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.

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 a 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 models 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 [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]. This model is based on a two- or three-dimensional square lattice of particles. Each particle is connected to all of its Moore 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].

3 Contribution

3.1 Method

3.2 Challenges

Acronyms

CiS Cells in Silico. 2

CPM Cellular Potts Model. 1–3

CPU Central Processing Unit. 1

ECM Extracellular Matrix. 1–3

FEM Finite Element Method. 2

GPU Graphics Processing Unit. 1

LBM Lattice Boltzmann Method. 3

MCS Monte-Carlo Step. 1, 2

MPI Message Passing Interface. 2

NAStJA Neoteric Autonomous Stencil code for Jolly Algorithms. 2

SLS Standard Linear Solid. 3

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