Project plan:
Agent-based modelling for prostate cancer

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1. INTRODUCTION

Computational modelling is widely applied across biotechnology, such as in simulating disease control, drug side effects, and cancer cell interactions with tissue (NIBIB, 2009; Nicolò Cogno, et al., 2024). Mathematical modelling reduces costs and labour by predicting outcomes like cancer cell interactions, while in silico experiments enable rapid hypothesis testing through parallel simulations (Puniya et al., 2024). In this simulation, agent-based modelling (ABM) is used to visualise tumour cell interactions within a controlled environment where agents follow predefined rules ('Agent-Based Modeling — Project in Mathematical Modeling,' 2024).

Prostate cancer has over 300 000 deaths annually and more than 1.4 million new cases among men, making it the second most common cancer for men worldwide. Thus, it is highly relevant to examine and try to understand its mechanisms (Cancer Research UK, 2017). Prostate cancer is often treated with local interventions like surgery or radiation. However, survival rates drop significantly once the cancer metastasizes, spreading to secondary sites in the body (Zhou et al., 2015).

2. BACKGROUND

2.1 PROSTATE CANCER

Prostate cancer growth is influenced by the androgens, which are hormones that can impact the male reproductive system, by binding to the androgen receptors in prostate cells and stimulate them to grow (Britannica, 2024). To solve this, androgen receptor therapy is the most effective treatment used. This method will decrease the androgen levels or block their effects to slow down or diminish the cancer (Zhou et al., 2015). The problem is that despite the low androgens levels the cancer can reoccur and start growing again, which is known as Castration-Resistant Prostate Cancer. The cells will adapt and find ways to grow with the decreased levels of androgens.

Furthermore, the tumour microenvironment (TME) also has an effect in the development and progression of prostate cancer. The prostate TME consists of fibroblasts and macrophages and these cells will promote cancer cell growth through chemical and physical interactions. The fibroblast are cells with the primary function to form connective tissue and in the TME the fibroblasts become active, which puts them in a state similar to wound healing. In this activated state they are referred to as cancer-associated fibroblasts (CAFs). These activated cells support prostate cancer growth by excretion of TGF-β1 which causes the cancer cells to become more invasive (D'Arcangelo et al, 2020) and also aids in tissue remodelling.

The macrophages are immune cells and they are divided into two different types in the TME. The pro-inflammatory macrophages, also referred to as M1 macrophages, are anti-tumorigenic which means that they work to kill the tumour. The other type is an alternatively activated anti-inflammatory macrophage, called M2 macrophages, which will have a positive impact on the tumour growth (van Genderen et al., 2024).

2.2 NUTRIENT REQUIREMENTS IN MAMMALIAN CELLS

Extracellular nutrient accommodation by metazoan cells, i.e. multicellular animal cells, is essential for facilitation of basic metabolic processes. Examples being providing reduced substrate for energy production through oxidative phosphorylation and crucial macromolecules for non-dissimilatory processes such as protein synthesis and gluconeogenesis. Many essential vitamins and fatty acids that the cells lack the capability to synthesise, need to be sourced from the extracellular environment in order to accommodate for synthesis of macromolecules that are required for maintaining normal cellular function. The specific nutritional requirements of multicellular organisms depend on factors such as the cell's current metabolic states; that is whether they exist in maintenance and are committed to proliferation, as well as their physiological functions in the tissue.

2.3 NUTRIENT ACQUISITION IN TISSUE

Nutrient availability can regulate interactions with transporters in single-celled organisms, while metazoan cells often use cell-intrinsic signalling pathways. Many kinases involved in cell cycle regulation also influence nutrient uptake (Huber, et al. 2020). Specifically non-soluble nutrients such as cholesterol or hydrophobic amino acids are transported into the cell using diffusion while others use dedicated membrane transport protein (Palm, et al. 2017). However, in the case of depleted nutrient levels, cells must undergo various metabolic changes in order to regulate processes accordingly. Examples being upregulation of certain enzymes that facilitate conversion of metabolites throughout glycolysis (Ramakrishanan, et al. 2014).

A prevalent cause for nutrient, and oxygen deficiency is the manifestation of concentration gradients across tissues that arise as a consequence of cells further away from vascular systems have a harder time acquiring nutrients than more proximal cells (Rademakers, et al. 2019). To counteract the occurrence of oxygen deprived tissue environments, called hypoxic regions, some tissues express capabilities of promoting neovascularization (angiogenesis) in the direction of where hypoxia is experienced (Krock, et al. 2011). The sprouting angiogenesis mechanism is the most predominant and well-known one for angiogenesis (Run et al., 2024). This mechanism works by growth factors (signal molecules) that cause endothelial cells to expand the pre-existing blood vessels as well as creating entirely new blood vessel branches to supply the tumour cells with nutrients and oxygen (Run et al., 2024).

