Analysis of an Age-Structured Model of Chemotherapy-Induced Neutropenia

by

Lee Safranek

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Name: Lee Safranek

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Examining Committee:

Chair: Dr. Tom Archibald, Professor
Department of Mathematics

Dr. Nilima Nigam
Senior Supervisor
Professor
Department of Mathematics

Dr. Razvan Fetecau
Co-Supervisor
Associate Professor
Department of Mathematics

Dr. Weiran Sun
Internal Examiner
Assistant Professor
Department of Mathematics

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ABSTRACT

Neutropenia is a blood disorder characterized by low levels of neutrophils and is a common side effect of chemotherapy. Administration of granulocyte-colony stimulating factor (G-CSF) is a typical treatment that helps stabilize the level of neutrophils. However, it is not known if changes to the frequency and dosage of administered G-CSF will lead to better treatment. We analyze a nonlinear hyperbolic system of coupled integro-differential equations aimed at quantifying the effect of treatment plans on patients with chemotherapy-induced neutropenia. We show how this age-structured model can be decoupled for short time. We then investigate the equivalence of an integral equation with a related nonlinear PDE and prove existence and uniqueness of solutions of the integral equation. This is used to finally demonstrate existence and uniqueness of solutions to the full PDE system.

Keywords: neutropenia; hyperbolic partial differential equations; age-structure models

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Chapter 1

Introduction and Motivation

This thesis is concerned with the well-posedness of a mathematical model of a particular blood disorder. We focus on some theoretical results of this model, which consists of a system of nonlinear hyperbolic integro-differential equations. This model was developed by C. Foley [5] to describe various cell populations in an individual with chemotherapy-induced neutropenia. Each dependent variable in the system represents a density of some cell type. The coupling between components of the system, along with the nonlocal nature of the partial differential equation (PDE), renders establishing existence and uniqueness of solutions challenging. These challenges are typical of age-structured population models.

We start this chapter by investigating a much simpler population model. Let us first examine a single population whose total population at time t is given by $P(t)$. Velhurst in [16] used the following model to describe the growth of the population $P(t)$:

$$\frac{dP}{dt} = rP\left(1 - \frac{P}{K}\right), \quad P(0) = P_0.$$

Here K is the so-called *carrying capacity* and r is related to the growth rate of the population. This model assumes all individuals are identical and that the rate of growth of the population is related to the total population as well as to the amount of available resources. We can solve the ODE exactly:

$$P(t) = \frac{KP_0e^{rt}}{K + P_0\left(e^{rt} - 1\right)}, \quad \text{for } t \geq 0.$$

We see that in the limit as $t \to \infty$ we have

$$\lim_{t\to\infty} P(t) = K.$$

It is clear now why K is called the carrying capacity: for any starting value of $P(t)$ we see that the population will tend toward the steady state K. This is the stable size of the population.

Unfortunately, the model assumption that all individuals are identical is too strong for our

context. We will be examining populations of cells whose death rate and ability to reproduce is dependent on their level of maturation. A model which takes into account the influence of maturation is said to have age-structure.

1.1 Age-Structured Populations

Let us examine a population divided into n classes and follow their dynamics at discrete points in time, $0, \Delta t, 2\Delta t, \ldots$. Let $u_i(t)$ denote the amount of individuals of class i at time t. The population of individuals in all classes at time t can be represented as the vector

$$\vec{u} = (u_1(t), u_2(t), \ldots, u_n(t))^T .$$

Between every two states we define a probability, p_{ij}, of an individual changing from some state j to state i. Similarly let b_{ij} denote the amount of offspring of state i from state j. Generally p_{ij}, b_{ij} can be time dependent. See Figure 1.1 for an illustration of the notation. Letting $P = (p_{ij})$ and $B = (b_{ij})$ we can write the following update formula for $\vec{u}$:

$$\vec{u}(t + \Delta t) = (P + B)\vec{u}.$$

The *Leslie matrix model* has particularly simple forms for P and B:

$$\vec{u}(t+\Delta t) = \begin{bmatrix} 0 & 0 & \cdots & 0 & 0 \\ p_{21} & 0 & \cdots & 0 & 0 \\ 0 & p_{32} & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & p_{n,n-1} & 0 \end{bmatrix} \vec{u} + \begin{bmatrix} b_{11} & b_{12} & \cdots & b_{1,n-1} & b_{1,n} \\ 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 0 & 0 \end{bmatrix} \vec{u}.$$

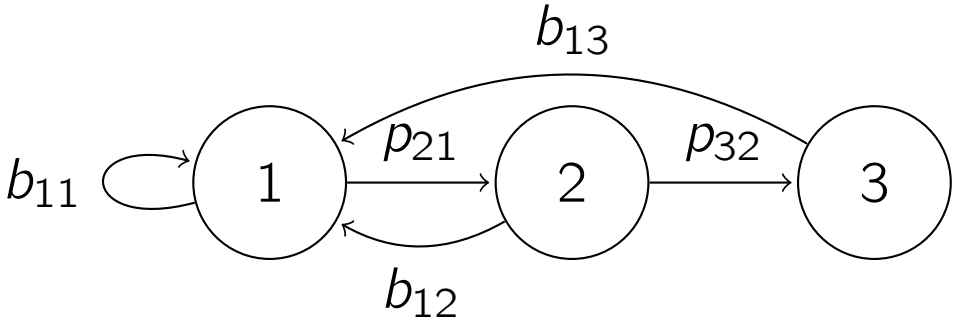

Figure 1.1: Simple state diagram for a population of 3 states demonstrating notation.

In this model individuals in each state produce offspring of state 1 and only transition to

'older' states. The long term behavior of this model can be investigate by looking at the spectral properties of the matrix $(P + B)$. If we examine the number of individuals that do not survive transitioning to state $j + 1$ from j per unit time, Δt, we see that:

$$\begin{aligned}\frac{u_j(t) - u_{j+1}(t + \Delta t)}{\Delta t} &= \frac{u_j(t) - p_{j+1,j}u_j(t)}{\Delta t}, \\ &= \frac{1 - p_{j+1,j}}{\Delta t}u_j(t).\end{aligned}$$

Recall that $p_{j+1,j}$ is the probability that an individual survives transitioning from state j to $j+1$, the quantity $1 - p_{j+1,j}$ is the probability that an individual does not survive this process. It is not difficult to see that we can arrive at a continuum model by taking appropriate limits. This limiting process can be seen in Chapter 2 of the text [3].

Some of the earliest and most referenced work on continuum age-structured models can be seen in [6] where population models of the following form were studied:

$$\frac{\partial \rho}{\partial t} + \frac{\partial \rho}{\partial a} + \lambda(a, P(t))\rho(t, a) = 0, \qquad (t, a) \in \mathbb{R}^+ \times \mathbb{R}^+, \tag{1.1a}$$

$$\rho(t, 0) = \int_0^\infty \beta(a, P(t))\rho(t, a)\, da, \qquad t > 0, \tag{1.1b}$$

$$\rho(0, a) = \rho_0(a), \qquad 0 \leq a \leq \infty, \tag{1.1c}$$

$$P(t) = \int_0^\infty \rho(t, a)\, da, \qquad t \geq 0. \tag{1.1d}$$

This integro-PDE, referred to in this thesis as the *Gurtin-MacCamy model*, is defined for $(t, a) \in \mathbb{R}^+ \times \mathbb{R}^+$ where a represents an individual's age and t represents time. The unknown function $\rho(t, a)$, which we will refer to as the population density, represents the number of individuals of age a at time t. The total population, $P(t)$, takes the form of an integral of the density $\rho(t, a)$ with respect to age. It is reasonable to assume that the number of individuals in a population that die and reproduce are dependent on the amount of resources available, which will depend in turn on the total population. We see that the total population, $P(t)$ appears in Equation (1.1a) and Equation (1.1b) as arguments for the functions $\lambda(a, P)$ and $\beta(a, P)$ respectively. The term $\lambda(a, P(t))$ is referred to as the *death modulus*. Similarly, $\beta(a, P(t))$ is called the *birth modulus*.

Equation (1.1b) is called the renewal equation. The number of offspring of age zero is assumed to be well modeled by a weighted average, with weights given by the birth modulus of the population density $\rho(t, a)$. We note that this boundary condition for $\rho(t, 0)$ is unusual as it is not known a priori. It is unclear whether such a boundary condition makes sense in a mathematical context, and we investigate this issue for a specific system.

The existence of solutions to Equations (1.1) is established in [6] by the use of a fixed point argument on a related integral formulation of the problem. Defining $B(t) := \rho(t, 0)$,

the integral formulation in [6] is given by the following coupled integral equations

$$\begin{aligned} P(t) &= \int_0^t K(t-a,t;P)B(a)\ da + \int_0^\infty L(a,t;P)\rho_0(a)\ da \\ B(t) &= \int_0^t \beta(t-a,P(t))K(t-a,t;P)B(a)\ da \\ &\quad + \int_0^\infty \beta(a+t,P(t))L(a,t;P)\rho_0(a)\ da \end{aligned}$$

where K and L are smooth kernels related to the death modulus of (1.1).

In this thesis we will provide a similar treatment of a mathematical model of chemotherapy-induced neutropenia. However, our model does not fall into the form of Equations (1.1).

Many generalizations of the Gurtin-MacCamy model have been proposed, see [4][8][13][14].

In [8], models of the following form are studied:

$$\frac{\partial \rho}{\partial t} + \frac{\partial}{\partial a}(V(t,a)\rho) = G(\rho(t,\cdot))(a), \qquad a \in [0,l), 0 \le t \le T, \tag{1.2a}$$

$$V(t,0)\rho(t,0) = C(t) + F(\rho(t,\cdot)), \qquad 0 \le t \le T, \tag{1.2b}$$

$$\rho(0,a) = \rho_0(a), \qquad a \in [0,l). \tag{1.2c}$$

By $G(\rho(t,\cdot)(a)$ we mean that for a fixed a and t, G is a functional over the variable suppressed by $(\cdot)$. If we let:

$$F(\rho(t,\cdot)) = \int_0^l \beta(a,P)\rho(t,a)\ da, \quad G(\rho(t,\cdot))(a) = -\lambda(a,P(t))\rho(t,a), \quad V(t,a) \equiv 1,$$

with $P(t) = \int_0^l \rho(t,a)da$, we arrive at the Gurtin-MacCamy model (1.1) for populations with finite age l. Compared to the Gurtin-MacCamy model, (1.2) allows more general forms of the death and birth terms as well as allowing for variable maturation rates.

The population model given by (1.2) is for a single population in the domain $[0,l) \times [a,T]$ and has a forcing term $C(t)$ in the renewal equation (1.2b). Solutions of (1.2) are shown to exist in [8] for short time under suitable assumptions on the functions F, G, V and C.

Another generalization of the Gurtin-MacCamy model can be seen in [14]. A time lag between conception and birth is allowed, denoted as $\tau \ge 0$, which gives the following form for the renewal equation:

$$\rho(t,0) = \int_0^l \beta(a,P(t-\tau),t-\tau)\rho(t-\tau,a)\ da. \tag{1.3}$$

Here the populations are assumed to have a finite age l and the birth modulus is a function of the total population τ units of time in the past. An integral formulation of the population model

is derived in [14], though the time lag, τ, introduces challenges. Again, existence of solutions to the time lag model is proved using a fixed point argument. Of particular interest is the existence of periodic solutions, as they represent a limiting behavior of a population. Whether models with a renewal equation of the form (1.3) admit periodic solutions is investigated and answered by Swick in [15].

