (Trichas et al., 2012). However, because vertex models approximate the width of cell–cell boundaries to be zero, there is a transient condition that several boundaries with the zero-limit width meet at a certain point in the physical process of multicellular dynamics. This transient event cannot be recognized in the finite timescale of multicellular dynamics. Rather, in physical uses of vertex models, it seems more reasonable to approximate the vertices connected to more than the minimum number of edges to be a set of the vertices connected to the minimum number. Even using the graph with the minimum connected number, the rosette structure can be expressed using a physical constraint for a set of vertices gathering within a local area. Thus, in this study, we focus mainly on graph classes with the minimum connected numbers.

Notably, from a topological viewpoint, it is challenging to generalize the soundness and completeness to graph classes without the constraint of the connected number. The generalized graph classes are represented by $\mathcal{G}^{\mathrm{gen}}$ and $\mathcal{Q}^{\mathrm{gen}}$, as in Table 1.

Third, the graph class can be categorized by the presence or absence of changes in the number of cells. Topological changes in the multicellular structure result from certain cell behavior, such as cell rearrangements, division, and death. While the number of cells can be changed by cell division and death, it cannot be changed by cell rearrangement. Graph classes with a constant number of k cells are represented by $\mathcal{G}_{(k)}$ and $\mathcal{Q}_{(k)}$, which correspond to the multicellular dynamics without cell division or death. The other classes correspond to the multicellular dynamics under conditions including cell division and death (Table 1).