2.3.1 HYPOXIA DRIVEN ANGIOGENESIS

Pathological angiogenesis in tumour manifestation and refers to the expression of neovascularization, by paracrine signalling pathways that are upregulated by tumour cells, which induce epithelial cell growth in the direction of signalling. Over a dozen angiogenic markers have been identified (Nishida, et al. 2006), out of which members of the vascular endothelial growth factor (VEGF) family are known to play significant roles in the angiogenic activity related to carcinomas, and for which the regulatory mechanisms in both carcinomas and normal metazoan cells are well studied. The VEGF family consists of 4 variants, ranging from A to D that regulate specific mechanisms related to angiogenesis as well as lymphangiogenesis for non-cancerous tissue (Nishida, et al. 2006). Specifically, VEGF-A has received attention for its role as a major inducer of neovascularization, as it is the founding member of the VEGF protein family, while also being overexpressed in several carcinomas. VEGF-A is a heparin-b binding glycoprotein that acts by binding members of the

complementary vascular endothelial growth factor receptor family (VEGFR), VEGFR-1 and -2, (Dvorak 2002) situated on the membrane of endothelial cells. VEGFR in turn mediates intracellular transduction which upregulates both cell division and break down of ECM which otherwise blocks migration (Nishida, et al. 2006), as well as improving microvascular permeability of nutrients, oxygen, and other molecules (Dvorak 2002).

VEGF-A is synthesised by the cell into the ECM which follows by diffusion through the ECM towards the target receptors on the epithelial cell membrane. Synthesis of VEGF-A is upregulated by hypoxia-response systems that react to oxygen deficiency in the extracellular microenvironment. For tumour cells, hypoxia is experienced during proliferation resulting in an increasing distance between newly formed cells and existing local capillaries. Decreased oxygen levels are sensed by prolyl hydroxylases that switch based on varying oxygen levels. This in turn recruits hypoxia-induced factor (HIF-1) which is an upregulator of the genes that code for VEGF-A as well as other growth factors (Ramakrishanan, et al. 2014). After intracellular VEGF-A synthesis, the protein is excreted out from the cell into the ECM, where it diffuses to target receptors.

2.4 NUTRIENT DEPENDENCY AND TUMOR PROMOTED ANGIOGENESIS

Cancer formation usually occurs due to mutations in the genes regulating cell cycle commitment and apoptosis. Due to heightened nutritional requirements as a consequence of uncontrolled tissue growth in tumours, promotion of nutrient acquisition has been observed to be a common survival technique in many tumour types. An example is the previously mentioned induction of angiogenesis which is regulated by similar signal pathways that regulate vascularization in normal tissues (Nishida, et al. 2006).

3. AIM AND METHOD

3.1. PURPOSE AND RESEARCH QUESTIONS

ABM is going to be used for studying prostate cancer development in relation to different objects in its TME related to nutrient acquisition. This project is inspired by Van Genderen et al. 2024 that made a similar model simulating cancer development in relationship to immunological mechanisms in the TME. In our case, we aim to examine how cancer cells promote proliferation through nutrient acquisition strategies such as induction of angiogenesis, for increasing nutrient and oxygen supply in the TME, as well as how different nutrient transporters behave as a consequence of regulatory signals from the cancer cells.

The research questions:
How does cancerous cells affect non-cancerogenous cells in its TME?
How does the replication of tumour cells affect vascularization?
How will the different agents affect the cancerogenous cells?

3.2. METHOD

Agent-based modeling (ABM) is a computational model which imitates the interactions between individual agents. The agents can represent institutions, humans or microorganisms. The actions of the agents are autonomous and implemented through predetermined rules. Analyzing the interactions will result in further knowledge of the systems behavior and the possible results. The simulation will observe the behaviour in between the autonomous agents, as well as their interactions with the environment, which will then allow for an observation of the macroscopic phenomena. ABM is suitable for this project of studying prostate cancer considering the flexibility of the method. It considers the temporal and spatial structures, the heterogeneity and the ability to adapt which is beneficial to the complexities of the tumour cells. The advantage of ABM is the ability to address these features compared to other analytical methods which encounter difficulties in that aspect (Hammond, 2015).

