



**HAL**  
open science

## Tyssue: an epithelium simulation library

Sophie Theis, Magali Suzanne, Guillaume Gay

► **To cite this version:**

Sophie Theis, Magali Suzanne, Guillaume Gay. Tyssue: an epithelium simulation library. Journal of Open Source Software, 2021, 6 (62), pp.2973. 10.21105/joss.02973 . hal-03765428

**HAL Id: hal-03765428**

**<https://hal.science/hal-03765428>**

Submitted on 31 Aug 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

# Tyssue: an epithelium simulation library

Sophie Theis<sup>1, 2</sup>, Magali Suzanne<sup>2</sup>, and Guillaume Gay<sup>1, 3</sup>

1 Morphogénie Logiciels, 32110 St Martin d'Armagnac, France. 2 LBCMCP, Centre de Biologie Intégrative (CBI), Université de Toulouse, CNRS, UPS, Toulouse 31062, France. 3 Turing Center for Living Systems, Marseille, France

DOI: [10.21105/joss.02973](https://doi.org/10.21105/joss.02973)

## Software

- [Review](#) ↗
- [Repository](#) ↗
- [Archive](#) ↗

Editor: [Pierre de Buyl](#) ↗

## Reviewers:

- [@fcooper8472](#)
- [@SergeDmi](#)

Submitted: 04 December 2020

Published: 07 June 2021

## License

Authors of papers retain copyright and release the work under a Creative Commons Attribution 4.0 International License ([CC BY 4.0](#)).

## Summary

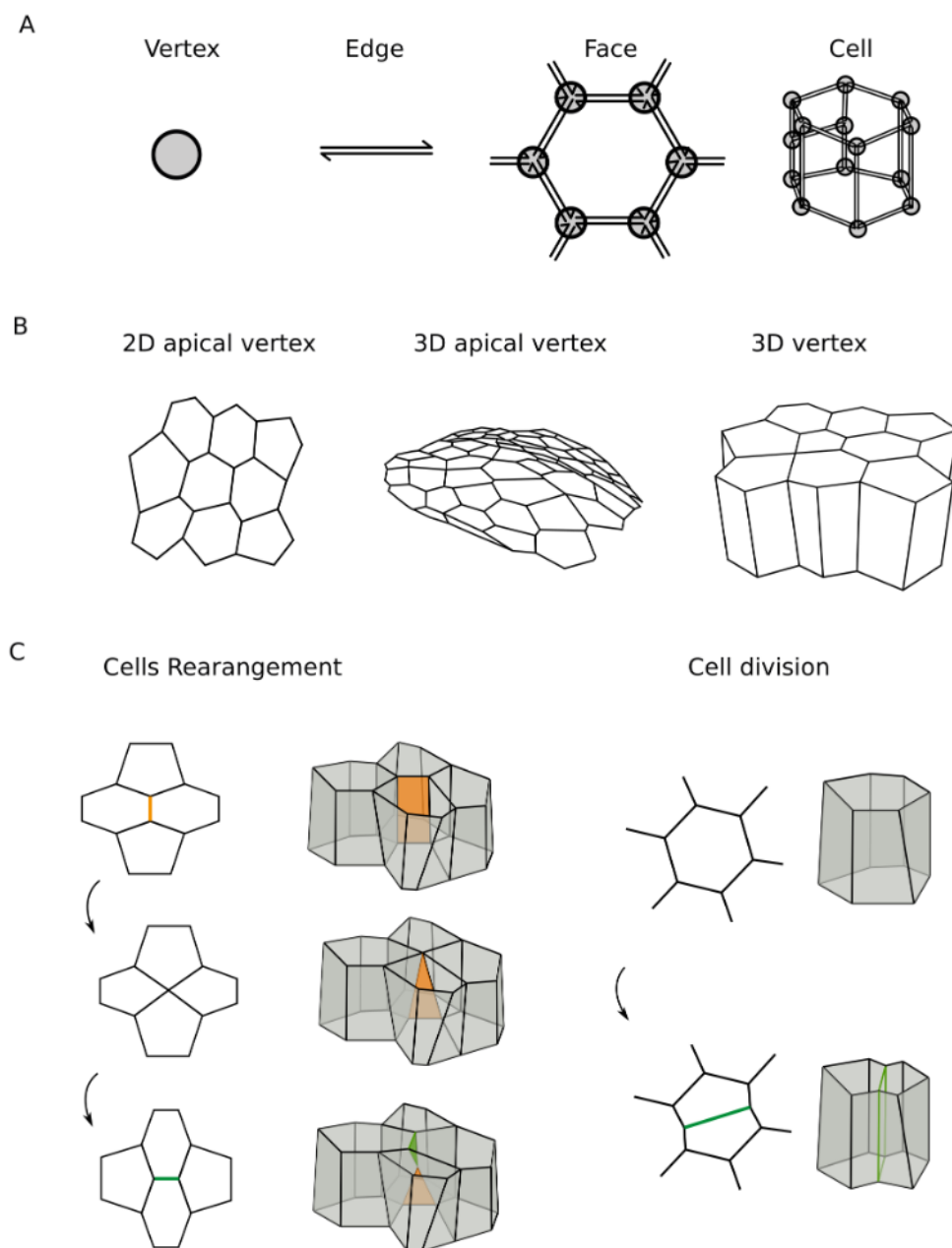
The `tyssue` Python library seeks to provide a unified interface to implement bio-mechanical models of living tissues. Its main focus is on vertex based epithelium models. `tyssue` allows to model the mechanical behavior of 2D, apical 3D or full 3D epithelia based on the numerical resolution of the equations 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

