On-lattice agent-based simulation of populations of cells within the open-source Chaste framework

Grazziela P. Figueredo
Tanvi Joshi
James Osborne
Helen Byrne
Markus Owen
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Introduction

2 and 3D in silico simulation of the dynamics of cell populations Diffusible fields such as nutrients and growth factors. Facilitate biological research in testing mechanisms such as:

• Interactions between different cell types
  • proliferating normal cells and cancer cells
  • non-proliferative macrophages
• Nutrient and growth-factor-dependent environment.
• Test potential new treatments for various pathologies, such as early-stage cancer.

Features:

• movement within a lattice in 2D and 3D
• regulation of cell cycle and factors, such as oxygen and other nutrients
• tumour hypoxia and effects of hypoxia in cell cycles of tumour and normal cells
Motivations
Objectives
The Vascular Tissue Modelling Environment Project

- Part of the (Virtual Physiological Human) VPH toolkit
- VTME is currently being implemented within the “Cancer, Heart and Soft Tissue Environment”
- Existing solvers/tools for simulating ODEs, PDEs and cell-based models.
- Software development employs rigorous testing, version control and documentation.
- Parallel Chaste developments relating to model curation, interfaces, etc.

http://www.cs.ox.ac.uk/chaste/
The Virtual Physiological Human: collaborative investigation of the human body as a single complex system.

An up-to-date list of projects funded by the EC’s VPH Initiative is available on http://vph-portal.eu/vph-projects.

The Virtual Physiological Human Network of Excellence (VPH NoE), 2008-2013, served as a rallying point and source of best-practice information for the VPH community. This role has now been passed to the VPH Institute (http://www.vph-institute.org). The tools and educational/outreach materials developed by the VPH NoE – and future contributions – will be maintained at the VPH Portal: http://vph-portal.eu/vph-noe-home.
Chaste

Chaste (Cancer, Heart and Soft Tissue Environment) is a general purpose simulation package aimed at multi-scale, computationally demanding problems arising in biology and physiology. Current functionality includes tissue and cell level electrophysiology, discrete tissue modelling, and soft tissue modelling. The package is being developed by a team mainly based in the Computational Biology Group at the Department of Computer Science, University of Oxford, and development draws on expertise from software engineering, high performance computing, mathematical modelling and scientific computing. Read more...

To get started with Chaste, download the code and browse the documentation.
The Multi-scale Model

Diffusible species
- Oxygen
- Nutrient 1
- Nutrient 2

Cellular layer
- Cycle-based cells
  - Normal Cells
  - Cancer Cells
- Lifespan-based cells
  - Macrophages

Subcellular layer
- Cell cycle
- Apoptosis

- Cell division and reinforced random walks of cells on a lattice
- ODEs for subcellular networks that regulate the cell cycle and growth factors
- PDEs for the transport, release and uptake of diffusible substances

Link to the paper: http://ima.ac.uk/papers/Figueredo2013a.pdf
On lattice simulations

- Cells are placed inside a lattice
- 2D and 3D on lattice simulations
- An on lattice model was considered
  - As cells interact within their neighbour cells
  - It is an effective way to discretise the space to control mechanisms such as
    - Population growth per area
    - Oxygen uptake and nutrient concentration at a certain region
    - Cellular dynamics (such as movement and birth) given the amount of cells in its neighbourhood
Cell Population - Features

- Cells occupy only one lattice site (not a Potts model).
- Each cell has a neighbourhood, following the concepts of Cellular Automata, for cell movement.
- There can be lattice sites with no cell associated.
- Cells are added (cellular birth) and removed (cellular death) from the lattice over the course of a simulation.
- Cells move in the lattice randomly or chemotactically.
- Different cell types within a lattice (e.g. normal cells, tumour cells, macrophages).
- There can be more than one cell per lattice site.
- Lattice sites have different carrying capacities.
Cell Population – Why?

