Studying effects of competition on adaptive therapy

A Thesis

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by

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Certificate

This is to certify that this dissertation entitled Studying effects of competition on adaptive therapytowards the partial fulfilment of the BS-MS dual degree programme at the Indian Institute of Science Education and Research, Pune represents study/work carried out by Harshavardhan BV at Indian Institute of Science Education and Research under the supervision of Prof. Sutirth Dey, Professor, Department of Biology , during the academic year 2020-2021.

Prof. Sutirth Dey

Committee:

Prof. Sutirth Dey

Dr. M.S. Madhusudhan

This thesis is dedicated to ?

Declaration

I hereby declare that the matter embodied in the report entitled Studying effects of competition on adaptive therapy are the results of the work carried out by me at the Department of Biology, Indian Institute of Science Education and Research, Pune, under the supervision of Prof. Sutirth Dey and the same has not been submitted elsewhere for any other degree.

Harshavardhan BV

Acknowledgments

Not more than 250 words

Abstract

Write your abstract here

Contents

List of Tables

List of Figures

Chapter 1

Introduction

1.1 What is Cancer?

Cancer is a collection of disease that is usually caused by uncontrolled division of cells and that has potential to spread to other parts of the body (cancer.gov, 2015). Cancer could be caused by various factors like tobacco usage, excess sun exposure, viral infection to name a few (Trichopoulos, Li, & Hunter, 1996). Although, the underlying mechanism from these causes usually involves genetic mutations or epigenetic changes that alter the DNA. These alterations usually trigger a cascade of events that eventually leads to uncontrolled growth of cells (GRØNBÆK, HOTHER, & JONES, 2007; Moolgavkar & Knudson, 1981).

Cancer is among the highest causes of death among human beings. In the year 2021, over 600,000 deaths are expected to be caused by cancer in the US alone (Siegel, Miller, Fuchs, & Jemal, 2021). Cancer systems has been of research interest for several decades due to the massive impact it has on human lives. Through such research, we have been able to understand the causes and mechanism of how cancer arises and then develop new therapies and drugs that target them. Although, the mortality among some types of cancer have been reduced significantly, we were not so lucky among other types of cancers and, the overall mortality still remains pretty high.

1.2 Conventional therapy against cancer

The most popular strategies to control cancer are radiotherapy, chemotherapy, immunotherapy, and surgery. Depeneding on the type and stage of cancer, some of these strategies may not be effective.

Among chemotherapy, the standard clinical protocol, Standard of Care (SOC) followed for most cancer is to administer cytotoxic drugs at the maximum tolerated dosage (MTD) (Frei & Canellos, 1980). The aim of this method is to kill the maximum number of tumour cells as fast as possible. This minimises the tumour burden quickly and should give better standard of living if it's the case.

However, evolutionarily thinking, a tumour would consist of cells with heterogenous sensitivity towards a cytotoxic drug. Under normal conditions, that is, in the absence of therapy, these cells would compete with each other and keep the number of resistant phenotype in check. On adminitering the drug at MTD, the most sensitive cells are killed off first and this leads to a "competitive release" of the resistant phenotype (Scott & Marusyk, 2017). The resistant phenotype now grows without inhibition and takes over the population. These resistant phenotypes don't respond to further dose administered and the therapy fails. This is illustrated in Figure 1.1.

Competitive release could happen for other methods of therapy as well, if there are resisitant phenotypes for that particular therapy method present in the population.

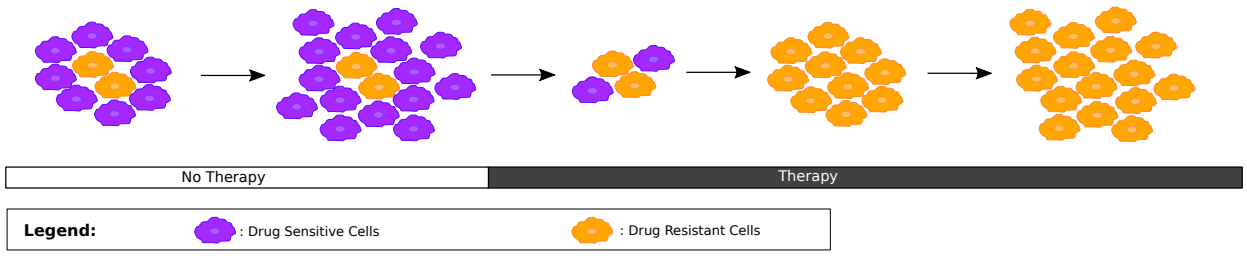

Figure 1.1: Illustration of competitive release under SOC

1.3 Adaptive therapy

When competitive release happens, one could try to combat the cells with another drug or therapy method. However, these cells could potentially be resistant to the new drug as well and developing new drugs is research intensive. The best method would be to avoid such a competitive release in the first place.