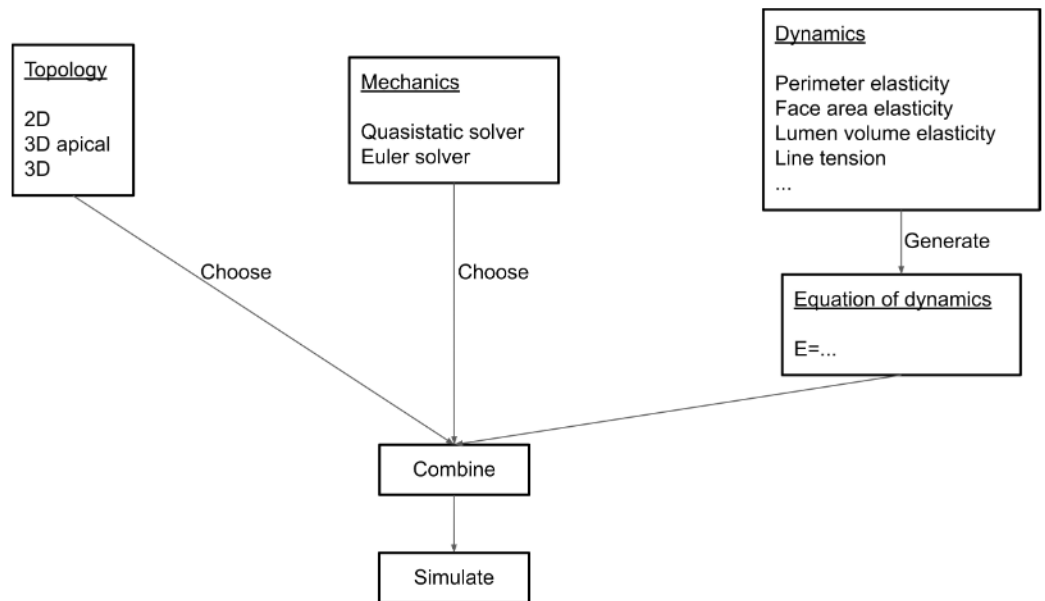
In `tyssue`, the dynamical behavior of epithelium is described by solving the equation of motions following Newton's principle. At the scales of the studied processes, the inertia is negligible compared to other forces such as friction, adhesion or contraction of the actin cytoskeleton.

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 tissue**

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.

## Acknowledgements

The development of `tyssue` was supported by grants from the European Research Council (ERC) under the European Union Horizon 2020 research and innovation program (grant number EPAF: 648001), and from the Association Nationale de la recherche et de la Technologie (ANRT). `tyssue` has benefited from the contributions of [Hadrien Mary](#), [George Courcoubetis](#), [Bertrand Caré](#) and [Félix Quinton](#).

