The Journal of Open Source Software

cellular_raza: Agent-based Modeling of Cellular Systems from a Clean Slate

Jonas Pleyer [1] **and Christian Fleck**[1]

1 Freiburg Center for Data-Analysis and Modeling

DOI: 10.xxxxxx/draft

Software

- Review
- Repository
- Archive

Editor: Open Journals

Reviewers:

- @openjournals

Submitted: 01 January 1970
Published: unpublished

Summary

`cellular_raza` is a cellular agent-based modeling framework which allows researchers to construct models from a clean slate. In contrast to other agent-based modeling toolkits, `cellular_raza` was designed to be free of assumptions about the underlying cellular representation. This enables researchers to build up complex models while retaining full control over every parameter introduced. It comes with predefined building blocks for agents and their physical domain to quickly construct new simulations bottom-up. Furthermore, `cellular_raza` has been used with the `pyo3` and `maturin` packages to create python bindings and can thus act as a numerical backend to a python package.

Statement of Need

Agent-based models have become popular in cellular biology (Cess & Finley, 2022; Delile et al., 2017a, 2017b; Mogilner & Manhart, 2016). While these tools have proven to be effective for targeted research questions, they often lack the ability to be applied for multiple distinct use-cases in a more generic context. However, core functionalities such as numerical solvers, storage solutions, domain decomposition methods and functions to construct these simulations could be shared between models if written in a generic fashion. In order to combat this issue and build up models from first principles without any assumptions on the underlying complexity or abstraction level, we developed `cellular_raza`.

State of Field

General-Purpose Agent-Based Modeling Toolkits

General-purpose agent-based toolkits are mostly designed with multiple applications in mind (Abar et al., 2017; Wilensky, 1999; **Datseries2022?**). They are often able to define agents bottom-up and can be a good choice if they allow for the desired cellular representation. However, they lack the explicit forethough to be applied in cellular systems and may implement global rules rather than individual-based ones. Furthermore, since they are required to solve a wider range of problems they are not able to make assumptions on the type of agent or the nature of their interactions and thus miss out on possible performance optimizations and advanced numerical solvers.

Cellular Agent-Based Frameworks

In our previous efforts (Pleyer & Fleck, 2023) we have assessed the overall state of modeling toolkits for individual-based cellular simulations. The inspected frameworks are all crafted for specific use-cases and may require a many parameters. These parameters are often not known in practice and are cumbersome to determine experimentally. This creates problems

for the extendability of the software and the ability to properly interpret results. Only few modeling frameworks exist which provide a significant level of flexibility and customizability in their definition of cell-agents. Chaste (Cooper et al., 2020) allows to reuse individual components of their simulation code such as ODE and PDE solvers but is only partially cell-based. Biocellion (Kang et al., 2014) has support for different cell shapes such as spheres and cylinders but acknowledges that their current approach lacks flexibility in the subcellular description. BioDynaMo (Breitwieser et al., 2021) offers some modularity in the choice for components of cellular agents but can not freely customize the cellular representation.

Examples

Examples and simulaton code are explained in full detail at cellular-raza.com/showcase.

Cell Sorting

Cell sorting is a naturally occurring phenomenon (Graner & Glazier, 1992; Steinberg, 1963). While the underlying biological reality can be quite complex, it is rather simple to describe such a system in its most basic form. Fundamentally, any cellular `Interaction` is specific to their species. We consider two distinct species represented by soft spheres which physically attract each other at close proximity if their species is identical. Cells are placed randomly inside a cube with reflective boundary conditions. In the final snapshot, we can clearly see the phase-separation between the different species.

