



MATHEMATICAL MODELLING OF DRUG RESISTANCE IN MALIGNANT
TUMOUR TREATMENT

A DISSERTATION SUBMITTED TO THE UNIVERSITY OF KWAZULU-NATAL
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Abstract

Resistance to conventional chemotherapies, especially to anti-cancer agents, is rapidly becoming a global pandemic. Mutations, in combination with genetic instabilities, play an important role in the molecular heterogeneity of cancerous cells that display resistance to chemotherapeutic drugs. Currently, mechanisms involved in drug resistance phenotype resulting from the interaction of a tumour and anti-cancer agents are not fully understood. In this dissertation, we propose two new dynamical models for the interaction between a tumour and a chemotherapeutic drug. Our focus is only on resistance which is caused by random genetic point mutations. The models consist of coupled systems of ordinary and partial differential equations. Tumour cells are divided into two classes, namely; sensitive and resistant cells. We determine the equilibrium points of the model equations and investigate their stability. In the first instance, after reviewing the basic modelling assumptions and main results found in the mathematical modelling literature on drug resistance, we present the ordinary differential equation (ODE) model. To account for spatial growth effects, we then extend the model to a partial differential equation (PDE) model that describes the local interaction of the tumour with the anti-cancer agent through convection, reaction and diffusion processes. Some analytical solutions of the PDE model that are comparable to those found in the literature are obtained. One novel outcome of the models in this dissertation is the qualitative demonstration of the possible success of the therapy for certain initial conditions, number of sensitive cells and their interaction with the chemotherapeutic drug. Parameter sensitivity analysis is carried out to determine the influence of each individual parameter in the model. For all the models, numerical solutions which showed the effect of therapeutic agents on the growth and spread of the tumour cells, subject to evolving drug resistance phenomenon, were attained and presented here.

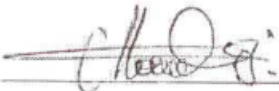
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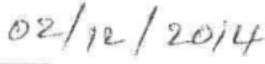
I declare that this dissertation presents my original work and effort. It was carried out under the supervision of Dr. H. Mambili-Mamboundou and Prof. P. Sibanda, in the School of Mathematics, Statistics and Computer Sciences, University of KwaZulu-Natal, Pietermaritzburg Campus.

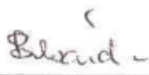
It has not been submitted in any form to any university or institution of higher learning for any degree or qualification. Where use has been made of the work of others it is duly acknowledged.

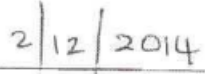
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Dedication

This dissertation is dedicated to my beautiful wife, Macharles Mahasa, and my son, Charles Mahasa, and daughter, Lerato Mahasa.

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Chapter 1

Introduction

1.1 Overview

Cancer is a major global health problem and a leading cause of deaths worldwide [6]. According to the International Agency for Research on Cancer, there were 12.7 million new cases of cancer in 2008. The global cancer burden is expected to double to 21.4 million cases with the corresponding deaths of 13.5 million by 2030 [7]. Some cancers can be treated successfully even with current medical treatment options [8,9]. However, to date, there is still no cure for most cancers [10,11].

Cancer is generally defined as an unrestrained growth of abnormal cells in any part of the body. There are various distinct types of cancers, which can change substantially in their phenotype (the appearance of a cancerous cell resulting from its interaction with a surrounding environment) and response to treatment. Normal cells have regulatory mechanisms that govern cell proliferation (i.e a cellular division or increase in number), differentiation (the degree of tumours capacity in relation to invasiveness and mortality), survival and death of the individual cells. Cancer cells, on the other hand, behave quite differently. Cancer can occur when there is either a fast unbounded growth of abnormal cells or cells have lost their ability to die; thereby resulting in the formation of a mass called a tumour. Tumours can be classified in two ways, namely benign or malignant tumours. A benign tumour usually remains confined to its tissue of origin. Benign tumours may be harmful due to their interference in body regulatory mechanisms that accompany the cellular proliferation, growth and death of individual cells. So they can be harmful, although they are usually considered less dangerous and or less invasive than malignant tumours. A malignant tumour is one that can metastasize (i.e

invade the surrounding tissues, and spread to other distant body sites). The metastatic tumours initially grow locally in the primary tissue before they can spread to other distant sites through the bloodstream and the lymphatic system.

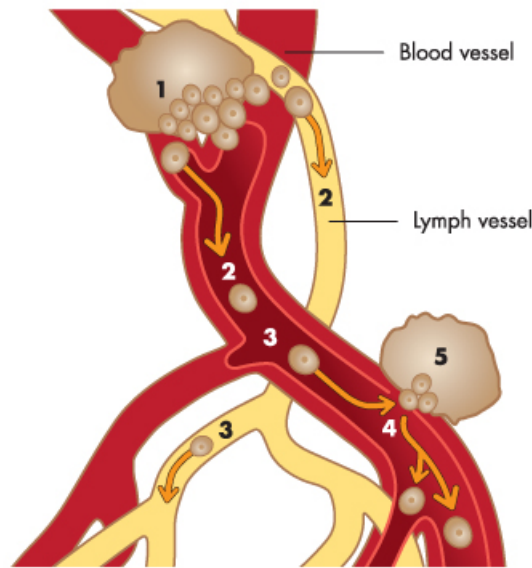


Figure 1.1: The stages of tumour metastasis, Source [1].

Figure 1.1 gives a summary of the metastatic processes. Step (1) illustrates the state at which the tumour grows at its primary site, (2) represents the state at which the tumour has broken away from the original site and entered the bloodstream or lymphatic system, (3) shows the cancerous cells travelling through the bloodstream or lymphatic system to other parts of the body, (4) denotes the state at which the tumour escapes the bloodstream or lymphatic system and breaks into the nearby tissue, and finally (5) represents the state at which the tumour has now invaded the nearby tissue and started to grow into a new tumour [1]. Metastasis has been reported as the most frequent cause of cancer death, therefore, systemic or targeted therapies are required to improve patients health [12–16].

There are many causes of cancer that have been identified to date, including excessive exposure to sunlight, drinking excessive alcohol, exposure to certain chemicals and genetic differences [17]. However, many of the cancer causing agents are still unknown [18]. In the case of known cancer types, there exist a considerable number of treatment options for patients including chemotherapy [19–24], surgery [25], immunotherapy [6, 20, 26–32], radiotherapy [33, 34], anti-angiogenesis [8, 33, 35], and oncolytic virus therapy (virotherapy) [36, 37]. Treatment usually improves the patients quality of life or brings about remission of the cancer [10, 11]. However, mathematical and biological knowledge of

these treatment modalities is still in its infancy.

The effectiveness of cancer treatment varies between patients and with the type of cancer. Some cancers may remain undetectable for years, while others may grow and metastasize rapidly, and cause death within a short period. Nevertheless, in as much as there are numerous distinct cancer types, Hanahan and Weinberg [38] showed that, in their rapid cell growth, most human cancers have six basic properties, to be specific:

- (i) unbounded replicative potential,
- (ii) insensitivity to growth-inhibitory signals,
- (iii) tissue invasion and metastasis,
- (iv) self-sufficiency in growth signals,
- (v) evasion of programmed cell death, and finally
- (vi) sustained angiogenesis (development of new blood vessels)

Conventional cancer treatments follow three principal regimens. Firstly surgery, may be appropriate where the tumour is of a detectable size and is localized; that is, it is unlikely to have metastasized. A second therapy option is radiotherapy, which uses radiation to kill the cancerous cells. However it may cause a further problem of killing healthy surrounding tissues if tumour has metastasized. The third option is chemotherapy, where cytotoxic drugs are used to invade the rapidly proliferating cells. However, a major limitation of chemotherapy is that it also kills any normal healthy cells that also have a rapid proliferation rate, such as those found in bone marrow [8]. Furthermore, despite great advances in both biological and clinical understanding of cancer, there remain only a few cancer types that are known to be sensitive to standard therapies and which are thus potentially curable. These include many pediatric tumours, several hematological cancers and germ cell tumours such as those found in the testis [9]. Therefore, despite great advances in both biological and clinical understanding of drug sensitivity, drug-resistant tumour populations remain a major challenge for both scientific and clinical researchers [9, 39–43].

Resistance to a single chemotherapeutic drug has been reported in many mathematical, biological and oncological studies [5, 44–49]. Although many tumour cells may be intrinsically resistant to chemotherapy, such resistance being caused by mutant genes, in some cases, a tumour may also

develop resistance to a chemotherapeutic agent later during therapy due to cell mutations in response to signals from the micro-environment. This later development may then confer resistance to a specific chemotherapeutic drug [43]. Examples of reported acquired drug resistance studies include breast cancers that show a loss of estrogen receptor following the emergence of tamoxifen resistance [50]; the development of mutations that render chronic myelogenous leukemia (CML) cells resistance to the drug imatinib [51], and non small cell lung cancer (NSCLC) resistance to the drug gefitinib [52]. With diverse underlying evolutionary mechanisms and pathways to drug resistance, the development of tumour sub-populations, which modify the overall sensitivity of the drug sensitive cells, still remains a problem in clinical oncology [46]. Due to drug resistance, there is a need for better understanding of the roles played by various treatments modalities for the inhibition of tumour growth and metastasis. This is an exceptionally difficult task since cancer cells are usually composed of cells that may be in different phases of their cell cycle [10]. Furthermore, for any given type of cancer, the macroscopic properties of the tumour may depend on the number of the cancer cells present at that instant. As a result, mathematical modelling of malignant tumours faces challenges in terms of which parameters to prioritise, because there are no consistent data about the properties of a given cancer [10, 20, 53]. In response to this challenge, mathematical models developed in this dissertation will provide a theoretical description of dynamical systems concerned in the spread of cancerous cells. These models will thus provide qualitative and quantitative understanding of the effects of various treatment options on cancerous cells.

There are two major aims in this study. We seek to understand, and model, the biological aspects of cancer that concern:

- (i) cell population growth describing the production of offspring through cell proliferation, death and local interaction between tumour cells and cancer anti-agents,
- (ii) spatial distribution dynamics of the cell populations through reaction, convection and diffusion which describe the random mobility of cells, and biological phenomenon which are involved in the migration of cancer anti-agents towards tumour cells.

In particular, we aim to answer the following questions;

- (a) How do tumour cells escape cancer drugs or treatment?
- (b) What interventions can be implemented to reduce or minimise this escape?

As a first approach to answering these questions, we develop deterministic mathematical models that;

- (1) take into consideration the local population growth and reaction kinetics,
- (2) model the dynamics of spatial distribution of the tumour sub-populations through reaction, convection and diffusion,
- (3) enhance our understanding of the effect of different interventions on the tumour cell sub-populations through qualitative and numerical analyses.

1.2 A review of mathematical models for drug resistance

Along with biological and clinical research, many mathematical models have been developed to model the development of drug resistance in cancer. Such mathematical models have the advantage over clinical studies in that they provide significant insights into the dynamics of the drug resistance before the model could be used in carrying out the clinical trials. Economically, this help to save money that could be used to implement the dimly understood drug resistance phenomenon. Further, conclusions from mathematical models could provide a valuable information to clinical researchers to develop new trials with a more refined focus, and in some cases lead to new clinical trials [45]. In earlier studies [39–41], the evolution of drug resistance was identified as the major source of failure in many chemotherapies. Mathematical models that take into account the undesirable effects of drug-resistance can be found in [10, 11, 22, 41, 54–56] with succinct reviews published in [45, 46]. These studies range from deterministic to stochastic models, and from discrete (agent-based) to continuum models. The models include those composed of ordinary differential equations (ODEs), partial differential equations (PDEs), delayed differential equations (DDEs), and integro differential equations (IDEs) [45, 46].

In literature, there are mathematical models which consider the mechanism of genetic point mutations and gene amplification. Gene amplification comes as a result of an overproduction of a particular gene or genes. This means that larger portion of the genome would be replaced by copies of one gene, which, in turn, confer resistance to a particular drug. By using branching stochastic processes, mathematical models of drug resistance due to gene amplification were done in [57, 58]. Point mutations are random genetic changes that occur during cell division. The models of this type have been considered in earlier works of Coldman and Goldie [5]. One novel feature of their model is that small tumours

have a higher probability of not having drug resistance than large solid tumours. However, more recent reports of stochastic models of point mutations are found in Komarova [54, 59]. By using PDEs and probabilistic methods, Komarova [59] showed that the tumour pre-treatment phase is more important in the development of drug resistance than the treatment phase. Further, Komarova and Wodarz [54] showed, within the assumptions of their model, that using a combination of three drugs with different specificities might overcome the problem of resistance. Another mathematical report on genetic point mutations is by Iwasa et al [60] in which the branching processes were used to compute the probability of resistance at the time the tumour is detected.

From these studies it can be seen that there has been considerable work on modelling of drug resistance using stochastic processes. However, there is not enough information on the mechanisms of how do cancer cells elude chemotherapy. It is nevertheless important to note that there are diverse underlying evolutionary mechanisms and pathways to drug resistance. The development of the drug-resistant tumour sub-populations which modify the overall sensitivity of the drug sensitive cells still remains a major problem in clinical oncology [46]. Even though there are many treatment options available for cancer patients, particularly in the early stages of the disease, the mortality rate is still high [61]. We describe two particular ODE models here which will be used as starting points for our PDE model which takes into account the effects of spatial dynamics of the tumour cells.

The first model we describe is the ODE model of Tomasetti and Levy [47] which describes the probability of the development of drug resistance based on the number of cancerous cells at the time of detection, the mutation rate and the turnover rate of the cancer cells. In their study, they first distinguished two types of cells: the wild-type (cells that are sensitive to the drug), $N(t)$, and the cells that have undergone mutations and hence resistant to the drug, $R(t)$. They further delineated the branching processes that lead to drug resistance due to genetic point mutations. The model may be described by the equations

$$\begin{cases} N'(t) = (L - D)N(t), \\ R'(t) = (L - D)R(t) + \mu N(t), \end{cases} \quad t \leq t^*$$

$$\begin{cases} N'(t) = (L - D - H)N(t), \\ R'(t) = (L - D - H)R(t) + \mu N(t), \end{cases} \quad t > t^*$$

where $N(t)$ is the number of wild-type cancer cells that are sensitive to a drug at time t , $R(t)$ denotes the cancer cells that have undergone mutations and are therefore resistant to the drug. L, D, μ denote

the natural cell birth, death and mutation rates, respectively, while H denotes the drug-induced death rate. An interesting finding from this model is that the levels of resistance, before the start of the treatment and present at some given time afterwards, always depends on the turnover rate D/L , regardless of the number of chemotherapeutic drugs used simultaneously in the treatment [8].

The mathematical model by Jackson and Byrne [48] played an important role in the development of further mathematical models for drug resistance in solid tumours. Their spatially- dependant mathematical model considered the response of vascular tumours and drug resistance to chemotherapeutic treatment. In that study, two tumour cell types are distinguished with respect to their responsiveness to a chemotherapeutic agent: a rapidly dividing population, $p(r, t)$, which is highly susceptible to the drug, and the other population, $q(r, t)$, which has lower drug susceptibility. They further assumed that the tumour spheroid expands or shrinks at a rate which depends upon the balance between cell growth and division, and cell death within the tumour, in which the latter state is being modified by the presence of the drug. $d(r, t)$ denotes a chemotherapeutic drug concentration at time t , and $\mathbf{u}(r, t)$ presents a local cell velocity. The model is described by the following equations:

$$\frac{\partial d}{\partial t} + \nabla \cdot (\mathbf{u}d) = \nabla \cdot (D(r)\nabla d) + \Gamma(r)(d_B(t) - d) - \lambda d, \quad (1.1)$$

$$\frac{\partial p}{\partial t} + \nabla \cdot (\mathbf{u}p) = D_p\Delta p + F_p(p) - C_p(p, d), \quad (1.2)$$

$$\frac{\partial q}{\partial t} + \nabla \cdot (\mathbf{u}q) = D_q\Delta q + F_q(q) - C_q(q, d), \quad (1.3)$$

where $D(r)$ and $\Gamma(r)$ are radial diffusion and coefficient of blood-tissue transfer, respectively. λ and d_B are the respective drug decay and prescribed drug concentration in the tumour vasculature. D_p and D_q are the constant random motility coefficients of the two types of tumour cells and $F_p(p)$ and $F_q(q)$ are their respective net proliferation rates. The functions $C_p(p, d)$ and $C_q(q, d)$ represent the effect of the chemotherapy on each tumour sub-population. This model illustrates how the vasculature exchange would affect the tumour's response to therapy. Using this model, Jackson and Byrne [48] found that the spatially- dependent blood-tissue transfer gave rise to the largest reduction in tumour volume as compared to no blood-tissue transfer and constant blood-tissue transfer. Furthermore, when the tumour consisted of only sensitive cells, minimum tumour radius was determined. From this model, it could be seen that while under certain conditions the drug resistant sub-population could be eliminated, nevertheless, tumour re-growth is possible.

In this dissertation, we draw some important tumour modelling assumptions on previous studies, such as those outlined above to develop new mathematical models of drug resistance which take into

account the effects of genetic point mutations. We will use both ordinary and partial differential equations. We will then use computational methods to solve these differential equations. The numerical schemes used include a hybrid fourth and fifth order Runge-Kutta differential solvers such as *ode45* and *pdepe* solvers.

1.3 Steady states analysis

In mathematical analysis of biological systems, particularly in anti-cancer modelling, the study of the equilibria of the system and stability analysis are important tasks because stability conditions usually indicate the conditions where tumour eradication is feasible [62,63]. Furthermore, it is important to note that the orbital portraits of one steady state may differ from those of nearby steady states [62]. Thus, any categorisation of the steady state must be local.

There are two methods of determining the stability of any system, namely graphical stability analysis and linearisation stability analysis. Because the models are comprised of nonlinear ODEs, for the purposes of this study, we use the linearisation stability analysis. In effect, linearisation simply means that we approximate a function by a first-order Taylor series expansion about the steady state. If the linearization is performed, then the nonlinear system behaves more like a linear system, which is easy to determine its stability, in the neighbourhood of equilibrium point.

For the purpose of this study, we use the linearisation method and deduce the stability of each steady state based on the Rough-Hurwitz stability criterion [62,64–66], as described below.

To illustrate the linearisation technique, consider a biological system that is described by three differential equations. The derivatives about the equilibrium point are given as

$$\begin{aligned} \frac{dx}{dt} &= f_1(x, y, z) \approx x \frac{\partial f_1}{\partial x} + y \frac{\partial f_1}{\partial y} + z \frac{\partial f_1}{\partial z}, \\ \frac{dy}{dt} &= f_2(x, y, z) \approx x \frac{\partial f_2}{\partial x} + y \frac{\partial f_2}{\partial y} + z \frac{\partial f_2}{\partial z}, \\ \frac{dz}{dt} &= f_3(x, y, z) \approx x \frac{\partial f_3}{\partial x} + y \frac{\partial f_3}{\partial y} + z \frac{\partial f_3}{\partial z}. \end{aligned}$$

We re-write this system in matrix notation as

$$\dot{\mathbf{x}} = \mathbf{J}(\mathbf{x}) = \begin{pmatrix} \frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} & \frac{\partial f_1}{\partial z} \\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y} & \frac{\partial f_2}{\partial z} \\ \frac{\partial f_3}{\partial x} & \frac{\partial f_3}{\partial y} & \frac{\partial f_3}{\partial z} \end{pmatrix} \begin{pmatrix} x \\ y \\ z \end{pmatrix}, \quad (1.4)$$

where the matrix \mathbf{J} is the Jacobian matrix of the system. We find the eigenvalues of the Jacobian matrix in order to deduce the stability of the system via the Routh-Hurwitz stability criterion, as will be shown in Section 2.4 and 2.6.

1.3.1 Rough-Hurwitz stability criterion

In a complex dynamical system, determination of the stability of the system may not be easy. However, the Routh-Hurwitz criterion provides necessary and sufficient conditions for the stability of a system with n state variables [62, 64–66]. May [64] provides a full description of the Routh-Hurwitz stability criterion based on $m = 1, 2, \dots, 5$ state variables. In brief, the criterion can be given as follows. Suppose the characteristic polynomial associated with the Jacobian matrix of the system of differential equations with n state variables is

$$P(\gamma) = \gamma^n + a_1\gamma^{n-1} + \dots + a_{n-1}\gamma + a_n, \quad (1.5)$$

where the coefficients a_1, a_2, \dots, a_n are real constants. We define the Hurwitz matrices corresponding to the number of the state variables as

$$H_1 = (a_1), \quad H_2 = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix}, \quad H_3 = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix}, \dots, \quad (1.6)$$

$$H_n = \begin{pmatrix} a_1 & 1 & 0 & 0 & \dots & 0 \\ a_3 & a_2 & a_1 & 1 & \dots & 0 \\ a_5 & a_4 & a_3 & a_2 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \dots & a_n \end{pmatrix}, \quad (1.7)$$

with $a_i = 0$ whenever $j > n$. If all the roots of the polynomial (1.5) are negative or have a negative real part, then the determinants of the Hurwitz matrices, (1.6) – (1.7) are positive. That is,

$$\det(H_i) > 0, \quad i = 1, 2, \dots, n. \quad (1.8)$$

In summary, the Rough-Hurwitz stability criterion for $n = 2, 3, 4$ and 5 is

$$\left. \begin{aligned} n = 2 : a_1 > 0 \text{ and } a_2 > 0, \\ n = 3 : a_1 > 0, a_3 > 0 \text{ and } a_1 a_2 > a_3, \\ n = 4 : a_1 > 0, a_3 > 0, a_4 > 0, \text{ and } a_1 a_2 a_3 > a_3^2 + a_1^2 a_4, \\ n = 5 : a_i > 0, i = 2, 3, 4, 5, a_1 a_2 a_3 > a_3^2 + a_1^2 a_4, \text{ and} \\ (a_1 a_4 - a_5)(a_1 a_2 a_3 - a_3^2 - a_1^2 a_4) > a_5(a_1 a_2 - a_3)^2 + a_1 a_5^2 \end{aligned} \right\} \quad (1.9)$$

The proof of this criterion is given by Gantmacher [66] for $n = 2$. We use this criterion because the models considered here have more than two state variables. If there is no drug in the tumour, then the system (2.4) – (2.6) reduces to a system of two state variables. Thus the Rough-Hurwitz criterion would be helpful in determining the stability of the system.

1.3.2 Dulac's criterion

Dulac's Criterion is an important theorem used to determine if the system of differential equations has no periodic orbits [67]. This criterion would be vital for the models considered in this study because the periodic orbits might show the condition at which a tumour eradication is feasible or not. This means that after a chemotherapeutic drug has killed some sensitive cells, then other cells, possibly the resistant cells, might bring cancer remission later or not. In this study, it is also important to investigate if tumour eradication is possible under the constraints of the models considered in this study.

Consider a smooth differential equation system

$$\dot{x} = f(x, y), \quad (1.10)$$

$$\dot{y} = g(x, y). \quad (1.11)$$

Dulac's criterion states that if there is a smooth function $B(x, y)$ defined on a simply connected region $\Omega \subset \mathbb{R}^n$ such that

$$\frac{\partial}{\partial x}(B \cdot f) + \frac{\partial}{\partial y}(B \cdot g) \quad (1.12)$$

is not identically zero and of a fixed sign on Ω , then the system (1.10) – (1.11) has no periodic solution on Ω . The main disadvantage of Dulac's criterion is that there is no systematic way of finding the function $B(x, y)$. For this reason, the method is not always possible to use. Consequently, instead, we make use of the Poincaré-Bendixson theorem.

1.3.3 Poincaré-Bendixson Theorem

Dulac's criterion is useful for demonstrating the existence of periodic solutions. To show that it a periodic solution exists, a necessary and sufficient condition is that the Poincaré-Bendixson theorem is satisfied. We state, without proof, the Poincaré-Bendixson theorem that is useful for demonstrating the existence of the limit cycle of the system of differential equations [68].

Theorem 1.3.1. *Suppose there is a function $f \in C^1(E)$, where E is an open subset of \mathbb{R}^2 , and ϕ is the solution of the system $\dot{\mathbf{x}} = f(\mathbf{x})$. If Ω is a non-empty compact ω -limit set of ϕ , and Ω does not contain a rest point (i.e. stable equilibrium point), then Ω is a periodic orbit.*

Corollary 1.3.4. *This Corollary follows directly from Theorem 1.3.1. If E contains a periodic orbit Γ of the system $\dot{\mathbf{x}} = f(\mathbf{x})$ and its interior U , then U contains at least one rest point of the system, [68].*

In order to determine the stability of the ODE systems, developed in this dissertation, about any steady state, we shall use the Routh-Hurwitz stability criterion. Additionally, to show the existence of a globally asymptotic stable point, in Section 2.4.2, we will use the Dulac's criterion and a corollary of the Poincaré-Bendixson theorem to show that there exist no periodic solutions associated with the models considered in this study.