Another form of time delay in the renewal condition is explored in [4] where averages over past information are used. The renewal equation is as follows:

$$\rho(t,0) = \int_0^\infty \int_{-r}^0 \beta(a, P(t+s))\rho(t+s,a)\, dsda, \qquad t > 0, \tag{1.4a}$$

$$\rho(s,a) = \phi(s,a), \qquad s \in [-r, 0] \geq 0, \tag{1.4b}$$

We see that instead of simply integrating over age as in (1.1), we have an additional integral which takes into account the past total population up to r units of time. This same model is put into a semigroup framework in [12], similar to the treatment in Chapter 2 of the text [17]. This renewal equation is generalized for multiple populations . A model for multiple populations with delays similar to (1.4a) is explored in [13]. Once again, existence of solutions to this system is proved through a fixed point argument on a related integral operator.

As these models are aimed to quantify the behavior of populations, numerical methods to compute solutions are of interest. Various numerical methods have been developed to compute solutions of age-structure models. An upwinding scheme in [9] is shown to be stable and convergent under suitable assumptions on the data. Both discontinuous and continuous finite element methods have been employed in [10] and [11] respectively on an age-structured model. In summary, many generalizations of the Gurtin-MacCamy model have been studied. The common strategy for showing existence of solutions to these models is to formulate an integral operator related to the original PDE. These integral operators are then shown to admit a fixed point, under suitable assumptions, which are related to solutions of the PDE. We will employ similar techniques to an age-structured model, which does not fall into the above categories of models, aimed at quantifying treatment of chemotherapy-induced neutropenia.

1.2 Background: Neutropenia

White blood cells are vital to the immune system. Neutrophils are the most common type of white blood cell in the innate immune system, sometimes referred to as the first line of defence. Cyclical neutropenia is a hematological disease that prevents neutrophils from maintaining a constant cell count. The oscillatory behavior seen in individuals with the disease prevents the immune response from functioning properly. This disease, although rare, is the subject of a large amount of research.

Altering the rate of cell death of the neutrophils, as achieved with treatments of granulocyte colony stimulating factor (G-CSF), is one method of attempting to stabilize the neutrophil count. Effective usage of G-CSF requires treatment some time after the neutrophil count starts to decline. The period between injections of G-CSF should be chosen to minimize oscillations and consequently stabilize the neutrophil count.

The aim of the mathematical model of chemotherapy-induced neutropenia developed by [5] is to predict the influence of G-CSF treatment on the relevant cell populations. The model consists of five cell compartments each governed by a PDE. The cell compartments are as follows: resting stem cells, proliferative stem cells, proliferative precursor cells, non-proliferative precursor cells, and neutrophils. We discuss this model in detail in the following chapter, and examine its well-posedness in subsequent chapters.

1.3 Goals

The main focus of this thesis is to establish existence and uniqueness of solutions to an age-structured model developed by C. Foley in [5]. There is also some investigation of steady states of the model. Chapters 3 and 4 are novel contributions.

This thesis is arrange as follows.

- Chapter 2 - Overview of chemotherapy-induced neutropenia and the important biological processes involved in the PDE model. Steady states of system are investigated.
- Chapter 3 - An analytical look at the PDE model. A method for decoupling the system for short time is derived. This is a novel contribution.
- Chapter 4 - The existence and uniqueness of solutions to the full PDE model for global time is established. This is a novel contribution.
- Chapter 5 - A summary of the work in this thesis, possible future work.

Chapter 2

Mathematical Model

In this chapter, we investigate a mathematical model of chemotherapy-induced neutropenia. We begin by introducing the biological factors of the production of neutrophils that are important to capture in the modeling process. We then introduce a model, developed in [5], that captures the dynamics of the neutrophils and G-CSF concentration seen in patients with chemotherapy-induced neutropenia. We then end the chapter by examining steady states of the PDE system.

2.1 Biology of Neutropenia

The number of neutrophils, the most common type of white blood cell, can reach dangerously low levels when patients undergo chemotherapy. The pathological state of low levels of neutrophil counts is referred to as neutropenia. Granulocyte-colony stimulating factor (G-CSF) is produced naturally in the body and stimulates the production of neutrophils in bone marrow. For this reason, G-CSF is a common treatment for chemotherapy-induced neutropenia and cyclical neutropenia (CN). Periodic subcutaneous (under the skin) injections of G-CSF have been shown to help stabilize levels of neutrophils in individuals with CN. However, these injections can be very expensive ($\$45,000$ a year for a $70kg$ adult given daily injections [5]). Changing the dosage and period between injections might lead to better, cheaper treatment plans. For patients who undergo chemotherapy, two forms of G-CSF are used for treatment: filgrastim (daily doses) and pegfilgrastim (one time dosage per chemotherapy cycle).The desire for better treatment is a leading motivator for quantifying the effect of G-CSF on the population of neutrophils.

The production of blood cells, called hematopoiesis, takes place in the bone marrow. Stem cells in the bone marrow can differentiate (change cell types) into many types of cells, including neutrophils. We are mainly interested in how the concentration of G-CSF affects the following processes: differentiation of *hematopoietic stem cells* (HSCs) into neutrophils

as well as the creation of HSCs through proliferation and replication. HSCs that have begun the differentiation process and have yet to become a mature neutrophils are called *neutrophil precursors*. These cells mature and divide at a rate dependent on the G-CSF concentration. The time the neutrophil precursors take to become mature neutrophils is called the *transit time*. The HSCs that do not differentiate into neutrophils enter the proliferative cycle and either die or produce two daughter HSCs.

2.2 Mathematical Model

The mathematical model developed by C. Foley in [5] tracks the population of five different types of cells. In addition to the total population of these cells, we are interested in their age distribution. The independent variables in this model are time and age, denoted as t and a respectively. The types of cells in the model are the following:

- Proliferative stem cells, denoted $m(t, a)$,
- Resting stem cells, denoted $s(t, a)$,
- Proliferative precursor cells, denoted $p(t, a)$,
- Non-proliferative precursor cells, denoted $n(t, a)$,
- White blood cells, denoted $w(t, a)$.

Note that the neutrophil precursor cells are split into two kinds: *proliferative precursor cells*, $p(t, a)$, and *non-proliferative precursor cells*, $n(t, a)$. The total populations of all five types of cells can be represented as integrals over age. We denote the total populations of the five different cells as follows:

$$M(t) = \int_0^{\tau_s} m(t, a)\, da,\ S(t) = \int_0^{\infty} s(t, a)\, da,\ P(t) = \int_0^{\tau_p} p(t, a)\, da,$$

$$N(t) = \int_0^{\tau_n} n(t, a)\, da,\ W(t) = \int_0^{\infty} w(t, a)\, da.$$

Note that the integrals have different limits of integration depending on the type of cell. Cell types m, p, n have a finite terminal age (τ_s, τ_p, and τ_n respectively) while cells of types s, w can be of any age. The amount of circulating G-CSF is denoted as $G(t)$.

The model assumptions given by [5] can be summarized by the following:

- Apoptosis (cell death) takes place in every type of cell, except the resting stem cells ($s(t, a)$), and is affected by the amount of circulating G-CSF. For cell compartments

$i = m, p, n$ the apoptosis rate has the form:

$$\gamma_i(G(t)) = \left(\gamma_i^{min} - \gamma_i^{max}\right) \frac{G(t)}{8} + \gamma_i^{max}.$$

This is a decreasing linear function of the argument $G(t)$. The higher the G-CSF concentration, the lower the apoptosis rates. The apoptosis rate of the neutrophils, γ_w is assumed to be constant.

- Cell maturation is assumed to be constant in all cell types except the non-proliferative precursor cells, $n(t, a)$, where the maturation rate is assumed to have the form:

$$V_n(G(t)) = (V_{max} - 1)\frac{G(t)}{G(t) + b_v} + 1.$$

The maturation rate of the non-proliferative precursors becomes larger as the G-CSF concentration increases. This insures that the transit time decreases as G-CSF increases. This function is bounded between 1 and V_{max}. The parameter $b_v > 0$ determines how quickly the function $V_n(G(t))$ saturates to the fastest maturity rate, V_{max}.

- Resting stem cells can reenter proliferation at a rate of $\beta(S)$ or differentiate into proliferative precursor cells at a rate of $\delta(W)$. These functions are assumed to be Hill functions of the following forms:

$$\beta(S) = k_0 \frac{\theta_2^2}{\theta_2^2 + S^2}, \quad \text{and} \quad \delta(W) = f_0 \frac{\theta_1}{\theta_1 + W}.$$

Note that $\beta(S)$ is a decreasing function of S. More resting stem cells, $s(t, a)$, enter the proliferation cycle if their number is low. The function $\beta(S)$ is bounded above by k_0 which means k_0 is the highest rate at which resting stem cells reenter proliferation. Similarly, for $\delta(W)$, the rate that HSCs enter the neutrophil line increase when the neutrophil count is low and is bounded above by f_0.

- Proliferative stem cells, $m(t, a)$, exiting the proliferation phase, $m(t, \tau_s)$, split into two daughter cells and become resting stem cells, $s(t, 0)$.

- The number of cell divisions between the proliferative precursor compartment and the non-proliferative precursor compartment is assumed to have the form:

$$A(G(t)) = (A_{max} - A_{min})\frac{G(t)}{G(t) + b_A} + A_{min}.$$

Here $A(G(t))$ is an increasing function of G-CSF. Higher amounts of circulating G-CSF increases the number of cell divisions in the neutrophil line.

The PDE governing these cells and their interactions is the following age-structured population model

$$\frac{\partial m}{\partial t} + \frac{\partial m}{\partial a} = -\gamma_s(G(t))m, \quad t > 0, a \in [0, \tau_s], \tag{2.1a}$$

$$\frac{\partial s}{\partial t} + \frac{\partial s}{\partial a} = -\delta(W)s - \beta(S)s, \quad t > 0, a \in [0, \infty), \tag{2.1b}$$

$$\frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} = -\gamma_p(G(t))p, \quad t > 0, a \in [0, \tau_p], \tag{2.1c}$$

$$\frac{\partial n}{\partial t} + V_n(G(t))\frac{\partial n}{\partial a} = -\gamma_n(G(t))n, \quad t > 0, a \in [0, \tau_n], \tag{2.1d}$$

$$\frac{\partial w}{\partial t} + \frac{\partial w}{\partial a} = -\gamma_w w, \quad t > 0, a \in [0, \infty). \tag{2.1e}$$

with initial and boundary conditions of the form

$$m(0,a) = \phi_m(a), \qquad m(t,0) = \beta(S(t))S(t), \qquad t > 0, a \in [0, \tau_s], \tag{2.2a}$$

$$s(0,a) = \phi_s(a), \qquad s(t,0) = 2m(t,\tau_s), \qquad t > 0, a \in [0, \infty), \tag{2.2b}$$

$$p(0,a) = \phi_p(a), \qquad p(t,0) = \delta(W(t))S(t), \qquad t > 0, a \in [0, \tau_p], \tag{2.2c}$$

$$n(0,a) = \phi_n(a), \qquad n(t,0) = A(G(t))p(t,\tau_p), \qquad t > 0, a \in [0, \tau_n], \tag{2.2d}$$

$$w(0,a) = \phi_w(a), \qquad w(t,0) = n(t,\tau_n), \qquad t > 0, a \in [0, \infty). \tag{2.2e}$$

The boundary conditions in the second column of (2.2) are called the *renewal equations*. The right hand sides of the renewal equations in (2.2) contain terms which are initially unknown, e.g. $m(t,\tau_s)$, $p(t,\tau_p)$, $n(t,\tau_n)$. For an illustration of the renewal equations and the coupling of the system see Figure 2.2.

