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Tyssue: an epithelium simulation library

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Software

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Summary

The `tyssue` Python library seeks to provide a unified interface to implement bio-mechanical models of living tissues. Its main focus is on vertex based epithelium models. `tyssue` allows to model the mechanical behavior of 2D, apical 3D or full 3D epithelia based on the numerical resolution of the equations of motion for the mesh vertices. Biological processes are modeled through changes in the topological and dynamical properties of the mesh. `tyssue` is a modular library. Starting with the same tissue geometry, the choice of constraints, energy potential terms and parameters increases the possibility to answer different biological questions and easily explore mechanical hypotheses.

Statement of Need

Tissue remodeling is a complex process integrating a large number of inputs such as gene expression pattern, cell adherent properties or cell mechanics. It can be difficult to manipulate specific aspects genetically. It can even be hard to simply capture, when the process takes only few minutes. Furthermore, morphogenesis is inherently a mechanical process. To execute complex morphogenetic movements, epithelia are driven by in-plane forces, like constriction of apical cell surface (Heer et al., 2017), and/or out-of-plane forces, such as the apico-basal cable in apoptotic cell (Gracia et al., 2019; Monier et al., 2015) or lateral tension (Sherrard et al., 2010; Sui et al., 2018). Modeling these processes help us to understand how tissues acquire their shape, in complement of the experimental systems, and beyond their limitations. Several vertex models have been developed in the past few years to describe the physics of epithelia (for a review, see (Alt et al., 2017)), and common features can be identified. Several kinds of models have already been published. The apical vertex model has been used several times to study topology changes during morphogenetic movement in *Drosophila, Hydra and Xenopus* (Aegerter-Wilmsen et al., 2012; Aigouy et al., 2010; Farhadifar et al., 2007). Associated with protein dynamics, it has been used to study the effect of protein position on tissue organisation in zebrafish retina (Salbreux et al., 2012). 3D vertex model have been used to study epithelium deformation due to normal development or to cancer development (Eritano et al., 2020; Okuda et al., 2015). Most of the time, models are developed for a specific biological question and are difficult to adapt to other systems, for several reasons. However, there is some exception like Chaste (Cooper et al., 2020), which propose an open source C++ library to model cell populations or how specific events arise at the system level. With the `tyssue` library, we propose models which are adaptable and scalable with the field of research and the biological question. Topology and mechanics are implemented independently to improve the versatility of models.

The `tyssue` library defines epithelium as meshes. A vertex model defines a tissue as an assembly of vertices and edges, which can form polygonal face (in 2D) or polyhedron (in 3D).

For now, we assume that cell junctions are straight lines. In `tyssue`, each edge is split, so that every face is limited by oriented "half-edges" (see figure 1 A), in a structure identical to the Linear Cell Complex in the CGAL library. The `tyssue` library allows to produce different kinds of tissue, from 2D to 3D tissue (see figure 1 B). The library implements concepts and mechanisms common to all vertex models, for both topological and mechanical aspects.

