

A Model and Pipeline for Interactive Simulation of Morphological Biology

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Abstract

In this work, we present our current efforts towards a comprehensive, human-in-the-loop modelling framework for the study of complex morphogenetic systems. The state of our physical cell model providing localized surface-based interactions and built on top of a real-time capable particle-based physics engine is summarized. We further outline our long-term concept towards an integrated pipeline for automated model generation and refinement based on empirical data and human-in-the-loop simulations. With it, we strive to seamlessly integrate with a biologist’s workflow, for example through appropriate import and annotation tools for empirically obtained data, and intuitive and accessible tools and languages for behaviour description. To integrate the different software components into a real-time interactive system, we use *UnrealEngine4*, a state-of-the-art game engine.

Introduction

We aim to provide an interactive, immersive, and real-time framework for the modelling and simulation of morphogenetic systems, see Figure 1. At its core, our concept envisions a cell-centred simulation approach, where biological cells are represented as autonomous spatial agents with explicit physical shape and local, surface-based interactions embedded in a fluid dynamic simulation for substance diffusion. This core model needs to be augmented with an accessible user interface for modelling of cellular behaviour. By including the “human in the loop”, modelling, retracing and exploring complex system behaviours is facilitated (Narayanan, 2011). Also, the study of and interaction with of complex morphologies benefit from spatial visualisation and freedom of exploration made possible by means of immersive virtual reality interfaces.

In order to closely align the resulting model with biologically valid empirical data and also in order to inform the biologists’ work, our targeted framework needs to go beyond offering an extensible cell model and interactive simulation mechanics. To make use of the vast amount of empirical data generated by biologists, import and processing pipelines must be provided that seamlessly tie into the biologists’ established toolchains. The user must be able to

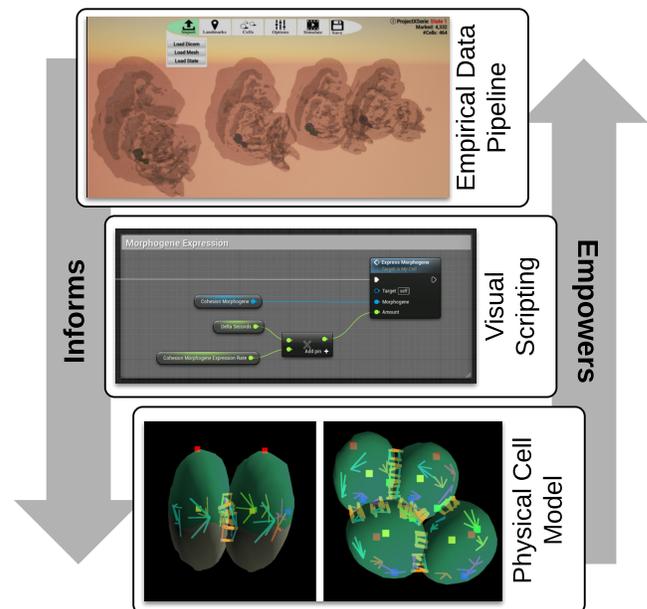


Figure 1: The basic components of our proposed concept. An interactive, particle-based physical cell model (bottom) can be programmed using accessible tools such as visual scripting languages (middle) and integrated directly with empirically obtained data (top). For the latter, a comprehensive import and annotation pipeline is provided. Based on this foundation, algorithms to generate or optimise models based on empirical data and simulation performance allow for automated model refinement.

quickly and comprehensively define and test models, and to optimize their parameters. In addition, the integration of automated model-finding routines that mine the biological data are highly desirable.

In this extended abstract, we support our vision with outlines of system components that we have already implemented. In particular, we briefly present two implementations that should be merged in the near future: One that helps to utilise biological data and another one that focusses on the refinement of a real-time capable virtual cell model.

Related Work

Merks (2005) point to the importance of cell-centred models and the similarities between current models of biological cells and the concept of autonomous agents. Recently, the importance of physical interactions in the simulation of complex behaviour of cellular systems has been stressed (Drasdo, 2007; Hamant, 2008; Uyttewaal, 2010). One approach is to model spherical, elastic bodies in a system of constraints (e.g. the Johnson-Kendall-Roberts model (Chu, 2005)). CellSys (Hoehme, 2010) and CompuCell3D (Swat, 2012) offer examples for an integrated design and visualisation approach. Several physical cell models have been realised and evaluated successfully (Delile, 2017; Hoehme, 2010; Disset, 2015; Swat, 2012), however without real-time interaction capabilities.

With regards to our long-term vision of integrated developmental frameworks with automated model building, recent progress has been made. For example, Faure (2016) realized a pipeline for the reconstruction and visual analysis of cell lineages from developmental time series of embryonic cells in the form of image data.

Methodology

To create a rich real-time interactive experience, we draw from the available technology of state-of-the-art game engines. These systems provide efficient, high-quality visualisations, facilities for the design of accessible user interfaces, compatibility with current virtual reality interfaces, and a modular, extensible software design. Also, accessible visual scripting environments are often provided. We currently use UnrealEngine4 (EPIC Inc., 2017). We exploit the capabilities of current hardware through massive parallelization, off-loading work to the GPU.

To create an interactive, cell-centred and physical simulation model, fast, efficient, and dynamic soft body simulation is required. Our current cell model is built on top of FleX, a real-time physics simulation that can provide plausible results at interactive speeds (Bender, 2013). Individual cells are modelled by a set of particles combined with internal constraints, allowing the simulation of deformable exteriors and localized interactions, such as adhesion. Fluid dynamics and diffusion simulation can be used to retrace the emergence of morphogen gradients, a fundamental mechanism in the appearance of distinct morphological features. The features of the model can be presented to the user at arbitrary degrees of complexity, e.g. through visual scripting.

First results towards an integrated developmental biology pipeline that integrates empirical data and automated parameter optimization have been made (Däschinger, 2017b). The system allows to parse volumetric data from CT scans and annotate it, defining time series data of the developmental stages of certain regions of the tissue. Such regions can then be populated with (various types of) cells, and their parametrization will be continuously optimized by the

means of an genetic algorithm. This process is an example of Guided Self-Organisation (Däschinger, 2017a).

Future Work

The presented cell model and the steps towards a pipeline for automated parameter refinement and model building are at early stages. The cell model requires a quantitative analysis with respect to the accuracy of the model. Consequently, it is desirable to define clear implementation and usage constraints on NVidia's FleX physics solver that guarantee for consistent and sufficiently accurate simulation results. The current fluid dynamics and diffusion model is overly simplistic and, though highly parallelized, still lacks in accuracy and scalability. Integrating different models for cellular behaviour on top of the physical model, such as Gene Regulatory Networks, should be investigated. The pipeline was currently limited both in the kind of data used as an input as well as the algorithms implemented for the parameter refinement. Also, the task of integrating the two projects remains.

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