INTER-CLONAL INTERACTIONS IN CANCER

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There is evidence that subclones within tumours can cooperate. In breast cancer, minor subpopulations can drive metastatic progression by modulating the tumour microenvironment.

A minor subclone secretes IL11 which influences neutrophils to create changes which allow metastasis. A minor subclone also secretes FIGF which increases angiogenesis and vascular permeability. These sub clones represent 1 - 5% of tumour cells [Janiszewska et al. 2019].

In Wnt-driven breast tumours, cooperation between Hras mutant and wild type clones was required for efficient tumour propagation that relied on luminary produced Wnt. The Hras mutant cells have basal identity whilst the wild type cells have luminal identity. Hras is an oncogene, and so once mutants arise it would normally be expected that they dominate the tumour, but the requirement for Wnt production meant that the fraction of Has mutants was <0.3 [Cleary et al. 2014].

In breast cancer, IL11 clones enhanced tumour growth non-cell autonomously. IL11 appeared to have an indirect effect enhancing cell proliferation via increased vascularisation and remodelling of the extracellular matrix [Marusyk et al. 2014].

Mathematical models lead to the rejection of the hypothesis of independent clonal growth rates, and the most likely hypothesis was that IL11 clones increased the growth rates of all clones.

PROPOSITION

Interspecies interactions have been the subject of much study in ecology. In this summer project, we propose to apply ecological multi-species models to studying inter-clonal interactions in cancer.

In doing so, we consider tumour growth through oncogenic cooperation of different mutations in separate clones of cells.

INTRODUCTION

The development of tumours occur when cells undergo certain mutations in their genetic code, which lead to a growth advantage for that cell. It is thought that the malignancy of cells relies heavily on the production of diffusible growth factors. Changes in this chemical production can alter self-sufficiency in growth signals, insensitivity to anti-growth signals,

evading apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion, and metastasis [Renton et al. 2019]. We must therefore look at the effect of the production of these growth factors on cell populations organised into tissues. This enables us to examine the role of cellular cooperation in tumour growth.

We will examine the evolution of cooperation for diffusible growth factors by modelling the cells as a periodic lattice to represent the organised structure of cell populations in tissues. There is a significant effect of tissue structure on the evolutionary dynamics, favouring cellular cooperation compared to well mixed cells.

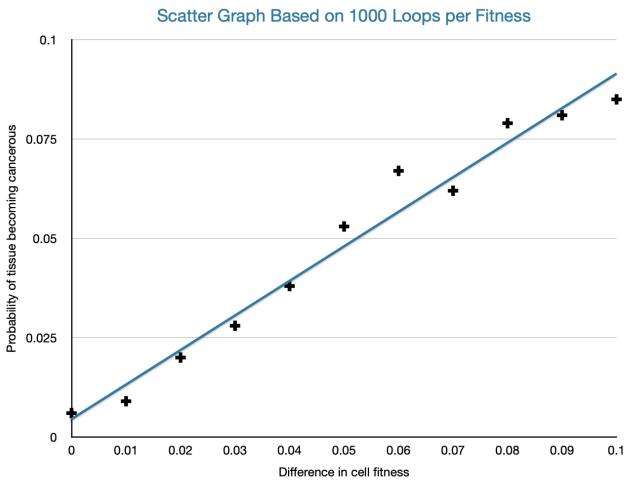
A focus will be placed on incorporating Evolutionary Graph Theory (EGT) to model cell games on the structured tissue population. We therefore aim to develop a model by placing each cell on the vertex of a graph, joined to its neighbours by edges. These cells will then interact and play games with each other, deriving their fitnesses, before we incorporate the diffusion of growth factors into our model.

Our models initially look at the evolution of traits on fixed population structures, where each cell is represented by the vertex of a static graph and the edges correspond to neighbouring cellular connections.