2.3 Granulocyte Colony Stimulating Factor (G-CSF)

We have yet to describe what governs the level of circulating G-CSF in the blood stream. Injections of G-CSF are modeled by an input function $I(t)$ for $t \in [t_a, t_b]$. The dosage of injection is given by $\int_{t_a}^{t_b} I(t)\ dt$. We aim to keep track of concentration of G-CSF in the tissue as well as the circulating concentration. The concentration of G-CSF in the tissue is denoted $X(t)$ and measured in units of $\mu g/kg$ (body weight) while the circulating G-CSF in the blood is denoted $G(t)$ and measured in units $\mu g/mL$. These two quantities are coupled by the following system:

$$\frac{dX}{dt} = I(t) + k_T V_B G - k_B X, \tag{2.3}$$
$$\frac{dG}{dt} = G_{prod} + \frac{k_B X}{V_B} - k_T G - (\gamma_G + \sigma W F(G))\, G. \tag{2.4}$$

The subcutaneous injection of G-CSF, $I(t)$, enters the tissue and is absorbed into the bloodstream at a rate k_B. Similarly, the G-CSF in the blood, $G(t)$, is absorbed back into the tissue at a rate k_T. Since $X(t)$ is measured in $\mu g/kg$ (body weight) and $G(t)$ is measured in $\mu g/mL$ the exchange between compartments needs to be scaled by a volume, denoted V_B. G_{prod} represents the G-CSF naturally produced in the body. The clearance rate of circulating G-CSF is given by $\gamma_G + \sigma W F(G)$. The clearance of G-CSF in the blood stream is modeled to incorporate two factors: degradation of G-CSF by the kidneys at a rate γ_G, and binding of G-CSF to free receptors on neutrophils. An illustration of the coupling between the levels of G-CSF in the tissue and blood can be seen in Figure 2.1.

Note that the right hand side of (2.4) depends on the number of neutrophils, $W(t)$. The parameter σ and the function $F(G)$ are assumed to be nonnegative; thus the term $-\sigma W F(G)$ is always nonpositive.

The terms $-\sigma W F(G) G$ and $-\gamma_G G$ (from (2.4)) both cause exponential decay in the amount of circulating G-CSF. This term will not change the overall dynamics of the G-CSF concentration as it will only further stabilize $G(t)$. In this thesis, we will assume $G(t)$ is given, continuous, and uncoupled from $W(t)$.

2.4 Equilibrium Age Distributions

It is of interest to know the possible steady states of the PDE system (2.1), if any. In this section, assuming parameter values from Foley [5], we show the existence of two possible steady states. One of these is the trivial case where all cell compartments are empty. Showing the existence of a unique nontrivial steady state is a relatively straightforward calculation. Some details are omitted from the algebra for the sake of readability.

In the steady state, all parameters and cell compartments will be independent of time. We use the notation $\tilde{s}(a)$ to denote the cell density $s(t, a)$ in steady state, i.e., $\tilde{s} = \lim_{t\to\infty} s(t, a)$. Similarly, let $\tilde{m}$, $\tilde{p}$, $\tilde{n}$, and $\tilde{w}$ denote the steady states of their respective cell densities. Furthermore, we denote $\tilde{G} = \lim_{t\to\infty} G(t)$, $\tilde{A} = A(\tilde{G})$, $\tilde{V}_n = V_n(\tilde{G})$, and $\tilde{\gamma}_i = \gamma_i(\tilde{G})$ for $i = m, p, n, w$. In the steady state, the total populations of the resting stem cells and the neutrophils ($S(t)$ and $W(t)$) will be constant and denoted $\tilde{S}$ and $\tilde{W}$ respectively. In steady state the PDE

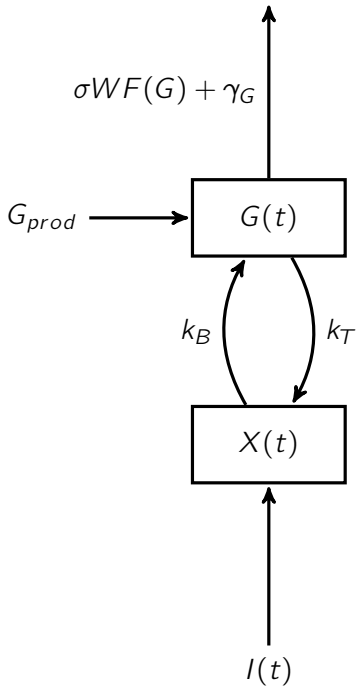

Figure 2.1: Schematic of model of Granucolyte-colony stimulating factor (G-CSF). $G(t)$ denotes the amount of circulating G-CSF. $X(t)$ denotes the amount of G-CSF in the tissue.

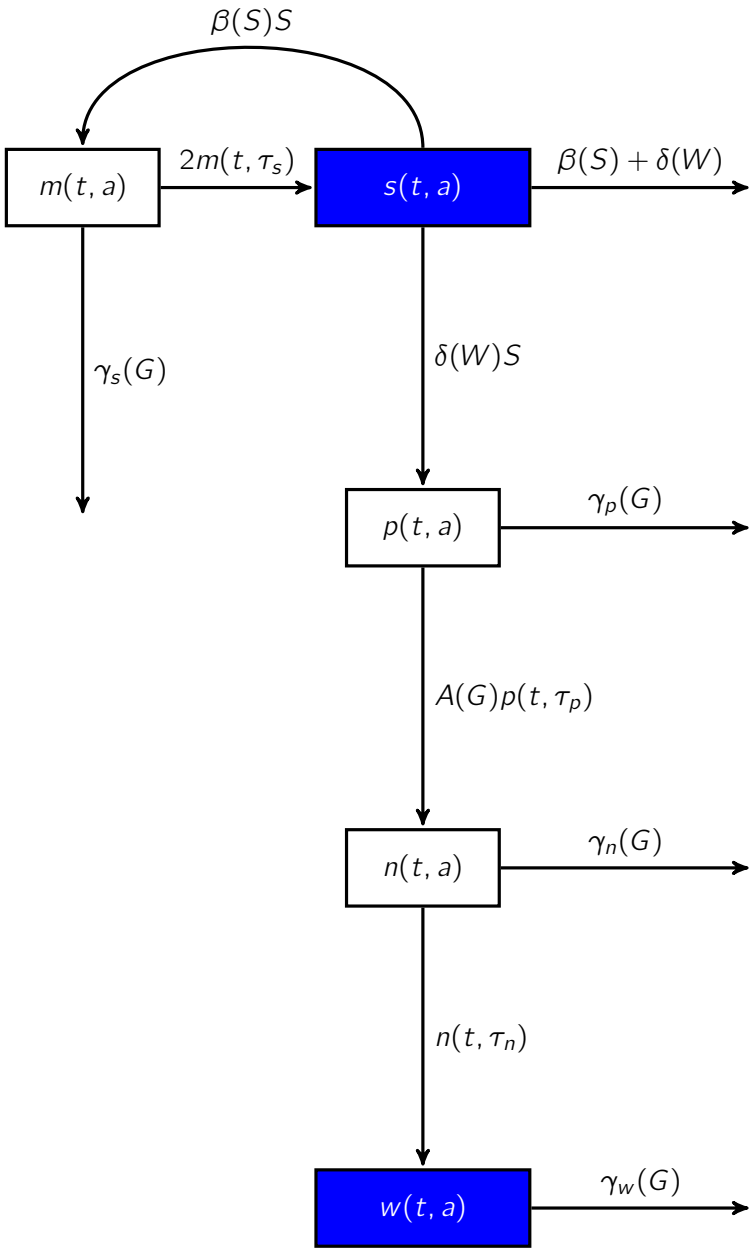

Figure 2.2: Diagram of cell compartments with renewal equations.The γ_i represent the apoptosis rates of the respective cells. Arrows between compartments represent the renewal equations given by the system (2.1). The white compartments, m, p, n, represent cells with a terminal age. Arrows between compartments represent the renewal equations given by the system.

system (2.1) reduces to the following:

$$\partial_a \tilde{m} = -\tilde{\gamma}_s \tilde{m}, \qquad \tilde{m}(0) = \beta(\tilde{S})\tilde{S} \tag{2.5}$$

$$\partial_a \tilde{s} = -\left(\beta(\tilde{S}) + \delta(\tilde{W})\right)\tilde{s}, \qquad \tilde{s}(0) = 2\tilde{m}(\tau_s) \tag{2.6}$$

$$\partial_a \tilde{p} = -\tilde{\gamma}_p \tilde{p}, \qquad \tilde{p}(0) = \delta(\tilde{W})\tilde{S} \tag{2.7}$$

$$\partial_a \tilde{n} = -\frac{\tilde{\gamma}_n}{\tilde{V}_n}\tilde{n}, \qquad \tilde{n}(0) = \tilde{A}\tilde{p}(\tau_p) \tag{2.8}$$

$$\partial_a \tilde{w} = -\tilde{\gamma}_w \tilde{w}, \qquad \tilde{w}(0) = \tilde{n}(\tau_n). \tag{2.9}$$

Solving the above ODEs and applying the Cauchy conditions give the following forms of solutions:

$$\tilde{m}(a) = \beta(\tilde{S})\tilde{S}e^{-\tilde{\gamma}_s a}, \tag{2.10a}$$

$$\tilde{s}(a) = 2\beta(\tilde{S})\tilde{S}e^{-\tilde{\gamma}_s \tau_s}e^{-\left(\beta(\tilde{S})+\delta(\tilde{W})\right)a}, \tag{2.10b}$$

$$\tilde{p}(a) = \delta(\tilde{W})\tilde{S}e^{-\tilde{\gamma}_p a}, \tag{2.10c}$$

$$\tilde{n}(a) = \tilde{A}\delta(\tilde{W})\tilde{S}e^{-\tilde{\gamma}_p \tau_p}e^{-\frac{\tilde{\gamma}_n}{\tilde{V}_n}a}, \tag{2.10d}$$

$$\tilde{w}(a) = \tilde{A}\delta(\tilde{W})\tilde{S}e^{-\tilde{\gamma}_p \tau_p}e^{-\frac{\tilde{\gamma}_n}{\tilde{V}_n}\tau_n}e^{-\tilde{\gamma}_w a}. \tag{2.10e}$$

Note that these solutions are not explicit since the total population of resting stem cells $\tilde{S}$ appears on the right hand side for the solution of $\tilde{s}(a)$. It is also worth noting that the amount of cells leaving finite age cell compartments is proportional to the amount of cells entering the compartment. We define π_s as the proportion of cells that become resting stem cells after reentering proliferation. This ratio can be expressed as:

$$\pi_s := 2e^{-\tilde{\gamma}_s \tau_s}.$$

Similarly we define π_w to be the proportion of cells that differentiate from the population of stem cells and survive to become a neutrophil. This quantity has the expression:

$$\pi_w := \tilde{A}e^{-\tilde{\gamma}_p \tau_p - \frac{\tilde{\gamma}_n}{\tilde{V}_n}\tau_n}.$$

The equations for $\tilde{s}(a)$ and $\tilde{w}(a)$ become:

$$\tilde{s}(a) = \pi_s \beta(\tilde{S})\tilde{S}e^{-\left(\beta(\tilde{S})+\delta(\tilde{W})\right)a} \tag{2.11}$$

$$\tilde{w}(a) = \pi_w \delta(\tilde{W})\tilde{S}e^{-\tilde{\gamma}_w a}. \tag{2.12}$$

Next we integrate $\tilde{s}(a)$ and $\tilde{w}(a)$ with respect to a to arrive at the equations:

$$\tilde{S} = \frac{\pi_s \beta(\tilde{S})\tilde{S}}{\beta(\tilde{S}) + \delta(\tilde{W})}, \tag{2.13}$$

$$\tilde{W} = \frac{\pi_w}{\tilde{\gamma}_w}\delta(\tilde{W})\tilde{S}. \tag{2.14}$$

