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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 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. Nevertheless, core functionalities such as numerical solvers, storage solutions, domain decomposition methods and functions to construct these simulations could be shared between models if written generically. In order to address this issue and construct models from first principles without any assumptions regarding 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 often designed without specific applications in mind (Abar et al., 2017; Datseris et al., 2022; Wilensky, 1999). 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. 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 assessed the overall state of modelling toolkits for individual-based cellular simulations. The frameworks reviewed are all designed for specific use cases and often require a large number of parameters which are often unknown in practice and difficult to determine experimentally. This is an inherent problem for the applicability of the software and the ability to properly interpret results. Few modelling frameworks exist

that provide a significant degree of flexibility and customisation in the definition of cell agents. Chaste (Cooper et al., 2020) allows reuse of individual components of its 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 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 freely customise the cellular representation.

cellular_raza

We distinguish between different simulation aspects, e.g., mechanics, cell cycle, 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 a fully customised bottom-up approach, if desired. 'cellular_raza' utilises macros to generate code contingent on the simulation aspects being solved numerically. It makes extensive use of generics and provides abstract numerical solvers. 'cellular_raza' hides 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 within the macros. Consequently, users are able to fully and deeply customise the representation and behaviour of the agents. Each simulation aspect is formulated as a trait in Rust's type system, which provides the necessary abstractions. The getting-started guide provides a good entry point and explains every step from building, running to visualising.

Examples

In the following, we present four different examples how to use `cellular_raza` (see 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.

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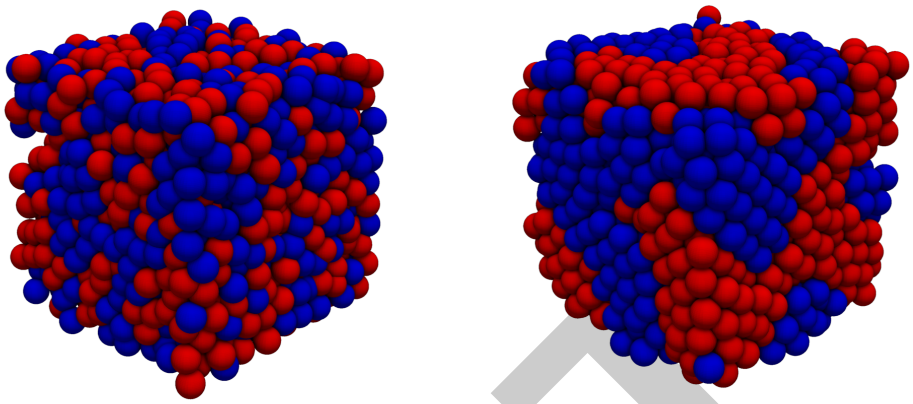

Figure 1: The initial random placement of cells reorders into a phase-separated spatial pattern.

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.

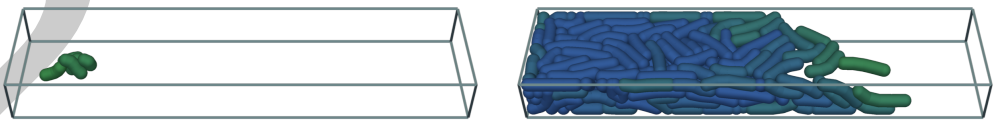

Figure 2: The bacteria extend from the initial placement in the left side towards the right side. Their elongated shape and the confined space favour the orientation facing along the growth direction.

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.

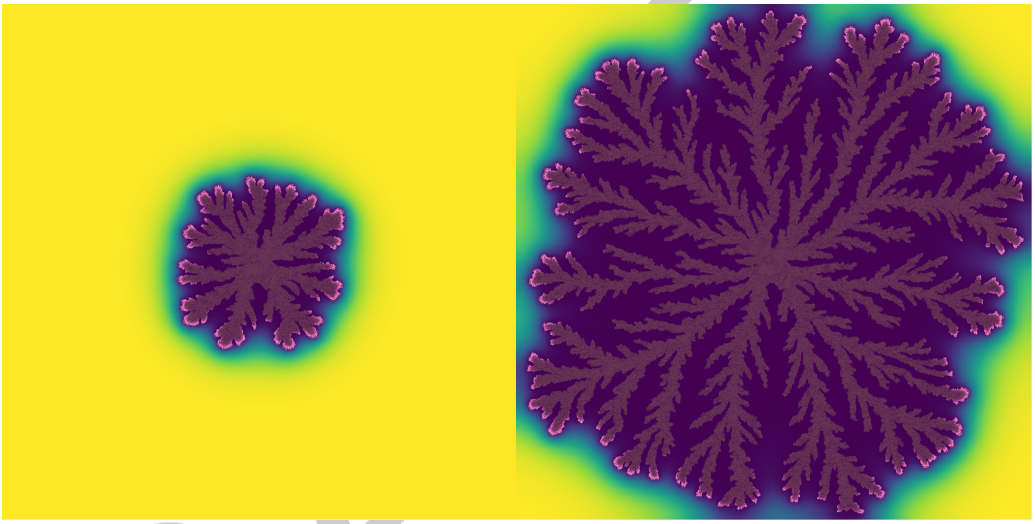

Figure 3: The bacterial colony grows outwards towards the nutrient-rich parts of the domain thus forming branches in the process.

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.

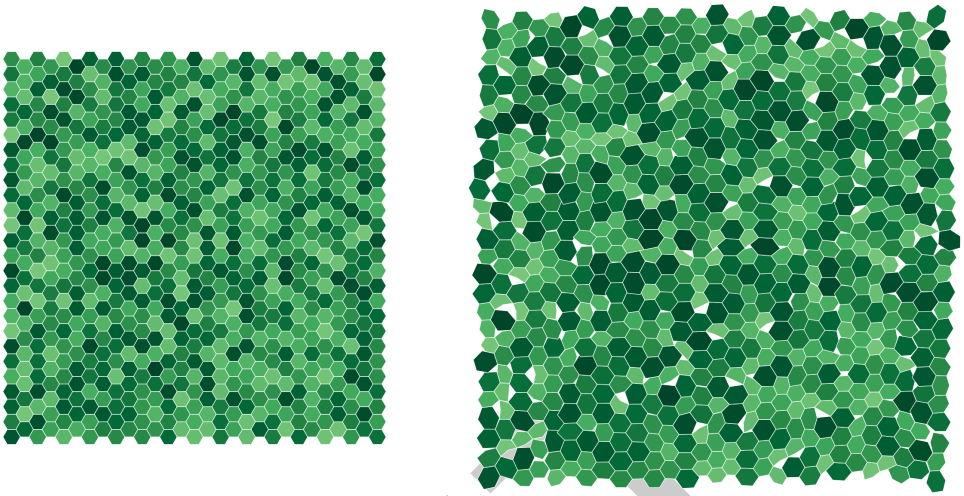

Figure 4: During growth the cells push on each other thus creating small spaces in between them as the collection expands. These forces also lead to deviations in the otherwise perfect hexagonal shape.

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