A Mathematical Model of Cancer Stem Cell Lineage Population Dynamics with Mutation

Accumulation and Telomere Length Hierarchies

By

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Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in

Mathematics

August, 2012

Nashville, Tennessee

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ACKNOWLEDGMENTS

First and foremost, I would like to that my adviser, professor Glenn Webb, for his teaching me not only the ways of Mathematics but the ways of the Mathematical society. I would also like to thank professors Gieri Simonett and Alexander Powell for steering me, without their knowledge, toward a career in analysis and biomathematics in particular. I would especially like to thank professor Joanna Wares for her lecture on biomath. Thirty minutes in, I was sold.

Last, but not least, I would like to thank my mother, Korneliya, for encouraging me to come to the United States ten years ago.

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CHAPTER I

INTRODUCTION

Telomeres are the ends of chromosomes in eukaryotic cells. They are repeated DNA sequences that do not contain genetic information. A cell goes through several phases in its cycle, the final being mitosis - division of the cell into two daughters. Although both daughters are genetically identical to the mother, the splitting of chromosomes is not symmetrical - there is DNA loss. This loss occurs at the ends of the chromosomes, so it is only loss of telomeres. Each cell has a finite number of telomeres, therefore its descendants can only divide a finite number of times (the cells that cannot divide any further eventually die). The number of those divisions is called a Hayflick limit [28][40][31].

At the top of the telomere hierarchy is the stem cell. The stem cell has two properties that characterize it: self-renewal and potency. Self-renewal is the ability of the cell to divide and reproduce itself without differentiation (i.e. one daughter of the stem cell remains a stem cell). Potency is the ability of the stem cell to differentiate into specialized cell types (i.e. the other daughter will be a cell with more specific functions)(Figure I.1). Those two abilities allow the stem cells to create organs and tissues: self-renewal guarantees constant supply of cells, and differentiation guarantees the production of cells whose functions are essential for the tissue [40][31]. Other types of cells in the differentiation hierarchy are progenitor cells, and differentiated (mature) cells. Differentiated cells perform very specific functions in the body. They cannot self-renew. Progenitor cells are a middle stage between stem cells and differentiated cells.

A hierarchy imposed in the model divides cells into classes, based on how long their telomeres are, which coincides with how differentiated they are. The more differentiated cells have the shortest and the least differentiated cells, the stem cells, have the longest telomeres.

There is strong evidence that cancer develops after several stages of mutagenesis of normal cells (Figure I.2). Mutations can not only change the characteristics and functions of the cell but

also alter its capability of survival. Cancer cells generally proliferate faster, are more competitive for resources, and grow larger than normal cells [48][37][12].

In the present model a mutation can occur only during replication of DNA (i.e. during cell division). This mutation would be exhibited by the daughter cells. The daughter cells also inherit the mutations their mother cell has accumulated before division. The descendants of the daughter cells can acquire further mutations until, eventually, their descendants reach the number (and type) of mutations necessary for the formation of a cancer cell. Thus, we impose a hierarchial structure upon the cells, based on how many mutations they have accumulated (which is equivalent to how close they are to being cancerous). However, both non-cancer and cancer cells exhibit the telomere hierarchy. Therefore, combining both hierarchies, we can split cells into classes depending on the number of acquired mutations, and the number of differentiations left until their descendants become fully differentiated.

The main objective of the model presented in this article is to describe the interactions between cells of several levels of differentiation and malignancy by tracking their lineages. The model tries to address three questions:

1. Considering cell mutation as a dynamic population process, rather than a one-time random event, what can we show about cancer cell population growth in relation to the growth of the populations of non-cancer cells?

2. What is the role of stem cells in the cell population dynamics?

3. Is the cancer stem cell count as small as scientists have claimed (some results claim that only one in ten thousand cancer cells is a cancer stem cell[13][9])?

The model addresses these questions through both mathematical analysis and numerical simulations and the answers appear in the Discussion.

Difficulty in observing and experimenting with stem cells has led to a rise in mathematical models, which can describe cell growth and interaction. Several previous models have considered a telomere or differentiation hierarchy [32][30]. In [2], Arino, Kimmel, and Webb looked at a model

of telomere loss in both discrete and continuous time. Under their assumptions, the cells grew in polynomial time, the fastest growing cells being the ones with the least telomeres. However, it is the initial reservoir of the cells with highest amount of telomeres that determines the size of the asymptotic population. In [3], Arino, Sánchez, and Webb looked at telomere loss using a continuous model involving a linear system of partial differential equations. In fact, the model presented here can be considered an expansion of their model. Their result was consistent with [3] - polynomial growth of all cell classes and faster growth of cells with less telomeres. In [28], Levy, et al, gave another discrete model of telomere loss, exploring its connection to cell senescence. Discrete classification of maturity and tracking of a cell cohort during successive divisions have been done previously in [7] by Bernard, Pujo-Menjouet, and Mackey. These authors considered cells in two phases: resting phase and proliferative phase. Their results are consistent with experimental data and their model is a good framework for characterization of different cell subpopulations. In [22] Fearon and Vogelstein introduced a model for sequential accumulation of mutations, known as a "Vogelgram". Their hypothesis, that a cell goes through several mutations to become cancerous, is a very important assumption for our model. In [23], Gentry, Ashkenazi, and Jackson developed a model that combined cell hierarchy with sequential accumulation of mutations. They focused on the effect different types of mutations had on cancer growth. The mathematical model proposed in the present paper differs from theirs in several ways. In [23], the model considers cell maturity as a continuous variable correlated to differentiation, while in the present work differentiation is discrete and determines cell classes. The present model tracks cell lineages through multiple generations, not unlike [7], and focuses on the role of the stem cells as generators of this lineage.

The model presented here is an age-dependent structured population model, represented by a system of partial differential equations. Models of this type are originally known from works by Sharpe, Lotka, and McKendrick, extended by M. Gurtin and R. MacCamy. A general treatment of age-dependent population dynamics models is given by Glenn Webb in [45]. Such models are also often used as examples within the field of semigroups of linear operators and their applications [20].
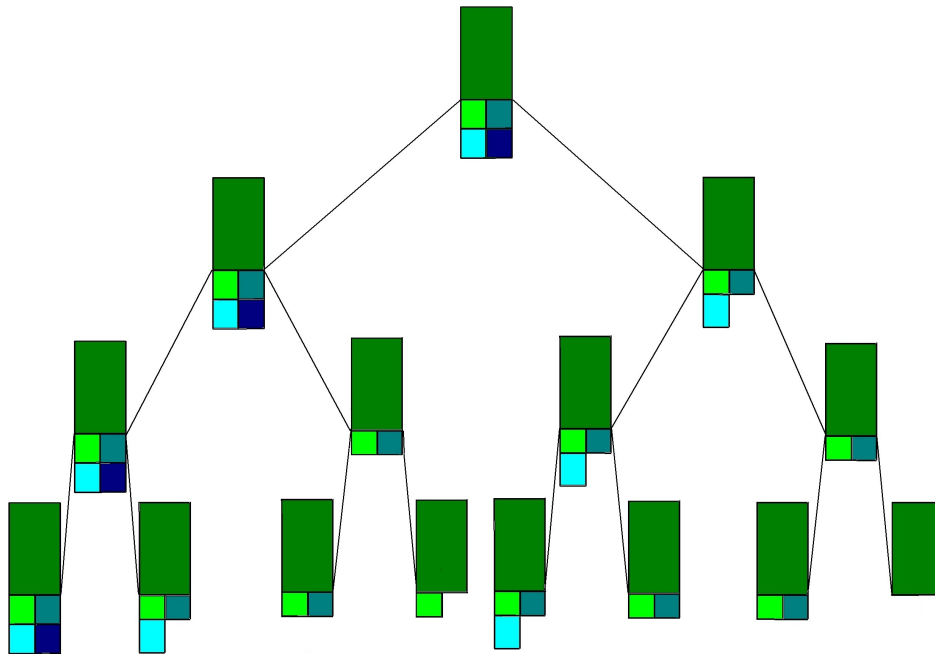
Figure I.1: The process of asymmetrical telomere shortening as a cell divides. The top cell is a stem cell with full length chromosomes. The leftmost branch of division consists of stem cells (self-renewal). The other branches depict more differentiated cells. They exhibit loss of chromosome ends - telomeres [28]. Note that a cell may lose different telomere lengths when dividing.
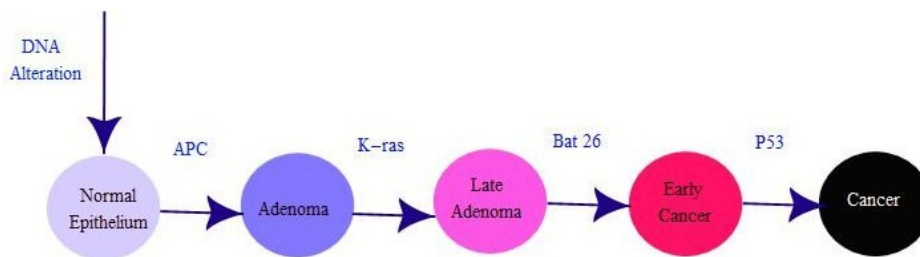
Figure I.2: A Genetic Model for Colorectal Tumorigenesis. This is an example of a Vogelgram - multistep cancer progression model [22]

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THE LINEAR MODEL

The assumptions of the model are:

1. Telomere loss only occurs during division. There is no loss of telomeres driven by outside sources (oxidation, etc.[1][50]).

2. If a mutation occurs during the division of a cell, the mutation is exhibited by the daughters of the cell and not by the mother cell.

The model is formulated as the following system of partial differential equations:

$$\begin{cases} \frac{\partial u_{j,i}(a,t)}{\partial t} + \frac{\partial u_{j,i}(a,t)}{\partial a} = -(\mu_{j,i}(a) + \beta_{j,i}(a))u_{j,i}(a,t) \\ u_{j,i}(0,t) = 2\sum_{k=j}^{n}(p_{j,k,i}\int_{0}^{\infty}\beta_{k,i}(a)u_{k,i}(a,t)da+ \\ q_{j,k,i-1}\int_{0}^{\infty}\beta_{k,i-1}(a)u_{k,i-1}(a,t)da) \\ u_{j,i}(a,0) = \phi_{j,i}(a), \end{cases} \qquad (\text{II.1})$$

where:

Definition II.1.

1. $j = 1, ..., n; i = 0, ..., m - 1$; also, for the rest of the paper, let $N = nm$.

2. j represents the number of telomeres of a cell, $1 \leq j \leq n$. Hence it also represents the number of divisions a cell has to go through until one of its descendants cannot divide any further. Moreover, it is the number of differentiation stages the lineage of a cell goes through until a fully differentiated cell is produced.

3. i is the number of mutations a cell has accumulated, $0 \leq i \leq m - 1$.

4. For $t \geq 0, u_{j,i}(a, t) \in L_1([0, \infty))$, represents the density of cells with age a at time t, in the jth telomere class, with i mutations.

5. $\mu_{j,i}(a) \geq 0$, is the age-specific mortality rate of cells in the jth telomere, i^{th} mutation class.

6. $\beta_{j,i}(a) > 0$, is the age-specific proliferation rate of cells in the jth telomere, i^{th} mutation class.

7. $\mu_{j,i}(a) \in L^\infty[0, \infty)$.

8. $\beta_{j,i}(a) \in L^\infty[0, \infty)$.

9. Therefore, we can define $\bar{\beta}$, such that $\bar{\beta} \geq \beta_{j,i}(a), \forall 1 \leq j \leq n, 0 \leq i \leq m-1, \forall a \in [0, \infty)$.

10. Similarly, define $\bar{\mu}$, such that $\bar{\mu} \geq \mu_{j,i}(a), \forall 1 \leq j \leq n, 0 \leq i \leq m-1, \forall a \in [0, \infty)$.

11. $p_{j,k,i} > 0$, is the probability that one of the daughters of a cell in the kth telomere and i^{th} mutation class will be a cell in the jth telomere, i^{th} mutation class.

12. $q_{j,k,i-1} > 0$, is the probability that a cell in the kth telomere, $(i-1)^{th}$ mutation class will produce, by acquiring a mutation during division, a cell in the jth telomere, i^{th} mutation class.

Remark II.2. In Equation II.1, if $i = 0, q_{j,k,i-1} = 0, 1 \leq j \leq n, j \leq k \leq n$.

Hypothesis II.3. A mother cell in the jth telomere, i^{th} mutation class, $j = 1, ..., n; i = 0, ..., m-1$, produces one daughter cell in the same class. The other daughter could be either in a lower telomere, same mutation class, lower telomere, $(i+1)^{th}$ mutation class, or same telomere, $(i+1)^{th}$ mutation class. We do not keep track of cells in the 0th telomere class (they cannot divide). A cell with $m-1$ mutations is considered cancerous and cannot acquire any further mutations.

The hypothesis means that:

1. $p_{j,j,i} = \frac{1}{2}, \forall 1 \leq j \leq n, 0 \leq i \leq m-1$.

2. $p_{j,k,i} = 0$ for $j > k, \forall 2 \leq j \leq n, 0 \leq i \leq m-1$.

3. $q_{j,k,i} = 0$ for $j > k, \forall 2 \le j \le n, 0 \le i \le m - 1$.

4. $\sum_{k=j+1}^{n} p_{j,k,i} + \sum_{k=j}^{n} q_{j,k,i} = \frac{1}{2}, \forall 1 \le j \le n; 0 \le i \le m - 2$.

Remark II.4. Since we do not track the 0th telomere class, the probabilities regarding the offspring of cells of telomere class (j, i), $j = 1, 0 \le i \le m - 1$, need not add up to 1.

Hypothesis II.5. $\int_0^\infty \beta_{j,i}(a) e^{-\int_0^a \beta_{j,i}(x)dx} da = 1, \forall 1 \le j \le n, 0 \le i \le m - 1$.

Hypothesis II.5 presents the *net reproduction rate* $\int_0^\infty \beta_{j,i}(a) e^{-\int_0^a \beta_{j,i}(x)dx} da$. In population models, the *net reproduction rate* generally refers to the expected number of offspring a population unit (cell in our case) is expected to have within its lifetime. For our model, $\int_0^\infty \beta_{j,i}(a) e^{-\int_0^a \beta_{j,i}(x)dx} da$ is the probability that a cell in class (j, i) will go into mitosis and produce a cell in the same class, if it does not die. From Hypothesis II.3, this probability is 1, hence the balance law given by Hypothesis II.5.

ANALYSIS OF THE LINEAR MODEL RECAST AS AN ORDINARY DIFFERENTIAL

EQUATION

III.1 The Total Population Ordinary Differential Equation

Hypothesis III.1. $\mu_{j,i}(a) = \mu_{j,i} \geq 0$ and $\beta_{j,i}(a) = \beta_{j,i} > 0, \forall 1 \leq j \leq n; 0 \leq i \leq m - 1$ (i.e. they are constants).

Remark III.2. Hypothesis II.5 is automatically satisfied if $\beta_{j,i}(a)$ is a constant.

Integrating II.1 with respect to a over $[0, \infty)$, we get:

$$\int_0^\infty \frac{\partial u_{j,i}(a,t)}{\partial t} da - u_{j,i}(0,t) = -(\mu_{j,i} + \beta_{j,i}) \int_0^\infty u_{j,i}(a,t) da \qquad \text{(III.1)}$$

Since $u_{j,i}(a,t)$ is a density function, $\int_0^\infty u_{j,i}(a,t) da$ gives the total population of the $(j,i)^{th}$ class of cells. Call it $U_{j,i}(t)$. Also,

$$u_{j,i}(0,t) = 2 \sum_{k=j}^n \left(p_{j,k,i} \int_0^\infty \beta_{k,i} u_{k,i}(a,t) da + q_{j,k,i-1} \int_0^\infty \beta_{k,i-1} u_{k,i-1}(a,t) da \right).$$

Then, the problem is recast as a system of ordinary differential equations:

$$U'_{j,i}(t) = -(\mu_{j,i} + \beta_{j,i}) U_{j,i}(t) + 2 \sum_{k=j}^n (p_{j,k,i} \beta_{k,i} U_{k,i}(t) + q_{j,k,i-1} \beta_{k,i-1} U_{k,i-1}(t))$$

$$= -(\mu_{j,i} + \beta_{j,i}) U_{j,i}(t) + 2 p_{j,j,i} \beta_{j,i} U_{j,i}(t) +$$

$$+ 2 \sum_{k=j+1}^n p_{j,k,i} \beta_{k,i} U_{k,i}(t) + 2 \sum_{k=j}^n q_{j,k,i-1} \beta_{k,i-1} U_{k,i-1}(t)$$

From Hypotheses II.3, since $p_{j,j,i} = \frac{1}{2}$, the equation above simplifies to:

$$U'_{j,i}(t) = -\mu_{j,i}U_{j,i}(t) + 2\sum_{k=j+1}^{n} p_{j,k,i}\beta_{k,i}U_{k,i}(t) + 2\sum_{k=j}^{n} q_{j,k,i-1}\beta_{k,i-1}U_{k,i-1}(t) \qquad \text{(III.2)}$$

Let $\vec{U}(t) = (U_{1,0}(t), ..., U_{n,0}(t), U_{1,1}(t), ..., U_{n,1}(t), ..., U_{j,i}(t), ..., U_{n,m-1}(t))^{\top}$, where $\vec{v}^{\top}$ is the transpose of $\vec{v}$. Then, the system of equations can be rewritten as:

$$\begin{cases} \vec{U}'(t) = A\vec{U}(t) \\ \vec{U}(0) = \vec{\Phi} \end{cases} \qquad \text{(III.3)}$$

where:

1. A is an $N \times N$ matrix that can be described as an $m \times m$ block matrix. Each block is an $n \times n$ matrix. A is a lower-triangular block matrix.

