Interactive, Agent-Based Biological Cell Simulations for Morphogenesis

Andreas Knote and Sebastian von Mammen

University of Würzburg
Germany
{andreas.knote,sebastian.von.mammen}@uni-wuerzburg.de

Abstract. Inspired by the success of interactive simulations in the analysis of complex systems, we investigate interactive simulations of biological systems, especially multicellular organisms. Such interactive biological simulations would aid biologists in understanding the behavior of simulation models, in the deliberate search for model inconsistencies, in guiding model development, and in the design and preparation of wet lab experiments. We currently focus our research on the formation of structure and shape, a process called morphogenesis. Cellular biological systems can be modeled as self-organizing systems of cells acting as autonomous agents. In terms of sensors and actuators, chemical messaging and physical interactions between the cells are an essential requirement for modeling the agents' behaviors. Simulations combining these aspects have high computational demands, and existing simulations in the biological domain often use optimizations that limit their real-time capability which is required for human-computer interaction. In this chapter, we first report the key results of an interactive, immersive biological cell simulation prototype. Based on this, we lay out and prioritize the next steps to tackle the problems of complexity, interaction, visualization, and integration with the workflow.

Keywords: Interactive Simulation · Biological Cell Simulation · Complex Systems · Developmental Biology.

1 Introduction

Empirical sciences strive for accurate and comprehensive models of reality. In biology, such models have inherently great complexity and are hard to unearth fully. On the one hand, there is a large number of factors whose impact to investigate, and on the other hand, empirical assays are time and resource intense.

1.1 Interactive Simulations for Complex System Analysis

Interactive simulations have proven their usefulness in the analysis, development and refinement of complex system models [2,14]. We aim at transferring this usefulness to biological systems, especially multicellular organisms, supporting biologists in three different ways:

Model Exploration First, they allow users to better understand the behavior of simulation models through interactive exploration of simulation setups, thereby improving their proficiency. For example, they are interested in exploring the impact of directed proliferation and over-proliferation on the resulting shape of tissue. Also, merely observing interactions between different tissue layers, or exploring diffusion gradients of different gene products, or tracing which cells see which see which signals would allow deepening insights into emerging properties of the cellular system.

Model Analysis Second, they can be used in the search for model inconsistencies based on a researcher's knowledge and experience, thereby guiding model development. As the exploration of the simulation landscape and its dynamics becomes more accessible, the user can effortlessly refocus on possibly unexpected developments during the runtime of the simulation.

Synthesis Ultimately, alleviating the burden of exploring models can lead to faster convergence of hypotheses and models. Finally, given sufficiently plausible and tested models, costly wet-lab experiments can be planned and tested in dry simulations, improving efficiency.

1.2 Requirements of Interactive Biological Simulations

Such interactive simulations have a number of requirements, which we will detail in the subsequent paragraphs. First, a modeling paradigm for the biological system needs to be selected. Second, the necessary mathematical model(s) that power the simulation and their implementation raises issues with computational demand and scalability, which need to be addressed. Third, meaningful visualizations and interactions need to be designed. Fourth, existing data sources and sinks need to be integrated.

Cell-Centered Modeling Merks and Glazier [13] make a case for a mesoscale simulation of tissue, using cells as the central simulated units. To cope with the computational complexity of this approach, the cell model needs to be sufficiently abstract. Treating cells phenomenologically as agents that react to the influences from the environment with a basic set of responses can already be sufficient to explore the dynamics of tissue formation. Chemical messaging and physical interactions between the cells are a crucial requirement for the modeling of the mechanisms involved in the self-organization of cells. Cells can produce and sense chemical or electrical signals, which persist and propagate to their neighbors, for example through diffusion processes, which allows them to communicate indirectly by manipulation of the environment ("stigmergy", [18]).

Computational Requirements and Scalability The complexity of biological systems results in computationally very demanding simulations. It is not

unusual for biological simulations to run on high-performance clusters. Consequently, many existing simulations use optimizations that limit their usability in interactive setups or are very hard or impossible to adapt to support dynamic user interactions. Even though millions of cells might be necessary to represent significant portions of organic tissue, meaningful effects in the simulated biological populations can already be observed when only considering several hundred or thousands of cells [6,16]. Still, even at this number, the demands for an interactive simulation are high, and the implementation and hardware requirements rise accordingly. Therefore, sleek algorithmic designs, exploiting parallelization, distributed computing, and efficient algorithms as well as selecting apt optimizations and modeling approaches are paramount.

