Exposé

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July 2023

1 Introduction

Computational models of cell behavior can be useful to simulate and reproduce experiments. In addition, they show us how well our understanding models reality. A popular approach is the Cellular Potts Model (CPM), where each cell is modeled as a set of connected pixels or voxels on a two- or three-dimensional lattice. To simulate biological processes involving thousands of cells, large lattices are needed. Due to the local nature of the computations involved, the CPM lends itself well to distributed programming. I will base my work on Cells in Silico (CiS), which is a distributed implementation of the CPM based on the Neoteric Autonomous Stencil code for Jolly Algorithms (NAStJA) framework.

In order to be true to *in vivo*/*in vitro* findings, such *in silico* models must take into account a multitude of factors influencing cell behavior. One such factor is the interaction with the Extracellular Matrix (ECM), the structural scaffold which cells are embedded in. In this work I will focus on the viscoelasticity of the collagen networks in the ECM. I will explore models of viscoelasticity that, similar to the CPM itself, employ local interactions to model global effects. This is required to fit the implementation into the NAStJA framework so that it can be seamlessly integrated with CiS. Additionally, I will investigate the performance of my model using different implementations on both CPUs and GPUs.

2 Research

2.1 The Cellular Potts Model (CPM)

The CPM [6] models cells as sets of connected sites on a square lattice. Each lattice site is assigned the integer cell ID of the cell it belongs to.

The behavior of the cells is regulated by the Hamiltonian H, which represents the energy of a particular lattice. The Hamiltonian contains at the least a cell-cell adhesion and cell volume, but is usually extended by other terms such as cell surface or alignment.

To advance the CPM, a Monte-Carlo Step (MCS) is performed: The cell ID of a random lattice site is changed to the cell ID of one of its neighbors and the difference in energy ΔH is calculated. The update is always accepted if the energy decreases. If the energy does not decrease, the update is accepted probabilistically (e.g. by the Metropolis criterion), where greater increases are less probable. Repeated MCSs minimize H.

From an implementor's perspective, the CPM has a great advantage over other approaches: Since updates happen on a square lattice and changes in energy can be calculated locally, it lends itself well to distributed programming. Cells in Silico (CiS) [3] is a parallel implementation of the CPM based on the Neoteric Autonomous Stencil code for Jolly Algorithms (NAStJA) framework [2]. NAStJA offers an abstraction layer for implementing stencil codes using Message Passing Interface (MPI), making it possible to leverage large-scale parallelism for CiS. NAStJA divides the simulation domain into blocks. After the stencil is computed for each block, the *halo*, i.e. the boundary region between blocks is exchanged such that each block has the data necessary to compute the stencil again.

2.2 The Extracellular Matrix (ECM)

The ECM is the part of a tissue that surrounds the cells. It provides their physical and biochemical environment, thereby influencing cell behavior [5].

While the ECM consists of a variety of components, I focus on a single essential component: Fibrous collagen networks and their viscoelasticity. ECM viscoelasticity has been established as an important factor in cell behavior [4]. For example, the ECM confines cells and restricts processes such as migration, spreading, growth and mitosis. These processes also affect the ECM and can lead to permanent deformation. In turn, this deformation can have an influence on cell behavior, resulting in a string coupling between the behavior of the ECM and the behavior of the cells.

2.3 Models of the ECM in the CPM

In this section I list current approaches to modeling the ECM in CPM simulations. I present approaches that explicitly model the plasticity of ECM collagens.

Static Cell A starting point is to model the ECM as a static cell. In this model, a cell ID is chosen to represent the solid parts of the ECM. Cell-matrix interactions are regulated by the Hamiltonian just like cell-cell interactions. ECM lattice sites do not copy their neighbors and can not be copied by their neighbors during a MCS. Instead, simulations using this approach usually allow cells to degrade adjacent matrix sites over time. This approach is used for example in [1], where the ECM is initialized by randomly placing fiber bundles across the domain and [18], which investigates cell behavior in ECMs with regular patterns.

Hybrid CPM-FEM An approach using a Finite Element Method (FEM) is presented in [15] and expanded upon in [16, 17]. Each lattice site is assigned a local directional strain on the ECM. Cells exert traction forces on the ECM used to calculate the lattice strains by a FEM. The hamiltonian of the CPM is modified such that cells respond to the strain.