NON INTERACTING CELL MODEL

In this model we start with the whole population of healthy cells and one cancerous, mutated cell. An individual cell is chosen to die uniformly at random. It is then replaced by the offspring of a neighbouring cell, chosen with probability proportional to the fitness. We keep the fitness of a healthy cell constant (set it equal to 1), and vary the fitness of the mutated cell.

By running multiple loops of our code we can observe the links between fitness value, probability of the cancer over-ruling the tumour, and length of time for this to occur.



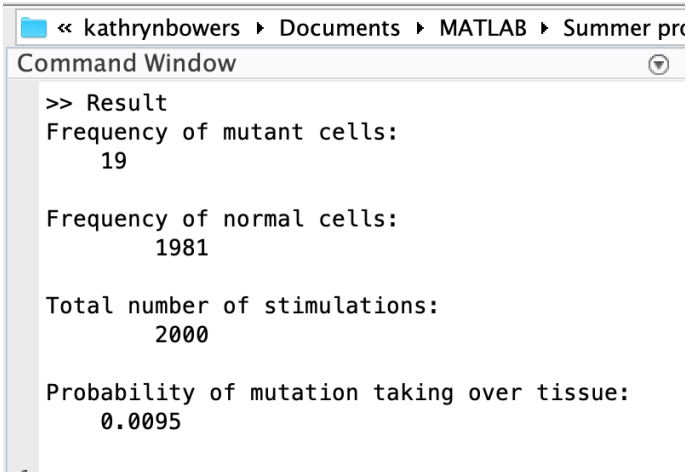
INTERACTING CELL MODEL

We then developed the interacting cell model to introduce cooperator cells. These cells provide some benefit to cells in a near vicinity, increasing their fitness, but at a cost to the fitness of the cooperator cell itself.

In this model we used cooperation with neighbouring cells, and introduced cost and benefit values for cooperation. By formulating a pay-off matrix and then determining the pay-off to an individual cell from its neighbours, we can calculate the fitnesses and control them by using a selection strength parameter.

It is possible to check our model by setting the cost to the cooperator cell to be 0.01, and the benefit it provides as 0.04.

By running our code multiple times, we should calculate the probability of the cooperator cell taking over to be 1/100 (using a 10x10 cell grid).



PUBLIC GOODS GAME

Though the interacting cell model incorporates cooperator cells, it is necessary to further develop our model to take into consideration the ratio of diffusion rate to utilisation rate (λ).

It is very common for the public goods dilemmas to appear in microbes, where the benefits from the cooperator cell are distributed to the surrounding cells (excluding the producer).

We denote the colony of cells as a matrix, and assign the edges that join neighbouring cells a "weight" proportional to the frequency of diffusion along it. We then normalise these weights so that they represent the relative frequencies.

Edge weights: e_{ij}

Normalisation of weights: $\sum_j e_{ij} = 1$

Note that we are only modelling intercellular diffusion so $e_{ii} = 0$ (no summation convention) for each i, and bi-transitive symmetry, so $e_{ij} = e_{ji}$ for all i and j.

We assume that the cooperator cell produces one unit of public good that has a direct benefit per unit of time.

By denoting the local public goods concentration (produced by the cooperator) at each node i as Ψ_i, we model the rate of change in concentration as:

$$\dot{\Psi}_i = s_i - \Psi_i - \lambda\Psi_i + \lambda \sum_j e_{ji}\Psi_j$$

We specify the value of $s_i \in \{0,1\}$ to represent the current cell being a defector or cooperator respectively, and thus the public goods production.

The utilisation of public goods and diffusion outwards are represented by $-\Psi_i$ and $-\lambda\Psi_i$ respectively, with the diffusion inwards from neighbouring cells being represented by the remaining term, $\lambda \sum_j e_{ji}\Psi_j$.

(In our case we set $e_{ij} = 0.25$ between direct neighbours and $e_{ij} = 0$ otherwise).

