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Modeling Stem Cell Population Dynamics

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MODELING STEM CELL POPULATION DYNAMICS

by

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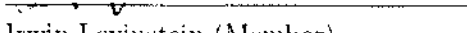Requirements for the Degree of

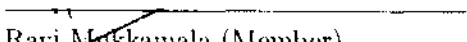DOCTOR OF PHILOSOPHY
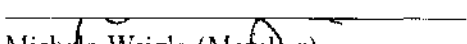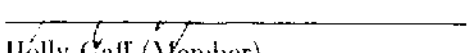
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ABSTRACT

MODELING STEM CELL POPULATION DYNAMICS

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Old Dominion University, 2014
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Because of the stochastic nature of biological systems, mathematical and computational modeling approaches have become more acceptable to experimentalists and clinicians in recent years as contributing to new understandings of complicated cell mechanisms and tissue physiology. Indeed, even single cell or small tissue samples are complex dynamic systems that adapt to environmental challenges in space and time which is poorly understood. Mathematical models and computer simulations can explain and uncover unknown aspects of cell behavior and tissue functions. Models based on key biological mechanisms can give interesting insights and formulate predictions that cannot be derived from physical experiments or statistical data alone. Therefore, novel research approaches should incorporate interdisciplinary dialogues between Biology, Mathematics and Computational Sciences to validate experimental data and non-intuitive scenarios such as the stem cell hypothesis. The tissue of a higher organism such as a human being can be described as a set of a large number of cells with certain functions and morphology. However, most of the mature cells are deprived of the potential to replenish themselves. Such imperfection of mature cells is compensated by the presence of a population of stem cells which possesses the capability to self renew and to differentiate into various cell lineages. This process of continual cell replacement, is called homeostasis, is critical for the maintenance of adult tissues, and is maintained through the presence of different control mechanisms. The homeostatic replacement of cells varies substantially among different tissues. Unquestionably, the most important ability of a stem cell is to maintain the homeostasis by continuously supplying specialized cells. The decision for an individual stem cell to either renew or differentiate can be described as a stochastic process. Several research programs supported by hospitals and health institutes are trying to understand the underlying mechanism of how stem cells proliferate, differentiate, and maintain equilibrium with or without feedback. At this stage researchers are not able to answer key questions, for example the rate of proliferation, stem cell homeostasis and feedback that plays a crucial role in tissue equilibrium. This dissertation work

is within the realm of Bioinformatics where computer scientists have to face more algorithmic challenges because of the huge amount of data with exception, numerous rules and conditions. This thesis attempts to present stochastic models which can predict stem cell growth, understand stem cell homeostasis characteristics, and formalize mathematical relationships of tissue lineage homeostasis.

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My parents have been a great source of mental strength and emotional support during this period. They were always there for me whenever I was faced with difficulties. They gave me the necessary encouragement to pursue lofty academics goals from a very early stage of my life. I would also like to thank my elder sisters Jabin and Munira for supporting me throughout my life. My friends have also been an endless source of support and inspiration during these years, and their patience with me despite my packed schedules was something that I always cherished. Lastly, I have to thank all my teachers from BRAC University, Bangladesh, especially Dr. Mumit Khan and Dr. Ziauddin Ahmed for encouraging me to pursue graduate studies abroad.

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CHAPTER 1

INTRODUCTION

To some degree, our life comprises of a multitude of biochemical processes on very different scales. Such processes are inherently stochastic. Stochasticity is unavoidable when considering biological systems and processes, both at the macro scale with populations surviving in rapidly and unpredictably changing environments, but also and especially at the molecular level [37, 23, 53], where entropic considerations can have significant implications.

Due to the stochastic representation of the biological systems, mathematical and computational modeling approaches have become more acceptable by experimentalists and clinicians. Several new contributions have been made to understand complicated cell mechanisms and tissue physiology. Even a single cell or a tissue segment is a complex dynamical systems that adapts to environmental challenges in space and time. Which makes them appropriate for modeling. Mathematical models and computer simulations can explain and uncover unknown details of cell behavior and tissue functions [25, 9]. Models based on key biological mechanisms can give interesting insights and formulate predictions that cannot be derived from actual physical experiments [27]. Therefore, novel research approaches should incorporate interdisciplinary interactions to validate experimental data and non-intuitive scenarios such as the stem cell hypothesis [40].

The tissues of higher organisms such as human beings can be described as a set of a large number of cells with various functions and morphology. However, most of the mature cells are deprived of the potential to replenish themselves indefinitely. Such imperfection of mature cells is compensated by the presence of a population of stem cells, which possess capability to self renew and to differentiate into various cell lineages. These processes of self-renewal, differentiation, and proliferation are fundamental in the functioning of stem cells. Li and Xie [28] have described a delicate balance between stem cell self-renewal and differentiation, and the understanding of this point is a basis for understanding of how stem cells regulate the body, their role in tumor growth and formation, and their therapeutic use in treating human disease.

Scientists were led to the concept of stem cell niche by observing the role of the surrounding environment in regulation of stem cell function and determination of the course of their development. The concept of niche refers to the micro-environment for the adult stem cells and a more specific understanding of niche includes a thorough description of cell to cell interactions and extracellular signaling. The stem cell niche is the means by which the body interacts with the stem cells to determine development, maintaining a state of quiescence, and self-renewal under normal conditions, but stimulating proliferation and differentiation when additional cells are required by the body, such as times of external stress. Although the concept of niche is derived from the micro-environment of the stem cell within the organism, scientists are attempting to reproduce these conditions in vitro, and the concept of niche also extends to regulation of stem cells in this environment. Moreover, the decision for individual stem cells to either renew or differentiate can also be represented by a stochastic process. Several research programs [27, 60, 26] supported by hospitals and health institutes are trying to understand underlying mechanism how a stem cell proliferates, differentiates and maintains equilibrium with or without feedback. At this stage the rate of stem cell proliferation, stem cell homeostasis mechanism in tissue equilibrium are not properly understood. The main goal of this thesis is to employ stochastic modeling and computer simulations to understand stem cell growth, homeostasis and tissue lineage homeostasis.

1.1 MOTIVATION

In recent decades the biological research community has come to view cell lineages as fundamental unit of tissue and organ development, maintenance and regeneration. At the starting point of lineage, particularly in self-renewing tissues such as blood, epidermis and the intestinal lining, stem cells are present in small number. As scientists and clinicians have become ever so interested in harnessing the proliferation and differentiation power of stem cells to repair injuries and cure disease, there has also been a surge of interest in the mechanisms underlying the execution and regulation of cell lineages [14, 16].

Stem cells have tremendous capabilities to develop into many different cell types in the body during early life and growth. Additionally, in many tissues they are the only source of internal repair system, dividing frequently to replenish other cells as long as the person or animal's life time. As a stem cell divides, each new stem
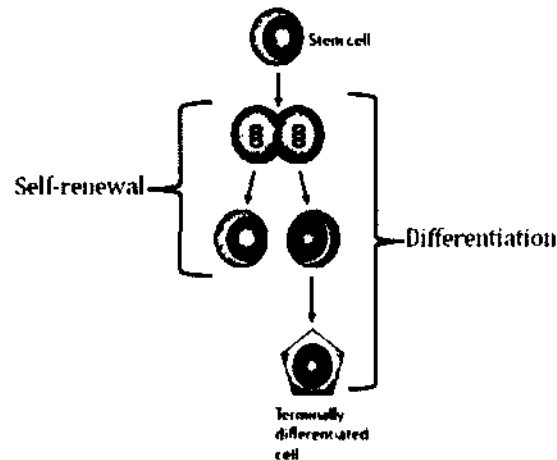
FIG. 1: **Self-renewal and Differentiation.** from *Wilson et. al.* Stem cells are capable of repopulating undifferentated cell populations (self-renewal) and forming more specialized cell types (differentation).[63]

cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell. Understanding the life cycle and transition of stem cell within tissue to a fully developed differentiated cell holds much promise to tackle different problems in regenerative medicine and cancer cures.The transformation of a single stem cell to a specific cell type within the body happens in multiple stages. In the intermediary stages stem cells are called transit amplifying cells (TA). Since stem cells and TA cells cannot be readily distinguished from each other, to infer the number of stem cells, the process has to be indirect. One approach is to develop stochastic models for the evolution of tissue and infer the number of stem cells from molecular markers in a sample of cell taken from tissue [57]. Hence, it is believed in many sections of the research community, building proper stochastic models is of paramount importance to understand the growth of stem cells, homeostasis, and cell lineage within tissue.

1.2 OBJECTIVE

The most important objective of this work is to develop a mathematical model for tissue level cell lineage to understand cell progression from pure stem cell to fully differentiated mature cells in the body. A compartmental structure of tissue comprising of stem cell compartment (SC), transit-amplifying (TA) cell compartment,

and fully mature cell compartment (FC) has been proposed in this thesis for this purpose.

The key problems in pursuit of this complete tissue cell lineage model is to understand individual compartments and their intricacies. The most important of these compartments is the stem cell compartment, which holds the main proliferation capability of any tissue within the body. As a result, stem cell growth model and stem cell homeostasis model were independently developed in this work.

1.3 THESIS STATEMENT

With the inherent stochastic nature of stem cell characteristics and the complex nature of multistage cell progression within tissue, stochastic models are required to fully understand and comprehend these complex phenomena. In this thesis several different stochastic models with mathematically tractable closed forms have been revealed and their theoretical predictions have also been compared with computational simulation results.

1.4 CONTRIBUTIONS

The main objective is to understand stem cell proliferation, cell lineage within tissue, homeostasis, and to depict the progression of mutant cells from normal stem cells within tissue. These are all accomplished through five different independent mathematical models, which are the main contributions of this work:

- The first model shows the growth kinetics of stem cells independently. Since differentiated cells are incapable of self-renewal, a crucial component of stem cell research is modeling the proliferation capacity of the undifferentiated stem cell phenotype. Therefore, it is an important research topic to identify mathematical growth models for stem cells that are inherently heterogeneous and account in a unified way for division, stagnation, deterioration and death. Somewhat surprisingly, the overwhelming majority of stem cell growth models proposed in the literature, including the well known Sherley model [50] and hyperbolastic model [54], are deterministic. While simple and tractable, deterministic models are too rigid, lacking the flexibility and versatility needed to accurately describe stem cell proliferation which has high variability and heterogeneity.

- In the second model, simple stem cell dynamics within tissue was modeled to

accurately predict the number of stem cell within a particular tissue after each cell cycle finishes. In the light of the increased interest in stem cell research, fueled by the promises that cell based therapies hold, it is hardly surprising that various mathematical models have been proposed for illustrating the intricate dynamics of stem cell self-renewal, differentiation, and fully maturing cell production. Most of the models in current literature are again deterministic [5, 10], with only a handful of them taking a stochastic approach [58]. In addition, virtually all approaches to modeling stem cell dynamics assume only specific cell division patterns (typically, symmetric) ignoring the asymmetric division regimen. In addition to being stochastic, this model accommodates all types of cell divisions. One of the interesting features of this model is that it suggests that, with the absence of spontaneous mutations or external molecular feedback, the Markov process is a martingale indicating that the stem cell population is in stochastic equilibrium.

- The main goal of the third model is to offer a comprehensive mathematical model of tissue level homeostasis. In order to model the dynamics of individual compartments, two local parameters are employed. They are the rate at which cells divide and the rate at which they undergo apoptosis. In the current literature asymmetric cell divisions are not taken into consideration [25, 27]. But in this model all forms of division have been taken into consideration. It also presents a stochastic mathematical model to study stem cell population dynamics and stem cell homeostasis, both applicable in the hematopoietic system and other tissues. Highlighting the quantitative aspects of stem cell biology. In spite of its simplicity, this model reveals the intricate interplay between local and global equilibrium (i.e., homeostasis) requirements.

- The last of the models depicts how mutant stem cells within tissue evolve from wild type stem cells. Again stochastic approach has been employed to model the evolution of mutant stem cells.

1.5 OUTLINE

This work is organized in the following order:

- Chapter 2 gives a short overview of different biological terms and short functional description of their roles within organisms.

- Chapter 3 presents a background on current mathematical and computational models in stem cell proliferation, differentiation, homeostasis and an overview of different models in mathematical biology.

- Chapter 4 presents a simple stochastic growth model for stem cell proliferation.

- Chapter 5 shows a discrete time Markov model for stem cell homeostasis within tissue.

- Chapter 6 depicts a comprehensive tissue cell lineage and homeostasis model at tissue level.

- Chapter 7 presents a simple stochastic model to depict mutant cell evolution.

- Chapter 8 concludes with the summary of the work and brief discussion on future research directions.

CHAPTER 2

TERMINOLOGY

In this chapter, some of the basic biological terminology will be discussed in brief to lay foundations for the mathematical models in later chapters. Some specific tissue will also be discuss in preparation for tissue lineage homeostasis model, which will be discussed in chapter 6.

All living creatures are made of *cells* which are small membrane-bounded units filled with a concentrated aqueous solution of chemicals and endowed with the extraordinary ability to create copies of themselves by growing and dividing. The simplest forms of life are solitary cells. Higher organism such as human beings are communities of cells derived by growth and division from a single founder cell. Most cells are very small; most are indistinguishable without using a microscope. Cells are enclosed by a cell membrane and come in many different shapes. The contents of a cell are called the protoplasm.

The following is a glossary of animal cell terms:

- **Cell membrane -** The thin layer of protein and fat that surrounds the cell. The cell membrane is semipermeable, allowing some substances to pass into the cell and blocking others.

- **Centrosome -** (also called the microtubule organizing center) A small body located near the nucleus and it has a dense center and radiating tubules. The centrosomes is where microtubules are made. During cell division (mitosis), the centrosome divides and the two parts move to opposite sides of the dividing cell. The centriole is the dense center of the centrosome.

- **Cytoplasm -** The jellylike material outside the cell nucleus in which the organelles are located.

- **Golgi body -** (also called the Golgi apparatus or golgi complex) A flattened, layered, sac-like organelle that looks like a stack of pancakes and is located near the nucleus. It produces the membranes that surround the lysosomes.

The Golgi body packages proteins and carbohydrates into membrane-bound vesicles for export from the cell.

- **Lysosome** - (also called cell vesicles) round organelles surrounded by a membrane and containing digestive enzymes. This is where the digestion of cell nutrients takes place.

- **Mitochondrion** - Spherical to rod-shaped organelles with a double membrane. The inner membrane is infolded many times, forming a series of projections (called cristae). The mitochondrion converts the energy stored in glucose into ATP (adenosine triphosphate) for the cell.

- **Nuclear membrane** - The membrane that surrounds the nucleus.

- **Nucleolus** - This is an organelle within the nucleus. It is where ribosomal RNA is produced. Some cells have more than one nucleolus.

- **Nucleus** - A spherical body containing many organelles, including the nucleolus. The nucleus controls many of the functions of the cell (by controlling protein synthesis) and contains DNA (in chromosomes). The nucleus is surrounded by the nuclear membrane.

- **Ribosome** - A small organelles composed of RNA-rich cytoplasmic granules that are sites of protein synthesis.

2.0.1 EUCARYOTIC CELL

Cells do not all contain the same organelles in the same proportions. Indeed, one vast and evolutionarily ancient class of cells, the bacteria, contain essentially no organelle. The presence or absence of a nucleus is used as the basis for a simple but fundamental classification of all living organisms. Those whose cells have a nucleus are called *eucaryotes*. Those cells that do not have it are called *procaryotes*.

2.0.2 PHENOTYPE

The one defining character or observable marker of a cell or organism is called phenotype. A phenotype results from the expression of an organism's genes as well as the influence of environmental factors and the interactions between the two.

2.0.3 CELL CYCLE

Reproductive cycle of the cell, the orderly sequence of events by which a cell duplicates its contents and divides into two. the cell cycle can be divided in three periods. First phase is known as interphase, during which the cell grows, accumulating nutrients needed for mitosis and duplication of its DNA. The second phase is known as mitotic phase, during which the cell splits itself into two distinct cells, often called daughter cells. The final phase where the cell is completely divided.

2.0.4 CELL DIVISION

Separation of a cell into two daughter cells. In eucaryotic cells it entails division of the nucleus (mitosis) closely followed by divison of the cytoplasm.

2.0.5 CELL SENESCENCE

The normal aging of cells from one location to another. Particularly the migration of a cell over a surface.

2.0.6 CELL SIGNALING

Communication between cells by extracellular chemical singals; especially the molecular mechanisms by which cells detect and respond to these signals.

2.0.7 MITOSIS

The most common form of stem cell division is called *mitosis*. It is used for growth and repair. During mitosis, a cell makes an exact copy of itself and splits into two new cells. Each cell contains an exact copy of the original cell's chromosomes in their 23 pairs. This is the reason why all the cells in an organism are genetically identical. The process of mitosis is fast and highly complex. The sequence of events is divided into stages corresponding to the completion of one set of activities and the start of the next. Mitosis is closely controlled by the genes inside every cell. Errors in mitosis can either kill a cell through apoptosis or cause mutations. Certain types of cancer can arise from such mutations. Sometimes this control can go wrong. If that happens in just a single cell, it can replicate itself to make new cells that are also out of control. These are cancer cells. They continue to replicate rapidly without the

control systems that normal cells have. Cancer cells will form lumps, or *tumors*, that damage the surrounding tissues. Sometimes, cancer cells break off from the original tumor and spreads in the blood to other parts of the body. When a tumor spreads to another part of the body it is said to have *metastasized*. The cancer cells continue to replicate and make more tumors. These are called secondary tumors. Proper control of mitosis is one of the main regulatory concerns of stem cell homeostasis.

2.0.8 CELL MUTATION

When a cell replicates using mitosis, the ideal result is a perfectly identical sister cell. When a cell replicates and the resulting cell is different than the original cell, it is called a mutation.

2.0.9 APOPTOSIS

A genetically determined process of cell self-destruction that is marked by the fragmentation of nuclear DNA. It is activated either by the presence of a stimulus or by the removal of a stimulus or suppressing agent. This is a normal physiological process eliminating DNA-damaged, superfluous, or unwanted cells, and when halted (as by genetic mutation) may result in uncontrolled cell growth and tumor formation. This is also known as programmed cell death (PCD).

2.0.10 TISSUE

Tissue is an organized assembly of specialized cells that forms a distinct part of a plant or an animal. It is nothing but an ensemble of similar cells from the same origin that together carry out a specific function. Body organs are formed by the functional grouping together of multiple different tissues.

2.1 STEM CELLS

Stem cells are a class of undifferentiated cells that are able to differentiate into specialized cell types. Commonly, stem cells come from two main sources. *Embryonic* stem cells are derived from a four or five day old human embryo that is in the blastocyst phase of development. These are generally *totipotent cells*. So, these cells have total potential to develop into any cell in the body. *Adult* or *somatic* stem cells exist throughout the body after embryonic development and are found inside

of different types of tissue. These stem cells have been found in tissues such as the brain, bone marrow, blood, blood vessels, skeletal muscles, skin, and the liver.

The main characteristics of stem cells can be summarized as follow:

- They have the potential to replace cell tissue that has been damaged or destroyed by severe illnesses or injury.

- They can replicate over and over again for a very long time.

- Understanding the growth and replication of stem cells into healthy tissues and disease prone tissues will assist the search for cures.

- Embryonic stem cells generated through therapeutic cloning have also been proposed as promising candidates for future therapies.

The ability to differentiate is the potential to develop into other cell types. A totipotent stem cell (e.g. fertilized egg) can develop into all cell types including embryonic membranes. A pleuripotent stem cell can develop into cells from all three germinal layers (e.g cells from the inner cell mass). Other cells can be oligopotent, bipotent, or unipotent depending on their ability to develop into few, two, or one other cell type(s), respectively.

Self-regeneration is the ability of stem cells to divide and produce more stem cells. During early development, the cell division is symmetrical, i.e. each cell divides to gives rise to daughter cells each with the same potential.

2.1.1 TYPES OF STEM CELLS

Several adjectives are used to describe the developmental potential of stem cells; that is, the number of different kinds of differentiated cell that they can become.

- **Totipotent cells.** In mammals, totipotent cells have the potential to become any type in the adult body and any cell of the extraembryonic membranes (e.g., placenta). The only totipotent cells are the fertilized egg and the first four or so cells produced by its cleavage. In mammals, the expression totipotent stem cells is a misnomer as totipotent cells cannot make more of themselves.

- **Pluripotent stem cells.** These are the group of stem cells, with the potential to make any differentiated cell in the body. Three types of pluripotent stem cells that occur naturally:

Embryonic Stem (ES) Cells. These can be isolated from the inner cell mass (ICM) of the *blastocyst*. This is the stage of embryonic development when implantation occurs. For humans, excess embryos produced during in vitro fertilization (IVF) procedures are used. Harvesting ES cells from human blastocysts is controversial because it destroys the embryo, which could have been implanted to produce another baby (but often was simply going to be discarded).

– **Embryonic Germ (EG) Cells.** These can be isolated from the precursor to the gonads in aborted fetuses.

– **Embryonic Carcinoma (EC) Cells.** These can be isolated from *teratocarcinomas*, a tumor that occasionally occurs in a gonad of a fetus.

- **Multipotent stem cells.** These stem cells can only differentiate into a limited number of differentiated types. For example, the bone marrow contains multipotent stem cells that give rise to all the cells of the blood but not to other types of cells. Multipotent stem cells are found in adult animals; perhaps most organs in the body (e.g., brain, liver, lungs) contain them where they can replace dead or damaged cells. These adult stem cells may also be the cells that when one accumulates sufficient mutations, produce a clone of cancer cells.

2.2 IDENTIFICATION OF STEM CELLS

Although there is not complete agreement among scientists of how to identify stem cells, most tests are based on making sure that stem cells are undifferentiated and capable of self-renewal. Tests are often conducted in the laboratory to check for these properties.

Two Canadian researchers Till and McCulloch first discovered stem cells [58]. They irradiated mice with enough X-rays to kill the animals within 30 days if they did not receive a transplant of fresh, undamaged bone marrow cells. The researchers then injected varying amounts of cells to determine how many cells were necessary to keep the animals alive. Ten days after injecting the cells, McCulloch observed nodules in the spleens of the surviving mice. With a background in bacteriology, Dr. McCullough suspected that the blood cells were forming the equivalent of a bacterial colony and that this was the source of the new blood cells that were keeping the animals alive.

One way to identify stem cells in a lab, and the standard procedure for testing bone marrow or hematopoietic stem cell (HSC), is by transplanting one cell to save an individual without HSCs. If the stem cell produces new blood and immune cells, it demonstrates its potency.

Clonogenic assays (a laboratory procedure) can also be employed in vitro to test whether single cells can differentiate and self-renew. Researchers may also inspect cells under a microscope to see if they are healthy and undifferentiated or they may examine chromosomes.

To test whether human embryonic stem cells are pluripotent, scientists allow the cells to differentiate spontaneously in cell culture, manipulate the cells so they will differentiate to form specific cell types, or inject the cells into an immuno suppressed mouse to test for the formation of a teratoma (a benign tumor containing a mixture of differentiated cells).

Both embryonic and adult stem cells share the properties of self-renewal, differentiation, and proliferation which characterize stem cells; however, there are some important differences. The main difference is in differentiation, pluripotency versus multipotency. Although embryonic stem cells may be grown effectively outside the body, adult stem cells have shown resistance to production in large numbers. All the above issues of self-renewal, differentiation, and proliferation are critical areas within the field of stem cell research. For many stem cell therapies, the efficacy of the treatment will depend on the number of stem cells available, thus a mathematical model representing the size and rate of growth of stem cells would be highly useful.

2.3 STEM CELL NICHE

The microenvironment where stem cells are found, which interacts with stem cells to regulate cell fate is known as stem cell niche. In a *Nature* review [47], stem cell populations are established in niches, specific anatomic locations that regulate how they participate in tissue generation, maintenance, and repair. The niche saves stem cells from depletion, while protecting the host from over-exuberant stem-cell proliferation. It constitutes a basic unit of tissue physiology, integrating signals that mediate the balanced response of stem cells to the needs of organisms. Yet the niche may also induce pathologies by imposing aberrant function on stem cells or other targets. The interplay between stem cells and their niche creates the dynamic system necessary for sustaining tissues, and for the ultimate design of stem-cell therapeutics.The

simple location of stem cells is not sufficient to define a niche. The niche must have both anatomic and functional dimension. The word *niche* can be in reference to the in vivo or in vitro stem cell micro-environment. During embryonic development, various niche factors act on embryonic stem cells to alter gene expression and induce their proliferation or differentiation for the development of the fetus. Within the human body, stem cell niches maintain adult stem cells in a quiescent state, but after tissue injury, the surrounding micro-environment actively signals to stem cells to either promote self renewal or differentiation to form new tissues. Scientists are studying the various components of the niche and trying to replicate the in vivo niche conditions in vitro. This is because for regenerative therapies, cell proliferation and differentiation must be controlled in flasks or plates, so that sufficient quantity of the proper cell type are produced prior to being introduced back into the patient for therapy.

2.4 HOMEOSTASIS

In order to function properly and for longevity, cells must maintain homeostasis. Homeostasis is a state in which everything within the cell is in equilibrium and functioning properly. The state of homeostasis keeps the cell constant with what it needs to function. For stem cells it is even more important as stem cells have enormous proliferation capability which other normal cells lack. The waste is being transported away from the cell while it receives the nutrients it needs to continue to function. Homeostasis keeps the cell stable. When cells are in homeostasis, they work to help the organism function properly. It is important for cells to maintain homeostasis for the organism to remain healthy. Different parts of the cell work to constantly maintain homeostasis in the cell.

The main part of the cell that works to maintain homeostasis is the cell membrane. That is the outer wall between the cell and the outside world. Essentially, it protects the cell from outside stimuli that could disrupt a cell's homeostasis. The cell membrane acts as the gatekeeper to what goes into and leaves the cell. It is made up of mostly fats (lipids) and protein and is selectively permeable, meaning it only lets certain molecules pass through the membrane.

When there is too much of a certain molecule inside the cell, the cell membrane allows some of the molecules to permeate the membrane and leave the cell. Conversely, when there is too much of a molecule outside the cell and not enough inside

the cell, the cell membrane will allow enough of the molecule to permeate to maintain homeostasis. Charged molecules and large molecules cannot pass through the cell membrane, while small and uncharged molecules can.