2. The blocks that form A are of three types:

   (a) 0 blocks ($n \times n$ 0 matrix)

   (b) P_i blocks (they occupy the main block-diagonal of A): $n \times n$ upper-triangular matrices that describe the proliferation dynamics within the ith mutation class of cells. The diagonal of a P_i matrix consists of the mortality rates $-\mu_{j,i}, 1 \leq j \leq n$, where the j corresponds to the telomere class of the cells whose mortality $\mu_{j,i}$ describes and also the row $-\mu_{j,i}$ occupies in P_i. P_i is an upper-triangular matrix, so its other non-zero elements (all are strictly positive) are located above the main diagonal and consist of the rates $2p_{j,k,i}\beta_{k,i}$ with which cells in class (k,i) produce cells in class (j,i) during mitosis ($1 \leq j \leq n-1; j+1 \leq k \leq n; 0 \leq i \leq m-1$). $2p_{j,k,i}\beta_{k,i}$ is the $(j,k)^{th}$ element of P_i.

   (c) Q_i blocks (they occupy the first block subdiagonal of A): $n \times n$ upper-triangular matrices that describe the mutation dynamics between the $(i-1)^{th}$ and the ith mutation classes (the cells of mutation class $i-1$ mutate into cells of class i, $1 \leq i \leq m-1$). Its elements are the rates $2q_{j,k,i-1}\beta_{k,i-1}$ with which cells of class $(k, i-1)$ produce cells of

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class (j, i) during mitosis $(1 \leq j \leq n - 1; j \leq k \leq n; 1 \leq i \leq m - 1)$. $2q_{j,k,i-1}\beta_{k,i-1}$ is the $(j, k)^{th}$ element of Q_i.

(d) $\vec{\Phi} = \{\Phi_{j,i}\}_{1 \leq j \leq n; 0 \leq i \leq m-1}$. $\Phi_{j,i} \geq 0$, $1 \leq j \leq n; 0 \leq i \leq m - 1$.

The following equation is an example for the case n = 3, m = 3:

$$
\begin{pmatrix}
U'_{1,0}(t) \\
U'_{2,0}(t) \\
U'_{3,0}(t) \\
U'_{1,1}(t) \\
U'_{2,1}(t) \\
U'_{3,1}(t) \\
U'_{1,2}(t) \\
U'_{2,2}(t) \\
U'_{3,2}(t)
\end{pmatrix}
=
\begin{pmatrix}
P_0 & 0 & 0 \\
Q_1 & P_1 & 0 \\
0 & Q_2 & P_2
\end{pmatrix}
\cdot
\begin{pmatrix}
U_{1,0}(t) \\
U_{2,0}(t) \\
U_{3,0}(t) \\
U_{1,1}(t) \\
U_{2,1}(t) \\
U_{3,1}(t) \\
U_{1,2}(t) \\
U_{2,2}(t) \\
U_{3,2}(t)
\end{pmatrix},
$$

where

$$
P_0 =
\begin{pmatrix}
-\mu_{1,0} & 2p_{1,2,0}\beta_{2,0} & 2p_{1,3,0}\beta_{3,0} \\
0 & -\mu_{2,0} & 2p_{2,3,0}\beta_{3,0} \\
0 & 0 & -\mu_{3,0}
\end{pmatrix}
$$

$$
P_1 =
\begin{pmatrix}
-\mu_{1,1} & 2p_{1,2,1}\beta_{2,1} & 2p_{1,3,1}\beta_{3,1} \\
0 & -\mu_{2,1} & 2p_{2,3,1}\beta_{3,1} \\
0 & 0 & -\mu_{3,1}
\end{pmatrix}
$$

$$
P_2 =
\begin{pmatrix}
-\mu_{1,2} & 2p_{1,2,2}\beta_{2,2} & 2p_{1,3,2}\beta_{3,2} \\
0 & -\mu_{2,2} & 2p_{2,3,2}\beta_{3,2} \\
0 & 0 & -\mu_{3,2}
\end{pmatrix}
$$

$$Q_1 = \begin{pmatrix} 2q_{1,1,0}\beta_{1,0} & 2q_{1,2,0}\beta_{2,0} & 2q_{1,3,0}\beta_{3,0} \\ 0 & 2q_{2,2,0}\beta_{2,0} & 2q_{2,3,0}\beta_{3,0} \\ 0 & 0 & 2q_{3,3,0}\beta_{3,0} \end{pmatrix}$$

$$Q_2 = \begin{pmatrix} 2q_{1,1,1}\beta_{1,1} & 2q_{1,2,1}\beta_{2,1} & 2q_{1,3,1}\beta_{3,1} \\ 0 & 2q_{2,2,1}\beta_{2,1} & 2q_{2,3,1}\beta_{3,1} \\ 0 & 0 & 2q_{3,3,1}\beta_{3,1} \end{pmatrix}$$

So, $A =$

$$\begin{pmatrix} -\mu_{1,0} & 2p_{1,2,0}\beta_{2,0} & 2p_{1,3,0}\beta_{3,0} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\mu_{2,0} & 2p_{2,3,0}\beta_{3,0} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\mu_{3,0} & 0 & 0 & 0 & 0 & 0 & 0 \\ 2q_{1,1,0}\beta_{1,0} & 2q_{1,2,0}\beta_{2,0} & 2q_{1,3,0}\beta_{3,0} & -\mu_{1,1} & 2p_{1,2,1}\beta_{2,1} & 2p_{1,3,1}\beta_{3,1} & 0 & 0 & 0 \\ 0 & 2q_{2,2,0}\beta_{2,0} & 2q_{2,3,0}\beta_{3,0} & 0 & -\mu_{2,1} & 2p_{2,3,1}\beta_{3,1} & 0 & 0 & 0 \\ 0 & 0 & 2q_{3,3,0}\beta_{3,0} & 0 & 0 & -\mu_{3,1} & 0 & 0 & 0 \\ 0 & 0 & 0 & 2q_{1,1,1}\beta_{1,1} & 2q_{1,2,1}\beta_{2,1} & 2q_{1,3,1}\beta_{3,1} & -\mu_{1,2} & 2p_{1,2,2}\beta_{2,2} & 2p_{1,3,2}\beta_{3,2} \\ 0 & 0 & 0 & 0 & 2q_{2,2,1}\beta_{2,1} & 2q_{2,3,1}\beta_{3,1} & 0 & -\mu_{2,2} & 2p_{2,3,2}\beta_{3,2} \\ 0 & 0 & 0 & 0 & 0 & 2q_{3,3,1}\beta_{3,1} & 0 & 0 & -\mu_{3,2} \end{pmatrix}$$

The solution to equation III.3 is:

$$\vec{U}(t) = e^{tA}\vec{\Phi} \tag{III.4}$$

III.2 Asymptotic Analysis

Theorem III.4. *Let hypotheses II.3 and III.1 hold and let $\vec{U}(t)$ be the unique solution of Equation III.3. Then:*

1. *If, for every $1 \leq j \leq n$ and for every $0 \leq i \leq m-1$, $\mu_{j,i} > 0$, then $\lim_{t \to \infty} U_{j,i}(t) = 0$.*

2. *If, for every $1 \leq j \leq n$ and for every $0 \leq i \leq m-1$, $\mu_{j,i} = 0$, then $U_{j,i}(t)$ is a polynomial in t of degree $n - j + i$. Furthermore, the coefficient of t^{n-j+i} of this polynomial is a multiple of $\Phi_{n,0}$.*

Proof. Case 1: $\forall 1 \leq j \leq n, 0 \leq i \leq m-1, \mu_{j,i} > 0$

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Matrix A is a lower-triangular block matrix. Therefore, from [8], $det(A - \lambda I_N) = \Pi_{i=0}^{m-1} det(P_i - \lambda I_n)$, where P_i are the matrices described above and I_k is the identity $k \times k$ matrix ($k = n, N$). Each P_i is an upper-triangular matrix. Therefore, $det(P_i - \lambda I_n) = \Pi_{j=1}^{n}(-\mu_{j,i} - \lambda)$. So, $det(A - \lambda I_N) = \Pi_{i=0}^{m-1}\Pi_{j=1}^{n}(-\mu_{j,i} - \lambda)$. The equation implies that eigenvalues of matrix A are $\{-\mu_{j,i}\}_{1 \leq j \leq n; 0 \leq i \leq m-1}$. Since they are all negative, $\lim_{t \to \infty} e^{tA}\vec{\Phi} = 0$ (see e.g. [33]). Hence, $\lim_{t \to \infty} U_{j,i}(t) = 0$.

Case 2: $\forall 1 \leq j \leq n, 0 \leq i \leq m-1, \mu_{j,i} = 0$

Note, for the remainder of the proof:

1. A block refers to an $n \times n$ matrix within the block matrix A and the powers of A. A is an $m \times m$ block matrix and so are its powers.

2. Consider an indexing on the block subdiagonals of a matrix such that the main block diagonal is the 0th subdiagonal.

3. Consider an indexing on the superdiagonals of the blocks such that the main diagonal is the 0th superdiagonal.

4. $M_{k,l}$ refers to the $(k,l)^{th}$ block of block-matrix M, where k is the block row, $1 \leq k \leq m$ and l is the block-column $1 \leq l \leq m$.

5. P_i and $Q_{i+1}, 0 \leq i \leq m-1$ are the same matrices defined earlier in the section but with one important difference: P_i's main diagonal is zero.

6. All non-zero elements of the matrices we consider are positive.

7. For the remainder of the proof, a matrix is considered "positive", if it is non-zero and all of its non-zero elements are positive.

8. A block row, a block column, or a block subdiagonal is referred to as "positive" if it consists of matrices that are "positive", according to the definition above.

Throughout the proof, we use a Lemma, which is proved in the Appendix:

Lemma III.5. *Let C and B be $n \times n$ positive upper-triangular matrices. Let the first k super-diagonals of C (the main diagonal is also considered a superdiagonal) be zero and the first m superdiagonals of B be zero, $0 \le k, m \le n-1$. Assume every element on the lth superdiagonal of C, $k \le l \le n-1$, and r^{th} superdiagonal of B, $m \le r \le n-1$ is positive. Then CB and BC are upper-triangular matrices in which exactly the first $k+m$ superdiagonals are zero (if $k+m \ge n$, CB and BC will be the zero matrix) and every element of the sth superdiagonal, $k+m \le s \le n$, is positive.*

We encourage the reader to refer to Example III.6 as an illustration of the Lemmas that follow.

Example III.6. *(n = 3, m = 3):*

$$
P_0 = \begin{pmatrix} 0 & 2p_{1,2,0}\beta_{2,0} & 2p_{1,3,0}\beta_{3,0} \\ 0 & 0 & 2p_{2,3,0}\beta_{3,0} \\ 0 & 0 & 0 \end{pmatrix}
$$

$$
P_1 = \begin{pmatrix} 0 & 2p_{1,2,1}\beta_{2,1} & 2p_{1,3,1}\beta_{3,1} \\ 0 & 0 & 2p_{2,3,1}\beta_{3,1} \\ 0 & 0 & 0 \end{pmatrix}
$$

$$
P_2 = \begin{pmatrix} 0 & 2p_{1,2,2}\beta_{2,2} & 2p_{1,3,2}\beta_{3,2} \\ 0 & 0 & 2p_{2,3,2}\beta_{3,2} \\ 0 & 0 & 0 \end{pmatrix}
$$

$$
Q_1 = \begin{pmatrix} 2q_{1,1,0}\beta_{1,0} & 2q_{1,2,0}\beta_{2,0} & 2q_{1,3,0}\beta_{3,0} \\ 0 & 2q_{2,2,0}\beta_{2,0} & 2q_{2,3,0}\beta_{3,0} \\ 0 & 0 & 2q_{3,3,0}\beta_{3,0} \end{pmatrix}
$$

$$
Q_2 = \begin{pmatrix} 2q_{1,1,1}\beta_{1,1} & 2q_{1,2,1}\beta_{2,1} & 2q_{1,3,1}\beta_{3,1} \\ 0 & 2q_{2,2,1}\beta_{2,1} & 2q_{2,3,1}\beta_{3,1} \\ 0 & 0 & 2q_{3,3,1}\beta_{3,1} \end{pmatrix}
$$

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$$A =$$

$$
\begin{pmatrix}
0 & 2p_{1,2,0}\beta_{2,0} & 2p_{1,3,0}\beta_{3,0} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 2p_{2,3,0}\beta_{3,0} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
2q_{1,1,0}\beta_{1,0} & 2q_{1,2,0}\beta_{2,0} & 2q_{1,3,0}\beta_{3,0} & 0 & 2p_{1,2,1}\beta_{2,1} & 2p_{1,3,1}\beta_{3,1} & 0 & 0 & 0 \\
0 & 2q_{2,2,0}\beta_{2,0} & 2q_{2,3,0}\beta_{3,0} & 0 & 0 & 2p_{2,3,1}\beta_{3,1} & 0 & 0 & 0 \\
0 & 0 & 2q_{3,3,0}\beta_{3,0} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 2q_{1,1,1}\beta_{1,1} & 2q_{1,2,1}\beta_{2,1} & 2q_{1,3,1}\beta_{3,1} & 0 & 2p_{1,2,2}\beta_{2,2} & 2p_{1,3,2}\beta_{3,2} \\
0 & 0 & 0 & 0 & 2q_{2,2,1}\beta_{2,1} & 2q_{2,3,1}\beta_{3,1} & 0 & 0 & 2p_{2,3,2}\beta_{3,2} \\
0 & 0 & 0 & 0 & 0 & 2q_{3,3,1}\beta_{3,1} & 0 & 0 & 0
\end{pmatrix}
$$

$$
A = \begin{pmatrix}
P_0 & 0 & 0 \\
Q_1 & P_1 & 0 \\
0 & Q_2 & P_2
\end{pmatrix}
$$

$$
A^2 = \begin{pmatrix}
P_0^2 & 0 & 0 \\
Q_1 P_0 + P_1 Q_1 & P_1^2 & 0 \\
Q_2 Q_1 & Q_2 P_1 + P_2 Q_2 & P_2^2
\end{pmatrix}
$$

$$
P_0^2 = \begin{pmatrix}
0 & 0 & 4\beta_{2,0}\beta_{3,0}p_{1,2,0}p_{2,3,0} \\
0 & 0 & 0 \\
0 & 0 & 0
\end{pmatrix}
$$

$$Q_1 P_0 + P_1 Q_1 =$$

$$
\begin{pmatrix}
0 & 4\beta_{1,0}\beta_{2,0}p_{1,2,0}q_{1,1,0} + 4\beta_{2,0}\beta_{2,1}p_{1,2,1}q_{2,2,0} & 4\beta_{1,0}\beta_{3,0}p_{1,3,0}q_{1,1,0} + 4\beta_{2,0}\beta_{3,0}p_{2,3,0}q_{1,2,0} + 4\beta_{2,1}\beta_{3,0}p_{1,2,1}q_{2,3,0} + 4\beta_{3,0}\beta_{3,1}p_{1,3,1}q_{3,3,0} \\
0 & 0 & 4\beta_{2,0}\beta_{3,0}p_{2,3,0}q_{2,2,0} + 4\beta_{3,0}\beta_{3,1}p_{2,3,1}q_{3,3,0} \\
0 & 0 & 0
\end{pmatrix}
$$

$$Q_2 Q_1 =$$

$$
\begin{pmatrix}
4\beta_{1,0}\beta_{1,1}q_{1,1,0}q_{1,1,1} & 4\beta_{1,1}\beta_{2,0}q_{1,1,1}q_{1,2,0} + 4\beta_{2,0}\beta_{2,1}q_{1,2,1}q_{2,2,0} & 4\beta_{1,1}\beta_{3,0}q_{1,1,1}q_{1,3,0} + 4\beta_{2,1}\beta_{3,0}q_{1,2,1}q_{2,3,0} + 4\beta_{3,0}\beta_{3,1}q_{1,3,1}q_{3,3,0} \\
0 & 4\beta_{2,0}\beta_{2,1}q_{2,2,0}q_{2,2,1} & 4\beta_{2,1}\beta_{3,0}q_{2,2,1}q_{2,3,0} + 4\beta_{3,0}\beta_{3,1}q_{2,3,1}q_{3,3,0} \\
0 & 0 & 4\beta_{3,0}\beta_{3,1}q_{3,3,0}q_{3,3,1}
\end{pmatrix}
$$

$$A^3 = \begin{pmatrix} 0 & 0 & 0 \\ Q_1 P_0^2 + P_1 Q_1 P_0 + P_1^2 Q_1 & 0 & 0 \\ Q_2 Q_1 P_0 + Q_2 P_1 Q_1 + P_2 Q_2 Q_1 & Q_2 P_1^2 + P_2^2 Q_2 + P_2 Q_2 P_1 & 0 \end{pmatrix}$$

$$P_0^3 = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

$Q_1 P_0^2 + P_1 Q_1 P_0 + P_1^2 Q_1 =$

$$\begin{pmatrix} 0 & 0 & 8\beta_{1,0}\beta_{2,0}\beta_{3,0}p_{1,2,0}p_{2,3,0}q_{1,1,0} + 8\beta_{2,0}\beta_{2,1}\beta_{3,0}p_{1,2,1}p_{2,3,0}q_{2,2,0} + 8\beta_{2,1}\beta_{3,0}\beta_{3,1}p_{1,2,1} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

