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cellular_raza: Cellular Agent-based Modeling from a Clean Slate

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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` can be used with the `pyo3` and `maturin` packages and thus act as a numerical backend to a Python package.

Statement of Need

Agent-based models have become increasingly prevalent in the field of cellular biology (Cess & Finley, 2022; Delile et al., 2017a, 2017b; Mogilner & Manhart, 2016). Numerous tools have been developed that can delineate cellular systems with great precision (Abar et al., 2017; Pleyer & Fleck, 2023). While these tools have proven effective for specific research inquiries, they frequently lack the capacity to be applied more universally. In contrast, general-purpose ABM toolkits are not designed with particular applications in mind (Abar et al., 2017; Datseris et al., 2022; Wilensky, 1999). These toolkits often enable the definition of agents bottom-up and can be a suitable choice if they allow for the desired cellular representation. However, they lack the explicit forethought necessary for application in cellular systems and may not be able to describe every cellular aspect.

In contrast to classical particle simulations, agent-based models (ABMs) treat every cell individually. This implies that parameters can vary between agents and that every cell should be traceable throughout time and space. Additionally, they can describe growth, proliferation, death, and many other cellular processes and should also accurately model cell lineage. These models operate on the mesoscopic scale where the underlying complexity of the problem cannot be fully attributed to either intracellular or extracellular processes. Their applications include modeling of self-organization and emergent phenomena, but they can also be used to introduce spatial effects into existing population-based models. To address these issues and construct models from first principles without any assumptions regarding the underlying complexity or abstraction level, we developed "cellular_raza."

Cellular Agent-Based Frameworks

In our previous efforts (Pleyer & Fleck, 2023), we assessed the overall state of modeling toolkits for individual-based cellular simulations. These frameworks are designed for specific usages and often require many parameters which are unknown or difficult to determine experimentally. This poses an inherent problem for their applicability and the ability to properly interpret

results. Few modeling frameworks exist that provide a significant degree of flexibility and customization in the definition of cell agents. Chaste (Cooper et al., 2020) allows reuse of individual components , such as ODE and PDE solvers, but is only partially cell-based. Biocellion (Kang et al., 2014) supports different cell shapes such as spheres and cylinders, but admits that their current approach lacks flexibility in the subcellular description. BioDynaMo (Breitwieser et al., 2021) offers some modularity in the choice of components for cellular agents, but cannot deeply customize the cellular representation.

cellular_raza

We distinguish between different simulation aspects, i.e., mechanics, interaction, or cell cycle. These aspects are directly related to the properties of the cells, domain, or other external interactions. The user selects a cellular representation, which can be built from pre-existing building blocks or fully customized bottom-up. `cellular_raza` utilizes macros to generate code contingent on the simulation aspects. It makes extensive use of generics and provides abstract numerical solvers. `cellular_raza` encapsulates the inherent complexity of the code generation process, yet enables users to modify the specifics of the simulation through the use of additional keyword arguments. Consequently, users are able to fully and deeply customize the representation and behavior of the agents. Each simulation aspect is abstractly formulated as a trait in Rust's type system. The getting-started guide provides a good entry point and explains every step from building to running and visualizing.

Examples

In the following, we present four different examples of how to use `cellular_raza` (see cellular-raza.com/showcase).

Cell Sorting

Cell sorting is a naturally occurring phenomenon (Graner & Glazier, 1992; Steinberg, 1963), where the cellular interaction is species-specific. We consider two distinct types represented by soft spheres. They 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.

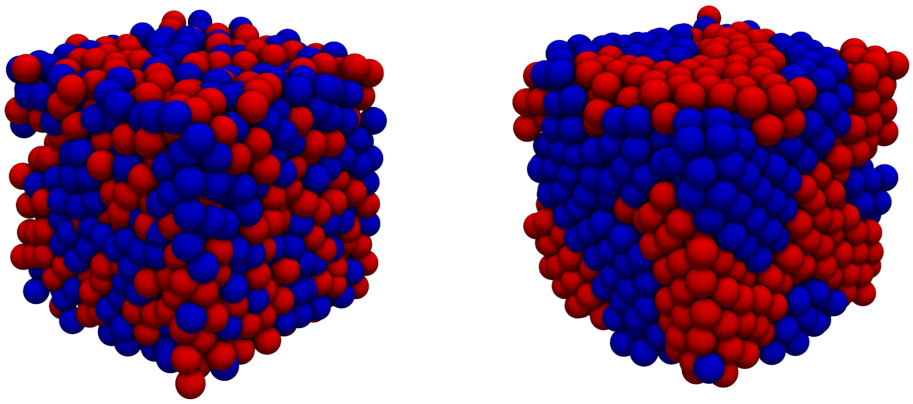

Figure 1: The initial random placement of cells reorders into a phase-separated spatial pattern.

Bacterial Rods

Bacteria come in various forms (Young, 2006; Zapun et al., 2008) such as elongated shapes (Billaudeau et al., 2017) which grow asymmetrically in the direction of elongation. Our model describes the physical mechanics of one cell as a collection of multiple vertices $\vec{v}_i$ which are connected by springs. Their relative angle α at each connecting vertex introduces a curvature force proportional to $2\tan(\alpha/2)$. 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. 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.