CHAPTER 3

STATE OF THE ART

Over the centuries, the task of understanding the dynamics of various biological phenomena noticed in nature and society have captured the interest of scholars and philosophers. However, with the exception of D. Bernoulli's attempt at modeling the outbreak of a smallpox epidemic, T. R. Malthus's population growth model and Verhulst formulation of the logistic growth model, most of the early efforts, including Gompertz's human mortality model [19], were empirical. The data available was highly unreliable, and the general sense of evidence was lacking by modern standards. All this changed in 1874 when Galton and Watson undertook the first systematic attempt at the extinction phenomena noticed in the social sciences that, nonetheless, could not be convincingly explained [61]. Their work was among the earliest systematic attempts at enlisting the help of probability theory in modeling, and thus, understanding, the dynamics of population growth. While their pioneering work had focused on a rather narrow problem, namely that of accounting for the wholesale extinction of family names in England, their mathematical methods turned out to be surprisingly powerful and general [21].

A mathematical model can be defined as description of a system using mathematical concepts and language. Usage of mathematical modeling in biology is widespread [30, 31]. For example, various mathematical models have been used in epidemics to study the mechanisms by which infectious diseases spread, predict the extent and course of outbreaks, evaluate the effectiveness of strategies to control and mitigate the resulting epidemics. Mathematical models have been used in biology to determine maximum harvest in agriculture, to understand the dynamics of biological invasions, and have numerous environmental conservation implications. Population models are also used to understand the spread of parasites, viruses, and disease. The realization of this dependence on environmental health has created a need to understand the dynamic interactions of the earths flora and fauna.

The mechanisms controlling stem cell self-renewal, maintenance and differentiation are still poorly understood, and there exists no general characterization of stem cells based on observable cell properties. To address these problems with the help of

mathematical models holds a promising research direction. The hard task of sorting and counting prized stem cells and their cancer causing cell (Cancer Stem Cells or CSC) has long frustrated scientists and medical practitioners looking for new ways to help people who have progressive diseases. Recent developments by University of Florida researchers [12] have devised a series of mathematical steps that accomplishes what the most powerful microscopes, high-throughput screening systems and protein assays have failed to do, that is, to assess how rapidly stem cells and their malignant cousins alter normal behavior to increase their numbers. By offering a method to evaluate the effects of diseases and treatments on stem cell activity in the tissue, as well as allowing the assessment of malignant stem like cells, researchers believe they can better evaluate potential therapies for incurable diseases. In the following section different types of mathematical models that are most prevalent in mathematical biology will be briefly discussed as a stepping stone to building modelings for stem cell dynamics and homeostasis.

3.1 DIFFERENT TYPES OF MATHEMATICAL MODELING IN BIOLOGY

Usually mathematical models in biology are segregated in two types, deterministic and stochastic. Deterministic models assume the future to be deterministic. Usually they are mathematically tractable and in widespread use. In most case they are rather unrealistic. Stochastic models assume the future to be stochastic/random. They are mathematically challenging and typically closed forms are much harder to obtain. Sections 3.1.1 and 3.1.2 give two important models of population growth based on reproduction of organisms: the exponential and the logistic models, both of which are deterministic, will be discussed. Section 3.1.3 gives a brief discussion of the Gompertz model, which is predominantly used in cancer research [34]. Then comes the important hyperbolastic growth model (3.1.4) which is used in stem cell growth modeling, tumor modeling and in other growth phenomena. Furthermore in section (3.1.5), Bass's growth model, the immensely popular model used in marketing research to predict, among other things, the time of adoption for durable consumer goods. Finally, to set the stage in section 3.1.6 a simple stochastic model proposed by Yule will be presented which turns out to be a linear growth-rate pure birth process.

3.1.1 THE EXPONENTIAL GROWTH MODEL

The exponential population growth model is usually associated with the work of T. R. Malthus (1766-1834) [49] who first realized that any species can potentially increase in numbers according to a geometric series. If a species has non-overlapping populations (e.g., annual plants), and each organism produces R offspring then the number, N_t, of individual in generation $t = 0, 1, 2, \cdots\cdots$ is given by

$$N_t = N_0 R^t,$$ (1)

where N_0 is the initial size of the population (i.e., at the 0-th generation). By writing $r = \ln R$, (1) becomes

$$N_t = N_0 e^{rt},$$ (2)

where, depending on the application domain. r is referred to as Malthusian parameter, intrinsic rate of increase. instantaneous rate of natural increase, or population growth rate.

A glance at (2) reveals that depending on the parameter r. there are three possible outcomes:

- if $r < 0$. the population declines exponentially;

- if $r > 0$, the population increases exponentially;

- if $r = 0$, the population does not change.

Some of the applications of the exponential model and equation (2) are in microbiology (growth of bacteria). conservation biology (restoration of disturbed populations or loss to extinction). insect rearing (prediction of yield). plant or insect quarantine (population growth of introduced species). fishery management (prediction of fish population dynamics) [1, 8].

In spite of its widespread use. a serious shortcoming of the exponential model is that it ignores the limitations to unbounded growth imposed by environmental factors and conditions [2].

3.1.2 THE LOGISTIC GROWTH MODEL

The logistic growth model was proposed by the Belgian mathematician P. Verhulst around 1838. Verhulst suggested that the rate of population increase may be limited.

as it may depend on the population size, $N = N(t)$, and on the growth rate, r, defined as

$$r = r_0 \left(1 - \frac{N}{K} \right).$$

where the parameter K represents the upper limit on population growth and is called *carrying capacity*. The carrying capacity of a biological species in a given environment is the largest population size of the species that the environment can sustain indefinitely, given the food, habitat, water and other necessities required.

Observe that when N is small relative to K, the population growth rate r is maximal and is nearly r_0. The parameter r_0 can be interpreted as the population growth rate in the absence of competition. The population growth rate declines with N and reaches 0 when $N = K$. If N exceeds K, the population growth rate becomes negative and the population declines, eventually becoming extinct. It can be easily seen population size N is a function of time t. The dynamics of population growth are captured by the following differential equation, with boundary condition $N = N_0$ at $t = 0$,

$$\frac{dN}{dt} = rN \left(1 - \frac{N}{K} \right). \tag{3}$$

Equation (3) tells that when N is small, the early unimpeded growth rate can be approximated by rN. Later, as N grows, $-\frac{rN^2}{K}$, becomes larger and larger, as some members of the population interfere with each other by competing for critical resource, such as food or living space. The competition diminishes the combined growth rate, until the value of N ceases to grow which indicated the saturation of the population in the given environment.

As it turns out, taking into account the boundary condition, equation (3) has the solution

$$N(t) = \frac{N_0 K}{N_0 + (K - N_0) e^{-rt}}. \tag{4}$$

Observe that

$$\lim_{t \to +\infty} N(t) = K$$

which is to say that the limiting value of N is K, the highest value that the population can reach given infinite time or come close to reaching in finite time.

3.1.3 THE GOMPERTZ GROWTH MODEL

Gompertz function is used to approximate growth up to certain limit. It is the most popular function to estimate growth,probability and proportion along with

logistic function. It is more general type than logistic function class.The right-hand or future value asymptote of the function is approached much more gradually by the curve than the left-hand or lower valued asymptote, in contrast to the logistic function in which both asymptotes are approached by the curve symmetrically.

$$G(x) = ae^{be^{cx}} \tag{5}$$

where $a \sim (0, \infty)$, $b \sim (-\infty, 0)$ and $c \sim (-\infty, 0)$. $G(t)$ usually denotes the number of individuals at time t.

The 3 coefficients control the shape of the function . The upper limit of the curve is controlled by the coefficient a. Whereas b is the growth rate and c is the acceleration rate .

3.1.4 THE HYPERBOLASTIC MODEL

Growth models such as logistic, Gompertz, Richards, and Weibull have been extensively studied and applied to a wide range of medical and biological studies. Tabatabai *et al.* [54] introduced a class of three and four parameter models called hyperbolastic models for accurately predicting and analyzing self-limited growth behavior that occurs, e.g, in tumors, stem cell growth. In the following three Hyperbolastic models H1, H2 and H3 will be briefly discussed.

First of the hyperbolastic model is the H1 hyperbolastic model which produces flexible asymmetric curves through nonlinear ordinary differential equations of the form

$$\frac{dP(t)}{dt} = \frac{1}{M} P(t)(M - P(t))\left(M\beta + \frac{\theta}{\sqrt{(1 + t^2)}}\right) \tag{6}$$

or

$$\frac{dP(t)}{dt} = \left(\beta M + \frac{\theta}{\sqrt{(1 + t^2)}}\right)P - \left(\frac{\theta}{M\sqrt{(1 + t^2)}} + \beta\right)P^2 = \beta_1(t)P - \beta_2(t)P^2 \tag{7}$$

With initial condition,

$$P(t_0) = P_0$$

where $P(t)$ represents the population size at time t, β is the parameter representing the intrinsic growth rate, θ is a parameter, and M represents the maximum

sustainable population (carrying capacity), which is assumed to be constant, though in general the carrying capacity may change over time. For growth curves, β has to be positive, leading to an eventually increasing curve with an asymptote at M; β can be negative only for eventual inhibition curves or decay profiles. If $\theta = 0$, then the equation (6) reduces to a logistic differential equation and equation (7) reduces to a general logistic model 3.1.2. Solving the equation (6) for the population P gives

$$P(t) = \frac{M}{1 + \alpha e^{[-M\beta t - \theta \operatorname{arcsinh}(t)]}} \tag{8}$$

where

$$\alpha = \frac{M - P_0}{P_0} e^{[M\beta t_0 + \theta \operatorname{arcsinh}(t_0)]}$$

and $\operatorname{arcsinh}(t)$ is the inverse hyperbolic sine function of t. The function $P(t)$ in equation (8) is the hyperbolastic growth model of type I or simply H1.

In the second type of Hyperbolastic models, an alternative growth curve through a nonlinear hyperbolastic differential equation of the form,

$$\frac{dP(t)}{dt} = \alpha \beta \gamma P^2(t) t^{\gamma - 1} \tanh\left[\frac{M - P(t)}{\alpha P(t)}\right] \tag{9}$$

with initial condition $P(t_0) = P0$ and $\gamma > 0$. where $\tanh$ stands for hyperbolic tangent function. M is the carrying capacity, and β and γ are parameters. As in the H1 model, parameter β has to be positive for increasing growth curves with an asymptote at M and is negative only for decay profiles. This equation (9) as the hyperbolastic differential equation of type II.

Solving equation (9) for population size P gives the three parameter model,

$$P(t) = \frac{M}{1 + \alpha \operatorname{arcsinh}\left[e^{(-M\beta t^\gamma)}\right]} \tag{10}$$

where

$$\alpha = \frac{M - P_0}{P_0 \left[e^{(-M\beta t_0^\gamma)}\right]}$$

The function $P(t)$ in equation (10) is the hyperbolastic growth model of type II or simply H2.

Finally, a third growth curve through the following nonlinear hyperbolastic differential equation of the form

$$\frac{dP(t)}{dt} = (M - P(t))\left(\beta\gamma t^{\gamma-1} + \frac{\theta}{\sqrt{1 + \theta^2 t^2}}\right) \tag{11}$$

with initial condition $P(t_0) = P_0$, where M is the carrying capacity and β, γ and θ are parameters. This equation (11) is known as the hyperbolastic ordinary differential equation of type III.

The solution to equation (11) is a four parameter model

$$P(t) = M - e^{[-\beta t^\gamma - \text{arcsinh}(t)]} \tag{12}$$

where

$$= (M - P_0)e^{[\beta t_0 - \text{arcsinh}(t_0)]}.$$

The function P(t) in equation (12) is the hyperbolastic growth model of type III or simply H3.

3.1.5 THE BASS GROWTH MODEL

The Bass growth model [3] was developed by Frank Bass to describe the process of how new products get adopted as an interaction between users and potential users. It has been described as one of the most famous empirical generalizations in marketing. Based on very simple behavioral observations, Bass's model became immensely popular. In spite of its deceiving simplicity, the Bass model is an excellent predictor of new-product sales and is still heavily used.

The model is based on number of empirical observations. First, that there exists an intrinsic tendency of some individuals to make a purchase, independent of the number of previous adopters. Bass calls these individuals the *innovators*. In contrast to the innovators, some people buys a product due media and social pressure. Bass refers to these folks as *imitators*. Bass's second major assumption is that the probability that an initial purchase will be made at time t is a linear function of the number of previous buyers. Under these assumptions Bass postulates that

$$\frac{dN(t)}{dt} = [M - N(t)][p + \frac{q}{M}N(t)] \tag{13}$$

where

- p and q be two parameters that quantify the extent of the influence of innovators and imitators, respectively;

- M the market potential of a given product, that is, the size of the potential consumer population;

- $N(t)$ the cumulative number of adopters in $[0, t]$

- $M - N(t)$ is the size of the remaining population, and

- $p + q/MN(t)$ is the instantaneous adoption rate of every individual in the remaining population.

The differential equation (13) with boundary condition $N(0) = 0$) has solution

$$N(t) = M \frac{e^{(p+q)t} - 1}{e^{(p+q)t} + \frac{q}{p}} \tag{14}$$

It is easy to confirm that

$$\lim_{t \to \infty} N(t) = M$$

and that $N(t)$ has an S-shaped graph characteristics of many other growth models, for example the logistic growth model.

It was recently pointed out by Yan *et al.* [65] that Bass's growth model is a common generalization of the exponential and logistic models. Indeed,

- for $q = 0$, Bass's model reduces to the exponential model;

- for $p = 0$, Bass's model reduces to the logistic model.

The accuracy of Bass's model depends on the three parameters, M, p, and q. In the case of a new product, these parameters are obtained by using existing sales data for previous versions of the same product or by extrapolating from sales data for similar products.

3.1.6 THE YULE MODEL

No doubt one of the earliest stochastic processes was proposed in 1924 by G. U. Yule in his mathematical theory of evolution [66]. In Yule's model, $\{Y(t) \mid t \geq 0\}$ represents the number of species in some genus of plants or animals [36]. Yule's model assumes that evolution begins with a single species at time $t = 0$ and that species do

not die out. If there are $Y(t)$ species at time t, then $\lambda Y(t)\delta$ is the probability that a new species will be created in the time interval $[t, t + \delta]$ for some very small $\delta > 0$.

More formally, the process $\{Y(t) \mid t \geq 0\}$ has boundary conditions $P_1(0) = 1$ and $P_i(0) = 0$ for $i \neq 1$ and transition rate λ_n such that:

$$\forall n \in \mathbb{N}, \quad \lambda_n = n\lambda > 0.$$

So, the Kolmogorov differential equations are,

$$\begin{cases} \frac{dP_n(t)}{dt} = -n\lambda P_n(t) + (n-1)\lambda P_{n-1}(t) & \text{if } n \geq 2; \\ \frac{dP_n(t)}{dt} = -\lambda P_1(t) & \text{if } n = 1. \end{cases}$$

Now, the second equation above yields $P_1(t) = e^{-\lambda(t)}$

An easy inductive argument confirms that $\forall t \geq 0$

$$P_n(t) = e^{-\lambda t}(1 - e^{-\lambda t})^{n-1} \tag{15}$$

It follows that In Yule's growth model the events $\{Y(t) = n\}$ are geometrically distributed with success probability $e^{-\lambda t}$.

It is clear that because of its underlying assumptions, the Yule model is not sufficiently flexible to deal with growth phenomena encountered in real-life application. In addition to the assumed linear growth rate, the Yule model assumes unbounded growth and, consequently, cannot be used to model growth in limited-capacity situations.

3.2 STEM CELL GROWTH

Stem cells are capable of dividing and renewing themselves for long periods, in some tissues for the entire life period of the animal. Unlike muscle cells, blood cells, or nerve cells, which do not normally replicate themselves, stem cells may replicate many times, or proliferate. A starting population of stem cells that proliferates for many months in the laboratory can yield millions of cells. This property was first observed in the laboratory by James Till and Ernest McCulloch [58]. If the resulting cells continue to be non specialized, like the parent stem cells, the cells are said to be capable of long-term self-renewal. Understanding this self-renewal and proliferation capability may hold the key for a lot of important discoveries in regenerative medicine and artificial muscle production for food consumption. Till and McCulloch [58] also established the fact stem cell compartment contains cells with extensive proliferation

capacity which have the ability to give rise to new stem cells and to differentiate unboundedly. Secondly, they also established all the differentiated cell have minimum or no capacity to proliferate and within tissue stem cells are the only cell capable of mass growth. Their work was the first to realize that stem cells have an enormous capacity to renew and differentiate.

Afterward several different mathematical model have been proposed for stem cell proliferation. One of the mathematical model that was proposed is the Sherley's model [50]. This method is based on the implicit assumption that, within a cell population under study, all division events give rise to daughter cells that always divide. When a cell population does not adhere to this assumption, use of the exponential growth equation leads to errors in the determination of both population doubling time and cell generation time. Also a new derivation a more general growth equation that defines cell growth in terms of the dividing fraction of daughter cells was proposed. This equation can account for population growth kinetics that derive from the generation of both dividing and non-dividing cells. As such, it provides a sensitive method for detecting non-exponential division dynamics. In addition, this equation can be used to determine when it is appropriate to use the standard exponential growth equation for the estimation of doubling time and generation time.

Deasy *et al.* presented a model [11] where they evaluate the assumptions of the Sherley model [50]. Then it was augmented by incorporating terms to account for the alternative stem cell fates of apoptosis and differentiation. They offered two modified models for cell growth in the presence of cell loss or cell differentiation. Using muscle-derived stem cells (MDSC's) induced to apoptose or to undergo differentiation, it was observed good fits in the presence of these events. The models presented in [11] was expected to facilitate the development of both a biological and mathematical understanding of stem cell dynamics and heterogeneity. These tools allowed to quantitatively assess parameters of stem cell population growth subject to both intrinsic and extrinsic regulation. An increased understanding of inter cellular and micro-environmental determinants of stem cell fate teamed with appropriate growth models will eventually allow for the development of bio-reactor systems designed for the large scale generation of phenotypical stem cells to be used in cellular therapy strategies.

In recent times hyperbolastic growth models have been used by Tabatabai *et al.* [55]. It was argued the mathematical models prevalently used to represent stem cell

proliferation do not have the level of accuracy that might be desired and hyperbolastic growth models promise a greater degree of precision in representing data of stem cell proliferation. In the embryonic stem cells the results were compared with other popular models, including the Deasy model [10], which is used predominantly for stem cell growth. It was demonstrated that hyperbolastic model H3 can accurately represent the dynamics of stem cell proliferation for both embryonic and adult mesenchymnal stem cells. Although it was shown that model's stem cell proliferation predictions are close to real experiment data but more test is needed to accurately use this model generally. Another argument against this model that it is a very simple deterministic model whereas stem cell proliferation at cellular level is more accurately described by a stochastic model.

3.3 HOMEOSTASIS

Each of the tissues of an adult mammal seems to be in a state of equilibrium and all except the most highly modified types of cells, to be poised between an unstable functional state and a stable routine of recurring mitosis. It is pretty obvious that an understanding of the nature of the mechanisms that determine and maintain the actual point of balance with each tissue is of the greatest possible theoretical and practical importance. One common idea is that there exists a tissue level mitotic inhibitor which controls the tissue mass by suppressing cell division [51]. The earliest indication that this concept was correct came from observations on organ regeneration and in particular from studies of the regeneration of kidney and liver in adult mice and rats. The first successful extraction of tissue-specific mitotic control inhibitors appear to that have been the works of Saetren [45, 46].

Regulation of stem cells occurs at many different levels. Cell intrinsic factors as well as extrinsic signals from the surrounding cells and environment may modulate cell division, stem cell maintenance, and the differentiation process. In adult tissues, an amazing balance exists between stem cell proliferation and the generation of differentiated mature cells. Previously, it has been argued that this balance is obtained at the level of a single stem cell, which divides strictly into a new stem cell and a progenitor. However, recent evidence suggests that balance can also be achieved at the level of the stem cell population. Some stem cells might be lost due to differentiation or damage, whereas others divide symmetrically to fill this gap. In a standard scenario tissue only undergoes asymmetric divisions. That means a single

stem cell divides into one stem cell and one transit-amplifying cell which eventually differentiates into fully mature cell of the tissue. It has been noticed that without external duress usually tissue stem cells undergo asymmetrical division most of the time [59].

In [4] the general strategies for stem cell self-renewal and evidence for stochastic stem cell fate in adult tissues across a range of tissue types and organisms have been discussed. Alongside self-renewal and multipotency, stem cell potential is frequently associated with quiescence. Now in case of extensive growth, quiescence period can play a inhibitory role for regulating homeostasis. The factors controlling the balance between proliferation and differentiation in adult tissues have placed emphasis on mechanisms promoting asymmetrical division of individual stem cells, leading to stem cell longevity and clonal persistence. In recent years, the development of inducible genetic labeling systems has allowed such preconceptions to be challenged. Studies [4] have revealed that, in many cycling tissues, stem cells follow an active and stochastic pattern of behavior in which frequent stem cell loss is compensated by proliferation of neighbors leading to progressive expansion of some clones and extinction of others.

3.4 TISSUE CELL POPULATON DYNAMICS

There have been a number of models that have studied cell population dynamics mostly computational in [38, 39, 17]. The process of maintaining the number of mature cells is a well regulated multistage process consisting of differentiation of stem cells and their progeny and of the self-renewal of the stem cells population. The process of differentiation may be broken down into several stages. The capability to self renew characterizes not only the stem cells but also the population of cells at different stages of differentiation [32]. When the progeny of stem cells jumps to the higher stage of differentiation, its ability to differentiate is reduced and ultimately lost at the stage of mature cells. Mechanism of regulation of this complex process are not well understood. Due to the increasing interests in stem cells applications, such as stem cells based therapies for impaired organs, degenerative diseases [15, 18] or reconstitution of blood structure after chemotherapy in treatment of leukemia [48], wide spectrum of methods have been chosen to enlarge the knowledge on the rules of this process. Several mathematical and numerical models have been developed to help in understanding stem cells differentiation [52, 58, 32, 64].

These models present different mathematical approaches to describe processes of

differentiation and self renewal [52, 15, 13] involving stem cells proliferation [58] and mechanisms of stem cell fate decision [64] or stem cells regulation system [7]. All those models describe different parts of the process of homeostasis in adult tissue. However, an important difference is how an environmental and exterior disturbances during those processes are considered, and if they have a reflection in the mathematical form of the models.

One of the earliest and most influential models is that of Tomlinson and Bodmer [60], which was used as a starting point in later model by Jhonston et al. [25]. That earlier model assumes that the cells in the colonic crypt can be assigned to one of three different compartments: stem cells, semi-differentiate cells (transit-amplifying cells, TA) and fully differentiated cells. This is the first model where compartmental view was taken on board. It was a strictly deterministic model with each cell cycle comprising synchronous cell division on different compartments. The later on models such as Johnston tried to develop on that basic model by taking careful account of different cell cycle times of stem and semi-differentiated cells to accommodate asynchronous division which Bodmer's model failed to address. This resulted in much more complicated set of differential equations compare to the earlier primitive model because the enhanced model needs to keep track not only of the number of cells but also to their age distribution. In order to evade the complexity Johnston et al. [25] formulated a simpler model in which growth occurs continuously rather than in discrete multiples of cell cycle. Such assumption made it easier to analyze, and showed parameters in it may be related to those in more detailed age-structured model. To achieve homeostasis in physical or biological system, some degree of feedback mechanism is necessary. Jhonston model achieved that by varying the proportions of death, differentiation and renewal population as individual compartment sizes changed.

Many tissues and organs grow to precise sizes and, when injured regenerate accurate and rapidly. In [27], Lander et. al. investigated whether the organization of cells into lineages, are necessary elements of control strategies that make such behavior possible. Thus drawing on mathematical modeling and experimental results they showed fast regeneration from a variety of initial conditions, and maintenance of high ratios of differentiated to undifferentiated cells, can be simultaneously achieved through a combination of lineage structures and feedback mechanisms. The feedback mechanism that was proposed also explains how the distinctive proliferation

behaviors of stem cell and transit-amplifying cell populations can emerge as a consequence of feedback effects, rather than intrinsic programming of cell types. Unlike Bodmer's model they have structured semi-differentiated or transit-amplifying cell compartment into multiple stages with each stage having feedback to their prior stage.

CHAPTER 4

STEM CELL GROWTH

4.1 GROWTH MODELING IN STEM CELL RESEARCH

The past decade has seen a phenomenal surge of interest in stem cell research fueled by the immense potential stem cell based therapies holds in regenerative medicine and cancer research. In particular, there is an increasing demand for an accurate mathematical model to represent and describe its growth kinetics. Since once differentiated stem cells are incapable of mitosis, a crucial component of stem cell research is modeling the proliferation capacity of the undifferentiated stem cell phenotype. Therefore, it is an important research topic to identify mathematical growth models for stem cells that are inherently heterogeneous and account in a unied way for mitosis, quiescence, senescence and death. Somewhat surprisingly, the overwhelming majority of stem cell growth models proposed in the literature, including the well known Sherley and hyperbolastic models [50, 55, 6] are deterministic. While simple and tractable, deterministic models are too rigid, lacking the exibility and versatility needed to accurately describe stem cell population dynamics that have high variability and heterogeneity.

Stochastic growth models have a chance of making real progress. In this chapter, a simple and versatile stochastic model is presented to mimic stem cell growth phenomena.

A starting population of stem cells that proliferates for many months in the laboratory can yield millions of cells. If the resulting cells continue to be not specialized, like the parent stem cells, the cells are said to be capable of long-term self-renewal. These processes of self-renewal, differentiation and proliferation are fundamental in the functioning of stem cells. Lie and Xie [28] have described a delicate balance between stem cell self renewal and differentiation. This provides a basis for understanding of how stem cells regulate the body and also their therapeutic use in treating disease.

The main contribution of this chapter is to present a three-parameter version of the pure-birth growth model [41] as a versatile and effective means of tracking the

dynamics of stem cell growth. Using public-domain experimental data made available by NIH [35], a comparison is shown to illustrate the realistic nature of the model on stem cells growth characteristics.

For many stem cell based therapies, the efficacy of the treatment will depend on the number of undifferentiated stem cells available for transfer [56, 20]. An early model using a system of differential equations was proposed by Loeffler and Wichman [62] to model the stem cell growth within blood tissue. Cowan and Morris [33] introduced a two-parameter model representing the number of new daughter cells and the rate per proliferation cell per day. Similar in concept is the growth model proposed by Sherley et al. [50] to describe the generation of both dividing and non-dividing cells. Deasy et al. [9] applied the Sherley model to describe the mechanisms of muscle stem cell expansion with cytokines. Jankowski et al. [24] used this model to investigate the role of CD34 expression and cellular fusion in the regression capacity of cells. Deasy et al. [11] expanded the Sherley's growth model by incorporating a term to account for cell loss and cell differentiation Till et al. [58] presented the first stochastic model for stem cells growth. The growth model that would be presented later in the section is strictly stochastic. It is also a continuous model unlike most of the growth models for stem cells present in the literature.