Taking all of this into consideration, we are going to have the following agents, i.e. types of cells: tumour cells, fibroblast, macrophages (macrophage M1, macrophage M2), and endothelial cells (for modelling the angiogenesis). We are assuming that sprouting angiogenesis (see 2.3) is the only mechanism affecting angiogenesis in our simulation. The tumour cells will have a binary parameter that can be switched on and off depending on its condition, i.e. cancerous or non-cancerous. The agents will exist and act across a 2-dimensional square grid (125 x 125) for the simulation due to time-limitations and feasibility of the project. Each square will be the size of the tumour, assuming a tumour cell is circular and 143 μm^2, the entire grid square will be 1.48mm^2.

A parent class called “CellAgent” where all of the fundamental and general information of all the cells are stored will be used for the basis of our code. Here several child classes and subclasses will be constructed. Here the cell specific properties and actions are stored in their respective methods. We will initiate the simulation by letting one tumour cell be present at start. The tumour cell will have the ability to replicate. The parameter for the probability of proliferation for the tumour will be 0.0846 (see appendix 6.2). We aim to couple this characteristic to an increase in vascularization to simulate how the tumour proliferates as a consequence of increased nutrient supply. In addition to these classes, we also need a “ProstateCancerModel” class where all of the agents (cell-types) are initialised and the grid – representative of the TME – is formed as well as the class that is responsible for the for-loop for the number of steps is operated. This is the frame for the mathematical model (tumour development simulation).

The parameters for the agents are: the tumours probability of death parameter will be set as 0.00284. The initial number of fibroblast, M1 and M2 will be set as 0. The fibroblast proliferation probability parameter as 0.0838, with an initial proliferation capacity of 4. M1, whose parameters will mainly be about its killing rate capacity of the growing cells, will be set to 11, while its killing probability is set to 0.0306. The other type of macrophage, called M2, will have similar parameters except that M2 has a killing probability set as 0.0127 (see appendix 6.2). The parameters for endothelial cells are not yet determined and will be using literature studies for the initial parameters.

4. PROJECT MANAGEMENT AND PROCEDURES

We will have weekly meetings either on site at KTH or on Zoom where the meeting will be documented. Documents will be shared through google drive and program code will be shared through Github. During the preliminary sprint, a basic framework for the model code will be constructed in parallel with researching for the appropriate parameters values and agent's predefined rules. An outline for the tasks that needs to be done during a certain sprint will be divided amongst the group members using google sheets to document the progress as well as a Gantt chart which will be updated as the project progresses (see Appendix 6.1). Throughout the project, weekly meetings might be replaced with hackathons where the team meets up to work in parallel.