Interaction and Visualization At the same time, considerable efforts have to be invested in interfaces that make the user aware of the relevant data in a meaningful way and provide precise and powerful interaction modalities. The demands in terms of visualization and interaction might vary strongly between different simulation models and goals. For example, for the analysis of pressure and strain created by internal forces of a cellular organism, these might be visualized through vector fields or colored overlays, while analyzing specific disruptive events might best be identified using break conditions and highlighting of cell states.

Integration Lastly, to provide a useful tool for biologists and to support them in their research, it is necessary to integrate the interactive simulation with the existing methodological ecosystem. For instance, the import and use of empirically obtained data, such as volumetric CT data, should be as effortless as possible.

In Section 2, we introduce related work on biological cell simulations and agent-based simulations. In Section 3, we give an overview of a prototypical interactive, immersive biological cell simulation used to obtain feedback from domain experts. We discuss feedback and technical issues and derive the resulting next steps in Section 4 before we conclude this work in Section 6

2 Related Work

In the following, we provide related work that inspires and grounds our research, with which we try to occupy a niche in between existing cell simulations by demanding (real-time) interactivity.

2.1 Cell and Cell-Centered Modeling

Merks [13] points to the importance of cell-centered models, emphasizing the view of biological systems as complex systems. Biological cells and the concept of autonomous agents both draw from high autonomy and low central control.

2.2 (Mechanical) Cell Models

MecaCell [6] provides a framework for the integration of physical and behavioral models into a biological simulation. CellSys [9] and CompuCell3D [17] offer examples for an integrated design and visualisation approach. MecaGen [5] offers a full development environment including behavioral programming through gene regulatory networks. However, these simulations are not interactive in the sense of giving the user the ability to interfere with the simulation state directly at runtime.

2.3 Interactive Cell Simulations

An interactive simulation based on the Cellular Potts Model is found in Morpheus [16]. In the domain of molecular simulations, several works on interactive simulations of the processes of interest have been published. Lv et al. [12] research an interactive molecular visualization system based on the Unity game engine. Frey et al. [7] developed a generic system to link molecular simulations with interactive front-ends called MDdriver. Molecule position and energy data are transferred via networks to the visualization engine, and user input is, in turn, converted to physical force to be applied to the simulation.

2.4 Large-Scale Agent-Based Cell Simulations

Large-scale and distributed agent-based simulations on parallel and distributed platforms are an active area of research [10,1]. Timothy [3] is a recent example of a large-scale, agent-based modeling framework for the simulation of biological cell colonies on massively parallel systems. It allows for simulations of up to 10^9 cells (1cm^3 of tissue).

3 Real-Time Interaction Prototype to Generate Feedback from Domain Experts

We have created an interactive simulation prototype that combines a virtual biological cell model with an immersive visualization [11]. It allows to observe and interact with virtual biological cell agents [8,13] in a mock-up experiment using virtual reality gear, as shown in Figure 1.

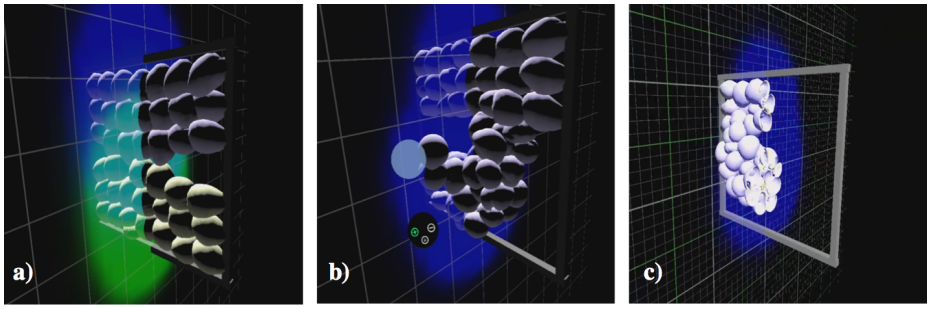

Fig. 1. The interactive simulation prototype as seen through a head-mounted display (cropped field of view). (a) Two types of virtual cells are initially placed in an unstable equilibrium, controlled by two competing signaling substances which are produced by the cells. (b) The balance can be easily disturbed by the user by the introducing new cells or changing the local substance density, causing a phase of uncontrolled proliferation of one cell type and the extinction of the other, until the inducing chemical agent is depleted. (c) The shape and composition of the cell cluster can be visually inspected throughout the simulation. Taken from [11] © 2018 IEEE.