Recall that the functions $\delta(\tilde{W}), \beta(\tilde{S})$ have the following forms:

$$\beta(\tilde{S}) := k_0 \frac{\theta_2^2}{\theta_2^2 + \tilde{S}^2}, \tag{2.15}$$

$$\delta(\tilde{W}) := f_0 \frac{\theta_1}{\theta_1 + \tilde{W}}. \tag{2.16}$$

If we are able to find solutions $\tilde{S}$ and $\tilde{W}$ to (2.13) and (2.14) then from Equations (2.10) we can construct explicit solutions for the equilibrium age distribution. We show that there are solutions to (2.13) and (2.14) using the specific forms of β, δ. As mentioned before, there is a steady state where all compartments are empty which would require $\tilde{S} = 0$. Assuming $\tilde{S} \neq 0$, we can simplify Equation (2.13) to

$$\delta(\tilde{W}) = (\pi_s - 1)\beta(\tilde{S}). \tag{2.17}$$

Since both $\delta(\tilde{W})$ and $\beta(\tilde{S})$ are positive when $\tilde{S}$ and $\tilde{W}$ are positive, we need $\pi_s > 1$ for the above equation to be satisfied and physically relevant. For parameter values from Foley [5], namely $\tau_s = 2.8$ and $\tilde{\gamma}_s = 0.05$, we have that $\pi_s \approx 1.7$. We can now explicitly solve Equation (2.14) for $\tilde{S}$ in terms of $\tilde{W}$,

$$\tilde{S} = \frac{\tilde{\gamma}_w}{\pi_w}\frac{\tilde{W}}{\delta(\tilde{W})}. \tag{2.18}$$

Substituting (2.18) into (2.14) we get a single equation in terms of $\tilde{W}$:

$$\delta(\tilde{W}) = (\pi_s - 1)\beta\left(\frac{\tilde{\gamma}_w}{\pi_w}\frac{\tilde{W}}{\delta(\tilde{W})}\right). \tag{2.19}$$

Using (2.15) and (2.16), the reciprocal of Equation (2.19) becomes:

$$\frac{\theta_1 + \tilde{W}}{f_0\theta_1} = (\pi_s - 1)^{-1}\left(k_0\theta_2^2\right)^{-1}\left(\theta_2^2 + \frac{\tilde{\gamma}_w^2}{\pi_w^2}\left(\frac{\tilde{W}(\theta_1 + \tilde{W})}{f_0\theta_1}\right)^2\right). \tag{2.20}$$

Equation (2.20) is a fourth degree polynomial in $\tilde{W}$. We are interested in positive real roots of this polynomial as they represent the possible limiting levels of neutrophils. Note that the

right hand side of Equation 2.20 has no linear term and the quadratic, cubic and quartic terms have positive coefficients. If we expand the above polynomial and move everything to the right hand side we get:

$$c_4\tilde{W}^4 + c_3\tilde{W}^3 + c_2\tilde{W}^2 + c_1\tilde{W} + c_0 = 0 \tag{2.21}$$

where c_4, c_3, c_2, c_1, c_0 are combinations of parameters in the model. We know that c_4, c_3, c_2 are positive from Equation (2.20). Furthermore, we know that c_1 is negative since the only linear term in the polynomial comes from the left hand side of Equation (2.20). The constant term has the form:

$$c_0 = \frac{1}{(\pi_s - 1)k_0} - \frac{1}{f_0}.$$

Substituting parameter values from Foley [5] gives $c_0 \approx -1.5 < 0$. We emphasize the sign of the coefficient as the sequence c_4, c_3, c_2, c_1, c_0 only has one sign change. This is important because we can claim existence of a unique positive $\tilde{W}$ that satisfies Equation (2.20) by using Descartes' Rule of Signs [1]. Descartes' Rule of Signs states that the number of sign changes in the sequence of coefficients is an upper bound for the number of positive real roots and it also states that the difference in the number of sign changes and the number of positive roots must be even. As there is only one sign change in our polynomial, the number of positive roots must be one.

The condition $c_0 < 0$ can be rewritten as

$$\pi_s - \frac{f_0}{k_0} > 1. \tag{2.22}$$

Note that (2.22) is a necessary and sufficient condition for the existence of a nontrivial steady state of (2.1). A similar result is available in [5] where the condition

$$\pi_s - \frac{2f_0}{k_0} > 1 \tag{2.23}$$

is found to be sufficient for the existence of a nontrivial steady state.

Chapter 3

Model Decoupling and Solution Strategy

3.1 Introduction

The mathematical model of chemotherapy-induce neutropenia (2.1) consists of five first order hyperbolic equations. Neglecting the Cauchy conditions, the PDE governing the cells m, n, p and w from (2.1) are linear. As these compartments are governed by first order linear hyperbolic equations, in theory, they can be solved explicitly in terms of their Cauchy conditions. We will show, for some short time, that enough Cauchy conditions are known initially to solve the linear equations for m, p, n, w for short time. Using the solutions of m, p, n, w, we can specify the Cauchy conditions and death modulus for the PDE governing $s(t, a)$. This procedure ensures we can decouple the PDE system (2.1), at least for short time. The cell compartments with dependence on other cell densities are shown in Figure 2.2.

3.2 Method of Characteristics

As Equations (2.1) are first order hyperbolic PDE, a natural method to try and solve the system is the method of characteristics. Consider the following variable aging PDE:

$$\frac{\partial x}{\partial t} + Q(t)\frac{\partial x}{\partial a} = -P(t)x, \qquad (t, a) \in \mathbb{R}^+ \times [0, \tau_x]. \tag{3.1a}$$

$$x(t, 0) = B_x(t), \qquad t \in \mathbb{R}^+, \tag{3.1b}$$

$$x(0, a) = \phi_x(a), \qquad a \in [0, \tau_x]. \tag{3.1c}$$

Assuming $Q(t)$ is nonnegative and bounded, recall we can solve Equations (3.1) using the method of characteristics. Let $(t(s), a(s))$ denote a curve parameterized by s in the upper

right quadrant. Then we have

$$\frac{dx(t(s),a(s))}{ds} = \frac{dt(s)}{ds}\frac{\partial x}{\partial t} + \frac{da(s)}{ds}\frac{\partial x}{\partial a}. \tag{3.2}$$

If we have

$$\frac{dt}{ds} = 1, \quad \frac{da}{ds} = Q(t(s)), \tag{3.3}$$

then we obtain the characteristic equation for x given by

$$\frac{dx}{ds} = -P(t(s))x. \tag{3.4}$$

Solving Equations (3.3) with initial conditions $t(0) = t_0,\ a(0) = a_0$ gives:

$$t(s) = s + t_0, \quad a(s) = \int_0^s Q(t(\alpha))\ d\alpha + a_0$$

from which we get

$$a(s) = \int_{t_0}^t Q(\alpha)\ d\alpha + a_0. \tag{3.5}$$

From Equation (3.4) we have a solution of PDE (3.1) of the form:

$$x(s) = x_0 \exp\left\{-\int_0^s P(t(\alpha))\ d\alpha\right\}, \tag{3.6}$$

where x_0 depends on the curve $(t(s), a(s))$.

Given that our domain is $\{(t,a)|t \geq 0,\ a \geq 0\}$, the characteristic curves must originate at either the t-axis or the a-axis. We define the following sets:

$$R_1 := \left\{(t,a) \;\middle|\; a - \int_0^t Q(\alpha)\ d\alpha \geq 0\right\}, \quad R_2 := \left\{(t,a) \;\middle|\; a - \int_0^t Q(\alpha)\ d\alpha < 0\right\}.$$

The set R_1 represents the set of points in the upper right quadrant whose characteristic curves originate at the a-axis. This can be seen from setting $t_0 = 0$ in Equation (3.5) and enforcing the resulting a_0 to be nonnegative. Similar reasoning can be applied to R_2, which represents the set of points whose characteristic curves originate at the t-axis. Note that if $(t,a) \in R_2$ we have $a_0 = 0$ and a unique $t_0 \geq 0$ that satisfies

$$a = \int_{t_0}^t Q(\alpha)\ d\alpha, \tag{3.7}$$

(from the definition of R_2 and our assumptions on $Q(t)$ being nonnegative and bounded). This ensures that characteristics do not cross. We can now write a solution of Equations (3.1) as

follows

$$x(t,a) = \begin{cases} \phi_x(a_0) \exp\left\{ -\int_0^t P(\alpha)\, d\alpha \right\}, & (t,a) \in R_1, \\ B_x(t_0) \exp\left\{ -\int_{t_0}^t P(\alpha)\, d\alpha \right\}, & (t,a) \in R_2, \end{cases} \tag{3.8}$$

where (t_0, a_0) satisfy Equation (3.5). We note that (3.8) suggests we can still make sense of a solution to (3.1) if the data ϕ_x, B_x is non smooth. If $x(t,a)$ satisfies (3.8) almost everywhere we say $x(t,a)$ is a *weak solution* to (3.1). We will require B_x and ϕ_x to be piecewise continuous and will call $x(t,a)$ a solution of (3.1) if $x(t,a)$ satisfies (3.8). This notion of a solution only requires $x(t,a)$ to be smooth along characteristics, not necessarily between them.

We also note that solutions of (3.1) are unique. To see this, suppose by contradiction $x_1(t,a), x_2(t,a)$ are both solutions to (3.1). Letting $e(t,a) = x_1(t,a) - x_2(t,a)$ we see that $e(t,a)$ satisfies

$$\begin{aligned} &\frac{de}{dt} + Q(t)\frac{de}{da} = -P(t)e, && (t,a) \in \mathbb{R}^+ \times [0, \tau_x], \\ &e(t,0) = 0, && t \in \mathbb{R}^+, \\ &e(0,a) = 0, && a \in [0, \tau_x]. \end{aligned}$$

We see that this is of the form (3.1) and hence admits solutions of the form (3.8), which simply gives $e = 0$. It follows that $x_1(t,a) = x_2(t,a)$, a contradiction.

3.3 Decoupled Problem

The cell density $s(t,a)$ is governed by the following PDE:

$$\frac{\partial s}{\partial t} + \frac{\partial s}{\partial a} = -\left(\beta(S(t)) + \delta(W(t))\right) s, \qquad (t,a) \in \mathbb{R}^+ \times \mathbb{R}^+, \tag{3.9a}$$

$$S(t) = \int_0^\infty s(t,a)\, da, \qquad t \in \mathbb{R}^+, \tag{3.9b}$$

$$W(t) = \int_0^\infty w(t,a)\, da, \qquad t \in \mathbb{R}^+, \tag{3.9c}$$

$$s(0,a) = \phi_s(a), \qquad a \in \mathbb{R}^+, \tag{3.9d}$$

$$s(t,0) = B_s(t) = 2m(t,\tau_s), \qquad t \in \mathbb{R}^+. \tag{3.9e}$$

Here we see that $s(t,a)$ depends only on $m(t,a)$ and $w(t,a)$ explicitly. The renewal equation $B_s(t)$ is dependant solely on m, and the death modulus depends on s and w. As mentioned earlier, the PDE governing m and w are linear. We show that we can decouple $m(t,a), s(t,a)$, and $w(t,a)$, for short time. First we show $m(t,a)$ and $s(t,a)$ can be decoupled. Then we decouple $w(t,a)$ and $s(t,a)$ using a similar method.