1.4 Sensitivity analysis

The modelling of complex biological system involves estimation and analysis of model parameters. However, as indicated above, understanding of the multi-drug-tumour system may be limited by lack of values for parameters. This deficiency can be partially addressed through a technique called sensitivity analysis (SA). SA investigates the relationship between particular model parameters and the characteristics of the observable outcome; thus indicating some phenotypic behaviour of the system under study [69]. SA can be utilised, not only for identification of the model parameters that are highly correlated with the state variables, but also to help prioritise research on those essential parameters [70], particularly where there is no available medical literature for some of the model parameters. To be specific, we will here identify the parameters that are most influential in the dynamical behaviour of our systems.

1.4.1 Partial rank correlation coefficient

We use the partial rank correlation coefficient (PRCC) test, to determine the statistical significance of the model parameters on the outcome of the state variables. In particular we consider those model state variables that have a monotonic but non-linear behaviour [71, 72]. PRCC uses the Latin hypercube sampling technique (LHS). To implement the LHS, we first generate a random sample of N vectors in the parameter space using the Latin hypercube sampling. LHS attempts to sample the whole parameter space by separating the bounded subsets of the parameter space into N compartments and then choosing a random value in each compartment from a uniform distribution [72, 73]. To perform this task, we first needed to write a Matlab code and use the Matlab built-in function *lhsdesign* to generate a matrix of parameter values between 0 and 1. Each parameter set needed to be rescaled by the tumour carrying capacity 5×10^7 , [74]. By letting M be the resultant matrix of the *lhsdesign*, then, using the output of the LHS, we could generate a vector, Y , where y_i represents a model value at any time t using the given parameter value of i^{th} row of the matrix M .

The first step in the implementation of PRCC test is to rank the transformed matrices, which take M and Y as inputs and return the matrices \underline{M} and \underline{Y} with the same dimensions, in which each column contains all the integers from 1 to N . Note that the ordering of the integers in \underline{M} and \underline{Y} corresponds to ordering of the integer values in the original matrices, where a 1 in the k^{th} column of \underline{M} corresponds to the position of the lowest value in the k^{th} column of M , and N corresponds to the highest value.

Utilising the rank transformed matrices, \underline{M} and \underline{Y} , we can now fit a linear regression model for each of the parameters, say \bar{p}_k , defined as

$$\bar{p}_k = a_0 + a_1 p_1 + \cdots + a_{k-1} p_{k-1} + a_{k+1} p_{k+1} + \cdots + a_n p_n, \quad (1.13)$$

which expresses a selected parameter p_k as a linear combination of all other model parameters.

Equation (1.13) can be solved by

$$\underline{a} = (X^T X)^{-1} (X^T \underline{p}_k), \quad \underline{a} = \begin{bmatrix} a_0 \\ a_1 \\ \vdots \\ a_n \end{bmatrix}, \quad \text{and} \quad X = \begin{bmatrix} 1, p_1, p_2, \dots, p_n \end{bmatrix}. \quad (1.14)$$

Similarly, we define

$$\bar{Y}_{p_k} = b_0 + b_1 p_1 + \cdots + b_{k-1} p_{k-1} + b_{k+1} p_{k+1} + \cdots + b_n p_n, \quad (1.15)$$

of which can be solved by

$$\underline{b} = (X^T X)^{-1} (X^T \underline{Y}), \quad \underline{b} = \begin{bmatrix} b_0 \\ b_1 \\ \vdots \\ b_n \end{bmatrix}, \quad \text{and} \quad X = \begin{bmatrix} 1, p_1, p_2, \dots, p_n \end{bmatrix}. \quad (1.16)$$

The values \bar{p}_k and \bar{Y}_{p_k} , together with \underline{p}_k and \underline{Y} , are used to compute the residuals, $\text{res}(p_k) = \underline{p}_k - \bar{p}_k$ and $\text{res}(Y_{p_k}) = \underline{Y} - \bar{Y}_{p_k}$, between the two data sets. The correlation coefficients between $\text{res}(p_k)$ and $\text{res}(Y_{p_k})$ are computed via the Matlab built-in function *corrcoeff*. These correlation coefficients are the required results of the PRCC, and measure the strength of the relationship between the two given parameters, or the degree of association between a given state variable and a given parameter. A correlation coefficient value close to 1 indicates a strong positive linear relationship between the given state variable and the parameter in question, whereas a negative correlation coefficient value close to -1 shows a strong negative relationship between the state variable and the given parameter. Therefore, the sign indicates the qualitative relationship between the state variable and the parameter in question. If the correlation coefficient is either $-\frac{1}{2}$ or $\frac{1}{2}$, then there is no linear relationship between the state variable and the parameter in question. Thus, the parameters with large PRCC values greater than 0.5 or less than -0.5 are the most important [75]. The PRCC test is applicable only in mathematical models that have two or more parameters. This is true for the ODE models in this study. The quantitative results of the sensitivity analysis are presented in Chapter 4.

1.5 Dissertation structure

The remainder of the dissertation comprises four chapters where the major contributions to the chemotherapeutic modelling of drug resistance in cancer are presented. In particular, two new mathematical models describing the interactions between tumour cells and chemotherapeutic agent(s) are presented.

In Chapter 2, two new compartmental models describing the interactions between tumour cells and chemotherapeutic drug(s) are constructed. In order to model these interactions, the system of several

ordinary differential equations that take into account the effects of drug resistance to one and then two chemotherapeutic agents are constructed. The steady states and stability of the systems are investigated. The fixed points are important since they highlight the system solutions that might bring about cancer eradication or remission. The stable points are solutions that might bring about effective disease control and prolong the quality of life, while unstable points are solutions of the uncontrolled state (i.e the state that usually leads to metastasis).

In Chapter 3, to account for the spatial distribution dynamics of the tumour sub-populations, a partial differential equation model is constructed. Some analytical solutions of this model are presented. Model simulations and parameter sensitivity analysis of the ODE models is presented in Chapter 4. Numerical simulations provide a plausible dynamical model behaviour and interactions of tumour sub-populations and chemotherapeutics drugs. In Chapter 5, the overall conclusions from the studies are brought together and discussed in the light of previously published work. This highlights some further points for future research. In the Appendix, a glossary of relevant biological terms is given.

Chapter 2

A two compartmental ODE model for drug resistance

2.1 Introduction

The use of ordinary differential equations (ODEs) to model tumour growth has a long history in cancer modelling, [24, 76–82]. See specifically the work of Tomasetti and Levy [47] described in the previous chapter. While ODEs can capture many important features of cell divisions in large cell populations they have the added advantage of being computationally easy to work with. Nevertheless, using ODEs in cancer modelling requires a number of simplifying assumptions to represent a three-dimensional tumour. Thus, identifying the constituent components in any biological system is a vital step to ensure robust mathematical and computational analysis. In this regard, it is important to note that within a single tumour, there are likely to be a number of sub-populations that could each be characterised by different intrinsic growth rates and treatment susceptibilities [83]. Thus, in order to monitor the growth of the tumour, it is vital to track the total number of cells within it, while also keeping track of each sub-population within it [24, 84–86]. However, with biological phenomena, it is often difficult to adequately delineate which tumour components are present in the system because some components or processes may not be well understood. Nevertheless, many biological phenomena involving time-evolved systems can be analysed using ODEs consisting of two cell populations [33, 47].

Furthermore, there are some mathematical models in which partial resistance, and its corresponding

correlation to the amount of the drug present, have been addressed [49, 87]. In this chapter, we develop a non cell-cycle specific system of ODEs that govern the development of tumour cells under the intervention of chemotherapeutic drug(s). We give the criteria and theorems needed to show stability and non-existence of periodic solutions. The numerical solutions of these system of equations are given in Chapter 4.

2.2 Chemotherapeutic model formulation

As explained in the previous chapter, one of the defining attributes of malignant tumours is their ability to metastasise [88]. Furthermore, human cancer cells may include a sub-population with an intrinsic drug resistance. In this section we develop a mathematical model that considers the case in which the tumour develops the resistance to a single chemotherapeutic drug due to genetic point mutations. We have also considered a similar biological setting to that proposed by Goldie and Goldman [5], where, even-though the malignant cancer cells are highly heterogeneous, the tumour is viewed as a single compartmental population composed of two types of cell sub-populations. The first sub-population group consists of rapidly proliferating cells that are highly susceptible to the drug, $S(t)$, and the second sub-group consists of the cells that are drug resistant, $R(t)$. Thus:

$$N(t) = S(t) + R(t), \tag{2.1}$$

where $N(t)$ is the total number of the tumour cells at time t .

2.2.1 Model assumptions

As mentioned earlier, modelling of biological system requires a number of simplifications. Therefore, in constructing the first ODE model the following assumptions were made:

- (i) There is a logistic growth in both types of cells, when there is no drug in the tumour, and the intrinsic growth rates are different. It is reasonable to assume different growth rates because, in [46], it was found experimentally that the sensitive tumour cells usually grow faster than the resistant cells. Furthermore, it has been shown that in lung cancer cells, resistant to the chemotherapeutic drug, gemcitabine, are less invasive and grow slowly than their drug sensitive counterparts [89].

- (ii) The drug kills only the sensitive cells and has no effect on the resistant cell population.
- (iii) Mutation happens in only one direction (i.e. during mitosis, one of the daughter cells mutates to a resistant cell and not vice-versa). This is a standard assumption when modelling resistance due to genetic point mutations, rather than resistance caused by gene amplification [47].
- (iv) We assume that an interaction between the chemotherapeutic drug and the tumour cells follows an exponential saturation kinetics as in [21]. This exponential form has been validated by [90] for a reasonable number of chemotherapeutic drugs.

By distinguishing between only two types of tumour cells, the model variables are;

- (a) $D(t)$, the chemotherapeutic drug concentration at time t ,
- (b) $S(t)$, the number of tumour cells that are sensitive to the drug at time t ,
- (c) $R(t)$, the number of tumour cells that are resistant to the drug at time t .

The model parameters, λ_S and λ_R are the intrinsic growth rates of sensitive and resistant cells, respectively. λ_D represents a drug decay rate, μ is the mutation rate coefficient resulting from cell division. k_S is the susceptibility coefficient of the sensitive cells to the drug, while k is the drug saturation coefficient for the tumour. $V(t)$ represents an external time dependent influx of the chemotherapeutic drug, and θ is the limiting size, commonly called maximum carrying capacity of the tumour.

With these parameters, we model the dynamics of the chemotherapeutic drug by the equation

$$\frac{dD(t)}{dt} = V(t) - \lambda_D D, \quad (2.2)$$

with the following baseline conditions:

$$D(t) = \begin{cases} 0 & \text{if } t = 0, \\ D_c(t) & \text{if } t > 0, \end{cases} \quad (2.3)$$

where $D_c(t)$ is the drug concentration in the tumour (which depends on the external influx $V(t)$ and the natural decay rate of the drug, λ_D), at any time t . We assume that $\lambda_D \geq 0$, with inclusion of a mathematical limit state $\lambda_D = 0$ to represent a situation of having no chemotherapeutic drug decay in the tumour. We have assumed that, initially at time $t = 0$, there is no drug in the tumour,

so $D(0) = 0$, as in Krabs and von Wolfersdorf [91]. We have further assumed that the amount of the chemotherapeutic drug entering the patient is bounded above, that is $0 \leq V(t) \leq V_{max}(t)$, in accordance with [19, 24, 91–93].

During chemotherapy, the basic growth kinetics of the tumour cells is usually perturbed by the intravenous infusion of the cytotoxic agent at any time t [94]. Thus, we write our full model as

$$\frac{dD(t)}{dt} = V(t) - \lambda_D D, \quad (2.4)$$

$$\frac{dS(t)}{dt} = \lambda_S S \left(1 - \frac{S}{\theta}\right) - k_S (1 - e^{-kD}) S - \mu S, \quad (2.5)$$

$$\frac{dR(t)}{dt} = \lambda_R R \left(1 - \frac{R}{\theta}\right) + \mu S. \quad (2.6)$$

The corresponding initial conditions for the system (2.4) – (2.6), given by the initial drug concentration, the initial number of the sensitive and resistant cells, are

$$D(0) = 0, \quad S(0) = S_0, \quad R(0) = R_0, \quad (2.7)$$

where each of the above initial values is non-negative. In order to determine the effects of the chemotherapeutic drug, we have assumed that there is at least one tumour cell that is sensitive to the drug at the start of the therapy. The domain of the model is $[0, T_f]$, where $T_f \in \mathbb{R}^+$ is a fixed time of chemotherapy. In the second equation (2.5), the last term denotes the loss term (i.e the sensitive cells death due to the presence of the drug at the tumour site.) In both tumour sub-populations, equations (2.5) and (2.6), the first term denotes the logistic growth of tumour cells. This model obeys the growth laws on a finite interval $[0, \theta]$, as in [78–82].

This model shares some similarities with the recent model of Tomasetti and Levy [47], but instead of modelling an intrinsic drug resistance in chemotherapy, we focus on the dynamics of the drug effects after the treatment has begun. We are mainly concerned with minimising the escape of the malignant tumours once the drug is introduced. In addition, in contrast with Tomasetti and Levy [47], we allow for logistic growth of the tumour cell population. Tumour growth, in reality, is limited by the carrying capacity of the host tissue, as well as the availability of oxygen and nutrients necessary for its growth. Models of this type have been found to be appropriate for modelling tumour growth [95, 96]. Furthermore, our mathematical model is in line with many other mathematical models that describe the dynamics of the drug based on the decay of the external influx of the drug [24, 78–82]. To be specific, here we are primarily concerned with the effects of the drugs on the tumour sensitive cells, while also taking into account the evolution of a resistant cell sub-population as the treatment progresses.

2.2.2 Non-dimensionalisation of model equations

In order to facilitate the numerical simulation of the system, we need to non-dimensionalize the systems. The rationale behind this process is to determine which parameter variations have a more significant effect on the system and, possibly, to reduce the number of parameters. We take the drug concentration, D , as a non-dimensional variable, as in [29]. We denote by S^* the non-dimensionalised version of the state variable S and then choose the size of the cell population scale as S_0 , where S_0 is an initial number of sensitive cells. Note, here we have assumed that the eternal drug influx, V , is constant for the duration of a chemotherapeutic treatment. Thus the non-dimensionalised state variables for respective tumour sub-populations and drug concentration using equations (2.4) – (2.6) are

$$S = S^* \bar{S}, \quad D = D^* \bar{D}, \quad \bar{D} = \frac{1}{k}, \quad R = R^* \bar{R}, \quad t = t^* \bar{t}, \quad t_0 = \frac{1}{\lambda_D}, \quad R_0 = \theta, \quad (2.8)$$

and the corresponding model parameters are

$$V^* = \alpha V, \quad \alpha = \frac{t_0}{D}, \quad \mu_1 = \mu t_0, \quad a_1 = \lambda_S t_0, \quad \theta_1 = \frac{S_0}{\theta}, \quad (2.9)$$

$$\eta = k_S t_0, \quad a_2 = \lambda_R t_0, \quad \mu_2 = \frac{S_0 t_0 \mu}{\theta}, \quad \bar{S} = S_0, \quad \bar{R} = R_0. \quad (2.10)$$

Writing the system (2.4) – (2.6) in these new dimensionless variables and parameters, and dropping the stars for notational convenience, we have

$$\frac{dD(t)}{dt} = V - D, \quad (2.11)$$

$$\frac{dS(t)}{dt} = a_1 S \left(1 - \frac{S}{\theta_1}\right) - \eta(1 - e^{-D})S - \mu_1 S, \quad (2.12)$$

$$\frac{dR(t)}{dt} = a_2 R(1 - R) + \mu_2 S, \quad (2.13)$$

and corresponding initial conditions are

$$D(0) = 0, \quad S(0) = 1, \quad R(0) = 1, \quad (2.14)$$

where the number of initial sensitive cells are given by $S_0 > 0$ and the number of resistant cells are given by $R_0 \geq 0$.

2.3 Boundedness, positive invariance and dissipativity

In this section, we establish some important properties of the system (2.11)–(2.13), which ensure that we have non-negative solutions. The same assurance will be needed for other equations (2.59)–(2.63)

later in the chapter.

2.3.1 Positive Invariance

All solutions with positive values shall always remain positive. From equation (2.12), one solution is $S \equiv 0$; therefore, we observe that no solution $S(t)$ with $t > 0$ can be zero in finite time, hence all solutions are non-negative. Similarly, it can be shown that the same analysis leads to positive solutions of equation (2.13). Finally, from equation (2.11), we note that

$$\frac{dD(t)}{dt} = V - D, \quad D_0 = 0, \quad (2.15)$$

where D_0 is the initial drug concentration at the time $t = 0$ and V is a constant external drug influx; hence there is no solution of equation (2.11) with $D(t) > 0$ that can be zero.

2.3.2 Dissipativity

A dissipative system is a system whose solutions starting from a certain region, say B , in \mathbb{R}^n either approach, enter or remain in B . For the system (2.11) – (2.13), dissipativity imply that all trajectories evolve to an attracting region in \mathbb{R}_+^3 . However, one should note that the non-negative initial conditions of the system, does not guarantee that all the solutions shall also be non-negative. From equation (2.12), if $S_0 > 0$, then we realise that

$$\begin{aligned} \frac{dS(t)}{dt} &= a_1 S \left(1 - \frac{S}{\theta_1} \right) - \eta(1 - e^{-D})S - \mu_1 S, \\ \frac{dS(t)}{dt} &\leq a_1 S \left(1 - \frac{S}{\theta_1} \right) \end{aligned} \quad (2.16)$$

Separating the variable from equation (2.16), we obtain

$$\frac{dS}{S \left(1 - \frac{S}{\theta_1} \right)} \leq a_1 dt. \quad (2.17)$$

Solving the inequality equation (2.17) we get

$$S(t) \leq \frac{\theta_1}{1 + Ae^{-a_1 t}}, \quad (2.18)$$

where A is a constant. Taking the limits on both sides, we have that

$$\limsup_{t \rightarrow \infty} S(t) \leq \lim_{t \rightarrow \infty} \frac{\theta_1}{1 + Ae^{-a_1 t}} = \theta_1. \quad (2.19)$$

Now, considering equation (2.13), let $R_0 \geq 0$ and $S(t) = \theta_1$, then

$$\begin{aligned} \frac{dR(t)}{dt} &\leq a_2 R(1 - R) + \mu_2 \theta_1, \\ R(t) &\leq \frac{1}{2C} \left\{ a_2 \theta_1 + \rho \tanh \left[\frac{\rho}{2\theta_1} (t + A) \right] \right\}, \end{aligned} \quad (2.20)$$

where

$$\rho = \sqrt{4\mu_2 a_2 \theta_1 + (a_2 \theta_1)^2}, \quad (2.21)$$

and C, A are constants. Taking the limits on both sides of equation (2.20) we obtain

$$\limsup_{t \rightarrow \infty} R(t) \leq \frac{1}{2C} (a_2 \theta_1 + \rho). \quad (2.22)$$

Similarly, from equation (2.11), we have

$$\frac{dD(t)}{dt} \leq V - D, \quad (2.23)$$

$$\limsup_{t \rightarrow \infty} D(t) \leq V. \quad (2.24)$$

Hence we have the region

$$\mathbf{B} = \left\{ (D, S, R) \in \mathbb{R}_+^3 \mid 0 \leq S \leq \theta_1, \quad 0 \leq R \leq \frac{1}{2C} (a_2 \theta_1 + \rho), \quad 0 \leq D \leq V \right\} \quad (2.25)$$

as the attracting invariant region of the system.

2.3.3 Boundedness

All the solutions of the system (2.11) – (2.13), with positive initial values are bounded in the region in \mathbb{R}_+^3 and are attracted to the region \mathbf{B} . It is important to note that because we are modelling a biological system, we can never have negative tumour sub-populations.

2.4 Equilibria and stability analysis: single drug resistance

Determining the solutions of a non-linear system may not be a trivial task. However, through stability analysis, one can determine the long term behaviour of the system without having to indulge in a tedious search for solutions. For the models, equations (2.11) – (2.13) and (2.59) – (2.63), stability analysis is most significant because a stable solution may imply a full remission of the

tumour sub-populations or at least a condition at which the tumour sub-populations may remain controllable. Conversely, unstable steady states may imply the relapse of the tumour sub-populations, corresponding to unsuccessful chemotherapy.

It is of particular interest in this study to determine the asymptotic local stability of the systems. To achieve this, we linearise equations (2.11) – (2.13) about each of the steady states and determine the stability of the system.

2.4.1 Drug free equilibrium: single drug resistance

We first investigate the equilibria of equations (2.11) – (2.13) when there is no drug ($D(t) = 0$ for all time t). This helps to shed light on how the two tumour sub-populations grow if there is no drug in the patient’s body. The steady states of the system is found by making the respective derivatives zero. We have the following reduced system:

$$a_1 S \left(1 - \frac{S}{\theta_1}\right) - \mu_1 S = 0, \tag{2.26}$$

$$a_2 R (1 - R) + \mu_2 S = 0, \tag{2.27}$$

Solving equation (2.26), we obtain the following:

$$S = 0 \quad \text{or} \quad S = \frac{\theta_1(a_1 - \mu_1)}{a_1}. \tag{2.28}$$

Substituting $S = 0$ into equation (2.27), we find that

$$R = 0 \quad \text{or} \quad R = 1. \tag{2.29}$$

If we substitute $S = \frac{\theta_1(a_1 - \mu_1)}{a_1}$ into equation (2.27), we observe that

$$a_2 a_1 R^2 - a_2 a_1 R - \mu_2 \theta_1 (a_1 - \mu_1) = 0, \tag{2.30}$$

which is quadratic in R . Thus we solve it to obtain

$$R = \left(\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\mu_2 \theta_1}{a_1 a_2} (a_1 - \mu_1)} \right). \tag{2.31}$$

Because we are modelling a biological system, we are only interested in steady states which are positive and real; thus we can only take a positive value for R provided that the discriminant is non-negative. That is,

$$\mu_1 < a_1. \tag{2.32}$$

Denoting the equilibrium point by $E_i = (S^*, R^*)$, $i = 0, 1, 2$, and using equations (2.28), (2.29) and a positive value for R in equation (2.31), we obtain the following steady states:

$$E_0 = (0, 0), \quad (2.33)$$

$$E_1 = (0, 1), \quad (2.34)$$

$$E_2 = \left(\frac{\theta_1 (a_1 - \mu_1)}{a_1}, \left(\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\mu_2 \theta_1}{a_1 a_2} (a_1 - \mu_1)} \right) \right). \quad (2.35)$$

E_2 exists if and only if $\mu_1 < a_1$. Note, if $\mu_1 = a_1$, then E_2 reduces to E_1 . This generally means that equilibrium point E_2 exists if the intrinsic growth rate of sensitive population is higher or equal to the mutation rate of cancerous cells. This is intuitive valid because if the mutations do not occur at a faster rate than growth of sensitive sub-population, then it might be plausible to inhibit the occurrence of resistant sub-population. The Jacobian of the linearised system with no drug is given by

$$J = \begin{pmatrix} a_1 \left(1 - \frac{2S}{\theta_1}\right) - \mu_1 & 0 \\ \mu_2 & a_2(1 - 2R) \end{pmatrix}. \quad (2.36)$$

We first evaluate the Jacobian matrix (2.36) about the trivial equilibrium point E_0 . This reduces to the matrix

$$J(E_0) = \begin{pmatrix} a_1 - \mu_1 & 0 \\ \mu_2 & a_2 \end{pmatrix}. \quad (2.37)$$

The corresponding characteristic polynomial is given by

$$\gamma^2 + (\mu_1 - a_2 - a_1) \gamma + a_2 a_1 - a_2 \mu_2 = 0. \quad (2.38)$$

Now, using Routh-Hurwitz conditions for stability [62], the eigenvalue $\gamma_2 = a_2 > 0$, then no matter the sign of the eigenvalue $\gamma_1 = a_1 - \mu_1$ can be, (i.e. either $a_1 - \mu_1 < 0$ or $a_1 - \mu_1 > 0$) we shall always have an unstable steady state.