3.1 Cell Model

Multiple cell types can be defined, each with custom logic programmed in C++ or using a visual scripting language. Cells can interface with their environment by, e.g. (1) producing substances and executing logical routines based on the measured concentration of substances in their surroundings, (2) controlling their growth, (3) attaching and detaching regions of their surface to/from other cells, (4) active motion, (5) proliferation/division, or (6) cell death (apoptosis). These mechanisms form the basis of bottom-up modeling of the behavior of multicellular organisms with the goal of recreating their emergent properties. The governing parameters might be subjected to manual, automatic, or guided (self-)optimization cp. [4].

3.2 Methodology

A GPU-driven physics engine, NVidia FleX [15], originally developed for visual effects, was repurposed to provide baseline performance. We further implemented a simple diffusion simulation on the GPU that allows for basic diffusion-evaporation simulation of multiple substances, based on a grid lattice. The system has not been validated for physical correctness for this use case, but was meant to provide plausible behavior for the interactive evaluation by domain experts. More specifically, it should provide actively and passively deformable cells, e.g., growth, stress, and the ability to have the user exert forces on the cells ("pushing"). Most importantly, it should allow the user to *actively, intuitively and dynamically engage* with the simulation. For this prototype, no integration of empirical data was implemented.

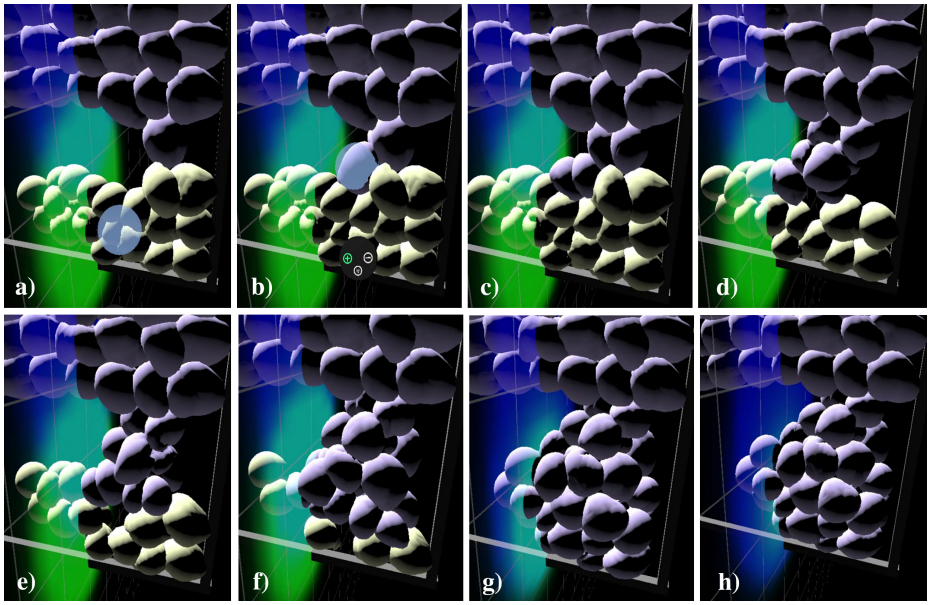

Fig. 2. The interactive simulation prototype as seen through a head-mounted display (cropped field of view). Exemplary user interaction sequence: (a) 00:00:00 The initial configuration of two populations of A- and B-cells (green resp. blue), homogeneously grouped, is mechanically suspended in a rigid frame. (b) 00:00:02 The user places a new A-cell near the line of segregation. (c) 00:00:03 The A-type cells are proliferating due to the presence of B-type signaling substances (green). (d)-(g) 00:00:05-00:00:12 A-cells continue to proliferate and produce signaling substances (blue) that cause B-cells to die. (h) 00:00:13 The concentration of A-cell signaling substances diminishes, and the proliferation comes to a halt.

3.3 Interaction and Visualization

All interaction takes place using tracked motion controllers. The user can place and remove cells of different types, exert physical forces, and modify the local concentration of the chemicals. Morphogen density can be visualized using a relocatable 2D plane. A cutting plane can be used to inspect the interior of the cell cluster.

3.4 Mock-Up Experiment

We prepared a mock-up experiment containing two types of cells, A- and B-type. A-type cells produce a substance that induces cell death in B-cells. B-type cells produce a substance that induces proliferation in A-cells. Initially, a matrix of homogenously distributed cells of each type is mechanically suspended in a rigid frame, as shown in Figure 1. This configuration quickly settles in an unstable equilibrium, with a gap dividing the two populations. As shown in Figure 2,

the user can now place new cells or increase the local concentration of the two cell products, to excite the cells and destroy the equilibrium, usually leading to domination of the A cells.

