

Exposé

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1 Introduction

Computational models of cell behavior can be useful to simulate and reiterate experiments. In addition, they can 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.

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) that cells exist in. In this work we will focus on the viscoelasticity of the collagen networks in the ECM. We explore models of viscoelasticity that, similar to the CPM itself, employ local interactions to model global effects. In this manner the simulations remain parallelizable. Additionally, we investigate the performance of our 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 sites on a square lattice which are usually connected. 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 term for the adhesion between cells on the lattice, but can be extended by other terms such as cell volume 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, where greater increases are less probable. Repeated MCSs minimize H .

From an implementor's perspective, the CPM has a great advantage over other approaches to cell simulation such as agent-based modeling: 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 on the Message Passing Interface (MPI), making it possible to leverage large-scale parallelism for CiS. NASTJA divides the domain into blocks, computing each stencil locally, then performing an halo exchanges of the border regions.

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, we 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 self-reinforcing effects (see for example [10]).

2.3 Models of the ECM in the CPM

In this section we list current approaches to modeling the ECM in CPM simulations. We focus on 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 [17, 16]. 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 viscous (damper-like) behavior. The behavior of such viscoelastic materials is modeled by serial or parallel configurations of springs and dampers [19, 10]. 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, we researched approaches that model viscoelastic materials on square lattices.

Discrete Particle Method A model for viscoelastic solids is presented in [12]. 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 [12, 14, 13, 11].

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 we will explore lattice-based viscoelastic simulations of the ECM in the CPM.

3.1 Method

For the CPM we use the distributed implementation CiS. CiS is based on the NASTJA framework implemented using the MPI, which we will use to develop our model of the ECM. The model will likely be based on the viscoelastic discrete particle method, as preliminary experiments based on a simplified implementation show promising results.

In order to model cell-matrix interactions, we will develop a method that allows cells to influence the ECM simulation. To model matrix-cell interactions, we 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 our model to simulate the self-reinforcing interactions of cells and ECM.

3.2 Challenges

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

Spatial Scale While we 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 our 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, we 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 compute needed by our 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. We will experiment with these techniques and evaluate the possible improvements.

Acronyms

CiS	Cells in Silico. 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, 3
NASStJA	Neoteric Autonomous Stencil code for Jolly Algorithms. 2–4
SLS	Standard Linear Solid. 3

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