$Q_2 Q_1 P_0 + Q_2 P_1 Q_1 + P_2 Q_2 Q_1 =$

$$\begin{pmatrix} 0 & c_{1,2} & c_{1,3} \\ 0 & 0 & c_{2,3} \\ 0 & 0 & 0 \end{pmatrix},$$

where

$c_{1,2} = 8\beta_{1,0}\beta_{1,1}\beta_{2,0}p_{1,2,0}q_{1,1,0}q_{1,1,1} + 8\beta_{1,1}\beta_{2,0}\beta_{2,1}p_{1,2,1}q_{1,1,1}q_{2,2,0} + 8\beta_{2,0}\beta_{2,1}\beta_{2,2}p_{1,2,2}q_{2,2,0}q_{2,2,1}$

$c_{1,3} = 8\beta_{1,0}\beta_{1,1}\beta_{3,0}p_{1,3,0}q_{1,1,0}q_{1,1,1} + 2\beta_{3,0}p_{2,3,0}(4\beta_{1,1}\beta_{2,0}q_{1,1,1}q_{1,2,0} + 4\beta_{2,0}\beta_{2,1}q_{1,2,1}q_{2,2,0}) +$

$+ 8\beta_{1,1}\beta_{2,1}\beta_{3,0}p_{1,2,1}q_{1,1,1}q_{2,3,0} + 8\beta_{2,1}\beta_{2,2}\beta_{3,0}p_{1,2,2}q_{2,2,1}q_{2,3,0} +$

$+ 2\beta_{3,0}(4\beta_{1,1}\beta_{3,1}p_{1,3,1}q_{1,1,1} + 4\beta_{2,1}\beta_{3,1}p_{2,3,1}q_{1,2,1})q_{3,3,0} +$

$+ 2\beta_{3,0}q_{3,3,0}(4\beta_{2,2}\beta_{3,1}p_{1,2,2}q_{2,3,1} + 4\beta_{3,1}\beta_{3,2}p_{1,3,2}q_{3,3,1})$

$c_{2,3} = 8\beta_{2,0}\beta_{2,1}\beta_{3,0}p_{2,3,0}q_{2,2,0}q_{2,2,1} + 8\beta_{2,1}\beta_{3,0}\beta_{3,1}p_{2,3,1}q_{2,2,1}q_{3,3,0} + 8\beta_{3,0}\beta_{3,1}\beta_{3,2}p_{2,3,2}q_{3,3,0}q_{3,3,1}$

$$A^4 =$$

$$
\begin{pmatrix}
 & 0 & & 0 & 0 \\
 & 0 & & 0 & 0 \\
Q_2Q_1P_0^2 + Q_2P_1Q_1P_0 + P_2Q_2Q_1P_0 + Q_2P_1^2Q_1 + P_2^2Q_2Q_1 + P_2Q_2P_1Q_1 & 0 & 0
\end{pmatrix}
$$

$$Q_2Q_1P_0^2 + Q_2P_1Q_1P_0 + P_2Q_2Q_1P_0 + Q_2P_1^2Q_1 + P_2^2Q_2Q_1 + P_2Q_2P_1Q_1 =$$

$$
\begin{pmatrix}
0 & 0 & c_{1,3}^1 \\
0 & 0 & 0 \\
0 & 0 & 0
\end{pmatrix},
$$

where

$$c_{1,3}^1 = 16\beta_{1,0}\beta_{1,1}\beta_{2,0}\beta_{3,0}p_{1,2,0}p_{2,3,0}q_{1,1,0}q_{1,1,1} + 16\beta_{1,1}\beta_{2,0}\beta_{2,1}\beta_{3,0}p_{1,2,1}p_{2,3,0}q_{1,1,1}q_{2,2,0} +$$

$$+ 16\beta_{2,0}\beta_{2,1}\beta_{2,2}\beta_{3,0}p_{1,2,2}p_{2,3,0}q_{2,2,0}q_{2,2,1} + 16\beta_{1,1}\beta_{2,1}\beta_{3,0}\beta_{3,1}p_{1,2,1}p_{2,3,1}q_{1,1,1}q_{3,3,0} +$$

$$+ 16\beta_{2,1}\beta_{2,2}\beta_{3,0}\beta_{3,1}p_{1,2,2}p_{2,3,1}q_{2,2,1}q_{3,3,0} + 16\beta_{2,2}\beta_{3,0}\beta_{3,1}\beta_{3,2}p_{1,2,2}p_{2,3,2}q_{3,3,0}q_{3,3,1}$$

$$
A^5 =
\begin{pmatrix}
0 & 0 & 0 \\
0 & 0 & 0 \\
0 & 0 & 0
\end{pmatrix}
$$

The proof also uses the following three lemmas, which are also proved in the Appendix:

Lemma III.7. *If $1 \le k \le m - 1$, the kth block subdiagonal is the highest indexed positive block subdiagonal of A^k. Any block subdiagonal of higher index is 0.*

Lemma III.8. *In $A^k, 1 \le k \le m + n$, any block element of a positive block subdiagonal indexed by $i, 0 \le i \le m - 1$, is an upper-triangular matrix in which exactly the first $k - i$ superdiagonals (including the main diagonal) are 0.*

Lemma III.9. *If $n \le k < n+m$, the $(k-n+1)^{th}$ block subdiagonal is the lowest indexed positive block subdiagonal of A^k. Any block subdiagonal of lower index is 0.*

All eigenvalues of A are zero, therefore, $A^{n+m} = 0$, A is nilpotent, and $e^{tA}\vec{\Phi}$ is a finite polynomial vector in t. Thus, each cell class has a polynomial growth in t.

First, we need to determine the polynomials in t that describe the growth of each mutation class. This is equivalent to determining the polynomials in t that corresponds to a block-row i in $e^{tA} = I + tA + \frac{t^2 A^2}{2} + ... + \frac{t^{m+n-1}A^{m+n-1}}{(m+n-1)!}, 1 \le i \le m$. This is, in turn, equivalent to determining for which powers k of A^k, the block row corresponding to the mutation class is positive.

From Lemma III.7, the power k, for which a block subdiagonal indexed $(i-1)$ in A^k becomes positive (i.e. the power for which this block becomes the highest indexed positive block in A^k) is $(i-1)$. So, any polynomial in t that describes the growth of cells in mutation class corresponding to block row $i, 1 \le i \le m$, is at least t^{i-1}.

From Lemma III.9, it follows that a block row $i, 1 \le i \le m$, becomes 0 only when the $(i-1)^{th}$ block subdiagonal, which contains the block element $A_{i,1}^k$, becomes 0 for some power k of $A^k, k \ge n$. Therefore, one can conclude that when $k = n+i-2$, the $(i-1)^{th}$ block subdiagonal is positive in A^{n+i-2} and when $k = n+i-1$, it is 0 in A^{n+i-1}.

Therefore, any polynomial in t that describes the growth of cells in mutation class corresponding to block row $i, 1 \le i \le m$, is at most t^{n+i-2}.

What needs to be determined next is what polynomials describe the growth of the cells within the telomere classes of mutation class $i-1$. This is equivalent to determining the highest power of k for which a row $j, 1 \le j \le n$ remains positive in $A_{i,1}^k, i-1 \le k \le n+i-1$. The last statement, in turn, is equivalent to determining the highest power of k for which the superdiagonal indexed $n-j$ remains positive in $A_{i,1}^k$. From Lemma III.8, this power is $k = i+n-j-1$. Therefore, the row j in block row i corresponds to a polynomial in t of power $t^{i+n-j-1}, 1 \le i \le m, 1 \le j \le n$. If we switch the indexing of i to make it correspondent to how many mutations a class of cells a block row represents, the growth of cells in mutation class $i, 0 \le i \le m-1$, telomere class $j, 1 \le j \le n$ is determined by a polynomial in t of power t^{i+n-j}.

Example III.10. *(n = 2, m = 2):*

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$$A = \begin{pmatrix} 0 & 2p_{1,2,0}\beta_{2,0} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 2q_{1,1,0}\beta_{1,0} & 2q_{1,2,0}\beta_{2,0} & 0 & 2p_{1,2,1}\beta_{2,1} \\ 0 & 2q_{2,2,0}\beta_{2,0} & 0 & 0 \end{pmatrix}$$

$$\begin{pmatrix} U_{1,0} \\ U_{2,0} \\ U_{1,1} \\ U_{2,1} \end{pmatrix} = e^{tA}.\vec{\Phi} =$$

$$= \begin{pmatrix} \Phi_{1,0} + 2p_{2,1,0}\beta_{2,0}\Phi_{2,0}t \\ \Phi_{2,0} \\ \Phi_{1,1} + 2p_{2,1,1}\beta_{2,1}\Phi_{2,1}t + 2\Phi_{1,0}q_{1,1,0}\beta_{1,0}t + 2\Phi_{2,0}(q_{1,2,0}\beta_{2,0}t + p_{2,1,0}\beta_{2,0}q_{1,1,0}\beta_{1,0}t^2 + p_{2,1,1}\beta_{2,1}q_{2,2,0}\beta_{2,0}t^2) \\ \Phi_{2,1} + 2\Phi_{2,0}q_{2,2,0}\beta_{2,0}t \end{pmatrix}$$

From Lemma III.8 and the above, the element that contains the highest power of t, t^{i+n-j}, in row j, block row i in e^{tA}, $1 \le j \le n; 1 \le i \le m$, is in the nth column of block $e^{tA}_{i,1}$. This column contains the elements that are matrix multiplied by $\Phi_{n,0}$ when determining $e^{tA}\vec{\Phi}$. Hence, the coefficient of $t^{n-j+i}, 1 \le j \le n; 0 \le i \le m - 1$, is a multiple of $\Phi_{n,0}$ □

In Theorem III.4.1, the model depicts a situation in which cell mortality has profound effect on the outcome - eventually all cells die. It can predict the cell dynamics in a long-term *in vitro* or *in vivo* experiment. Theorem III.4.2 presents a model, more suitable to depict short term *in vitro* and *in vivo* interaction between the different cell classes, because cell mortality does not play a major role in short term experiments. Part 2 of the theorem shows that the more differentiated a cell population is, the faster it grows. This result is consistent with our knowledge of the distribution of cells within the cell hierarchy of the human body, for example the hierarchy of human hematopoiesis [29]. Further, the theorem also shows that cell populations that have acquired a higher number of malignant mutations grow faster. This result is consistent with the nature of aggressive cancer growth [48][39][24]. Note that Theorem III.4 makes no assumption about the proliferation rate, $\beta_{j,i}$, of different classes. Therefore, the increased growth can be explained by the processes of cell differentiation and mutation accumulation. In the model, those processes are presented in Equation II.1, which describes the sources of new cells for the different cell classes. This fact suggests that

mutation acquisition is reason enough for cancer cells to grow faster than normal cells. A more complete treatment of the issue is given in the Discussion section.

CHAPTER IV

ANALYSIS OF THE ORIGINAL LINEAR MODEL AS A PARTIAL DIFFERENTIAL EQUATION - THE ABSTRACT PROBLEM

We would like to introduce some notation for convenience:

Let X be an N-dimensional Banach space, $\vec{v} \in X$ and $Q \in L(X)$, where $L(X)$ is the space of linear operators on X. Then:

1. $\{v_k\}_\vee = \vec{v}$, where v_k is the kth component of $\vec{v}$, $1 \leq k \leq N$, $1 \leq k \leq N$.

2. Qv_k is the kth component of $Q\vec{v}$, $1 \leq k \leq N$.

3. $\displaystyle\sum_{j=1,i=0}^{j=n,i=m-1} v_{j,i} = v_{1,0} + v_{2,0} + ... + v_{n,0} + v_{1,1} + ... + v_{n,1} + ...v_{1,m-1} + ...v_{n,m-1}$, where j and i are the indexes referring to the telomere and mutation classes of cell populations, respectively.

4. $diag[a_k]$ is a diagonal matrix with dimension N whose diagonal entries are $a_1, a_2, ..., a_N$.

IV.1   Solution of the Original Problem

Let us refer to Equation II.1, together with Hypothesis II.3 and Definition II.1, as the Original Problem (OP).

Let $X := L_1(\mathbb{R}_+; \mathbb{R}^N)$ with the norm $||\vec{v}||_X = \displaystyle\sum_{k=1}^{N} ||v_k||_{L_1(\mathbb{R})}$, where $||v_k||_{L_1(\mathbb{R})} = \int_0^\infty |v_k(x)|dx$, $1 \leq k \leq N$.

Remark IV.1. For convenience, if $\vec{v} \in \mathbb{R}^\mathbb{N}$, we define $||\vec{v}||_X := ||\vec{v}||_{l_1} = \displaystyle\sum_{k=1}^{N} |v_k|$.

The (OP) can be recast as the following abstract Cauchy problem:

$$\begin{cases} \frac{d}{dt}\vec{u}(a,t) = A\vec{u}(a,t) \\ \vec{u}(0,t) = N\vec{u}(a,t) \\ \vec{u}(a,0) = \vec{\phi}(a), \end{cases} \qquad \text{(IV.1)}$$

where A and N are linear operators on X.

Remark IV.2.

1. $A\vec{v} := -\frac{d}{da}\vec{v}(a) - diag[\beta_{j,i}(a) + \mu_{j,i}(a)]\vec{v}(a)$, $1 \leq j \leq n$, $0 \leq i \leq m-1$, $\forall \vec{v} \in D(A)$, the domain of A.

2. $D(A) := \{\vec{v} \in X : \frac{d}{da}\vec{v}(a) \in X, \vec{v}(0) = N\vec{v}\}$.

3. $N\vec{v} := M\{\int_0^\infty \beta_{j,i}(a)v_{j,i}(a)da\}_\vee, 1 \leq j \leq n, 0 \leq i \leq m-1$, where M is the matrix involving the probabilities for class distributions of daughter cells of dividing cells, as in Definition II.1.

The matrix M has the following structure:

1. M is an $N \times N$ matrix that can be described as an $m \times m$ block matrix. Each block is an $n \times n$ matrix. M is a lower-triangular block matrix.

2. The blocks that form M are of three types:

   (a) 0 blocks ($n \times n$ 0 matrix)

   (b) P_i blocks (they occupy the main block-diagonal of M): $n \times n$ upper-triangular matrices that describe the proliferation dynamics within the ith mutation class of cells. The elements on the diagonal of a P_i matrix is $2p_{j,j,i} = 1$ (from Hypothesis II.3), $\forall 1 \leq j \leq n$. P_i is an upper-triangular matrix, so its other non-zero elements (all are strictly

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positive) are located above the main diagonal and consist of the probabilities $2p_{j,k,i}$ for the daughters of cells in class (k,i) to be cells in class (j,i) ($1 \leq j \leq n-1; j+1 \leq k \leq n; 0 \leq i \leq m-1$). $2p_{j,k,i}$ is the $(j,k)^{th}$ element of P_i.

(c) Q_i blocks (they occupy the first block subdiagonal of M): $n \times n$ upper-triangular matrices that describe the mutation dynamics between the $(i-1)^{th}$ and the ith mutation classes (the cells of mutation class $i-1$ mutate into cells of class i, $1 \leq i \leq m-1$). Its elements are the probabilities $2q_{j,k,i-1}$ for the daughters of cells of class $(k,i-1)$ to be cells of class (j,i) ($1 \leq j \leq n-1; j \leq k \leq n; 1 \leq i \leq m-1$). $2q_{j,k,i-1}$ is the $(j,k)^{th}$ element of Q_i.

The following matrix is an example for the case n = 3, m = 3:

Example IV.3.

$$
\begin{pmatrix}
P_0 & 0 & 0 \\
Q_1 & P_1 & 0 \\
0 & Q_2 & P_2
\end{pmatrix},
$$

where

$$
P_0 =
\begin{pmatrix}
1 & 2p_{1,2,0} & 2p_{1,3,0} \\
0 & 1 & 2p_{2,3,0} \\
0 & 0 & 1
\end{pmatrix}
$$

$$
P_1 =
\begin{pmatrix}
1 & 2p_{1,2,1} & 2p_{1,3,1} \\
0 & 1 & 2p_{2,3,1} \\
0 & 0 & 1
\end{pmatrix}
$$

$$P_2 = \begin{pmatrix} 1 & 2p_{1,2,2} & 2p_{1,3,2} \\ 0 & 1 & 2p_{2,3,2} \\ 0 & 0 & 1 \end{pmatrix}$$

$$Q_1 = \begin{pmatrix} 2q_{1,1,0} & 2q_{1,2,0} & 2q_{1,3,0} \\ 0 & 2q_{2,2,0} & 2q_{2,3,0} \\ 0 & 0 & 2q_{3,3,0} \end{pmatrix}$$

$$Q_2 = \begin{pmatrix} 2q_{1,1,1} & 2q_{1,2,1} & 2q_{1,3,1} \\ 0 & 2q_{2,2,1} & 2q_{2,3,1} \\ 0 & 0 & 2q_{3,3,1} \end{pmatrix}$$

So, $M =$

$$\begin{pmatrix}
1 & 2p_{1,2,0} & 2p_{1,3,0} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 2p_{2,3,0} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\
2q_{1,1,0} & 2q_{1,2,0} & 2q_{1,3,0} & 1 & 2p_{1,2,1} & 2p_{1,3,1} & 0 & 0 & 0 \\
0 & 2q_{2,2,0} & 2q_{2,3,0} & 0 & 1 & 2p_{2,3,1} & 0 & 0 & 0 \\
0 & 0 & 2q_{3,3,0} & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 2q_{1,1,1} & 2q_{1,2,1} & 2q_{1,3,1} & 1 & 2p_{1,2,2} & 2p_{1,3,2} \\
0 & 0 & 0 & 0 & 2q_{2,2,1} & 2q_{2,3,1} & 0 & 1 & 2p_{2,3,2} \\
0 & 0 & 0 & 0 & 0 & 2q_{3,3,1} & 0 & 0 & 1
\end{pmatrix}$$

Remark IV.4. Note that $||M||_{B(X)} = 2, \forall N \geq 1$, because of the distribution of probabilities. We use the column matrix norm for our calculations.