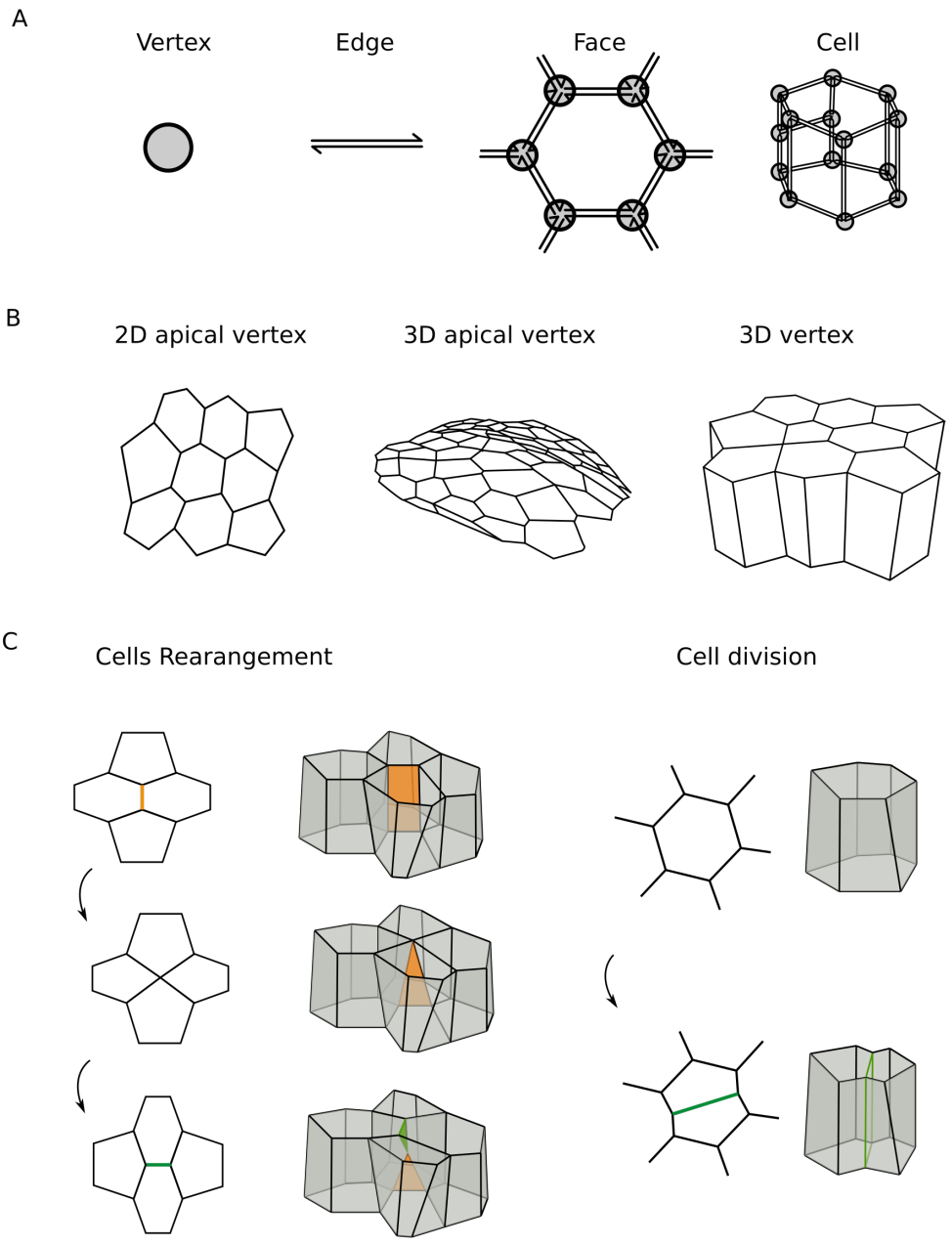

Figure 1: Description of tyssue geometry. *A-Composition of a tissue from a vertex to a cell. B-Three kind of geometry that can be used in tyssue. C-Example of cell dynamics usable in 2D and 3D.*

Features of tyssue

Topology

Common cellular processes are implemented in our library such as cell elimination, division or rearrangements. We implemented those processes based on previous works.

Cell division is modeled as the splitting of a cell by a straight line (or plane in 3D) (Brodland & Veldhuis, 2002), the angle and position of the division plane can be decided (see Figure 1 C, right panel).

Changes in cell neighbors - also called rearrangements - happen when the size of the boundary between two neighboring cells passes below a certain threshold length in 2D (type 1 transition), or area in 3D (I-H or H-I transition) (Okuda et al., 2015). In that case, the linked vertices fuse and are separated again, which can lead to a change in the local topology (see Figure 1 C, left panel).

Cell elimination happens when a cell area (volume) reaches a low threshold. When this happens, cell starts to lose contact with neighboring cells through series of rearrangements. Once the cell is reduced to a triangle (in 2D) or a tetrahedron (in 3D) the remaining vertices are merged to create a new vertex.

Although it was customary to assume the neighbor exchange to be a single-step process, we follow the work by Finegan et al. which describes cell exchange as a multistep, stochastic process (Tara M Finegan et al., 2019). As a consequence, in `tyssue`, vertices are not limited to 3 (in 2D) or 4 (in 3D) linked edges, but can form "rosettes" - see type1 and rosette examples.