2.4.2 Existence of a globally asymptotically stable point for a drug free case

Since equations (2.11) – (2.13), are dissipative, as shown in Section 2.3.2, then it suffices to only prove that there are no periodic orbits associated with the system.

If there exists a periodic orbit in the system, then using Corollary 1.3.4 of the Poincaré-Bendixson Theorem, we note that it should enclose the steady state, E_0 in this case. Note that if a periodic orbit existed, then part of the orbit must lie in the dissipative region \mathbf{B} in equation (2.25), hence the orbit cannot be periodic, but rather approach the steady state E_0 . Therefore, E_0 must be a globally asymptotically stable steady state.

However, we have already shown above that the steady state E_0 is unstable; hence there exists at least one other steady state that is globally asymptotically stable. This can be established from realisation that when there is no drug infused, equations (2.11) – (2.13) reduce to a two dimensional system. Thus we can state the following result:

Theorem 2.4.1. *If the equilibrium solutions $E_i, i = 1, 2$ exist, then at least one of the equilibrium solutions is globally asymptotically stable in $\mathbb{R}^2 \setminus E_0$.*

Proof. Since we have already established that the steady state, E_0 is unstable, and the system is dissipative, then it suffices to show that there are no periodic solutions. To prove this, we shall utilise the Dulac's theorem by choosing $B(S, R) = \frac{1}{S \cdot R}$. Applying this to equations (2.11) – (2.13), with $D = 0$, we have that

$$\begin{aligned} & \frac{\partial}{\partial S} \left\{ \frac{1}{S \cdot R} \left(a_1 S \left(1 - \frac{S}{\theta_1} \right) - \mu_1 S \right) \right\} + \frac{\partial}{\partial R} \left\{ \frac{1}{S \cdot R} \left(a_2 R \left(1 - \frac{R}{\theta_1} \right) + \mu_2 S \right) \right\} \\ &= \frac{\partial}{\partial S} \left\{ \frac{a_1}{R} \left(1 - \frac{S}{\theta_1} \right) - \frac{\mu_1}{R} \right\} + \frac{\partial}{\partial R} \left\{ \frac{a_2}{S} \left(1 - \frac{R}{\theta_1} \right) + \frac{\mu_2}{R} \right\} \\ &= - \left(\frac{a_1}{R\theta_1} + \frac{a_2}{\theta_1 S} + \frac{\mu_2}{R^2} \right) < 0. \end{aligned}$$

This is always true for any two dimensional system, $(S, R) \in \mathbb{R}_+^2$. Therefore, by Dulac's criterion the reduced system does not have periodic solutions. \square

We study the stability of the system about the non-trivial steady state in order to gain an understanding of the long term behaviour of the system. The steady state, $E_1 = (0, 1)$, represents the case where the tumour grows to its carrying capacity. This is the most undesirable state because this state could suggest that chemotherapy is unlikely to be successful. The Jacobian matrix (2.36) corresponding to the second steady state, $E_1 = (0, 1)$, is

$$J(E_1) = \begin{pmatrix} a_1 - \mu_1 & 0 \\ \mu_2 & -a_2 \end{pmatrix}. \tag{2.39}$$

We note that the steady state E_1 is locally asymptotically stable only if $a_1 < \mu_1$ because we have $\gamma_2 = -a_2 < 0$. The condition $a_1 < \mu_1$ is plausible in cancer treatment [5] because here it indicates that the impact of random mutations acquisition on drug resistance is time dependent. In this case more resistant cells are continuously produced despite the lack of growth of sensitive cells [5]. The steady state E_1 can be the unstable saddle point if $\mu_1 < a_1$.

The Jacobian matrix (2.36) at the steady state, E_2 , is

$$J(E_2) = \begin{pmatrix} \mu_1 - a_1 & 0 \\ \mu_2 & -2a_1\sqrt{\frac{1}{4} + \frac{\mu_2}{a_1 a_2}(a_1 - \mu_1)} \end{pmatrix}. \quad (2.40)$$

The equilibrium point E_2 would to be locally asymptotically stable only if

$$\mu_1 < a_1. \quad (2.41)$$

Otherwise, E_2 , would be an unstable.

Therefore, we have the following cases for E_0 , E_1 and E_2 :

- (i) If $a_1 < \mu_1$, then E_0 is unstable, but E_1 is stable and E_2 does not exist.
- (ii) If $a_1 > \mu_1$, then E_0 and E_1 are unstable, but E_2 is stable.

Using parameters from the literature, $a_1 = 0.18$ from [97], $a_2 = 0.16$ and $\theta = 1.2 \times 10^6$ from [98], $\mu = 3.67 \times 10^{-6}$ from [74], and plotting the phase portraits of the system corresponding to E_0 , E_1 and E_2 , we obtain Figure 2.1.

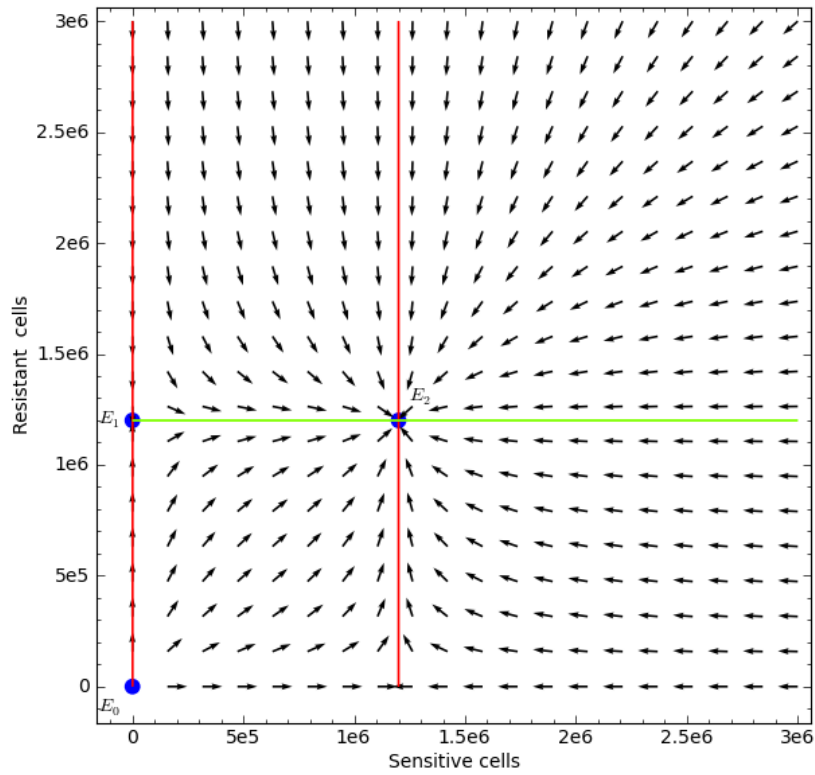


Figure 2.1: The phase portraits corresponding to the equilibrium points when $\mu_1 < a_1$.

In Figure 2.1, the points, E_0 , E_1 and E_2 , denote the equilibrium points of the system, and the arrows indicate the direction of the trajectories away from or towards the equilibrium points.

It is important to note that, in the absence of the drug, the system reduces to a two-dimensional autonomous system. We have used a phase plane analysis to capture the significant features of the system. The steady state E_2 is globally asymptotically stable as shown in Figure 2.1. This confirms the existence of a global steady state as discussed earlier in this section.

When mutation rate is higher than the intrinsic growth of sensitive sub-population, we have the following phase portrait:

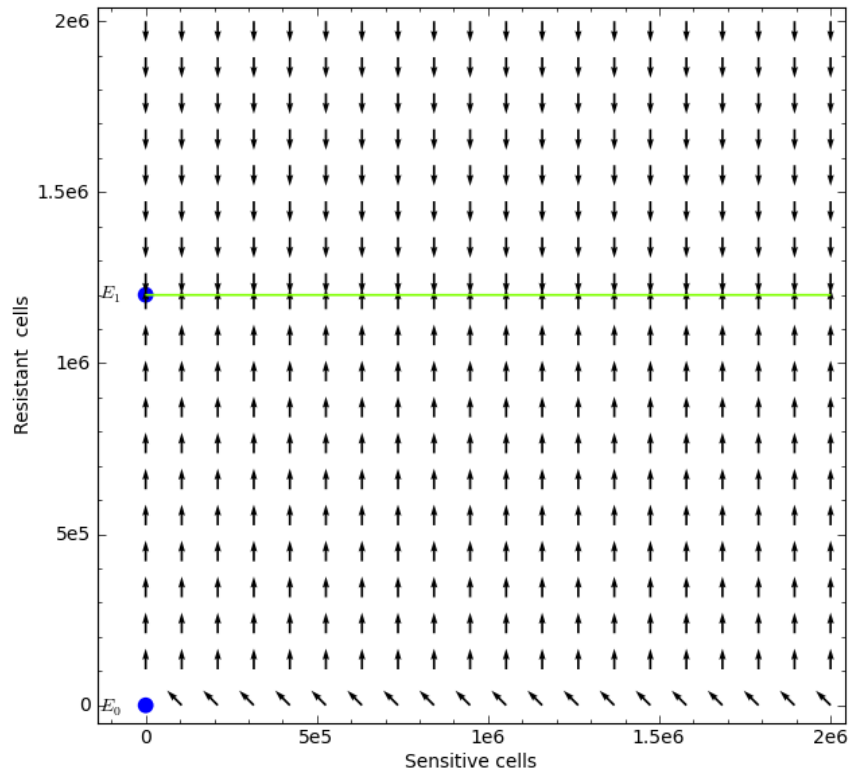


Figure 2.2: The phase portraits corresponding to the equilibrium points when $a_1 < \mu_1$.

From Figure 2.2, we note that the steady state E_1 is stable, but not asymptotically. In this case, we only have two equilibrium points, E_0 , which is unstable, and E_1 , which is stable. Intuitively, this means that if the treatment is taken, then tumour sub-populations would still be driven to extinction, but not exponentially like in the case when $\mu_1 < a_1$ as indicated in Figure 2.1.

2.4.3 Treatment equilibrium: single drug resistance

Having shown the dynamical behaviour of the model when there is no drug in at the tumour site, we next consider the classification of the equilibrium points in the presence of a therapeutic drug. The equilibrium points, denoted by $T(E_i) = (S^*, R^*, D^*)$, $i = 0, 1, 2$ are found by solving the non-linear system (2.11)–(2.13), with the left sides equated to zero. As before in Section 2.4, the stability of the system should be found in the same manner. However, the model now involves exponential terms, which pose a challenge in terms of solving the system algebraically, hence we used the computer

package SAGE [99] to find the steady states. We found the following plausible steady states:

$$T(E_0) = (0, 0, V), \quad (2.42)$$

$$T(E_1) = (0, 1, V), \quad (2.43)$$

$$T(E_2) = (S^*, R^*, D^*), \quad (2.44)$$

where

$$S^* = \frac{\theta_1}{a_1} (a_1 - (\mu_1 + \eta(1 - e^{-V}))),$$

$$R^* = \left(\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\mu_2 \theta_1}{a_1 a_2} (a_1 - (\mu_1 + \eta(1 - e^{-V})))} \right),$$

$$D^* = V.$$

Since $e^{-V} < 1$, then R^* exists only if the following conditions is satisfied:

$$\mu_1 + \eta(1 - e^{-V}) < a_1. \quad (2.45)$$

If condition (2.45) is satisfied, then S^* and R^* are positive. This is another necessary condition for existence of positive solutions in this model. We require positive solutions because we are dealing with biological populations; hence we cannot have negative populations.

The Jacobian matrix, for $i = 0, 1, 2$ is,

$$J(T(E_i)) = \begin{pmatrix} -1 & 0 & 0 \\ -\eta e^{-D^*} S^* & -2\frac{a_1}{\theta_1} S^* + \frac{a_1}{\theta} S^* & 0 \\ 0 & \mu_2 & a_2(1 - 2R^*) \end{pmatrix}. \quad (2.46)$$

Evaluating the Jacobian matrix (2.46) of the system about the steady state, $T(E_0)$, we obtain the following:

$$J(T(E_0)) = \begin{pmatrix} -1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & \mu_2 & a_2 \end{pmatrix}. \quad (2.47)$$

Here, we observe that the eigenvalue $\gamma_1 = -1 < 0$, but the eigenvalue $\gamma_3 = a_2 > 0$, hence the steady state, $T(E_0)$, is an unstable saddle point.

The Jacobian matrix corresponding to the steady state, $T(E_1)$ is

$$J(T(E_1)) = \begin{pmatrix} -1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & \mu_2 & -a_2 \end{pmatrix}. \quad (2.48)$$

Since the first eigenvalue $\gamma_1 = -1 < 0$, and the third eigenvalue $\gamma_3 = -a_2 < 0$, then the steady state $T(E_1)$ is stable, but not asymptotically.

At the steady state, $T(E_2)$, we have the following result:

$$J(T(E_2)) = \begin{pmatrix} M_{11} & M_{12} & M_{13} \\ M_{21} & M_{22} & M_{23} \\ M_{31} & M_{32} & M_{33} \end{pmatrix}, \quad (2.49)$$

where

$$\begin{aligned} M_{11} &= -1, & M_{12} &= 0, & M_{13} &= 0, \\ M_{21} &= \frac{\theta_1}{a_1} (a_1 - (\mu_1 + \eta(1 - e^{-V}))), \\ M_{22} &= - (a_1 - (\mu_1 + \eta(1 - e^{-V}))), & M_{23} &= 0, \\ M_{31} &= 0, & M_{32} &= \mu_2, \\ M_{33} &= -2a_2 \sqrt{\frac{1}{4} + \frac{\mu_2}{a_1 a_2} (a_1 - (\mu_1 + \eta(1 - e^{-V})))}. \end{aligned}$$

Since $e^{-V} \leq 1$ and given that the condition (2.45) is satisfied, then the eigenvalue $\gamma_2 = M_{22}$ is negative. Furthermore, if the condition (2.45) is satisfied, then the eigenvalue $\gamma_3 = M_{33} < 0$ only if

$$\mu_1 + \eta(1 - e^{-V}) < a_1. \quad (2.50)$$

Since $\gamma_1 = -1 < 0$, then the steady state $T(E_2)$ would be locally asymptotically stable.

2.5 The two drug case

One of the major questions in this dissertation is to determine how cancer cells elude the chemotherapeutic drugs. In such a biologically complex situation, the mathematical model is similarly complex. Apart from the tumour's heterogeneity, there are many factors which might substantially alter the tumour's responsiveness to the chemotherapeutic drugs. The investigation of these factors has been a

central focus of both clinical and mathematical oncologists in the last decades [2,45,46,100,101]. The prevalence of these adverse factors usually leads to the development multi-drug resistance (MDR).

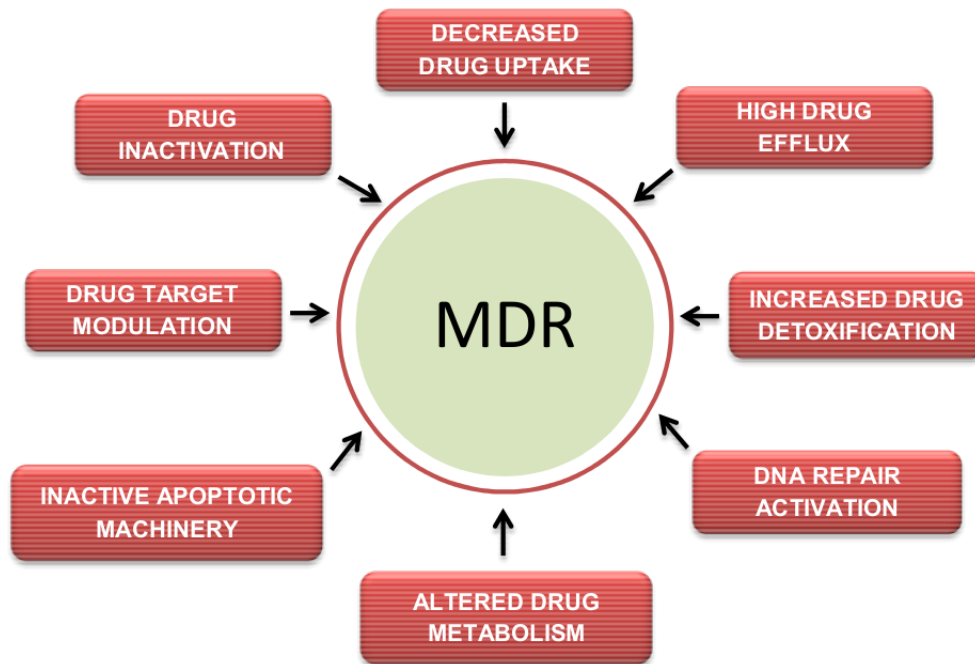


Figure 2.3: The schematic view of the mechanisms that contribute to the development of the multi-drug resistance (MDR), Source: [2].

Figure 2.3 gives a summary of the factors involved in the evolution of MDR. In many studies, MDR has been described as the most likely route by which the malignant tumour cells elude the chemotherapeutic drugs [2, 11, 42, 45–47, 54, 100, 101]. Since some cancer cells may be resistant to one drug, but be vulnerable to other drug, it is important to consider the evolution of a multi-drug resistance phenomenon in mathematical modelling. The combination of drugs used in clinical studies usually includes both cytostatic and cytotoxic drugs. Cytostatic drugs, assist in slowing down the rapid proliferation of the tumour cells, possibly by inhibiting their growth [55] or by inhibiting in the growth of the tumour host tissue, and some specific cell functions that are involved in tumour invasion [102,103]. For instance, Tamoxifen is a drug that is utilised to treat breast cancer by binding to estrogen receptors on the tumour cells and so inhibiting transcription of estrogen-responsive genes [104]. In lower dosages, cytostatic drugs are not considered harmful to the normal cells [45, 47, 56, 105].

Cytotoxic drugs, on the other hand, can destroy the tumour cells. However, they present problems of not only the inevitable evolution of multi-drug resistance, but their toxicity to normal tissues [106].

Furthermore, during chemotherapy, cytotoxic drug kills sensitive cells [8, 44, 45, 47], but the resistant cells may actually increase; consequently leading to a failure of the therapy. Therefore both drug types may be used together. Accordingly, in modelling the effects of acquired drug resistance we aim to minimize the number of resistant cells through studying the effect of two drugs on the tumour sensitive cells. At present this study is limited to the effect of two drugs, although extension of this model to account for three or more drugs is possible.

We denote by $R_1(t)$ and $R_2(t)$ the populations of tumour cells that are resistant to the first and second drugs, respectively, at time t after the start of the treatment. We further denote with $R_{12}(t)$ the tumour cells that are resistant to both the first and second drugs. We have also assumed that the non-cross resistant sub-populations mutate into cross resistant sub-population. We assume that the drugs are combined (e.g Lapatinib is a combination of two drugs [107]) and hence are infused simultaneously as a combination into the targeted tumour site. With these notations, we can now write the model as

$$\frac{dD(t)}{dt} = V(t) - \lambda_D D, \quad (2.51)$$

$$\frac{dS(t)}{dt} = \lambda_S S \left(1 - \frac{S}{\theta}\right) - k_S (1 - e^{-kD}) S - \mu S, \quad (2.52)$$

$$\frac{dR_1(t)}{dt} = \lambda_{R_1} R_1 \left(1 - \frac{R_1}{\theta}\right) + \frac{\mu}{3} S - k_{R_1} (1 - e^{-kD}) R_1 - \mu R_1(t), \quad (2.53)$$

$$\frac{dR_2(t)}{dt} = \lambda_{R_2} R_2 \left(1 - \frac{R_2}{\theta}\right) + \frac{\mu}{3} S - k_{R_2} (1 - e^{-kD}) R_2 - \mu R_2(t), \quad (2.54)$$

$$\frac{dR_{12}(t)}{dt} = \lambda_{R_{12}} R_{12} \left(1 - \frac{R_{12}}{\theta}\right) + \frac{\mu}{3} S + \mu R_1(t) + \mu R_2(t). \quad (2.55)$$

The initial conditions of the system (2.51) – (2.55) are given as

$$D(0) = 0, \quad S(0) = S_0, \quad R_1(0) = R_{01}, \quad R_2(0) = R_{02}, \quad R_{12}(0) = R_{012}, \quad (2.56)$$

where each of the initial values is non-negative. Again, we emphasise that the chemotherapeutic drug, D , represents the combination of two chemotherapeutic drugs, for instance, a combination of cytotoxic and cytostatic drugs [15, 16, 47, 55, 56, 102, 105–110] or a cytotoxic drug with an ABC-transport inhibitor [111]. This model setting provides valuable information because if a particular tumour cell is resistant to one drug, then it may be still vulnerable to the other drug and D remains the same as in Tomasetti and Levy [47].

2.5.1 Non-dimensionalisation

As we did in Section 2.2.2 for the simpler model, we again now create dimensionless variables. We denote by S^* the non-dimensionalised state variable S for sensitive cells and choose the order of magnitude of the cell population scale to be S_0 . The dimensionless state variables for a two drug-resistance model, equations (2.51) – (2.55), are

$$\begin{aligned} S &= S^* \bar{S}, & D &= D^* \bar{D}, & \bar{D} &= \frac{1}{k}, & R_1 &= \theta R_1^*, & R_2 &= \theta R_2^*, & R_{12} &= \theta R_{12}^*, \\ t &= t^* \bar{t}, & t_0 &= \frac{1}{\lambda_D}, & \bar{S} &= S_0 \end{aligned} \quad (2.57)$$

The additional dimensionless parameters to baseline parameters (2.9) – (2.10) are

$$\begin{aligned} V^* &= \alpha V, & \alpha &= \frac{t_0}{\bar{D}}, & \mu_1 &= \mu_3 = \mu_5 = \mu t_0, & a_1 &= \lambda_S t_0, & \theta_1 &= \frac{S_0}{\theta}, & \eta &= k_S t_0, & a_{R_1} &= \lambda_{R_1} t_0, \\ \mu_2 &= \frac{\mu t_0 S_0}{3R_{01}}, & \eta_1 &= k_{R_1} t_0, & a_{R_2} &= \lambda_{R_2} t_0, & \mu_4 &= \frac{\mu t_0 S_0}{3R_{02}}, & \eta_2 &= k_{R_2} t_0, & a_{R_{12}} &= \lambda_{R_{12}} t_0, \\ \mu_6 &= \frac{\mu t_0 S_0}{3R_{012}}, & \mu_7 &= \frac{\mu t_0 R_{01}}{R_{012}}, & \mu_8 &= \frac{\mu t_0 R_{02}}{R_{012}}, & R_{01}^* &= \frac{R_{01}}{\theta}, & R_{02}^* &= \frac{R_{02}}{\theta}, & R_{012}^* &= \frac{R_{012}}{\theta}. \end{aligned} \quad (2.58)$$

Dropping the asterisks for notational convenience, we write equations (2.51) – (2.55), in terms of the dimensionless state variables (2.57) as follows:

$$\frac{dD(t)}{dt} = V - D, \quad (2.59)$$

$$\frac{dS(t)}{dt} = a_1 S \left(1 - \frac{S}{\theta_1}\right) - \eta(1 - e^{-D})S - \mu_1 S, \quad (2.60)$$

$$\frac{dR_1(t)}{dt} = a_{R_1} R_1 (1 - R_1) + \mu_2 S - \eta_1(1 - e^{-D})R_1 - \mu_3 R_1, \quad (2.61)$$

$$\frac{dR_2(t)}{dt} = a_{R_2} R_2 (1 - R_2) + \mu_4 S - \eta_2(1 - e^{-D})R_2 - \mu_5 R_2, \quad (2.62)$$

$$\frac{dR_{12}(t)}{dt} = a_{R_{12}} R_{12} (1 - R_{12}) + \mu_6 S + \mu_7 R_1(t) + \mu_8 R_2(t), \quad (2.63)$$

The initial conditions of the dimensionless system (2.59) – (2.63) are given as

$$D(0) = 0, \quad S(0) = 1, \quad R_1(0) = R_{01}, \quad R_2(0) = R_{02}, \quad R_{12}(0) = R_{012}, \quad (2.64)$$

where each of the initial values is non-negative. We shall solve equations (2.11) – (2.13) and (2.59) – (2.63), using the Matlab numerical solver, *ode45*, to determine the effects of the chemotherapeutic drug on tumour reduction.