Definition IV.5. (From [20]) Let X be a Banach space. A *strongly continuous semigroup* (C_0-semigroup) in X is a family of bounded linear operators $\{T(t)\}_{t\geq0}$, such that:

1. $T(t+s) = T(t)T(s), \forall t, s \geq 0$.

2. $T(0) = I$, where I is the identity operator in $B(X)$.

3. The map $t \rightarrow T(t)v$ is continuous from $\mathbb{R}_+$ to X for each fixed $v \in X$.

Definition IV.6. (From [20]) Let X be a Banach space and let $\{T(t)\}_{t\geq0}$ be a C_0-semigroup. The

infinitesimal generator of $\{T(t)\}_{t \geq 0}$ is the mapping A from a subset of X to X, such that:

$$Av := \lim_{t \to 0^+} \frac{T(t)v - v}{t}$$

with domain $D(A) := \{v \in X : \lim_{t \to 0^+} \dfrac{T(t)v - v}{t} \text{ exists }\}$.

Then the properties of the solution are given in following Proposition:

Proposition IV.7. *$\vec{u}(a, t)$ is a generalized solution to (OP) iff it is a solution to Equation IV.1. It satisfies the following properties:*

1. *The problem is well-posed, i.e. there exists a unique solution for every initial $\vec{\phi} \in D(A)$.*

2. *The maximal interval of existence with respect to t is $[0, \infty)$.*

3. *$\forall t \geq 0$, if $\vec{\phi}$ is in X_+, the positive cone of X, so is $\vec{u}(a, t)$, i.e. if $\phi_{j,i}(a, t) \geq 0$, $\forall t \geq 0, a \geq 0$, then $u_{j,i}(a, t) \geq 0$, $\forall t \geq 0, a \geq 0$, $1 \leq j \leq n, 0 \leq i \leq m - 1$. We are obviously only interested in non-negative solutions.*

4. *$\forall t \geq 0, \vec{u}(\cdot, t)$ is a continuous mapping from $[0, \infty)$ to $D(A)$.*

5. *$\vec{u}(a, t) = (T(t)\vec{\phi})(a)$, where $T := \{T(t)\}_{t \geq 0}$ is a strongly continuous semigroup of bounded linear operators from X to itself. A is the infinitesimal generator of T.*

6. *$\overline{D(A)} = X$, i.e. $D(A)$ is dense in X.*

The Proposition is a result of the well-known properties of age-dependent population models and proofs of it can be found in [45] and [3]. We will use the method of characteristics to establish a form for the solution that will help us prove results in the further analysis.

Let:

1. $t - a = c.$

2. $w_{j,i}^c(t) := u_{j,i}(t - c, t),\ 1 \leq j \leq n, 0 \leq i \leq m - 1$.

3. $t_c := max\{0, c\}$.

4. $t \geq t_c$.

$$\frac{\partial w_{j,i}^c}{\partial t} = \lim_{h \to 0^+} \frac{u_{j,i}(t + h - c, t + h) - u_{j,i}(t - c, t)}{h}$$

$$= (-\mu_{j,i}(t - c) - \beta_{j,i}(t - c))w_{j,i}^c(t), t \geq t_c$$

So, $w_{j,i}^c(t) = w_{j,i}^c(t_c)e^{-\int_{t_c}^t \mu_{j,i}(s-c)+\beta_{j,i}(s-c)ds}, t \geq t_c$

If $c = t - a$, then $t \geq a, c \geq 0, t_c = c$, and $w_{j,i}^c(t) = w_{j,i}^c(c)e^{-\int_c^t \mu_{j,i}(s-c)+\beta_{j,i}(s-c)ds}$

Therefore, $u_{j,i}(a, t) = u_{j,i}(0, t - a)e^{-\int_{t-a}^t \mu_{j,i}(s-c)+\beta_{j,i}(s-c)ds}, t > a$

If $c = t - a$, then $t \leq a, c \leq 0, t_c = 0$, and $w_{j,i}^c(t) = w_{j,i}^c(0)e^{-\int_0^t \mu_{j,i}(s-t+a)+\beta_{j,i}(s-t+a)ds}$

So, $u_{j,i}(a, t) = u_{j,i}(a - t, 0)e^{-\int_0^t \mu_{j,i}(s-t+a)+\beta_{j,i}(s-t+a)ds}, a \geq t$

Combining them:

$$u_{j,i}(a, t) = \begin{cases} \phi_{j,i}(a - t)e^{-\int_{a-t}^a \mu_{j,i}(s)+\beta_{j,i}(s)ds}, t \leq a, 1 \leq j \leq n, 0 \leq i \leq m - 1 \\ u_{j,i}(0, t - a)e^{-\int_0^a \mu_{j,i}(s)+\beta_{j,i}(s)ds}, t > a, 1 \leq j \leq n, 0 \leq i \leq m - 1 \end{cases} \tag{IV.2}$$

IV.2   Preliminary Results from the Theory of Semigroups of Bounded Linear Operators

We would like to introduce several definitions and propositions referring to strongly continuous semigroups that will be used in the analysis of the (OP).

Lemma IV.8. *(Proved in [20]) Let $\{T(t)\}_{t \geq 0}$ be a C_0-semigroup on a Banach space X. Then $\forall t_0 \geq 0, \exists C(t_0) \in \mathbb{R}_+$, such that $||T(t)||_{B(X)} \leq C(t_0), \forall t \in [0, t_0]$.*

Lemma IV.9. *(Proved in [20]) For a C_0-semigroup $\{T(t)\}_{t \geq 0}$ on a Banach space X, $\lim_{t \to 0} T(t)v = v, \forall v \in X$.*

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Lemma IV.10. *(Proved in [20]) For every C_0-semigroup $\{T(t)\}_{t \geq 0}$, there are constants $\omega \in \mathbb{R}, C \geq 1$, such that $||T(t)||_{B(X)} \leq C e^{\omega t}, \forall t \geq 0$.*

Definition IV.11. (From [20]) For a C_0-semigroup $\{T(t)\}_{t \geq 0}$, we define $\omega_0(T) := \inf\{\omega : \omega$ is defined as in Lemma IV.10$\}$.

Definition IV.12. Let X be a Banach space and let A be a linear operator on X. Then:

1. The *resolvent* of A, $\rho(A) := \{\lambda : (\lambda - A)^{-1} \in B(X)\}$ and $D((\lambda - A)^{-1})$ is dense in $X\}$.

2. The *spectrum* of A, $\sigma(A) := \mathbb{C}/\rho(A)$.

3. The *spectral bound* of A, $s(A) := sup\{Re\lambda : \lambda \in \sigma(A)\}$.

4. An *eigenvector* corresponding to the eigenvalue λ of A is a $\vec{v} \in D(A), \vec{v} \neq 0$, such that $(\lambda - A)\vec{v} = 0$.

5. An *eigenspace* corresponding to the eigenvalue λ of A is the subspace X_λ of X, spanned by all the eigenvectors, associated with λ.

6. An *eigenprojection* corresponding to the eigenvalue λ is a linear operator Π_λ, such that $\Pi_\lambda^2 = \Pi_\lambda$ and $\forall \vec{v} \in X, \Pi_\lambda \vec{v} \in X_\lambda$.

Definition IV.13. A linear operator on a Banach space X is compact if it maps bounded sets in X into sets with compact closure in X.

Definition IV.14. (From [20]) Let X be a Banach space. Let $K(X)$ be the space of all compact linear operators on X. Then, for every linear operator T on X, $||T||_{ess} := dist(T, K(X))$.

Definition IV.15. (From [20]) Let A be the infinitesimal generator of C_0-semigroup $\{T(t)\}_{t \geq 0}$. Then the *essential growth bound* of A, $\omega_{ess} := \inf_{t > 0} \frac{1}{t} \log ||T(t)||_{ess}$.

Remark IV.16. Note that if $A \in K(X)$, then $\omega_{ess}(A) = -\infty$.

Lemma IV.17. *(Proved in [20]) Let $\{T(t)\}_{t\geq 0}$ be a C_0-semigroup of a Banach space X with generator A. Then*

$$\omega_0 = max\{\omega_{ess}, s(A)\}$$

Moreover, for every $\omega > \omega_{ess}$, the set $\sigma_\omega := \sigma(A) \cap \{\lambda \in \mathbb{C} : Re\lambda \geq \omega\}$ is finite and the corresponding spectral projection has finite rank.

Definition IV.18. (From [20]) A C_0-semigroup $\{T(t)\}_{t\geq 0}$ on a Banach space X is called *uniformly exponentially stable* if there exists $\epsilon > 0$ such that $\lim_{t\to\infty} e^{\epsilon t}||T(t)||_{B(X)} = 0$

Lemma IV.19. *(Proved in [20]) For a C_0-semigroup $\{T(t)\}_{t\geq 0}$, if $\omega_0 < 0$, T is a uniformly exponentially stable semigroup.*

Definition IV.20. (From [20]) A C_0-semigroup $\{T(t)\}_{t\geq 0}$ on a Banach space X is called *quasi-compact* if

$$\lim_{t\to\infty} \inf\{||T(t) - S|| : S \in K(X)\} = 0$$

.

IV.3   Compactness of the Trajectories and Asymptotic Stability

Define for all $\vec{\phi} \in X$:

$$(V(t)\vec{\phi})(a) = \begin{cases} 0 & a.e. \ a \in (0, t) \\ (T(t)\vec{\phi})(a) & a.e. \ a \in (t, \infty) \end{cases} \tag{IV.3}$$

$$(W(t)\vec{\phi})(a) = \begin{cases} (T(t)\vec{\phi})(a) & a.e. \ a \in (0, t) \\ 0 & a.e. \ a \in (t, \infty) \end{cases} \tag{IV.4}$$

Proposition IV.21. *Let $\{T(t)\}_{t\geq 0}$, be the C_0-semigroup associated with (OP). Assume $\exists \ \mu > 0$,*

such that $\underline{\mu} \leq \mu_{j,i}(a), \forall 1 \leq j \leq n, 0 \leq i \leq m-1, a \in [0, \infty)$. Then, for all $\vec{\phi} \in X$, $t \geq 0$,

$$||V(t)\vec{\phi}||_X \leq e^{-\underline{\mu}t}||\vec{\phi}||_X$$

.

Proof. From IV.2,

$$
\begin{aligned}
||V(t)\vec{\phi}||_X &= \sum_{j=1,i=0}^{j=n,i=m-1} \int_t^\infty \phi_{j,i}(a-t)e^{-\int_{a-t}^a \mu_{j,i}(x)+\beta_{j,i}(x)dx}da \\
&\leq \sum_{j=1,i=0}^{j=n,i=m-1} \int_t^\infty \phi_{j,i}(a-t)e^{-\int_{a-t}^a \underline{\mu}\, dx}da \\
&= \sum_{j=1,i=0}^{j=n,i=m-1} \int_t^\infty \phi_{j,i}(a-t)e^{-\underline{\mu}t}da \\
&= e^{-\underline{\mu}t} \sum_{j=1,i=0}^{j=n,i=m-1} \int_t^\infty \phi_{j,i}(a-t)da \\
&= e^{-\underline{\mu}t}||\vec{\phi}||_X
\end{aligned}
$$

$\square$

Lemma IV.22. *(Proved in [17]) A closed and bounded subset C of L_1 is compact iff the following two conditions hold:*

$$\lim_{h \to 0} \int_0^\infty |\phi(a) - \phi(a+h)|da = 0 \qquad (\text{IV.5})$$

uniformly for $\phi \in C$ ($\phi(a+h) := 0$ if $a + h < 0$).

$$\lim_{h \to \infty} \int_h^\infty |\phi(a)|da = 0 \qquad (\text{IV.6})$$

uniformly for $\phi \in C$.

Proposition IV.23. *Consider the strongly continuous semigroup $\{T(t)\}_{t \geq 0}$, associated with the*

solution to the (OP). For every $t > 0$, the operator $W(t)$, defined in IV.4, is compact on X.

Proof. Fix t. Consider the set $\{\vec{\phi} \in X : ||\vec{\phi}||_X \leq C_1\}$. Also, from IV.8, $\exists r > 0$, such that $||T(s)||_{B(X)} \leq r, \forall s \in [0, t]$. From Equations IV.2 and IV.4,

$$(W(t)\vec{\phi})(a) = (T(t-a)N\phi_{j,i})(a)e^{-\int_0^a \mu_{j,i}(x)+\beta_{j,i}(x)dx}\vee$$

We want to show that $W(t)$ maps bounded sets in $D(A)$ to precompact sets in X. Since $T(t)$ is a bounded operator, so is $W(t)$, hence $W(t)$ maps bounded sets of $D(A)$ to bounded sets in X. Hence, if we show that the set $W(t)X$ satisfies the requirements of Lemma IV.22, then its closure will be a compact set in X.

Pick $h > t$. Then $\int_h^\infty (W(t)\vec{\phi})(a)da = 0$, from $a > t$, the definition of $W(t)$ and IV.2. Therefore, IV.6 is satisfied.

Pick $h < t$. From IV.2:

$$\sum_{j=1,i=0}^{j=n,i=m-1} \int_0^\infty |(W(t)\phi_{j,i})(a+h) - (W(t)\phi_{j,i})(a)|da$$

$$\leq \sum_{j=1,i=0}^{j=n,i=m-1} \int_0^{t-h} |(W(t)\phi_{j,i})(a+h) - (W(t)\phi_{j,i})(a)|da$$

$$+ \sum_{j=1,i=0}^{j=n,i=m-1} \int_{t-h}^t |(W(t)\phi_{j,i})(a+h) - (W(t)\phi_{j,i})(a)|da.$$

Let's concentrate on the first integral:

$$\sum_{j=1,i=0}^{j=n,i=m-1} \int_0^{t-h} |(W(t)\phi_{j,i})(a+h) - (W(t)\phi_{j,i})(a)| da$$

$$= \sum_{j=1,i=0}^{j=n,i=m-1} \int_0^{t-h} |(T(t-(a+h))N\phi_{j,i})(a)e^{-\int_0^{a+h} \mu_{j,i}(x)+\beta_{j,i}(x)dx}$$

$$- (T(t-(a+h))N\phi_{j,i})(a)e^{-\int_0^a \mu_{j,i}(x)+\beta_{j,i}(x)dx}$$

$$+ (T(t-(a+h))N\phi_{j,i})(a)e^{-\int_0^a \mu_{j,i}(x)+\beta_{j,i}(x)dx}$$

$$- (T(t-a)N\phi_{j,i})(a)e^{-\int_0^a \mu_{j,i}(x)+\beta_{j,i}(x)dx}| da$$

$$\leq \sum_{j=1,i=0}^{j=n,i=m-1} \int_0^{t-h} |(T(t-(a+h))N\phi_{j,i})(a)[e^{-\int_0^{a+h} \mu_{j,i}(x)+\beta_{j,i}(x)dx} - e^{-\int_0^a \mu_{j,i}(x)+\beta_{j,i}(x)dx}]| da$$

$$+ \sum_{j=1,i=0}^{j=n,i=m-1} \int_0^{t-h} e^{-\int_0^{a+h} \mu_{j,i}(x)dx} |(T(t-(a+h))N\phi_{j,i})(a) - (T(t-a)N\phi_{j,i})(a)| da$$

Let:

$$J_1(j,i) := \int_0^{t-h} |(T(t-(a+h))N\phi_{j,i})(a)[e^{-\int_0^{a+h} \mu_{j,i}(x)+\beta_{j,i}(x)dx} - e^{-\int_0^a \mu_{j,i}(x)+\beta_{j,i}(x)dx}]| da,$$

$$1 \leq j \leq n, 0 \leq i \leq m-1.$$

$$J_2(j,i) := \int_0^{t-h} e^{-\int_0^{a+h} \mu_{j,i}(x)dx} |(T(t-(a+h))N\phi_{j,i})(a) - (T(t-a)\phi_{j,i})(0)| da,$$

$$1 \leq j \leq n, 0 \leq i \leq m-1.$$

Note that

$$e^{-\int_0^{a+h} \mu_{j,i}(x)+\beta_{j,i}(x)dx} - e^{-\int_0^a \mu_{j,i}(x)+\beta_{j,i}(x)dx}$$

$$= \int_0^h (\mu_{j,i}(a+b) + \beta_{j,i}(a+b))e^{-\int_0^{a+b} \mu_{j,i}(x)+\beta_{j,i}(x)dx} db$$

$$\leq h(\bar{\beta} + \bar{\mu}).$$

Therefore, from above and the definition of $D(A)$,

$$J_1(j,i) \leq rh(\bar{\beta} + \bar{\mu}) \int_0^{t-h} N\phi_{j,i}(a)da$$

$$= rh(\bar{\beta} + \bar{\mu}) \int_0^{t-h} M \int_0^\infty \beta_{j,i}(x)\phi_{j,i}(x)dx\, da$$

$$\leq 2rh\bar{\beta}(\bar{\beta} + \bar{\mu})C_1(t-h).$$

So, $\displaystyle\lim_{h \to 0} \sum_{j=1,i=0}^{j=n,i=m-1} J_1(j,i) = 0.$

On the other hand,

$$J_2(j,i) \leq \int_0^{t-h} |(T(t-(a+h))N\phi_{j,i})(a) - (T(t-a)N\phi_{j,i})(a)|da,$$

$1 \leq j \leq n, 0 \leq i \leq m-1.$

If $h > 0$,

$$\int_0^{t-h} |(T(t-(a+h))N\phi_{j,i})(a) - (T(t-a)N\phi_{j,i})(a)|da$$

$$= \int_0^{t-h} (I - T(h))(T(t-(a+h))N\phi_{j,i})(a)da$$

$$= \int_0^{t-h} (I - T(h))T(t-(a+h))M \int_0^\infty \beta_{j,i}(x)\phi_{j,i}(x)dx\, da$$

$\leq 2(t-h)r\bar{\beta}||(I - T(h))\phi_{j,i}||_X \to 0$ as $h \to 0^+$, for $1 \leq j \leq n, 0 \leq i \leq m-1,$

from IV.9.