3.3.1 Renewal Equation

Here we will write $B_s(t)$ from Equation (3.9e) explicitly in terms of ϕ_m. We do this by using the method of characteristics on the linear PDE governing $m(t,a)$ to write out $m(t,\tau_s)$ in terms of known quantities. The cell density $m(t,a)$ is governed by the following linear problem:

$$\begin{aligned}
&\frac{\partial m}{\partial t} + \frac{\partial m}{\partial a} = -\gamma_s(G(t))m(t,a), && (t,a) \in \mathbb{R}^+ \times [0,\tau_s],\\
&m(t,0) = B_m(t) = \beta(S(t))S(t), && t \in \mathbb{R}^+,\\
&m(0,a) = \phi_m(a), && a \in [0,\tau_s].
\end{aligned}$$

From Equation (3.8) we can write the solution for $m(t,a)$ as:

$$m(t,a) = \begin{cases} \phi_m(a-t)\exp\left\{-\int_0^t \gamma_s(G(\alpha))\,d\alpha\right\}, & a-t \geq 0,\\ \beta(S(t-a))S(t-a)\exp\left\{-\int_{t-a}^t \gamma_s(G(\alpha))\,d\alpha\right\}, & a-t < 0. \end{cases}$$

In particular, for $0 \leq t \leq \tau_s$, we can write the solution of m at its terminal age as

$$m(t,\tau_s) = \phi_m(\tau_s - t)\exp\left\{-\int_0^t \gamma_s(G(\alpha))\,d\alpha\right\}.$$

Consequently we can write $B_s(t)$ in Equation (3.9e) explicitly in terms of known quantities for $0 \leq t \leq \tau_s$ as

$$B_s(t) = 2m(t,\tau_s) = 2\phi_m(\tau_s - t)\exp\left\{-\int_0^t \gamma_s(G(\alpha))\,d\alpha\right\}.$$

We define the set:

$$A_1 := \{(t,a) \mid 0 \leq t \leq \tau_s,\ t \leq a \leq \tau_s\}.$$

This is precisely the set of points whose characteristic curves originate at the a-axis for the cell density $m(t,a)$. We can solve for $m(t,a)$ in terms of ϕ_m (the initial data) for $(t,a) \in A_1$. We also define the set:

$$A_2 := \{(t,a) \mid 0 \leq t \leq \tau_s,\ a \geq 0\}.$$

The set A_2 is the region where the birth condition for $s(t,a)$ (namely B_s in Equation (3.9e)) is known. An illustration of these sets can be seen in Figure 3.1.

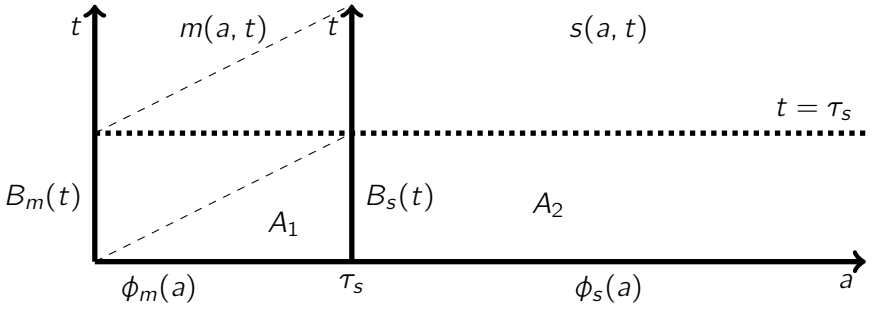

Figure 3.1: Domains for cell densities m and s shown side by side. Resting stem cells ($s(t,a)$) entering the proliferative phase ($m(t,0)$) take τ_s units of time to become resting stem cells again ($(s(t,0))$).

3.3.2 Death Modulus

The death modulus in Equation (3.9a) is a function of $w(t,a)$ which is initially unknown. In a similar manner to the preceding subsection, we will use the method of characteristics to build a solution $w(t,a)$ for short time in terms of known quantities. As was seen in Figure 2.2, the cells entering the differentiation process from compartment s enter compartment p, then go to compartment n, and finally enter compartment w. We will show that $w(t,a)$ can be written in terms of ϕ_p and ϕ_n for some short time.

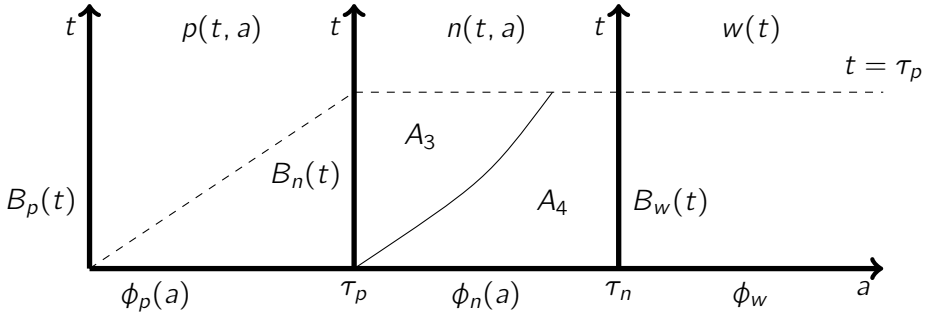

Figure 3.2: Domains for cell densities p, n and w shown side by side. A_4 represents the domain where n can be solved in terms of ϕ_n. Terminal data of p can be used to solve for n in A_3.

Recall the entire PDE system given by Equations (2.1). The PDE governing the compartments for p and n are given by

$$\frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} = -\gamma_p(G(t)), \qquad t > 0, a \in [0, \tau_p], \tag{3.11a}$$

$$p(0,a) = \phi_p(a), \qquad a \in [0, \tau_p], \tag{3.11b}$$

$$p(t,0) = \delta(W(t))S(t), \qquad t > 0, \tag{3.11c}$$

and

$$\frac{\partial n}{\partial t} + V_n(G(t))\frac{\partial n}{\partial a} = -\gamma_n(G(t))n, \qquad t > 0, a \in [0, \tau_n], \tag{3.12a}$$

$$n(0, a) = \phi_n(a), \qquad a \in [0, \tau_n], \tag{3.12b}$$

$$n(t, 0) = A(G(t))p(t, \tau_p), \qquad t > 0. \tag{3.12c}$$

Note that Equation (3.12c) depends on the terminal age of cell density p. From Equation (3.8) we can write the solution of (3.11) as

$$p(t, \tau_p) = \phi_p(\tau_p - t) \exp\left\{-\int_0^t \gamma_p(G(\alpha))\, d\alpha\right\}, \quad 0 \le t \le \tau_p. \tag{3.13}$$

We define the following sets:

$$A_3 = \left\{(t, a)\middle| a - \int_0^t V_n(G(\alpha))\, d\alpha \ge 0, t \le \tau_p, a \le \tau_n\right\}, \tag{3.14}$$

$$A_4 = \left\{(t, a)\middle| a - \int_0^t V_n(G(\alpha))\, d\alpha < 0, t \le \tau_p, a \le \tau_n\right\}. \tag{3.15}$$

An illustration of these sets can be seen in Figure 3.2.

Equations (3.12) are of the form Equations (3.1) for $0 \le t \le \tau_p$. There exists a solution to Equations (3.12) for given $(t, a) \in [0, \tau_p] \times [0, \tau_p]$ of the form:

$$n(t, a) = \begin{cases} \phi_n(a_0) \exp\left\{-\int_0^t \gamma_n(G(\alpha))\, d\alpha\right\}, & (t, a) \in A_3, \\ A(G(t_0))p(t_0, \tau_p) \exp\left\{-\int_0^t \gamma_p(G(\alpha))\, d\alpha\right\}, & (t, a) \in A_4, \end{cases} \tag{3.16}$$

where (t_0, a_0) satisfy the following:

$$a = \int_{t_0}^t V_n(G(\alpha))\, d\alpha + a_0. \tag{3.17}$$

We have successfully constructed, albeit in terms of G, a solution $n(t, a)$ for $0 \le t \le \tau_p$. From Equations (2.1) we can readily see for $0 \le t \le \tau_p$:

$$w(t, a) = \begin{cases} \phi_w(a - t)e^{-\gamma_w t}, & a - t \ge 0, \\ n(t - a, \tau_n)e^{-\gamma_w(t-a)}, & a - t < 0. \end{cases} \tag{3.18}$$

We have shown $w(t, a)$ is dependent only on known quantities up to $t = \tau_p$. Consequently the total population of $w(t, a)$,

$$W(t) = \int_0^\infty w(t, a)\, d\alpha, \tag{3.19}$$

is also dependent only on known quantities. As $W(t)$ is known and independent of $s(t,a)$, up to $t = \tau_p$, the death modulus of Equation (3.9a) can be thought of as solely dependent on $S(t)$.

3.3.3 Summary

We have used the method of characteristics on the linear PDE in Equations (2.1) to show existence of $m(t,\tau_s)$ and $W(t)$ independent of $s(t,a)$ up to time τ_s and τ_p respectively. We now define:

$$\tau = \min(\tau_s, \tau_p). \tag{3.20}$$

For $0 \leq t \leq \tau$ we have existence of $m(t,\tau_s)$ and $W(t)$ independent of s. We can then examine the following system for s where the dependence of m and w are suppressed,

$$\frac{\partial s}{\partial a} + \frac{\partial s}{\partial t} = -\lambda_s(S(t))s(t,a), \qquad (t,a) \in [0,\tau] \times \mathbb{R}^+, \tag{3.21a}$$

$$s(t,0) = B_s(t), \qquad 0 \leq t \leq \tau, \tag{3.21b}$$

$$s(0,a) = \phi_s(a), \qquad a \geq 0, \tag{3.21c}$$

$$S(t) = \int_0^\infty s(t,a)\, da, \qquad 0 \leq t \leq \tau. \tag{3.21d}$$

We will refer to this system as the decoupled problem for s. Supposing we can solve the system (3.21), we can then solve for $m(t,a)$ and $p(t,a)$ for $0 \leq t \leq \tau$ using the method of characteristics. After doing so all five compartments in the model will be known up to time $t = \tau$. We can then repeat this process using terminal data as initial data and solve for compartments up to $t = 2\tau$. The next chapter is devoted to proving existence of solutions to Equations (3.21) and consequently (2.1) .

Chapter 4

Existence

Typically, first order hyperbolic PDEs have *a priori* prescribed Cauchy conditions. One of the main difficulties in working with age-structured models is dealing with a renewal condition that is dependent on the solution in the domain. Since the solution is not known before hand, neither is the renewal condition. Solutions for the Gurtin-MacCamy model (see [6]) exist for suitable conditions on various functions and parameters. The model for chemotherapy-induced neutropenia developed by C. Foley in [5] is more complex. The PDE system governs five cell compartments whose renewal conditions are coupled through the birth conditions at $a = 0$. Existence of solutions to this PDE system is unknown due to the coupling of the unknown Cauchy conditions as well as the non-local nature of the death modulus. In this chapter we prove existence of solutions to the full PDE model (2.1) for global time.

4.1 System

We aim to show existence of solutions to the following equations:

$$\frac{\partial m}{\partial t} + \frac{\partial m}{\partial a} = -\gamma_s(G)m, \qquad t > 0, a \in [0, \tau_s], \tag{4.1a}$$

$$\frac{\partial s}{\partial t} + \frac{\partial s}{\partial a} = -\delta(W)s - \beta(S)s, \qquad t > 0, a > 0, \tag{4.1b}$$

$$\frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} = -\gamma_p(G)p, \qquad t > 0, a \in [0, \tau_p], \tag{4.1c}$$

$$\frac{\partial n}{\partial t} + V_n(G)\frac{\partial n}{\partial a} = -\gamma_n(G)n, \qquad t > 0, a \in [0, \tau_n], \tag{4.1d}$$

$$\frac{\partial w}{\partial t} + \frac{\partial w}{\partial a} = -\gamma_w w, \qquad t > 0, a > 0, \tag{4.1e}$$

given the initial and renewal conditions:

$$\begin{aligned}
m(0,a) &= \phi_m(a), & m(t,0) &= \beta(S(t))S(t), & t>0, a\in[0,\tau_s],\\
s(0,a) &= \phi_s(a), & s(t,0) &= 2m(t,\tau_s), & t>0, a\in[0,\infty),\\
p(0,a) &= \phi_p(a), & p(t,0) &= \delta(W(t))S(t), & t>0, a\in[0,\tau_p],\\
n(0,a) &= \phi_n(a), & n(t,0) &= A(G(t))p(t,\tau_p), & t>0, a\in[0,\tau_n],\\
w(0,a) &= \phi_w(a), & w(t,0) &= n(t,\tau_n), & t>0, a\in[0,\infty).
\end{aligned}$$

We do this by using the method described in Chapter 3 to decouple the full system (4.1), leading to the decoupled problem (3.21). In this chapter, we first focus on the decoupled problem for $s(t,a)$ given by (3.21). We create an integral operator related to (3.21) and prove it admits a fixed point. This fixed point is then used to create a solution of (3.21), which is only valid until $t=\tau$, with τ given by (3.20). We then show we can use the solution of the reduced problem up until $t=\tau$ to update the remaining cell compartments. Finally, we show can repeat this process and build solutions to (4.1) for global time.