4.2 DERIVATION OF THE VERSATILE STOCHASTIC GROWTH MODEL

Consider a stochastic process $\{N(t) \mid t \geq 0\}$ of continuous parameter t, where for every positive integer k, $(1 \leq k \leq N)$, the event $\{N(t) = k\}$ occurs if the colony contains k cells at time t.

For simplicity, assume that at time $t = 0$ the population starts with a single individual and assume an upper bound N on the total size of the population. It is worth noting that in many, if not most, practical situations this assumption is violated. However, it is rather straightforward to see that the case of n_0 initials reduces to the n_0-fold convolution of independent simple processes.

When the population contains k individuals, λ_k captures the growth rate of the population. The growth rates are subject to the mild restriction. Namely,

$$\lambda_i \neq \lambda_j \tag{16}$$

for all $1 \leq i, j \leq N$; moreover, since N is the largest size the population assumed, so it deduces, $\lambda_N = 0$.

It will become apparent in the following, condition (16) is not unduly restrictive since one can instantiate the λ_ks in such a way that (16) is satisfied.

To model the stem cell growth process, the instantiation of λ_k, $(1 \leq k \leq N)$ as

$$\lambda_k = k^\alpha (N - k)^\beta \tag{17}$$

where α and β are positive real numbers, assumed to be of infinite precision, and N is a parameter that described the largest desirable size of the stem cell colony. This allows to tweak α and β in such a way that $\lambda_i \neq \lambda_j$ for $i \neq j$, thereby satisfying condition (16). It is observed that $k * \alpha$ is the driving force of cell growth where k is the current number of cells. I

Furthermore, $P_k(t) = \Pr[\{N(t) = k\}]$. Which says the probability of the event of having k stem cells at time t is represented by $P_k(t)$.

4.2.1 DERIVING A CLOSED FORM FOR $P_K(T)$, $1 \leq K < N$

It is fairly obvious that for $k > 1$ and for a small $h > 0$, $P_k(t+h)$ has the following components:

- $P_k(t)[1 - h\lambda_k + o(h)]$, which describes the probability of staying at state k.

- $P_{k-1}(t)[h\lambda_{k-1} + o(h)]$, which describes the probability of reaching to the state k from state $k - 1$.

This allows the following:

$$
\begin{aligned}
P_k(t + h) &= P_k(t)[1 - h\lambda_k + o(h)] + P_{k-1}(t)[h\lambda_{k-1} + o(h)] + o(h) \\
&= P_k(t)[1 - h\lambda_k] + P_{k-1}(t)h\lambda_{k-1} + o(h).
\end{aligned}
$$

Transposing $P_k(t)$ and dividing with h yields

$$\frac{P_k(t + h) - P_k(t)}{(t + h) - t} = -\lambda_k P_k(t) + \lambda_{k-1} P_{k-1}(t) + \frac{o(h)}{h}.$$

Taking limits on both sides of this equality as $h \to 0$ yields the differential equation

$$\frac{dP_k(t)}{dt} = -\lambda_k P_k(t) + \lambda_{k-1} P_{k-1}(t) \tag{18}$$

with the boundary condition $P_k(0) = 0$. Proceeding similarly for $k = 1$, the following differential equation is obtained.

$$P_1(t + h) = P_1(t)[1 - h\lambda_1] + o(h).$$

Transposing $P_1(t)$ and dividing with h yields

$$\frac{P_1(t+h) - P_1(t)}{(t+h) - t} = -\lambda_1 P_1(t) + \frac{o(h)}{h}.$$

Taking limits on both sides of this equality as $h \to 0$ yields the differential equation

$$\frac{dP_1(t)}{dt} = -\lambda_1 P_1(t) \tag{19}$$

with the boundary condition $P_1(0) = 1$. This latter equation can be easily solved to obtain

$$P_1(t) = e^{-\lambda_1 t}. \tag{20}$$

Having obtained $P_1(t)$, using the differential equation (22), a closed form of $P_2(t)$ can be achieved similarly. This process is then continued iteratively, until a closed form is obtained for $P_k(t)$ for $(1 \leq k \leq N)$. The details of the derivation, as well as the proof of Theorem 4.1 can be found in Appendix A. To summarize, the following result can be stated.

Theorem 4.1. *For all $t \geq 0$,*

$$P_k(t) = \begin{cases} \lambda_1 \lambda_2 \cdots \lambda_{k-1} \sum_{i=1}^{k} \dfrac{e^{-\lambda_i t}}{\prod\limits_{\substack{j=1 \\ j \neq i}}^{k}(\lambda_j - \lambda_i)} & \text{for } 1 \leq k \leq N-1 \\[3em] 1 - \sum_{i=1}^{N-1} \left(\prod\limits_{\substack{j=1 \\ j \neq i}}^{N-1} \left[\dfrac{\lambda_j}{\lambda_j - \lambda_i} \right] e^{-\lambda_i t} \right) & \text{for } k = N. \end{cases} \tag{21}$$

Above theorem gives a formula to obtain the probability of having k stem cells at any given time t. Using this formula all the probabilities $P_1, P_2, \cdots \cdots$ can be computed as it has been already been state that $1 \leq k \leq N$.

4.3 DERIVING A CLOSED FORM FOR $P_K(T)$, $1 \leq K < N$

For $k > 1$, $P_k(t+h)$ has the following components:

- $P_k(t)[1 - h\lambda_k + o(h)]$

- $P_{k-1}(t)[h\lambda_{k-1} + o(h)]$.

This allows to write

$$\begin{aligned} P_k(t+h) &= P_k(t)[1 - h\lambda_k + o(h)] + P_{k-1}(t)[h\lambda_{k-1} + o(h)] + o(h) \\ &= P_k(t)[1 - h\lambda_k] + P_{k-1}(t)h\lambda_{k-1} + o(h). \end{aligned}$$

Transposing $P_k(t)$ and dividing with h yields

$$\frac{P_k(t+h) - P_k(t)}{(t+h) - t} = -\lambda_k P_k(t) + \lambda_{k-1} P_{k-1}(t) + \frac{o(h)}{h}.$$

Taking limits on both sides of this equality as $h \to 0$ yields the differential equation

$$\frac{dP_k(t)}{dt} = -\lambda_k P_k(t) + \lambda_{k-1} P_{k-1}(t) \tag{22}$$

with the boundary condition $P_k(0) = 0$.

Proceeding similarly, when $k = 1$,

$$\begin{aligned} P_1(t+h) &= P_1(t)[1 - h\lambda_1 + o(h)] + o(h) \\ &= P_1(t)[1 - h\lambda_1] + o(h). \end{aligned}$$

Transposing $P_1(t)$ and dividing with h yields

$$\frac{P_1(t+h) - P_1(t)}{(t+h) - t} = -\lambda_1 P_1 t) + \frac{o(h)}{h}.$$

Taking limits on both sides of this equality as $h \to 0$ yields the differential equation

$$\frac{dP_1(t)}{dt} = -\lambda_1 P_1(t) \tag{23}$$

with the boundary condition $P_1(0) = 1$. This latter equation can be easily solved to obtain

$$P_1(t) = e^{-\lambda_1 t}. \tag{24}$$

Having obtained $P_1(t)$, Let compute $P_2(t)$. For this purpose, a suitable instantiation of (22) allows to write

$$\frac{dP_2(t)}{dt} = -\lambda_2 P_2(t) + \lambda_1 P_1(t).$$

Solving for $P_2(t)$ yields

$$\begin{aligned} P_2(t) &= \frac{\lambda_1}{\lambda_2 - \lambda_1} \left[e^{-\lambda_1 t} - e^{-\lambda_2 t} \right] \\ &= \lambda_1 \left[\frac{e^{-\lambda_1 t}}{\lambda_2 - \lambda_1} + \frac{e^{-\lambda_2 t}}{\lambda_1 - \lambda_2} \right] \end{aligned} \tag{25}$$

Having obtained $P_2(t)$, it is easy to compute $P_3(t)$. Indeed, (22) allows to write

$$\frac{dP_3(t)}{dt} = -\lambda_3 P_2(t) + \lambda_2 P_1(t).$$

This latter equation yields

$$P_3(t) = \lambda_1 \lambda_2 \left[\frac{e^{-\lambda_1 t}}{(\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)} + \frac{e^{-\lambda_2 t}}{(\lambda_1 - \lambda_2)(\lambda_3 - \lambda_2)} + \frac{e^{-\lambda_3 t}}{(\lambda_1 - \lambda_3)(\lambda_2 - \lambda_3)} \right].$$

It is instructive to verify that the boundary condition $P_3(0) = 0$ holds. Indeed,

$$
\begin{aligned}
P_3(0) &= \lambda_1 \lambda_2 \left[\frac{1}{(\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)} + \frac{1}{(\lambda_1 - \lambda_2)(\lambda_3 - \lambda_2)} + \frac{1}{(\lambda_1 - \lambda_3)(\lambda_2 - \lambda_3)} \right] \\
&= 0
\end{aligned}
$$

With insight gleaned from the resolution of these special cases, now the proof the following general result is,

Theorem 4.2. *For $1 < k < N$ and $t \geq 0$,*

$$P_k(t) = \lambda_1 \lambda_2 \cdots \lambda_{k-1} \sum_{i=1}^{k} \frac{e^{-\lambda_i t}}{\prod_{\substack{1 \leq j \leq k \\ j \neq i}} (\lambda_j - \lambda_i)}. \tag{26}$$

Proof. It can be proceeded by induction on k. The base case, corresponding to $k = 2$, is verified as confirmed by (25).

Let k, $(2 \leq k \leq N - 2)$, be arbitrary and assume that (26) holds for the chosen value of k. It is needed to show that

$$P_{k+1}(t) = \lambda_1 \lambda_2 \cdots \lambda_k \sum_{i=1}^{k+1} \frac{e^{-\lambda_i t}}{\prod_{\substack{1 \leq j \leq k+1 \\ j \neq i}} (\lambda_j - \lambda_i)} \tag{27}$$

holds as well.

$P_{k+1}(t)$ obeys the differential equation

$$\frac{dP_{k+1}(t)}{dt} = -\lambda_{k+1} P_{k+1}(t) + \lambda_k P_k(t)$$

with the boundary condition $P_{k+1}(0) = 0$.

To simplify the notation write

$$y(t) = P_{k+1}(t).$$

In this notation, the previous differential equation reads

$$\frac{dy(t)}{dt} + \lambda_{k+1} y(t) = \lambda_k P_k(t)$$

with $y(0) = 0$.

To solve the latter differential equation, an integrating factor $p(t)$ is needed in such a way that

$$\frac{d(p(t)y(t))}{dt} = p(t)\lambda_k P_k(t).$$

(28)

A bit of algebra reveals that

$$p(t) = e^{\lambda_{k+1}t}.$$

Now, both sides of (28) can be integrated to obtain

$$
\begin{aligned}
p(t)y(t) &= \int \lambda_k e^{\lambda_{k+1}t} P_k(t)dt + C \\
&= \int \lambda_1\lambda_2\cdots\lambda_k e^{\lambda_{k+1}t} \sum_{i=1}^{k} \frac{e^{-\lambda_i t}}{\prod_{\substack{1 \le j \le k \\ j \neq i}}(\lambda_j - \lambda_i)}dt + C \quad \text{[by (26)]} \\
&= \lambda_1\lambda_2\cdots\lambda_k \int \sum_{i=1}^{k} \frac{e^{(\lambda_{k+1}-\lambda_i)t}}{\prod_{\substack{1 \le j \le k \\ j \neq i}}(\lambda_j - \lambda_i)}dt + C \\
&= \lambda_1\lambda_2\cdots\lambda_k \sum_{i=1}^{k} \int \frac{e^{(\lambda_{k+1}-\lambda_i)t}}{\prod_{\substack{1 \le j \le k \\ j \neq i}}(\lambda_j - \lambda_i)}dt + C \\
&= \lambda_1\lambda_2\cdots\lambda_k \sum_{i=1}^{k} \frac{e^{(\lambda_{k+1}-\lambda_i)t}}{(\lambda_{k+1} - \lambda_i)\prod_{\substack{1 \le j \le k \\ j \neq i}}(\lambda_j - \lambda_i)} + C.
\end{aligned}
$$

(29)

From (29) it follows immediately that

$$
\begin{aligned}
P_{k+1}(t) &= y(t) \\
&= \lambda_1\lambda_2\cdots\lambda_k \sum_{i=1}^{k} \frac{e^{-\lambda_i t}}{(\lambda_{k+1} - \lambda_i)\prod_{\substack{1 \le j \le k \\ j \neq i}}(\lambda_j - \lambda_i)} + Ce^{-\lambda_{k+1}t} \\
&= \lambda_1\lambda_2\cdots\lambda_k \sum_{i=1}^{k} \frac{e^{-\lambda_i t}}{\prod_{\substack{1 \le j \le k+1 \\ j \neq i}}(\lambda_j - \lambda_i)} + Ce^{-\lambda_{k+1}t}.
\end{aligned}
$$

(30)

The constant C can be determined from the boundary condition $P_{k+1}(0) = 0$. This is equivalent to

$$\lambda_1\lambda_2\cdots\lambda_k \sum_{i=1}^{k} \frac{1}{\prod_{\substack{1 \le j \le k+1 \\ j \neq i}}(\lambda_j - \lambda_i)} + C = 0.$$

Solving for C to obtain

$$
\begin{aligned}
C &= -\lambda_1\lambda_2\cdots\lambda_k \sum_{i=1}^{k} \frac{1}{\prod_{\substack{1\le j\le k+1 \\ j\ne i}}(\lambda_j - \lambda_i)} \\
&= \lambda_1\lambda_2\cdots\lambda_k \left(\sum_{i=1}^{k} \frac{1}{\prod_{\substack{1\le j\le k+1 \\ j\ne i}}(\lambda_j - \lambda_i)} \right) \\
&= \lambda_1\lambda_2\cdots\lambda_k \frac{1}{\prod_{1\le j\le k+1}(\lambda_j - \lambda_{k+1})}.
\end{aligned}
\tag{31}
$$

Finally, (30) and (31), combined yield

$$
\begin{aligned}
P_{k+1}(t) &= \lambda_1\lambda_2\cdots\lambda_k \sum_{i=1}^{k} \frac{e^{-\lambda_i t}}{\prod_{\substack{1\le j\le k+1 \\ j\ne i}}(\lambda_j - \lambda_i)} + Ce^{-\lambda_{k+1}t} \\
&= \lambda_1\lambda_2\cdots\lambda_k \left[\sum_{i=1}^{k} \frac{e^{-\lambda_i t}}{\prod_{\substack{1\le j\le k+1 \\ j\ne i}}(\lambda_j - \lambda_i)} + \frac{1}{\prod_{1\le j\le k+1}(\lambda_j - \lambda_{k+1})} \right] \\
&= \lambda_1\lambda_2\cdots\lambda_k \sum_{i=1}^{k+1} \frac{e^{-\lambda_i t}}{\prod_{\substack{1\le j\le k+1 \\ j\ne i}}(\lambda_j - \lambda_i)}
\end{aligned}
$$

confirming that (27) holds true.

This completes the proof of Theorem 4.2. □

4.4 APPLICATION OF VERSATILE STOCHASTIC GROWTH MODEL

In Section 4.3 a simple formula was derived for the state probabilities for a three parameter pure-birth process growth model. The main goal of this section is to show that by a suitable instantiation of the λ_ks, the three parameter pure-birth process can be used to model stem cell growth phenomenon.

Specifically, in Appendix A (26) allows to compute the probability of having k individuals at any given time t. In turn, once the state probabilities are computed, then the expected number, $E[\{N(t)\}] = \sum_{k=1}^{N} kP_k(t)$ of individuals at any given time t.

The NIH stem cell growth data [35] which is available online have been taken to compare with the predictions from versatile stochastic growth model. In Figure 3 a comparison between data generated by the three parameter birth model and the NIH embryonic stem cell growth data is presented. It has to be noted that growth model predicts the expected number of cells present at any given time period. It
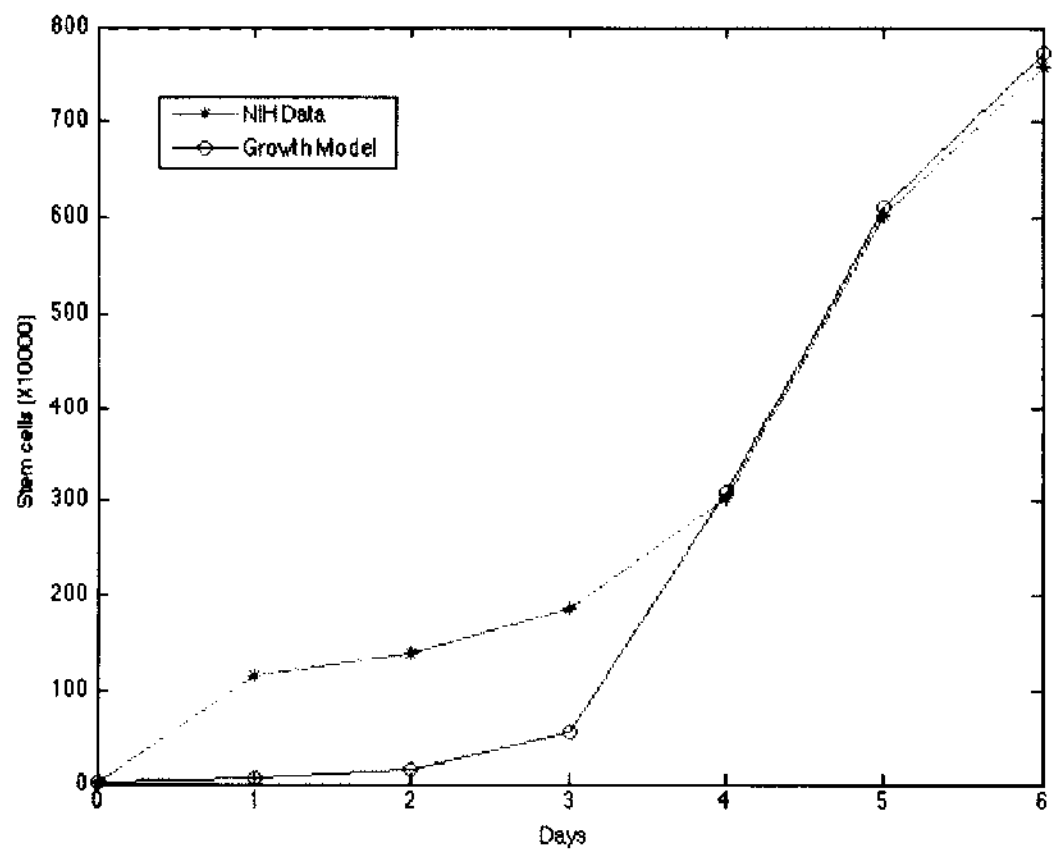
FIG. 2: NIH data [35] and expected number of embryonic stem cells
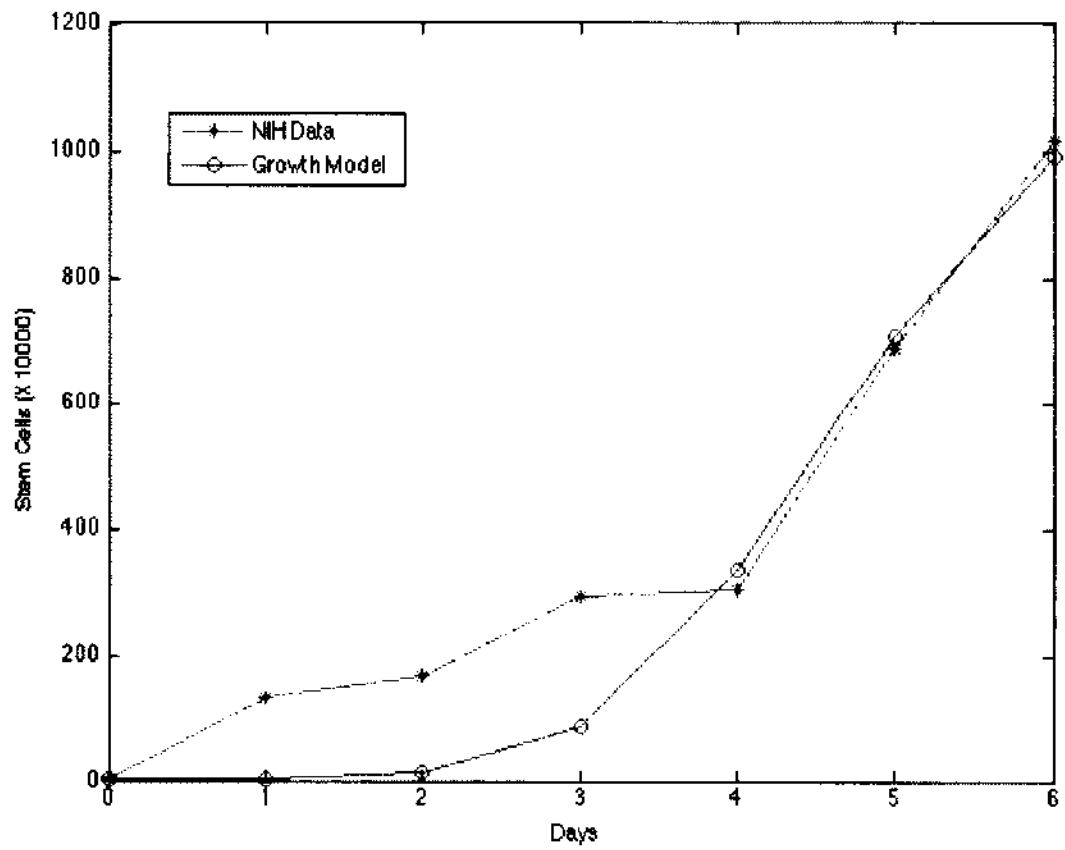
FIG. 3: NIH data [35] and expected number of adult stem cells

can be deduced that the three parameter pure birth process growth model roughly follows the experimental data of stem cell growth. Similarly in Figure 4 signifies results generated by three parameter model against adult stem cell experimental data. Unlike the deterministic models where for any given time there could only be one result, in stochastic three parameter growth model there can be numerous outcomes which is more in tune with realistic experimentation. The calculation of expected number of cells is basically taking the mean of all possible values. It is further possible that if data of stem cell growth from a series of experiments are tested, the average will match predictive results from this model even more accurately.

The three parameter pure-birth versatile growth model is sufficiently accurate to predict the dynamic behavior of stem cells. This model can be used to understand the growth dynamics of cell populations such as cell proliferation and quiescence rates both in vivo and in vitro. Although it must be emphasized at this moment due to lack experimental data at this stage this model cannot be compared vigorously but this could be a good lead in the research of stochastic growth models for stem cell.

CHAPTER 5

STEM CELL HOMEOSTASIS

The equilibrium of stem cell numbers are usually observed in all living organism. Results show [5, 27] that an increase in stem cell self-renewal, low apoptosis rates, and less differentiation can lead to the growth of cancers. Consequently, it is of great interest to understand the dynamics of homeostasis at the stem cell population level.

Long-term maintenance of tissue equilibrium relies on the accurate regulation of stem cell activity. Stem cells have to respond to tissue damage and proliferate according to tissue requirements while avoiding over proliferation. The regulatory mechanisms involved in these responses are now being unraveled [60, 27, 33] providing new insight into strategies and mechanisms of stem cell regulation. In the following section a new approach to investigate the dynamics of the stem cell compartment is presented.

Stem cells constitute a population of cells that continues to divide in adult organisms and produces cells for tissue regeneration. Stem cells can self-renew, can produce both differentiating cells, and cells that maintain stem-cell identity. They are pluripotent meaning they can give rise to all cell types in a given organ. Most stem cells actually divide very slowly and differentiating cells are produced from a partly lineage-restricted, rapidly dividing, cell population, the so-called transient amplifying pool. Stem cells are usually identified by tissue culture procedures: under certain culture conditions, individual cells from a tissue can produce all cell types present in this tissue. If the progeny of such a cell contains at least one cell that also fulfills these pluripotency criteria, the mother cell could self-renew and is by definition a stem cell.

In the light of the increased interest in stem cell research, fueled by the promises that cell-based therapies hold, it is hardly surprising that various mathematical models have been proposed for elucidating the intricate dynamics of stem cell self-renewal and differentiation. Most of these models are deterministic [5, 10] with only a handful of them taking a stochastic approach [58]. In addition, virtually all approaches to modeling stem cell dynamics of which assume only specific cell division patterns (typically, symmetric) ignoring the asymmetric division regimen.

The main contribution of this model is to propose a simple and intuitive Markov chain to model the internal underpinnings of stem cell dynamics. In addition to being stochastic, this model accommodates all types of cell divisions. One of the interesting features is that it suggests that, absent of spontaneous mutations or external molecular feedback, the Markov process is a Martingale indicating that the stem cell population is in stochastic equilibrium.

The remainder of this chapter is organized as follows: Section 5.1 introduces Markov chain that models the dynamics of the stem cell compartment, and Section 5.2 discusses the empirical validation of the model by way of simulation.

5.1 MODELING STEM CELL DYNAMICS

A Markov chain Figure 5 with states $0, 1, 2, 3, \cdots$ with the obvious semantics, namely that when in state i, the stem cell compartment comprises of i stem cells. Also it is worth noting that state 0 is absorbing, capturing the fact that the stem cell compartment becomes extinct and no further dynamics are of interest.
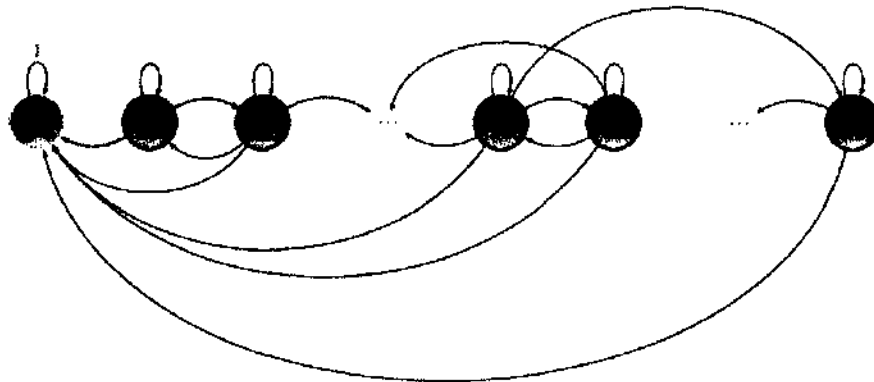
FIG. 4: Markov chain for stem cell homeostasis

Some experiments seem to indicate that should the stem cell compartment become extinct, molecular-level feedback induces one or several semi-differentiated cells, also known as transit amplifying cells, to revert back to stem cell state. However, since this reversal does not seem to be widely accepted in the literature, it was not taken into consideration for this model.