Similarly, if $h < 0$,

$$\int_0^{t-h} |(T(t-(a+h))N\phi_{j,i})(a) - (T(t-a)N\phi_{j,i})(a)|da$$

$$= \int_0^{t-h} (T(-h) - I)(T(t-a)N\phi_{j,i})(a)da$$

$\leq 2(t-h)r\bar{\beta}||(T(-h) - I)\phi_{j,i}||_X \to 0$ as $h \to 0^-.$

So, $\displaystyle\lim_{h \to 0} \sum_{j=1,i=0}^{j=n,i=m-1} J_2(j,i) = 0.$

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If $h > 0$, from IV.4,

$$\int_{t-h}^{t} |(W(t)\phi_{j,i})(a+h) - (W(t)\phi_{j,i})(a)|da$$

$$= \int_{t-h}^{t} (W(t)\phi_{j,i})(a)da$$

$$= \int_{t-h}^{t} (T(t-a)N\phi_{j,i})(a)da$$

$\leq 2hr\bar{\beta}C_1 \to 0$ as $h \to 0^+$.

If $h < 0$,

$$\int_{t-h}^{t} |(W(t)\phi_{j,i})(a+h) - (W(t)\phi_{j,i})(a)|da$$

$$= \int_{t-h}^{t} (W(t)\phi_{j,i})(a+h)da$$

$$= \int_{t-h}^{t} (T(t-(a+h))N\phi_{j,i})(a)da$$

$\leq 2|h|r\bar{\beta}C_1 \to 0$ as $h \to 0^-$, for $1 \leq j \leq n, 0 \leq i \leq m-1$.

Therefore, from the above results
$\lim\limits_{h\to 0} \sum\limits_{j=1,i=0}^{j=n,i=m-1} \int_0^\infty |(W(t)\phi_{j,i})(a+h) - (W(t)\phi_{j,i})(a)|da = 0$, so IV.5 is satisfied. Therefore, $W(t)$
is a compact operator on X for every $t \geq 0$. $\qquad\square$

Proposition IV.24. *Assume $\exists \underline{\mu} > 0$, such that $\underline{\mu} < \mu_{j,i}(a), \forall 1 \leq j \leq n, 0 \leq i \leq m-1, a \in$*

$[0, \infty)$. Then the spectral bound of the strongly continuous semigroup $\{T(t)\}_{t\geq 0}$, associated with

the solution to the (OP), is negative.

Proof. What we want to do is show that the resolvent set $\rho(A)$ is the complex numbers to the right

of the line $Re\lambda = -\underline{\mu}, \ \lambda \in \mathbb{C}$. From Definition IV.12, since $D(A)$ is dense in X, what we need to

show that if $Re\lambda > -\underline{\mu}, (\lambda - A)^{-1}$ is in $B(X)$. Consider the characteristic equation for the (OP):

$\lambda\vec{\phi} - A\vec{\phi} = \vec{f}, f \in X$. It is equivalent to:

$$
\begin{cases}
\lambda\vec{\phi}(a) + \vec{\phi}'(a) + diag[\mu_{j,i}(a) + \beta_{j,i}(a)]\vec{\phi}(a) = \vec{f}(a), 1 \leq j \leq n, 0 \leq i \leq m-1 \\
\vec{\phi_{j,i}}(0) = M\{\int_0^\infty \beta_{j,i}(a)\phi_{j,i}(a)da\}_\vee, 1 \leq j \leq n, 0 \leq i \leq m-1
\end{cases}
\tag{IV.7}
$$

The general solution is:

$\vec{\phi}(a) = \{\phi_{j,i}(0)e^{-\int_0^a \lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx}\}_\vee + \{\int_0^a e^{-\int_y^a \lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx} f_{j,i}(y)dy\}_\vee, 1 \leq j \leq n, 0 \leq$

$i \leq m-1$. Apply $diag[\beta_{j,i}(a)], 1 \leq j \leq n, 0 \leq i \leq m-1$, integrate from 0 to ∞ with respect to

a, and apply M on both sides. Then, for $1 \leq j \leq n, 0 \leq i \leq m-1$:

$$
\begin{aligned}
&M\{\int_0^\infty \beta_{j,i}(a)\phi_{j,i}(a)da\}_\vee \\
&= M\{\phi_{j,i}(0)\int_0^\infty \beta_{j,i}(a)e^{-\int_0^a \lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx}da\}_\vee \\
&+ M\{\int_0^\infty \beta_{j,i}(a)\int_0^a e^{-\int_y^a \lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx} f_{j,i}(y)dyda\}_\vee.
\end{aligned}
$$

Note that $M\{\int_0^\infty \beta_{j,i}(a)\phi_{j,i}(a)da\}_\vee = \{\phi_{j,i}(0)\}_\vee$.

Therefore, for $1 \leq j \leq n, 0 \leq i \leq m-1$

$(I_N - Mdiag[\int_0^\infty \beta_{j,i}(a)e^{-\int_0^a \lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx}da])\vec{\phi}(0)$

$= M\{\int_0^\infty \beta_{j,i}(a)\int_0^a e^{-\int_y^a \lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx} f_{j,i}(y)dy\, da\}_\vee$,

where I_N is the $N \times N$ identity matrix.

Let $H(\lambda) := I_N - Mdiag[\int_0^\infty \beta_{j,i}(a)e^{-\int_0^a \lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx}da]$

Let us look at the structure of $H(\lambda)$ for two cases.

Example IV.25. *n = 2, m = 1. Then*

$$
M = \begin{pmatrix} 1 & 1 \\ 0 & 1 \end{pmatrix},
$$

$$diag[\int_0^\infty \beta_{j,i}(a)e^{-\int_0^a \lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx}da] =$$

$$\begin{pmatrix} \int_0^\infty \beta_{1,0}(a)e^{-\int_0^a \lambda+\mu_{1,0}(x)+\beta_{1,0}(x)dx}da & 0 \\ 0 & \int_0^\infty \beta_{2,0}(a)e^{-\int_0^a \lambda+\mu_{2,0}(x)+\beta_{2,0}(x)dx}da \end{pmatrix}.$$

So,

$$H(\lambda) = \begin{pmatrix} 1 - \int_0^\infty \beta_{1,0}(a)e^{-\int_0^a \lambda+\mu_{1,0}(x)+\beta_{1,0}(x)dx}da & \int_0^\infty \beta_{2,0}(a)e^{-\int_0^a \lambda+\mu_{2,0}(x)+\beta_{2,0}(x)dx}da \\ 0 & 1 - \int_0^\infty \beta_{2,0}(a)e^{-\int_0^a \lambda+\mu_{2,0}(x)+\beta_{2,0}(x)dx}da \end{pmatrix}.$$

Example IV.26. *n = 2, m = 2. Let* $h_{j,i}(\lambda) := \int_0^\infty \beta_{j,i}(a)e^{-\int_0^a \lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx}da$

$$M = \begin{pmatrix} 1 & p_{1,2,0} & 0 & 0 \\ 0 & 1 & 0 & 0 \\ q_{1,1,0} & q_{1,2,0} & 1 & 1 \\ 0 & q_{2,2,0} & 0 & 1 \end{pmatrix},$$

$$diag[\int_0^\infty \beta_{j,i}(a)e^{-\int_0^a \lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx}da] =$$

$$\begin{pmatrix} h_{1,0}(\lambda) & 0 & 0 & 0 \\ 0 & h_{1,0}(\lambda) & 0 & 0 \\ 0 & 0 & h_{1,0}(\lambda) & 0 \\ 0 & 0 & 0 & h_{1,0}(\lambda) \end{pmatrix}.$$

So,

$$H(\lambda) = \begin{pmatrix} 1 - h_{1,0}(\lambda) & p_{1,2,0}h_{2,0}(\lambda) & 0 & 0 \\ 0 & 1 - h_{2,0}(\lambda) & 0 & 0 \\ q_{1,1,0}h_{1,0}(\lambda) & q_{1,2,0}h_{2,0}(\lambda) & 1 - h_{1,1}(\lambda) & 1 \\ 0 & q_{2,2,0}h_{2,0}(\lambda) & 0 & 1 - h_{2,1}(\lambda) \end{pmatrix}.$$

We return to the general case. The matrix $H(\lambda)$ is invertible if and only if its determinant does not equal 0. Since $H(\lambda)$ is a lower-triangular block matrix,

$$det(H(\lambda)) = \prod_{j=1,i=0}^{j=n,i=m-1} (1 - \int_0^\infty \beta_{j,i}(a)e^{-\int_0^a \lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx} da).$$

Let $\lambda = \alpha + i\gamma$. Let us consider and arbitrary pair (j,i), $1 \le j \le n$, $0 \le i \le m - 1$. Then

$$1 - \int_0^\infty \beta_{j,i}(a)e^{-\int_0^a \lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx} da$$
$$= 1 - \int_0^\infty \beta_{j,i}(a)e^{-\int_0^a \beta_{j,i}(x)dx}e^\alpha \cos(\gamma)e^{-\int_0^a \mu_{j,i}(x)dx} da$$
$$+ i \int_0^\infty \beta_{j,i}(a)e^{-\int_0^a \beta_{j,i}(x)dx}e^\alpha \sin(\gamma)e^{-\int_0^a \mu_{j,i}(x)dx} da.$$

If $Re\lambda > -\underline{\mu}$,

$$Re \int_0^\infty \beta_{j,i}(a)e^{-\int_0^a \lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx} da$$
$$\le \int_0^\infty \beta_{j,i}(a)e^{-\int_0^a Re\lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx} da < 1,$$

since

$$e^{Re\lambda}e^{-\int_0^a \mu_{j,i}(x)dx} < e^{-\int_0^a \mu_{j,i}(x)-\underline{\mu}dx} < 1, \forall a > 0.$$

Therefore, if $Re\lambda > -\underline{\mu}$, $det(H(\lambda)) \ne 0$, so the matrix $H(\lambda)$ is invertible. We continue the analysis with the assumption that $Re\lambda > -\underline{\mu}$.

From II.1,

$$\sum_{j=1,i=0}^{j=n,i=m-1} M\{\int_0^\infty |\beta_{j,i}(a) \int_0^a e^{-\int_y^a \lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx} f_{j,i}(y)dy|da\}_\vee$$

$$\leq \bar{\beta} \sum_{j=1,i=0}^{j=n,i=m-1} M\{\int_0^\infty |\int_0^a e^{-\int_y^a \lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx} f_{j,i}(y)dy|da\}_\vee$$

$$\leq \bar{\beta} \sum_{j=1,i=0}^{j=n,i=m-1} M\{\int_0^\infty |\int_0^a e^{-(\lambda+\underline{\mu})(a-y)} f_{j,i}(y)dy|da\}_\vee,$$

which, by Young's Inequality,

$$\leq \bar{\beta}||f||_X \int_0^\infty |e^{-(\lambda+\underline{\mu})a}|da$$

$$\leq \frac{\bar{\beta}||f||_X}{|Re\lambda+\underline{\mu}|}.$$

Therefore, $||\phi(0)||_X \leq \frac{\bar{\beta}||H(\lambda)^{-1}||_{B(X)}||f||_X}{|Re\lambda+\underline{\mu}|}$

Let $C_2(\lambda) := \frac{\bar{\beta}||H(\lambda)^{-1}||_{B(X)}}{|Re\lambda+\underline{\mu}|}$. Therefore, by an argument, similar to the ones above,

$$||\phi||_X \leq \sum_{j=1,i=0}^{j=n,i=m-1} ||\phi_{j,i}(0)||_X \int_0^\infty |e^{-\int_0^a \lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx}|da$$

$$+ \sum_{j=1,i=0}^{j=n,i=m-1} \int_0^\infty |\int_0^a e^{-\int_y^a \lambda+\mu_{j,i}(x)+\beta_{j,i}(x)dx} f_{j,i}(y)dy|da$$

$$\leq \frac{C_2(\lambda)+1}{|Re\lambda+\underline{\mu}|}||f||_X.$$

Therefore, if $Re\lambda > -\underline{\mu}$, $(\lambda - A)^{-1}$ is a bounded linear operator on $D(A)$ and $(-\underline{\mu}, \infty) \in \rho(A)$. Hence, $s(A) \leq -\underline{\mu}$. $\qquad\square$

Theorem IV.27. *Assume $\exists \underline{\mu} > 0$, such that $\underline{\mu} < \mu_{j,i}(a), \forall 1 \leq j \leq n, 0 \leq i \leq m-1, a \in [0, \infty)$. Then, the strongly continuous semigroup $\{T(t)\}_{t\geq 0}$, associated with the solution to the (OP), is uniformly stable and $\omega_0 \leq -\underline{\mu}$.*

Proof. Note that $T(t) = V(t) + W(t)$ from IV.3 and IV.4. From Proposition IV.23, $W(t) \in K(X)$. Then, from IV.21,

$\lim_{t\to\infty} ||T(t) - W(t)||_{B(X)} = \lim_{t\to\infty} ||V(t) + W(t) - W(t)||_{B(X)}$

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$= \lim_{t \to \infty} ||V(t)||_{B(X)} \leq \lim_{t \to \infty} e^{-\underline{\mu} t} = 0.$

Therefore, from Definition IV.20 the semigroup $\{T(t)\}_{t \geq 0}$ is quasi-compact. From Definitions IV.15 and IV.15, $\omega_{ess} \leq -\underline{\mu}$. From Proposition IV.24, $s(A) \leq -\underline{\mu}$, so, from Lemma IV.17, $\omega_0 \leq -\underline{\mu}$. Then $\{T(t)\}_{t \geq 0}$ is uniformly stable from Lemma IV.19. $\qquad \square$

The result is the equivalent of Theorem III.4.2 for the (OP): when we have positive mortality, all cell classes eventually go to extinction.

CHAPTER V

A NONLINEAR VERSION OF THE ORDINARY DIFFERENTIAL EQUATION MODEL

V.1 Introduction to the Logistic Equation

We introduce a crowding term in equation III.3:

$$
\begin{cases}
\vec{U}'(t) = A\vec{U}(t) - F(\vec{U}(t))\vec{U}(t) \\
\vec{U}(0) = \vec{\Phi},
\end{cases}
\tag{V.1}
$$

where A is the matrix defined in the linear case, $\vec{U}(t)$, as before, is the vector representing the total number of cells of the different telomere and mutation classes, $\vec{\Phi}$ is the vector of the initial cell populations, and for fixed $t \geq 0$, F is a positive linear functional from $L_1(\mathbb{R}^N_+)$ to $\mathbb{R}_+$. The "crowding" term, $F(\vec{U}(t))\vec{U}(t)$, describes a situation under which the growth of the total cell population, or the population of certain cell classes, slows down. The biological interpretations are numerous. Crowding can occur because of limited nutrients, space, or events during which cells get signals to cease proliferation. The model presented in Equation V.1 does not choose a specific crowding term in this section. In the next section, Numerical Simulations, we choose a specific linear functional F and a biological interpretation. However, the mathematical results that follow do not depend on the biological interpretation of the crowding term. The following assumptions hold:

Hypothesis V.1.

1. $\mu_{j,i}(a) = \mu_{j,i} > 0, \forall 1 \leq j \leq n; 0 \leq i \leq m - 1$

2. $\beta_{j,i}(a) = \beta_{j,i} > 0, \forall 1 \leq j \leq n; 0 \leq i \leq m - 1$

3. $p_{j,k,i} = 0$ for $j > k, \forall 1 \leq j \leq n; 0 \leq i \leq m - 1$.