3.5 Performance

The simulation is capable of simulating up to 250 cells for a VR simulation (Test Setup: Intel i7-7600K, 16 GiB RAM, NVidia GeForce GTX1080 8 GiB) and up to 1024 cells at above 30 frames per second without VR visualization.

4 Discussion and Next Steps

The horizontal prototype of our interactive simulation allowed us to receive feedback from experts in biology on multiple occasions.

4.1 Interacting with Virtual Cells

Even though the prototype did not aim for scientific accuracy, the feedback on the ability to "program" cells using visual scripting, and consequently interact with a simulation interactively at runtime was met with interest and support. Exerting forces by pushing cells, guiding development or triggering disruptive events by distributing signaling molecules in strategic places, and the ability to look and reach below or behind spatial virtual objects proved rather attractive to the testers.

4.2 Lessions Learned

To obtain the prototype, we tried to re-use existing components from real-time interactive simulations and game engines. On the one hand, this allowed creating an immersive visualization with little overhead. On the other hand, it brought a tight coupling between the simulation and visualization loop, which limits scalability. The use of off-the-shelf physics engines needs to further scrutinized to assert the validity (in terms of simulation accuracy) and advantage (in terms of adaptability, extensibility, maintainability) of their use.

5 Next Steps

Besides system design and implementation, evaluation and validation of the user interaction design are of high importance. We expect the following three objectives to be most important in driving forward the development of real-time interactive biological cell simulations (in order of priority).

(1) Decoupled Simulation-Interaction / Visualization: Alongside with a selection of other models including the MecaCell framework [6], we plan to investigate decoupled simulation-interaction/visualization approaches. Providing an interface layer that allows communicating the meaningful state data in a compressed manner between simulation and visualization, and providing a back channel for user interactions, would allow to scale and distribute the simulation setups. The use of (remote) high-performance computing might alleviate some constraints imposed by current standard workstation hardware.

(2) Identifying Parameters and Variables: The precise parameters and state variables of the simulation that are of interest to biologists need to be elicited based on more detailed inquiries. Also, research needs to be done to identify the visualization methods and metaphors most apt to effectively communicate the state of the simulation. To this end, staying in a tight loop with biologists and related researchers is essential.

(3) (Off-The-Shelf) GPU-Based Real-Time Physics: The FleX soft body physics simulation, selected for its anticipated speed and flexibility, will need additional scrutiny. The mechanical cell model should be transferred into a stand-alone simulation setup. The introduction of flexible boundaries representing enclosing layers of tissue and the restriction of the cell movement to two dimensions might allow research in the generation of pressure through cell proliferation and the resulting deformation of tissue. Also, taking lessons from the highly-optimized implementation might benefit the development of strongly GPU-driven, more accurate and interactive physics simulations that could drive more scientifically accurate, future simulations. Both might further benefit the scientific community in using off-the-shelf components for research.

6 Conclusion

In this work, we have summarised our motivation for the development of real-time interactive biological cell simulations to support biologists in exploring the complex behavior of cellular organisms. Seeing cells as autonomous agents and modeling them accordingly provides the path for interactive, high-impact, in-silico exploration of biological systems. We pointed out the critical issues that lie in the way to the creation of such a system. First, a suitable cell model needs to be found that captures all relevant aspects. Agent-based simulations with divergent agent models are computationally expensive and often limit real-time applicability. Nonetheless, such a system should ideally be able to cope with several thousand cells of multiple types or even greater scales. The user interfaces need to be suitable for the investigation by biologists, providing apt interaction methods and visualizations while also scaling with high numbers of cells. Providing a visualization at the appropriate scale, measurement tools of the appropriate granularity and, especially, tools for the retracing of development *over time*, are expected to provide high value. The system might offer to replicate

different stages of the same organism, or different configurations of the same protocol, side-by-side. To be useful for biologists, the system needs to integrate with existing sources of empirical data, such as CT scans. We summarised the results from a first horizontal real-time-interactive prototype, which led us to the following three next steps: Accordingly, we plan to (1) decouple simulation and interaction/visualization to improve performance and scalability, elicit (2) the critical parameters and visualization methods and metaphors need, and (3) further investigate of the use of GPGPU for interactive biological simulations.