Time is divided into *slots* of identical duration. In each time slot, each stem cell divides with a constant probability p, independent of other stem cells and of the time

slot itself. A dividing stem cell has a 1/3 probability of producing two, one or zero stem cells, independent of the time slot when the division occurs and of how cells divide.

Suppose that for some n, $(n \geq 0)$, the event $\{X_n = i\}$ has occurred, that is, in time slot n the stem cell compartment contains i cells. Here the point of interest is in the conditional probability of the event $\{X_{n+1} = j\}$ that there will be j stem cells in time slot $n + 1$. Observe that for a fixed value of i

$$0 \leq j \leq 2i \tag{32}$$

which holds because the largest possible number of stem cells produced by i dividing stem cells is $2i$.

5.1.1 A STEPPING STONE

As a first step towards computing $\Pr[\{X_{n+1} = j\}|\{X_n = i\}]$, The following probablity needs to be computed first.

$$\Pr[\{X_{n+1} = j\}|\{X_n = i\} \cap \{k \text{ stem cells divide in time slot n}\}]. \tag{33}$$
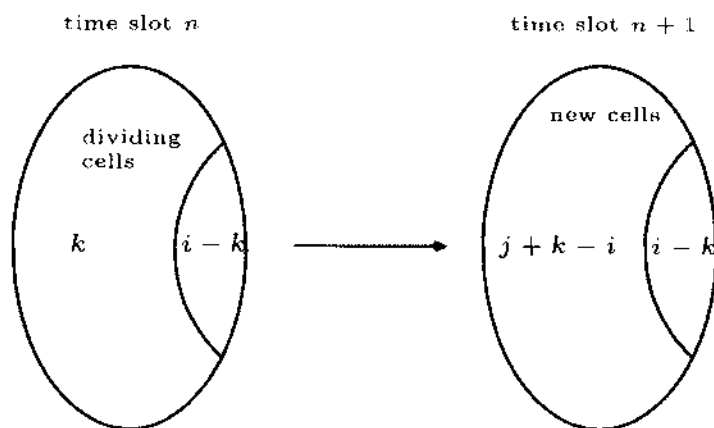
FIG. 5: Illustrating the case where k cells divide in time slot n.

Referring to Figure 6, imagine that k stem cells divide in time slot n. In order for the stem cells compartment to contain j stem cells in time slot $n+1$, $k+j-i$ new stem cells have to be produced as a result of the k divisions occurring in time slot n. Since each of the dividing stem cells can produce at most two stem cells, it must be that $k+j-i \leq 2k$ and so

$$j - i \leq k \leq i. \tag{34}$$

On the other hand, if $i \geq j$ then, since $i - k$ stem cells have not divided, it must be the case that $i - k \leq j$ and so

$$i - j \leq k \leq i. \tag{35}$$

Now, (34) and (35), combined, imply

$$|i - j| \leq k \leq i. \tag{36}$$
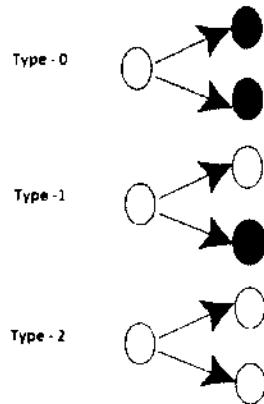
FIG. 6: Illustrating three cases of division with Type-0 producing zero stem cell and two differentiated cells, Type-1 producing one stem cell and one differentiated cell, Type-2 producing two stem cells

A dividing stem cell is said to be of Type r, $(r = 0, 1, 2)$, if it produces r stem cells. Since the stem cells are morphologically indistinguishable, the number

of *distinct* configurations of Types 0, 1 and 2 arising from the division of k stem cells can be obtained using the well-known Bose-Einstein statistics. Recall that in the Bose-Einstein statistics, m indistinguishable balls are placed at random into n distinguishable bins and each of the resulting $\binom{n+m-1}{m}$ distinct outcomes has the same probability, namely

$$\frac{1}{\binom{n+m-1}{m}}.$$

In this case, $m = k$ and $n = 3$ and so the number of distinct outcomes is $\binom{k+3-1}{k}$ $= \binom{k+2}{2}$, each with probability

$$\frac{1}{\binom{k+2}{2}}.$$

Let x_1, x_2, x_3 be the number of dividing stem cells of Type 2, Type 1, and Type 0 respectively. It is clear that x_1, x_2, x_3 must satisfy the following conditions

$$\begin{cases} x_1 + x_2 + x_3 = k \\ 2x_1 + x_2 = j - i + k. \end{cases}$$

Assuming x_3 to be a parameter, it can be solved for x_1 and x_2

$$\begin{cases} x_1 = j - i + x_3 \\ x_2 = k + i - j - 2x_3. \end{cases}$$

Since both x_1 and x_2 are non-negative, it follows that

$$\max\{0, i - j\} \leq x_3 \leq \left\lfloor \frac{k - (j - i)}{2} \right\rfloor. \tag{37}$$

Since x_3 is an integer, the number of values of x_3 that satisfy (37) is determined as follows:

- First, if $i \leq j$ the possible values of x_3 are $0, 1, 2, \cdots, \left\lfloor \frac{k-(j-i)}{2} \right\rfloor$, for a total of

$$1 + \left\lfloor \frac{k - (j - i)}{2} \right\rfloor$$

distinct values;

- Second, if $i > j$ then by (37), the possible values of x_3 are

$$i - j, \; i - j + 1, \; \cdots, \; \left\lfloor \frac{k - (j - i)}{2} \right\rfloor$$

for a total of

$$\left\lfloor \frac{k-(j-i)}{2} \right\rfloor - (i-j) + 1 = 1 + \left\lfloor \frac{k-(i-j)}{2} \right\rfloor$$

distinct values.

To summarize, regardless of whether $i \leq j$ or $i \geq j$, x_3 can take on exactly

$$1 + \left\lfloor \frac{k - |i-j|}{2} \right\rfloor \tag{38}$$

distinct values.

Consequently, since each value of x_3 uniquely determines a value for x_1 and a value for x_2 and since by the Bose-Einstein statistics each is equiprobable, with probability $\binom{k+2}{2}^{-1}$, then,

$$\Pr[\{X_{n+1} = j\}|\{X_n = i\} \cap \{k \text{ stem cells divide in time slot n}\}] \ = \ \frac{1 + \left\lfloor \frac{k-|i-j|}{2} \right\rfloor}{\binom{k+2}{2}}. \tag{39}$$

Thus, (33) holds true.

5.1.2 COMPUTING THE ONE-STEP TRANSITION PROBABILITIES

Let i and j be arbitrary non-negative integers. Since state 0 is absorbing, it is clear that

$$\Pr[\{X_{n+1} = j\}|\{X_n = 0\}] = 0.$$

Therefore, from now on it is assumed $i \geq 1$. By (32), $\Pr[\{X_{n+1} = j\}|\{X_n = i\}] = 0$ whenever $j > 2i$.

Theorem 5.1. *Let $i \geq 1$. For all j, $(0 \leq j \leq 2i)$,*

$$\Pr[\{X_{n+1} = j\}|\{X_n = i\}] = \sum_{k=|i-j|}^{i} \binom{i}{k} p^k (1-p)^{i-k} \frac{1 + \left\lfloor \frac{k-|i-j|}{2} \right\rfloor}{\binom{k+2}{2}}. \tag{40}$$

Proof. By Theorem B.1 in Appendix B,

$$
\begin{aligned}
\Pr[\{X_{n+1} = j\}|\{X_n = i\}] &= \sum_{k=|i-j|}^{i} \Pr[\{X_{n+1} = j\}|\{X_n = i\}] \\
&\quad \cap \{k \text{ stem cells divide in time slot } n\}] \\
&\quad \Pr[\{k \text{ stem cells divide in time slot } n\}|\{X_n = i\}] \\
&= \sum_{k=|i-j|}^{i} \binom{i}{k} p^k (1-p)^{i-k} \frac{1 + \left\lfloor \frac{k-|i-j|}{2} \right\rfloor}{\binom{k+2}{2}} \quad \text{[by (39)]}.
\end{aligned}
$$

$$(41)$$

In the above expression

- $\binom{i}{k} p^k (1-p)^{i-k}$ is the probability that exactly k of the i stem cells divide in time slot n;

- $\dfrac{1 + \left\lfloor \frac{k-|i-j|}{2} \right\rfloor}{\binom{k+2}{2}}$ is the conditional probability that j stem cells will be present in time slot $(n+1)$, given that there were i stem cells in time slot n and that k of them have divided.

With this the proof of Theorem 5.1 is complete. □

Corollary 5.2. *Let* $i \geq 1$. *For all* r, $(0 \leq r \leq i)$,

$$
\Pr[\{X_{n+1} = r\}|\{X_n = i\}] = \Pr[\{X_{n+1} = 2i - r\}|\{X_n = i\}]. \tag{42}
$$

Proof. It follows directly from (41) which tells that the underlying Markov chain has symmetric transitions about i. □

Thus, for example, letting $p_{i,j}$ stand for $\Pr[\{X_{n+1} = j\}|\{X_n = i\}]$, $p_{i,0} = p_{i,2i}$, $p_{i,1} = p_{i,2i-1}$ and, in general, $p_{i,r} = p_{i,2i-r}$ for $0 \leq r \leq i$.

5.1.3 VERIFYING THAT THE TRANSITION MATRIX IS STOCHASTIC

Having obtained the various one-step transition probabilities, it is important to show they for all i and for all n, $\sum_{j=0} \Pr[\{X_{n+1} = r\}|\{X_n = i\}] = 1$, in other words, that the transition matrix is stochastic.

Theorem 5.3. *For all i and for all $n \in \mathbb{N}$,*

$$\sum_{j=0} \Pr[\{X_{n+1} = j\}|\{X_n = i\}] = 1$$

Proof. The proof relies heavily on Theorem 5.1 and Corollary 5.2. For a given i, evaluating $\sum_{j=0}^{2i} \Pr[\{X_{n+1} = j\}|\{X_n = i\}]$ as follows

$$
\begin{aligned}
\sum_{j=0} \Pr[\{X_{n+1} = j\}|\{X_n = i\}] &= \sum_{j=0}^{2i} \Pr[\{X_{n+1} = j\}|\{X_n = i\}] \\
&= \sum_{j=0}^{2i} \sum_{k=|i-j|}^{i} \binom{i}{k} p^k (1-p)^{i-k} \frac{1 + \left\lfloor \frac{k-|i-j|}{2} \right\rfloor}{\binom{k+2}{2}} \\
&= \sum_{j=0}^{i-1} \sum_{k=|i-j|}^{i} \binom{i}{k} p^k (1-p)^{i-k} \frac{1 + \left\lfloor \frac{k-|i-j|}{2} \right\rfloor}{\binom{k+2}{2}} \\
&+ \sum_{j=i} \sum_{k=|i-j|}^{i} \binom{i}{k} p^k (1-p)^{i-k} \frac{1 + \left\lfloor \frac{k-|i-j|}{2} \right\rfloor}{\binom{k+2}{2}} \\
&+ \sum_{j=i+1}^{2i} \sum_{k=|i-j|}^{i} \binom{i}{k} p^k (1-p)^{i-k} \frac{1 + \left\lfloor \frac{k-|i-j|}{2} \right\rfloor}{\binom{k+2}{2}}.
\end{aligned}
$$

Let $t = |i - j|$ and note that

$$
\sum_{j=0}^{i-1} \sum_{k=|i-j|}^{i} \binom{i}{k} p^k (1-p)^{i-k} \frac{1 + \left\lfloor \frac{k-|i-j|}{2} \right\rfloor}{\binom{k+2}{2}} = \sum_{j=i+1}^{2i} \sum_{k=|i-j|}^{i} \binom{i}{k} p^k (1-p)^{i-k} \frac{1 + \left\lfloor \frac{k-|i-j|}{2} \right\rfloor}{\binom{k+2}{2}}
$$

$$
= \sum_{t=1}^{i} \sum_{k=t}^{i} \binom{i}{k} p^k (1-p)^{i-k} \frac{1 + \left\lfloor \frac{k-t}{2} \right\rfloor}{\binom{k+2}{2}}.
$$

With this, the expression of $\sum_{j=0}^{2i} \Pr[\{X_{n+1} = j\}|\{X_n = i\}]$ becomes

$$
\begin{aligned}
\sum_{j=0}^{2i} \Pr[\{X_{n+1} = j\}|\{X_n = i\}] &= \sum_{k=0}^{i} \binom{i}{k} p^k (1-p)^{i-k} \frac{1 + \left\lfloor \frac{k}{2} \right\rfloor}{\binom{k+2}{2}} \\
&+ 2 \sum_{t=1}^{i} \sum_{k=t}^{i} \binom{i}{k} p^k (1-p)^{i-k} \frac{1 + \left\lfloor \frac{k-t}{2} \right\rfloor}{\binom{k+2}{2}}. \quad (43)
\end{aligned}
$$

Let r be an arbitrary value of t and consider all the terms corresponding to $k = r$ in the previous sums.

First, in the sum $\sum_{k=0}^{i} \binom{i}{k} p^k (1-p)^{i-k} \dfrac{1 + \left\lfloor \frac{k}{2} \right\rfloor}{\binom{k+2}{2}}$ the corresponding term is

$$\binom{i}{r} p^r (1-p)^{i-r} \frac{1 + \left\lfloor \frac{r}{2} \right\rfloor}{\binom{r+2}{2}};$$

Second, in the sum $2 \sum_{t=1}^{i} \sum_{k=t}^{i} \binom{i}{k} p^k (1-p)^{i-k} \dfrac{1 + \left\lfloor \frac{k-t}{2} \right\rfloor}{\binom{k+2}{2}}$ the corresponding terms are

$$\frac{\binom{i}{r}}{\binom{r+2}{2}} p^r (1-p)^{i-r} \left[\left(1 + \left\lfloor \frac{r-1}{2} \right\rfloor \right) + \left(1 + \left\lfloor \frac{r-2}{2} \right\rfloor \right) + \cdots \right.$$
$$\left. + \left(1 + \left\lfloor \frac{r-(r-1)}{2} \right\rfloor \right) + \left(1 + \left\lfloor \frac{r-r}{2} \right\rfloor \right) \right]$$

which reduces to

$$\frac{\binom{i}{r}}{\binom{r+2}{2}} p^r (1-p)^{i-r} \left[2r + 2 \left(\left\lfloor \frac{r-1}{2} \right\rfloor + \left\lfloor \frac{r-1}{2} \right\rfloor + \cdots + \left\lfloor \frac{1}{2} \right\rfloor \right) \right].$$

By Theorem B.5 in Appendix B, this reduces further to

$$\frac{\binom{i}{r}}{\binom{r+2}{2}} p^r (1-p)^{i-r} \left[2r + \frac{r(r-1)}{2} - \left\lfloor \frac{r}{2} \right\rfloor \right].$$

Thus, altogether, the coefficient corresponding to $t = r$ in

$$\sum_{j=0}^{2i} \sum_{k=|i-j|}^{i} \binom{i}{k} p^k (1-p)^{i-k} \frac{1 + \left\lfloor \frac{k-|i-j|}{2} \right\rfloor}{\binom{k+2}{2}}$$

turns out to be

$$\binom{i}{r} p^r (1-p)^{i-r} \frac{1 + \left\lfloor \frac{r}{2} \right\rfloor + 2r + \frac{r(r-1)}{2} - \left\lfloor \frac{r}{2} \right\rfloor}{\binom{r+2}{2}} = \binom{i}{r} p^r (1-p)^{i-r} \frac{\frac{r^2 + 3r + 2}{2}}{\binom{r+2}{2}}$$
$$= \binom{i}{r} p^r (1-p)^{i-r} \frac{\frac{(r+2)(r+1)}{2}}{\binom{r+2}{2}}$$
$$= \binom{i}{r} p^r (1-p)^{i-r}.$$

Since, r was arbitrary it follows that

$$\sum_{j=0}^{2i} P[\{X_{n+1} = j\}|\{X_n = i\}] = \sum_{r=0}^{i} \binom{i}{r} p^r (1-p)^{i-r} = (p + 1 - p)^r = 1,$$

and the proof of the theorem is complete. $\square$

5.1.4 EVALUATING THE CONDITIONAL EXPECTATION OF X_{N+1}

Having determined the one-step transition probabilities, it is of great theoretical interest to determine for a given state i, the expected state in which the Markov chain will find itself once it leaves i. Put differently, what is of interest is in the conditional expectation $E[X_{n+1}|\{X_n = i\}]$. The somewhat surprising answer to this natural question is given by the following result.

Theorem 5.4. *For all non-negative integers n, and for all $i \geq 1$, $E[X_{n+1}|\{X_n = i\}] = i$.*

Proof. By the Law of Total Expectation

$$E[X_{n+1}|\{X_n = i\}] = \sum_{j=0}^{2i} j \Pr[\{X_{n+1} = j\}|\{X_n = i\}]$$

$$= \sum_{j=0}^{2i} j \sum_{k=|i-j|}^{i} \binom{i}{k} p^k (1-p)^{i-k} \frac{1 + \left\lfloor \frac{k-|i-j|}{2} \right\rfloor}{\binom{k+2}{2}}$$

$$= \sum_{j=0}^{i-1} j \sum_{k=|i-j|}^{i} \binom{i}{k} p^k (1-p)^{i-k} \frac{1 + \left\lfloor \frac{k-|i-j|}{2} \right\rfloor}{\binom{k+2}{2}}$$

$$+ \sum_{j=i}^{i} j \sum_{k=|i-j|}^{i} \binom{i}{k} p^k (1-p)^{i-k} \frac{1 + \left\lfloor \frac{k-|i-j|}{2} \right\rfloor}{\binom{k+2}{2}}$$

$$+ \sum_{j=i+1}^{2i} j \sum_{k=|i-j|}^{i} \binom{i}{k} p^k (1-p)^{i-k} \frac{1 + \left\lfloor \frac{k-|i-j|}{2} \right\rfloor}{\binom{k+2}{2}}.$$

Write $t = |i - j|$ and observe that

- if $j = 0, 1, \cdots, i-1$ then $t = i, i-1, \cdots, 1$ and $j = i - t$;

- if $j = i + 1,\ i + 2,\ \cdots,\ 2i$ then $t = 1,\ 2,\ \cdots,\ i$ and $j = i + t$;

- finally, if $j = i$ then $t = |i - j| = 0$.

After the change of variable $t = |i - j|$, the expression of $E[X_{n+1}|\{X_n = i\}]$ becomes

$$
\begin{aligned}
E[X_{n+1}|\{X_n = i\}] &= \sum_{t=1}^{i}(i-t)\sum_{k=t}^{i}\binom{i}{k}p^k(1-p)^{i-k}\frac{1+\left\lfloor\frac{k-t}{2}\right\rfloor}{\binom{k+2}{2}} \\
&+ i\sum_{k=0}^{i}\binom{i}{k}p^k(1-p)^{i-k}\frac{1+\left\lfloor\frac{k-t}{2}\right\rfloor}{\binom{k+2}{2}} \\
&+ \sum_{t=1}^{i}(i+t)\sum_{k=t}^{i}\binom{i}{k}p^k(1-p)^{i-k}\frac{1+\left\lfloor\frac{k-t}{2}\right\rfloor}{\binom{k+2}{2}} \\
&= i\sum_{k=0}^{i}\binom{i}{k}p^k(1-p)^{i-k}\frac{1+\left\lfloor\frac{k-t}{2}\right\rfloor}{\binom{k+2}{2}} \\
&+ \sum_{t=1}^{i}[(i+t)+(i-t)]\sum_{k=t}^{i}\binom{i}{k}p^k(1-p)^{i-k}\frac{1+\left\lfloor\frac{k-t}{2}\right\rfloor}{\binom{k+2}{2}} \\
&= i\sum_{k=0}^{i}\binom{i}{k}p^k(1-p)^{i-k}\frac{1+\left\lfloor\frac{k-t}{2}\right\rfloor}{\binom{k+2}{2}} \\
&+ \sum_{t=1}^{i}2i\sum_{k=t}^{i}\binom{i}{k}p^k(1-p)^{i-k}\frac{1+\left\lfloor\frac{k-t}{2}\right\rfloor}{\binom{k+2}{2}} \\
&= i\left[\sum_{k=0}^{i}\binom{i}{k}p^k(1-p)^{i-k}\frac{1+\left\lfloor\frac{k-t}{2}\right\rfloor}{\binom{k+2}{2}}\right. \\
&+ \left. 2\sum_{t=1}^{i}\sum_{k=t}^{i}\binom{i}{k}p^k(1-p)^{i-k}\frac{1+\left\lfloor\frac{k-t}{2}\right\rfloor}{\binom{k+2}{2}}\right] \\
&= i \quad [\text{by Theorem 5.3 and (43), the terms add up to 1.}]
\end{aligned}
$$

With this, the proof of Theorem 5.4 is complete. $\square$

Theorem 5.4 states that if every dividing stem cell has an equal chance of producing, two, one, or no stem cells then, stochastically, the system is in *equilibrium*,

in the sense that if the stem cell compartment contains i cells in time slot n, then the expected number of stem cells it contains in time slot $n + 1$ is also i. More formally, it can now be stated the following important consequence of Theorem 5.4.

Corollary 5.5. *The process $\{X_n\}$ is a martingale.*

Proof. By Theorem 5.4, for all positive i and non-negative integer n, $E[X_{n+1}|\{X_n = i\}] = i$. This, combined with the fact that $x_n = i$ implies that $E[X_{n+1}|\{X_n = i\}] = X_n$. Now, applying the expectation operation on both sides yields

$$
\begin{aligned}
E[X_n] &= E[E[X_{n+1}|\{X_n = i\}]] \\
&= E[X_{n+1}], \quad \text{[by the Law of Total Expectation]}
\end{aligned}
$$

confirming that $\{X_n\}$ is a martingale. □

5.2 SIMULATIONS

In this section simulation analysis will be conducted to demonstrate the model's effective predictions. All these simulations were implemented on MATLAB.

5.2.1 EXPERIMENTAL SETUP

In order confirm empirically the theoretical findings above and especially the predictions of Theorem 5.4, the following simulation plan was implemented:

1. Firstly, the number n of time slots was taken as independent parameter for the simulation and also the initial distribution, i, of the number of stem cells. In the first and second experiments initial number of stem cells i was, $i = 50$ and $i = 100$ respectively. While the number n of time slots was 100 in both experiments;

2. In each time slot simulated, from the current number of stem cells i, randomly k stem cells were selected to divide in that time slot. The number k was selected following a binomial distribution with success probability $p = 0.3$;

3. Each of these k dividing stem cells produced either 0, 1, or 2 stem cells according to the Bose-Einstein statistics;
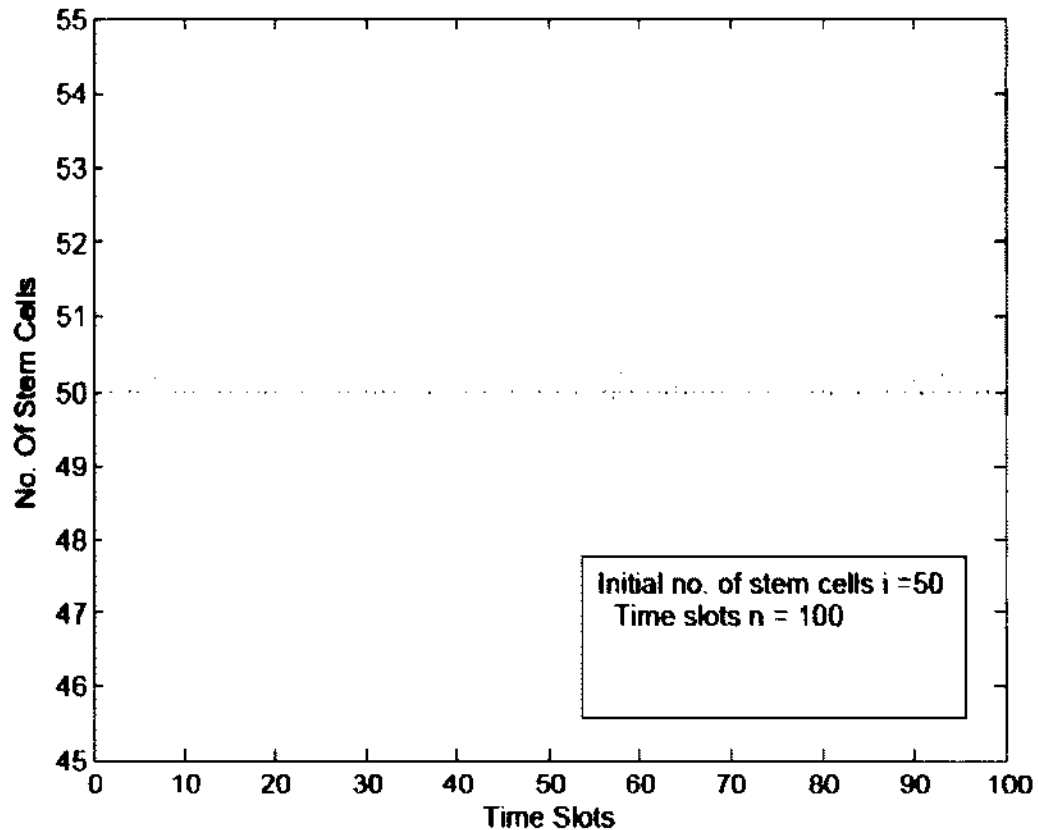
FIG. 7: Simulation results for initial stem cell populations of 50

4. The track of the number of stem cells were kept after all k divisions and updated the total number of stem cells accordingly. The same procedure was repeated for 100 time slots.

All the steps above are then run ten thousand times and averages were taken to produce the final outcome.

5.2.2 RESULTS

As previously discussed in Section 5.2.1 a simulation script was written in MAT-LAB to produce all the predictive results. A glance at Figure 8 and Figure 9 reveals that at the end of 100 time slots, the number of stem cells found is roughly equal to the same initial number of stem cells at the start. In other words, as predicted by Theorem 5.4, the expected number of stem cells that would be seen in the next time

slot is equal to the stem cell seen at current time slot. In the first experiment initially the experiment had $i = 50$ stem cells. Then the script was run independently 10,000 times. After averaging individual runs of all the trial runs the results were observed and plotted. From Figure 8 demonstrates stem cell numbers did fluctuate above the initial number of cells $i = 50$ during runs but on an average after 100 time units, they remained the same number from starting point, reflecting stem cell homeostasis.