We wish to thank all past and present members of Magali Suzanne's team for their continuous support and for providing valuable insight on epithelium biology, Cyprien Gay for the discussions on the physics of epithelia, and the scientific python community for the core tools ([Harris et al., 2020](#); [Hunter, 2007](#); [McKinney, 2010](#); [Virtanen et al., 2020](#)) we use in this project.

## Correspondence

Please contact [guillaume@damcb.com](mailto:guillaume@damcb.com)

## 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](#).



## References

- Aegerter-Wilmsen, T., Heimlicher, M. B., Smith, A. C., Reuille, P. B. de, Smith, R. S., Aegerter, C. M., & Konrad, B. (2012). Integrating force-sensing and signaling pathways in a model for the regulation of wing imaginal disc size. *Development*. <https://doi.org/10.1242/dev.082800>
- Aigouy, B., Farhadifar, R., Staple, D. B., Sagner, A., Röper, J.-C., Jülicher, F., & Eaton, S. (2010). Cell Flow Reorients the Axis of Planar Polarity in the Wing Epithelium of *Drosophila*. *Cell*, *142*, 773–786. <https://doi.org/10.1016/j.cell.2010.07.042>
- Alt, S., Ganguly, P., & Salbreux, G. (2017). Vertex models: from cell mechanics to tissue morphogenesis. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *372*(1720), 20150520. <https://doi.org/10.1098/rstb.2015.0520>
- Bi, D., Lopez, J. H., Schwarz, J. M., & Manning, M. L. (2015). A density-independent rigidity transition in biological tissues. *Nature Physics*, *11*(12), 1074–1079. <https://doi.org/10.1038/nphys3471>
- Brodland, G. W., & Veldhuis, J. H. (2002). Computer simulations of mitosis and interdependencies between mitosis orientation, cell shape and epithelia reshaping. *Journal of Biomechanics*, *35*(5), 673–681. [https://doi.org/10.1016/S0021-9290\(02\)00006-4](https://doi.org/10.1016/S0021-9290(02)00006-4)
- Cooper, F., Baker, R., Bernabeu, M., Bordas, R., Bowler, L., Bueno-Orovio, A., Byrne, H., Carapella, V., Cardone-Noott, L., Cooper, J., Dutta, S., Evans, B., Fletcher, A., Grogan, J., Guo, W., Harvey, D., Hendrix, M., Kay, D., Kursawe, J., ... Gavaghan, D. (2020). Chaste: Cancer, Heart and Soft Tissue Environment. *Journal of Open Source Software*, *5*(47), 1848. <https://doi.org/10.21105/joss.01848>
- Eritano, A. S., Bromley, C. L., Bolea Albero, A., Schütz, L., Wen, F.-L., Shibata, T., Takeda, M., Sami, M. M., Lemke, S., & Wang, Y.-C. (2020). Tissue-Scale Mechanical Coupling Reduces Morphogenetic Noise to Ensure Precision During Epithelial Folding. *Developmental Cell*, *53*, 1–17. <https://doi.org/10.2139/ssrn.3378007>
- Farhadifar, R., Röper, J.-C., Aigouy, B., Eaton, S., & Jülicher, F. (2007). The Influence of Cell Mechanics, Cell-Cell Interactions, and Proliferation on Epithelial Packing. *Current Biology*, *17*(24), 2095–2104. <https://doi.org/10.1016/J.CUB.2007.11.049>
- Gracia, M., Theis, S., Proag, A., Gay, G., Benassayag, C., & Suzanne, M. (2019). Mechanical impact of epithelial–mesenchymal transition on epithelial morphogenesis in *Drosophila*. *Nature Communications*, *10*(1), 2951. <https://doi.org/10.1038/s41467-019-10720-0>
- Harris, C. R., Millman, K. J., Walt, S. J. van der, Gommers, R., Virtanen, P., Cournapeau, D., Wieser, E., Taylor, J., Berg, S., Smith, N. J., Kern, R., Picus, M., Hoyer, S., Kerkwijk, M. H. van, Brett, M., Haldane, A., Fernández del Río, J., Wiebe, M., Peterson, P., ... Oliphant, T. E. (2020). Array programming with NumPy. *Nature*, *585*, 357–362. <https://doi.org/10.1038/s41586-020-2649-2>
- Heer, N. C., Miller, P. W., Chanet, S., Stoop, N., Dunkel, J., & Martin, A. C. (2017). Actomyosin-based tissue folding requires a multicellular myosin gradient. *Development*, *144*(10), 1876–1886. <https://doi.org/10.1242/dev.146761>
- Honda, H. (1978). Description of cellular patterns by dirichlet domains: The two-dimensional case. *Journal of Theoretical Biology*, *72*(3), 523–543. [https://doi.org/10.1016/0022-5193\(78\)90315-6](https://doi.org/10.1016/0022-5193(78)90315-6)
- Honda, H. (1983). Geometrical models for cells in tissues. *International Review of Cytology*, *81*, 191–248. [https://doi.org/10.1016/S0074-7696\(08\)62339-6](https://doi.org/10.1016/S0074-7696(08)62339-6)
- Hunter, J. D. (2007). Matplotlib: A 2D graphics environment. *Computing in Science Engineering*, *9*(3), 90–95. <https://doi.org/10.1109/MCSE.2007.55>