Adaptive therapy (AT) is one such novel technique under development to avoid competitive release. In AT, the cytotoxic drug is administered at lower and fluctuating doses. This doesn't kill off all the sensitive cells and the probability of a competitive release is minimised. The resistant cells cannot take over due to competitive pressure from the still remaining sensitive cells and the tumour burden is maintained under control due to further doses being able to kill the sensitive cells that grow back. This is illustrated in

The dose adminitered at a given point is usually related to the tumour size at that given point (Gatenby, Silva, Gillies, & Frieden, 2009). The challenge with designing AT regimens is to balance between the inhibition of resistant phenotype and the inhibition of the overall tumour size.

Even with this, AT may not be able to achieve control indefinitely. It'll only attempt to maximise the survival time compared to other regimens. AT, however, ignores the possibility of a cure, where the standard of care method would yield the best results. The patient has to live with the tumour for the rest of their life and other complications could arise due to this. (put in discussion maybe?)

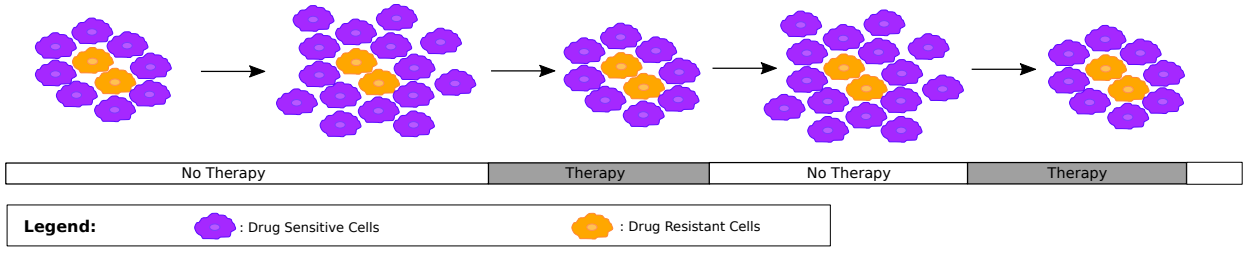

Figure 1.2: Illustration of control under AT

1.4 Importance of competition in adaptive therapy

The only way of controlling the resistant phenotype for a fixed drug in AT is through competition by the sensitive cells. Therefore, the success of AT in containing the tumour depends on the effectiveness of competition between sensitive and resistant cells. Although, previously it was thought that resistant cells are required to have an inherent disadvantage for AT to be successful, even without it the survival time can be prolonged by competition between the cells (Strobl et al., 2020).

Cells can use different strategies such as higher proliferation rate, better survival at suboptimal conditions or lower death rate to compete with each other, and several such strategies are seen to be acquired over the course of cancer progression, as shown by the "hallmarks of cancer" framework (Hanahan & Weinberg, 2011).

1.5 System of Study

The metastatic castration resistant prostate cancer (mCRPC) was chosen to be the system of study. The mCRPC system already has a history of AT work done on it, although in different contexts (Cunningham, Brown, Gatenby, & Staňková, 2018; Zhang, Cunningham, Brown, & Gatenby, 2017).

Prostate cells express androgen receptors (ARs) that require testosterone or its metabolite, 5α-dihydrotestosterone to activate. Activated AR bind to promoters of genes responsible for proliferation (Heinlein & Chang, 2004). Without testosterone, proliferation is halted and the cells die of apoptosis. When cancerous cells evolve from prostate cells, the AR mechanism is preserved and such prostate cancer remains testosterone dependent.

This system is usually modelled as consisting of three different types of cells: T^+, T^p and T^-. T^+ is the baseline population for prostate cancer which require testosterone for survival. The standard therapy for prostate cancer is castration or androgen deprivation therapy (ADT) which blocks external production of testosterone and would kill the T^+ cells in a normal castration sensitive prostate cancer. However, castration resistant prostate cancer soon develops, as the T^p cells can produce testosterone and sustain the T^+ cells. T^p cells are also dependent on testosterone, and they produce testosterone from cholesterol

through upregulation of CYP17α (Dillard, Lin, & Khan, 2008). The T^- cells on the other hand do not require testosterone as they have mutated ARs that remain active even in the absence of testosterone.

Abiraterone is a drug developed against mCRPC that inhibits the CYP17α and can be effective against both T^+ and T^p, however, not against T^-. And, this could lead to competitive release of the resistant T^- cells if adminitered in the standard clinical protocol. Abiraterone is usually adminitered after ADT as the system develops into a mCRPC. For our study, we shall only consider AT protocols on abiraterone under ADT.