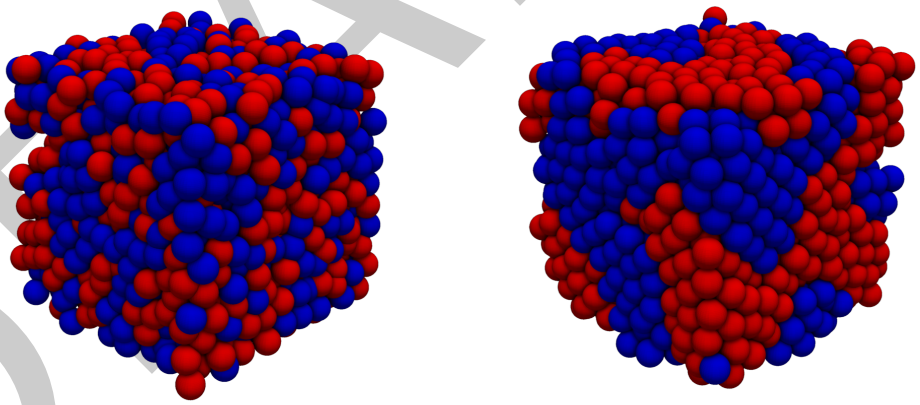

Figure 1: The initial random placement of cells reorders into a phase-separated spatial pattern.

Bacterial Rods

Bacteria come in various forms (Young, 2006; Zapun et al., 2008) such as elongated shapes (Billaudeau et al., 2017) which grows asymmetrically in the direction of elongation. Our model describes the physical mechancis of one cell as a collection of multiple vertices $\vec{v}_i$ which are connected by springs. Their relative angle at each connecting vertex introduces a stiffening force which is proportional to the angle difference $\alpha - 180°$. Cells interact via a soft-sphere force potential with short-ranged attraction. Multiple contributions are calculated between every vertex and the closest point on the other cells edges. In addition, the cell cycle introduces growth of the bacteria until it divides in the middle into two new cells. This growth is downregulated by an increasing number of neighboring cells which is a phenomenological

but effective choice for the transition into the stationary phase of the bacterial colony. Cells are placed inside the left-hand side of an elongated box with reflective boundary conditions. Their colors range from green for fast growth to blue for dormant cells.

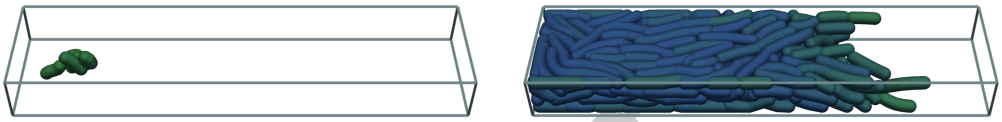

Figure 2: The bacteria extend from the initial placement in the left side towards the right side. Their elongated shape and the confined space favour the orientation facing along the growth direction.

Branching of *Bacillus Subtilis*

Spatio-temporal patterns of bacterial growth such as in *Bacillus Subtilis* have been studied for numerous years (Kawasaki et al., 1997; Matsushita et al., 1998). Cells are modeled by soft spheres which interact with the domain by taking up nutrients. By consuming intracellular nutrients, the cell grows continuously and divides upon reaching a threshold. The initial placement of the cells is inside of a centered square. From there, cells start consuming nutrients and growing outwards towards the nutrient-rich area. Cells are colored bright purple while they are actively growing and dividing while dark cells are not subject to growth anymore. The outer domain is colored by the intensity of present nutrients. A lighter color indicates that more nutrients are available while a dark color signifies a lack thereof.