Letting $A = diag(1,1,1,V_n(G(t)),1)$, note that (4.1) can be written as

$$\vec{u}_t + A\vec{u}_a = \vec{f}(u,G) \tag{4.3}$$

where $\vec{u} = [m,s,p,n,w]^T$. This PDE system is hyperbolic as the matrix A is diagonalizable with real eigenvalues.

4.2 Existence

In this section we show existence of solutions, $s(t,a)$, to the reduced problem (3.21). The proof uses a fixed point argument on an integral operator related to Equation (4.1). First we define the following operator:

$$Ds(t,a) := \lim_{h\to 0} \frac{s(t+h,a+h)-s(t,a)}{h}.$$

Note that for $s\in C^1$ we have $Ds = \frac{\partial s}{\partial t} + \frac{\partial s}{\partial a}$. However, we would like to relax our assumptions on the regularity of s to allow for more general types of initial data. We require that the initial data, $\phi_i,\ i = m,s,p,n,w$, be piece-wise continuous and integrable on their respective domains. We will assume this for the remainder of the chapter.

4.2.1 Integral Equation Formulation

We restate the reduced problem for $s(t,a)$ up to time T.

$$Ds(t,a) = -\lambda_s(S(t))s(t,a), \qquad (t,a) \in [0,T] \times \mathbb{R}^+, \tag{4.4a}$$

$$s(t,0) = B_s(t), \qquad 0 \le t \le T, \tag{4.4b}$$

$$s(0,a) = \phi_s(a), \qquad a \ge 0, \tag{4.4c}$$

$$S(t) = \int_0^\infty s(t,a)\, da, \qquad 0 \le t \le T. \tag{4.4d}$$

Recall that the reduced problem is only valid for $T \le \tau$ as defined in (3.20). We also note that we require λ_s to be a continuous function. Next we define what we mean by a solution to (4.4).

Definition 4.2.1. A function $s : [0,T] \times \mathbb{R}^+ \to \mathbb{R}^+$ with the following properties is a solution of (4.4) up to time T:

1. $s(t,\cdot) \in L^1(\mathbb{R}^+)$ for all $t \in [0,T]$,
2. $Ds(t,a)$ exists for $(t,a) \in [0,T] \times \mathbb{R}^+$,
3. Equations (4.4) are satisfied.

The above definition is similar to the notion of a solution of the Gurtin-MacCamy model in [6]. Our first theorem establishes an integral equation formulation of the PDE (4.4).

Theorem 1. *A solution $s(t,a)$ to (4.4) up to time $T \le \tau$ satisfies the following integral equation:*

$$S(t) = \int_0^t K(t-a,t;S)B_s(a)\, da + \int_0^\infty L(a,t;S)\phi_s(a)\, da, \tag{4.5}$$

where the kernels K and L are given by:

$$K(\alpha,t;S) = \exp\left\{-\int_{t-\alpha}^t \lambda_s(S(\tau))\, d\tau\right\}, \tag{4.6a}$$

$$L(\alpha,t;S) = \exp\left\{-\int_0^t \lambda_s(S(\tau))\, d\tau\right\}. \tag{4.6b}$$

Proof. If $S(t)$ is known, then (4.4) is of the form (3.1) and admits solutions of the form (3.8). That is, for $t \le T \le \tau$ we have

$$s(t,a) = \begin{cases} \phi_s(a-t)\exp\left\{-\int_0^t \lambda_s(S(\alpha))\, d\alpha\right\}, & a > t, \\ B_s(t-a)\exp\left\{-\int_0^a \lambda_s(S(t-a+\alpha))\, d\alpha\right\}, & t < a. \end{cases} \tag{4.7}$$

Therefore,

$$\begin{aligned} S(t) &= \int_0^\infty s(t,a)\ da, \\ &= \int_0^t s(t,a)\ da + \int_t^\infty s(t,a)\ da, \\ &= \int_0^t B_s(t-a)\exp\left\{-\int_0^a \lambda_s(S(t-a+\alpha))\ d\alpha\right\}\ da \\ &+ \int_t^\infty \phi_s(a-t)\exp\left\{-\int_0^t \lambda_s(S(\alpha))\ d\alpha\right\}\ da. \end{aligned} \tag{4.8}$$

A change of variables, $a^* = t - a, \bar{a} = a - t$ for the first and second terms respectively gives the result. □

Next we show that the total population $S(t)$ can be used to recreate $s(t,a)$.

Theorem 2. *Suppose $S(t) \geq 0$ and satisfies (4.5) up to time $T < \tau$, then $s(t,a)$ defined by (4.7) satisfies (4.4)*

Proof. We prove this directly. Equation (4.7) show $s(t,a)$ satisfies the conditions: $s(0,a) = \phi_s(a)$ and $s(t,0) = B_s(t)$. We have $S(t) = \int_0^\infty s(t,a)\ da$ from (4.8). Next we show $s(t,a)$ satisfies the PDE (4.4).

Letting $s_0(h) = s(t+h, a+h)$ and $\lambda_0(h) = \lambda_s(S(t+h))$ for $a > t$ and $t < T$ we have:

$$s_0(h) = \phi_s(a-t)\exp\left\{-\int_0^{t+h} \lambda_s(S(\alpha))\ d\alpha\right\}$$

$$\frac{ds_0}{dh} = \phi_s(a-t)\exp\left\{-\int_0^{t+h} \lambda_s(S(\alpha))\ d\alpha\right\}[-\lambda_s(S(t+h))] = -s_0(h)\lambda_0(h)$$

For $a < t$, similarly we have:

$$\frac{ds_0}{dh} = B_s(t-a)\exp\left\{-\int_0^{a+h} \lambda_s(S(t-a+\alpha))\ d\alpha\right\}[-\lambda_s(S(t+h))] = -s_0(h)\lambda_0(h)$$

The characteristic equations are satisfied; hence $s(t,a)$ defined by (4.7) satisfies (4.4). □

4.2.2 Local Existence

Let us first state and prove a lemma that will be used shortly.

Lemma 4.2.1. *For $x \in \mathbb{R}$, the following inequality is true:*

$$|e^x - 1| \leq |x|e^{|x|}$$

Proof. We prove this directly. Recall the power series for the exponential function,

$$e^x = 1 + x + \frac{x^2}{2} + \cdots .$$

We then have:

$$\begin{aligned} |e^x - 1| &= \left| \left(1 + x + \frac{x^2}{2} + \cdots\right) - 1 \right| \\ &= \left| x + \frac{x^2}{2} + \cdots \right| \\ &= |x| \left| 1 + \frac{x}{2} + \frac{x^2}{6} + \cdots \right| \\ &\leq |x| \left(1 + |x| + \left|\frac{x^2}{2}\right| + \cdots\right) \\ &= |x| e^{|x|}. \end{aligned}$$

□

Let $C^+[0,T]$ denote the set of nonnegative continuous functions on the interval $[0,T]$. We define the integral operator $\mathscr{S}_T$ on $C^+[0,T]$ by,

$$\mathscr{S}_T(S)(t) = \int_0^t K(t-a,t;S)B_s(a)\ da + \int_0^\infty L(a,t;S)\phi_s(a)\ da \tag{4.9}$$

We aim to show local existence by showing the integral operator $\mathscr{S}_T(S)(t)$ admits a fixed point for sufficiently small T. To show this we need to impose some conditions on the death modulus, $\lambda_s(S(t))$, and the birth modulus, $B_s(t)$. For given $T \geq 0$ and $r \geq 0$ we define the following:

$$\Phi = \int_0^\infty \phi_s(a)\ da, \tag{4.10a}$$

$$\Psi_t = \int_0^t B_s(a)\ da, \tag{4.10b}$$

$$||\cdot||_T = \sup_{0\leq t\leq T} |\cdot|, \tag{4.10c}$$

$$\Sigma_T = \left\{ f \in C^+[0,T] \ \mid \ ||f - (\Psi_t + \Phi)||_T \leq r \right\}, \tag{4.10d}$$

$$\lambda_1 = \sup_{S\geq 0} |\lambda_s(S))|, \tag{4.10e}$$

$$\lambda_2 = \sup_{S,\bar{S}\geq 0} \left| \frac{\lambda_s(S) - \lambda_s(\bar{S})}{S - \bar{S}} \right|, \tag{4.10f}$$

$$\beta_1 = ||B_s||_T. \tag{4.10g}$$

The quantity $\Psi_t + \Phi$ is the total number of cells introduced into the system up to time t. Σ_T is the set of nonnegative continuous functions that are 'close' to the total number of cells introduced to the compartment. λ_1 is an upper bound for λ_s and λ_2 is the Lipschitz constant. We are now ready to prove the integral operator defined by (4.9) admits a point.

Theorem 3. *Suppose $\lambda_1, \lambda_2 < \infty$ and $\Psi_t < \infty, \forall\ t \leq \tau$ where λ_1, λ_2 and Ψ_t are as defined in (4.10). Then there exists a time T, $0 < T \leq \tau$, such that the operator $\mathscr{S}_T(S)(t) : C^+[0,T] \to C^+[0,T]$ defined by (4.9) admits a unique fixed point.*

Proof. $C[0,T]$ with $||\cdot||_T$ is a Banach Space. For given $r > 0$, we want to use the Banach Fixed Point Theorem. To invoke this theorem, we need to find a T such that Σ_T is closed, $\mathscr{S}_T$ maps Σ_T into itself, and is contractive.

First we show Σ_T is closed. Suppose $\{f_n\} \subset \Sigma_T$ such that $f_n \to f$ with respect to $||\cdot||_T$. Then the f_n are converging uniformly and hence converge to a continuous function f. We also have for all $n \in \mathbb{N}$

$$||f_n - (\Phi + \Psi_t)||_T \leq r.$$

Taking the limit as $n \to \infty$ gives $f \in \Sigma_T$.

Let $S \in \Sigma_T$, we show $||\mathscr{S}_T(S)(t) - (\Psi_t + \Phi)\,||_T$ is arbitrarily small with respect to a particular choice of T.

$$\begin{aligned}
|\mathscr{S}_T(S)(t) - (\Psi_t + \Phi)\,| &= \left| \int_0^t K(t-a,t;S)B_s(a)\ da + \int_0^\infty L(a,t;S)\phi_s(a)\ da \right. \\
&\quad \left. - \int_0^t B_s(a)\ da - \int_0^\infty \phi(a)\ da \right| \\
&\leq \int_0^t |K(t-a,t;S) - 1|\, B_s(a)\ da + \int_0^\infty [L(a,t;S) - 1]\,\phi(a)\ da \\
&\leq \Psi_t \sup_{a \geq 0, 0 \leq t \leq T} |K(t-a,t;S) - 1| + \Phi \sup_{(a \geq 0, 0 \leq t \leq T)} |L(a,t;S) - 1|\,.
\end{aligned}$$

The last step uses boundedness of B_s (by assumption) and Hölders inequality.