1.6 Goal of the Project

The goal of the project is to:

1. Develop a model of the chosen system of study with their respective resource dependence.
2. Study the dynamics of the system under different conditions in the absence of therapy.
3. Compare the dynamics under effect of different therapy regimens.
4. Find the corresponding optimal therapy regimen that maximises the survival time for particular conditions.

Chapter 2

Methods

2.1 System of Equations

The system of study was modelled using coupled Ordinary Differential Equations (ODEs). The model is based on a logistic framework modified with a dynamic carrying capacity that depends on the environmental conditions. The "environment" consists of the resources, oxygen and testosterone which have their own equations for production and consumption. We make the simplifying assumption that every other resource required by cells are present in non-limiting concentrations. Additionally, the cell types were assumed to not mutate and hence cannot change their types. No spatial structure is considered and the system is assumed to be well mixed and the resource available in bulk for all the cells. The ODEs are given below:

For $i \in \{T^+, T^p, T^-\}$ and $res \in \{O_2, test\}$

$$\frac{dy_i}{dt} = r_i y_i (1 - \frac{\sum_j y_j}{1 + K_{i,max} f_i(O_2) f_i(test)}) - \delta_i y_i \tag{2.1}$$

$$\frac{dO_2}{dt} = p_{O_2} - \sum_i \mu_{O_2,i} y_i - \lambda_{O_2} O_2 \tag{2.2}$$

$$\frac{dtest}{dt} = p_{test} y_{T^p} - \sum_i \mu_{test,i} y_i - \lambda_{test} test \tag{2.3}$$

$$f_i(res) = \begin{cases} 1 & \text{if } ul_{res,i} \leq res \\ \frac{res - ll_{res,i}}{ul_{res,i} - ll_{res,i}} & \text{if } ll_{res,i} < res < ul_{res,i} \\ 0 & \text{if } res \leq ll_{res,i} \end{cases} \tag{2.4}$$

The cell count equation involves growth and death terms. The effective growth rate decreases as the overall tumour size approaches the carrying capacity, while the effective death rate remains constant. Competition between the cell types happens in two ways, one through the density dependence over all the cell types, and the other through the implicit dependence and consumption of resources.

The equation for oxygen involves terms for external production, uptake by all the cells and decay. Similarly, the equation for testosterone involves terms for production by T^p cells, uptake by T^+ and T^p, and decay.

The functional dependence $f_i(res) \in [0, 1]$. Below the lower limit, $ll_{res,i}$ the function is 0,representative of no growth, and increases linearly above it upto the upper limit, $ul_{res,i}$ and the function saturates to 1, representative of the maximum growth, for any resource levels above that.

Note that these equations are defined only for positive values of cell count and resource level to be biologically relevant. To mitigate the problem of having a continuous variable for cell count, $y_i < 1$ is defined as extinction of the cell type i and $\frac{dy_i}{dt} = 0$ in such a case.

2.2 Parameters Used

Table 2.1 gives a brief description of the parameters from the above equations, the values used, and the sources for these values where applicable. Note that all the resource parameters are normalised to tissue levels of that resource. For the literature values, the following cell lines were considered to correspond to the cell types assumed in the model.

- T^+ = LNCaP
- T^p = 22Rv1
- T^- = PC3

Constraint equations given below were used to determine the values of some parameters for which direct sources were not available.

$$r_i = \frac{ln(2)}{\tau_{d,i}} + \delta_i \tag{2.5}$$

$$K_{i,max} = \frac{r_i}{r_i - \delta_i} y_i^* \tag{2.6}$$

$$p_{O_2} = \lambda_{O_2} O_2^* + y_i^* \mu_i \tag{2.7}$$

$$p_{test} - \mu_{test,T^p} = \frac{test^* \lambda_{test}}{y_{T^p}^*} = 4 \times 10^{-4} \tag{2.8}$$

2.3 Code Implemetation

The code is written in Python 3 and with dependencies of numpy, scipy, pandas, matplotlib and seaborn libraries. The system of equations were solved numerically by the LSODA algorithm provided by the `scipy.integrate.ode` function. The code is designed to run the different parameters of a set parallely over multiple threads, however, the actual solver is sequential and single threaded.

The code, at each time step checks if the values are non-negative and sets them to 0 if it be the case. This is since the equations are not defined in these range of values and numerical errors can give rise to negative values. A similar implementation is done for $y_i < 1$.

The source code along with the data is available at the following Github repository: https://www.github.com/harshavardhan-bv/cancer-compe-strat.