2.6 Equilibria and stability analysis: multi-drug resistance

In this section, we determine all biologically feasible equilibria admitted by system (2.59) – (2.63) and study the dynamics around each equilibrium point. We first determine the steady states when there is no chemotherapeutic drug in the tumour. Second, we find all equilibrium points of the system when there is a dose of the combination drug in the tumour.

2.6.1 Drug free equilibrium: multi-drug resistance

Let the steady states be $E_i = (S, R_1, R_2, R_{12})$. Then in order to better understand the dynamical behaviour of the system, with no chemotherapy, set

$$a_1 S \left(1 - \frac{S}{\theta_1}\right) - \mu_1 S = 0, \quad (2.65)$$

$$a_{R_1} R_1 (1 - R_1) + \mu_2 S - \mu_3 R_1 = 0, \quad (2.66)$$

$$a_{R_2} R_2 (1 - R_2) + \mu_4 S - \mu_5 R_2 = 0, \quad (2.67)$$

$$a_{R_{12}} R_{12} (1 - R_{12}) + \mu_6 S + \mu_7 R_1(t) + \mu_8 R_2(t) = 0, \quad (2.68)$$

and solve for the state variables. From equation (2.65) we find that

$$S = 0, \quad \text{and} \quad S = \frac{\theta_1(a_1 - \mu_1)}{a_1}. \quad (2.69)$$

Thus we have two cases:

(i) $S = 0$,

(ii) $S = \frac{\theta_1(a_1 - \mu_1)}{a_1}$.

Now, we have the following analysis:

(i) If $S = 0$, from equation (2.66) we find that

$$R_1 = 0, \quad \text{and} \quad R_1 = \frac{a_{R_1} - \mu_3}{a_{R_1}}, \quad (2.70)$$

and from equation (2.67), we have that

$$R_2 = 0, \quad \text{and} \quad R_2 = \frac{a_{R_2} - \mu_5}{a_{R_2}}. \quad (2.71)$$

When $S = R_1 = R_2 = 0$, from equation (2.68), we note that

$$R_{12} = 0, \quad \text{and} \quad R_{12} = 1, \quad (2.72)$$

and with $S = R_1 = 0$ and $R_2 = \frac{a_{R_2} - \mu_5}{a_{R_2}}$, from equation (2.68) we have that

$$R_{12} = \frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\mu_8}{a_{R_2} a_{R_{12}}}(a_{R_2} - \mu_5)}. \quad (2.73)$$

Since we are modelling a biological system, we take the positive R_{12} provided that $\mu_5 < a_{R_2}$.

Similarly, when $R_1 = \frac{a_{R_1} - \mu_3}{a_{R_1}}$ and $S = R_2 = 0$, from equation (2.68) we note that

$$R_{12} = \frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\mu_7}{a_{R_1} a_{R_{12}}}(a_{R_1} - \mu_3)}, \quad (2.74)$$

provided $\mu_3 < a_{R_1}$. If $S = 0$, $R_1 = \frac{a_{R_1} - \mu_3}{a_{R_1}}$ and $R_2 = \frac{a_{R_2} - \mu_5}{a_{R_2}}$, from equation (2.68) we find that

$$R_{12} = \frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\mu_7}{a_{R_1} a_{12}}(a_{R_1} - \mu_3) + \frac{\mu_8}{a_{R_2} a_{12}}(a_{R_2} - \mu_5)}. \quad (2.75)$$

We only take a positive value for R_{12} provided that $\mu_3 < a_{R_1}$ and $\mu_5 < a_{R_2}$.

Thus, for the case $S = 0$, we obtained the following five biologically meaningful steady states:

$$E_0^* = (0, 0, 0, 0), \quad (2.76)$$

$$E_1^* = (0, 0, 0, 1), \quad (2.77)$$

$$E_2^* = (0, 0, R_2^{**}, R_{12}^{**}), \quad (2.78)$$

$$E_3^* = (0, R_1^{***}, 0, R_{12}^{***}), \quad (2.79)$$

$$E_4^{4*} = (0, R_1^{4*}, R_2^{4*}, R_{12}^{4*}), \quad (2.80)$$

where

$$R_2^{**} = \frac{a_{R_2} - \mu_5}{a_{R_2}}, \quad R_{12}^{**} = \frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\mu_8}{a_{R_2} a_{R_{12}}}(a_{R_2} - \mu_5)},$$

$$R_1^{***} = \frac{a_{R_1} - \mu_3}{a_{R_1}}, \quad R_{12}^{***} = \frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\mu_7}{a_{R_1} a_{R_{12}}}(a_{R_1} - \mu_3)},$$

$$R_1^{4*} = \frac{a_{R_1} - \mu_3}{a_{R_1}}, \quad R_2^{4*} = \frac{a_{R_2} - \mu_5}{a_{R_2}},$$

$$R_{12}^{4*} = \frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\mu_7}{a_{R_1} a_{12}}(a_{R_1} - \mu_3) + \frac{\mu_8}{a_{R_2} a_{12}}(a_{R_2} - \mu_5)}.$$

The Jacobian of the system, for $i = 0, 1, 2, 3, 4$, is given by

$$J(E_i^*) = \begin{pmatrix} a_1 - \frac{2a_1S}{\theta_1} - \mu_1 & 0 & 0 & 0 \\ \mu_2 & a_{R_1}(1 - 2R_1) - \mu_3 & 0 & 0 \\ \mu_4 & 0 & a_{R_2}(1 - 2R_2) - \mu_5 & 0 \\ \mu_6 & \mu_7 & \mu_8 & a_{R_{12}}(1 - 2R_{12}) \end{pmatrix}. \quad (2.81)$$

Evaluating the Jacobian matrix about the trivial steady state, E_0^* , we have that

$$J(E_0^*) = \begin{pmatrix} a_1 - \mu_1 & 0 & 0 & 0 \\ \mu_2 & a_{R_1} - \mu_3 & 0 & 0 \\ \mu_4 & 0 & a_{R_2} - \mu_5 & 0 \\ \mu_6 & \mu_7 & \mu_8 & a_{R_{12}} \end{pmatrix}. \quad (2.82)$$

We observe that the trivial steady state is unstable because the eigenvalue $\gamma_4 = a_{R_{12}} > 0$. The other eigenvalues $\gamma_1 = a_1 - \mu_1$, $\gamma_2 = a_{R_1} - \mu_3$, $\gamma_3 = a_{R_2} - \mu_5$ can either be negative or positive. Thus, in any case, E_0^* would still be unstable.

The Jacobian matrix corresponding to the second steady state, E_1^* , is

$$J(E_1^*) = \begin{pmatrix} a_1 - \mu_1 & 0 & 0 & 0 \\ \mu_2 & a_{R_1} - \mu_3 & 0 & 0 \\ \mu_4 & 0 & a_{R_2} - \mu_5 & 0 \\ \mu_6 & \mu_7 & \mu_8 & -a_{R_{12}} \end{pmatrix}. \quad (2.83)$$

Here we realise that because the fourth eigenvalue $\gamma_4 = -a_{R_{12}} < 0$, then the steady state E_1^* is locally asymptotically stable if and only if $a_1 < \mu_1$, $a_{R_1} < \mu_3$, and $a_{R_2} < \mu_5$, otherwise, it remains unstable.

The Jacobian matrix about the steady state, E_2^* , is given by

$$J(E_2^*) = \begin{pmatrix} a_1 - \mu_1 & 0 & 0 & 0 \\ \mu_2 & a_{R_1} - \mu_3 & 0 & 0 \\ \mu_4 & 0 & M_{33} & 0 \\ \mu_6 & \mu_7 & \mu_8 & M_{44} \end{pmatrix}, \quad (2.84)$$

where

$$M_{33} = -(a_{R_2} - \mu_5), \quad M_{44} = -2a_{R_{12}} \sqrt{\frac{1}{4} + \frac{\mu_8}{a_{R_2} a_{R_{12}}} (a_{R_2} - \mu_5)} \quad (2.85)$$

The eigenvalues $\gamma_4 = M_{44} < 0$ only if $\mu_5 < a_{R_2}$. The eigenvalue $\gamma_3 = -(a_{R_2} - \mu_5) < 0$ provided $\mu_5 < a_{R_2}$, hence the steady state E_2^* is locally asymptotically stable only if the eigenvalues $\gamma_2 = a_{R_1} - \mu_3 < 0$ if and only if $a_{R_1} < \mu_3$ and $\gamma_1 = a_S - \mu_1 < 0$ only if $a_1 < \mu_1$, otherwise it is unstable.

The Jacobian resulting from the steady state, E_3^* , is

$$J(E_3^*) = \begin{pmatrix} a_1 - \mu_1 & 0 & 0 & 0 \\ \mu_2 & M_{22} & 0 & 0 \\ \mu_4 & 0 & -(a_{R_2} - \mu_5) & 0 \\ \mu_6 & \mu_7 & \mu_8 & M_{44} \end{pmatrix}, \quad (2.86)$$

where

$$M_{22} = -(a_{R_1} - \mu_3), \quad M_{44} = -2a_{R_{12}} \sqrt{\frac{1}{4} + \frac{\mu_7}{a_{R_1} a_{R_{12}}} (a_{R_1} - \mu_3)} \quad (2.87)$$

We note that $\gamma_4 = M_{44} < 0$ only if $\mu_5 < a_{R_2}$. The eigenvalue $\gamma_3 = M_{22} < 0$ only if $\mu_5 < a_{R_2}$. The steady state E_3^* would be locally asymptotically stable only if the eigenvalues $\gamma_3 = a_{R_2} - \mu_5 < 0$ if and only if $a_{R_2} < \mu_5$, $\gamma_1 = a_1 - \mu_1 < 0$ only if $a_1 < \mu_1$, $\gamma_4 = M_{44} < 0$ and $\gamma_3 = M_{22} < 0$; otherwise it would be unstable.

Evaluating the Jacobian matrix about the steady state E_4^* , we have the following:

$$J(E_4^*) = \begin{pmatrix} a_1 - \mu_1 & 0 & 0 & 0 \\ \mu_2 & M_{22} & 0 & 0 \\ \mu_4 & 0 & -M_{33} & 0 \\ \mu_6 & \mu_7 & \mu_8 & M_{44} \end{pmatrix}, \quad (2.88)$$

where

$$M_{22} = -(a_{R_1} - \mu_3), \quad M_{33} = -(a_{R_2} - \mu_5), \quad (2.89)$$

$$M_{44} = -2a_{R_{12}} \sqrt{\frac{1}{4} + \frac{\mu_7}{a_{R_1} a_{12}} (a_{R_1} - \mu_3) + \frac{\mu_8}{a_{R_2} a_{12}} (a_{R_2} - \mu_5)} \quad (2.90)$$

Here, given that $\mu_3 < a_{R_1}$ and $\mu_5 < a_{R_2}$, then the eigenvalues $\gamma_2 = M_{22} < 0$, $\gamma_3 = M_{33} < 0$ and $\gamma_4 = M_{44} < 0$. Hence, the steady state E_4^* would be asymptotically locally stable if $a_1 < \mu_1$; otherwise it would be unstable point.

(ii) When $S^\# = \frac{\theta_1(a_1 - \mu_1)}{a_1}$, we have the following solutions for the resistant sub-populations:

$$R_1^\# = \frac{1}{2a_{R_1}} (a_{R_1} - \mu_3) + \sqrt{\frac{1}{4a_{R_1}^2} (a_{R_1} - \mu_3)^2 + \frac{\mu_2\theta_1}{a_1 a_{R_1}} (a_1 - \mu_1)}, \quad (2.91)$$

$$R_2^\# = \frac{1}{2a_{R_2}} (a_{R_2} - \mu_5) + \sqrt{\frac{1}{4a_{R_2}^2} (a_{R_2} - \mu_5)^2 + \frac{\mu_4\theta_1}{a_1 a_{R_2}} (a_1 - \mu_1)}, \quad (2.92)$$

$$R_{12}^\# = \frac{1}{2} + \sqrt{\frac{1}{4} + \frac{1}{a_{12}} (\mu_6 S^\# + \mu_7 R_1^\# + \mu_8 R_2^\#)}, \quad (2.93)$$

provided that

$$S^\# > 0, \quad R_1^\# > 0, \quad R_2^\# > 0, \quad \text{whenever } \mu_1 < a_1, \quad \mu_3 < a_2, \quad \mu_5 < a_2. \quad (2.94)$$

For this case, $S^\# = \frac{\theta_1(a_1 - \mu_1)}{a_1}$, we obtained the following steady state:

$$E^{P^\star} = (S^\#, R_1^\#, R_2^\#, R_{12}^\#), \quad (2.95)$$

The Jacobian matrix of this steady state, E^{P^\star} , is

$$J(E^{P^\star}) = \begin{pmatrix} M_{11} & 0 & 0 & 0 \\ \mu_2 & M_{22} & 0 & 0 \\ \mu_4 & 0 & -M_{33} & 0 \\ \mu_6 & \mu_7 & \mu_8 & M_{44} \end{pmatrix}, \quad (2.96)$$

where

$$M_{11} = -(a_1 - \mu_1), \quad M_{22} = - \left((a_{R_1} - \mu_3) + 2a_{R_1} \sqrt{\frac{1}{4a_{R_1}^2} (a_{R_1} - \mu_3)^2 + \frac{\mu_2\theta_1}{a_1 a_{R_1}} (a_1 - \mu_1)} \right),$$

$$M_{33} = - \left((a_{R_2} - \mu_5) + 2a_{R_2} \sqrt{\frac{1}{4a_{R_2}^2} (a_{R_2} - \mu_5)^2 + \frac{\mu_4\theta_1}{a_1 a_{R_2}} (a_1 - \mu_1)} \right),$$

$$M_{44} = -2a_{R_{12}} \sqrt{\frac{1}{4} + \frac{1}{a_{12}} (\mu_6 S^\# + \mu_7 R_1^\# + \mu_8 R_2^\#)},$$

where $S^\#, R_1^\#$ and $R_2^\#$ are given in (2.91 – 2.93) and satisfy condition (2.94). We realise that if condition (2.91 – 2.93) is satisfied, then all the eigenvalues, $\gamma_1 = M_{11}, \gamma_2 = M_{22}, \gamma_3 = M_{33}$ and $\gamma_4 = M_{44}$ are negative. Thus, the steady state, E^{P^\star} , is locally asymptotically stable. Otherwise, it would be unstable.

In this section, we have investigated the dynamics of the tumour growth when there is no treatment given. It is important to note that the existence of stable steady states indicates the plausible points when cancerous cells may not be harmful to a patient. It is also important to note that some tumours may remain undetectable for years, while others may grow and metastasize rapidly, and cause death with a short period [38].

2.6.2 Treatment equilibrium: multi-drug resistance

Determining the steady states of the system (2.59 – 2.63) is quite tedious; however, we obtained the following steady states denoted by $T(E_i^{q^i}) = (D^{q^i}, S^{q^i}, R_1^{q^i}, R_2^{q^i}, R_{12}^{q^i})$, for $i = 0, \dots, 5$:

$$T(E_0^{q^0}) = (V, 0, 0, 0, 0), \quad (2.97)$$

$$T(E_1^{q^1}) = (V, 0, 0, 0, 1), \quad (2.98)$$

$$T(E_2^{q^2}) = (V, 0, R_1^{q^2}, 0, R_{12}^{q^2}), \quad (2.99)$$

$$T(E_3^{q^3}) = (V, 0, 0, R_2^{q^3}, R_{12}^{q^3}), \quad (2.100)$$

$$T(E_4^{q^4}) = (V, 0, R_1^{q^4}, R_2^{q^4}, R_{12}^{q^4}), \quad (2.101)$$

$$T(E_5^{q^5}) = (V, S^{q^5}, R_1^{q^5}, R_2^{q^5}, R_{12}^{q^5}), \quad (2.102)$$

where

$$R_1^{q^2} = \frac{1}{a_{R_1}} (a_{R_1} - (\mu_3 + \eta_1 (1 - e^{-V}))), \quad R_{12}^{q^2} = \frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\mu_7}{a_{R_{12}}} R_1^{q^2}}, \quad (2.103)$$

$$R_2^{q^3} = \frac{1}{a_{R_2}} (a_{R_2} - (\mu_5 + \eta_2 (1 - e^{-V}))), \quad R_{12}^{q^3} = \frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\mu_8}{a_{R_{12}}} R_2^{q^3}}, \quad (2.104)$$

$$R_1^{q^4} = R_1^{q^2}, \quad R_2^{q^4} = R_2^{q^3}, \quad R_{12}^{q^4} = \frac{1}{2} + \sqrt{\frac{1}{4} + \frac{1}{a_{R_{12}}} (\mu_7 R_1^{q^4} + \mu_8 R_2^{q^4})}, \quad (2.105)$$

$$S^{q^5} = \frac{\theta_1}{a_1} (a_1 - (\mu_1 + \eta (1 - e^{-V}))), \quad R_1^{q^5} = R_1^{q^2}, \quad R_2^{q^5} = R_2^{q^3}, \quad (2.106)$$

$$R_{12}^{q^5} = \frac{1}{2} + \sqrt{\frac{1}{4} + \frac{1}{a_{R_{12}}} (\mu_6 S^{q^5} + \mu_7 R_1^{q^5} + \mu_8 R_2^{q^5})}. \quad (2.107)$$

Since $e^{-V} \leq 1$, then the equilibrium points $T(E_2^{q^2}), T(E_3^{q^3}), T(E_4^{q^4})$ and $T(E_5^{q^5})$ exist only if

$$\mu_1 + \eta (1 - e^{-V}) < a_1, \quad (2.108)$$

$$\mu_3 + \eta_1 (1 - e^{-V}) < a_{R_1}, \quad (2.109)$$

$$\mu_5 + \eta_2 (1 - e^{-V}) < a_{R_2} \quad (2.110)$$

The Jacobian matrix for the system, for $i = 0, 1, 2, 3, 4, 5$, is given by

$$J(T(E_i^{q_i})) = \begin{pmatrix} -1 & 0 & 0 & 0 & 0 \\ -\eta e^{-D} S & TS & 0 & 0 & 0 \\ -\eta_1 e^{-D} R_1 & m\mu_2 & TR_1 & 0 & 0 \\ -\eta_2 e^{-D} R_2 & \mu_4 & 0 & TR_2 & 0 \\ 0 & \mu_6 & \mu_7 & \mu_8 & TR_{12} \end{pmatrix}, \quad (2.111)$$

where

$$TS = -\frac{2a_1}{\theta_1} S + (a_1 - (\mu_1 + \eta(1 - e^{-D}))), \quad (2.112)$$

$$TR_1 = -2a_{R_1} R_1 + (a_{R_1} - (\mu_3 + \eta_1(1 - e^{-D}))), \quad (2.113)$$

$$TR_2 = -2a_{R_2} R_2 + (a_{R_2} - (\mu_5 + \eta_2(1 - e^{-D}))), \quad (2.114)$$

$$TR_{12} = a_{R_{12}}(1 - 2R_{12}). \quad (2.115)$$

and given that conditions are satisfied (2.108 – 2.110).

Evaluating the Jacobian matrix (2.111) about the steady state $T(E_0^{q_0})$, we have

$$J(T(E_0^{q_0})) = \begin{pmatrix} -1 & 0 & 0 & 0 & 0 \\ 0 & a_1 - \mu_1 & 0 & 0 & 0 \\ 0 & \mu_2 & a_{R_1} - \mu_3 & 0 & 0 \\ 0 & \mu_4 & 0 & a_{R_2} - \mu_5 & 0 \\ 0 & \mu_6 & \mu_7 & \mu_8 & a_{R_{12}} \end{pmatrix}. \quad (2.116)$$

We observe that the eigenvalue $\gamma_1 = -1 < 0$, but $\gamma_5 = a_{R_{12}} > 0$, hence the steady state $T(E_0^{q_0})$ is an unstable saddle point.

Evaluating the Jacobian matrix (2.111) about the steady state $T(E_1^{q_1})$, we obtain

$$J(T(E_1^{q_1})) = \begin{pmatrix} -1 & 0 & 0 & 0 & 0 \\ 0 & a_1 - \mu_1 & 0 & 0 & 0 \\ 0 & \mu_2 & a_{R_1} - \mu_3 & 0 & 0 \\ 0 & \mu_4 & 0 & a_{R_2} - \mu_5 & 0 \\ 0 & \mu_6 & \mu_7 & \mu_8 & -a_{R_{12}} \end{pmatrix}. \quad (2.117)$$

This implies that the second eigenvalue, $\gamma_2 = a_1 - \mu_1$, is negative only if $a_1 < \mu_1$. In that case, the mutation rate is higher than the growth of sensitive cells. This indicates the impact of random

mutations whereby the drug resistance acquisition is time dependent. It means that more resistant cells would be continuously produced, despite the lack of growth of sensitive cells [5]. The eigenvalue, $\gamma_3 = a_{R_1} - \mu_3$ and $\gamma_4 = a_{R_2} - \mu_5$ would be negative only if $a_{R_1} < \mu_3$ and $a_{R_2} < \mu_5$, respectively. Because $\gamma_1 = -1 < 0$ and $\gamma_5 = -a_{R_{12}} < 0$, then the state $T(E_1^{q1})$ is stable if and only if $a_1 < \mu_1$, $a_{R_1} < \mu_3$ and $a_{R_2} < \mu_5$.

The Jacobian matrix corresponding to $T(E_2^{q2})$ is given as

$$J(T(E_2^{q2})) = \begin{pmatrix} -1 & 0 & 0 & 0 & 0 \\ 0 & a_1 - \mu_1 & 0 & 0 & 0 \\ -\eta_1 e^{-V} R_1 & \mu_2 & TR_1 & 0 & 0 \\ 0 & \mu_4 & 0 & a_{R_2} - \mu_5 & 0 \\ 0 & \mu_6 & \mu_7 & \mu_8 & TR_{12} \end{pmatrix}, \quad (2.118)$$

where

$$TR_1 = - (a_{R_1} - (\mu_3 + \eta_1 (1 - e^{-V}))),$$

$$TR_{12} = -2a_{R_{12}} \sqrt{\frac{1}{4} + \frac{\mu_8}{a_{R_{12}}} R_2^{q3}}.$$

If condition (2.109) is satisfied, then both eigenvalues, $\gamma_3 = TR_1$ and γ_5 are negative. Thus, the steady state, $T(E_2^{q2})$, would be locally asymptotically stable if $a_1 < \mu_1$ and $a_{R_2} < \mu_5$. Otherwise, it would be an unstable point.

Evaluating the Jacobian matrix, (2.111), about the steady state $T(E_3^{q3})$, we have the following outcome:

$$J(T(E_3^{q3})) = \begin{pmatrix} -1 & 0 & 0 & 0 & 0 \\ 0 & a_1 - \mu_1 & 0 & 0 & 0 \\ 0 & \mu_2 & a_{R_2} - \mu_3 & 0 & 0 \\ -\eta_2 e^{-V} R_2 & \mu_4 & 0 & TR_2 & 0 \\ 0 & \mu_6 & \mu_7 & \mu_8 & TR_{12} \end{pmatrix}, \quad (2.119)$$

where

$$TR_2 = - (a_{R_2} - (\mu_5 + \eta_1 (1 - e^{-V}))),$$

$$TR_{12} = -2a_{R_{12}} \sqrt{\frac{1}{4} + \frac{\mu_7}{a_{R_{12}}} R_1^{q2}}.$$

Similarly, if condition (2.110) is satisfied, then both the third and fifth eigenvalues, $\gamma_3 = TR_1$ and γ_5 , are negative. Hence, the steady state, $T(E_3^{q3})$, would be locally asymptotically stable only if $a_1 < \mu_1$ and $a_{R_1} < \mu_3$. Otherwise, it would be unstable.