4. $q_{j,k,i} = 0$ for $j > k, \forall 2 \le j \le n, 0 \le i \le m - 1$.

Note: $p_{j,j,i}$ need not equal $\frac{1}{2}, \forall 1 \le j \le n, 0 \le i \le m - 1$

By an argument similar to the one in the proof of Theorem III.4, Case 1, the eigenvalues of A are of the form:$-\mu_{j,i} - \beta_{j,i} + 2p_{j,j,i}\beta_{j,i}$. Let λ_0 denote the dominant eigenvalue, that is $\lambda_0 > \lambda$, where λ is any other eigenvalue of A.

Hypothesis V.2. $\lambda_0 = -\mu_{n,m-1} - \beta_{n,m-1} + 2p_{n,n,m-1}\beta_{n,m-1}$.

In other words, the dominant eigenvalue is associated with the growth of the cancer stem cells. We can assume this since stem cells have higher degree of self-renewal than other cells, hence $p_{n,n,m-1} \ge p_{j,j,i}, \forall 1 \le j \le n; 0 \le i \le m - 1$ [44][23][43]. Also, cancer cells are assumed to have higher proliferation rate than normal cells, hence $\beta_{n,m-1} \ge \beta_{j,i}, \forall 1 \le j \le n, 0 \le i \le m - 1$ [12][37][44][23]. Note that if $p_{n,n,m-1} > \frac{1}{2}$ and $\beta_{n,m-1} > \frac{\mu_{n,m-1}}{2p_{n,n,m-1}-1}$, then $\lambda_0 > 0$.

Let $\lambda_0 > 0$. Let $A' := A - \lambda_0 I$. A' is a block matrix with structure similar to A, the only difference being the diagonal entries, hence the only difference being the P_i blocks. For simplicity of notation, let:

$$\bar{m}_{j,i} := -\mu_{j,i} - \beta_{j,i} + 2p_{j,j,i}\beta_{j,i} - (-\mu_{n,m-1} - \beta_{n,m-1} + 2p_{n,n,m-1}\beta_{n,m-1})$$

and

$$\bar{p}_{j,k,i} := 2p_{j,k,i}\beta_{k,i}, 1 \le j \le n - 1, 0 \le i \le m - 1, k > j.$$

Then , for $0 \le i < m - 1$,

$$P_i' := \begin{pmatrix} \bar{m}_{1,i} & \bar{p}_{1,2,i} & \cdots & \cdots \\ 0 & \bar{m}_{2,i} & \bar{p}_{2,3,i} & \ddots \\ \vdots & \ddots & \ddots & \ddots \\ 0 & \cdots & \cdots & \bar{m}_{n,i} \end{pmatrix}.$$

For $i = m$,

$$P'_{m-1} := \begin{pmatrix} \bar{m}_{1,i} & \bar{p}_{1,2,i} & \cdots & \cdots \\ 0 & \bar{m}_{2,i} & \bar{p}_{2,3,i} & \ddots \\ \vdots & \ddots & \ddots & \ddots \\ 0 & \cdots & \cdots & 0 \end{pmatrix}.$$

Therefore,

$$A' = \begin{pmatrix} P'_0 & 0 & \cdots & 0 \\ Q_1 & P'_1 & \cdots & \vdots \\ \ddots & \ddots & \ddots & \ddots \\ 0 & \cdots & Q_n & P'_{m-1} \end{pmatrix}$$

V.2 Asymptotic Behavior

Theorem V.3. *Assume Hypotheses V.1 and V.2. Then, Equation V.1 has a unique solution and the eigenspace of the dominant eigenvalue λ_0 of A is one dimensional. Further, if Π_0 is the eigenprojection associated with λ_0, $\vec{U}(t)$ is the unique solution to Equation V.1, and $\vec{\Psi}$ is an eigenvector of λ_0, then the first $N - n$ entries of $\vec{\Psi}$ are 0, the last n are non-zero, and $\lim_{t\to\infty} \vec{U}(t) = \frac{\lambda_0 \Pi_0 \vec{\Phi}}{F(\Pi_0 \vec{\Phi})} = \frac{\lambda_0 \vec{\Psi}}{F(\vec{\Psi})}$.*

Before we go into the proof, let us remark on the solution to Equation V.1 as a semigroup of nonlinear operators and introduce two Lemmas that describe the connection between a semigroup and its dominant eigenvalue in more detail.

Remark V.4.

1. The matrix A is the infinitesimal generator of semigroup $T := \{T(t)\}_{t\geq 0}$, given by $T(t)\vec{v} := e^{tA}\vec{v} = \sum_{k=1}^{\infty} \frac{t^k A^k \vec{v}}{k!}$.

2. The unique solution of Equation V.1 is given by the nonlinear semigroup $S(t)\vec{v} := \frac{T(t)\vec{v}}{1+\int_0^t F(T(s)\vec{v})ds}$, a result proved in [18].

3. Note that since A is an $N \times N$ matrix, it is a compact operator on $\mathbb{R}^{\mathbb{N}}$.

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Lemma V.5. *(Proved in [20]) Let $T := \{T(t)\}_{t \geq 0}$ be a C_0 semigroup on a Banach space X with generator A and take $\lambda_1, ..., \lambda_m \in \sigma(A)$ satisfying $Re\lambda_1, ..., Re\lambda_m > \omega_{ess}(A)$. Then $\lambda_1, ..., \lambda_m$ are isolated spectral values of A with finite algebraic multiplicity. If $\Pi_1, ..., \Pi_m$ denote the corresponding spectral projections and $k_1, ..., k_m$ the corresponding indexes (multiplicities), then*

$$T(t) = T_1(t) + \cdots + T_m(t) + R_m(t),$$

where

$$T_n(t) = e^{\lambda_n t} \sum_{j=0}^{k_n-1} \frac{t^j}{j!} (A - \lambda_n)^j \Pi_n , n = 1, ..., m.$$

Moreover, for every $\omega > sup\{\omega_{ess}(A)\} \cup \{Re\lambda : \lambda \in \sigma(A) \setminus \{\lambda_1, ..., \lambda_m\}\}$, there exists $C_\omega > 0$ such that

$$||R_m(t)||_{B(X)} \leq C_\omega e^{\omega t}, \forall t \geq 0.$$

Remark V.6. From the proof of the above lemma, found in [20], if $\Pi := \sum_{n=1}^m \Pi_n$ is the spectral projection of A corresponding to the spectral set $\{\lambda_1, ..., \lambda_m\}$, then $T(t) = T(t)\Pi + T(t)(I - \Pi)$, so $R_m(t) = T(t)(I - \Pi)$, where $I - \Pi$ is the projection to $X \setminus \Pi X$.

Lemma V.7. *(Proved in [46]) Let X be a Banach space and let X_+ denote the the cone of nonnegative elements of X. Let $T = \{T(t)\}_{t \geq 0}$ be a C_0 semigroup of bounded linear operators in X with infinitesimal generator A and $T(t)x \in X_+$, for $x \in X_+$. Let there exist a real number λ_0 and a direct sum decomposition $X = X_0 \oplus X_1$ with associated projections Π_i, $\Pi_i X = X_i$, $i = 0, 1$, such that $\Pi_i T(t) = T(t)\Pi_i$, $i = 0, 1$, $T(t)\Pi_0 = e^{\lambda_0}\Pi_0$, $t \geq 0$, and for some constants $C_\omega \geq 1$, $\omega < \lambda_0$, $||T(t)\Pi_1||_{B(X)} \leq C_\omega e^{\omega t}||\Pi_1||_{B(X)}$, $t \geq 0$. Let F be a bounded linear functional on X such that $Fx > 0$ for $x \in X_+ - \{0\}$. Then Equation V.1 has a unique solution. Moreover, if $\lambda_0 > 0$, then $\lim_{t \to \infty} S(t)\vec{v} = \frac{\lambda_0 \Pi_0 \vec{v}}{F(\Pi_0 \vec{v})}$.*

Proof of Theorem V.3 From Remark V.4, we know $\vec{U}(t) := S(t)\Phi$ defines a unique solution to equation V.1. Since A is a matrix on a finite dimensional space X, A is a compact linear operator

and from Remark IV.16, $\omega_{ess}(A) = -\infty$. Then, from Lemma V.5,

$$T(t) = e^{\lambda_0 t}\Pi_0 + R_0(t).$$

From V.6, $R_0(t) = T(t)(I - \Pi_0)$. Referring to Lemma V.7,

$X_0 := \Pi_0 X$, $X_1 := (I - \Pi_0)X$, and $X = X_0 \oplus X_1$.

Moreover,

$$T(t)\Pi_0 = e^{\lambda_0}\Pi_0^2 + R_0(t)\Pi_0 = e^{\lambda_0}\Pi_0.$$

Let $T(t)_{|Ker(\Pi_0)}$ be the restriction of $T(t)$ to the kernel of Π_0, which is the range of $I - \Pi_0$. The infinitesimal generator of $T(t)_{|Ker(\Pi_0)}$ is $A_{|Ker(\Pi_0)}$ from [20], and

$$\omega_0(A_{|Ker(\Pi_0)}) = \sup\{\omega_{ess}(A_{|Ker(\Pi_0)}), s(A_{|Ker(\Pi_0)})\}.$$

Since $A_{|Ker(\Pi_0)}$ is a finite matrix, $\omega_{ess}(A_{|Ker(\Pi_0)}) = -\infty$.

$$s(A_{|Ker(\Pi_0)}) = \sup\{Re\lambda : \lambda \in \sigma(A) \setminus \{\lambda_0\}\}.$$

Therefore, from Lemma IV.10, $\exists \omega$ such that

$$\omega_0(A_{|Ker(\Pi_0)}) < \omega < \lambda_0$$

and $\exists C_\omega \geq 1$, such that

$$||T(t)_{|Ker(\Pi_0)}||_{B(X)} \leq C_\omega e^\omega.$$

Therefore,

$$||R_0(t)||_{B(X)} = ||T(t)(I - \Pi_0)||_{B(X)} \leq ||T(t)_{|Ker(\Pi_0)}||_{B(X)}||I - \Pi_0||_{B(X)} \leq C_\omega e^\omega ||I - \Pi_0||_{B(X)}$$

Therefore, by Lemma V.7, $\lim_{t \to \infty} \vec{U}(t) = \frac{\lambda_0 \Pi_0 \vec{\Phi}}{F(\Pi_0 \vec{\Phi})}$.

We are interested in finding the eigenvector of λ_0, in other words $\vec{\Psi} \in \mathbb{R}^N$, such that $A'\vec{\Psi} = 0$. Let us initially restrict our attention to solutions of $P_0'\vec{\Psi}_0 = 0$, where $\vec{\Psi}_0$ is the vector of the first n entries of $\vec{\Psi}$. Refer to Example V.8 throughout the proof.

Example V.8. *(n = 3):*

$$
P_0' = \begin{pmatrix} \bar{m}_{1,0} & \bar{p}_{1,2,0} & \bar{p}_{1,3,0} \\ 0 & \bar{m}_{2,0} & \bar{p}_{2,3,0} \\ 0 & 0 & \bar{m}_{3,0} \end{pmatrix},
$$

$$
\vec{\Psi}_0 = \begin{pmatrix} \Psi_{1,0} \\ \Psi_{2,0} \\ \Psi_{3,0} \end{pmatrix}.
$$

So,

$$
P_0'.\vec{\Psi}_0 = \begin{pmatrix} \bar{m}_{1,0}\Psi_{1,0} + \bar{p}_{1,2,0}\Psi_{2,0} + \bar{p}_{1,3,0}\Psi_{3,0} \\ \bar{m}_{2,0}\Psi_{2,0} + \bar{p}_{2,3,0}\Psi_{3,0} \\ \bar{m}_{3,0}\Psi_{3,0} \end{pmatrix} = 0.
$$

Hence, $\Psi_{3,0} = 0 \Rightarrow \Psi_{2,0} = 0 \Rightarrow \Psi_{1,0} = 0.$

$$
P_{m-1}' = \begin{pmatrix} \bar{m}_{1,m-1} & \bar{p}_{1,2,m-1} & \bar{p}_{1,3,m-1} \\ 0 & \bar{m}_{2,m-1} & \bar{p}_{2,3,m-1} \\ 0 & 0 & 0 \end{pmatrix},
$$

$$
\vec{\Psi}_{m-1} = \begin{pmatrix} \Psi_{1,m-1} \\ \Psi_{2,m-1} \\ \Psi_{3,m-1} \end{pmatrix},
$$

$$P'_{m-1} \cdot \vec{\Psi}_{m-1} = 0,$$

hence $\Psi_{3,m-1}$ is a free variable, $\Psi_{2,m-1} = \frac{-\bar{p}_{2,3,m-1}}{\bar{m}_{2,m-1}} \Psi_{3,m-1}$,

and $\Psi_{1,m-1} = \left(\frac{\bar{p}_{1,2,m-1} \bar{p}_{2,3,m-1}}{\bar{m}_{1,m-1} \bar{m}_{2,m-1}} - \frac{\bar{p}_{1,3,m-1}}{\bar{m}_{1,m-1}} \right) \Psi_{3,m-1}$

$P'_0 \vec{\Psi}_0 = 0$ is a system of n equations of n variables. Note that since P'_0 is positive and upper-triangular, each variable $\Psi_{j,0}, 1 \leq j \leq n$ is linearly dependent on all variables $\Psi_{k,0}, j < k \leq n$. The last equation of the system is $m_{n,0} \vec{\Psi}_{n,0} = 0$, therefore $\vec{\Psi}_{n,0} = 0$. The $(n-1)^{th}$ equation is $m_{n-1,0} \vec{\Psi}_{n-1,0} + \bar{p}_{n-1,n,0} \vec{\Psi}_{n,0} = 0$, so $\vec{\Psi}_{n-1,0} = 0$. By similar arguments for the other elements $\Psi_{j,0}, 1 \leq j < n-1$, in $\vec{\Psi}_0$, $\vec{\Psi}_0 = 0$.

Let us consider the second block-row of A'. We need to solve, in block-matrix form, the equation:

$$\begin{pmatrix} Q_1 & P'_1 \end{pmatrix} \cdot \begin{pmatrix} \Psi_{1,0} \\ \vdots \\ \Psi_{n,1} \end{pmatrix} = 0.$$

The first elements of $(\Psi_{1,0}...\Psi_{n,1})^\top = \vec{\Psi}_0$ are zero. So, from the argument above and the rules of matrix multiplication, Q_1 does not contribute to the solution of the system. Therefore, the equation above is reduced to :

$$\begin{pmatrix} P'_1 \end{pmatrix} \cdot \begin{pmatrix} \Psi_{1,1} \\ \vdots \\ \Psi_{n,1} \end{pmatrix} = 0.$$

By an argument similar to the one above, $(\Psi_{1,1}, ..., \Psi_{n,1})^\top = 0$. By a similar inductive argument, it is easy to show that $(\Psi_{1,0}...\Psi_{n,m-2})^\top = 0$.

The solution to the equation $A'\vec{\Psi} = 0$ is reduced to solving:

$$\begin{pmatrix} P'_{m-1} \end{pmatrix} \cdot \begin{pmatrix} \Psi_{1,m-1} \\ \vdots \\ \Psi_{n,m-1} \end{pmatrix} = 0,$$

which is a system of n equations and n variables, one of them free. The last row of P'_{m-1} is zero, so the free variable is $\Psi_{n,m-1}$. P'_{m-1} is an upper-triangular, positive (except for its nth, last row, which is 0) matrix. Therefore, every variable $\Psi_{j,m-1}$ is linearly dependent on the variables $\Psi_{k,m-1}, j < k \leq n$. Therefore, each $\Psi_{l,m-1}, 1 \leq l \leq n$ can be expressed as a positive multiple of $\Psi_{n,m-1}$. So, the eigenvector associated with λ_0, $\vec{\Psi}$, is unique up to a choice of $\Psi_{n,m-1}$. Its first $N - n$ entries are 0 and the last n entries are positive multiples of $\Psi_{n,m-1}$. Fix $\Psi_{n,m-1} > 0$ and let $\vec{\Psi}$ be the so defined eigenvector of the eigenspace of A, associated with λ_0. Thus, the eigenspace is one-dimensional. Hence $\frac{\lambda_0 \Pi_0 \vec{\Phi}}{F(\Pi_0 \vec{\Phi})} = \frac{\lambda_0 C \vec{\Psi}}{F(C\vec{\Psi})} = \frac{\lambda_0 C \vec{\Psi}}{CF(\vec{\Psi})} = \frac{\lambda_0 \vec{\Psi}}{F(\vec{\Psi})}$, $C \in \mathbb{C}$. $F(\vec{\Psi})$ is a constant, hence $\lim_{t\to\infty} \vec{U}(t) = \frac{\lambda_0 \vec{\Psi}}{F(\vec{\Psi})}$, an N-dimensional vector, whose only non-zero elements correspond to the telomere classes of the cancer cells. $\qquad\square$

The biological interpretation of the result of Theorem V.3 is that all cell populations converge to a steady state, in which only cancer cells survive. Given the assumptions about the higher proliferation rate and higher probability of self-renewal of the cancer stem cell, $p_{n,n,m}$, the cancer cells eventually overtake all other existing cells. However, they also reach an equilibrium determined by the fact that there is a crowding effect in the cell environment. Therefore, the cancer cells, by being more competitive, have taken over the somatic cellular tissue. However, because of limited resources they cannot increase their population indefinitely.