By solving this matrix equation, and assuming that the public goods gets set to a steady state, we can determine the values for Ψ_i and use this to give us the fitnesses of individual cells (F_i).

$$F_i = 1 + b\Psi_i - cs_i$$

From our model, we can verify that for public goods cooperation to be favoured we must have:

$$\frac{b}{c} > \frac{1}{\Psi_i + \sum_j e_{ji}\Psi_j}$$

(This is for a state in which we only have one cooperator cell i)

For our model, we consider a stationary public goods distribution, meaning that we set the rate of change in concentration to be zero ($\dot{\Psi}_i = 0$).

This yields a simpler equation to solve:

$$(1+\lambda)\Psi_i = s_i + \lambda \sum_j e_{ji}\Psi_j$$

In the case where only cell i is a cooperator, we can therefore obtain:

$$\frac{b}{c} > \frac{\lambda}{\Psi_i(1+2\lambda) - 1}$$

We can use this to test our code by finding the critical values of b and c for a given λ.

Another way that help convince us that the model is indeed valid is by setting $c = b = 0$.

```
Command Window
>> Result
Frequency of mutant cells:
     1

Frequency of normal cells:
    99

Total number of stimulations:
   100

Average generation for mutant cells to take over:
        6479

Average generation for normal cells to take over:
  525.6768

Probability of mutation taking over tissue:
    0.0100
```

For a lattice of 100 cells and by introducing a single mutant cell, we would expect the mutant cell would take over the tissue once per 100 runs of the model.

VORONOI TESSELLATION MODEL

We will explore how the structure of the cells in a two-dimensional tissue affects our models. To do this we still rely on a fixed domain with periodic boundary conditions. By first performing the Voronoi tessellation, we can identify the neighbouring cells. Following this, by implementing the Delaunay triangulation, we are able to partition the "tissue plane" into triangles joining the cell centres.

In this model we will assume the free-movement of cells in the fixed tissue domain. Spring-like forces act along the Delaunay triangulation edges with a fixed natural separation (s) for all neighbouring pairs.

However, when we consider cell reproduction to form sister cells, it is essential to formulate a rule for the separation of the newborn sister cell to the original.

Our model will assume that the natural separation between the cells grows linearly from an arbitrarily small distance ϵ to s over the course of an hour.

Force exerted on cell j by neighbour i:

$$F_{ij}(t) = -\mu\hat{r}_{ij}(t)(|r_{ij}(t)| - s)$$

Where μ is the spring constant, r_i is the position vector of cell i, and $r_{ij} = r_i - r_j$ (the displacement of cell j from cell i.

Total force acting on cell i :

$$F_i(t) = \sum_{j \in N_i(t)} F_{ij}(t)$$

Where $N_i(t)$ is the set of cells neighbouring cell i.

We can generalise our situation to a first-order differential equation by considering the nature of the friction acting on each cell.

Differential equation:

$$\eta \frac{dr_i}{dt} = F_i(t)$$

Where η is the damping constant.

We solve this discretely for a fixed change in time, chosen sufficiently small to ensure numerical stability e.g. every 0.005 hours (18 seconds).

For each cell birth and death, we must re-calculate the Delaunay transformation due to the movement of cells.

DISCUSSION

Though our models are becoming a more accurate representation of cancer growth, there are many alterations to still consider.

Our final model involved a constant cell population size, where the birth and death of cells occurred simultaneously. It would be interesting to consider the implications of cell death not occurring, but instead one clone being dominant over the others. This act of dispensing with cell death will lead to a growing population.

In addition, we assumed the birth rates to be proportional to the cell fitness, but we need to further develop a model for different relative fitnesses of 2 clones.

In vitro, it is unrealistic that the death of a cell is followed by the reproduction of a neighbouring cell, though we cannot exclude the possibility that the birth and death of cells have some spatial dependence.

Finally, a model should be developed in order to study a change in colony dimensionality. In this project, we only looked at two-dimensional structures.

Yet for tumours like breast cancer, three-dimensional structures are required. It could be hypothesised that progressing to three-dimensional space would reduce the advantage of cell cooperation.

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