The Jacobian matrix corresponding to $T(E_4^{q4})$ is given by

$$J(T(E_4^{q4})) = \begin{pmatrix} -1 & 0 & 0 & 0 & 0 \\ 0 & a_1 - \mu_1 & 0 & 0 & 0 \\ -\eta_1 e^{-V} R_1 & \mu_2 & TR_1 & 0 & 0 \\ -\eta_2 e^{-V} R_2 & \mu_4 & 0 & TR_2 & 0 \\ 0 & \mu_6 & \mu_7 & \mu_8 & TR_{12} \end{pmatrix}, \quad (2.120)$$

where

$$\begin{aligned} TR_1 &= - (a_{R_1} - (\mu_3 + \eta_1 (1 - e^{-V}))), \\ TR_2 &= - (a_{R_2} - (\mu_5 + \eta_1 (1 - e^{-V}))), \\ TR_{12} &= -2a_{R_{12}} \sqrt{\frac{1}{4} + \frac{1}{a_{R_{12}}} (\mu_7 R_1^{q4} + \mu_8 R_2^{q4})}. \end{aligned}$$

Now, if conditions (2.109 – 2.110) are satisfied, then the eigenvalues, $\gamma_3 = TR_1$, $\gamma_4 = TR_2$ and $\gamma_5 = TR_{12}$, are all negative. Therefore, the steady state, $T(E_4^{q4})$, is locally asymptotically stable only if $a_1 < \mu_1$ because the first eigenvalue, $\gamma_1 = -1$, is negative.

Finally, the Jacobian matrix corresponding to the endemic equilibrium point, $T(E_5^{q5})$, is given as

$$J(T(E_5^{q5})) = \begin{pmatrix} -1 & 0 & 0 & 0 & 0 \\ -\eta e^{-V} S & TS & 0 & 0 & 0 \\ -\eta_1 e^{-V} R_1 & \mu_2 & TR_1 & 0 & 0 \\ -\eta_2 e^{-V} R_2 & \mu_4 & 0 & TR_2 & 0 \\ 0 & \mu_6 & \mu_7 & \mu_8 & TR_{12} \end{pmatrix}, \quad (2.121)$$

where

$$\begin{aligned} TS &= - (a_1 - (\mu_1 + \eta (1 - e^{-D}))), \\ TR_1 &= - (a_{R_1} - (\mu_3 + \eta_1 (1 - e^{-V}))), \\ TR_2 &= - (a_{R_2} - (\mu_5 + \eta_1 (1 - e^{-V}))), \\ TR_{12} &= -2a_{R_{12}} \sqrt{\frac{1}{4} + \frac{1}{a_{R_{12}}} (\mu_6 S^{q5} + \mu_7 R_1^{q5} + \mu_8 R_2^{q5})}. \end{aligned}$$

If conditions (2.108 – 2.110) are satisfied, then the endemic equilibrium point, $T(E_5^{q5})$, is locally asymptotically stable. Otherwise, it would be unstable. This equilibrium point denotes the point that could bring cancer cell sub-populations to extinction when the chemotherapeutic drug is induced into the tumour.

2.7 Summary

In this chapter, two mathematical models describing local interaction of malignant tumour and anti-cancer agents have been presented. These models are based on compartmentalisation of tumour cells into drug sensitive and drug resistant sub-populations. The first model developed in this chapter describes the dynamics of tumour cells' interaction with a single chemotherapeutic drug. In the second model, we incorporated the dynamics of a multi-drug resistant phenotype. Equilibrium points of the model equations and their stability analysis were investigated, and show that the model is stable under certain conditions. However, because those conditions depend upon the parameter values, the stable conditionality of model does not always hold. Such stability analysis of the equilibria is an important aspect of mathematical modelling because a stable point could represent the state where tumour eradication is feasible, and this point, could then be a target point for chemotherapy. In this way we have increased our qualitative understanding of the model dynamics in relation to its stability. In Chapter 3, the model with single drug resistance will be extended to include the spatial interactions of tumour cells with a chemotherapeutic drug. In Chapter 4, numerical techniques will be applied to obtain quantitative results for both single and multi-drug resistance cases.

Chapter 3

A PDE model for drug resistance

3.1 Introduction

Even though ODE models can capture many vital biological processes, some processes can only be adequately addressed through partial differential equation (PDE) models. Such processes include the changes in age of the cells (i.e., the time elapsed since mitosis occurred), volume or density of the cells, their degrees of resistance to treatment, their DNA content or the size of the induced metastases. Analysis based on spatial and temporal processes takes into account the interactions between the tumour cells and their environment.

In this chapter, the goal is to develop a deterministic PDE model that describes tumour reduction by introducing chemotherapeutic drug, while simultaneously attempting to minimise the evolution of drug resistant phenotype. Our convection-reaction-diffusion model takes into account three important processes. To be specific, firstly, in order to account for the spatial dynamics of tumour cells, we have considered a spatial transport equation (based on convection) that governs the concentrations of tumour cells in response to the chemotherapeutic drug, for a given fixed period of the treatment. The model also incorporates the local chemical reactions that indicate the tumour's response to the chemotherapeutic drug while distinguishing between the drug sensitive and drug resistant tumour sub-populations. Finally, diffusion is the most significant mode of transport in the interstitial space around the tumour. Being the dominant transport process once the drug leaves the blood vessels it accounts for the intra-cellular spread of substances such as drug molecules.

In this way, the model describes the tumour's response to the chemotherapeutic drug by taking into

account the fact that chemotherapy is a localised treatment. That is to say, the drug is delivered from the patient’s vasculature into the tumour by means of blood vessels, which are often dense around the tumour surface, as shown below

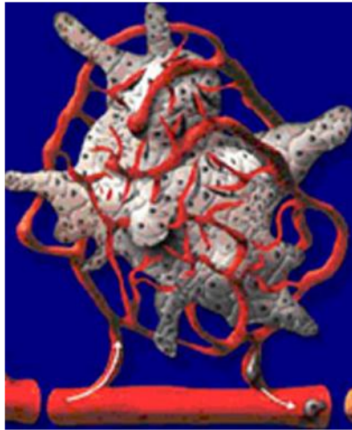
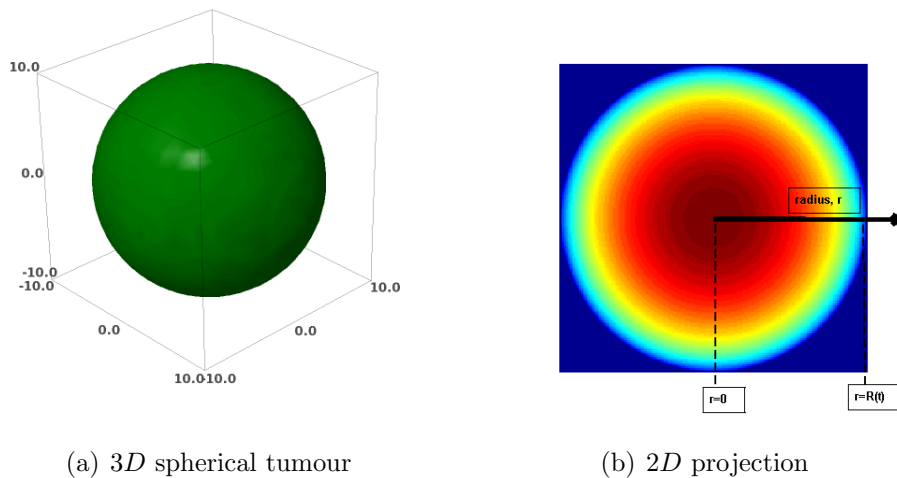


Figure 3.1: The blood vessels that vascularise the tumour, Source: [3].

It can be seen in Figure 3.1 that the tumour is surrounded by blood vessels to transport oxygen and minerals, which are essential for maintaining tumour growth and allowing for metastasis.

In our model, as in Jackson and Byrne [48], the tumour is viewed as a radially symmetric packed sphere, of radius $R(t)$, consisting of two types of sub-populations; the drug sensitive and drug resistant cells. There is an evidence that tumours grown in vitro (see Appendix) have a nearly spherical shape, but tumours grown in vivo are not [48, 112]. It is thus a moving boundary model, as illustrated in Figure 3.2(b).



(a) 3D spherical tumour

(b) 2D projection

Figure 3.2: The schematic view of a spherically symmetric tumour. The spatial domain is a moving boundary $[0, R(t)]$ with a radius $r = R(t)$.

Figure 3.2(a) show a schematic view of a spherical tumour in 3 dimensional space, while Figure 3.2(b) shows its projection of 2 dimensional setting in order to show a corresponding moving radius.

The geometry of this moving boundary problem, where cell movement is associated only with local volume changes that accompany cell proliferation and death, has been considered in various studies such as in [48,113–115]. However, there are models that associate the moving boundary of the tumour not only with concentration gradients of the chemicals inside the tumour, but also with interstitial pressure [113]. Because we are mainly interested in the tumour’s response to the chemotherapeutic agent, in this model we have not considered the impact of interstitial pressure.

We have developed a new model similar to the model of Jackson and Byrne [48], as well as Jackson [113], where the chemotherapeutic drug kills all types of tumour cells, subject to different susceptibilities, by assuming that the drug kills only sensitive cells, and does not have any impact on the resistant cells. This is a reasonable assumption because the model developed in this study is non cell-cycle specific. In cell cycle-specific models, chemotherapeutic drugs kill cancerous cells only in specific phases of the cell cycle [116]. The problem with cell cycle-specific chemotherapies is that drugs target cells only in certain phases of the cell cycle, and consequently spare some tumour cells that are not in the targeted phases [117]. We have further assumed that the resistant sub-population in the tumour is due to genetic point mutations, as in Tomasetti and Levy [47]. Since we are modelling a malignant tumour, we have also assumed the tumour to possess its own vasculature so that it can receive nourishment sufficient to maintain its growth and malignancy, through both diffusion and blood-tissue transfer [48,114].

3.2 PDE model formulation

There are many important biological processes involved in the distribution of drugs into the targeted cancerous cells, as shown in Figure 3.3.

The physical processes involved in the movement of drugs into or out of the tumour cells. Normally, drug molecules could either traverse from the vasculature (blood vessels) by means of advection (sometimes called convection) or diffuse through the interstitial space around the tumour; they are usually subject to some natural decay before they could be up-taken by the tumour cells. During advective movement, drug molecules are carried with a bulk flow of interstitial fluid. This flow could result from pressure differences within a tumour tissue or from the drainage of fluids into the

lymphatic circulation system [4].

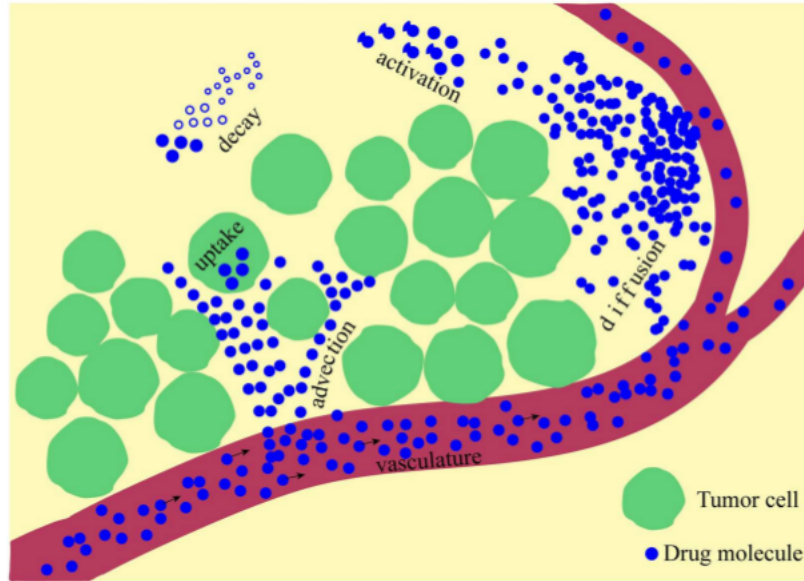


Figure 3.3: The biological processes involved in the migration of the drug molecules into the tumour cells, Source [4].

In some cases, drug molecules are boosted (activated) to increase an efficacy of the chemotherapeutic compounds as well as to increase the time of drug survival within the tumour tissue beyond its half-life [4]. For mathematical simplicity, in our model we consider diffusion and convection processes. Diffusion accounts for the random motility of drug molecules due to gradients in their concentration while convection usually accounts for the motion of the drug due to bulk motion in the carrying environment [118].

In order to account for the spatial dynamics of tumour cell sub-populations, where the density of any species depends on time and space, the ODE model is now extended to a system of partial differential equations (PDEs). We make the following assumptions for the vascular tumour growth model:

- (i) The chemotherapeutic drug reaches the tumour cells mainly by constant diffusion from nearby vasculature. There is little convective movement of the drug at the tumour site.
- (ii) The chemotherapeutic drug diffuses both ways between the tumour vasculature and the tumour-host tissue at a rate that is proportional to the difference in the drug concentrations in the blood and tumour.
- (iii) The drug sensitive tumour cells are uniformly susceptible to the drug, and the drug does not have any effects on the resistant cells.

- (iv) The tumour cells grow logistically in the absence of the chemotherapeutic drug [21, 48].
- (v) A portion of the drug gets inactivated as it interacts with the tumour cells. As in the ODE model, we assume that the interaction of the drug with the tumour cells follows an exponential saturation kinetics.

The model is comprised of a system of partial differential equations that describe spatial interaction of the chemotherapeutic drug with two tumour sub-populations. The first tumour sub-population comprises cells that are sensitive to the drug, $S(r, t)$, while the second sub-population is made up of cells that are resistant to the drug, $R(r, t)$. We follow a similar modelling approach to that adopted by Byrne and Jackson [48] by considering a vascular exchange between blood and the tumour. We denote by $D(\mathbf{r}, t)$ a drug concentration within the tumour, and by $D_b(t)$ the drug concentration within the blood. We consider a constant rate of transfer of the drug from the nearby vasculature to the tumour as in [114]. Tumour cell movement is described by the local volume changes that accompany proliferation and death of individual cells. Such movement is usually associated with a local cell velocity, $\mathbf{u}(r, t)$.

The following are the baseline parameters for our spatially symmetric tumour model:

- (i) d_D denotes the diffusion coefficient of the drug,
- (ii) d_S represents the growth rate of the sensitive cells,
- (iii) d_R denotes the growth rate of resistant cells,
- (iv) μ represents the mutation rate coefficient resulting from cell division,
- (v) λ_D denotes the chemotherapeutic decay,
- (vi) λ_S represents an intrinsic growth rate of sensitive cells,
- (vii) λ_R denotes an intrinsic growth rate of resistant cells,
- (viii) Γ represents the permeability coefficient between the tumour and nearby tissue vasculature,
- (ix) u_S represents a rate of inactivation of the drug from an interaction of sensitive cells, $S(r, t)$, and the chemotherapeutic drug, $D(r, t)$,
- (x) k_S denotes a susceptibility coefficient of the sensitive cells,

(xi) k denotes a saturation coefficient of the drug,

(xii) θ represents a maximum carrying capacity of the tumour.

Applying the principle of conservation of mass on each tumour sub-population and drug concentration, then the model is written as follow:

$$\frac{\partial D}{\partial t} + \nabla \cdot (\mathbf{u}D) = d_D \nabla^2 D + \Gamma(D_b(t) - D) - \lambda_D D - u_S I_{SD}(S, D), \quad (3.1)$$

$$\frac{\partial S}{\partial t} + \nabla \cdot (\mathbf{u}S) = d_S \nabla^2 S + \lambda_S S \left(1 - \frac{S}{\theta}\right) - I_{SD}(S, D) - \mu S, \quad (3.2)$$

$$\frac{\partial R}{\partial t} + \nabla \cdot (\mathbf{u}R) = d_R \nabla^2 R + \lambda_R R \left(1 - \frac{R}{\theta}\right) + \mu S. \quad (3.3)$$

This model shares some similarities with that of Jackson and Byrne [48] in that the local concentration of each tumour sub-population is subject to both diffusion and convection processes. However, in this model, reduction of drug concentration does not depend only on natural drug decay, as considered by Jackson and Byrne [48], but also to inactivation of the drug resulting from drug interaction with the sensitive cells. To account for this interaction between the tumour and the sensitive cells, we have denoted this interaction by a term I , for instance, $I_{SD}(S, D)$, represents the interaction of the drug and the sensitive cells. This interaction, in principle, depends only on the local concentrations of the sensitive tumour cells, S , and the chemotherapeutic drug, D . In addition, we considered an influence of genetic point mutations, μ , in the acquisition of resistance phenotype of tumour cells. We also note that all types of tumour sub-populations have distinct intrinsic growth rates, with the sensitive cells growing faster than the resistant cells. Furthermore, the chemotherapeutic drug decays at some specific rate and also diffuses into, or out of, the tumour from the bloodstream in the surrounding tissue.

Unlike to Jackson and Byrne [48], who assumed Michaelis-Menten interaction kinetics between the tumour cells and the chemotherapeutic drug, instead because chemotherapeutic drugs are effective during certain phases of the cell division cycle, we take the interaction term between the sensitive cells and the drug to follow exponential kinetics as

$$I_{SD}(S, D) = k_S(1 - e^{-kD})S. \quad (3.4)$$

The interaction of the chemotherapeutic drug and sensitive cells is usually given by exponential saturation kinetics [97]. This interaction of the sensitive cells and the chemotherapeutic drug has been validated with medical data by Gardner [90].

To account for the spherical symmetry of the tumour, we define the tumour boundary by

$$B(r, t) = r - R(t) = 0, \quad (3.5)$$

and the radial unity vector by $\hat{\mathbf{r}}$; thus we have $\mathbf{u} = u(r, t)\hat{\mathbf{r}}$. Our system of equations can be written as

$$\frac{\partial D}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} (r^2 \mathbf{u} D) = \frac{d_D}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial D}{\partial r} \right) + \Gamma(D_b(t) - D) - \lambda_D D - u_S k_S (1 - e^{-kD}) S, \quad (3.6)$$

$$\frac{\partial S}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} (r^2 \mathbf{u} S) = \frac{d_S}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial S}{\partial r} \right) + \lambda_S S \left(1 - \frac{S}{\theta} \right) - k_S (1 - e^{-kD}) S - \mu S, \quad (3.7)$$

$$\frac{\partial R}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} (r^2 \mathbf{u} R) = \frac{d_R}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial R}{\partial r} \right) + \lambda_R R \left(1 - \frac{R}{\theta} \right) + \mu S. \quad (3.8)$$

To find the equation for the local cell velocity, \mathbf{u} , we first assume that there are no empty spaces within the tumour such that the fraction of the spheroid occupied by the tumour cells remains constant, and that the proportion of the vascular space within the tumour also remains constant. Under these assumptions, we can write the following relation for the two tumour sub-populations

$$S + R = c \equiv \text{constant}. \quad (3.9)$$

Adding equation (3.7) and (3.8), and using (3.9) we obtain

$$\begin{aligned} \frac{c}{r^2} \frac{\partial}{\partial r} (r^2 \mathbf{u}) &= \left(\frac{d_S - d_{(c-S)}}{r^2} \right) \frac{\partial}{\partial r} \left(r^2 \frac{\partial S}{\partial r} \right) + \lambda_S S \left(1 - \frac{S}{\theta} \right) + \lambda_{(c-S)} (c - S) \left(1 - \frac{(c - S)}{\theta} \right) \\ &\quad - k_S (1 - e^{-kD}) S, \\ \frac{c}{r^2} \frac{\partial}{\partial r} (r^2 \mathbf{u}) &= \frac{E}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial S}{\partial r} \right) + \lambda_S S \left(1 - \frac{S}{\theta} \right) + \lambda_R R \left(1 - \frac{R}{\theta} \right) - k_S (1 - e^{-kD}) S, \end{aligned} \quad (3.10)$$

where $E = (d_S - d_{(c-S)})$. Equation (3.10) is the equation for the local velocity, \mathbf{u} . It suffices to determine the drug concentration, D , and the radial velocity, \mathbf{u} .

To complete our system, we note that the tumour has a moving boundary; hence let $r = \mathbf{R}(t)$, then we impose the following initial conditions:

$$\mathbf{R}(0) = \mathbf{R}_0, \quad S(r, 0) = S_0, \quad R(r, 0) = 0, \quad D(r, 0) = 0, \quad D_b(0) = D_{b0} \quad (3.11)$$

These conditions imply that the tumour of a given radius \mathbf{R}_0 comprises only the sensitive cells, S_0 . There is no chemotherapeutic drug in the tumour at time $t = 0$, but there is some chemotherapeutic drug in the surrounding tumour vasculature.

To assess the tumour's response to the chemotherapeutic drug we study the evolution of the tumour's volume ($V = (4/3)\pi\mathbf{R}^3$), and note that under radial symmetry, the tumour expands at a rate that is equal to the radial velocity at the tumour boundary [48]. Hence we have

$$\frac{d\mathbf{R}}{dt} = \mathbf{u}(\mathbf{R}(t), t) \quad (3.12)$$

At $r = 0$, we further impose the following Neumann boundary conditions:

$$\frac{\partial D(0, t)}{\partial r} = 0, \quad \frac{\partial S(0, t)}{\partial r} = 0, \quad \frac{\partial R(0, t)}{\partial r} = 0, \quad \mathbf{u}(0, t) = 0. \quad (3.13)$$

Since the tumour is assumed to be spherical, then at $r = 0$ there is no influx of the drug and the local radial velocity is zero. We further propose that there is no flux of tumour cells at the tumour center. To model the temporal and spatio-temporal equations through the continuity conditions at the boundary, $B(r, t) = 0$, we have that

$$\frac{\partial D(r, t)}{\partial r} = C_0, \quad \frac{\partial S(r, t)}{\partial r} = 0, \quad \frac{\partial R(r, t)}{\partial r} = 0, \quad D(r, t) = D_N(t). \quad (3.14)$$

Here, we have denoted the local concentration of the drug at the tumour boundary by $D_N(t)$. For mathematical simplicity, the concentration of the drug in the blood, $D_b(t)$, and the amount of the drug at the tumour boundary, $D_N(t)$, are assumed to be constants as in [113]. In [48] they are regarded as bi-exponential functions.

As in previous chapters, we now define dimensionless variables and parameters where

$$D = D^*\bar{D}, \quad \lambda_D = \frac{1}{t_0}\lambda_D^*, \quad \lambda_S = \frac{1}{t_0}\lambda_S^*, \quad \lambda_R = \frac{1}{t_0}\lambda_R^*, \quad D_b = D_b^*\bar{D}, \quad S = S^*\bar{S}, \quad (3.15)$$

$$R = R^*\bar{R}, \quad d_D = \frac{\mathbf{R}_0^2}{t_0}d_D^*, \quad d_S = \frac{\mathbf{R}_0^2}{t_0}d_S^*, \quad d_R = \frac{\mathbf{R}_0^2}{t_0}d_R^*, \quad r = \mathbf{R}_0r^*, \quad t = t^*\bar{t}, \quad (3.16)$$

$$\mathbf{u} = \frac{\mathbf{R}_0}{t_0}\mathbf{u}^*, \quad \Gamma = \frac{\Gamma^*\mathbf{R}_0^2}{t_0}, \quad \frac{\partial}{\partial r} = \frac{1}{\mathbf{R}_0}\frac{\partial}{\partial r^*}, \quad \frac{\partial}{\partial t} = \frac{1}{t_0}\frac{\partial}{\partial t^*}, \quad k_S = \frac{D_0}{S_0}k_S^*, \quad u_S = \frac{1}{t_0}u_S^*, \quad (3.17)$$

$$k = \frac{1}{D_0}k^*, \quad \mu = \frac{D_0}{S_0t_0}\mu^*, \quad \epsilon = \mathbf{R}_0^2/d_D, \quad D_0 = \frac{1}{k}, \quad \rho_S = \frac{S_0^2\lambda_S}{d_S}, \quad \eta = \frac{S_0k_S}{d_s}, \quad (3.18)$$

$$\theta_1 = \frac{\theta}{S_0}, \quad \beta = R_0^2/d_D, \quad \rho_R = \frac{R_0^2\lambda_R}{d_R}, \quad \mu_2 = \frac{R_0\mu}{d_R}, \quad R^* = \frac{R_0}{\theta}, \quad \bar{S} = S_0. \quad (3.19)$$

Using these dimensionless variables and parameters, (3.15) – (3.19), in equations (3.6) – (3.8), and

dropping the asterisks for notational convenience, we have the dimensionless system of equations

$$\epsilon \left\{ \frac{\partial D}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} (r^2 \mathbf{u} D) \right\} = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial D}{\partial r} \right) + \frac{1}{d_D} (\Gamma(D_b(t) - D) - \lambda_D D - u_S k_S (1 - e^{-kD}) S), \quad (3.20)$$

$$\alpha \left\{ \frac{\partial S}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} (r^2 \mathbf{u} S) \right\} = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial S}{\partial r} \right) + \rho_S S \left(1 - \frac{S}{\theta_1} \right) - \eta (1 - e^{-D}) S - \mu_1 S, \quad (3.21)$$

$$\beta \left\{ \frac{\partial R}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} (r^2 \mathbf{u} R) \right\} = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial R}{\partial r} \right) + \rho_R R (1 - R) + \mu_2 S \quad (3.22)$$

The velocity dimensionless equation is

$$\frac{c}{r^2} \frac{\partial}{\partial r} (r^2 \mathbf{u}) = \frac{E}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial S}{\partial r} \right) + \rho_S S \left(1 - \frac{S}{\theta_1} \right) + \rho_R R (1 - R) - \eta (1 - e^{-D}) S. \quad (3.23)$$

In this section we have now developed a model to describe the spatial dynamics of the tumour sub-populations and their interaction with the chemotherapeutic drug. This would be helpful in demonstrating the importance of space for tumour modelling. Furthermore, this would also be helpful for investigating the partial distribution effects of drugs on tumour growth.