Figure 2.1: QR code for the Github repository

2.4 Simulations Done

With the above described model, the following simulations were done:

1. Absence of therapy
   (a) Pairwise T^p - T^-:
      i. changing lower limits of oxygen for T^p and T^-, while keeping others limits fixed
      ii. changing upper limits of oxygen for T^p and T^-, while keeping other limits fixed
      iii. changing both lower limits and upper limits of oxygen for T^p and T^-, while keeping others limits fixed
      iv. changing lower limit of testosterone for T^p, while keeping other limits fixed
      v. changing upper limit of testosterone for T^p, while keeping other limits fixed
      vi. changing both lower and upper limit of testosterone for T^p, while keeping other limits fixed
      vii. Brute force parameter search over all the limits
      viii. changing the initial conditions for interesting cases found from the above simulations
   (b) Pairwise T^+ - T^p:
      i. changing lower limits of oxygen for T^+ and T^p, while keeping others fixed
      ii. changing upper limits of oxygen for T^+ and T^p, while keeping other limts fixed
      iii. changing both lower limits and upper limits of oxygen for T^+ and T^p, while keeping others limits fixed
      iv. changing lower limits of testosterone for T^+ and T^p, while keeping others fixed
      v. changing upper limits of testosterone for T^+ and T^p, while keeping other limts fixed
      vi. changing both lower limits and upper limits of testosterone for T^+ and T^p, while keeping others limits fixed

vii. changing the initial conditions for interesting cases found from the above simulations

(c) All three T^+ - T^p - T^-

- changing the initial conditions for interesting cases that are some combinations of the pairwise cases
- different cases of efficiency of oxygen use for T^+, T^p and T^-
- different cases of efficiency of testosterone use for T^+, T^p and T^-

2. With Therapy

- All three T^+ - T^p - T^-

  (a) TBD

Parameter	Description	Value(s)	Source(s)
y_i	No. of cells of cell type i	N/A	N/A
r_i	Population growth rate of cell type i	T^+: 2.84×10^{-3} min^{-1} T^p: 2.79×10^{-3} min^{-1} T^-: 6.23×10^{-4} min^{-1}	Equation 2.5
δ_i	Population death rate of cell type i	T^+: 2.5×10^{-3} min^{-1} T^p: 2.5×10^{-3} min^{-1} T^-: 1.6×10^{-4} min^{-1}	(Jain, Clinton, Bhinder, & Friedman, 2011)
$K_{i,max}$	Maximum Carrying capacity, coming up through the environment/resources	T^+: 8.35×10^4 T^p: 9.62×10^4 T^-: 1.34×10^4	Equation 2.6
$f_{i,res}$	Functional dependence of cell type i on resource res, normalised to 1	$f_{T^-,test} = 1$	N/A
p_{res}	Production rate of resource, either as bulk or by cells	O_2: 0.11 min^{-1} $test$: 5×10^{-7} $\text{min}^{-1}\text{cell}^{-1}$	Equation 2.7, Equation 2.8
$\mu_{res,i}$	Uptake of resource res by cell type i	O_2, T^+: 1.63×10^{-6} $\text{min}^{-1}\text{cell}^{-1}$ O_2, T^p: 1.63×10^{-6} $\text{min}^{-1}\text{cell}^{-1}$ O_2, T^-: 1.04×10^{-6} $\text{min}^{-1}\text{cell}^{-1}$ $test$, T^+: 2.34×10^{-8} $\text{min}^{-1}\text{cell}^{-1}$ $test$, T^p: 6.00×10^{-8} $\text{min}^{-1}\text{cell}^{-1}$ $test$, T^-: 0 $\text{min}^{-1}\text{cell}^{-1}$	(Hail, Chen, & Bushman, 2010), Equation 2.8
λ_{res}	Decay rate of resource res	O_2: 0.100 min^{-1} $test$: 0.004 min^{-1}	(Jain et al., 2011)

Continued on next page

Parameter	**Description**	**Value(s)**	**Source(s)**
$ll_{res,i}$	Lower limit/threshold level of resource res for carrying capacity of cell type i	$\in [0,1]$	N/A
$ul_{res,i}$	Upper limit/saturation level of resource res for carrying capacity of cell type i	$\in [0,1]$	N/A
Supplementary Parameters			
τ_d	Doubling time of cell type i	T^+ 34 hr T^p 40 hr T^- 25 hr	(atcc.org, 2020)
y_i^*	Equilibrium value of cell number in absence of competition	10000	assumed
res^*	Equilibrium/Tissue levels of resource with one cell type present	O_2 2.5 mmHg $test$ 3.74 pmol/g tissue	(Stewart et al., 2010),(Titus, Schell, Lih, Tomer, & Mohler, 2005)

Table 2.1: Table of all parameters

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