- Overcomes disadvantages of traditional CAs.
- Max population size is not restricted to the size of the lattice.
- The number of cells is controlled by the carrying capacity of each site.
- Closer to what happens in biological systems.
- The lattice contains heterogeneous populations with distinct rules associated to each type of biological cell.
- The lattice sites do not have rules.
- Instead, they are just possible locations where the biological cells lie on.
Cell Population – Two types of cells

OO approach
Single Cell Random Movement

Loop through all active cells and assign probabilities for moving from a site $x$ to sites in the Moore/Neumann neighbourhood of $x$.

The probability of a cell moving from lattice $x$ to $y$, in time $\Delta t$, $Pr(x, y, t)$ is given by:

$$Pr(x, y, t) = \frac{D \Delta t}{2d_{x,y}^2} \left( \frac{N_m - N(y, t)}{N_m} \right) \left( 1 + \frac{\chi}{2D} (V(y, t) - V(x, t)) \right) \quad \text{for } x \neq y$$

Where

- $N(x,t)$ is the number of cells at site $x$,
- $V(x,t)$ is the VEGF level at site $x$.
- $D$ is the maximum cell motility in the absence of chemotaxis,
- $N_m$ is the carrying capacity for movement of the cell type attempting to move,
- $\chi$ is the chemotactic sensitivity
- $d_{x,y}$ is the distance between sites $x$ and $y$.
- Random motion without chemotaxis: $\chi = 0$. 

Single Cell Random Movement Simulation
Single Cell Random Movement Simulation

Cell trajectory: VTME results

Cell trajectory: VTME results
Cell Cycle

• It's like a clock inside a cell
• Determines when a cell is ready to divide
• Cell divides according to the oxygen levels (or any other nutrient(s), if you like 😊)
• The oxygen concentration is determined by an ODE system
Cellular Growth

- Cells replicate according to their cell cycle
- New cells are added:
  - If there is enough oxygen
  - If there is space available (according to the cells and lattice carrying capacity)
Cellular Growth - Simulation Video
Multiple Cells Growth

Initial state

After 10 days

After 20 days

Normal cells with cell cycle time = 3000 minutes and diffusion coefficient = 0.03 cm²/minutes

Cancer cells with cell cycle time = 1600 minutes and diffusion coefficient = 0.03 cm²/minutes

Macrophages with a mean life span = 300 days
Normal Cell Death

- Oxygen concentration within its neighbourhood falls below a prescribed threshold.
- This threshold increases when a normal cell is surrounded predominantly by cancer cells.
- This reflects differences in the micro-environment of normal tissue and tumours.
Tumour Cell Death

Check_Apoptosis_Process

Update Nutrient

Nutrient < Minimum

- false
  - Quiescence?
    - false
      - Nutrient > Minimum_2
        - false
          - Quiescent_Time = 0
        - true
          - Label for Apoptosis
    - true
      - Label for Apoptosis

- true
  - Quiescence?
    - false
      - Quiescent_Time > Maximum
        - false
          - Update Quiescent_Time
        - true
          - Label for Apoptosis
Oxygen-dependend Cell Proliferation
Cell Growth and Hypoxia
Multiple Cell Types
3D
Drug Response
Conclusions

• We presented an open source environment for cellular simulations
• Results validated with existing models
• Can also be used to aid research on some pathologies and their therapies
• The lattice scheme has many benefits compared to traditional CAs
• Available in the current Chaste release (3.1)
Future Work

• Add vasculature
• Develop an off lattice VTME
  – compare outcomes, performance, processes of validation
  – assess the benefits of on lattice vs off lattice approaches for vascular tissue modelling
Future Work - The Multi-scale Model

- Cell division and reinforced random walks of cells on a lattice
- ODEs for subcellular networks that regulate the cell cycle and growth factors
- PDEs for the transport, release and uptake of diffusible substances
- Fluid flow in a vessel network
- Integration of angiogenic and vasculogenic endothelial cells into the vascular network

Owen et al.. Cancer Research, 71:8, pages 2826-2837, 2011