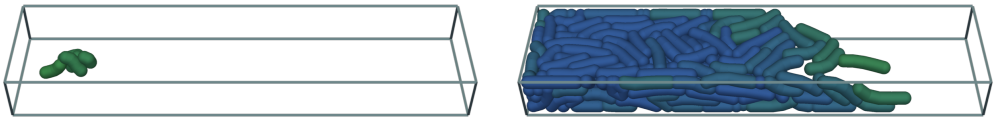

Figure 2: The bacteria extend from the initial placement in the left side towards the right side. Their elongated shape and the confined space favour the orientation facing along the growth direction.

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 as soft spheres which take up nutrients from the domain. By consuming intracellular nutrients, the cell grows continuously and divides upon reaching a threshold. Cells are initially placed inside a centered square after which they grow outwards into the nutrient-rich area. They are colored by the size of their radii from dark purple right after the division event to bright. A lighter color in the outer domain indicates that more nutrients are available while a dark color signifies a lack thereof.

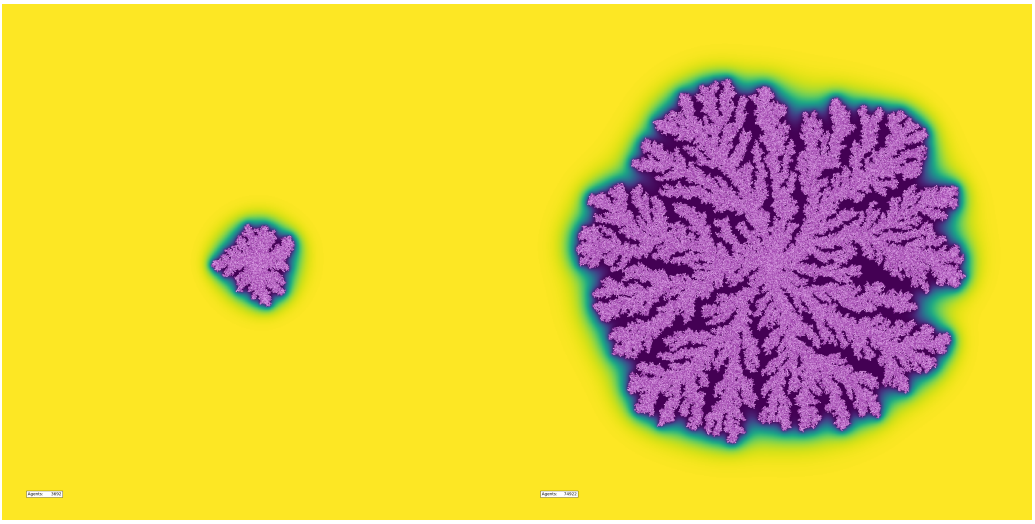

Figure 3: The bacterial colony grows outwards towards the nutrient-rich parts of the domain thus forming branches in the process.

Semi-Vertex Model for Epithelial and Plant Cells

Vertex models are actively being used 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 outwards, creating perfect hexagonal cells. Cells are attracting each other but whenever two polygons overlap, a repulsive force acts. They are placed in a perfect hexagonal grid such that edges and vertices align and assigned growth rates from a uniform distribution.

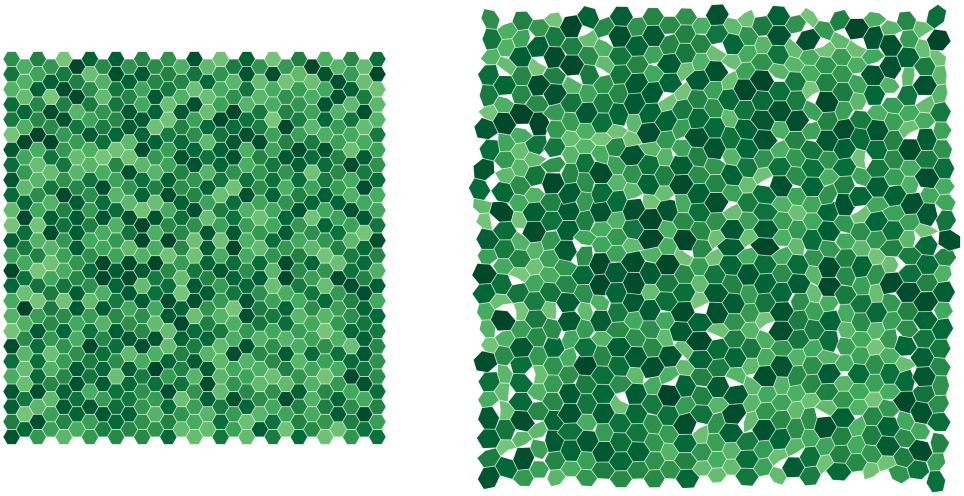

Figure 4: During growth the cells push on each other thus creating small spaces in between them as the collection expands. These forces also lead to deviations in the otherwise perfect hexagonal shape.

Further Information

The full documentation including guides, all examples from above and more is available at cellular-raza.com. `cellular_raza` can also be used as a numerical backend together with the

`pyo3` and `maturin` konsti (2025) crates.

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