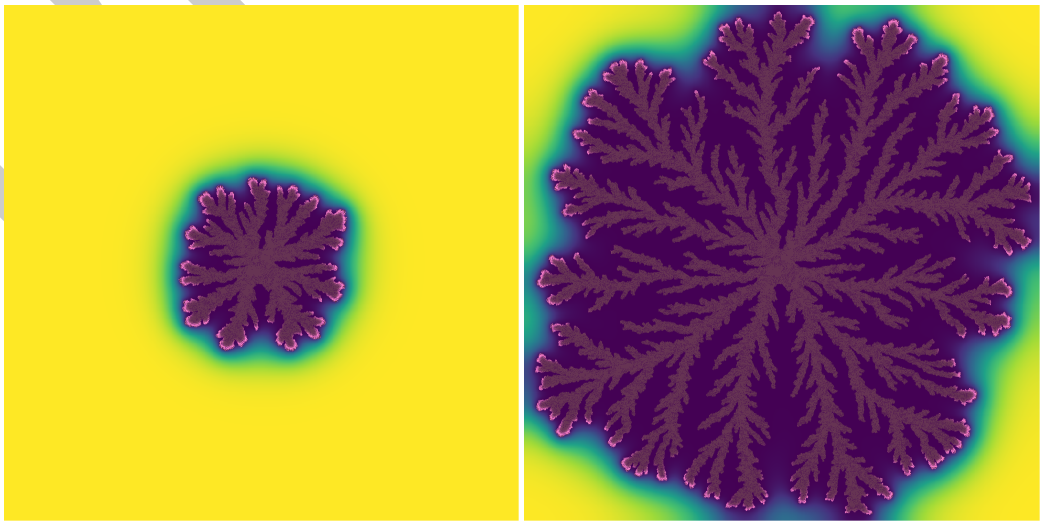

Figure 3: The bacterial colony grows outwards towards the nutrient-rich parts of the domain thus forming branches in the process.

Semi-Vertex Model for Epithelial and Plant Cells

Vertex models are a very popular choice in describing multicellular systems. They are actively being used in great variety such as to describe mechanical properties of plant cells (Merks et al., 2011) or organoid structures of epithelial cells (Barton et al., 2017; Fletcher et al., 2014).

We represent cells by a polygonal collection of vertices connected by springs. An inside pressure pushes vertices in an outwards direction. These two mechanisms by themselves create perfect hexagonal cells. Cells are attracting each other but in the case where two polygons overlap, a repulsive force acts between them. Cells are placed in a perfect hexagonal grid such that edges and vertices align. Their growth rates are chosen from a uniform distribution.

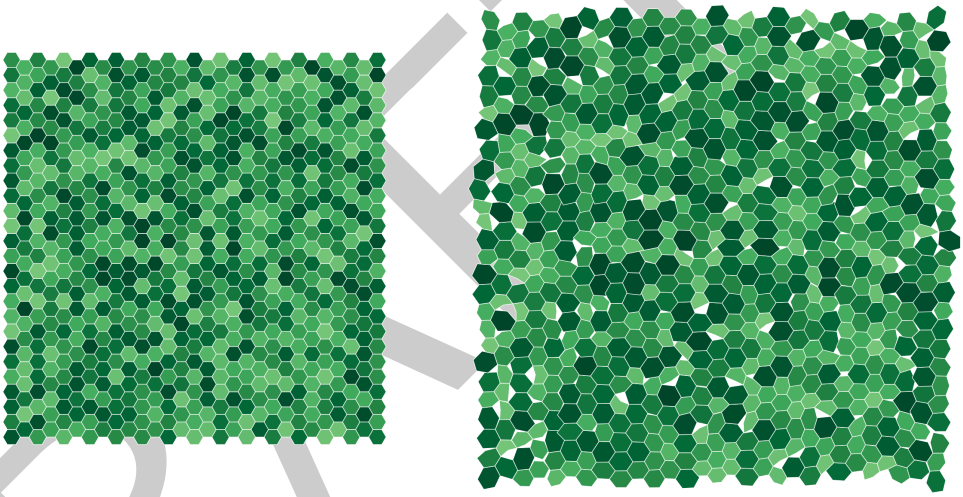

Figure 4: During growth the cells push on each other thus creating small spaces in between them as the collection expands. These forces also lead to deviations in the otherwise perfect hexagonal shape.

Acknowledgements

References

Abar, S., Theodoropoulos, G. K., Lemarinier, P., & O'Hare, G. M. P. (2017). Agent based modelling and simulation tools: A review of the state-of-art software. *Computer Science Review*, *24*, 13–33. https://doi.org/10.1016/j.cosrev.2017.03.001

Barton, D. L., Henkes, S., Weijer, C. J., & Sknepnek, R. (2017). Active vertex model for cell-resolution description of epithelial tissue mechanics. *PLOS Computational Biology*, *13*(6), e1005569. https://doi.org/10.1371/journal.pcbi.1005569

Billaudeau, C., Chastanet, A., Yao, Z., Cornilleau, C., Mirouze, N., Fromion, V., & Carballido-López, R. (2017). Contrasting mechanisms of growth in two model rod-shaped bacteria. *Nature Communications*, *8*(1). https://doi.org/10.1038/ncomms15370

Breitwieser, L., Hesam, A., Montigny, J. de, Vavourakis, V., Iosif, A., Jennings, J., Kaiser, M., Manca, M., Di Meglio, A., Al-Ars, Z., Rademakers, F., Mutlu, O., & Bauer, R.