- Martin, E., Theis, S., Gay, G., Monier, B., Rouvière, C., & Suzanne, M. (2021). Arp2/3-dependent mechanical control of morphogenetic robustness in an inherently challenging environment. *Developmental Cell*. <https://doi.org/10.1016/j.devcel.2021.01.005>
- McKinney, W. (2010). Data Structures for Statistical Computing in Python. In S. van der Walt & J. Millman (Eds.), *Proceedings of the 9th Python in Science Conference* (pp. 56–61). <https://doi.org/10.25080/Majora-92bf1922-00a>
- Monier, B., Gettings, M., Gay, G., Mangeat, T., Schott, S., Guarner, A., & Suzanne, M. (2015). Apico-basal forces exerted by apoptotic cells drive epithelium folding. *Nature*, *518*(7538), 245–248. <https://doi.org/10.1038/nature14152>
- Okuda, S., Inoue, Y., Eiraku, M., Adachi, T., & Sasai, Y. (2015). Modeling cell apoptosis for simulating three-dimensional multicellular morphogenesis based on a reversible network reconnection framework. *Biomechanics and Modeling in Mechanobiology*, *15*(4), 805–816. <https://doi.org/10.1007/s10237-015-0724-7>
- Salbreux, G., Barthel, L. K., Raymond, P. A., & Lubensky, D. K. (2012). Coupling Mechanical Deformations and Planar Cell Polarity to Create Regular Patterns in the Zebrafish Retina. *PLoS Computational Biology*, *8*(8), e1002618. <https://doi.org/10.1371/journal.pcbi.1002618>
- Sherrard, K., Robin, F., Lemaire, P., & Munro, E. (2010). Sequential Activation of Apical and Basolateral Contractility Drives Ascidian Endoderm Invagination. *Current Biology*, *20*(17), 1499–1510. <https://doi.org/10.1016/J.CUB.2010.06.075>
- Sui, L., Alt, S., Weigert, M., Dye, N., Eaton, S., Jug, F., Myers, E. W., Jülicher, F., Salbreux, G., & Dahmann, C. (2018). Differential lateral and basal tension drive folding of *Drosophila* wing discs through two distinct mechanisms. *Nature Communications*, *9*(1), 4620. <https://doi.org/10.1038/s41467-018-06497-3>
- Tara M Finegan, Nathan Hervieux, Alexander Nestor-Bergmann, Alexander G. Fletcher, Guy B. Blanchard, Sanson, B., Finegan, T. M., Hervieux, N., Nestor-Bergmann, A., Fletcher, A. G., Blanchard, G. B., & Sanson, B. (2019). The tricellular vertex-specific adhesion molecule Sidekick facilitates polarised cell intercalation during *Drosophila* axis extension. *PLOS Biology*, *17*(12), e3000522. <https://doi.org/10.1101/704932>
- Virtanen, P., Gommers, R., Oliphant, T. E., Haberland, M., Reddy, T., Cournapeau, D., Burovski, E., Peterson, P., Weckesser, W., Bright, J., van der Walt, S. J., Brett, M., Wilson, J., Millman, K. J., Mayorov, N., Nelson, A. R. J., Jones, E., Kern, R., Larson, E., ... SciPy 1.0 Contributors. (2020). SciPy 1.0: Fundamental Algorithms for Scientific Computing in Python. *Nature Methods*, *17*, 261–272. <https://doi.org/10.1038/s41592-019-0686-2>