Secondly, the experiment had $i = 50$ stem cells to start with. Then the script was run independently again 10,000 times. After averaging individual runs of all the trial runs the results were observed and plotted. From Figure 9 demonstrates stem cell numbers did fluctuated above the initial number of cells $i = 100$ during runs but on an average after 100 time units, they remained the same number from starting point, meaning stem cell homeostasis was achieved. These show that stem cells number fluctuate up and down because of the type of division occurs randomly at cellular level, but overall the number of stem cells remains the same and constant. Meaning the homeostasis of stem cell is conserved within tissue.

In the last of the figures, Figure 9 shows results from a single simulation run. This is presented here to demonstrate the reasoning behind 10,000 runs from last two results above. Rather than averaging numerous runs, a single run is observed. As seen from Figure 10 that unlike the previous two simulations it is not smooth and shows more movements upwards and downwards although results are practically same as stem cell numbers hovers close to initial number as suggested from the theoretical findings.

In Figure 11 stem cell compartment homeostasis is studied at different levels with influence of feedback mechanism. Feedback mechanisms provide sharp increase or decrease in the total number of stem cells. The green line signifies period of homeostasis whereas red line denotes explosive growth or reduction in stem cell compartment. In the first experiment, Figure 11 stem cell compartment initially started with 1000 cells then continued upto 450 time units when feedback mechanism triggered an explosion of stem cell growth for 50 time units. After that brief period of growth stem cell number reaches to roughly 1400. In this period of growth the feedback works in such a way which promotes only division where one stem cell produces two new stem cells in each cycle. Similarly, we see another growth period at time unit 1000 and later we see a significant reduction of stem cell number at time unit 1550. In reduction period, feedback mechanism works in such a way where cell division produces two
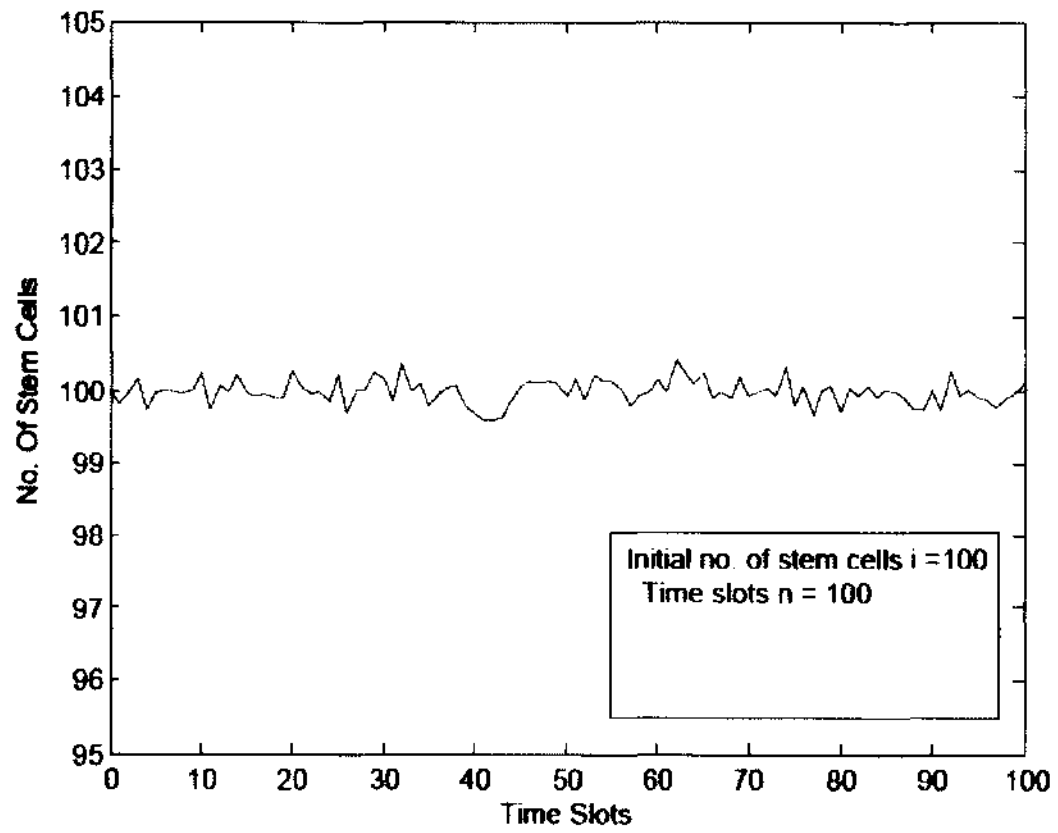
FIG. 8: Simulation results for initial stem cell populations of 100
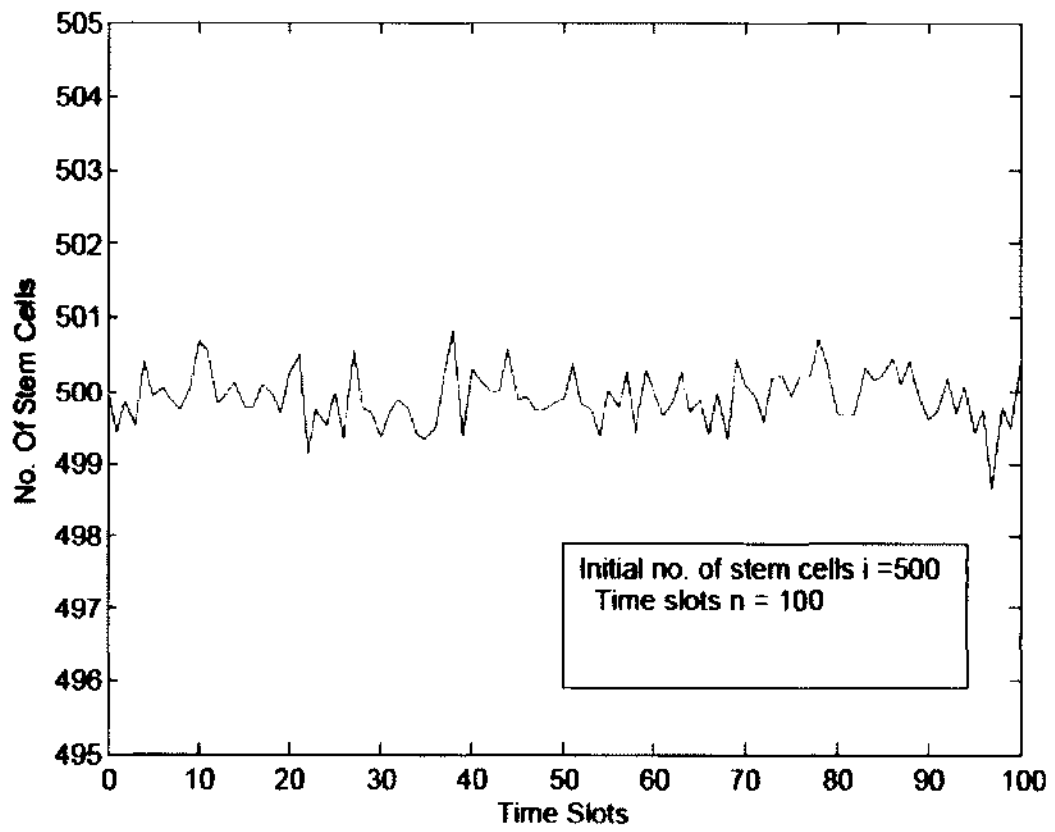
FIG. 9: Illustrating simulation results for initial stem cell populations of 500 with just a single run
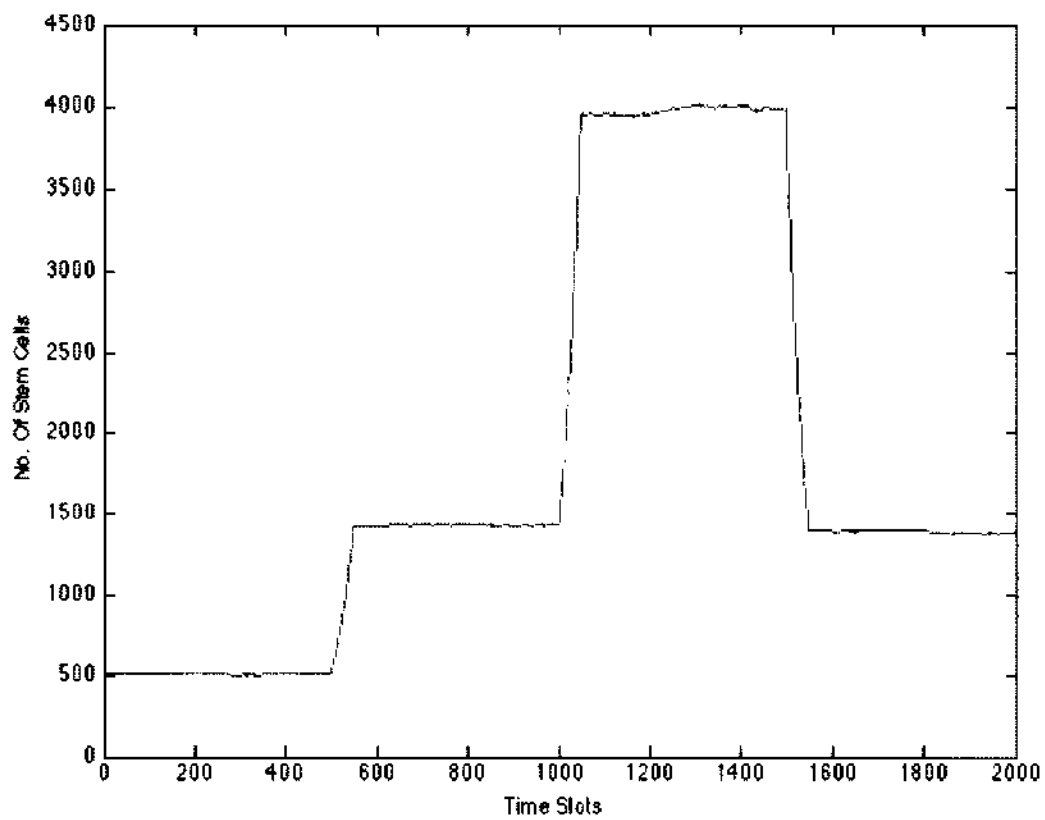
FIG. 10: Stem Cell Compartment Homeostasis at different level starting with 1000 stem cells
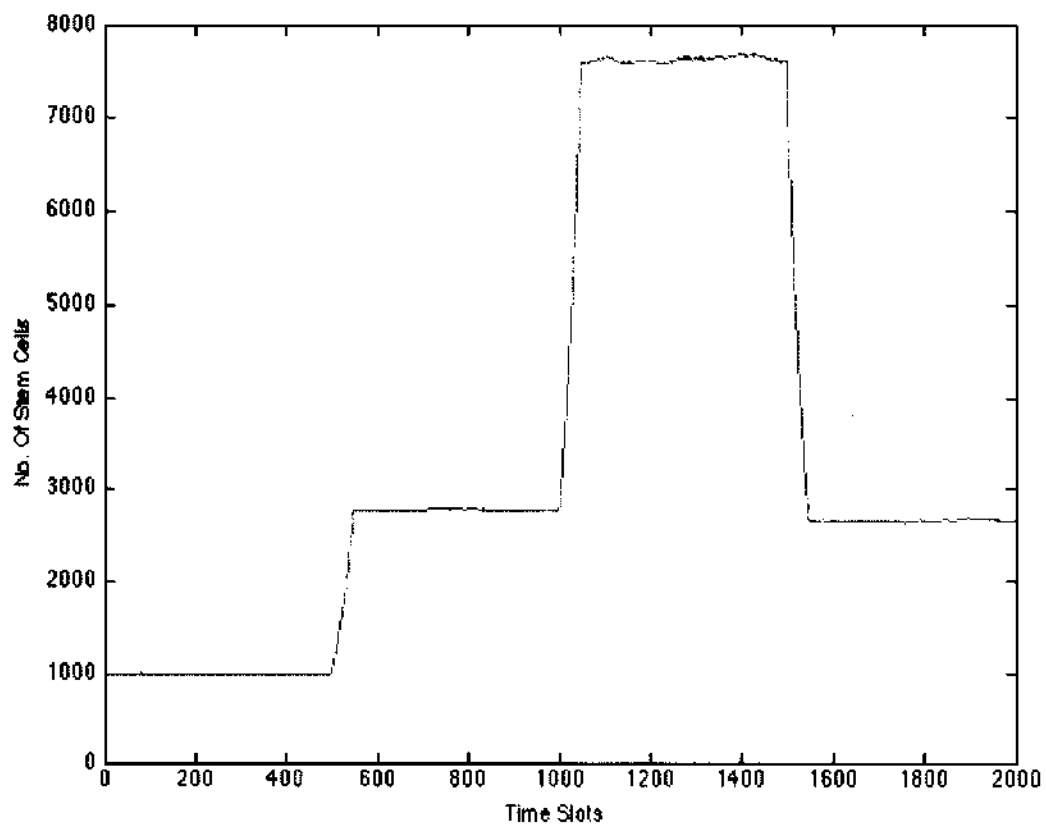
FIG. 11: Stem Cell Compartment Homeostasis at different level starting with 1000 stem cells

differentiated cells and no new stem cell, thus triggering reduction in total number of stem cells. The purpose of these two experiments is to show even with the feedback mechanism in place from the environment stem compartment maintain homeostasis at different level. A similar event occurs for Figure 12 where we homeostasis achieved at different levels where initially the simulation had 500 stem cells.

CHAPTER 6

REASONING ABOUT HOMEOSTASIS IN TISSUE

LINEAGES

The main goal of this chapter is to offer a mathematical model of tissue-level homeostasis. The modeling of the dynamics of individual compartments by two local parameters, namely the rate at which cells divide as well as the rate at which they undergo apoptosis. In spite of its simplicity, this model reveals the intricate interplay between local and global equilibrium (i.e., homeostasis) requirements. In turn, these requirements must be reflected in the prevailing feedback mechanisms.

The main results include:

- a necessary and sufficient condition for homeostasis of the stem cell (SC) compartment;

- a necessary and sufficient condition for homeostasis of the transit amplifying (TA) cell compartment;

- a necessary and sufficient condition for homeostasis of the differentiated cell (post-mitotic) compartment

- a proof of the fact that that the TA compartment cannot be homeostatic unless the stem cell compartment is also homeostatic.

It has been assumed existence of a complex and integrated feedback mechanism responsible for maintaining homeostasis at the tissue level. While in this model it was not concerned with the exact way in which the feedback mechanism operates, but local equilibrium equations spell out conditions that the feedback mechanism must address in one form or another.

It has also been assumed that the signaling by which the feedback mechanism regulates the biological processes in the tissue compartments occurs in pulses. The pulses are nearly instantaneous changes in compartment parameters. In the time intervals between these pulses, the various compartment parameters remain constant.

6.1 THE STEM CELL COMPARTMENT

Let $X_0(t)$ denote the size of the SC compartment at time $t \geq 0$, with $X_0(0) = n_0 \geq 1$. For $h > 0$, let

- $\nu_0(h)$ denote the fraction of the stem cells that divide in the interval $(t, t + h]$;

- $\gamma_0(h)$ denote the fraction of the stem cells that undergo apoptosis in the interval $(t, t + h]$.

Also it has been assumed that the two limits $\lim_{h \to 0} \frac{\nu_0(h)}{h} = \nu_0$ and $\lim_{h \to 0} \frac{\gamma_0(h)}{h} = \gamma_0$ exist and are finite.

Clearly, ν_0 represents the rate at which stem cells divide. Similarly, γ_0 represents the rate at which stem cells are lost to apoptosis. Previously it has been mentioned that the assumption over large time intervals both γ_0 and ν_0 are constants. This assumption is in line with the fact that both γ_0 and ν_0 change in response to regulatory feedback loops whose cycle is measured in days [7]. Since the ratio $\frac{\gamma_0}{\nu_0}$ will appear quite often in the derivations, it is convenient to write,

$$\theta_0 = \frac{\gamma_0}{\nu_0}. \tag{44}$$

For a dividing stem cell let,

- α_1 denote the probability that the cell produces two daughter stem cells;

- α_2 denote the probability that the cell produces one daughter stem cell and one TA cell;

- α_3 denote the probability that the cell produces two TA cells.

Naturally,

$$\alpha_1 + \alpha_2 + \alpha_3 = 1. \tag{45}$$

For later reference observe that $\alpha_1 \neq 1$. Otherwise, by (45), $\alpha_2 = \alpha_3 = 0$ which makes no biological sense, for the stem cells would produce no TA cells at all.

In the above notation, $\nu_0(h)X_0(t)$ and $\nu_0(h)X_0(t)$ denote, respectively, the expected number of stem cells that divide and those that undergo apoptosis in the time interval $(t, t + h]$. It should be fairly obvious that the size, $X_0(t + h)$, of the SC

compartment at time $t + h$ can be expressed as

$$
\begin{aligned}
X_0(t + h) &= X_0(t) - \nu_0(h)X_0(t) - X_0(t)\gamma_0(h) + X_0(t)\nu_0(h)[2\alpha_1 + \alpha_2] \\
&= X_0(t) + X_0(t)\nu_0(h)[2\alpha_1 + \alpha_2 - 1] - X_0(t)\gamma_0(h) \\
&= X_0(t) + X_0(t)\nu_0(h)[\alpha_1 - \alpha_3] - X_0(t)\gamma_0(h). \quad [\text{by } (45)]
\end{aligned}
$$

After transposing $X_0(t)$ and dividing both sides by h,

$$
\frac{X_0(t + h) - X_0(t)}{h} = \frac{\nu_0(h)}{h} X_0(t)[\alpha_1 - \alpha_3] - \frac{\gamma_0(h)}{h} X_0(t)
$$

which, upon taking limits as $h \to 0$, yields the differential equation

$$
\begin{aligned}
\frac{\mathrm{d}X_0(t)}{\mathrm{d}t} &= \lim_{h \to 0} \frac{\nu_0(h)}{h} X_0(t)[\alpha_1 - \alpha_3] - \lim_{h \to 0} \frac{\gamma_0(h)}{h} X_0(t) \\
&= X_0(t)\left[\nu_0(\alpha_1 - \alpha_3) - \gamma_0\right]
\end{aligned}
\tag{46}
$$

with the boundary condition $X_0(0) = n_0$. By solving (46) for $X_0(t)$,

$$
X_0(t) = n_0 e^{[\nu_0(\alpha_1 - \alpha_3) - \gamma_0]t}.
\tag{47}
$$

Since the ratio $\frac{\gamma_0}{\nu_0}$ will appear quite often in our derivations, it is convenient to write

$$
\theta_0 = \frac{\gamma_0}{\nu_0}.
\tag{48}
$$

Now taking note of a conceptually useful result implied by (47).

Corollary 6.1. *Unless $\theta_0 < 1$, the SC compartment cannot be homeostatic.*

Proof. Since both α_1 and α_3 are probabilities, and since $\alpha_1 \neq 1$, the difference $\alpha_1 - \alpha_3$ is strictly less than one. As a consequence, $\gamma_0 \geq \nu_0$ implies $\gamma_0 > \nu_0(\alpha_1 - \alpha_3)$ which, by (47), guarantees that $X_0(t)$ is a decreasing function of time. □

In turn, Corollary 6.1 confirms the intuitive feeling that if the SC compartment is to be homeostatic then the rate at which stem cells are lost to apoptosis must be strictly smaller than the rate at which they divide. However, it is conceivable that the condition $\theta_0 < 1$ might be violated for short, transient periods of time in the wider context of time-dependent feedback mechanisms.

$$X_0(t)\nu_0[1 + (\alpha_1 - \alpha_3)]$$

$$X_0(t)\nu_0[1 - (\alpha_1 - \alpha_3)]$$

$$X_0(t)\gamma_0$$
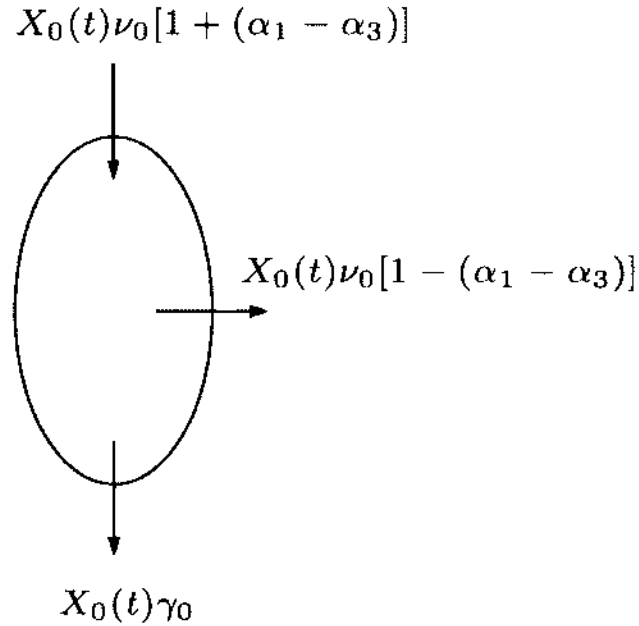
FIG. 12: Illustrating the dynamics of the SC compartment.

The dynamics of the stem cell compartment are illustrated in Figure 13. The direction of the arrows suggest the flow of cells going inside or outside of the stem cell compartment. Specifically, it is easy to confirm that:

- new stem cells are being produced as a result of cell divisions at the rate of $X_0(t)\nu_0(2\alpha_1 + \alpha_2) = X_0(t)\nu_0[1 + (\alpha_1 - \alpha_3)]$;

- stem cells are being lost to apoptosis at the rate of $X_0(t)\gamma_0$;

- TA cells are being produced at the rate of $X_0(t)\nu_0(\alpha_2 + 2\alpha_3) = X_0(t)\nu_0[1 - (\alpha_1 - \alpha_3)]$.

With all these condition stated, the following fundamental result is implied by (47).

Theorem 6.2. *A necessary and sufficient condition for homeostasis of the SC compartment is*

$$\gamma_0 = (\alpha_1 - \alpha_3)\nu_0. \tag{49}$$

Proof. First, if (49) holds then, by virtue of (47), $X_0(t) = n_0$, independent of t, indicating that the SC compartment is homeostatic.

Conversely, suppose that the SC compartment is homeostatic. This implies that $X_0(t) = n_0$, independent of t. Now, (47) implies that $\nu_0(\alpha_1 - \alpha_3) - \gamma_0 = 0$ and so (49) must hold, as claimed. □

It is interesting to note that $(\alpha - 1 - \alpha - 3)\nu_0$ is the rate at which stem cells accumulate due to symmetric divisions. Theorem 6.2 tells that in order for the SC compartment to be homeostatic this accumulation rate must match the rate at which stems cells are lost to apoptosis.

Observe that (49) can be written as

$$\alpha_1 - \alpha_3 = \theta_0,$$

emphasising the fact that θ_0 is a *critical* value as far as homeostasis of the SC compartment is concerned. Indeed, if $\alpha_1 - \alpha_3 > \frac{\gamma_0}{\nu_0}$ the SC compartment grows exponentially. On the other hand, if $\alpha_1 - \alpha_3 < \frac{\gamma_0}{\nu_0}$ then the SC compartment decreases exponentially.

Also noting that homeostasis of the SC compartment in the special case where $\gamma_0 = 0$ and only symmetric divisions occur, that is $\alpha_2 = 0$, has been studied extensively in the literature [25, 26, 27, 60]. As several of these authors pointed out, in that particular case, homeostasis of the SC compartment hinges on the very strong condition $\alpha_1 = \alpha_3 = \frac{1}{2}$ which shows that the system is inherently unstable.

At this point,

- equation (49) is independent of n_0, the number of cells in the SC compartment. In turn, this seems to suggest that any feedback mechanism that maintains SC compartment homeostasis must act on ν_0, γ_0, or, indeed, the probabilities α_1, α_2, α_3 subject to (49);

- as will be discussed later in some detail, the rate at which TA cells are produced by cell division in the stem cell compartment depends on $\alpha_1 - \alpha_3$. Thus, the lower $\alpha_1 - \alpha_3$, the more TA cells are being produced per unit time;

- somewhat surprisingly, the probabilities α_1 and α_3 only occur in (49) through the expression $\alpha_1 - \alpha_3$. This seems to imply that as long as the probabilities of symmetric divisions are shifted up or down by equal amounts, homeostasis is preserved. The feasible ranges for these probabilities are investigated below.

Lemma 6.3. *For every value of α_1 in the range $\left[\theta_0, \frac{1+\theta_0}{2}\right]$ there exist feasible probabilities α_2 and α_3 that satisfy both (45) and (49).*

Proof. It is by justifying the stated range for α_1. For this purpose, recall that by (45), $2\alpha_1 + \alpha_2 = 1 + (\alpha_1 - \alpha_3)$. Since $\alpha_2 \geq 0$, (49) leads directly to

$$\alpha_1 \leq \frac{1 + \theta_0}{2}$$

which, combined with the fact that $\alpha_1 \geq \theta_0$ guarantees that

$$\theta_0 \leq \alpha_1 \leq \frac{1 + \theta_0}{2}.$$

To complete the proof, there has to be a need to show that for each value of α_1 in the range $\left[\theta_0, \frac{1+\theta_0}{2}\right]$ there exist probabilities α_2 and α_3 that satisfy (45) and (49). To see that this is the case, write $\alpha_1 = u$ for some arbitrary u in the interval $[\theta_0, \frac{1+\theta_0}{2}]$

By (49), the expression of α_3 must be $\alpha_3 = u - \theta_0$. It is observed that by the choice of u,

$$0 \leq \alpha_3 = u - \theta_0 \leq \frac{1 - \theta_0}{2}.$$

Next, is it easy to see that $\alpha_2 = 1 + \theta_0 - 2u$ and that by the choice of u,

$$0 \leq \alpha_2 \leq 1 - \theta_0.$$

Finally, it is easy to see that the expressions for α_1, α_2, α_3 obtained above satisfy (45) and (49), and the proof is complete. $\square$

Lemma 6.3 confirms the intuition that homeostasis of the SC compartment can occur for a large number of values of α_1 and, consequently, of α_2 and α_3. Moreover, as later it can been shown, as long as (49) holds, the rate at which new TA cells arise as a result of divisions in the SC compartment is independent of the actual values of α_1, α_2, α_3. It would be interesting to see if the feedback mechanism that keeps the SC compartment homeostatic favors some of these values over others.

Next, turning attention to the rate at which TA cells are being produced.