References

1. Aaby, B.G., Perumalla, K.S., Seal, S.K.: Efficient simulation of agent-based models on multi-gpu and multi-core clusters. Proceedings of the 3rd International ICST Conference on Simulation Tools and Techniques (2010)
2. Bell, P.C., O'Keefe, R.M.: Visual interactive simulation — history, recent developments, and major issues. SIMULATION **49**(3), 109–116 (Sep 1987)
3. Cytowski, M., Szymańska, Z., Umiński, P., Andrejczuk, G., Raszkowski, K.: Implementation of an agent-based parallel tissue modelling framework for the intel mic architecture. Scientific Programming **2017**, 1–11 (2017)
4. Däschinger, M., Knote, A., von Mammen, S.: An evolutionary approach to behavioural morphometrics. In: Bosman, P.A.N. (ed.) Genetic and Evolutionary Computation Conference, Berlin, Germany, July 15-19, 2017, Companion Material Proceedings. pp. 83–84. ACM (2017)
5. Delile, J., Herrmann, M., Peyriéras, N., Doursat, R.: A cell-based computational model of early embryogenesis coupling mechanical behaviour and gene regulation. Nature Communications **8**, 13929 (Jan 2017)
6. Disset, J., Cussat-Blanc, S., Duthen, Y.: MecaCell: An Open-source Efficient Cellular Physics Engine. In: 07/20/2015-07/24/2015. p. 67. The MIT Press (2015). https://doi.org/10.7551/978-0-262-33027-5-ch014
7. Férey, N., Delalande, O., Grasseau, G., Baaden, M.: From interactive to immersive molecular dynamics. In: Proceedings of the Fifth Workshop on Virtual Reality Interactions and Physical Simulations, VRIPHYS, 2008. pp. 89–96 (2008)
8. Gelfand, A.: The Biology of Interacting Things: The Intuitive Power of Agent-Based Models: Biomedical applications of ABMs are taking off. Biomedical Computation Review (2013), bluehttp://biomedicalcomputationreview.org/content/biology-interacting-things-intuitive-power-agent-based-models
9. Hoehme, S., Drasdo, D.: A Cell-Based Simulation Software for Multi-Cellular Systems. Bioinformatics **26**(20), 2641–2642 (2010). https://doi.org/10.1093/bioinformatics/btq437
10. Kiran, M., Richmond, P., Holcombe, M., Chin, L.S., Worth, D., Greenough, C.: Flame: Simulating large populations of agents on parallel hardware architectures. In: Proceedings of the 9th International Conference on Autonomous Agents and Multiagent Systems. AAMAS '10, vol. 1, pp. 1633–1636. International Foundation for Autonomous Agents and Multiagent Systems, Richland, SC (2010)
11. Knote, Andreas; von Mammen, S.: Adaptation and integration of gpu-driven physics for a biology research ris. In: 2018 IEEE 11th Workshop on Software Engineering and Architectures for Realtime Interactive Systems (SEARIS) ((in press))

12. Lv, Z., Tek, A., Da Silva, F., Empereur-mot, C., Chavent, M., Baaden, M.: Game on, science - how video game technology may help biologists tackle visualization challenges. PLoS ONE **8**(3), e57990 (Mar 2013)
13. Merks, R.M.H., Glazier, J.A.: A cell-centered approach to developmental biology. Physica A: Statistical Mechanics and its Applications **352**(1), 113–130 (2005). https://doi.org/10.1016/j.physa.2004.12.028
14. Narayanan, S., Kidambi, P.: Interactive simulations: History, features, and trends. Human-in-the-Loop Simulations pp. 1–13 (2011)
15. NVidia Corporation: NVidia Flex Physics. bluehttps://developer.nvidia.com/flex, last retrieved: 10.1.2018 (2018)
16. Starruß, J., de Back, W., Brusch, L., Deutsch, A.: Morpheus: A User-Friendly Modeling Environment for Multiscale and Multicellular Systems Biology. Bioinformatics **30**(9), 1331–1332 (2013). https://doi.org/10.1093/bioinformatics/btt772
17. Swat, M.H., Thomas, G.L., Belmonte, J.M., Shirinifard, A., Hmeljak, D., Glazier, J.A.: Chapter 13 - Multi-Scale Modeling of Tissues Using CompuCell3D. In: Arkin, A.R.A., P., A. (eds.) Methods In Cell Biology : Computational Methods In Cell Biology, vol. Volume 110, pp. 325–366. Academic Press (2012). https://doi.org/10.1016/B978-0-12-388403-9.00013-8
18. Theraulaz, G., Bonabeau, E.: A brief history of stigmergy. Artificial Life **5**(2), 97–116 (1999)