CHAPTER VI

NUMERICAL RESULTS FOR THE ORDINARY DIFFERENTIAL EQUATION MODEL

VI.1   Purpose and Data

Table VI.1: Numerical values for parameters in the model

Parameter	Range based on references	Simulation Value
Non-cancer cell proliferation rate, $\beta_{j,i}$, $1 \le j \le n, 0 \le i \le m-2$ (cells/week) [47][6]	0.5 - 3.36	0.65 (Stem Cell); 0.7 (Non-Stem Cell)
Cancer cell proliferation rate, $\beta_{j,m-1}$ (cells/week) [39][48]	0.35 to 13.44	3.0
Cell mortality rate, $\mu_{j,i}$ (cells/week) [6][23] $1 \le j \le n, 0 \le i \le m-1$ (cells/week)	0.001 - 1.68	0.001 (nonlinear simulation) 0 (linear simulation)
Mutation probability, $q_{j,k,i}$ [23] $1 \le j \le n, j \le k \le n, 0 \le i \le m-2$	0.00001	0.00001
Stem Cell self-renewal probability, $p_{j,j,i}, j = n, 0 \le i \le m-1$		0.65 (nonlinear simulation) 0.5 (linear simulation)
Non-Stem Cell self-renewal probability, $p_{j,j,i}, 1 \le j \le n-1, 0 \le i \le m-1$		0.5

The main purpose of this section is to show numerical simulations of the mathematical results and demonstrate them in a visual setting. In Table VI.1 one can see the parameters used, ranges for the values of the parameters, based on evidence or previous models, and the values used in the simulations.

The proliferation rate, $\beta_{j,i}$, depends on the type of cells it refers to (stem, differentiated, cancer, etc.). The numerical values used in the simulation have been chosen to have biological meaning (based on the references), as well as simulation convenience. The mortality rate, $\mu_{j,i}$, would also differ based on the type of cells it refers to. However, the values used in the simulations are the same for all cells. A more thorough discussion of this decision can be found in Section VII. The mutation probability is evenly distributed among the possible mutation outcomes. For example, a cell in class ($j = 3$ telomeres, $i = 0$ mutations) can produce mutated daughters in classes ($j = 3$ telomeres, $i = 1$ mutation), ($j = 2$ telomeres, $i = 1$ mutation), and ($j = 1$ telomere, $i = 1$
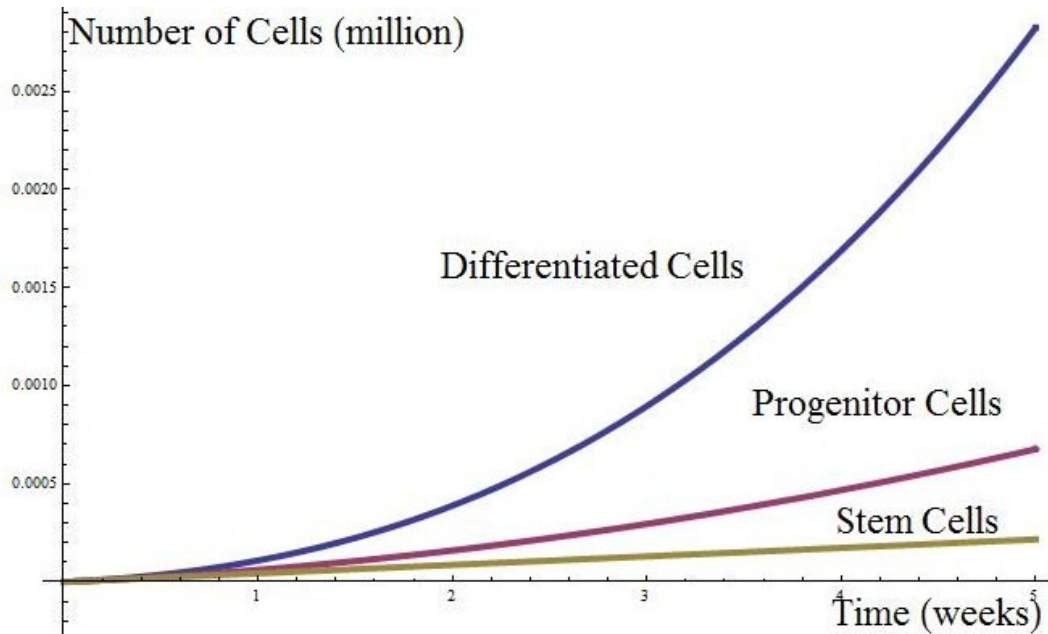
Figure VI.1: Linear model with n = 3 maximum number of telomeres and m = 3 mutation classes (2 mutations necessary to reach malignancy). Polynomial growth of cells with one mutation ($i = 1$ mutation), according to the results of Theorem III.4.2. Stem cells ($j = 3$ telomeres) grow linearly, progenitor cells ($j = 2$ telomeres) in t^2, and differentiated cells ($j = 1$ telomere) in t^3.
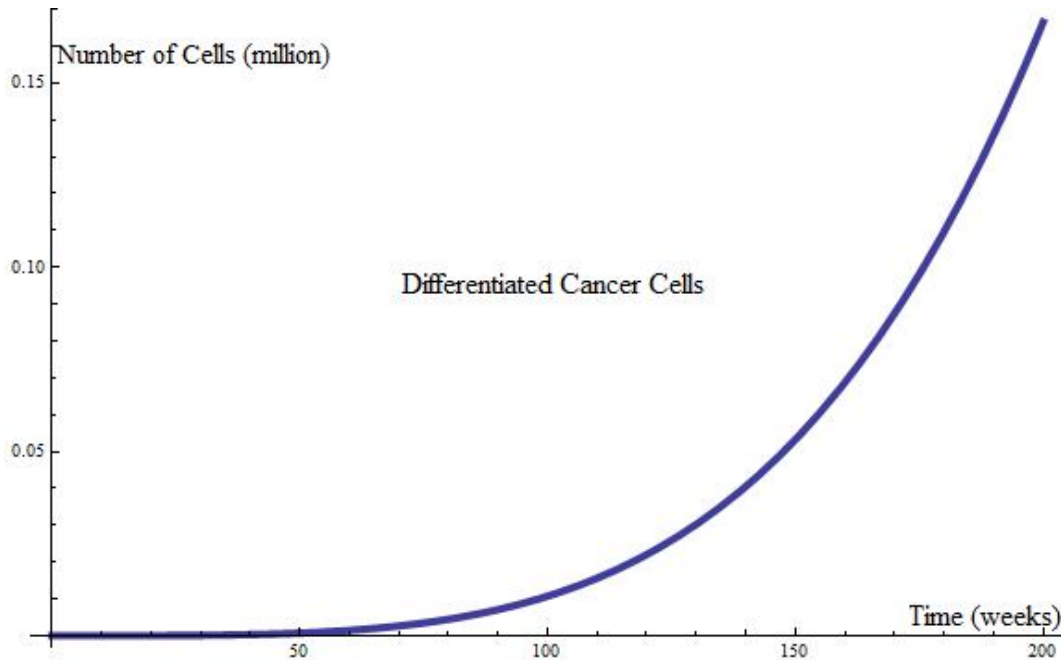

Figure VI.2: Linear model with n = 3 maximum number of telomeres and m = 3 mutation classes (2 mutations necessary to reach malignancy). Polynomial growth (t^4) of differentiated cancer cells($j = 1$ telomere, $i = 2$ mutations), according to the results of Theorem III.4.2.

mutation) with equal probability $\frac{1}{3} \times 10^{-5}$. The self-renewal probability of the cells refers to the asymmetric cell division assumption that one daughter of a cell will have the same characteristics
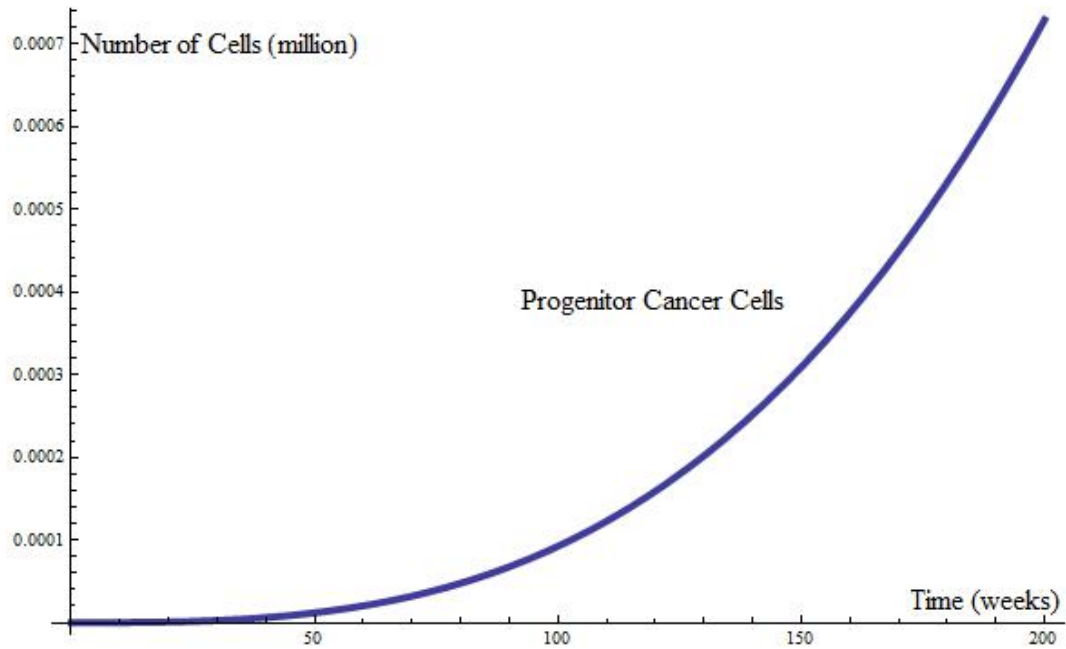
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Figure VI.3: Linear model with n = 3 maximum number of telomeres and m = 3 mutation classes (2 mutations necessary to reach malignancy). Polynomial growth (t^3) of progenitor cancer cells ($j = 2$ telomeres, $i = 2$ mutations), according to the results of Theorem III.4.2.
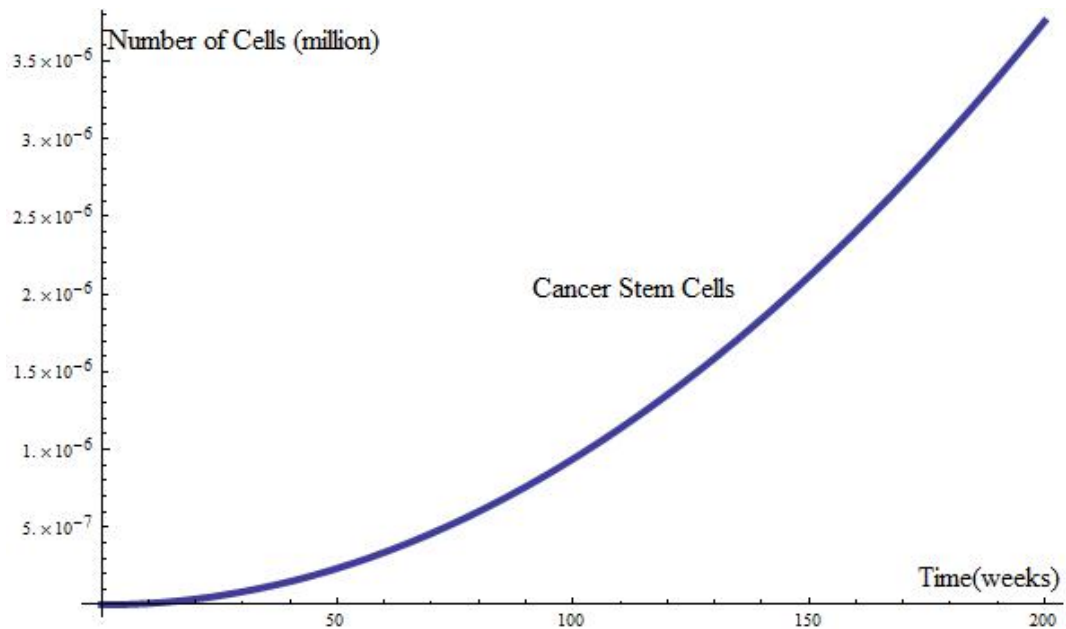
Figure VI.4: Linear model with n = 3 maximum number of telomeres and m = 3 mutation classes (2 mutations necessary to reach malignancy). Polynomial growth (t^2) of cancer stem cells ($j = 3$ telomeres, $i = 2$ mutations), according to the results of Theorem III.4.2.

(telomere length, in particular) as its mother. The remaining cell genealogy probabilities, referring to the daughter cell losing telomeres and not acquiring a mutation, are also evenly distributed among the possible outcomes. The figures were generated with *Mathematica* [49].

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VI.2   Linear Model Simulation

The simulation for the linear model (Equation III.3) represents an experiment of cellular dynamics with a relatively short duration. However, the main reason for the simulation is to present the different polynomial rates of growth for the different classes of cell population and to emphasize the fact that all cell types eventually develop, even though the initial cell population consists of only stem cells (which is implied in the result of Theorem III.4.2). Only three telomere classes (corresponding to stem ($j = 3$ telomeres), progenitor ($j = 2$ telomeres), and differentiated cells ($j = 1$ telomere)) and only three mutation classes (normal cells ($i = 0$ mutations), cells with one mutation ($i = 1$ mutation), and cancerous cells ($i = 2$ mutations)) are presented. Note that retinoblastoma is a cancer that develops after two mutations, which supports the assumption of the linear model simulation [26]. Initially, there are 10 million stem cells. Figures VI.1-VI.4 show the different rates of polynomial growth of the different cell classes. In Figure VI.4, after 100 weeks we get the first cancer stem cell. At 200 weeks we have around 4 cancer stem cells and 170 000 differentiated cancer cells. The ratio between the cancer stem cells and the differentiated cancer cells at that time is consistent with previous results [13].

VI.3   Nonlinear Model Simulation

The nonlinear model simulation was run with $n = 8$ telomere classes and $m = 6$ mutation classes and presents a more complex example of a "Vogelgram" [22]. In other words, $j = 8$ telomeres represents stem cells, $j = 1$ telomere is the index of the telomere class of differentiated cells, $i = 0$ mutations is the number of mutations for normal cells, and $i = 5$ mutations is the index of the mutation class for cancer cells (i.e. cancer cells develop after acquiring 5 mutations). The crowding function F is given by: $F(\vec{x}) = 0.0001||\vec{x}||_X, \vec{x} \in \mathbb{R}^N$. The choice of F describes loss of cells because the total cellular population is too large for the environment to handle because of spatial constraints. Therefore, cells stop proliferating or die and are not accounted for any further. One can view the scenario as cells entering a quiescent state. However, the numerical simulation is

mainly used to portray the steady state equilibrium that is achieved in the nonlinear model, rather than depict a very specific phenomenon.

Different tissues have different stages of differentiation but it is known that erythropoiesis
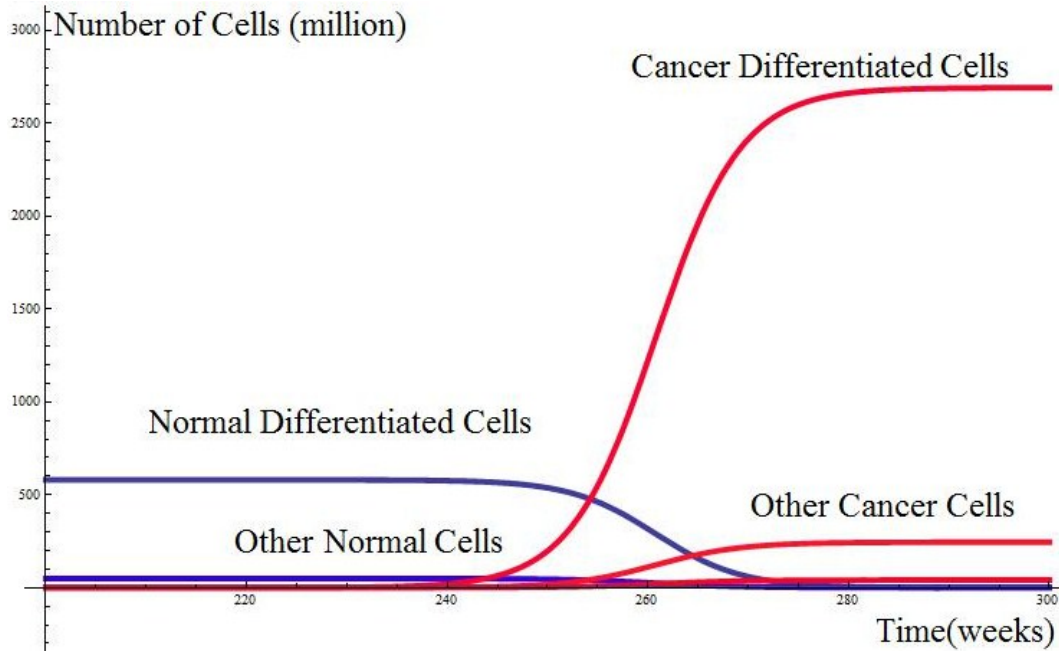

Figure VI.5: Nonlinear model with $n = 8$ maximum number of telomeres and $m = 6$ mutation classes (5 mutations necessary to reach malignancy). Cancer cells ($i = 5$ mutations) taking over the tissue environment according to the asymptotic steady state result in Theorem V.3.