Using the following inequality from Lemma 4.2.1,

$$|e^z - 1| \leq |z| e^{|z|}$$

we obtain:

$$\begin{aligned}
|L(a,t;S) - 1| &\leq \left| \int_0^t \lambda_s(\tau + a, S(\tau))\ d\tau \right| \exp\left\{ \int_0^t \lambda_s(\tau + a, S(\tau))\ d\tau \right\} \\
&\leq \lambda_1 T e^{\{\lambda_1 T\}}.
\end{aligned}$$

Similarly,

$$\begin{aligned}|K(a-t,t;S)-1| &\leq \left|\int_a^t \lambda_s(\tau-a,S(\tau))\,d\tau\right| \exp\left\{\int_a^t \lambda_s(\tau-a,S(\tau))\,d\tau\right\} \\ &\leq \lambda_1 T e^{\lambda_1 T}.\end{aligned}$$

Since $\lambda_1 < \infty$ by hypothesis,

$$\begin{aligned}|\mathscr{S}_T(S)(t)-(\Psi_t+\Phi)| &\leq \Psi_t \sup_{a\geq 0, 0\leq t\leq T} |K(a-t,t;S)-1| + \Phi \sup_{(a\geq 0, 0\leq t\leq T)} |L(a,t;S)-1|, \\ &\leq \lambda_1 T e^{\lambda_1 T}(\Psi_t+\Phi).\end{aligned}$$

Therefore, for any r we can find a T such that $\mathscr{S}_T : \Sigma_T \to \Sigma_T$. Now we show that there is a T such that the mapping $\mathscr{S}_T(S)(t)$ is a contraction on Σ_T. Letting $S,\ \bar{S} \in \Sigma_T$, we have

$$\begin{aligned}\left|\mathscr{S}_T(S)(t)-\mathscr{S}_T(\bar{S})(t)\right| \leq &\left|\left|\int_0^t \left(K(t-a,t;S)-K(t-a,t;\bar{S})\right) B_s(a)\,da\right|\right|_T \\ &+ \left|\left|\int_0^\infty \left(L(a,t;S)-L(a,t;\bar{S})\right)\phi_s(a)\,da\right|\right|_T.\end{aligned}$$

We bound the first term,

$$\begin{aligned}\left|L(a,t;S)-L(a,t;\bar{S})\right| &= \left|e^{-\int_0^t \lambda_s(S(\tau))\,d\tau} - e^{-\int_0^t \lambda_s(\bar{S}(\tau))\,d\tau}\right| \\ &\leq \left|1-\exp\left\{\int_0^t \left[\lambda_s(S(\tau))-\lambda_s(\bar{S}(\tau))\right]\,d\tau\right\}\right| \\ &\leq \left|\int_0^t \left[\lambda_s(S(\tau))-\lambda_s(\bar{S}(\tau))\right]\,d\tau\right| \exp\left\{\left|\int_0^t \left[\lambda_s(S(\tau))-\lambda_s(\bar{S}(\tau))\right]\,d\tau\right|\right\} \\ &\leq \int_0^T \lambda_2 \left|\left|S-\bar{S}\right|\right|_T\,d\tau e^{\int_0^T 2\lambda_1\,d\tau} \\ &= \lambda_2 T \left|\left|S-\bar{S}\right|\right|_T e^{2\lambda_1 T}.\end{aligned}$$

The third step uses Lemma 4.2.1. Similarly, for the second term we have:

$$\begin{aligned}\left|K(t-a,t;S)-K(t-a,t;\bar{S})\right| &\leq \left|1-e^{\int_a^t \lambda_s(S(\tau))-\lambda_s(\bar{S}(\tau))\,d\tau}\right| \\ &\leq \left|\int_a^t \left[\lambda_s(S(\tau))-\lambda_s(\bar{S}(\tau))\right]\,d\tau\right| e^{2\lambda_1 T} \\ &\leq \lambda_2 T \left|\left|S-\bar{S}\right|\right|_T e^{2\lambda_1 T}.\end{aligned}$$

Combining these inequalities we get:

$$\begin{aligned}|\mathscr{S}_T(S)(t) - \mathscr{S}_T(S)(t)| &\leq \left|\left|\int_0^t \left(K(t-a,t;S) - K(t-a,t;\bar{S})\right) B_s(a)\, da\right|\right|_T \\ &+ \left|\left|\int_0^\infty \left(L(a,t;S) - L(a,t;\bar{S})\right) \phi_s(a)\, da\right|\right|_T \\ &\leq \lambda_2 T \left|\left|S - \bar{S}\right|\right|_T e^{2\lambda_1 T} \left(\Psi_T + \Phi\right).\end{aligned}$$

Since $\lambda_1,\ \lambda_2, \Psi_T < \infty$, the operator $\mathscr{S}_T$ is a contraction on Σ_T for sufficiently small T. By the Banach Fixed Point Theorem $\mathscr{S}_T$ admits a unique fixed point in $\Sigma_T[0,T]$. We have shown uniqueness of a solution S only in $\Sigma_T[0,T]$, not in $C^+[0,T]$.

□

Note that Theorem 3 does not use a particular value of r from 4.10. A special value of r will be used in a later theorem to establish existence of solutions up to $t = \tau$.

Theorem 4. *A solution $S(t)$ of* (4.5) *up to time $T < \tau$ satisfies the following inequality:*

$$S(t) \leq \Psi_t + \Phi e^{-\underline{\lambda} t} \tag{4.11}$$

where Ψ_t and Φ are defined in (4.10) *and*

$$\underline{\lambda} := \inf_{S \geq 0} \lambda_s(S).$$

Proof. We show this directly. Recall the kernels L and K, given by (4.6), we have:

$$L(\alpha, t; S) = \exp\left\{-\int_{t-\alpha}^t \lambda_s(S(\tau))\, d\tau\right\} \leq e^{-\underline{\lambda} t},$$

$$K(\alpha, t; S) = \exp\left\{-\int_0^t \lambda_s(S(\tau))\, d\tau\right\} \leq 1.$$

Recall from (4.5) we have

$$\begin{aligned}S(t) &= \int_0^t K(t-a,t;S) B_s(a)\, da + \int_0^\infty L(a,t;S)\phi_s(a)\, da \\ &\leq \Psi_t + \int_t^\infty \phi(a) e^{-\underline{\lambda} t}\, da \\ &\leq \Psi_t + \Phi e^{-\underline{\lambda} t}.\end{aligned}$$

□

Now that we have shown that a solution $s(t,a)$ to (4.4) exists for $t \leq T$ (Theorems 3,

and 2) we want to use $s(T, a)$ as initial data for the interval of time $[T, 2T]$. However, since the choice of T from Theorem 3 depends on the Cauchy data, there is no guarantee that the integral operator will be a contraction on $[T, 2T]$. In the next theorem we use (4.11) to pick a T^* such that the integral operator given by (4.9) will be a contraction on each interval of length T^* even if the Cauchy data changes between intervals.

Theorem 5. *Suppose the conditions of Theorem 3 are satisfied. Then there is a solution $S(t)$ of (4.5) up to $t = \tau$.*

Proof. By Theorem 4 we have:

$$S(t) \leq \Psi_\tau + \Phi, \quad \forall\, t \in [0, \tau].$$

Recall that definitions 4.10a-4.10g depend on a choice of r. Let $r = \Psi_\tau + \Phi$. From the proof of Theorem 3 we have the following inequalities for $t \in [0, T]$:

$$||\mathscr{S}_T(S)(t) - (\Psi_t + \Phi)\,||_T \leq \lambda_1 T e^{\lambda_1 T}\,(\Psi_T + \Phi)\,, \tag{4.12}$$

$$||\mathscr{S}_T(S)(t) - \mathscr{S}_T(\bar{S})(t)||_T \leq \lambda_2 T \left|\left|S - \bar{S}\right|\right|_T e^{2\lambda_1 T}\,(\Psi_T + \Phi)\,. \tag{4.13}$$

The right hand side of Equation (4.12) being less than r means that $\mathscr{S}_T : \Sigma_T \to \Sigma_T$. The right hand side of Equation (4.13) being less than 1 means that the mapping $\mathscr{S}_T$ is a contraction mapping on Σ_T. We choose a value T^* such that the following hold:

$$\lambda_1 T^* e^{\lambda_1 T^*}\,(\Psi_\tau + \Phi) \leq r,$$

$$\lambda_2 T^* e^{2\lambda_1 T^*}\,(\Psi_\tau + \Phi) < 1.$$

Note that instead of $\Psi_{T^*} + \Phi$ as before we have $\Psi_\tau + \Phi$ which is larger and independent of T. This T^* ensures the existence of a solution $S(t)$ for $t \leq T^*$ by construction. Using terminal data of S at time T^* as initial data, we see that in the interval $t \in [T^*,\ 2T^*]$ the integral operator is still a contraction as

$$\begin{aligned} ||\mathscr{S}_{T^*}(S)(t) - \mathscr{S}_{T^*}(\bar{S})(t)||_{T^*} &\leq \lambda_2 T^* \left|\left|S - \bar{S}\right|\right|_{T^*} e^{2\lambda_1 T^*}\,(\Psi_{T^*} + \Phi) \\ &\leq \lambda_2 T^* \left|\left|S - \bar{S}\right|\right|_{T^*} e^{2\lambda_1 T^*}\,(\Psi_\tau + \Phi) < \left|\left|S - \bar{S}\right|\right|_{T^*}. \end{aligned}$$

Repeating this bootstrapping process clearly terminates in a finite number of steps; hence there exists a solution $S(t)$ of (4.5) for $0 \leq t \leq \tau$. □

Theorem 6. *Under the same assumptions as in Theorem 3, solutions $s(t, a)$ of (4.4) up to time τ are unique.*

Proof. Since we used a fixed point argument in Theorem 3 for existence we are guaranteed local uniqueness. In Theorem 5 we use Theorem 3 repeatedly on intervals of length T^* and hence we have local uniqueness in each interval. Consequently we have uniqueness for $t \in [0, \tau]$. □

To summarize, under reasonable assumptions on λ_1, λ_2 and B_s we have a solution $s(t, a)$ up to time $t = \tau$ by Theorem 5 and Theorem 2 . We would like to use $s(t, a), 0 \leq t \leq \tau$ to update the other cell densities and use Theorem 5 to give existence of a solution $s(t, a)$ up to time 2τ. This second level of bootstrapping is possible if there is no finite time blow up. The next section is devoted to finding bounds on the growth of the system and concludes in stating a theorem giving global existence of solutions to the full PDE system.

4.3 Bounded Growth

Below is a summary of ideas that we will use to show that solutions to the full PDE system (4.1) do not blow up in finite time.

- Show that removing death and prescribing larger Cauchy data will result in larger populations.
- Derive bounds on growth of system without death. Show that the original system will also be bounded by this growth.
- Conclude growth of populations is bounded by exponential growth.