3.3 Analytical solutions of the PDE model

Due to the complexity of the model, we do not expect to obtain the full analytical solutions of the model. Nevertheless, full solutions will be obtained derived numerically in Chapter 4. In the meantime, we can obtain analytical solutions for the local drug concentration and the local velocity, with transformation and additional assumptions. The full solution of the model shall be derived numerically in Chapter 4.

Firstly, we introduce a small parameter $0 \leq \epsilon = \mathbf{R}_0^2/d_D \ll 1$ which is a similar transformation as was used by [48, 113] to find steady states of their model solutions. Thus we can write equation (3.20) as

$$\epsilon \left\{ \frac{\partial D}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} (r^2 \mathbf{u} D) \right\} = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial D}{\partial r} \right) + \frac{1}{d_D} (\Gamma(D_b(t) - D) - \lambda_D D - u_S k_S (1 - e^{-kD}) S). \quad (3.24)$$

Then, following the method of multiple time scales [119, 120], we have adopted two time scales for our model: the intrinsic tumour growth scale (≈ 1 day), and the shorter diffusion time scale ($\mathbf{R}_0/d_D \approx 60$ seconds) [48]. Assuming that the chemotherapeutic drug diffuses much faster than the intrinsic growth of the tumour cells, then the quantity $\epsilon = \mathbf{R}_0^2/d_D \approx 0$ so that

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial D}{\partial r} \right) + \frac{1}{d_D} (\Gamma(D_b(t) - D) - \lambda_D D - u_S k_S (1 - e^{-kD}) S) = 0. \quad (3.25)$$

Note that equation (3.25) is a homogeneous first order partial differential equation; hence we can find the solution to it.

Next, if we further assume a low chemotherapeutic drug concentration, then $1 - e^{-kD} \approx kD$. This transforms the term $u_S k_S (1 - e^{-kD}) S$ to a linear term; hence equation (3.25) becomes

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial D}{\partial r} \right) - \left(\frac{\lambda_D + \Gamma + u_S k_S k S}{d_D} \right) D = -\frac{\Gamma}{d_D} D_b(t). \quad (3.26)$$

Now, let

$$\xi_D^2 = \frac{\lambda_D + \Gamma + u_S k_S k S}{d_D}, \quad (3.27)$$

then we have the following non-homogeneous PDE;

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial D}{\partial r} \right) - \xi_D^2 D = -\frac{\Gamma}{d_D} D_b(t). \quad (3.28)$$

Let us define another function $D = G(r, t)/r$, then we can write

$$G'' - \xi_D^2 G = -\frac{\Gamma}{d_D} D_b(t). \quad (3.29)$$

We choose the particular solution to equation (3.29) as $G_p = \frac{\Gamma}{d_D} D_b(t)$. The corresponding homogeneous equation to (3.29) is

$$G'' - \xi_D^2 G = 0. \quad (3.30)$$

Equation (3.28) is of the form

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial f_j}{\partial r} \right) - (k_j)^2 f_j + \gamma_j = 0, \quad (3.31)$$

which is a mass balance equation and could be solved with appropriate boundary conditions [121–124].

The formulation and solutions of the equations of this type are discussed in detail by Deen [123] and Bird et al [122].

The general solution to equation (3.28) is

$$D(r, t) = \frac{a(t) \sinh(\xi_D r) + b(t) \cosh(\xi_D r)}{r} + \frac{\Gamma}{d_D \xi_D^2} D_b(t), \quad (3.32)$$

where $a(t)$ and $b(t)$ are functions that are determined from the boundary conditions. To find the solution for the local drug concentration, we demand that the chemotherapeutic drug concentration approaches a steady state in the blood tissue. This can occur only if $a(t) + b(t) = 0$. Since we have assumed spherical tumour, then we require symmetry condition to be satisfied; hence we have that

$$\left. \frac{\partial D}{\partial r} \right|_{r=0} = 0, \quad \text{hence } b(t) = 0. \quad (3.33)$$

At $r = \mathbf{R}(t)$, we have

$$a(t) \frac{\sinh(\xi_D \mathbf{R}(t))}{\mathbf{R}(t)} + \frac{\Gamma}{d_D \xi_D^2} D_b(t) = D_N(t). \quad (3.34)$$

This gives

$$a(t) = \left(D_N(t) - \frac{\Gamma}{d_D \xi_D^2} D_b(t) \right) \frac{\mathbf{R}(t)}{\sinh(\xi_D \mathbf{R}(t))}. \quad (3.35)$$

Hence, the solution for the local drug concentration is

$$D(r, t) = \left(D_N(t) - \frac{\Gamma}{d_D \xi_D^2} D_b(t) \right) \frac{\mathbf{R}(t) \sinh(\xi_D r)}{r \sinh(\xi_D \mathbf{R}(t))} + \frac{\Gamma}{d_D \xi_D^2} D_b(t). \quad (3.36)$$

Here, we have only provided the analytical solution for the local drug concentration based on the assumption of induced low drug concentration at the tumour site. This solution is similar to the one attained by Jackson and Byrne [48]. The solution for high drug concentration can only be found numerically.

We next find the equation for the local velocity, $\mathbf{u}(r, t)$, by substituting equation (3.36) into equation (3.23). Let us first make the following assumptions;

- (i) The intra-tumour drug concentration, D , is low and constant. This implies that $1 - e^{-kD} \approx kD$. It is important to note that at relatively low drug concentrations, this interaction term is nearly linear, whereas at higher drug concentration, the drug concentration within the tumour reaches a saturation state (i.e a response curve plateaus). This exponential term corresponds to drug response kinetics suggested by Gardner [90].
- (ii) The tumour consists of only sensitive cells (i.e. one cell type, $S(r, t) = 1$). Thus, there are no resistant cells, $R(r, t) = 0$.

With these assumptions, the equation for the local velocity becomes

$$\frac{1}{r^2} \frac{\partial}{\partial r} (r^2 \mathbf{u}) = 1 - k_S k D. \quad (3.37)$$

Substituting equation (3.36) in the above equation we obtain

$$\frac{\partial}{\partial r} (r^2 \mathbf{u}) = \left(1 - \frac{k_S k \Gamma}{d_D \xi_D^2} D_b(t) \right) r^2 - k_S k \left(\left(D_N(t) - \frac{\Gamma}{d_D \xi_D^2} D_b(t) \right) \frac{\mathbf{R}(t) r \sinh(\xi_D r)}{\sinh(\xi_D \mathbf{R}(t))} \right). \quad (3.38)$$

Using integrating the above equation with respect to r and making use of the condition $u(0, t) = 0$, we have

$$\begin{aligned} \int \frac{\partial}{\partial r'} (r^2 \mathbf{u}) dr' &= \int \left(1 - \frac{k_S k \Gamma}{d_D \xi_D^2} D_b(t) \right) (r')^2 dr' \\ &\quad - k_S k \left(\left(D_N(t) - \frac{\Gamma}{d_D \xi_D^2} D_b(t) \right) \frac{\mathbf{R}(t)}{\sinh(\xi_D \mathbf{R}(t))} \int r' \sinh(\xi_D r') dr' \right), \end{aligned} \quad (3.39)$$

Integration by parts, equation (3.39) becomes

$$r^2 u(r, t) = u(0, t) + \left(1 - \frac{k_S k \Gamma}{d_D \xi_D^2} D_b(t)\right) \frac{r^3}{3} - k_S k \left(D_N(t) - \frac{\Gamma}{d_D \xi_D^2} D_b(t)\right) \frac{\mathbf{R}(t)}{\sinh(\xi_D \mathbf{R}(t))} \left(\frac{r}{\xi_D} \cosh(\xi_D r) - \frac{1}{\xi_D^2} \sinh(\xi_D r)\right). \quad (3.40)$$

Therefore the solution for the local velocity is

$$u(r, t) = \left(1 - \frac{k_S k \Gamma}{d_D \xi_D^2} D_b(t)\right) \frac{r}{3} - \frac{k_S k \mathbf{R}(t)}{\xi_D^2} \left(D_N(t) - \frac{\Gamma}{d_D \xi_D^2} D_b(t)\right) \frac{\xi_D r \cosh(\xi_D r) - \sinh(\xi_D r)}{r^2 \sinh(\xi_D \mathbf{R}(t))}. \quad (3.41)$$

With this solution for the local cell velocity, we can now follow the tumour's expansion by tracking the evolution of the tumour radius, given by

$$\frac{d\mathbf{R}}{dt} = \left(1 - \frac{k_S k \Gamma}{d_D \xi_D^2} D_b(t)\right) \frac{\mathbf{R}(t)}{3} - \frac{k_S k}{\xi_D^2} \left(D_N(t) - \frac{\Gamma}{d_D \xi_D^2} D_b(t)\right) \frac{\xi_D \mathbf{R}(t) \cosh(\xi_D \mathbf{R}(t)) - \sinh(\xi_D \mathbf{R}(t))}{\mathbf{R}(t) \sinh(\xi_D \mathbf{R}(t))}. \quad (3.42)$$

These solutions, when one type of tumour cell is present (primarily sensitive cells), is that tumours would usually regress once a chemotherapeutic drug is infused at the tumour site. When there are two types of the tumour sub-populations, the dynamics become complex. We shall attempt to capture some essential aspects of the model numerically in Chapter 4. We remark that the analysis and solutions provided here are only valid if we have a spherical geometry. These results would differ for non-spherical tumours and are not applicable where there are drug resistant tumour cells. More importantly, the establishment of these results is important because, by our model assumption, the resistant sub-population arise from mutation of a single sensitive cell. Thus, it is essential to track the dynamics of tumour growth prior to evolution of a drug-resistant sub-population. However, the model dynamics when there are two types of tumour sub-populations (i.e. the sensitive and resistant cells), will be investigated numerically in Chapter 4.

3.4 Summary

In this chapter, we enhanced our understanding of the spatial dynamics that underlie a tumour's growth with the intervention of a single chemotherapeutic drug. The presented model described the evolution of tumour sub-populations both in space and time. Our model shares some important similarity and analysis with that of Jackson and Byrne [48] for one cell type. The model follows the

evolution of tumour sub-populations in spherical geometry. Since the drug resistant tumour sub-population results from genetic point mutations of the sensitive cells, we analysed the model when one type of tumour cell exits. This analysis helped to follow the spatial evolution of the tumour as described by the radial velocity of the tumour at the boundary, $\mathbf{u}(R(t), t)$, shown in equation 3.42. In the following chapter, we shall provide numerical simulations of the model to better understand the model dynamics that could lead to fail or success of the treatment for combating tumour cells.

Chapter 4

Numerical results and discussion

The main goal of a chemotherapy treatment is to reduce the tumour volume to a smallest possible burden at the end of the therapy. Consequently we have already analysed the two ODE models in order to gain insight into the dynamical behaviour of models' response to small perturbations as illustrated by the stability of the models' equilibrium points. In this chapter, we now present the numerical findings for the ODE and PDE models that were developed earlier in Chapters 2 and 3. We solved the ODE model using Matlab's built-in solver, *ode45*. The *ode45* uses a Runge-Kutta method, with a variable time step, to compute a solution of a given differential equation. For the PDE model, we used Matlab's built-in solver, *pdepe*, which converts a PDE to a coupled set of ODEs using a second-order spatial discretization based on a fixed set of specified nodes. For intuitive analysis of the models, the dimensionless variables and parameters have now been re-defined in terms of the similar variables and parameters as in the original models.

4.1 Sensitivity analysis

In order to check for a monotonic dependence of sensitive cells on the baseline parameters, sensitivity analysis was performed on the ODE systems (2.11) – (2.13), and (2.59) – (2.63). Because we have assumed that only sensitive cells can mutate into a resistant sub-population, it is important to investigate the influence of the baseline parameters of the model relationship of on the sub-population of sensitive cells. If many sensitive cells could be eradicated by the chemotherapeutic drug, then there would be few or, possibly, no sensitive cells that might subsequently mutate into a resistant sub-population.

We provide the outcomes of the partial rank correlation coefficient (PRCC) analysis over 500 randomised parameter values, with respect to sensitive cells, using Latin hypercube sampling [71, 72]. We have regarded the external drug influx, V , as a one of the baseline parameters in order to check its contribution to the models monotonicity for tumour sensitive sub-population.

To effectively model drug resistance, we needed to deduce which parameters are in the model are most correlated with the sensitive sub-population. Thus the PRCC results allow us to determine which of the parameters could be most effectively controlled in order to mitigate cancer occurrence. Thus PRCC results are used to identify the key parameters that contribute most significantly to the sensitive cell density. The PRCCs were computed for each of the input baseline parameters and the state variable $S(t)$, representing the population of sensitive cells. Scatter plots for each baseline parameter and the number of sensitive cells were generated and examined for any monotonic dependence of the sensitive cell population on the given parameter.

As explained in Section 1.4, the magnitude of the PRCC illustrates the strength of correlation between the two quantities, while the sign of the PRCC indicates the qualitative relationship. Typically, a significant positive PRCC value implies that if values of one variable (i.e. the parameter under study) increases, then the values on the second parameter (i.e. sensitive sub-population), would also increase correspondingly, given that other parameters are held constant. Similarly, a significant negative PRCC tells us that as the input variable increase, then the outcome variable would correspondingly decrease. The PRCC results for equations (2.11) – (2.13) are given in Table 4.1, and for equations (2.59) – (2.63) in Table 4.2.

Table 4.1: The PRCCs between the input parameters for single drug resistance phenomenon and the output variable (sensitive cells).

Partial Rank Correlation Coefficients					
		Parameter	PRCC	Parameter	PRCC
Results		λ_D	-0.94542	λ_S	0.018136
		μ	0.041334	λ_R	0.060717
		k_S	0.025807	V	0.9152
		k	-0.070753	θ	-0.031957

It can be seen from Table 4.1 that the external drug influx (V) and the natural decay of the drug (λ_D) both have PRCC, in magnitude, close to 1. Thus we conclude that they contribute most significantly

to the density of the sensitive sub-population. This further highlights the role of the chemotherapeutic drug in minimising the survival opportunities of the tumour sensitive cells. Furthermore, we note that the positive value of PRCC for V indicates that an increase in the chemotherapeutic drug influx should result in the number of sensitive cells also increasing. Corresponding reasoning can be applied to the negative value of the PRCC for λ_D indicating that an increase in the drug decay rate would lead to a decrease in the number of sensitive cells.

Since we have many parameters in the model, the indices of the PRCC are also crucial in determining the effect of each individual parameter in metastasis dynamics and prevalence of multi-drug resistance. So similarly, we computed the PRCC for equations (2.59) – (2.63), and obtained the results in Table 4.2.

Table 4.2: PRCC results for the multi-drug resistance phenomenon

Partial Rank Correlation Coefficients				
Results	Parameter	PRCC	Parameter	PRCC
	$\lambda_{R_{12}}$	0.075714	k	-0.023531
	k_{R_2}	-0.025612	k_S	0.076146
	λ_{R_2}	0.072677	θ	-0.047579
	k_{R_1}	0.0089081	λ_S	0.04642
	λ_{R_1}	0.1137	λ_D	-0.94691
	μ	0.00078702	V	0.91861

As before, Table 4.2 illustrates the degree of influence of each parameter on the sensitive sub-population, given that all the influences of other parameters and variables could be completely removed. The results of the PRCC for the model with multi-drug resistance shown in Table 4.2 show that, again, the external drug influx, V , is a parameter that is highly positively correlated with the number of sensitive cells, while the drug decay, λ_D , is highly negatively correlated with the number of sensitive cells. The positive correlation implies that the number of sensitive cells would increase depending on the prevalence of the drug at the tumour site. This further suggests that if the number of sensitive cells increase, then the external drug influx should be increased. However, the increase of drug influx should be within tolerable toxicity constraints. Determination of an optimal drug influx shall constitute our future work on this model.

On the other hand, the negative correlation between drug decay and the number of sensitive cells

implies that when a drug with low decay rate is used, then the number of sensitive cells decreases. If the drug does not decay quickly, many sensitive cells would be killed by the drug elimination from a surrounding tumour tissue can take place due to natural decay [4]. Because chemotherapeutic drug molecules are subject to natural decay before they are taken up by cells [4], it clear that if the drug does not decay fast, then many drug molecules would interact with sensitive cells. These results appear to show that drug decay is an important aspect to consider for chemotherapeutic modelling. In this regard, Feizabadi et al. [24] argued that success of a chemotherapy regimen may be greatly influenced by the decay rate of the drug.

4.2 Solution of model with single drug resistance

In this Section, we investigate the dynamical behaviour of the model (2.4) – (2.6). We assumed that the resistant tumour sub-population is only resistant to one cytotoxic drug. The sensitivity analysis has shown that the external drug influx V , and the molecular drug decay, λ_D , are the most influential parameters in the model. Hence we shall separately investigate the dynamical response of the system to small variations in each of these two parameters.

We have taken the fixed time period of a chemotherapy simulation as $[0, 60]$ days and assumed the following initial conditions for the model: $S(0) = 1 \times 10^{12}$, $R(0) = 0$, $D(0) = 0$, as also used by Monro and Gaffney [11].

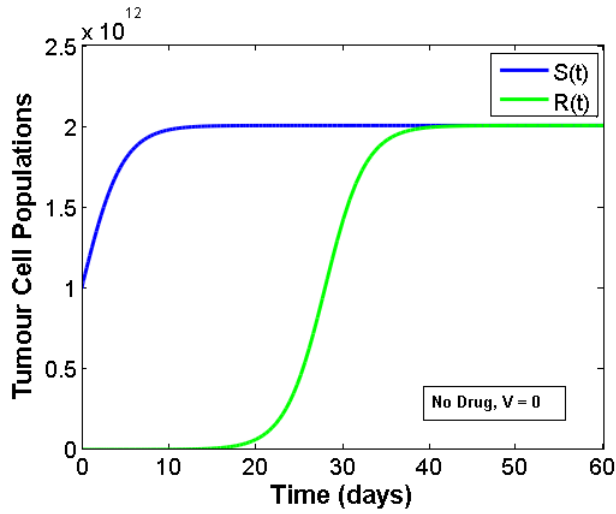
For the model simulations, we have used parameters from various literature sources that deal with the effects of drug resistance, and/or tumour burden reduction. However, there is no consistent plethora of tumour and chemotherapeutic drug interaction data available to choose from. Thus, for some parameters, we have estimated the values (parameter fitting) based on similar parameters from available literature sources. For instance, there is an evidence that resistant cells proliferate slower than sensitive cells [46]. The baseline parameters are given in Table 4.3.

Table 4.3: List of baseline parameter values utilised in the simulations of the model with single drug resistance and their sources.

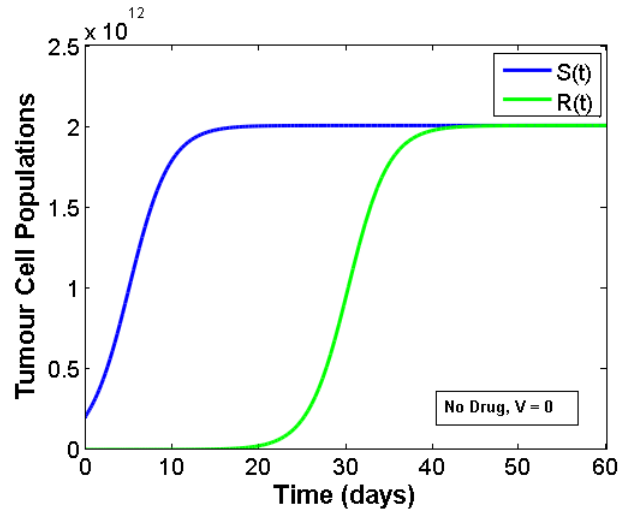
Parameter	Value	Source
λ_D	1.9/day	λ [48]
μ	1×10^{-6} /day	μ [83, 125]
k_S	0.6/day	d_1 [83]
k	1.179 mL/nmol	σ_T [29]
λ_S	4.31×10^{-1} /day	a [20]
λ_R	4.31×10^{-1} /day	Parameter Fitting
V	5.1/day	V [6]
θ	2×10^{12} nmol	N_∞ [11]

4.2.1 Results

We first investigated the tumour growth in the absence of the drug. Two numerical solutions using parameter values in Tables 4.3 but with different initial values for the sensitive cell population are presented in Figures 4.1(a) and 4.1(b). Figure 4.1(a) shows the growth of tumour sub-populations when the initial number of sensitive cells is $S(0) = 1 \times 10^{12}$, while in Figure 4.1(b) the initial number of sensitive cells is $S(0) = 0.2 \times 10^{12}$. In both figures, we note that all graphs reach the same asymptote, which indicates that the respective tumour sub-populations grow to the maximum carrying capacity in the host tissue in the absence of the drug. This suggest that once the tumour has been detected, there is an immediate need for medical treatment. Furthermore, comparing the two figures, it can be seen that if, at the start of the therapy, there are initially more sensitive cells, Figure 4.1(a) the tumour cells would quickly grow to the carrying capacity of the host more rapidly. With both graphs, in both figures, reaching the same asymptote imply that there are now equal number of sensitive and resistant cells.



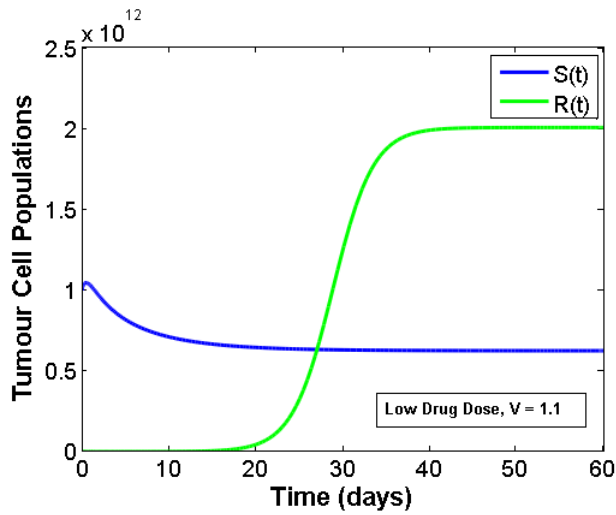
(a) $S(0) = 1 \times 10^{12}$.



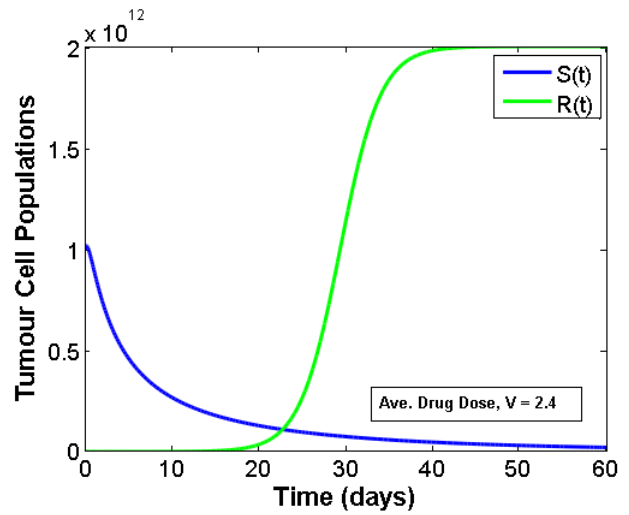
(b) $S(0) = 0.2 \times 10^{12}$.

Figure 4.1: The tumour growth when there is no chemotherapeutic drug.