Hybrid CPM and Molecular Dynamics Methods Another approach is presented in [21]. This work simulates matrix fibers using a bead-and-chain

model. Similar to the previous approach, the ECM model is coupled with the CPM. However, in this work, cells interact with the ECM only through a sparse subset of lattice sites.

2.4 Lattice Models of Viscoelastic Materials

The strain response of the collagen networks in the ECM is not fully elastic. It exhibits both elastic (spring-like) and viscuous (damper-like) behavior. The behavior of such viscoelastic materials is modeled by serial or parallel configurations of springs and dampers [10, 19]. The most common configurations for describing viscoelastic solids are

- the Maxwell model, consisting of a spring and a damper in series,
- the Kelvin-Voigt model, consisting of a spring and a damper in parallel
- and the Zener or Standard Linear Solid (SLS) model, which extends either the Maxwell or the Kelvin-Voigt model by another spring.

Depending on the specific viscoelastic characteristics that are to be predicted, a particular model can be chosen. In order to align the viscoelastic ECM model with the CPM, I consider approaches that model viscoelastic materials on square lattices. In particular, the following approaches might be relevant.

Discrete Particle Method A model for viscoelastic solids is presented in [11]. This work extends the discrete particle method for elastic solids presented in [20]. It is based on a two- or three-dimensional square lattice of particles. Each particle is connected to all of its cardinal and diagonal neighbors. The model for the force acting between two particles can be elastic or viscoelastic. Various models are explored in [11, 12, 13, 14].

Lattice Boltzmann Method (LBM) The LBM is an established approach for modeling the dynamics of fluids [7]. Also based on a square lattice, this model discretizes the particles moving at a particular lattice space into the cardinal and diagonal directions. Research suggests that the LBM can be used for modeling both solids [9] and viscoelastic fluids [8]. Perhaps for this particular use case, a LBM could be configured to model the ECM.

3 Contribution

In this work I will explore lattice-based viscoelastic simulations of the ECM in the CPM.

3.1 Method

In order to model cell-matrix interactions, I will develop a method that allows cells to influence the ECM simulation. To model matrix-cell interactions, I will expand the Hamiltonian of the CPM to include a term dependent on the local configuration of the ECM. This should make it possible for my model to simulate

the strong coupling of cells and ECM. I will explore which of the models listed above is the most promising and compare to them to existing approaches.

For the CPM I will use the distributed implementation CiS. CiS is based on the NAStJA framework implemented using MPI, which I will use to implement my model of the ECM.

In order to reduce simulation times I will employ implementation techniques such as GPU programming. As the implementation performance of my model will depend on several interconnected factors such as cache efficiency, network characteristics and GPU communication cost I will need to benchmark multiple implementations on a common test setup.

3.2 Challenges

My preliminary experiments have produced some questions and likely challenges that my work will need to address.

Spatial Scale While I could simply use the same lattice for the ECM model as for the CPM, it is not clear that this will deliver the best results. It could be useful to use a scaled lattice, e.g. where the lattice spacing of the ECM model is twice as long.

Temporal Scale Compared to cells, the waves in a viscoelastic material move quickly. It is likely that my model of the ECM will have to go through multiple time steps between the MCSs of the CPM. In the context of NAStJA, this means an increased number of halo exchanges between ranks per MCS. In order to reduce the number of halo exchanges, one could increase the width of the halo which allows the ECM simulation to run for multiple time steps between halo exchanges. As this approach necessarily leads to diminishing returns as the halo data gets bigger, an efficient configuration needs to be investigated.

Implementation Performance As CiS is designed to large and therefore compute-heavy simulations, it is worthwhile to measure the and optimize the computational resources needed by my implementation. Since the discrete particle method is a dense approach, it should be possible to leverage common parallelization techniques such as vectorization and GPU programming to improve performance. In particular, it might prove useful to run the CPM on CPUs and the ECM model of GPUs. I will experiment with these techniques and evaluate the possible improvements.

Acronyms

CiS Cells in Silico. 1, 2, 4

CPM Cellular Potts Model. 1–4

CPU Central Processing Unit. 1, 4

ECM Extracellular Matrix. 1–4

FEM Finite Element Method. 2

GPU Graphics Processing Unit. 1, 4

LBM Lattice Boltzmann Method. 3

MCS Monte-Carlo Step. 1, 2, 4

MPI Message Passing Interface. 2, 4

NAStJA Neoteric Autonomous Stencil code for Jolly Algorithms. 1, 2, 4

SLS Standard Linear Solid. 3

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