Lemma 4.3.1. *Solutions of the following PDE increase when $\gamma_i(t)$ decreases, $\phi_i(a)$ increases and $B(t)_i$ increases.*

$$\frac{\partial \rho_i}{\partial t} + \frac{\partial \rho_i}{\partial a} = -\gamma_i(t)\rho_i(t, a), \quad (a, t) \in [0, \tau_\rho] \times \mathbb{R}^+, \tag{4.14a}$$

$$\rho_i(0, a) = \phi_i(a), \tag{4.14b}$$

$$\rho_i(t, 0) = B_i(t). \tag{4.14c}$$

Proof. We know from Equation (3.8) that solutions to the above PDE have the form:

$$\rho(a, t) = \begin{cases} \phi_i(a - t) \exp\left\{-\int_0^t \gamma_i(\alpha)\, d\alpha\right\}, & t < a, \\ B_i(t - a) \exp\left\{-\int_0^a \gamma_i(t - a + \alpha)\, d\alpha\right\}, & t > a. \end{cases}$$

Let ρ_1 and ρ_2 be solutions of (4.14) for $i = 1, 2$ respectively. If $\gamma_1(t) \leq \gamma_2(t),\ B_1(t) \geq B_2(t)$,

and $\phi_1(a) \geq \phi_2(a),\ (a,t) \in [0,\tau_\rho] \times \mathbb{R}^+$, we have for $t < a$,

$$\begin{aligned}
\rho_1 - \rho_2 &= \phi_1(a-t)e^{-\int_0^t \gamma_1(\alpha)\,d\alpha} - \phi_2(a-t)e^{-\int_0^t \gamma_2(\alpha)\,d\alpha} \\
&= (\phi_1 - \phi_2)\, e^{-\int_0^t \gamma_1(\alpha)\,d\alpha} + \phi_2 \left(e^{-\int_0^t \gamma_2(\alpha)\,d\alpha} - e^{-\int_0^t \gamma_1(\alpha)\,d\alpha} \right) \\
&\geq 0, \qquad \text{since } \phi_1(a) \geq \phi_2(a),\ \gamma_1(t) \leq \gamma_2(t)
\end{aligned}$$

Similarly, for $t > a$ we have

$$\begin{aligned}
\rho_1 - \rho_2 &= B_1(t-1)e^{-\int_0^t \gamma_1(t-a+\alpha)\,d\alpha} - B_2(t-a)e^{-\int_0^t \gamma_2(t-a+\alpha)\,d\alpha} \\
&= (B_1 - B_2)\, e^{-\int_0^t \gamma_1(t-a+\alpha)\,d\alpha} + B_2 \left(e^{-\int_0^t \gamma_2(t-a+\alpha)\,d\alpha} - e^{-\int_0^t \gamma_1(t-a+\alpha)\,d\alpha} \right) \\
&\geq 0, \qquad \text{since } B_1(t) \geq B_2(t),\ \gamma_1(t) \leq \gamma_2(t).
\end{aligned}$$

□

It is clear that this result also holds for cell densities without a terminal age (compartments s and w) as well as cell densities with variable maturation rates (compartment n). We intend to examine a system where the death moduli are set to 0, thereby eliminating death from the system. We will show this gives an upper bound on the growth of solutions to the original system (4.1).

$$\partial_t m^* + \partial_a m^* = 0, \tag{4.15a}$$
$$\partial_t s^* + \partial_a s^* = 0, \tag{4.15b}$$
$$\partial_t p^* + \partial_a p^* = 0, \tag{4.15c}$$
$$\partial_t n^* + V_n(G(t))\partial_a n^* = 0, \tag{4.15d}$$
$$\partial_t w^* + \partial_a w^* = 0, \tag{4.15e}$$

with initial and renewal conditions given by:

$$\begin{aligned}
m^*(0,a) &= \phi_m(a) & m^*(t,0) &= \beta_1 S^*(t) & t > 0,\ a &\in [0,\tau_s] \\
s^*(0,a) &= \phi_s(a) & s^*(t,0) &= 2m^*(t,\tau_s) & t > 0,\ a &\in [0,\infty) \\
p^*(0,a) &= \phi_p(a) & p^*(t,0) &= \delta_1 S^*(t) & t > 0,\ a &\in [0,\tau_p] \\
n^*(0,a) &= \phi_n(a) & n^*(t,0) &= A_1 p^*(t,\tau_p) & t > 0,\ a &\in [0,\tau_n] \\
w^*(0,a) &= \phi_w(a) & w^*(t,0) &= n^*(t,\tau_n) & t > 0,\ a &\in [0,\infty),
\end{aligned}$$

where β_1, δ_1 and A_1 are given by:

$$\beta_1 = \sup_{S\geq 0} \beta(S), \quad \delta_1 = \sup_{W\geq 0} \delta(W), \quad A_1 = \sup_{G\geq 0} A(G). \tag{4.17}$$

Lemma 4.3.2. *If solutions m, s, p, n, w exist to the full PDE system (4.1) up to $t = \tau$ and β_1, δ_1, and A_1 as defined in (4.17) are finite then $m^* \geq m$, $s^* \geq s$, $p^* \geq p$, $n^* \geq n$, and $w^* \geq w$ (up to $t = \tau$), where the cell densities $(\cdot)^*$ are solutions to (4.15).*

Proof. The system for cell densities $(\cdot)^*$ are of the form (3.1); therefore, solutions exist up to $t = \tau$. Supposing that $S^*(t) \geq S(t)$, we have

$$\begin{aligned} p^*(t,0) &= \delta_1 S^*(t) \geq \delta(W(t))S(t) = p(t,0), \\ m^*(t,0) &= \beta_1 S^*(t) \geq \beta(S(t))S(t) = m(t,0). \end{aligned}$$

Then from Lemma 4.3.1 we see that $p^* \geq p$, $n^* \geq n$, $m^* \geq n$, $w^* \geq w$. Next we prove $S^*(t) \geq S(t)$. Let $B_s^*(t)$ denote the renewal condition for $s^*(t, a)$. Note that $B_s^*(t) \geq B_s(t)$ for $t \leq \tau$. By Theorem 1 we have:

$$\begin{aligned} S^*(t) - S(t) &= \int_0^t B_s^* \, dt + \int_0^\infty \phi_s^*(a) \, da - \int_0^t K(t-a,t;S)B_s(a) \, da - \int_0^\infty L(a,t;S)\phi_s(a) \, da \\ &= \int_0^t \left[(B_s^*(a) - B_s(a)) \, K(t-a,t;S) + (1 - K(t-a,t;S)) \, B_s^*(t) \right] \, da \\ &+ \int_0^\infty (1 - L(a,t;s))\phi_s^*(a) \, da + \int_0^\infty (\phi_s^*(a) - \phi_s(a))L(a,t;S) \, da \\ &\geq 0, \quad \text{since each term is non-negative} \end{aligned}$$

It remains to show $s^*(t, a) \geq s(t, a)$, this follows directly from (4.7). □

Lemma 4.3.2 gives that the cell densities which are solutions to (4.15) are larger than the corresponding solutions of (4.1) up to time $t = \tau$. The following theorem will prove this result up to an arbitrary time T.

Theorem 7. *If solutions $m, s, p, n,$ and w exist to (4.1) up to an arbitrary time T and $\beta_1, \delta_1,$ and $A_1 < \infty$ then $m^* \geq m$, $s^* \geq s$, $p^* \geq p$, $n^* \geq n$, and $w^* \geq w$ up to $t = T$, where the cell densities $(\cdot)^*$ are solutions to (4.15).*

Proof. Neglecting the Cauchy conditions, the PDE governing each compartment of (4.15) are of the form (3.1). Using the decoupling method from Chapter 3 we can use the method of characteristics to find solutions to (4.15) up until $t = \tau$. We would like to use terminal values of the cell densities $(\cdot)^*$ at $t = \tau$ and repeat this process on the interval $[\tau, 2\tau]$, but we need to ensure there is no finite time blow-up in any compartment.

To show the growth of s^* and w^* are bounded it is sufficient to show the growth of S^*, W^* are bounded by exponentials. First we show $S^*(t)$ has bounded growth. By Theorem 1 we have:

$$S^*(t) = \Phi_s + \int_0^t B_s^*(a)\, da. \tag{4.18}$$

The renewal equation for S^* has the form:

$$B_s^*(t) = \begin{cases} 2\phi_m^*(\tau_s - t), & t \le \tau_s, \\ 2\beta_1 S^*(t - \tau_s), & t > \tau_s. \end{cases}$$

S^* is monotonically increasing in time. Hence for $t > \tau_s$, $S^*(t) \ge S^*(t - \tau_s)$. Let

$$\bar{B}_s(t) := \begin{cases} 2\phi_m^*(\tau_s - t), & t \le \tau_s, \\ 2\beta_1 S^*(t), & t > \tau_s. \end{cases}$$

Since $\bar{B}_s \ge B_s^*$, from (4.18) we have

$$S^*(t) \le \phi_s^* + \int_0^t \bar{B}_s(a)\, da.$$

For $t \le \tau_s$, S^* is simply given by (4.18). For $t > \tau_s$, we have:

$$\begin{aligned} S^*(t) &\le \Phi_s^* + 2\Phi_m^* + 2\beta_1 \int_0^{t-\tau} S^*(a)\, da \\ &\le \Phi_s^* + 2\Phi_m^* + 2\beta_1 \int_0^{t} S^*(a)\, da \\ &\le (\Phi_s^* + 2\Phi_m^*)\, e^{2\beta_1 t}, \qquad \text{by Gronwall's inequality [2].} \end{aligned}$$

To show $W^*(t)$ has bounded growth we have a similar argument.

$$\begin{aligned} W^*(t) &\le \Phi_w^* + A_1\Phi_p^* + \Phi_n^* + \delta_1 A_1 \int_0^t S^*(a)\, da \\ &\le \Phi_w^* + A_1\Phi_p^* + \Phi_n^* + A_1\delta_1 \frac{\Phi_s^* + 2\Phi_m^*}{2\beta_1} e^{2\beta_1 t}. \end{aligned}$$

Since the growth of $S^*(t)$, $W^*(t)$ can be bounded by exponentials, we can use the decoupling method described in Chapter 3 along with (3.8) to build solutions to (4.15) in intervals of length τ.

Lemma 4.3.2 give $s^* \ge s$ up to $t = \tau$. Then we have

$$m^*(t, 0) = \beta_1 S^*(t) \ge \beta(S(t))S(t) = m(t, 0), \quad t = \tau.$$

It follows that by $m^* \geq m$ and $t \leq 2\tau$ by Lemma 4.3.1. Similarly we have

$$s^*(t,0) = m(t,\tau_s) = \beta_1 S^*(t-\tau_s) \geq m(t,\tau_s) = s(t,0), \quad t \in [\tau, 2\tau].$$

It follows that $s^* \geq s$ for $t \in [\tau, 2\tau]$ from Lemma 4.3.2. As growth of s is bounded, we can repeat this process without fear of finite-time blow up and conclude that $s^* \geq s$ up to $t = T$. The inequalities for the other cell densities follow similarly. □

Theorem 8. *Suppose* $\lambda_1, \lambda_2, \beta_1, \delta_1$, *and* A_1 *as defined in* (4.10) *and* (4.17) *are finite and all initial data,* ϕ_i *for* $i = m, s, p, n$, *and* w, *of* (4.1) *are piece-wise continuous and integrable. Then there are solutions of the full PDE* (4.1) *up to arbitrary time* T.

Proof. The conditions of Theorem 5 are satisfied by assumption so we have a solution $S(t)$ up to $t = \tau$ to the integral formulation (4.5). This S is then used to specify the renewal conditions for compartments m and p. Compartments for m, n, p and w all have linear governing PDE and can be solved up to $t = \tau$ using S. Considering the terminal data at $t = \tau$ as initial data we can repeat this argument as $S(t)$ has bounded growth by Theorem 7. □

4.4 Summary of theoretical results

Note that the forms of $\beta(S), \delta(W), \gamma_i(G)$ $(i = m, s, p, n, w)$ and $A(t)$ have not been used in the previous results. The actual forms of these functions, given in Chapter 2, satisfy the conditions of every theorem in this chapter. That is $\beta(S), \delta(W), \gamma_i(G)$ $(i = m, s, p, n, w)$ and $A(G)$ are Lipschitz continuous and bounded. Therefore, we have established existence of solutions to the full PDE system (4.1) for global time.

Chapter 5

Conclusion

In this thesis, we have discussed an age-structured model of chemotherapy-induced neutropenia. In Chapter 2, we gave necessary and sufficient conditions for the existence of a nontrivial steady state of the PDE system. In Chapter 3, we used the method of characteristics to decouple the system for short time. In Chapter 4, the existence of solutions to the decoupled problem for the resting stem cells was proved using a fixed point argument on a related integral operator. The solution to the decoupled problem was then used to find all cell densities up to time $t = \tau$. We then showed we can repeat this process due to bounds on the growth of the entire system.

As solutions are not necessarily continuous between characteristics, and the death modulus governing the resting stem cells is nonlocal, developing numerical methods for the full PDE system is difficult. Many assumptions were made about the full PDE system for the sake of numerical computation in [5]. Under similar assumptions, a variety of numerical methods were implemented in [7]. Future work might include developing a discontinuous finite element method to solve the full system without these assumptions.bioi

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