Lemma 6.4. *Under homeostatic conditions, the rate at which TA cells are being produced in the SC compartment is $n_0(\nu_0 - \gamma_0)$.*

Proof. Recall that the rate at which TA cells are being produced by cell division in the SC compartment is $X_0\nu_0(\alpha_2 + 2\alpha_3)$. Consequently, under homeostasis, It can be written,

$$
\begin{aligned}
X_0(t)\nu_0(\alpha_2 + 2\alpha_3) &= n_0\nu_0(\alpha_2 + 2\alpha_3) \\
&= n_0\nu_0[1 - (\alpha_1 - \alpha_3)] \\
&= n_0\nu_0(1 - \theta_0) \quad \text{[by (49)]} \\
&= n_0(\nu_0 - \gamma_0), \quad \text{[by (48)]}
\end{aligned}
$$

as claimed. □

$$n_0(\nu_0 + \gamma_0)$$

$$n_0(\nu_0 - \gamma_0)$$

$$n_0\gamma_0$$
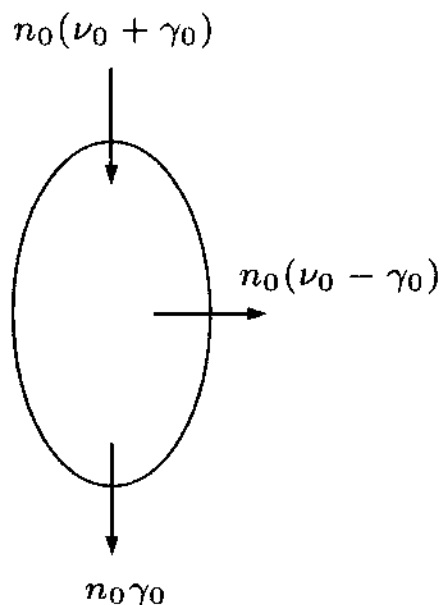
FIG. 13: Illustrating the dynamics of a homeostatic SC compartment.

To summarize, Figure 14 captures the dynamics of the SC compartment under homeostatic conditions. Indeed, with n_0 standing for the steady state number of stem cells:

- new stem cells are being produced at the rate of $n_0(\nu_0 + \gamma_0)$;

- stem cells are being lost to apoptosis at the rate of $n_0\gamma_0$;

- new TA cells are being produced at the rate of $n_0(\nu_0 - \gamma_0)$. Once created, these new TA cells join the dynamics of the TA compartment as described in Section 6.2.

6.2 THE TRANSIT AMPLIFYING CELL COMPARTMENT

Let $X_1(t)$ denote the size of the TA cell compartment at time $t \geq 0$, with $X_1(0) = n_1 \geq 1$. For $h > 0$, let

- $\nu_1(h)$ denote the fraction of TA cells that divide in the interval $(t, t + h]$;

- $\gamma_1(h)$ denote the fraction of TA cells that undergo apoptosis in the interval $(t, t + h]$.

Let assume that the two limits $\lim_{h \to 0} \frac{\nu_1(h)}{h} = \nu_1$ and $\lim_{h \to 0} \frac{\gamma_1(h)}{h} = \gamma_1$ exist and are finite. In this notation, ν_1 represents the rate at which TA cells divide, while γ_1 represents the rate at which TA cells undergo apoptosis. Since, as mentioned already, the model do not concern with time-dependent feedback mechanisms, both γ_1 and ν_1 are independent of time.

Further, for a dividing TA cell, let

- β_1 denote the probability that the cell produces two daughter TA cells;

- β_2 denote the probability that the cell produces one daughter TA cell and one differentiated cell;

- β_3 denote the probability that the cell produces two differentiated cells.

Clearly,

$$\beta_1 + \beta_2 + \beta_3 = 1. \tag{50}$$

For some small $h > 0$, let $X_1(t + h)$ denote the number of TA cells at time $t + h$. It is clear that $X_1(t + h)$ involves the following components

- $X_1(t) - \nu_1(h)X_1(t) - \gamma_1(h)X_1(t)$: the TA cells in existence at time t that have undergone neither division nor apoptosis in $(t, t + h]$;

- $X_0(t)\nu_0(h)[\alpha_2 + 2\alpha_3]$: the new TA cells generated in $(t, t + h]$ by divisions in the SC compartment;

- $X_1(t)\nu_1(h)[2\beta_1 + \beta_2]$: the new TA cells generated in $(t, t + h]$ by divisions of TA cells.

Visibly,

$$
\begin{aligned}
X_1(t + h) &= X_1(t) - \nu_1(h)X_1(t) - \gamma_1(h)X_1(t) + X_0(t)\nu_0(h)[2\alpha_2 + \alpha_3] + X_1(t)\nu_1(h)[2\beta_1 + \beta_2] \\
&= X_1(t) + X_1(t)\left[\nu_1(h)(\beta_1 - \beta_3) - \gamma_1(h)\right] + X_0(t)\nu_0(h)[\alpha_2 + 2\alpha_3].
\end{aligned}
$$

After simple algebraic manipulations of the above expression obtains

$$\frac{X_1(t+h) - X_1(t)}{h} = X_1(t)\left[\frac{\nu_1(h)}{h}(\beta_1 - \beta_3) - \frac{\gamma_1(h)}{h}\right] + X_0(t)\frac{\nu_0(h)}{h}[\alpha_2 + 2\alpha_3]$$

which, upon taking limits as $h \to 0$, yields the differential equation

$$\frac{dX_1(t)}{dt} = X_1(t)\left[\nu_1(\beta_1 - \beta_3) - \gamma_1\right] + X_0(t)\nu_0[\alpha_2 + 2\alpha_3] \tag{51}$$

with boundary condition $X_1(0) = n_1$.

By (47), the differential equation (51) with boundary condition $X_1(0) = n_1$ can be rewritten as

$$\frac{dX_1(t)}{dt} - AX_1(t) = \phi(t) \tag{52}$$

where

- $A = \nu_1(\beta_1 - \beta_3) - \gamma_1$, and

- $\phi(t) = n_0\nu_0(\alpha_2 + 2\alpha_3)e^{[\nu_0(\alpha_1 - \alpha_3) - \gamma_0]t} = n_0\nu_0[1 - (\alpha_1 - \alpha_3)]e^{[\nu_0(\alpha_1 - \alpha_3) - \gamma_0]t}$.

Using standard techniques, the solution of (52) turns out to be

$$X_1(t) = e^{At}\left[n_1 + \int_0^t e^{-Au}\phi(u)\,du\right] \tag{53}$$

which, upon evaluating the integral, becomes

$$X_1(t) = n_1 e^{At} + n_0\nu_0[1 - (\alpha_1 - \alpha_3)]\frac{e^{[\nu_0(\alpha_1 - \alpha_3) - \gamma_0]t} - e^{At}}{\nu_0(\alpha_1 - \alpha_3) - \gamma_0 - A} \tag{54}$$

where, recall, $A = \nu_1(\beta_1 - \beta_3) - \gamma_1$.

Now by this statement, and a prove of technical lemma that reveals the complexity of the feedback mechanism at work in tissue lineages.

Lemma 6.5. *If $A = \nu_0(\alpha_1 - \alpha_3) - \gamma_0$ then the TA compartment cannot be homeostatic.*

Proof. Suppose not; Lemma C.2 in the Appendix guarantees that as $A \to \nu_0(\alpha_1 - \alpha_3) - \gamma_0$

$$\frac{e^{[\nu_0(\alpha_1 - \alpha_3) - \gamma_0]t} - e^{At}}{\nu_0(\alpha_1 - \alpha_3) - \gamma_0 - A} \to te^{At}$$

and so the expression of $X_1(t)$ in (54) becomes

$$X_1(t) = e^{At}\left(n_1 + n_0\nu_0[1 - (\alpha_1 - \alpha_3)]t\right).$$

However, this latter expression shows that $X_1(t)$ is a function of t. Observe that $X_1(t)$ remains a function of t, even if $A = 0$ in which case $X_1(t) = n_1 + n_0\nu_0[1 - (\alpha_1 - \alpha_3)]t$ grows linearly with t. This completes the proof of the lemma. $\square$

Observe that the conclusion of Lemma 6.5 is independent of whether or not the SC compartment is homeostatic. The proof of Lemma 6.5 gives a hint of the growth regimens seen by the TA compartment it is happens not to be homeostatic. Refer to the Appendix C for details.

The following useful corollary follows directly from the proof of Lemma 6.5.

Corollary 6.6. *If the TA compartment is homeostatic then $A \neq 0$.*

Next, recalling that $A = \nu_1(\beta_1 - \beta_3) - \gamma_1$, Lemma 6.5 can be rephrased as follows:

Corollary 6.7. *If*

$$\beta_1 - \beta_3 = \frac{\gamma_1}{\nu_1} + \frac{\nu_0(\alpha_1 - \alpha_3) - \gamma_0}{\nu_1}$$

then the TA compartment cannot be homeostatic regardless of whether or not the SC compartment is.

The dynamics of the TA compartment are illustrated in Figure 15. Specifically, it is easy to confirm that:

- new TA cells are being produced as a result of TA cell divisions at the rate of $X_1(t)\nu_1(2\beta_1 + \beta_2) = X_1(t)\nu_1[1 + (\beta_1 - \beta_3)]$;

- new TA cells are being produced by divisions in the SC compartment at a rate of $X_0(t)\nu_0[1 - (\alpha_1 - \alpha_3)]$

- TA cells are being lost to apoptosis at the rate of $X_1(t)\gamma_1$;

- differentiated cells are being produced at the rate of $X_1(t)\nu_1(\beta_2 + 2\beta_3) = X_1(t)\nu_1[1 - (\beta_1 - \beta_3)]$.

As pointed out by several authors [25, 27, 60], accumulated empirical evidence suggests that if homeostasis is not present at the SC compartment, then neither can the TA compartment be homeostatic. To the best of current knowledge, there is no mathematical proof of this phenomenon in the literature. Next result provides such a proof.

Theorem 6.8. *If the TA compartment is homeostatic then so is the SC compartment.*

$$X_1(t)\nu_1[1 + (\beta_1 - \beta_3)]$$

$$X_0(t)\nu_0[1 - (\alpha_1 - \alpha_3)] \qquad X_1(t)\nu_1[1 - (\beta_1 - \beta_3)]$$

$$X_1(t)\gamma_1$$
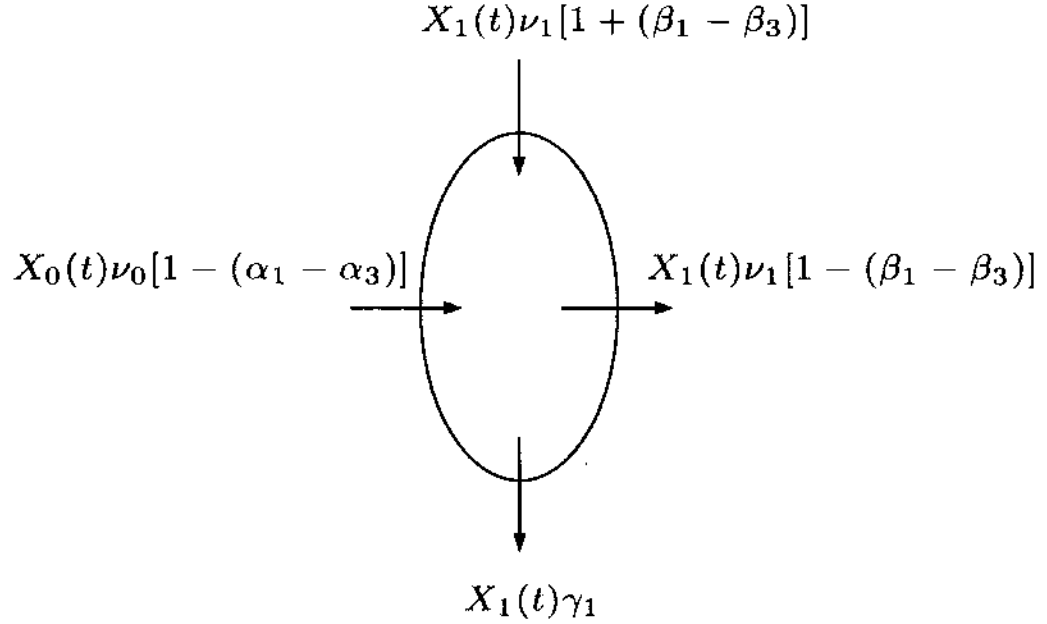
FIG. 14: Illustrating the dynamics of the TA cell compartment.

Proof. If the TA compartment is homeostatic, then $X_1(t) = n_1$ for all $t \geq 0$. After simple algebraic manipulations (54) can be written as

$$n_1\left[1 - e^{At}\right] = \frac{n_0\nu_0[1 - (\alpha_1 - \alpha_3)]}{\nu_0(\alpha_1 - \alpha_3) - \gamma_0 - A}\left[e^{[\nu_0(\alpha_1-\alpha_3)-\gamma_0]t} - e^{At}\right] \tag{55}$$

where, as a direct consequence of Corollary 6.6,

$$1 - e^{At} \neq 0.$$

After dividing (55) by $1 - e^{At}$ and some simple algebra, n_1 can be written as

$$\begin{aligned}
n_1 &= \frac{n_0\nu_0(\alpha_2 + 2\alpha_3)}{\nu_0(\alpha_1 - \alpha_3) - \gamma_0 - A} \cdot \frac{e^{[\nu_0(\alpha_1-\alpha_3)-\gamma_0]t} - e^{At}}{1 - e^{At}} \\
&= \frac{n_0\nu_0[1 - (\alpha_1 - \alpha_3)]}{\nu_0(\alpha_1 - \alpha_3) - \gamma_0 - A} \cdot \left[1 - \frac{1 - e^{[\nu_0(\alpha_1-\alpha_3)-\gamma_0]t}}{1 - e^{At}}\right].
\end{aligned} \tag{56}$$

Since the TA compartment is homeostatic, the right-hand side of (56) must be independent of t. Observe that $\frac{n_0\nu_0[1-(\alpha_1-\alpha_3)]}{\nu_0(\alpha_1-\alpha_3)-\gamma_0-A}$ is a constant and, therefore, in order for the right-hand side of (56) to be a constant the expression

$$\frac{1 - e^{[\nu_0(\alpha_1-\alpha_3)-\gamma_0]t}}{1 - e^{At}}$$

must be a constant. By Lemma C.1 in the Appendix C this happens if and only if $\nu_0(\alpha_1 - \alpha_3) - \gamma_0 = 0$. However, by (6.2) this guarantees that the SC compartment must be homeostatic.

One last point needs clarification, namely that the conditions of Lemma C.1 in the Appendix are verified. To see that they are with $a = \nu_0(\alpha_1 - \alpha_3) - \gamma_0$ and $b = A$ note that,

- by Corollary 6.6, $1 - e^{At} \neq 0$ and so, $b \neq 0$,

- by Lemma 6.5, $A \neq \nu_0(\alpha_1 - \alpha_3) - \gamma_0$ and so $a \neq b$,

confirming that Lemma C.1 does, indeed, apply.

This completes the proof of Theorem 6.8. □

Now the necessary and sufficient condition for the homeostasis of the TA compartment.

Theorem 6.9. *The TA compartment is homeostatic if and only if the SC compartment is homeostatic and, in addition,*

$$\beta_1 - \beta_3 = \frac{n_1\gamma_1 - n_0(\nu_0 - \gamma_0)}{n_1\nu_1}. \tag{57}$$

Proof. First, if the TA compartment is homeostatic, then by Theorem 6.8, the SC compartment is also homeostatic. Recall that by (49), $\alpha_1 - \alpha_3 = \frac{\gamma_0}{\nu_0}$. Thus, (56) can be re-written as

$$
\begin{aligned}
n_1 &= \frac{n_0\nu_0[1 - (\alpha_1 - \alpha_3)]}{\nu_0(\alpha_1 - \alpha_3) - \gamma_0 - A} \cdot \left[1 - \frac{1 - e^{[\nu_0(\alpha_1 - \alpha_3) - \gamma_0]t}}{1 - e^{At}} \right] \\
&= \frac{n_0\nu_0\left[1 - \frac{\gamma_0}{\nu_0}\right]}{-A} \\
&= \frac{-n_0(\nu_0 - \gamma_0)}{\nu_1(\beta_1 - \beta_3) - \gamma_1}. \tag{58}
\end{aligned}
$$

Now, simple algebra confirms that (58) yields (57).

Conversely, assumption that the stem cell department is homeostatic and that (57) holds. This requires now to show that the TA compartment is also homeostatic. Since the stem cell department is homeostatic, (49) guarantees that

- $n_0\nu_0(\alpha_2 + 2\alpha_3) = n_0(\nu_0 - \gamma_0)$;

- $A = \nu_1(\beta_1 - \beta_3) - \gamma_1 = \frac{-n_0(\nu_0 - \gamma_0)}{n_1}$;

- $\nu_0(\alpha_1 - \alpha_3) - \gamma_0 - A = -A = \frac{n_0(\nu_0 - \gamma_0)}{n_1}$;

- $e^{[\nu_0(\alpha_1 - \alpha_3) - \gamma_0]t} - e^{At} = 1 - e^{At}$.

Upon replacing the values of these expressions back into (54), this following can be obtained

$$X_1(t) = n_1 e^{At} + n_1 \left[1 - e^{At}\right] = n_1,$$

confirming that the TA compartment is homeostatic.

This completes the proof of the theorem. $\square$

It is worth observing that

- the probabilities β_1 and β_3 only occur in (57) through the expression $\beta_1 - \beta_3$. This seems to imply that, provided the SC compartment is homeostatic, as long as the probabilities of symmetric divisions are shifted up or down by equal amounts, homeostasis of the TA compartment is preserved;

- (57) relies on knowledge of the rate $n_0(\nu_0 - \gamma_0)$ at which TA cells are being produced in the SC compartment;

- contrary to what have been seen in the SC compartment, (57) depends on the size, n_1, of the TA compartment. How can the feedback mechanism keep track of, or approximate, n_1?

- further, (57) seems to suggest that homeostasis of the TA compartment may occur in two mutually exclusive ways, depending on the sign of the expression $\beta_1 - \beta_3$:

  Case 1: $\beta_1 - \beta_3 \geq 0$, in which case the probability that a dividing TA cell produces two daughter TA cells is larger than or equals the probability of producing two differentiated cells;

  Case 2: $\beta_1 - \beta_3 < 0$, in which case the probability that a dividing TA cell produces two daughter TA cells is strictly smaller than the probability that it produces two differentiated cells.

Now it can be argued that Case 1 above, while mathematically plausible, makes no biological sense. Indeed, assume that the TA cell compartment is homeostatic and $\beta_1 - \beta_3 \geq 0$. By (57) this implies that

$$n_1\gamma_1 \geq n_0(\nu_0 - \gamma_0) \geq 0.$$

In words, the number of TA cells lost to apoptosis per time unit equals or exceeds the influx of TA cells produced by the stem cell compartment per time unit. This does not make biological sense and so, in the remainder of the this model, Case 1 is dismissed.

For later reference,

Lemma 6.10. *Under homeostatic conditions in the TA compartment*

$$X_1(t)\nu_1(\beta_2 + 2\beta_3) = n_0(\nu_0 - \gamma_0) + n_1(\nu_1 - \gamma_1). \tag{59}$$

Proof. Under homeostasis, $X_1(t) = n_1$ independent of t. Thus

$$
\begin{aligned}
X_1(t)\nu_1(\beta_2 + 2\beta_3) &= n_1\nu_1(\beta_2 + 2\beta_3) \\
&= n_1\nu_1(1 - \beta_1 + \beta_3) \\
&= (n_0\nu_0 + n_1\nu_1) - (n_0\gamma_0 + n_1\gamma_1) \quad \text{[by Theorem 6.9]} \\
&= n_0(\nu_0 - \gamma_0) + n_1(\nu_1 - \gamma_1),
\end{aligned}
$$

completing the proof. $\square$

To summarize, Figure 16 captures the dynamics of the TA cell compartment under homeostatic conditions. Indeed, with n_1 standing for the steady state number of TA cells:

- new TA cells are being produced by divisions in the TA compartment at the rate of $n_1(\nu_1 + \gamma_1)$;

- new TA cells are being produced by divisions in the SC compartment at the rate of $n_0(\nu_0 + \gamma_0)$

- TA cells are being lost to apoptosis at the rate of $n_1\nu_1$;

- differentiated cells are being produced at the rate of $n_0(\nu_0 - \gamma_0) + n_1(\nu_1 - \gamma_1)$.
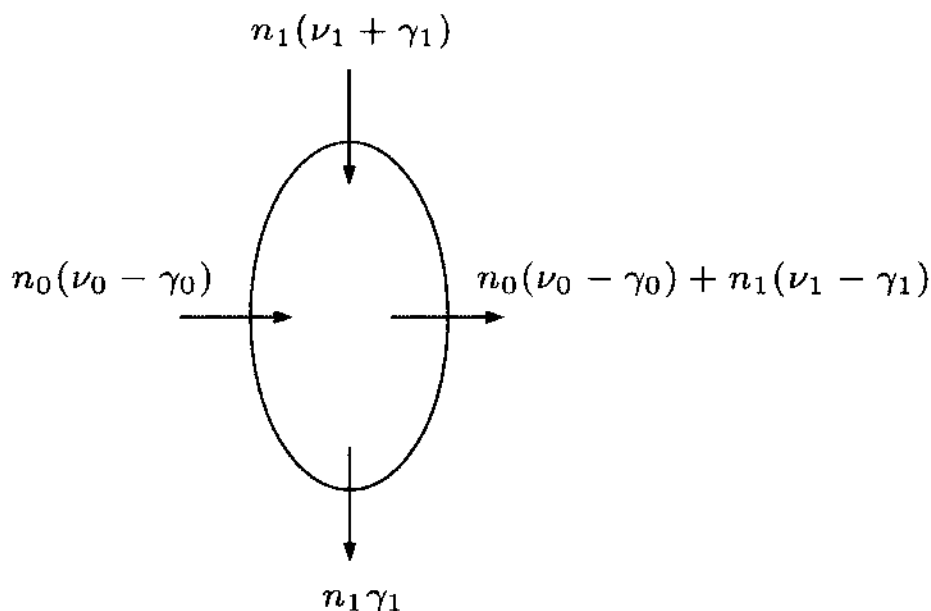
$$n_1(\nu_1 + \gamma_1)$$

$$n_0(\nu_0 - \gamma_0) \qquad\qquad n_0(\nu_0 - \gamma_0) + n_1(\nu_1 - \gamma_1)$$

$$n_1\gamma_1$$

FIG. 15: Illustrating the dynamics of the TA cell compartment under homeostasis.

6.3 THE DIFFERENTIATED CELL COMPARTMENT

Let $X_2(t)$ denote the size at time $t \geq 0$ of the differentiated (i.e. post-mitotic) cell compartment. Let assume that, $X_2(0) = n_2 \geq 0$.

For $h > 0$, let $\gamma_2(h)$ denote the fraction of the differentiated cell compartment that dies and is shed in $(t, t+h]$. Again assume that the limit $\lim_{h\to 0} \frac{\gamma_2(h)}{h} = \gamma_2$ exists and is finite. Clearly, γ_2 represents the rate at which differentiated cells die. Referring to Figure 17, consider what might happen in the time interval $(t, t+h]$:

- $X_1(t)\nu_1[\beta_2 + 2\beta_3]$ new differentiated cells are added from the TA cells compartment;

- $X_2(t)\gamma_2(h)$ differentiated cells die and are shed.

Visibly, $X_2(t + h)$ has the following components

$$X_2(t + h) = X_2(t) - X_2(t)\gamma_2(h) + X_1(t)\nu_1(h)[\beta_2 + 2\beta_3]$$

which can be written as

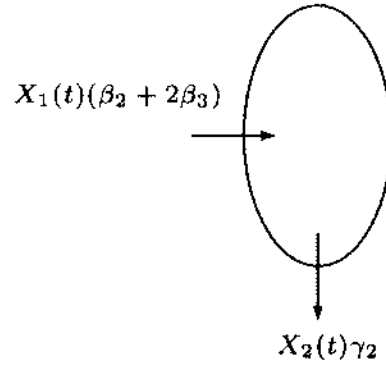$$\frac{X_2(t + h)X_2(t)}{h} = -\frac{\gamma_2(h)}{h}X_2(t) + \frac{\nu_1(h)}{h}X_1(t)[\beta_2 + 2\beta_3].$$

$$X_1(t)(\beta_2 + 2\beta_3)$$

$$X_2(t)\gamma_2$$

FIG. 16: Illustrating the dynamics of the differentiated cell compartment.

Upon taking limits as $h \to 0$ and using Lemma 6.10 the following differential equation can obtained,

$$\frac{dX_2(t)}{dt} + \gamma_2 X_2(t) = (n_0\nu_0 + n_1\nu_1) - (n_0\gamma_0 + n_1\gamma_1)$$

with boundary condition $X_2(0) = n_2$.

Using standard techniques the solution of this differential equation turns out to be

$$X_2(t) = e^{-\gamma_2 t} \left[n_2 - \frac{(n_0\nu_0 + n_1\nu_1) - (n_0\gamma_0 + n_1\gamma_1)}{\gamma_2} \right] + \frac{(n_0\nu_0 + n_1\nu_1) - (n_0\gamma_0 + n_1\gamma_1)}{\gamma_2}.$$

$$(60)$$

6.3.1 HOMEOSTASIS OF THE DIFFERENTIAL CELL COMPARTMENT

The crucial fact that there cannot exist homeostasis of the differentiated cell compartment unless both the stem cell and TA compartments are homeostatic.

If homeostasis to occur in the differentiated cell compartment, it must be that $X_2(t) = n_2$ independent of t. In particular, this observation along with (60) allow to write

$$n_2 = e^{-\gamma_2 t} \left[n_2 - \frac{(n_0\nu_0 + n_1\nu_1) - (n_0\gamma_0 + n_1\gamma_1)}{\gamma_2} \right] + \frac{(n_0\nu_0 + n_1\nu_1) - (n_0\gamma_0 + n_1\gamma_1)}{\gamma_2}$$

which, after suitable manipulations, yields

$$n_2 \left[1 - e^{-\gamma_2 t}\right] = \frac{(n_0 \nu_0 + n_1 \nu_1) - (n_0 \gamma_0 + n_1 \gamma_1)}{\gamma_2} \left[1 - e^{-\gamma_2 t}\right].$$

Since $\gamma_2 \neq 0$, the above becomes

$$n_2 = \frac{(n_0 \nu_0 + n_1 \nu_1) - (n_0 \gamma_0 + n_1 \gamma_1)}{\gamma_2}$$

or, equivalently,

$$n_0 \nu_0 + n_1 \nu_1 = n_0 \gamma_0 + n_1 \gamma_1 + n_2 \gamma_2. \tag{61}$$

Observe that equation (61) tells that the differentiate cell compartment is homeostatic only if the expected number of stems cells and TA cells produced by division per unit time matches the expected number of cells that die (in all compartments) per unit time.