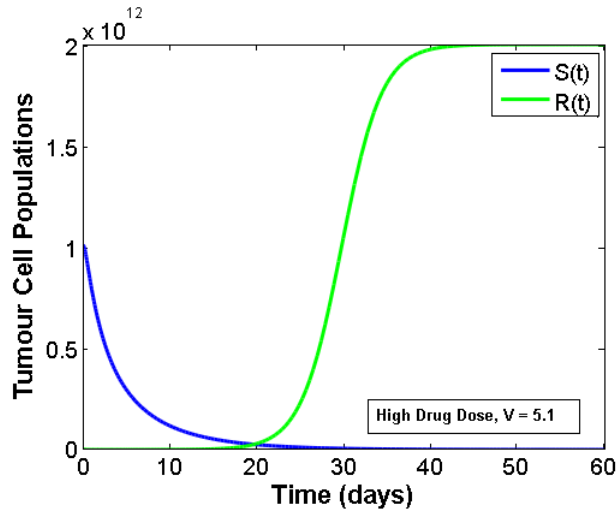
The first step in addressing drug resistance is to kill the drug sensitive cells, so as to give them no chance of mutating into the resistant sub-population. In this regard, the sensitivity analysis (Section 4.1) showed that the amount of the chemotherapeutic drug infused into the tumour can have considerable consequences on the success of the treatment. Thus, we varied the values of V , representing the cytotoxic drug dose. However, to avoid drug toxicity constraints, we have limited the values, while yet still maintaining a sufficient amount of the drug to induce lethal outcomes on the sensitive cells. Consequently, we have adopted the maximum drug dose as $V = 5.1$, as from [6], to obtain the results in Figures 4.2(a) – 4.2(c).



(a)



(b)

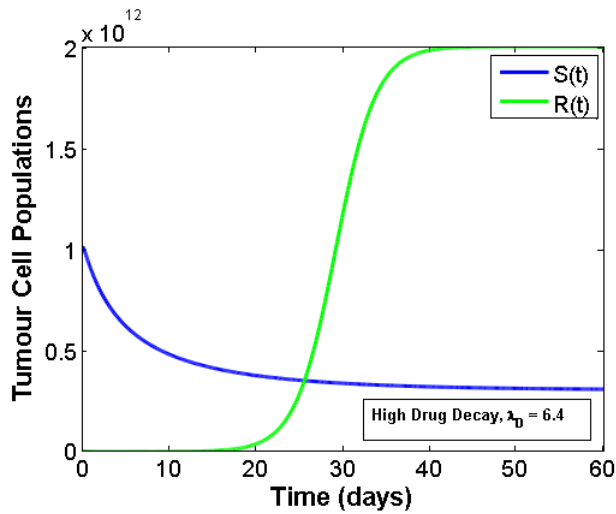


(c)

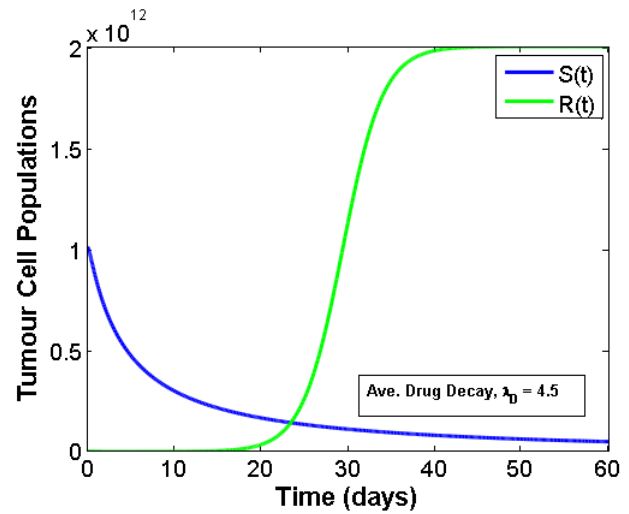
Figure 4.2: The finite continuous chemotherapeutic treatment on the sensitive cells with different drug doses.

The graphs of $S(t)$ in Figure 4.2(a) – 4.2(c) are all asymptotically decreasing. However, in Figure 4.2(a) this non-zero asymptote indicates that with a low chemotherapeutic drug dose ($V = 1.1$), the number of sensitive cells initially drops but then remains at more than half the initial value. This contrasts with the higher dosages represented in figures 4.2(b) and 4.2(c). In these, we note that the drug sensitive population is quickly reduced to an insignificant amount. Similar high dose strategies has been found to be effective against the more drug sensitive cells of the tumour, such as in lymphoma, leukemia and germ cell tumour [9]. In all three graphs it can be seen that the drug resistant cells continued to multiply to a maximum, unaffected by the treatment.

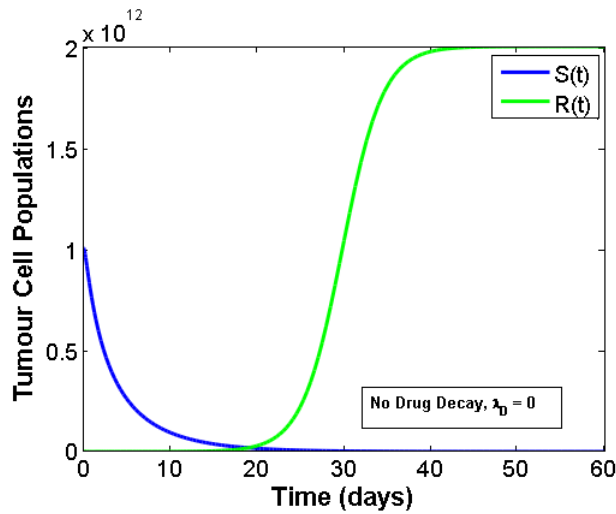
Other insightful results are obtained if we vary the drug decay rate, because if the drug does not decay too quickly, then for longer periods, there should be a reasonable amount of the drug available to kill the tumour. With drug dose now fixed at maximum tolerable content, $V = 5.1$ per day, we obtained the results shown in Figure 4.3(a) – 4.3(c).



(a)



(b)



(c)

Figure 4.3: Simulations tumour growth subject to different drug decay rate.

Figure 4.3(a) – 4.3(c) show reduction of the sensitive cells with different, reducing, drug decay rates. In Figure 4.3(a) fewer sensitive cells are killed, and moreover, their number remains as slightly less than half the initial amount. In Figure 4.3(b), we have a drug with an average decay rate of 4.5 and it can be seen that the graph does take longer time to reach an asymptotic horizontal value ($S(t) = 0$), but this is close to zero. Thus, we conclude that while eradication of sensitive cells takes a longer period of time, there ultimately remain very few sensitive cells. Mathematically, it is possible to have a limiting case of no drug decay as shown in Figure 4.3(c). This is presented for comparison, but in biological situations there is always a natural decay for each drug [24]. Once again it can be seen that the drug resistant cells were unaffected by the treatment.

Our results are in accordance with other published findings. In this regard, Feizabadi et al. [24] obtained results for different decay rates in their model, and argued that success of a chemotherapy regimen may be greatly influenced by the decay rate of the drug. Similar findings suggest that if the drug has a lower decay rate, then opportunities for successful treatment are increased, provided that the drugs effectively penetrate the tumour at lethal concentrations [43,126,127]. Such successful treatments would not allow the sensitive sub-population to accumulate enough mutations to become malignant.

4.3 Summary

In this section, we have provided results of the model with a single drug resistance. In particular, we have identified, through sensitivity analysis (Section 4.1), model parameters that are most influential to the number of sensitive cells. By varying those parameters, we have observed some significant reduction in the number of sensitive cells, which, if not eliminated, may contribute to an increase in the number of the resistant tumour sub-population. However, in all cases, development of resistant sub-population is inevitable. As highlighted in a recent review [111], the cancerous cells that recur after a single treatment may be resistant to multiple drugs. It was therefore important to investigate the dynamics of multi-drug resistance in this model. This is done in Section 4.4 below.

4.4 Solution of the ODE model for a multi-drug resistance

As pointed out in Section 2.5 one of the reasons ascribed to the failure of the chemotherapeutic treatment is the development of the multi-drug resistance phenomenon. In this section, we provide the simulated results for the multi-drug resistance with two chemotherapeutic drugs.

Again, as with the single drug case, some model parameters are not available in the literature, hence, for modelling purposes, we have estimated missing parameters (Parameter fitting) based on the available information pertaining to their properties. The baseline parameters of the model are given in Table 4.4,

Table 4.4: List of baseline parameter values used for simulations using equations (2.51) – (2.55).

Parameter	Value	Source
λ_D	1.9/day	λ [48]
μ	$10^{-1} - 10^{-6}$ /day	μ [83, 125]
k_S	0.6/day	d_1 [83]
k	1.179 mL/nmol	σ_T [29]
λ_S	4.31×10^{-2} /day	Modified a from [20]
λ_{R_1}	3.84×10^{-2} /day	Parameter Fitting
λ_{R_2}	2.81×10^{-2} /day	Parameter Fitting
$\lambda_{R_{12}}$	2.5×10^{-2} /day	Parameter Fitting
V	5.1/day	V [6]
θ	2×10^{12} nmol	N_∞ [11]

4.4.1 Results

Here, we are intrigued by the following question, “does increasing the number of drugs improve the opportunities of chemotherapeutic success?”. This question has been addressed in numerous studies, but there is no unique answer to it. In particular, we note the view of Komarova and Wodarz [54] who argued that success depends on the mutation rate and the death rate of the tumour cells. They emphasized that the higher the mutations acquisition, the lesser the effect of incremental increases in the number of drugs, with more likelihood of the tumour becoming difficult to treat. Using the baseline parameters given in Table 4.4, our results are shown in Figure 4.4.

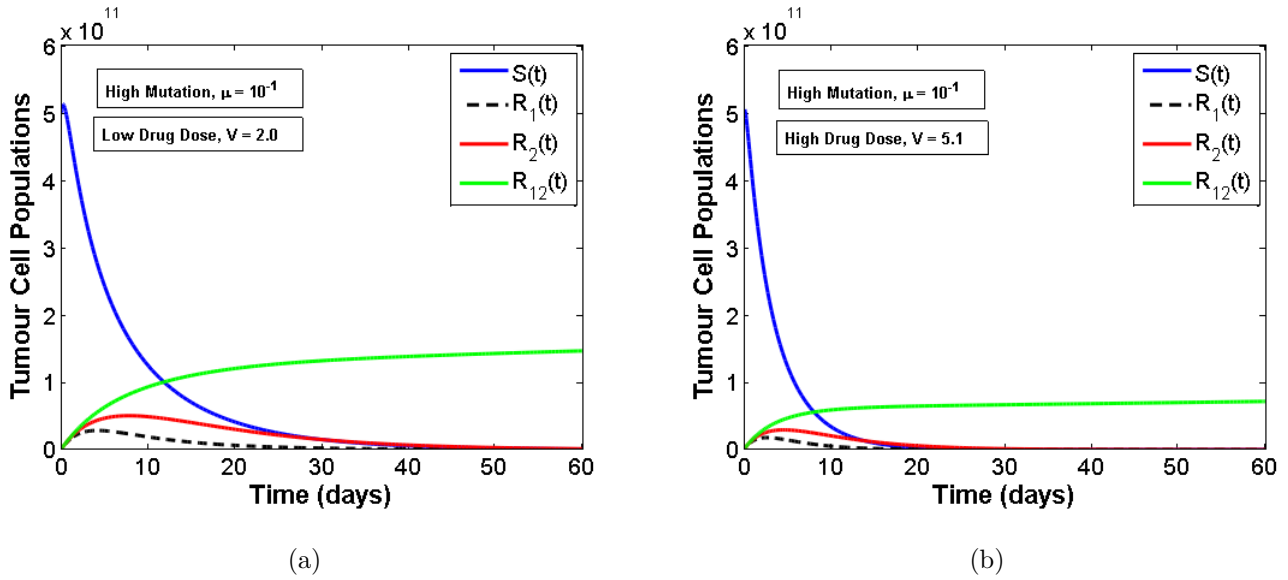


Figure 4.4: The dynamical behaviour of the tumour sub-populations, subject to high mutation rate and different drug doses.

Figures 4.4(a), we note that , with low drug dosage, if there are higher mutation variations in the tumour while the sub-populations represented as S , R_1 and R_2 do reduce by 40 days, the population of multi-drug resistant cells represented as R_{12} continues to increase, similar to the findings in [5, 41, 47, 51, 52, 54, 111, 125, 128]. To determine whether higher dosage would be even more beneficial, we investigated the effects of continuous infusion of high drug dose to the tumour site. The results are illustrated in Figures 4.4(b). When comparing Figures 4.4(a) and 4.4(b), we note that with a higher dose, the populations of sensitive cells are significantly decreased in less than 10 days while in Figure 4.4(a) takes more than 10 days to decrease to zero. Thus in comparing the results for low dosage in Figures 4.4(a) with high dosages in Figure 4.4(b), when we have high mutation rates, it appears that higher drug doses, within toxicity constraints, are more beneficial than lower drug doses in order to minimise the occurrence of non-cross resistant cells (i.e. cells that are not multi-drug resistant). Therefore, this partially explains some apparently contradictory findings in the literature. To be specific, in some studies low continuous drug dose has been identified as the most effective treatment dosing strategy for chemotherapy [54,129]. On the other hand, some studies, have suggested that higher concentrated drug doses are more beneficial [42,130]. However, our results show substantial advantages of high continuous drug dosing strategy in preventing the development of drug resistance, subject to high mutation rates, and partially inhibiting an increase in resistance in multidrug-resistant tumour sub-population.

These results highlight an important prediction by Goldie and Coldman [5] which links the success of a therapy to the number of cellular mutations. As described in [5], this relation is given by the following equation:

$$P(\alpha) = e^{-\alpha(N-1)}, \quad \text{where } N(t) = S(t) + R(t), \quad (4.1)$$

and α is the varying mutation rate, and $N(t)$ is the tumour density with drug sensitive, $S(t)$, and resistant, $R(t)$, sub-populations. As the number of mutations increases, the probability of having zero resistant sub-population declines. This result is shown in Figure 4.5.

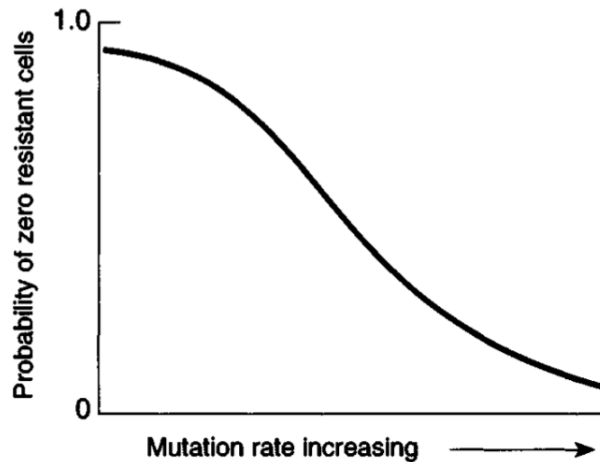


Figure 4.5: The probability of zero resistant cells as mutations increase [5].

Figure 4.5 shows the effect of mutation rate on the probability of attaining zero resistant tumour sub-population. The probability of zero resistant cells, is implicitly captured by our model as illustrated in Figure 4.4(a) and Figure 4.4(b), which both show a persistent increment in the cross resistant sub-population, R_{12} , despite multi-drug treatment.

As with the single drug resistance case, before investigating the effect of a multi-drug regimen, we establish a comparative baseline of following the evolution of the tumour sub-populations when there is no treatment given. We use the baseline parameters in Table 4.4 for the simulations. The results are given in Figure 4.6.

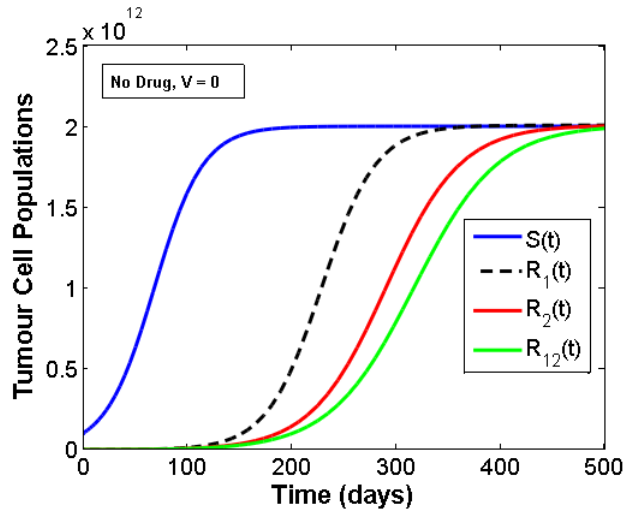


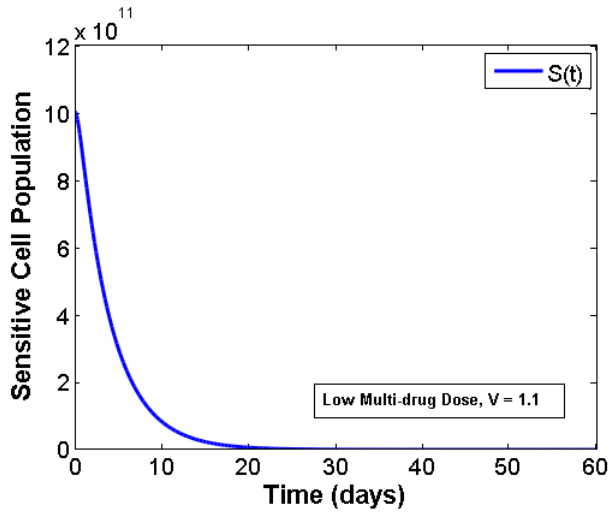
Figure 4.6: Relative growth of tumour sub-populations in the absence of the treatment, $t \in [0, 500]$ and $S(0) = 0.1 \times 10^{12}$.

Figure 4.6, it can be seen that the growth of all tumour sub-populations in the absence of a chemotherapeutic drug approach the maximum carrying capacity, $\theta = 2 \times 10^{12}$, and the population of sensitive cells quickly proliferates up to the maximum carrying capacity of the tumour.

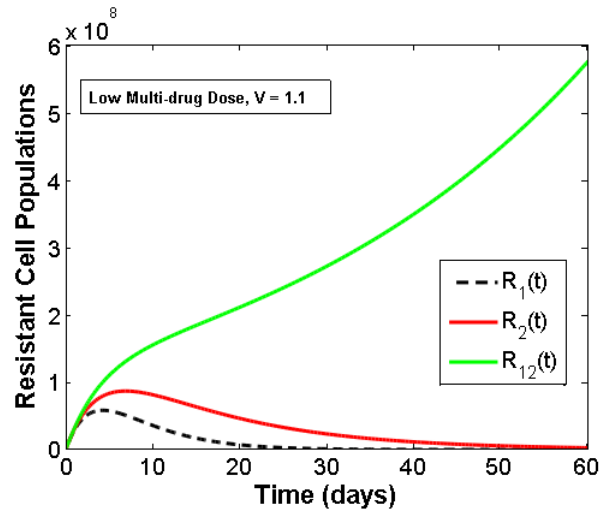
In order to gain insight into the dynamics of multi-drug resistance, we next investigated the effect of three different chemotherapeutic drug doses on the cell sub-populations. The results are shown in Figure 4.7(a) – (f)

From the graphs in Figure 4.7 it can be seen that with any dose, the graphs of S , R_1 and R_2 all follow similar patterns to S and R in the single drug resistant model. By this we mean that with a low dosage (a), the population of sensitive cells decreases, but not as quickly as in high dosage, (e). With higher dosages, $S(t)$ appears to drop to zero between 12 days (c) and 10 days (e). This indicates that a high infusion of the combination of chemotherapeutic drugs, V , might be a valuable strategy to eradicate the sensitive sub-population. And under any dosage, R_1 and R_2 , initially increase and then drop off to zero.

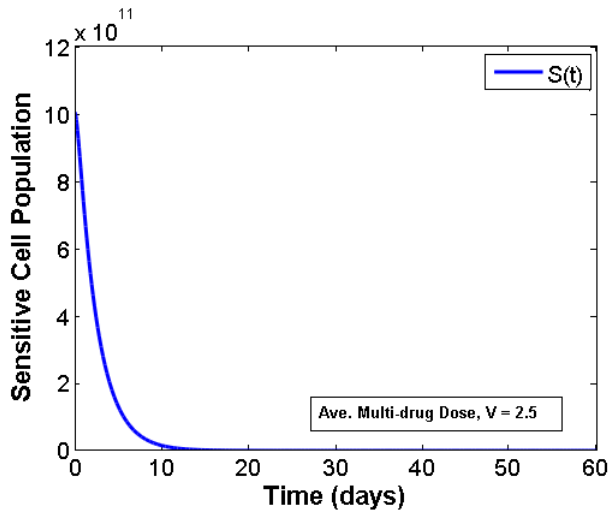
Nevertheless, the multi-drug resistant cells, shown by R_{12} , maintain the tumour's proliferation, up to the maximum carrying capacity of the tumour cell, under any dosage, although the higher the dosage, the less rapidly it increases. For the tumour this means that higher drug doses yield more efficacious outcomes. With the drug dose within the toxicity constraints, then the majority of both sensitive and non-cross drug resistant sub-populations are greatly reduced, but the cross resistant population remains a threat.



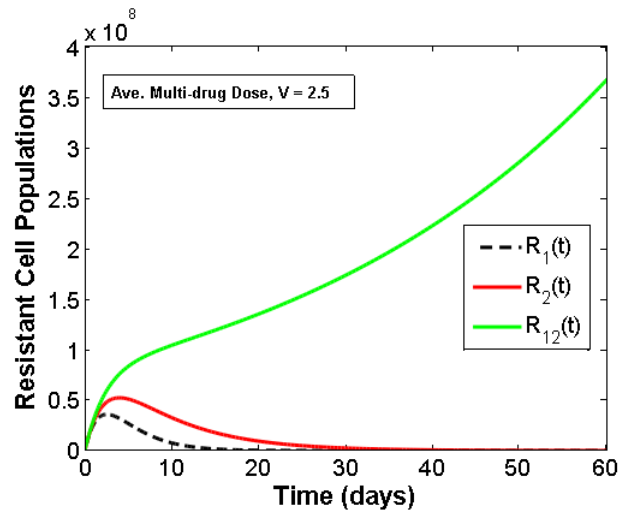
(a)



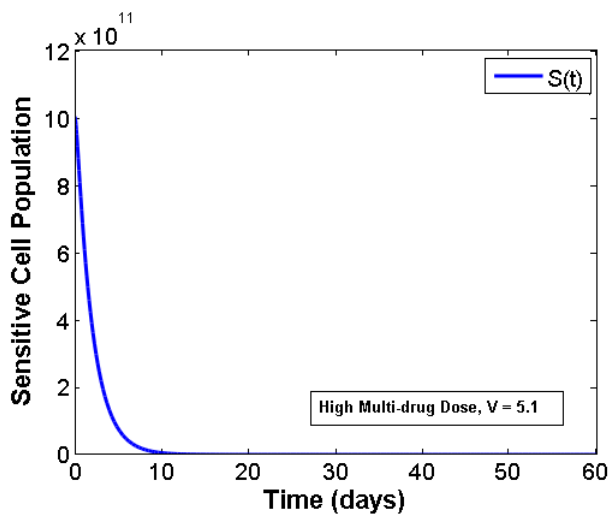
(b)



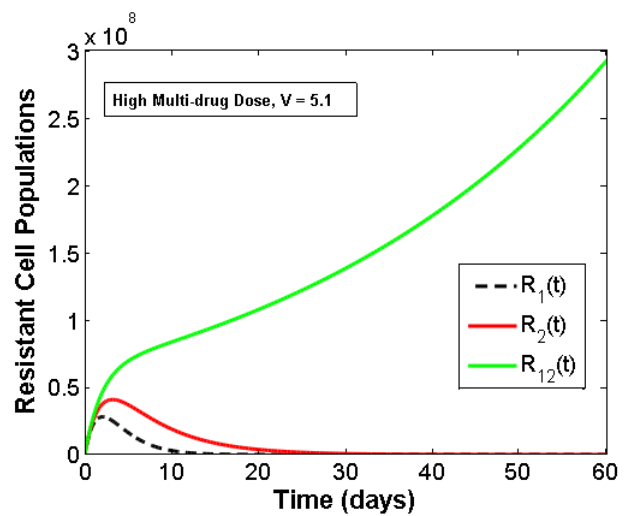
(c)



(d)



(e)



(f)

Figure 4.7: The response of the tumour sub-populations to various drug doses in multi-drug resistance case.

