In Silico Growth & Treatment of Cancer Cells

COMP90083 Assignment 2 Proposal (Group 18)

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Question

Are the Hallmarks of cancer cells effective and safe early drug targets for chemotherapies?

Previous Research

Cancer is one of the leading causes of mortality and morbidity worldwide[1]. This is largely attributed to the ability of cancer to arise through many different mutations, the aggressiveness of its spread and its resistance to chemoradiotherapy. To better understand the characteristics of cancer cells, Hanahan and Weinberg (2000) postulated six key hallmarks of cancer cells that provide them with their unique ability to proliferate and survive[2]. These six (phenotypic) traits are: sustained angiogenesis, evading apoptosis, sustaining growth signalling, resistance to anti-growth signals, tissue invasion and limitless replicative potential; they are believed be common amongst almost all malignancies. This approach to understanding cancer cells as a whole greatly differs from conventional molecular biology studies which typically focused on single genotypes causing cancer, instead of targeting the cancer phenotype as a whole. The benefits of holistic approaches to studying cancer are twofold. First, they offer an insight into the collective cellular mechanics that cause disease and how they could be exploited to control tumours and prevent metastatic spread. Second, they allow for the incorporation of big-data, which is quickly becoming the gold-standard for real-world analyses. Among the more popular computational models are differential equation-based models (EBMS)[3]. However, with EBMS, it is virtually impossible to capture the heterogeneity and complexity inherent in cancer cells and their disease dynamics. To this end, agent-based models (ABMs) are an increasingly popular alternative that are able to capture the emergent properties of the tumour/normal cell microenvironment[4], including that of the targeted chemotherapies. We propose an ABM that hopes to display some of the dynamics and emergent properties of drug targets for the phenotypic traits of cancer cells.

Overview- Purpose

To demonstrate the feasibility of early targeted chemotherapies specifically designed to "knockout" specific Hallmarks of cancer cells. This model simulates the growth of a new tumour, how it interacts with local tissue and how it responds to chemotherapy. This model will provide an insight into some of the possible emergent behaviours of this targeted chemotherapy on tumour cells as well as somatic tissue in a complex tumour\soma environment.

Entities, State Variables & Scales

Agents:

- *Tumour (cancer) & Somatic (normal) Cells.*[1] Have state variables: age, stem-cell potency and the six most prominent hallmarks of cancer:

  1. Sustained Angiogenesis
  2. Evading Apoptosis
  3. Growth Signals
  4. Resistance to Anti-Growth Signals
  5. Tissue Invasion
  6. Limitless Replicative Potential

- *Chemotherapy (drug) & Hormones.* Have state variables concentration and effect.

Environment:

[1] NB: Tumour and Somatic cells (due to their similar state variables) are collectively referred to as "cellular agents".

- A square grid that can be occupied by zero or more cellular agents and zero or more chemotherapy\hormone agents.
- The patches of this grid will represent the underlying extracellular matrix (ECM), artery wall and artery lumen. Cellular agents can move freely over the ECM patches, but not over the artery wall patches.[2] Chemotherapy agents can move freely throughout the environment.

Scale:

- Temporal: The time scale will be discrete; each tick will represent a second of time.
- Spatial: The spatial scale will be continuous and not spatially explicit.

Process Overview and Scheduling

As the model progresses, the environment setup by the patches (ECM, artery wall and lumen) and the cycling hormone agents does not change. However, how the cellular, response hormone and chemotherapy agents move and interact with the environment changes.The *response hormone* and *chemotherapy agents* move across a concentration gradient and eventually "die" as they are removed from the tissue.The *normal cell agents* divide, age and die in an equilibrium until they have to compete for space\resources with the tumour cell agents, or they are killed by the response hormone and\or chemotherapy agents. The *tumour cell agents* continue to divide and compete with the normal cell agents until their either take over the environment or are killed by the response hormone and\or chemotherapy agents. This control flow is given by the Scheduling algorithm (below).

Algorithm 1 Scheduling

```
1: Initialise (Environment, Agents, startChemo)
2: t ← 0 {set clock}
3: loop
4:    Divide(cancerCell), Divide(normalCell)
5:    Move(cyclingHormones)
6:    if t == startChemo then
7:       Move(chemo), Move(responseHormones)
8:       Interact(chemo, cancerCell), Interact(chemo, normalCell)
9:       Interact(responseHormones, cancerCell), Interact(responseHormones, normalCell)
10:   end if
11:   Interact(cyclingHormones, cancerCell), Interact(cyclingHormones, normalCell)
12:   CompeteOnPatch(cancerCell, cormalCell)
13:   t ← t + 1
14: end loop
```

Design Concepts

The **basic principle** at the heart of this model is growth via cell division, which can lead to the **emergence** of a tumour and, potentially, to metastasis. We model the **interaction** of cells, hormones, and a chemotherapy drug. **Stochasticity** is present in the initialisation and movement of hormones through the ECM. We **observe** the number of cancer/somatic cells and whether metastasis occurs.

Details- Initialisation

Patches are setup to represent the local solid tissue of interest (ECM, artery wall and artery lumen patches). ECM patches are initially occupied by somatic cells and tumour cells are limited to a single patch (site of the initial cancer stem cell). Cycling endogenous hormone agents are setup randomly across the environment. Chemotherapy agents and hormone agents that respond to tumour growth are not present at initialisation.

Input Data & Submodels

No input data is required for this model; however, this model could be expanded to incorporate real spatial data for generating the patches of the tumour\soma environment (amongst other expansions with input data). *Divide*, *Move*, *Interact*, and *CompeteOnPatch* (from Scheduling) will be described further in the Report.

[2] If an ECM patch is at a threshold value of tumour agents then the tumour agents can move into a neighbouring artery patch.

Previous Research References

1. Ferlay J., Steliarova-Foucher E., Lortet-Tieulent J., et al. *Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012.* European Journal of Cancer. 2013, 49:6, 1374-1403.
2. Hanahan D. & Weinberg RA. *Hallmarks of Cancer: The Next Generation.* Cell. 2011, 144: 5, 646-674.
3. Franssen LC., Lorenzi T., Burgess AEF., et at. *A Mathematical Framework for Modelling the Metastatic Spread of Cancer.* Bull Math Biol. 2019, 81:6, 1965-2010.
4. Zhang L., Wang Z., Sagotsky JA. et al. *Multiscale agent-based cancer modeling.* J Math Biol. 2009, 58:4-5, 545-59.