6.4 SIMULATIONS

In this section simulation analysis will actually demonstrate the model's effective predictions.

6.4.1 EXPERIMENTAL SETUP

In order to confirm empirically the theoretical findings above and especially the predictions of the model and condition (61), the following simulation plan was implemented:

1. Firstly, the number n of time slots was taken as independent parameter and also the initial distribution, n_0, of the number of stem cells, n_1, total number of TA cells and n_2, total of number of fully differentiated.

2. Each of the stem cells produces either $2, 1$ or 0 stem cells with α_1, α_2 and α_3 probabilities respectively. Whereas each of the TA cells produces either $2, 1,$ or 0 TA cells with $\beta_1, \beta_3,$ and β_3 probabilities respectively.

3. The apoptosis rates were taken as γ_0, γ_1 and γ_2 for stem, TA and fully differentiated cell compartments.

4. After each cell cycle stem cell compartment numbers were adjusted based on the number of new stem cells were produced and subtracted the shredded stem cells from apopotosis.

5. After each cell cycle TA cell compartment numbers were adjusted by adding new cells coming from stem cell compartment, newly produced TA cells and subtracting the dead TA cells.

6. For full differentiated cells, the numbers are adjusted by adding the cells arriving from TA cell compartment and subtracting the dead cells.

7. The total of number of cells in each compartment is adjusted after every cell cycle and for the entire duration of the experiment.

All the steps above are then run 10,000 times and averages were taken to produce the final outcome.

6.4.2 RESULTS

In the first group of results, stem cells, TA cells and fully differentiated cell compartments are observed after a certain period of time where they go through a finite number of cell cycles. For these group of results firstly apoptosis rates for different compartments were $\gamma_0 = 0.002, \gamma_1 = 0.003$ and $\gamma_2 = 0.019532$. Before each of the cell cycle, probabilities for stem cell compartment and TA cell compartment were chosen as such so that Lemma 6.3, and Lemma 6.7 were not violated. They were generated by a suitable random number generator. In Figure 18 initially there were $n_2 = 500$ fully differentiated cells along with $n_0 = 180$ stem cells and $n_1 = 170$ TA cells. Then the experiment started for 1000 time units where each time units represent one cell cycle. All the steps from Section 6.4.1 were performed correctly.

As expected from theoretical results stem cell, TA cell and fully differentiated compartments have all reached homeostasis within the 1000 unit time period. Similarly in Figure(19) initially there were $n_0 = 100$ stem cells, $n_1 = 120$ TA cells and $n_2 = 140$ fully differentiated cells, before the experiment was started and 500 time units were allotted. Again homeostatic conditions were observed for all three compartments before the the allotted 500 time units. Finally, in Figure 20 initially there were $n_0 = 50$ stem cells, $n_1 = 150$ TA cells and $n_2 = 200$ fully differentiated cells and again 500 time units were allotted. As expected homeostatic conditions were observed just expected by theoretical results.

In Figure 21 and 22 homeostasis condition is being observed for a special case. In both the experiments the fully differentiated cells are started initially substantially
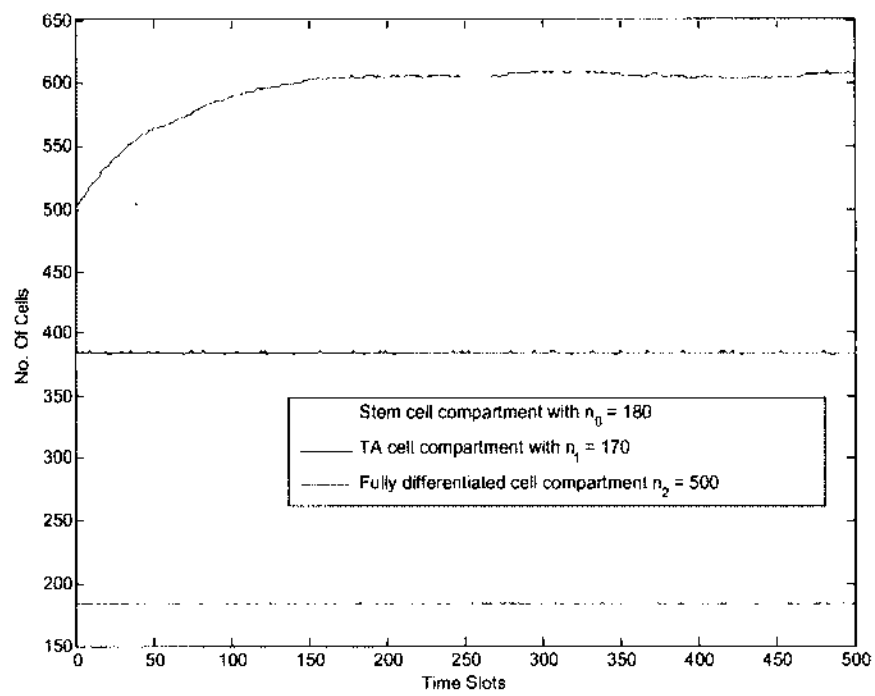
FIG. 17: Homeostatic condition observed at different compartments
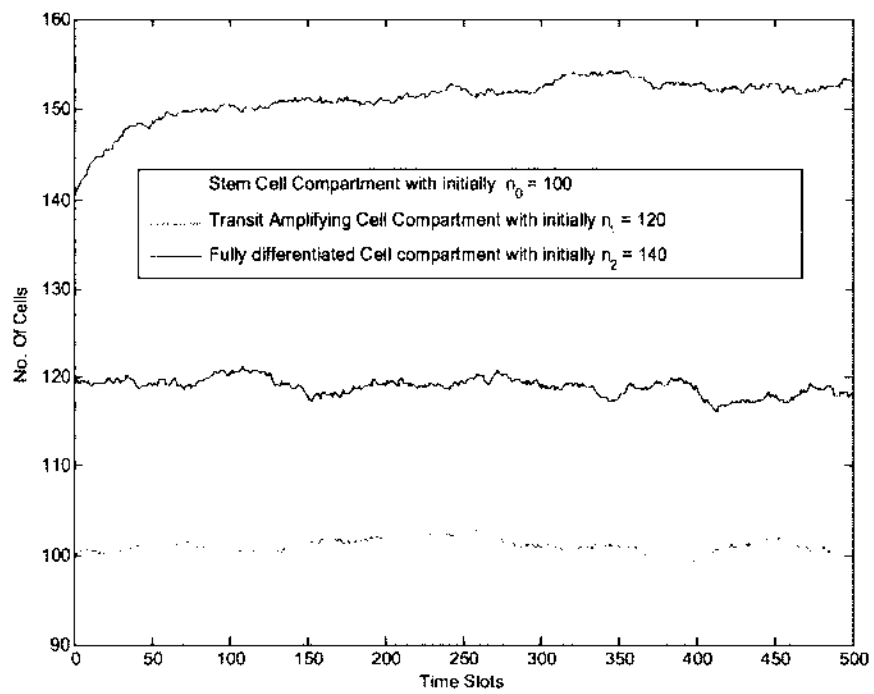
FIG. 18: Homeostatic condition observed at different compartments
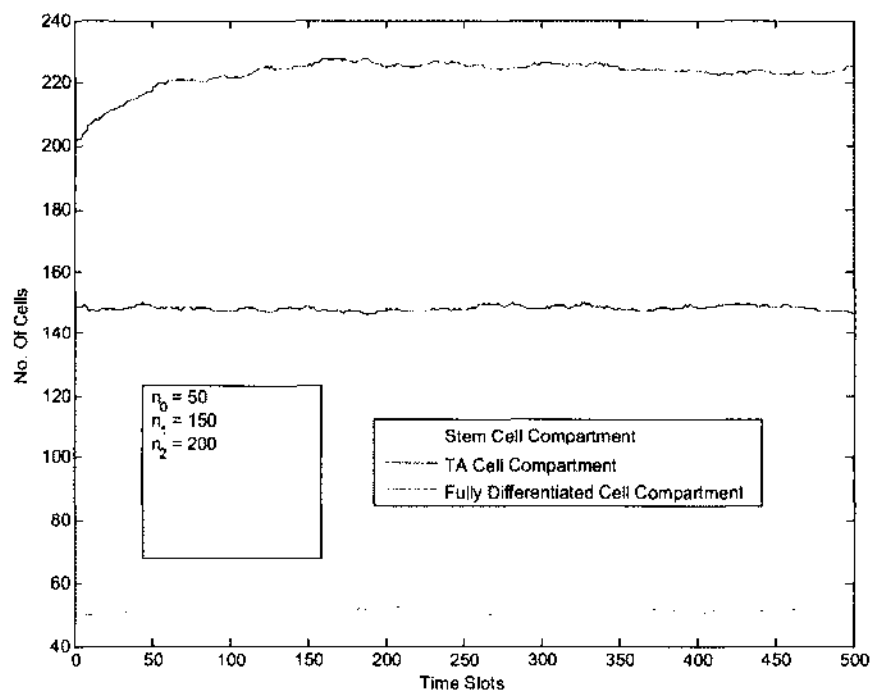
FIG. 19: Homeostatic condition observed at different compartments
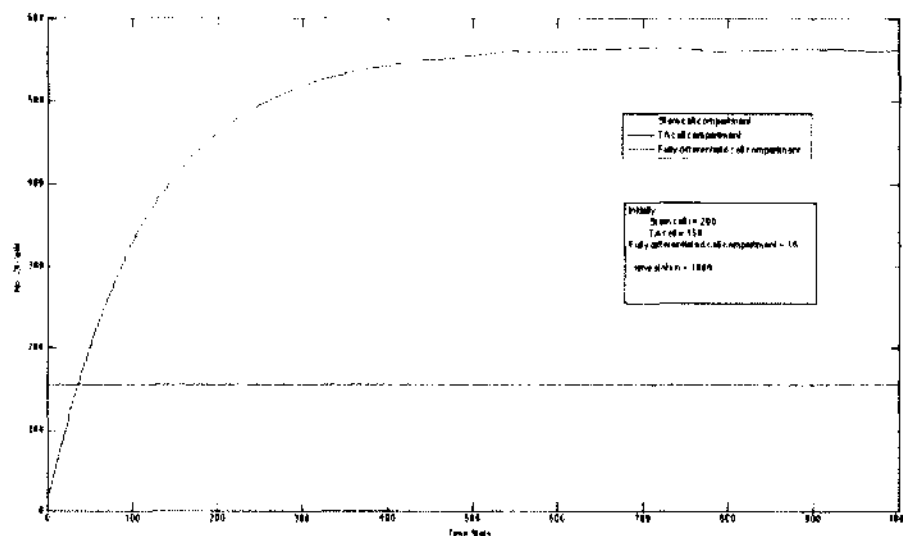
FIG. 20: Homeostatic Condition with lower fully differentiated cells at the start

lower than cell numbers in stem cell and TA cell compartment. This is actually the cases when external stressful situation is implied on tissue and tissue has to regenerate mature cells in quick succession to function properly. In Figure 21 and 22 this same phenomena is being observed. A steep rise of fully differentiated cell number is observed before homeostatic condition is reached and then production is ceased for fully differentiated cells. In ordinary circumstances fully matured cells are always larger in number than other type of cells. The main point to notice here that whenfully differentiated cell compartment number reduces significantly, a period of explosive growth is observed but eventually homeostasis will be preserved as we see at the tissues of living organisms.

FIG. 21: Homeostatic Condition with lower fully differentiated cells at the start

CHAPTER 7

MUTANT STEM CELL

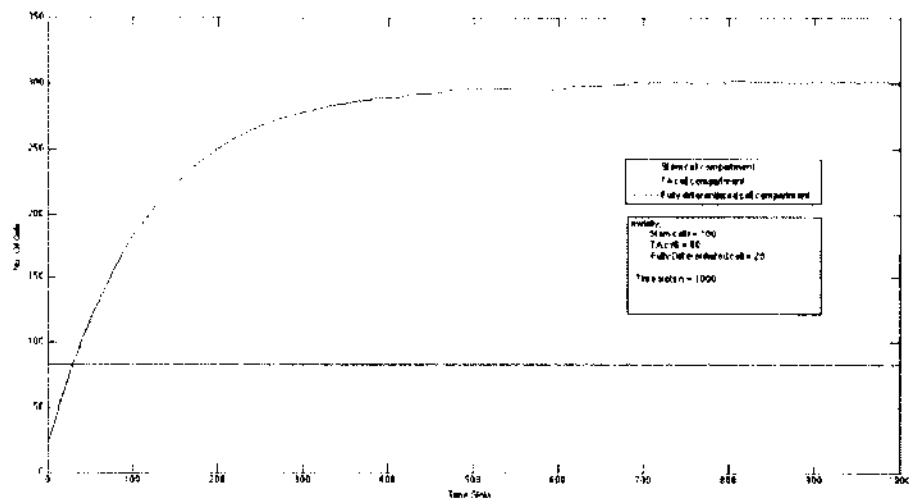As discussed in earlier chapters when a stem cell divides, it can either produce differentiated cells or self-renew to produce more stem cells. Because stem cells are thought to be the cells of origin for many types of cancer and other terminal diseases, understanding what controls this decision has become a central question in stem-cell and cancer research. But how is this decision altered when a stem cell acquires a cancer-driving mutation is being widely investigated [22]. Previous studies have shown that mutation increases the proliferation of stem cells that might tend to reduce the cells potential for differentiation. Enhanced proliferation and self-renewal has been prevalent more in mutated stem cells [29] . In this chapter a stochastic model is proposed to estimate the selective advantage of mutations by fitting the simulation curves to the real data.

Wild type cells will divide asymmetrically providing the population remains at a certain number say n whereas mutant cell divide symmetrically. Under initial condition model assume that cells divide symmetrically producing a type 2 division or production two stem cells any time the population is less than n. This can be made complex by assigning a probability of Type 0 and Type 2 symmetric divisions but homogeneity can be assumed so that P(type 0) = P(type 2). While total number of mutatnt stem cells remains under n , Type 2 division is favored or else Type 0 is favored. For this model such complexities are ignored. Mutant cells are identical to wild type cells except that they have an increased chance of a Type 2 division. In this model by assigning a probability of s per division that they divide symmetrically (Type 2). If this brings the population above n then a random cell in that niche is ejected and lost. If the model incorporated a feedback system this would not have been required.

7.1 MODELING MUTANT STEM CELLS PROGRESSION WITHOUT SELECTIVE ADVANTAGE

Let us consider an urn containing initially n white balls which are basically wild type stem cells. Then the cell cycles can be thought of an extraction of balls from the urn. A number of extractions are performed based on the following rules as follows:
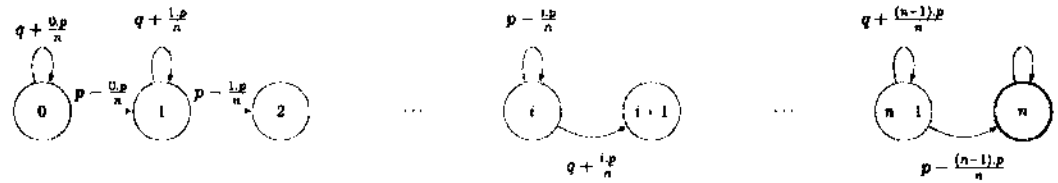
FIG. 22: Markov chain for mutant cell progression without selection

- If the ball extracted is white then a biased coin is flipped which gives heads with probability p and q is the probability of having tail. If head shows up a red ball is returned into the urn meaning a mutant cell is added to population after a cell cycle, otherwise the original ball is returned.

- If a red ball is extracted, it is promptly returned to the urn.

7.1.1 PROBLEM

Of interest is the expected number of such extractions that are performed until for the first time the urn contains all red balls only, meaning the population becomes filled with mutant stem cells only.

7.1.2 DERIVATION

This can be viewed as an Markov chain with states $0, 1, 2, \cdots\cdots, n$. When the state is in state i, there is i red balls in the urn.

Assume that without loss of any population, the Markov chain is in state i, $(0 \leq i \leq n$, where n is the total population. The probability that it stays in state i after the next extraction is the summation of the following probabilities:

- the probability that a red ball is extracted;

- the probability that a white ball is extraction times (1-p) or q.

So, the probability is ,

$$\frac{i}{n} + \frac{n-i}{n}(1-p) = 1 - p + \frac{ip}{n} = q + \frac{ip}{n}$$

On the other hand, the probability that at the end of the next extraction the Markov chain makes the transition to $i + 1$ is

- the probability that a white ball is extracted times p. That is,

$$p.\frac{n-i}{n} = p - \frac{ip}{n}$$

Now, it is easy to see that state n is the absorbing state as transition probability $p - \frac{np}{n} = 0$.

Now, $E(i)$ is the expected number of extractions that are necessary to reach the state i of the Markov chain. Recall that the markov chain starts out in state 0 and so $E(0) = 0$.

Assume the Markov chain is in state $i - 1$. By assumption, the expected number of transactions necessary to reach the state $i - 1$ is $E(i - 1)$. The expected number of transaction to reach state i can be expressed as follows:

$$
\begin{aligned}
E(i) &= \left[E(i-1)+1\right]\left(p - \frac{(i-1)p}{n}\right) + \left[E(i-1)+2\right]\left(q - \frac{(i-1)p}{n}\right)\left(p - \frac{(i-1)p}{n}\right) \\
&+ \left[E(i-1)+3\right]\left(q - \frac{(i-1)p}{n}\right)^2\left(p - \frac{(i-1)p}{n}\right)\cdots\cdots
\end{aligned}
$$

Let, $\alpha = p - \frac{(i-1)p}{n}$ so, $1 - \alpha = q + \frac{(i-1)p}{n}$ then,

$$
\begin{aligned}
E(i) &= \left[E(i-1)+1\right]\alpha + \left[E(i-1)+2\right]\alpha(1-\alpha) + \left[E(i-1)+3\right]\alpha(1-\alpha)^2 + \cdots\cdots \\
&= E(i-1)[\alpha + \alpha(1-\alpha) + \alpha(1-\alpha)^2 + \cdots\cdots] \\
&+ \alpha[1 + 2(1-\alpha) + 3(1-\alpha)^2 + \cdots\cdots] \\
&= E(i-1)\alpha[1 + (1-\alpha) + (1-\alpha)^2 + \cdots\cdots] \\
&+ \alpha[1 + 2(1-\alpha) + 3(1-\alpha)^2 + \cdots\cdots] \\
&= E(i-1).\alpha.\frac{1}{\alpha} + \alpha.\frac{1}{\alpha^2} \quad \text{[using (93])} \\
&= E(i-1) + \frac{1}{\alpha} \\
&= E(i-1) + \frac{1}{p(n-i+1)}
\end{aligned}
$$

So, $\forall i = 1, 2, \cdots\cdots n$,

$$E(i) = E(i-1) + \frac{1}{p(n-i+1)} \tag{62}$$

Now,

$$E(1) = E(0) + \frac{n}{p}\cdot\frac{1}{n}$$

$$E(2) = E(1) + \frac{n}{p}\cdot\frac{1}{n-1}$$

$$E(3) = E(2) + \frac{n}{p}\cdot\frac{1}{n-2}$$

$$\vdots$$

$$E(n) = E(n-1) + \frac{n}{p}$$

$$E(n) = \frac{n}{p}\left[\frac{1}{1} + \frac{1}{2} + \cdots + \frac{1}{n}\right]$$

Now, $\left[\frac{1}{1} + \frac{1}{2} + \cdots + \frac{1}{n}\right] = \ln n + \delta + \frac{1}{2n}$ where, δ is Euler's constant. $(\delta = 0.577..)$
Finally,

$$E(n) \cong \frac{1}{p}\left[n\ln n + \delta n - \frac{1}{2}\right] \tag{63}$$

More, generally, for any given i,

$$
\begin{aligned}
E(i) &= \frac{n}{p}\left[\frac{1}{n} + \frac{1}{n-1} + \cdots\cdots + \frac{1}{n-i+1}\right]\\
&= \frac{n}{p}\left[1 + \frac{1}{2} + \frac{1}{3} + \cdots\cdots + \frac{1}{n}\right]\\
&\quad - \frac{n}{p}\left[1 + \frac{1}{2} + \cdots\cdots + \frac{1}{n-i}\right]\\
&\cong \frac{n}{p}\left[\ln n + \delta + \frac{1}{2n} - \ln(n-i) - \delta - \frac{1}{2(n-i)}\right]\\
&= \frac{n}{p}\left[\ln\frac{n}{n-i} - \frac{i}{2n(n-i)}\right]\\
&= \frac{1}{p}\left[n\ln\frac{n}{n-i} - \frac{i}{2(n-i)}\right] \tag{64}
\end{aligned}
$$

7.2 MODELING MUTANT STEM CELLS PROGRESSION WITH SELECTION

Let us consider an urn that contains, for some $i(0 \le i \le n)$, i red balls and $n-i$ white balls. It can be thought here that red balls are mutant cells and white balls are wild types. Now after an certain time period when cells undergo divisions, these

model assumes an individual ball is being extracted. The model employs these two following extraction methods from the urn.

- **Suppose a white ball is extracted:** A biased coin is flipped that turns up heads with the probability p.

  - If the coin turns up heads, a red ball is returned into the urn. Meaning a mutant cell is added to the population.

  - If the coin turns up tails, the white ball is returned into the urn. Meaning a wild type cell is returned in the urn an no significant changes in population of wildtype and mutant stem cell.

- **Suppose a red ball is extracted:** A biased coid in flipped which turns up heads with probability r.

  - If head is obtained, an arbitrary ball is extracted from the urn and is replaced by two red balls. Meaning either wild type or mutant cell is replaced in the population with two mutant cell types.

  - If tails is obtained the red ball is returned meaning no changes in population comprising of wild type and mutant stem cell types.

7.2.1 PROBLEM

Suppose initially the population of n balls in the urn contains white balls only rather only wild type cells no mutant cell types. Of interest is the expected number of extractions as above stated rules, for the first time, the urn contains only red balls. In other words we are interested in the expected number cell cycles before we see a population of wild type cells converting into mutant cell types.

7.2.2 DERIVATION

Here the problem can be look as a Markov chain with states $0, 1, 2, \cdots\cdots, n$. In state $i, (0 \leq i \leq n)$, the urn contains i red balls. When the Markov chain is in state i, the claim is the probability of the Markov chain in state i after the next extraction is $1 - \frac{n-i}{n}\left[p + \frac{ir}{n-1}\right]$

To see this, consider separately the case where the next ball to be extracted is red or white.

- Upon extracting a white ball, the Markov chain stays in state i with probability $\left(\frac{n-i}{n}(1-p)\right)$

- Upon extracting a red ball, the Markov chain remain in state i if either,

  - tails show up with probability $(1-r)\frac{i}{n}$

  - heads show up but a red ball is extracted from the urn with probability $\left(r.\frac{i}{n}.\frac{i-1}{n-1}\right)$

To summarize total probability of staying at i state for the Markov chain is,

$$\left(\frac{n-i}{n}\right)(1-p) + \left(r.\frac{i}{n}\frac{i-1}{n-1}\right) = 1 - \frac{n-i}{n}.\left[p + \frac{ir}{n-1}\right]$$

Similarly, claim is the Markov chain is in state $i+1$, after the next extraction is $\frac{n-i}{n}\left[p + \frac{ir}{n-1}\right]$

As before we consider separately the case of where extracted ball was red or white.

- Upon extracting a white ball, the Markov chain goes to state $i+1$ with probability $\frac{n-i}{n}.p$

- Upon extracting a red ball, the Markov chain goes to state $i+1$ with probablity $\left(r.\frac{i}{n}.\frac{n-i}{n-1}\right)$

To summarize, the total probability is

$$\frac{n-i}{n}.p + \left(r.\frac{i}{n}.\frac{n-i}{n-1}\right) = \frac{n-i}{n}.\left[p + \frac{ir}{n-1}\right]$$

Let $E(i)$ be the expected member of extractions that, starts with an all white ball urn, end with an urn with i red balls and $n-i$ white balls. It is easy to see that $E(0) = 0$.

Next goal is to evaluate $E(i)$ recursively in respect to function of $E(i-1)$. To help visual the problem Figure 24 depicts the Markov chain,

It is easy to see that,

- $\forall i, (0 \le i \le n)$, the sum of probabilities leaving state i add up to 1.

- for $i = n$, state is absorbing
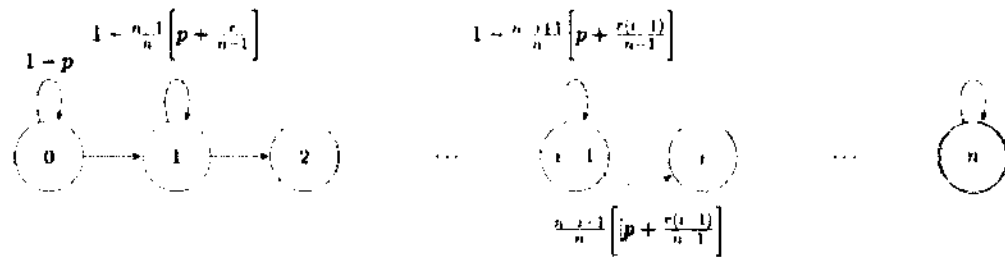
FIG. 23: Markov chain with state transition probabilities

For, $\forall i$ it can be shown using (62) that,

$$
\begin{aligned}
E(i) &= E(i-1) + \cfrac{1}{\frac{n-i+1}{n}\left[p + \frac{(i-1)r}{n-1}\right]} \\
&= E(i-1) + \frac{n(n-1)}{p} \cdot \frac{1}{(n-i+1)[n-1+(i-1)\theta]}
\end{aligned}
\tag{65}
$$

where, $\theta = \frac{r}{p}$.

Now, we simply sum up all the expected values to write,

$$
E(n) = \frac{n(n-1)}{p} \sum_{i=1}^{n} \frac{1}{(n-i+1)[n-1+(i-1)\theta]}
\tag{66}
$$

This also proves for $r = 0$, $i.e$ $\theta = 0$,

$$
\begin{aligned}
E(n) &= \frac{n(n-1)}{p} \sum_{i=1}^{n} \frac{1}{(n-i+1)(n-1)} \\
&= \frac{n}{p}\left[\frac{1}{1} + \frac{1}{2} + \cdots + \frac{1}{n}\right].
\end{aligned}
\tag{67}
$$

7.3 SIMULATION

Simulation was carried out for several values of n to match the prediction of theoretical results. In the simulation setup, the chances for heads to show up was

FIG. 24: Mutant cell progression from wildtype

taken as $p = 0.1$. In every cell cycle the steps were performed as described in the model. Different values of n was used to test the efficacy of the model's prediction. Figure 25 shows the simulation results. As it can be seen, the results show that the simulation results closely match with theoretical predictions. [1]

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[1] A special thanks has to go to Mr. Alex Nwala for his assistance with this simulation.