In all the figures for the resistant sub-populations in Figure 4.7, the curve for the multi-drug resistant sub-population, as indicated by R_{12} , keeps increasing to the maximum carrying capacity of the tumour. This highlights the fact that multi-drug resistant sub-population is, generally, not easy to control. That is why multi-drug resistance has always be ascribed as a major source of failure in many chemotherapeutic treatments [2].

4.5 Solution of the PDE model without the interstitial convection

In this section we provide the numerical solution of equations (3.20) – (3.22). These equations represent an interaction of the tumour cells with a single chemotherapeutic drug. The diffusive flux is a major modal transport by which the chemotherapeutic drug could reach the tumour. Hence, without loss of generality, interstitial convection could be regarded as zero. The model reduces to

$$\frac{\partial D}{\partial t} = \frac{d_D}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial D}{\partial r} \right) + \Gamma(D_b(t) - D) - \lambda_D D - u_S k_S (1 - e^{-kD}) S, \quad (4.2)$$

$$\frac{\partial S}{\partial t} = \frac{d_S}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial S}{\partial r} \right) + \lambda_S S \left(1 - \frac{S}{\theta} \right) - k_S (1 - e^{-kD}) S - \mu S, \quad (4.3)$$

$$\frac{\partial R}{\partial t} = \frac{d_R}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial R}{\partial r} \right) + \lambda_R R \left(1 - \frac{R}{\theta} \right) + \mu S. \quad (4.4)$$

First, in order to gain some insights into the mechanical behaviour of the model, we considered different initial conditions. The solutions presented in this section were found using a finite difference based PDE solver in Matlab, *pdepe*. We solved equations (4.2) – (4.4) with initial conditions (3.11), and boundary conditions (3.13) and (3.14). For the model simulations, we used the initial conditions $D_b(0) = 1.179$, $S(r, 0) = 4 \times 10^3$, $R(r, 0) = 0$, $D(r, 0) = 0$ to investigate the effects of the growing tumour subject to diffusion of the chemotherapeutic drug from the surrounding vasculature.

The parameter values used in the simulations are given in Table 4.5. We obtained some parameter values from Jackson’s models [48] and other literature relevant sources, as shown in the table. Because there is no consistent data for any type of cancer [10], we had to use some parameters that relate to a variety of cancer types. The baseline parameters and the initial conditions are varied in order to investigate the tumour’s behaviour with respect to different mutations.

Table 4.5: List of baseline parameter values utilised for simulations in the PDE model and their sources.

Parameter	Value	Source
d_D	1.7 cm ² /day	D [48]
d_S	0.0867 cm ² /day	Parameter Fitting
d_R	0.0845 cm ² /day	Parameter Fitting
λ_D	1.9/day	λ [48]
μ	1×10^{-3} /day	μ [125]
Γ	16/day	Γ [48]
u_S	0.021/day	Parameter Fitting
k_S	42.8/day	k_T [29]
k	1.179 mL/nmol	σ_T [29]
λ_S	0.18/day	a [97]
λ_R	0.15/day	Parameter Fitting
θ	2×10^6 /nmol	M [131]

4.5.1 Results

We begin by evaluating the model response to different initial numbers of sensitive tumour cells, because we assumed that the resistant sub-population evolves from the mitosis of the sensitive cells. This consideration is vital in those instances where the acquired drug resistance might be dependent on the size of the tumour. In this regard, the initial tumour size plays an important role predicting the equilibrium state from the start of the therapy [132]. When medical treatment is given to a cancer patient, the tumour cells could be driven to either no tumour equilibrium or large tumour equilibrium [132]. The latter state is usually held responsible for failure of many chemotherapies due to the evolution of drug resistance.

If we have no drug present, and initially only sensitive cells, we then investigate the effect of tumor size using $S(0) = 5 \times 10^{11}$ in Figure 4.8.

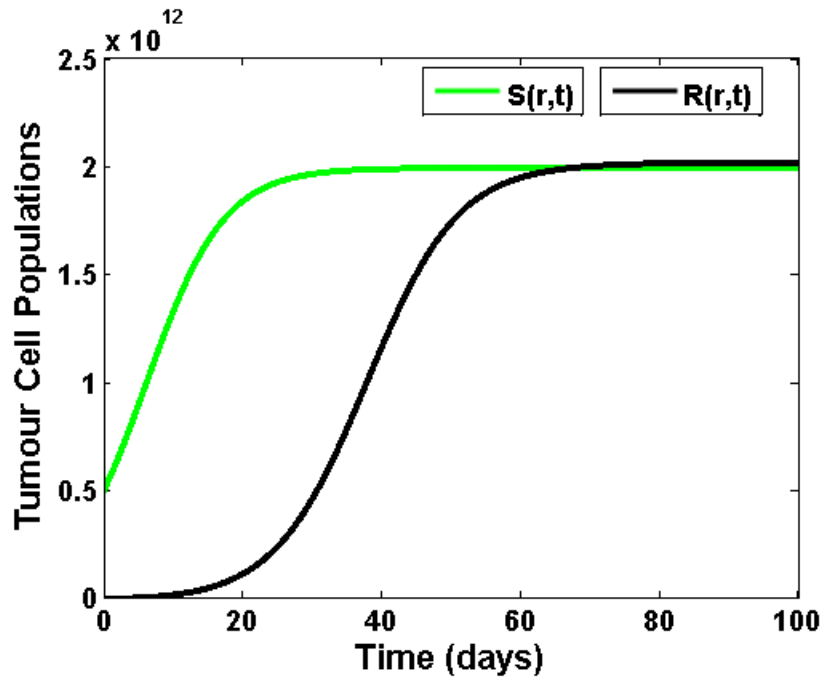


Figure 4.8: The comparison of the tumour sub-populations growth without drug.

As with the ODE model, equations (2.4) – (2.6), Figure 4.8 show that if there is no drug at the tumour site, and an initial tumour size is large, then the tumour sub-populations would rapidly proliferate to the maximum carrying capacity of the host tissue. This further indicates that larger tumours are more difficult to treat by chemotherapy or radiotherapy [133], and usually, the tumour would grow to a dangerous level if left untreated. However, if the initial numbers of sensitive tumour cells is small, $S(0) = 4 \times 10^3$, we obtain results in Figure 4.9.

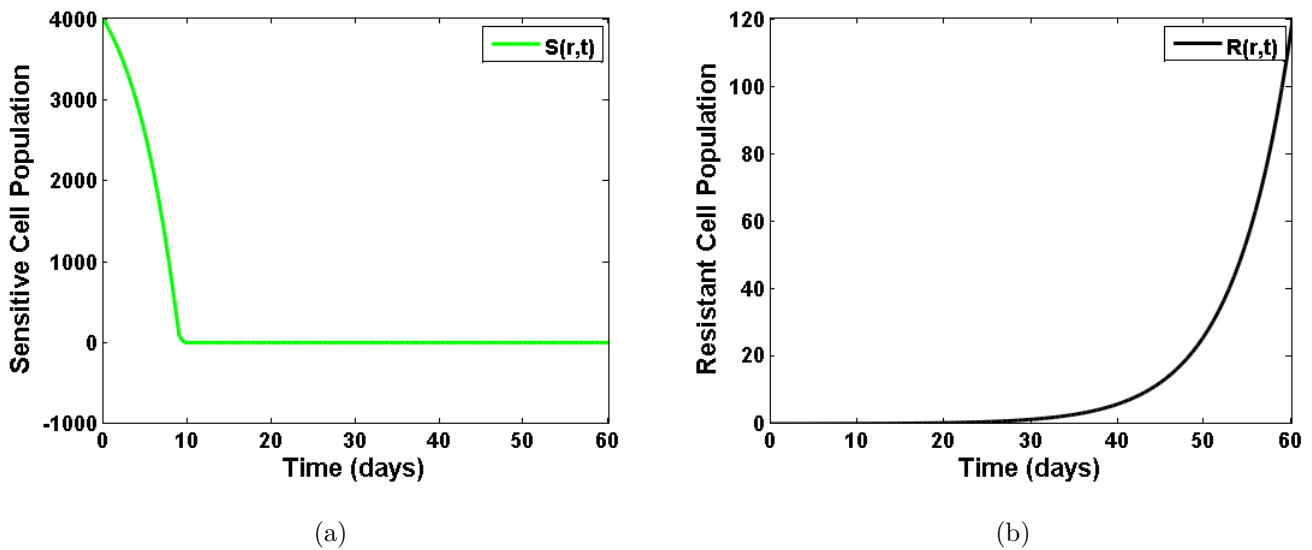


Figure 4.9: Tumour sub-populations with small initial size, $S_0 = 4 \times 10^3$.

Figure 4.9 gives a comparison of tumour growth for the two sub-populations when the initial number of sensitive cells is small. As shown in Figure 4.9(a), if the initial number of sensitive cells is small, then the tumour could be eradicated before the evolution of the drug resistant sub-population. This is shown in Figure 4.9(a) whereby the sensitive cells are eradicated on 10th day, while the evolution of the resistant tumour sub-population occurs on the 25th day as shown in Figure 4.9(b). From these results we note that treatment of small tumours may help to circumvent a problem of drug resistance because sensitive cells could be eradicated before the evolution of the resistant sub-population. However, small tumours may not be easily identified until they have reached a certain detectable size [20].

It was necessary to further explore an optimal time to eradicate a tumour with small initial number of sensitive cells at the start of therapy, $S_0 = 4 \times 10^3$, and we obtained the results shown in Figure 4.10.

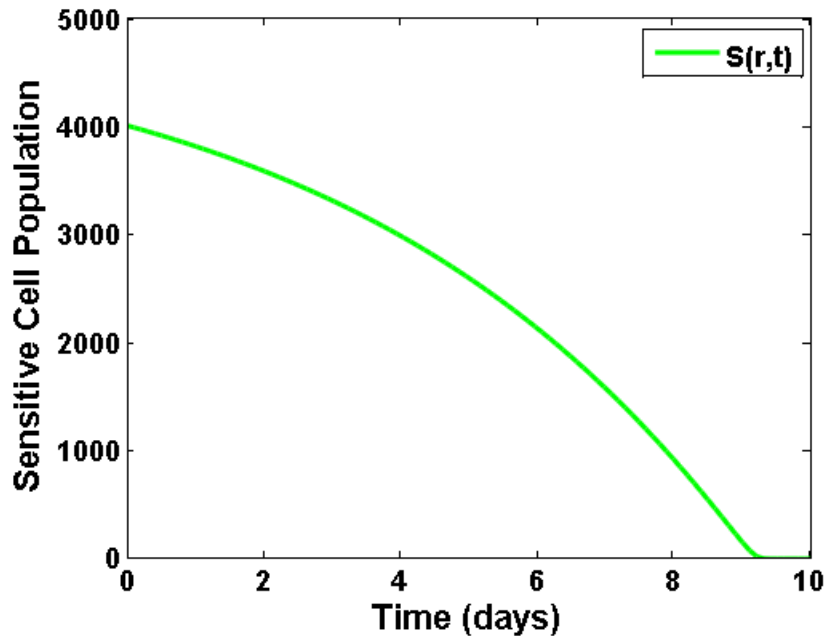


Figure 4.10: Simulation of the smallest time for the eradication of a tumour with small number of sensitive cells.

Figure 4.10 indicates that, under our model assumptions, the tumour’s eradication with a chemotherapeutic drug is plausibly within 9 days. This further shows that continuous infusion of chemotherapeutic drug is better strategy to reduce a tumour burden [134].

It is of particular interest to determine the dynamics of the tumour’s response to the chemotherapeutic drug. To achieve this, we have numerically solved the model with and without the drug and using $S_0 = 5 \times 10^3$, $\theta = 2 \times 10^{12}$ and $\mu = 1 \times 10^{-6}$ as recommended in [11]. We obtained the results shown in Figure 4.11.

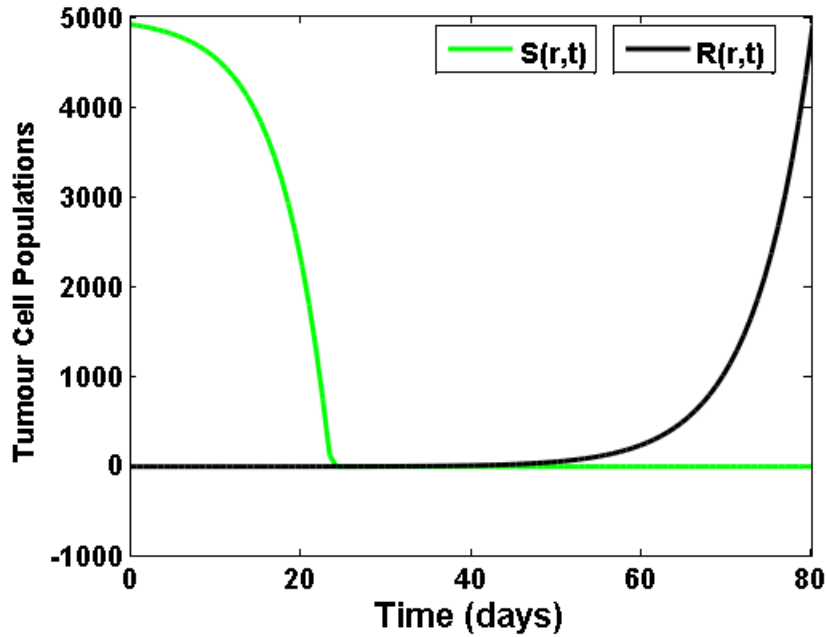


Figure 4.11: The solution of the model with a chemotherapeutic drug.

Figure 4.11 shows the tumour growth profile with interventions by chemotherapeutic drug. Compared to Figure 4.8, it can be seen that with no drug present there is the inevitable growth in cancer cells. However in Figure 4.11, as with many cytotoxic drug models, the simulations show that for certain initial and boundary conditions, eradication of the sensitive cells is possible. However, the evolution and growth of the resistant sub-population remain inevitable. Although further studies must be conducted, our results to date indicate that continuous infusion of a chemotherapeutic drug could be useful to eliminate the drug sensitive cells, while diminishing the opportunities for the development of drug resistance. This outcome is important for our model because we assumed that the resistant tumour sub-population arise from genetic mutations of sensitive cells. Thus, the benefits of this treatment strategy could help to combat drug resistance by giving sensitive cells no chance of quickly mutating into drug resistant sub-population.

4.6 Summary

Mathematical modelling and computer simulations are tools that provide a robust framework for better understanding of cancer progression and response to treatment. In this chapter, we solved numerically both the ODE and PDE models. Through sensitivity analysis of the ODE models, parameters that contribute most significantly to the tumour's response to therapy were identified as

external drug influx and drug decay. Numerical simulations obtained in this study demonstrate the qualitative effect of various initial conditions and boundary conditions of tumour sub-populations. Specifically we have shown that for the tumour with high genetic point mutations, high dosage of a chemotherapeutic drug could be used to eradicate sensitive cells, thereby minimising the development of resistant sub-population. For cases where diffusion of anti-cancer drugs into or out of the tumour is a major mode of transport, continuous infusion of the drug might help to eliminate drug sensitive sub-population. Because the development of drug resistance is a major impediment of chemotherapy success, the results presented in this study support the clinical implementation of a continuous infusion of a chemotherapeutic drug, within toxicity constraints, to prevent the development of drug resistance in tumours. The mathematical models developed in this study provide a significant level of new understanding of these interactions. Nevertheless, the complex interactions between a tumour and the anti-cancer agents are still poorly understood from biological and mathematical points of view. In particular, we need greater insight into how to prevent the resistant sub-population from proliferating.

Chapter 5

Conclusions

In this dissertation, we sought to understand and model local interactions between tumour cells and anti-cancer agents, while including the evolution of drug resistance. We further sought to enhance our understanding of the effect of different interventions on the tumour cell sub-populations through qualitative and numerical analysis. We formulated and analysed two mathematical models that take into account the effects of drug resistance in cancer. The numerical simulations showed that a combination of two drugs that are functionally and structurally different may succeed in eliminating the drug-sensitive and non-cross resistant cells. However, we found that multi drug resistant cells continued to proliferate.

In Chapter 2, we developed two new ODE models that describe the local interaction of the tumour cells and anti-cancer agent(s). These models comprise two tumour sub-populations, namely the drug sensitive cells, $S(t)$, and the resistant cells, $R(t)$. We considered two situations, specifically where there was resistance to one drug or two drug. The mechanisms underlying multi-drug resistance are both biologically and mathematically complex, but we were able to determine the stationary states of these systems and analysed their stability. In both models, non-trivial equilibrium states were found and the conditions that confer stability were determined. Biologically, these states and stability conditions indicated that conditions under which the tumour could be harmful or not if not eradicated from the body. In particular, a stable steady-state solution imply that the tumour can remain inside a host tissue of a patient for a long time without causing much evasion on the surrounding tissues [135]. On the other hand, an unstable tumour is likely to metastasise to other tissues [135]. These findings were different from those already published, in that they do not only give a qualitative understanding of a tumour progression and metastasis, but they also give a valuable

information on the conditions under which the tumour could confer resistance to chemotherapeutic drug(s). However, under certain conditions, the ODE models have certain limitations because they do not include the spatial dynamics of tumour cells. Normally, tumour sub-populations compete for space and resources necessary for their growth and metastasis [55]. We incorporate this feature into our partial differential equation (PDE) model in Chapter 3.

In Chapter 3, we presented a mathematical model that includes spatial dynamics of the tumour and chemotherapeutic agents. This is a convection-reaction-diffusion model type with spherical geometry. We distinguished between the sensitive, $S(r, t)$, and resistant, $R(r, t)$, sub-populations. Analytical solutions of the chemotherapeutic drug concentration and the local velocity of the tumour boundary were found. These solutions showed that when tumour consisted of one cell, sensitive cell, the temporal expansion of the tumour can be followed by tracking a radial change of the tumour boundary. This was achieved by introducing a local velocity, $\mathbf{u}(r, t)$, which described a cellular motion generated by the balance between tumour cell proliferation and death. An drug resistant sub-population might arise from mutations of the drug sensitive sub-population via mutations [41,130]. Thus, the derivation of these solutions served as a key step in comprehending the moving boundary conditions usually associated with the tumour surface, as well as the roles played by mutations in the evolution of the drug resistant sub-population. We have shown how the underlying assumptions influence model analytical solution feasibility. For example, assuming a lower chemotherapeutic drug concentration and one cell type lead to simplification (via Maclaurin series expansion) of an exponential term, which described the tumour's interaction with the chemotherapeutic drug, to a linear term which helped to attain analytical solutions for the drug and radial velocity of the tumour boundary. These findings are similar to those obtained by Jackson and Byrne [48]. Numerical solutions of this model further show the possibility of eradicating sensitive cells when diffusion of chemotherapeutic drug is a major mode of fluids transport into or out of the tumour. However, the success of the therapy depends on a low initial number of sensitive cells. Consequently, through the model, we have shown that early detection of the tumour is important aspect for the efficacious elimination of the tumour, which is in accordance with findings by [5,47].

In Chapter 4, sensitivity analysis was used to show that the model was most sensitive to the model parameters. Specifically, when the drug decay rate was high, there was an increase in the number of sensitive cell population, and when the external drug influx was increased, there was a corresponding drop in the number of sensitive cell population. From these observations we concluded that in order to

efficaciously eliminate the drug sensitive sub-population, it is important to use a chemotherapeutic drug with a low decay rate, while continuously infusing a drug influx within admissible toxicity constraints. These results are in accordance to other published findings such as [55, 129, 130, 134]. The numerical solutions for the models showed that it is possible to eradicate the sensitive sub-population, which, if not removed, could mutate into drug resistant sub-populations. The results indicate that for the first ODE model with a single drug, complete remission is not feasible, but the sensitive sub-population is significantly reduced. The reduction of the sensitive sub-population is slow, thus giving sensitive cell population an opportunity to mutate into a resistant sub-population. The model was extended to a two drug case where we further considered the effects of genetic point mutations that confer multi-drug resistance. Mutations have been shown in many studies [5, 41, 47, 51, 52, 105, 117, 125, 136] that they contribute significantly to the evolution of drug resistance. This model showed a significant reduction in the sensitive sub-population. Nevertheless, the persistent growth of the multi-drug resistant sub-population was unavoidable. Under high genetic point mutations, our results showed that continuous infusion of the chemotherapeutic drug, within toxicity constraints, is recommended to reduce the sensitive cell population. Furthermore, our results showed that there would still be a significant reduction on the number of the tumour sensitive sub-population when the chemotherapeutic drug with low decay rate was used.

The models presented in this study show how mathematical models may be used to reveal complex spatial and dynamical interactions between tumours and chemotherapeutic drugs. The interaction of between tumour cells and chemotherapeutic drugs, subject to drug resistance, has been done in many studies [5, 9, 42, 47, 48, 55, 58, 59, 102, 126]. The preliminary results here expand current knowledge of mathematical approaches to modelling drug resistance. The results provide a solid foundation of two compartmental modelling of tumour sub-populations for extending the model to more sophisticated representation of the biological processes and the chemotherapeutic drug interactions.

The models presented here have significant shortcomings that need to be addressed in order to make the models suitable for clinical validation. Firstly, the empirically determined parameters, for example the growth of resistant cells, λ_R for the first ODE model, and λ_{R_1} , λ_{R_2} and $\lambda_{R_{12}}$ for the second ODE models, need to be sourced from clinical data for the model results to be realistic. Thus, we have identified a need for more clinical or empirical research in this regard. The second limitation is that these models only include a tumour in a pre-metastatic state. As discussed in Chapter 1, when subgroups of cancer cells leave the primary tumour and travel to other distant site in the body

and begin to invade a new distant tissue and therein form a new tumour mass, they are said to have metastasised. Metastasis has been reported as the most frequent cause of cancer death [12–16]. Therefore, because early spread of tumour cells is usually not detected [137], it is important to prohibit the development of tumour cells prior to metastatic process with the chemotherapeutic drugs once the tumour is detected. In this regard, these models could possibly be extended to include the interaction of the tumour and the drug at the secondary site (that is, after the tumour has metastasised to a new site). This would, however, present a considerable mathematical challenge because, for instance, such an extension would mean that our first ODE model would consist of six coupled differential equations that have to be solved simultaneously. Moreover, chemotherapy can kill tumour cells only at certain stages in the cell cycle, so other tumour cells would be unaffected.

An exciting extension to our work could be to model chemotherapy and immunotherapy concomitantly. Alternatively, it is worth noting that there already exist a number of mathematical models that combine chemotherapy with immunotherapy [20, 26–28, 30–32]. Combining immunotherapy with anti-cancer drugs has the advantage of combating cancerous cells that elude an assault of chemotherapeutic drugs, and hence result in faster elimination of tumour cell sub-populations. A sophisticated model of this type was presented in [20] in which the immune system consists of three sub-populations, namely tumour antigen activated cells, natural killer cells and the circulating lymphocytes (white blood cells). This model has a great advantage of having already been validated with both mice and human data.

Our approach would be different from that in [20] and would seek to model the tumour’s interaction with the drugs, with evolving drug resistance to chemotherapy, but with the enhancement of the immunotherapy.

Appendix: Glossary of biological terms used in this dissertation

Apoptosis	programmed cell death.
Detoxification	the removal of toxic agents in a living organism.
Differentiation	In developmental biology, differentiation is the term used to denote the cells developmental capacity to perform a specific function by change of phenotype. However, in surgical pathology, differentiation, apart from being used as a classification of whether the tumour is benign or malignant, is used to grade the degree of tumours capacity in relation to invasiveness and mortality.
Lymphoma	a range of cancers that are associated with the lymphatic system, connecting network of nodes, organs, and vessels whose primary cell is the lymphocyte.
Malignant	A malignant tumour is the one that is capable of invading the neighbouring tissues and spreading to other body parts.
In vitro test	A medical trial, experiment or procedure that is usually carried outside the body of an animal or a patient.
In vivo test	A medical trial that is carried inside the body of an animal or a patient.
Metastasize	A tumour is said to have metastasized if it has spread to other distant body parts from the primary tumour site and has begun to form a new tumour there.
Mitosis	the process of molecular cell division.
Phenotype	the set of observable attributes or characteristics of an individual resulting from mutations in genes when they interact with a surrounding environment.

Angiogenesis	is the formation of new blood vessels from pre-existing blood vessels in the body. The newly formed blood vessels does not only supply oxygen and nutrients to cancerous cells, but they also provide an opportunity for tumour cells to get into blood vessels and spread to other parts of the body.
Proliferate	To reproduce/divide/increase in number.

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