(2021). BioDynaMo: a modular platform for high-performance agent-based simulation. *Bioinformatics*, *38*(2), 453–460. https://doi.org/10.1093/bioinformatics/btab649

Cess, C. G., & Finley, S. D. (2022). Multiscale modeling of tumor adaption and invasion following anti-angiogenic therapy. *Computational and Systems Oncology*, *2*(1). https://doi.org/10.1002/cso2.1032

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

Delile, J., Herrmann, M., Peyriéras, N., & Doursat, R. (2017a). A cell-based computational model of early embryogenesis coupling mechanical behaviour and gene regulation. *Nature Communications*, *8*(1). https://doi.org/10.1038/ncomms13929

Delile, J., Herrmann, M., Peyriéras, N., & Doursat, R. (2017b). A cell-based computational model of early embryogenesis coupling mechanical behaviour and gene regulation. In *Nature Communications* (No. 1; Vol. 8). Springer Science; Business Media LLC. https://doi.org/10.1038/ncomms13929

Fletcher, A. G., Osterfield, M., Baker, R. E., & Shvartsman, S. Y. (2014). Vertex models of epithelial morphogenesis. *Biophysical Journal*, *106*(11), 2291–2304. https://doi.org/10.1016/j.bpj.2013.11.4498

Graner, F., & Glazier, J. A. (1992). Simulation of biological cell sorting using a two-dimensional extended potts model. *Physical Review Letters*, *69*(13), 2013–2016. https://doi.org/10.1103/physrevlett.69.2013

Kang, S., Kahan, S., McDermott, J., Flann, N., & Shmulevich, I. (2014). Biocellion : Accelerating computer simulation of multicellular biological system models. *Bioinformatics*, *30*(21), 3101–3108. https://doi.org/10.1093/bioinformatics/btu498

Kawasaki, K., Mochizuki, A., Matsushita, M., Umeda, T., & Shigesada, N. (1997). *Modeling Spatio-Temporal Patterns Generated byBacillus subtilis*. https://doi.org/10.1006/jtbi.1997.0462

Matsushita, M., Wakita, J., Itoh, H., Ràfols, I., Matsuyama, T., Sakaguchi, H., & Mimura, M. (1998). *Interface growth and pattern formation in bacterial colonies*. https://doi.org/10.1016/S0378-4371(97)00511-6

Merks, R. M. H., Guravage, M., Inzé, D., & Beemster, G. T. S. (2011). VirtualLeaf: An open-source framework for cell-based modeling of plant tissue growth and development. *Plant Physiology*, *155*(2), 656–666. https://doi.org/10.1104/pp.110.167619

Mogilner, A., & Manhart, A. (2016). Agent-based modeling: Case study in cleavage furrow models. *Molecular Biology of the Cell*, *27*(22), 3379–3384. https://doi.org/10.1091/mbc.e16-01-0013

Pleyer, J., & Fleck, C. (2023). Agent-based models in cellular systems. *Frontiers in Physics*, *10*. https://doi.org/10.3389/fphy.2022.968409

Steinberg, M. S. (1963). Reconstruction of tissues by dissociated cells: Some morphogenetic tissue movements and the sorting out of embryonic cells may have a common explanation. *Science*, *141*(3579), 401–408. https://doi.org/10.1126/science.141.3579.401

Wilensky, U. (1999). *NetLogo* [Http://ccl.northwestern.edu/netlogo/]. Center for Connected Learning; Computer-Based Modeling. http://ccl.northwestern.edu/netlogo/

Young, K. D. (2006). The selective value of bacterial shape. *Microbiology and Molecular Biology Reviews*, *70*(3), 660–703. https://doi.org/10.1128/mmbr.00001-06

Zapun, A., Vernet, T., & Pinho, M. G. (2008). The different shapes of cocci. *FEMS Microbiology Reviews*, *32*(2), 345–360. https://doi.org/10.1111/j.1574-6976.2007.00098.x