(production of red blood cells) has about 8 stages of differentiation [29]. Also, although different types of cancer go through a different number of mutations, 4-7 is the general number of mutations a cell needs to acquire to become cancerous [4][22]. The scenario we assumed for the nonlinear model is that the cells in a region of an organ, or in a cell culture dish, have reached homeostasis, consisting of only normal cells ($i = 0$ mutations). Once homeostasis is established, mutations were introduced and, hence, the possibility for cancer development. Homeostatic values were established at 0.0402333 million stem cells ($j = 8$ telomeres) and 580.567 million differentiated cells ($j = 1$ telomere). The full vector of values for the different differentiation classes of normal cells is: $(580.567, 49.3302, 7.72654, 1.68346, 0.455944, 0.14457, 0.0517274, 0.0402333)^{\top}$. Once mutations are introduced, only cancer cells ($i = 5$ mutations) remain after around 280 weeks (Figure

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VI.5). The resulting vector of the cancer cell populations is $(2690.99, 244.64, 40.7741, 9.40954,$
$2.68848, 0.896172, 0.336069, 0.261392)^\top$, where the first number refers to the number, in millions,
of differentiated cancer cells ($j = 1$ telomere, $i = 5$ mutations) and the last - the number, in mil-
lions, of cancer stem cells ($j = 8$ telomeres, $i = 5$ mutations) in the region. The curve that shows
the growth of the cancer cells is similar to the Gompertzian curve, which is achieved in many
models [23][41][34]. The results, depending on the interpretation of the scenario, is that the cancer
cells overtake either the region in the organ or the cell culture dish.

CHAPTER VII

DISCUSSION

We have presented two models of intercellular dynamics: one linear and one nonlinear. Both models incorporate similar ideas: cells lose telomeres during mitosis and differentiation; cells can acquire mutations during division; when a normal cell acquires a certain number of mutations, it becomes cancerous[22][4].

In the Introduction, there were three questions we tried to address. Here are the answers, according to the presented models:

1. Question: Considering cell mutation as a dynamic population process, rather than a one-time random event, what can we show about cancer cell population growth in relation to the growth of the populations of non-cancer cells?

   Answer: Theorem III.4.2 proves that the number of cancer cells grows faster polynomially than any other type of cell (of the same telomere class). The Theorem does not assume any advantages of cancer cells in proliferation rates, mortality rates, and self-renewal probability. The only advantage cancer cells have over other cells, according to the model, is the number of mutations they have accumulated. According to Theorem III.4.2, the more mutations a cell population has, the faster it grows with respect to time. Therefore, it is the nature of mutation acquisition that may explain the higher population growth of cancer cells.

   However, Theorem III.4 does not address how quickly cancer develops and whether it develops within a human life. This question was answered by the numerical simulations, in particular of the nonlinear scenario. In the simulation, equilibrium of normal cells was reached first, after which, with the given initial conditions, mutations were introduced and, hence, the possibility for the development of cancer cells. The experiments were run for several values of the proliferation rate of cancer cells. In our simulations, $\beta_{j,5} = 3.0$ cells/week, $1 \leq j \leq 8$, gave the most realistic result as far as time-frame is concerned. From Figure

VI.5, one can see that cancer cells begin their invasion after about 240 weeks, become dominant after 250 weeks, and overtake the tissue (or cell dish) after 270 weeks. These results are consistent with the aggressive development of certain types of cancer, for example small cell lung cancer [36]. Therefore, according to the model and the current knowledge of the nature of cancer cells, cancer cells do need to exhibit high proliferation rate in order for their population to grow to levels dangerous for the organism in a realistic time frame.

2. Question: What is the role of stem cells in the cell population dynamics?

Answer: Theorem III.4.2 proves that the coefficient of the highest power of the polynomial that determines the growth of the cell populations, relative to time, is a multiple of the initial number of stem cells. Therefore, stem cells are crucial for the development of all other cell classes and are also important for the rate at which those different cell populations grow. The importance of stem cells for the development of the somatic cells is known: [19][14][31][40].

The significance of cancer stem cells is shown through Theorem V.3. The result does assume advantages for the cancer stem cell (higher proliferation rate, higher self-renewal probability), consistent with the characteristics associated with this type of cells [9][27] [15][16][12][37][5][24]. Under these assumptions, the cancer cells overtake the whole region of tissue (or cell culture dish), which confirms the importance of cancer stem cells for the aggressive development of cancer.

3. Question: Is the cancer stem cell count as small as scientists have claimed?

Answer: According to the numerical simulations, the ratio of cancer stem cells to overall cancer cell populations is quite small (order of 1 in 10000) and there has been evidence for similar ratios [13][9]. These specific results do depend on the different parameter values chosen for the simulations. However, mathematical evidence that cancer stem cells can be a small fraction of the total number cancer cells and still generate the cancer cell population can be found in Theorem III.4.2, where it's shown that they grow at a slower polynomial rate

than any other type of cancer cell, while differentiating into those types and, thus, constantly providing new cells for their lineage. Therefore, a relatively small subpopulation of cancer stem cells can generate the total population of cancer cells.

There are several assumptions of the basic framework of the model that should be commented on further. First, the model assumes that cancer stem cells mutate from normal stem cells. Although there is strong evidence for the existence of cancer cells that exhibit stem cell characteristics, their existence is still a hypothesis. Cancer stem cells have also been found only in certain types of cancer. Furthermore, the origin of cancer stem cells is ambiguous: some suggest they do come from mutated stem cells ([27]), others that they are mutated progenitor or differentiated cells. The model heavily relies on the assumption that stem cells mutate into cancer stem cells. In fact, it was designed to investigate the importance of this phenomenon and draw the conclusions above.

Second, Hypothesis II.3 assumes asymmetric cell division (one daughter cell is identical with the mother cell and the other is genetically different). Differentiation of cells and loss of telomeres are well-established: [25][40][11]. However, the literature is not conclusive with the rate of telomere loss [28], which may be dynamic [35]. Further, the role of the enzyme telomerase has not been explicitly included in the model. Asymmetric division of stem cells has been demonstrated. In fact, one of the main properties of stem cells is self-renewal [40][31]. Also, it is hypothesized that some progenitor cells could self-renew as well [11]. Therefore, the assumption of the model that cells can self-renew is supportable. This assumption is only used for the analysis of the linear model and has no effect on the result of Theorem V.3.

Third, Theorem III.4.2 assumes $\mu_{j,i} = 0$ for all cells and the nonlinear numerical simulation uses a constant mortality for all cell classes. For Theorem III.4.2, this assumption is made so that the various rates of population growth of the different cell types can be observed. Therefore, the linear model with zero mortality is suitable for modeling short-term *in vitro* or *in vivo* experiments (mortality of cells would have less of an effect on the outcome of the experiment).

As far as the mortality rate used for the simulations goes, the focus of the model analysis is on the interaction between cell populations and, to some extent, the role of the proliferation rate in

the inter-cellular dynamics. The mortality rate is, like the proliferation rate, dependent on the cell class. There exist mechanisms within the body that force mutated cells to go into apoptosis. Also, cancer cells often have lower mortality rate than normal cells [24]. One can explore those options by manipulating the mortality rate for certain cell classes. However, such investigation is beyond the scope of this paper.

Finally, the assumption that cells acquire their sequence of mutation in a particular order may be too simplistic [42]. However, the model does not address different types of mutation, only their number. So, the focus is on the process of mutation acquisition and not on the effect of specific mutations on the cell characteristics.

The linear model with zero mortality can be used to model short term *in vitro* and *in vivo* experiments: cell mortality does not play a major role in a short time span. Linear and polynomial rates of growth of cancer cell populations have been observed: [21][14][37][12][10][38]. Further, polynomial growth of high degree is similar in behavior to exponential growth if the time frame is short, and exponential models are often used to describe initial populations growth.

The numerical simulation of the nonlinear model shows growth of the cancer cell population similar to the Gompertzian curve, which is achieved in many models [23][41][34]. This result supports the usefulness of the model framework for modeling both *in-vivo* and *in-vitro* experiments by showing its consistency with previous work.

The strength of the modeling framework presented in the current paper lies within its flexibility. The linear model can predict short-term behavior, the nonlinear - long term behavior. Further, the choice of the operator F is up to the researcher and allows for the investigation of other questions within the intra-cellular dynamics. More, we have made suggestions for future researchers and how they can address different problems by simply modifying the parameters of the model. Those suggestions and different scenarios will be investigated in future work. Future work would also feature the addition of fitness and competition between healthy and cancer cells, investigating possible cellular Darwinism. Another flexibility of the model is the open number of telomere and mutation classes, which implies that one can mimic different tissues and different types of cancer.

Therefore, the presented models, although complex, can be readily used to describe a wide variety of cell interactions, which makes the model framework useful for researchers.

APPENDIX

Proof of Lemma III.5. Without loss of generality, let us look at the structure of the matrix CB. Since C and B are uppertriangular matrices, so is CB, so all its subdiagonals lower than the main diagonal, are automatically zero.

Consider an arbitrary element in the lth superdiagonal of CB, row j, $0 \leq l \leq k + m - 1, l \leq n - 1, 1 \leq j \leq n - l$. (note that the main diagonal is a superdiagonal of index 0). This element is element $(j, j + l)$ of CB and is equal to the matrix multiplication of row j in C and column $j + l$ in B.

The first $j + k - 1$ elements of row j in C are zero. The first $j + l - m$ elements in column $j + l$ in B are positive.

Therefore, the first positive element of row j in C is $(j, j + k)$. If $j + k > n$, then row j in C is zero, so the element $(j, j + l)$ of CB is zero. So, let's assume $j + k \leq n$.

The last positive element of column $j + l$ in B is $(j + l - m, j + l)$ If $j + l - m = 0$, column $j + l$ in B is zero, so the element $(j, j + l)$ of CB is zero. So, let's assume $j + l - m > 0$.

However, $j + l - m < j + k$ since $j < m + k$. Therefore, the CB element $(j, j + l)$ cannot be positive because all positive elements in row j of C will be multiplied by zero elements of column $j + l$ in C and vice versa. Therefore, it is zero.

Let $k + m \leq l$. If $k + m \geq n$, the argument above shows that the matrix CB is the zero matrix (all of its superdiagonals will be zero).

So, let $l < n$. Consider an arbitrary element in the lth superdiagonal of CB, row j, $1 \leq j \leq n - l$. From the argument above, the first positive element of row j in C is $(j, j + k)$. The last positive element of column $j + l$ in B is $(j + l - m, j + l)$.

Since $j + k \leq j + l - m$, elements $(j, j + k)$ in C and $(j + k, j + l)$ in B are both positive, therefore, so it element $(j, j + l)$ in CB. $\qquad \square$

Example VII.1.

$$C = \begin{pmatrix} 0 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

(The first 3 superdiagonals of C are 0),

$$B = \begin{pmatrix} 0 & 1 & 1 & 1 & 1 \\ 0 & 0 & 1 & 1 & 1 \\ 0 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

(The first superdiagonal of B is 0), then

$$BC = CB = \begin{pmatrix} 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

(The first 3+1 = 4 superdiagonals of BC and CB are 0).

Proof of Lemma III.7. (By induction) *Basic Step*: In A, by construction, the highest indexed positive block subdiagonal is its first block subdiagonal.

Inductive Step: Let the statement be true for $A^k, 1 \leq k \leq m - 2$. Pick an arbitrary block element in the $(k+1)^{th}$ block subdiagonal of A^{k+1}, $A^{k+1}_{l+k+1,l}, 1 \leq l \leq m - k - 2$. It is constructed by matrix multiplying the $(l + k + 1)^{th}$ block row of A^k with the lth block-column of A. From the structure of A, $A^{k+1}_{l+k+1,l} = A^k_{l+k+1,l}P_{l-1} + A^{l+k+1}_{l+1}Q_l$. From the inductive assumption, $A^k_{l+k+1,l} = 0$,

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since it is an element in the $(k+1)^{th}$ block subdiagonal of A^k. However, $A^k_{l+k+1,l+1}$, which is an element in the kth block subdiagonal of A^k, is positive. From Lemma III.5 and the fact that Q_l has no zero superdiagonals, $A^{l+k+1}_{l+1}Q_l \neq 0$. Therefore, the $(k+1)^{th}$ block subdiagonal of A^{k+1} is positive.

Consider the $(k+2)^{th}$ subdiagonal of A^{k+1}. If $k = m-2$, it does not exist. So, let $k < m-2$. Let $A^{k+1}_{l+k+2,l}, 1 \leq l \leq$ be an arbitrary element in the $(k+2)^{th}$ subdiagonal of A^{k+1}. By the rules of matrix multiplication, and the structure of A, $A^{k+1}_{l+k+2,l} = A^k_{l+k+2,l}P_{l-1} + A^k_{l+k+2,l+1}Q_l$. However, $A^k_{l+k+2,l}$ is an element in the $(k+2)^{th}$ block subdiagonal of A^k and $A^k_{l+k+2,l+1}$ is an element in the $(k+1)^{th}$ block subdiagonal of A^k. From the inductive assumption, both the $(k+1)^{th}$ and the $(k+2)^{th}$ block subdiagonals of A^k are 0. Therefore, the $(k+2)^{th}$ subdiagonal of A^{k+1} is 0, which proves the Lemma. $\square$

Proof of Lemma III.9. (By induction) *Basic Step*: Since A is a lower-triangular block matrix, the main block diagonal block elements of A^n, $A^n_{i,i} = P^n_{i-1}, 1 \leq i \leq m$. From Lemma III.5, since the main diagonal of P_{i-1} is 0, $P^n_{i-1} = 0$. From Lemma III.8, the first block subdiagonal of A^n consists of upper-triangular matrices, in which exactly the first $n-1$ superdiagonals are 0. Hence, the first block subdiagonal of A^n is positive.

Inductive step: Assume the statement is true for $A^k, n < k < n+m$. Then, from Lemma III.8, the $(k-n+2)^{th}$ block subdiagonal of A^k consists of upper-triangular matrices in which exactly the first $n-2$ superdiagonals are 0 and the $(k-n+1)^{th}$ block subdiagonal of A^k consists of upper-triangular matrices in which exactly the first $n-1$ superdiagonals are 0. Consider A^{k+1}. Pick and arbitrary block element in its $(k-n+2)^{th}$ block subdiagonal, $A^{k+1}_{l+k-n+2,l}, 1 \leq l \leq m-k+n-2$. It is constructed by matrix multiplying the $(l+k-n+2)^{th}$ block row of A^k with the lth block-column of A. The only positive block elements of the lth block-column of A are $A_{l,l} = P_{l-1}$ and $A_{l+1,l} = Q_l$. Therefore, by the rules of matrix multiplication, $A^{k+1}_{l+k-n+2,l} = A^k_{l+k-n+2,l}P_{l-1} + A^k_{l+k-n+2,l+1}Q_l$. $A^k_{l+k-n+2,l+1}$ is a block element in the $(k-n+1)^{th}$ block subdiagonal of A^k and Q_l is an upper-triangular matrix without 0 superdiagonals. Therefore, by Lemma III.5, the result of their matrix multiplication is an upper-triangular matrix in which exactly the first $n-1$ superdiagonals are 0.

$A_{l+k-n+2,l}^{k}$ is a block element in the $(k-n+2)^{th}$ block subdiagonal of A^k and P_{l-1} is an upper-triangular matrix whose main diagonal is 0. Therefore, by Lemma III.5, the result of their matrix multiplication is an upper-triangular matrix in which exactly the first $n-1$ superdiagonals are 0. Hence, $A_{l+k-n+2,l}^{k+1}$ is an upper-triangular matrix in which exactly the first $n-1$ superdiagonals are 0 and the last one is positive. Pick and arbitrary block element in the $(k-n+1)^{th}$ block subdiagonal of A^{k+1}, $A_{l+k-n+1,l}^{k+1}$, $1 \leq l \leq m-k+n-1$. It is constructed by matrix multiplying the $(l+k-n+1)^{th}$ block row of A^k with the lth block-column of A. The only positive block elements of the lth block-column of A are $A_{l,l} = P_{l-1}$ and $A_{l+1,l} = Q_l$. Therefore, by the rules of matrix multiplication, $A_{l+k-n+1,l}^{k+1} = A_{l+k-n+1,l}^{k} P_{l-1} + A_{l+k-n+1,l+1}^{k} Q_l$. $A_{l+k-n+1,l+1}^{k}$ is a block element in the $(k-n)^{th}$ block subdiagonal of A^k, so it is 0. $A_{l+k-n+1,l}^{k}$ is a block element in the $(k-n+1)^{th}$ block subdiagonal of A^k and P_{l-1} is an upper-triangular matrix whose main diagonal is 0. Therefore, by Lemma III.5, the result of their matrix multiplication is 0. Hence, $A_{l+k-n+1,l}^{k+1}$ is 0. Similar results would follow for any other lower indexed subdiagonal of A^{k+1}. $\square$

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