Mechanics

In `tyssue`, the dynamical behavior of epithelium is described by solving the equation of motions following Newton's principle. At the scales of the studied processes, the inertia is negligible compared to other forces such as friction, adhesion or contraction of the actin cytoskeleton.

Honda et al. assume that cell movements respond to mechanical forces in an overdamped manner and the vertices are driven by the sum of interfacial tension on cell boundaries and the resistance force against the deformation of cells (Honda, 1978, 1983). The `EulerSolver` class in `tyssue` allows to simulate such an over-damped movement.

Interactions in the epithelium are described as potentials depending on the mesh geometry, as described in Farhadifar et al., who showed that a 2D epithelium geometry and topology can be faithfully reproduced by finding the quasi-static equilibrium of energy depending on cell areas and junction lengths (Farhadifar et al., 2007). The `QSSolver` class allows to solve this gradient descent problem.

More recently, Bi et al. focused his work on tissue rigidity which allows or not cell displacement in an epithelium, based on the relation between area and perimeter of a cell (Bi et al., 2015). In `tyssue`, it is easy to define custom terms of the potential, through an object oriented model "factory" design, and use them to solve either the over-damped or gradient descent problem.

This way, it is easy to test various combinations of energy terms and find those that best fit the observed *in vivo* dynamics.

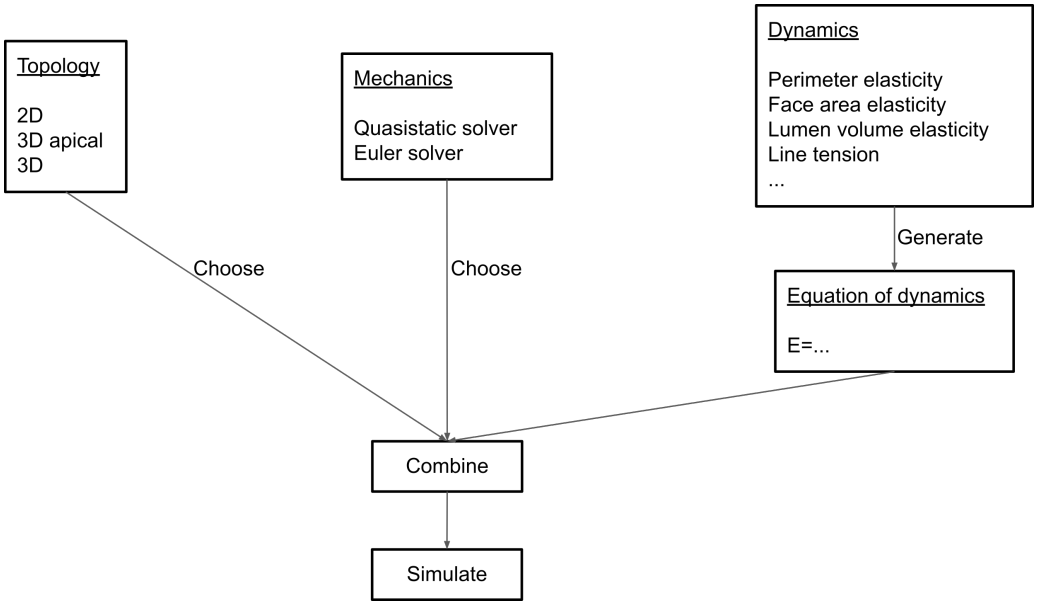

Figure 2: Organisation of different part of tyssue

Documentation of the `tyssue` Python library can be found here. Notebook introduction on how to use `tyssue` library can be found here.

The `tyssue` library has already been used in several studies with different context of epithelia morphogenesis, such as leg folding and mesoderm invagination in *Drosophila melanogaster* (Gracia et al., 2019; Martin et al., 2021; Monier et al., 2015). Github repository from those publications can be found here, here and here respectively.

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Code

tyssue is written in Python 3. Code and detailed installation instructions can be found here. Continuous integration is performed with Travis. The associated code coverage can be found at CodeCov.

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