5. REFERENCES

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6. APPENDIX

6.1 GANTT CHART

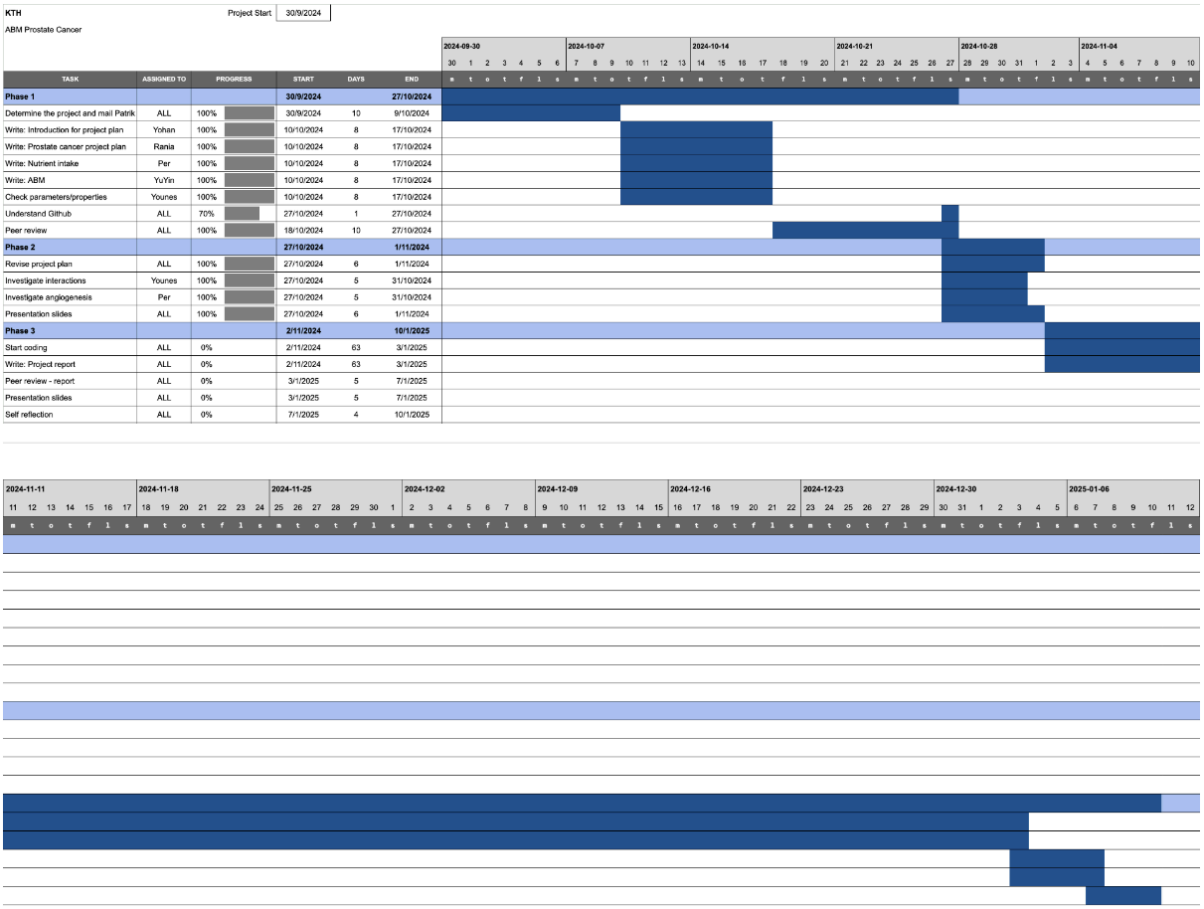

Figure 1. *A preliminary Gantt schedule of the project plan.*

6.2 PARAMETERS

```
%DEFINE TUMOR CELL PARAMETERS
mySystem.params.TUpprol = 0.0846;  %probability of proliferation
mySystem.params.TUpmig = 0.1167;     %probability of migration
mySystem.params.TUpdeath = 0.00284;%probability of death
mySystem.params.TUrwalk = 0.5;    %random influence on movement
mySystem.params.TUpmax = 4;   %initial proliferation capacity
mySystem.params.TUps = 0;          %probability of symmetric division
mySystem.params.TUcellNo = 1500;      %center first tumor cells or use multiple randomly distributed
mySystem.params.TUresNo = 0;        %seed some resitant cells
mySystem.params.TUpres = 0;        %probability of proliferation leading to resistant tumor cell
mySystem.params.TUpprolres = 0;    %probability of proliferation of resistant cells
mySystem.params.TUpmigres = 0;     %migration of resistant cells
mySystem.params.TUpmaxres = 0;      %poliferation capacity of resistant cells

%DEFINE MACROPHAGE TYPE 1 PARAMETERS
mySystem.params.M1kmax = 11;        %killing capacity
mySystem.params.M1pkill = 0.0306;   %probability of killing
mySystem.params.M1pmig = 0.2667;    %probability of migration
mySystem.params.M1pdeath = 0.0049;  %probability of death
mySystem.params.M1rwalk = 0.8;      %random influence on movement
mySystem.params.M1speed = 40;       %speed of movement
mySystem.params.M1influxProb = 0; %probability of influx
mySystem.params.M1influxRate = 1;   %number of cell influx
mySystem.params.M1cellNo = 0;       %number of initial cells
mySystem.params.M1engagementDuration = 60; %number of steps immune cell is engaged
```

```
%DEFINE MACROPHAGE TYPE 2 PARAMETERS
mySystem.params.M2kmax = 11;   %killing capacity
mySystem.params.M2pkill = 0.0127;   %probability of killing
mySystem.params.M2pkill = 0;        %probability of cell promotion
mySystem.params.M2pmig = 0.2667;    %probability of migration
mySystem.params.M2pdeath = 0.0049;  %probability of death
mySystem.params.M2rwalk = 0.8;      %random influence on movement
mySystem.params.M2speed = 40;       %speed of movement
mySystem.params.M2influxProb = 0; %probability of influx
mySystem.params.M2influxRate = 1;   %number of macrophages each influx
mySystem.params.M2cellNo = 0;       %number of initial cells
mySystem.params.M2TUadd = 0;         %Tumor promoting
mySystem.params.M2engagementDuration = 60; %number of steps immune cell is engaged

%DEFINE FIBROBLAST PARAMETERS
mySystem.params.Fpprol = 0.0838;      %probability of proliferation
mySystem.params.Fpmig = 0.4;       %probability of migration
mySystem.params.Fpdeath = 0.0018;    %probability of death
mySystem.params.Fpmax = 4;          %initial proliferation capacity
mySystem.params.Frwalk = 0.5;      %random influence on movement
mySystem.params.FcellNo = 0;     %ratio of initial number of cells
```

Figure 2. *Parameters for the tumour cell, fibroblasts, M1 and M2 (van Genderen et al., 2024).*