Agent-Based Biomechanical Modelling of Lung Adenocarcinoma and its Tumour-Immune-Microenvironment using PhysiCell

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Abstract

Lung cancer, of which **lung adenocarcinoma (LUAD**) is a subtype, is the leading cause of cancer death in the world[1]. The tumour-immune-microenvironment (T**IME)** contains complex interactions between **cancer cells, immune cells, and extracellular matrix (ECM) proteins** that contribute to tumour growth[3]. Immune cells can have **both pro- and anti-tumour roles[3].** In LUAD the ECM increases in stiffness and density, thus promoting tumour growth[4]. There is a gap in **in-silico modelling of the comprehensive TIME of lung cancer** using agent-based modelling, which this model seeks to address. The model presented expands the existing PhysiCell cancer-immune model to simulate **early LUAD**, through agent-based modelling of cancer cells, immune cells (CD8+ T, CD4+ T, *MDSC, M1 *TAM, M2 *TAM, γδ T, *Treg, and *TAN cells), CAFs, and ECM fibres. This can be used in conjunction to in-vivo or in-vitro experiments to **predict tumour growth, simulate patient specific prognostic predictions, and trial cancer therapies.** This project also provides **a stepwise methodology** for comprehensive simulation of specific cancer types including the TIME.

Methodology

Base model: PhysiCell cancer-immune model

Extensive literature search of A549 LUAD cell line properties, namely proliferation, oxygen uptake, cell volume, and migration speed

Expand generic “immune cell” type in base model to specific immune cells in lung adenocarcinoma: CD8+ T cells, CD4+ T cells, MDSC cells, M1 TAMS, M2 TAMS, γδ T cells, Treg cells, and TAN cells

Create Cancer Associated Fibroblast (CAF) cell type

Initialize and seed non-cancer cells

Seed cancer cells in spherical shape with varying oncoprotein levels

Initialize and seed ECM fibres to match lung tissue stiffness

Extensive literature search for parameter values of immune cells, CAFs, and ECM fibres

Implement rules cancer cells, immune cells, CAFs, and ECM fibre interactions

Legend

- cancer cell
- CD8+ T cell
- CD4+ T cell
- MDSC
- M1 TAM
- M2 TAM
- ydT cell
- Treg
- CAF
- TAN
- ecm

What is PhysiCell?

PhysiCell is software used to build mechanistic, multicellular, off-lattice agent-based models, predominantly for cancer. It is written in C++ and is open-source[5].

Mechanistic: based on scientific laws and rules[5]
Agent-based: each cell/fiber is an independent object with individual rules[5]
Off-lattice: cells not confined to predefined coordinates on a grid[5]

Each cell type is programmed with parameter values for cell cycling, apoptosis, necrosis, solid and fluid volume changes, mechanics, and motility, secretion/uptake, and rules for cell-cell interaction[5]. Custom parameters/rules can be added[5].

Results

Top: Cancer-immune sample

0 day	1 day, 0 hours	2 days, 0 hours
18317 agents	24180 agents	30981 agents

Bottom: LUAD model

0 day	1 day, 0 hours	2 days, 0 hours
36332 agents	48888 agents	281816 agents

Figure 1. Cross section of simulated LUAD and TIME at various timepoints.

Future Directions

1. **Ensure 3D simulation functionality and validity**
2. **More accurate spatial arrangement of cells** → Seed non-cancer cells in between cancerous cells
3. **ECM fibre subtypes** → expand generic ECM cell type to specific subtypes

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*MDSC = myeloid-derived suppressor cell, TAM = tumour-associated macrophage, Treg cell = regulatory T cell, TAN =- tumour-associated neutrophils

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