CHAPTER 8

CONCLUSION

In this chapter, the summary of the work and future research directions are discussed. The dissertation started with a look at stem cell growth. Then stem cell homeostasis and tissue cell lineage was explored before mutant stem cell progression was briefly studied to complete this work.

8.1 SUMMARY

Through a combination of the processes of self-renewal, differentiation, and proliferation, all the cell types needed in the tissue system are produced as daughter cells of the stem cells, while the stem cells themselves are maintained in constant numbers. For regenerative medicine and tissue healing, the number of stem cells in a tissue plays a vital role. The choice of an accurate growth model is an integral part of the analysis of the growth and will eventually aid researchers in attaining a better understanding of the progression and regression of the population size and the associated rates of change. In this work, a simple stochastic growth model proposes to fulfill the need for an growth model. This simple growth model with closed mathematical form is deceptively simple enough to compute and fairly accurate.

The regulation and equilibrium of stem cell numbers is normally observed in living organisms. Results show that an increase in cell renewal, which is equivalent to a failure of programmed cell death or of differentiation, can lead to the growth of cancers. So, understanding the ingrained homeostasis at cellular level is of great interest to researchers. In Chapter 5 a stem cell homeostasis is modeled using discrete time Markov chain which clearly shows mathematically that in long run stem cells maintain equilibrium.

Studies of developing and self-renewing tissues have shown that differentiated cell types are typically specified through the actions of multistage cell lineages. Such lineages commonly include a stem cell and multiple progenitor (TA) cell stages, which ultimately give rise to terminally differentiated (TD) cells. Understanding the cell lineage process through mathematical modeling is of paramount importance. Homeostasis at tissue lineage model in Chapter 6 addresses these issues.

Perhaps the most important and useful property of stem cells is that of self-renewal. Through this property, striking parallels can be found between stem cells and cancer cells: tumors may often originate from the transformation of normal stem cells, similar signaling pathways may regulate self-renewal in stem cells and cancer cells, and cancer cells may include cancer stem cells, rare cells with indefinite potential for self-renewal that drive tumorigenesis. Mutant stem cells are responsible mainly for tumorigenesis. Hence, understanding the genealogy of mutant stem cell is of vital importance. Mutant stem progression model in Chapter 7 tries to depict these important phenomena.

8.2 CONTRIBUTIONS

Firstly, the three parameter pure-birth growth model is sufficiently accurate to predict the dynamic behavior of stem cells. This model can be used to understand the growth dynamics of cell populations such as cell proliferation and quiescence rates both in vivo and lab experiment.

Secondly, a simple stochastic model for capturing the homeostasis of the stem cell compartment was proposed. By assuming that each dividing stem cell has an equal chance of producing two, one or no stem cells the stochastic model shows that homeostasis seems to be a default scenario of stem cell dynamics and that to get the stem cells out of this equilibrium either by spontaneous mutations that favor one specific division outcome or, otherwise, external feedback is required. One possible form of such feedback would alter the outcome of stem cell divisions favoring, perhaps on a transient basis, the number of stem cells produced. This feedback is of paramount importance in regenerative medicine where the stem cells need to be steered towards a controlled growth that will regenerate lost tissue cells.

Finally, simple mathematical equations have been derived for the three compartments of tissue. These equations along with strict conditions portrays a better understanding of homeostasis which has not been revealed in earlier research attempts [27, 26].

8.3 FUTURE WORK

From this dissertation, several clear directions for future work can be envisaged. These directions can be classified as further analysis of stem cell homeostasis, self-renewal and differentiation and also understanding reasoning behind cancerous stem

cell hypothesis.

Also justification of the models can be made more concrete by more rigorous simulation techniques and also by comparing with clinical data from vivo and vitro.

For stem cell growth model it would be ideal to get clinical data from real world. Especially, stem cell growth data for comparison with the predictive nature of model and better estimates of the three parameters. At this stage much cannot be said about the parameters from a biological stand point. May be with delving more with real world data and comparing with the model one can understand the parameters upper and lower bounds. Analyzing laboratory data in future will let growth model's individual parameter to precisely map the progression. The main strength of the growth data is to predict the time required to produce certain cell mass. In muscle regeneration this growth model holds a promising future. In recent times using stem cell's explosive growth ingredient, artificial beef production has been accomplished. This could be an interesting future research topic to predict the initial number of stem cell required to produce certain amount of tissue mass. A more robust growth model based on the simple model from Chapter 4 may be the answer for that.

Stem cell homeostasis and tissue lineage models are very important in better understanding the balance at tissue level for a living organism. In future work understanding the feedback mechanisms that was ignored in this work for this two models would be a novel addition. In biological organism complex feedback mechanisms work to control growth, death and differentiation. Although it was ignored here in these two models but these two model give a foundation to build more comprehensive models in future.

Mutant cell model that was proposed here needs further investigation in terms of more simulation and comparison with real world mutant cell progression data. Also it would be useful would add more parameter that triggers a wild type stem cell to convert into a mutant cell.

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APPENDIX A

THEOREMS AND LEMMA RELATING TO STEM CELL

GROWTH

A.0.1 DERIVING A CLOSED FORM FOR $P_N(T)$

In Section 4.3 closed form for $P_k(t)$ for $k < N$ was obtained. What can be said about $P_N(t)$?

Recalling that $\lambda_N = 0$, (22)

$$\frac{dP_N(t)}{dt} = \lambda_{N-1} P_{N-1}(t) \tag{68}$$

which implies that

$$P_N(t) = \lambda_{N-1} \int P_{N-1}(t)dt + D$$

where the constant D will be determined in such a way that the boundary condition $P_N(0) = 0$ is satisfied.

To determine D, $P_N(t)$ can be written as follows

$$
\begin{aligned}
P_N(t) &= \lambda_{N-1} \int P_{N-1}(t)dt + D \\
&= \lambda_1 \lambda_2 \cdots \lambda_{N-1} \int \sum_{i=1}^{N-1} \frac{e^{-\lambda_i t}dt}{\Pi_{\substack{1 < j < N \\ j \neq i}}(\lambda_j - \lambda_i)} + D \\
&= \lambda_1 \lambda_2 \cdots \lambda_{N-1} \sum_{i=1}^{N-1} \int \frac{e^{-\lambda_i t}dt}{\Pi_{\substack{1 < j \le N \\ j \neq i}}(\lambda_j \cdot \lambda_i)} + D \\
&= -\lambda_1 \lambda_2 \cdots \lambda_{N-1} \sum_{i=1}^{N-1} \frac{e^{-\lambda_i t}dt}{\lambda_i \Pi_{\substack{1 \le j \le N-1 \\ j \neq i}}(\lambda_j - \lambda_i)} + D \\
&= D - \sum_{i=1}^{N-1} \Pi_{\substack{1 < j \le N \\ j \neq i}} \left[\frac{\lambda_j}{\lambda_j - \lambda_i} e^{-\lambda_i t} \right]
\end{aligned}
\tag{69}
$$

Since $P_N(0) = 0$, (69) implies that

$$
\begin{aligned}
D &= \sum_{i=1}^{N-1} \Pi_{\substack{1 < j < N \\ j \neq i}} \frac{\lambda_j}{\lambda_j - \lambda_i} \\
&= 1. \quad \text{[by Theorem A.2 in the Appendix]}
\end{aligned}
$$

Replacing the value of D in (69)

$$P_N(t) = 1 - \Pi_{\substack{1 \le j \le N-1 \\ j \ne i}} \left[\frac{\lambda_j}{\lambda_j - \lambda_i} e^{-\lambda_i t} \right]. \tag{70}$$

Lemma A.1. *If* $a_1, a_2, \cdots, a_n$, $(n \ge 2)$, *are distinct real numbers then the following identity holds*

$$\sum_{i=1}^{n} \frac{1}{\displaystyle\prod_{\substack{j-1 \\ j \ne i}}^{n} (a_j - a_i)} = 0. \tag{71}$$

Proof. Proceeding by induction on n. To settle the basis, observe that

$$\frac{1}{a_2 - a_1} + \frac{1}{a_1 - a_2} = 0,$$

as expected.

For the inductive step, let n, $(n \ge 2)$, be arbitrary and assume that for the chosen value of n, (71) holds. With this assumption, goal becomes to show that

$$\sum_{i=1}^{n+1} \frac{1}{\displaystyle\prod_{\substack{j=1 \\ j \ne i}}^{n+1} (a_j - a_i)} = 0. \tag{72}$$

After multiplying (71) throughout by $\frac{1}{a_{n+1} - a_1}$ and after suitably transposing terms,

$$\frac{1}{\displaystyle\prod_{\substack{j=2 \\ j \ne i}}^{n+1} (a_j - a_1)} = -\sum_{i=2}^{n} \frac{1}{(a_{n+1} - a_1) \displaystyle\prod_{\substack{j=1 \\ j \ne i}}^{n} (a_j - a_i)}.$$

With this observation, the left-hand side of (72) becomes

$$\sum_{i=1}^{n+1} \frac{1}{\prod_{\substack{j=1\\j\neq i}}^{n+1}(a_j - a_i)} = -\sum_{i=2}^{n} \frac{1}{(a_{n+1} - a_1)\prod_{\substack{j=1\\j\neq i}}^{n}(a_j - a_i)} + \sum_{i=2}^{n} \frac{1}{\prod_{\substack{j=1\\j\neq i}}^{n+1}(a_j - a_i)} + \frac{1}{\prod_{j=1}^{n}(a_j - a_{n+1})}$$

$$= \sum_{i=2}^{n} \left[\frac{1}{\prod_{\substack{j=1\\j\neq i}}^{n+1}(a_j - a_i)} - \frac{1}{(a_{n+1} - a_1)\prod_{\substack{j=1\\j\neq i}}^{n}(a_j - a_i)} \right] + \frac{1}{\prod_{j=1}^{n}(a_j - a_{n+1})}$$

$$= -\sum_{i=2}^{n} \frac{(a_{n+1} - a_1) - (a_{n+1} - a_i)}{(a_{n+1} - a_1)\prod_{\substack{j=1\\j\neq i}}^{n+1}(a_j - a_i)} + \frac{1}{\prod_{j=1}^{n}(a_j - a_{n+1})}$$

$$= -\sum_{i=2}^{n} \frac{a_1 - a_i}{(a_{n+1} - a_1)\prod_{\substack{j=1\\j\neq i}}^{n+1}(a_j - a_i)} + \frac{1}{\prod_{j=1}^{n}(a_j - a_{n+1})}$$

$$= -\sum_{i=2}^{n} \frac{1}{(a_{n+1} - a_1)\prod_{\substack{j=2\\j\neq i}}^{n+1}(a_j - a_i)} + \frac{1}{\prod_{j=1}^{n}(a_j - a_{n+1})}$$

$$= -\sum_{i=2}^{n} \frac{1}{(a_{n+1} - a_1)\prod_{\substack{j=2\\j\neq i}}^{n+1}(a_j - a_i)} - \frac{1}{(a_{n+1} - a_1)\prod_{\substack{j=2\\j\neq i}}^{n}(a_j - a_{n+1})}$$

$$= -\frac{1}{a_{n+1} - a_1} \left[\sum_{i=2}^{n} \frac{1}{\prod_{\substack{j=2\\j\neq i}}^{n+1}(a_j - a_i)} + \frac{1}{\prod_{\substack{j=2\\j\neq i}}^{n}(a_j - a_{n+1})} \right]$$

$$= -\frac{1}{a_{n+1} - a_1} \cdot \sum_{i=2}^{n+1} \frac{1}{\prod_{\substack{j=2\\j\neq i}}^{n}(a_j - a_i)}$$

$$= 0. \quad \text{[as (74) is applied to the n-element sequence } a_2, a_3, \cdots, a_{n+1}\text{]}$$

$$(73)$$

□

A companion result to Lemma A.1 goes as follows.

Lemma A.2. *If $a_1, a_2, \cdots, a_n$, $(n \geq 2)$, are distinct real numbers then the following identity holds*

$$\sum_{i=1}^{n}\prod_{\substack{j=1\\j\neq i}}^{n} \frac{a_j}{a_j - a_i} = 1. \tag{74}$$

Proof. Proceeding by induction on n. To settle the basis, observe that

$$\frac{a_1}{a_2 - a_1} + \frac{a_2}{a_1 - a_2} = 1,$$

as desired.

For the inductive step, let n, $(n \geq 2)$, be arbitrary and assume that for the chosen value of n, (74) holds. With this assumption, goal becomes to show that

$$\sum_{i=1}^{n+1}\prod_{\substack{j=1\\j\neq i}}^{n+1} \frac{a_j}{a_j - a_i} = 1. \tag{75}$$

By writing,

$$\sum_{i=1}^{n+1}\prod_{\substack{j=1\\j\neq i}}^{n+1} \frac{a_j}{a_j - a_i} = \prod_{k=1}^{n+1} a_k \cdot \sum_{i=1}^{n+1} \frac{1}{a_i \prod_{\substack{j=1\\j\neq i}}^{n+1}(a_j - a_i)}$$

$$= \prod_{k=1}^{n+1} a_k \cdot \left[\frac{1}{a_1 \prod_{\substack{j=2\\j\neq i}}^{n+1}(a_j - a_1)} + \sum_{i=2}^{n+1} \frac{1}{a_i \prod_{\substack{j=1\\j\neq i}}^{n+1}(a_j - a_i)} \right] \tag{76}$$

Recall that by Lemma A.1

$$\sum_{i=1}^{n+1} \frac{1}{\prod_{\substack{j=1\\j\neq i}}^{n+1}(a_j - a_i)} = 0. \tag{77}$$

After multiplying (77) throughout by $\frac{1}{a_1}$ and after suitably transposing terms,

$$\frac{1}{a_1 \prod_{\substack{j=2 \\ j \neq i}}^{n+1}(a_j - a_1)} = -\sum_{i=2}^{n+1} \frac{1}{a_1 \prod_{\substack{j=1 \\ j \neq i}}^{n}(a_j - a_i)}. \tag{78}$$

By virtue of (78), (76) can be written as follows:

$$
\begin{aligned}
\sum_{i=1}^{n+1}\prod_{\substack{j=1 \\ j \neq i}}^{n+1}\frac{a_j}{a_j - a_i} &= \prod_{k=1}^{n+1} a_k \cdot \left[-\sum_{i=2}^{n+1}\frac{1}{a_1 \prod_{\substack{j=1 \\ j \neq i}}^{n}(a_j - a_i)} + \sum_{i=2}^{n+1}\frac{1}{a_i \prod_{\substack{j=1 \\ j \neq i}}^{n+1}(a_j - a_i)} \right] \\
&= \prod_{k=1}^{n+1} a_k \cdot \sum_{i=2}^{n+1}\left[\left(\frac{1}{a_i} - \frac{1}{a_1}\right)\frac{1}{\prod_{\substack{j=1 \\ j \neq i}}^{n+1}(a_j - a_i)} \right] \\
&= \prod_{k=1}^{n+1} a_k \cdot \sum_{i=2}^{n+1}\frac{a_1 - a_i}{a_1 a_i (a_1 - a_i)\prod_{\substack{j=2 \\ j \neq i}}^{n+1}(a_j - a_i)} \\
&= \prod_{k=1}^{n+1} a_k \cdot \sum_{i=2}^{n+1}\frac{1}{a_1 a_i \prod_{\substack{j=2 \\ j \neq i}}^{n+1}(a_j - a_i)} \\
&= \prod_{k=2}^{n+1} a_k \cdot \sum_{i=2}^{n+1}\frac{1}{a_i \prod_{\substack{j=2 \\ j \neq i}}^{n+1}(a_j - a_i)} \\
&= \sum_{i=2}^{n+1}\prod_{\substack{j=2 \\ j \neq i}}^{n+1}\frac{a_j}{a_j - a_i} \\
&= 1. \quad \text{[as (74) is applied to the n-element sequence } a_2, a_3, \cdots, a_{n+1}]
\end{aligned}
$$
$$\tag{79}$$

This completes the proof of Lemma A.2. □

Finally, take note of the following result.

Lemma A.3. *If $a_1, a_2, \cdots, a_n$, $(n \geq 2)$, are distinct real numbers then the following identity holds*

$$1 + \frac{a_1}{a_2 - a_1} + \frac{a_1 a_2}{(a_2 - a_1)(a_3 - a_1)} + \cdots + \frac{a_1 a_2 \cdots a_{n-1}}{(a_2 - a_1)(a_3 - a_1) \cdots (a_n - a_1)} = \prod_{j=2}^{n} \frac{a_j}{a_j - a_1}.$$
(80)

Proof. Proceeding by induction on n. To settle the basis, observe that

$$1 + \frac{a_1}{a_2 - a_1} = \frac{a_2}{a_2 - a_1},$$

as expected.

For the inductive step, let n, $(n \geq 2)$, be arbitrary and assume that for the chosen value of n, (80) holds. With this assumption, goal becomes to prove that

$$1 + \frac{a_1}{a_2 - a_1} + \frac{a_1 a_2}{(a_2 - a_1)(a_3 - a_1)} + \cdots + \frac{a_1 a_2 \cdots a_n}{(a_2 - a_1)(a_3 - a_1) \cdots (a_{n+1} - a_1)} = \prod_{j=2}^{n+1} \frac{a_j}{a_j - a_1}.$$
(81)

Writing,

$$
\begin{aligned}
&1 + \frac{a_1}{a_2 - a_1} + \frac{a_1 a_2}{(a_2 - a_1)(a_3 - a_1)} + \cdots + \frac{a_1 a_2 \cdots a_n}{(a_2 - a_1)(a_3 - a_1) \cdots (a_{n+1} - a_1)} \\
&= 1 + \frac{a_1}{a_2 - a_1} + \frac{a_1 a_2}{(a_2 - a_1)(a_3 - a_1)} \cdots + \frac{a_1 a_2 \cdots a_{n-1}}{(a_2 - a_1)(a_3 - a_1) \cdots (a_n - a_1)} \\
&\quad + \frac{a_1 a_2 \cdots a_n}{(a_2 - a_1)(a_3 - a_1) \cdots (a_{n+1} - a_1)} \\
&= \prod_{j=2}^{n} \frac{a_j}{a_j - a_1} + \frac{a_1 a_2 \cdots a_n}{(a_2 - a_1)(a_3 - a_1) \cdots (a_{n+1} - a_1)} \quad \text{[by the induction hypothesis]} \\
&= \prod_{j=2}^{n} \frac{a_j}{a_j - a_1} \left[1 + \frac{a_1}{a_{n+1} - a_1} \right] \\
&= \prod_{j=2}^{n} \frac{a_j}{a_j - a_1} \cdot \frac{a_{n+1}}{a_{n+1} - a_1} \\
&= \prod_{j=2}^{n+1} \frac{a_j}{a_j - a_1},
\end{aligned}
$$

as desired. This completes the proof of Lemma A.3. $\square$

A.0.2 THE SANITY CHECK

The major goal of this section is to prove that for all $t \geq 0$, the probabilities $P_k(t)$ add up to 1.

Theorem A.4. *For all* t, $(t \geq 0)$,

$$\sum_{k=1}^{N} P_k(t) = 1. \tag{82}$$

Proof. Recall that by Theorem 4.2, for $1 < k < N$ and for $t \geq 0$,

$$P_k(t) = \lambda_1 \lambda_2 \cdots \lambda_{k-1} \sum_{i=1}^{k} \frac{e^{-\lambda_i t}}{\prod_{\substack{j=1 \\ j \neq i}}^{k} (\lambda_j - \lambda_i)}.$$

Similarly, by Equation 70 for $t \geq 0$,

$$P_N(t) = 1 - \sum_{i=1}^{N-1} \left(\prod_{\substack{j=1 \\ j \neq i}}^{N-1} \left[\frac{\lambda_j}{\lambda_j - \lambda_i} \right] e^{-\lambda_i t} \right).$$

Thus, proving Theorem A.4 is tantamount to proving the following result.

Lemma A.5. *For all* $1 \leq i \leq N - 1$, *the coefficient of* $e^{-\lambda_i t}$ *in* $\sum_{k=1}^{N-1} P_k(t)$ *is*

$$\prod_{\substack{j=1 \\ j \neq i}}^{N-1} \frac{\lambda_j}{\lambda_j - \lambda_i}.$$

Proof. To begin, assume that $2 \leq i \leq N - 1$. It is easy to see that the coefficient of $e^{-\lambda_i t}$ in $\sum_{k=1}^{N-1} P_k(t)$ is

$$\frac{\lambda_1 \lambda_2 \cdots \lambda_{i-1}}{(\lambda_1 - \lambda_i)(\lambda_2 - \lambda_i) \cdots (\lambda_{i-1} - \lambda_i)} + \frac{\lambda_1 \lambda_2 \cdots \lambda_i}{(\lambda_1 - \lambda_i)(\lambda_2 - \lambda_i) \cdots (\lambda_{i-1} - \lambda_i)(\lambda_{i+1} - \lambda_i)}$$

$$+ \cdots + \frac{\lambda_1 \lambda_2 \cdots \lambda_{N-2}}{(\lambda_1 - \lambda_i)(\lambda_2 - \lambda_i) \cdots (\lambda_{i-1} - \lambda_i)(\lambda_{i+1} - \lambda_i) \cdots (\lambda_{N-1} - \lambda_i)}$$

$$= \frac{\lambda_1 \lambda_2 \cdots \lambda_{i-1}}{(\lambda_1 - \lambda_i)(\lambda_2 - \lambda_i) \cdots (\lambda_{i-1} - \lambda_i)} \tag{83}$$

$$\left[1 + \frac{\lambda_i}{\lambda_{i+1} - \lambda_i} + \frac{\lambda_i \lambda_{i+1}}{(\lambda_{i+1} - \lambda_i)(\lambda_{i+2} - \lambda_i)} + \cdots + \frac{\lambda_i \lambda_{i+1} \cdots \lambda_{N-2}}{(\lambda_{i+1} - \lambda_i)(\lambda_{i+2} - \lambda_i) \cdots (\lambda_{N-1} - \lambda_i)} \right].$$

$$\tag{84}$$

On the other hand, observe that with the assignment

$$a_1 = \lambda_i, \ a_2 = \lambda_{i+1}, \ \cdots$$

Lemma A.3 guarantees that

$$
\begin{aligned}
& 1 + \frac{\lambda_i}{\lambda_{i+1} - \lambda_i} + \frac{\lambda_i \lambda_{i+1}}{(\lambda_{i+1} - \lambda_i)(\lambda_{i+2} - \lambda_i)} + \cdots + \frac{\lambda_i \lambda_{i+1} \cdots \lambda_{N-2}}{(\lambda_{i+1} - \lambda_i)(\lambda_{i+2} - \lambda_i) \cdots (\lambda_{N-1} - \lambda_i)} \\
& = \frac{\lambda_{i+1} \lambda_{i+2} \cdots \lambda_{N-1}}{(\lambda_{i+1} - \lambda_i)(\lambda_{i+2} - \lambda_i) \cdots (\lambda_{N-1} - \lambda_i)}.
\end{aligned}
\tag{85}
$$

Finally, by (83) and (85), combined, the coefficient of $e^{-\lambda_i t}$ in $\sum_{k=1}^{N-1} P_k(t)$ is

$$
\begin{aligned}
& \frac{\lambda_1 \lambda_2 \cdots \lambda_{i-1}}{(\lambda_1 - \lambda_i)(\lambda_2 - \lambda_i) \cdots (\lambda_{i-1} - \lambda_i)} \cdot \frac{\lambda_{i+1} \lambda_{i+2} \cdots \lambda_{N-1}}{(\lambda_{i+1} - \lambda_i)(\lambda_{i+2} - \lambda_i) \cdots (\lambda_{N-1} - \lambda_i)} \\
& = \prod_{\substack{j=1 \\ j \neq i}}^{N-1} \frac{\lambda_j}{\lambda_j - \lambda_i}
\end{aligned}
$$

completing the proof of Lemma A.5. □

In turn, Lemma A.5 implies Theorem A.4.

Thus, for all t, $(t \geq 0)$,

$$
\sum_{k=1}^{N} P_k(t) = 1
$$

and the proof is complete. □

APPENDIX B

THEOREMS AND LEMMAS RELATING TO STEM

CELL HOMEOSTASIS

Theorem B.1. *Let A and B be events over a probability space $(\Omega, \mathcal{F}, \Pr)$ with $\Pr[B] \neq 0$. Let $C_0, C_1, C_2, \cdots \cdots$ be a partition of Ω that is, $\cup_{k \geq 0} C_k = \Omega$ and $C_i \cap C_j = \emptyset, \forall i \neq j$.*

Let, now state and prove a useful result from probability theory.

$$\Pr[A|B] = \sum_{k \geq 0} \Pr[A|C_k \cap B] \Pr[C_k|B]$$

Proof.

$$
\begin{aligned}
\Pr[A|B] &= \Pr[(A \cap \cup_{k \geq 0} C_k)|B] = \Pr[\cup_{k \geq 0}(A \cap C_k)|B] \\
&= \frac{\Pr[\cup_{k \geq 0}(A \cap C_k \cap B)]}{\Pr[B]} = \frac{\sum_{k \geq 0} \Pr[(A \cap C_k \cap B)]}{\Pr[B]} \\
&= \frac{\sum_{k \geq 0} \Pr[(A|C_k \cap B)] \Pr[C_k \cap B]}{\Pr[B]} \\
&= \frac{\sum_{k \geq 0} \Pr[(A|C_k \cap B)] \Pr[C_k|B] \Pr[B]}{\Pr[B]} \\
&= \sum_{k \geq 0} \Pr[(A|C_k \cap B)] \Pr[C_k|B],
\end{aligned}
$$

as claimed. $\square$

Lemma B.2. *For all non-negative integers r,*

$$\left\lfloor \frac{r}{2} \right\rfloor + \left\lfloor \frac{r-1}{2} \right\rfloor = r - 1$$

Proof. By proving a more general statement, namely that for all integers m, $(m \neq 0)$, and n

$$\left\lfloor \frac{n}{m} \right\rfloor + \left\lceil \frac{(m-1)n}{m} \right\rceil = n.$$

$$\left\lfloor \frac{n}{m} \right\rfloor + \left\lceil \frac{(m-1)n}{m} \right\rceil = \left\lfloor \frac{n}{m} \right\rfloor + \left\lceil \left(n - \frac{n}{m}\right) \right\rceil$$

$$= \left\lfloor \frac{n}{m} \right\rfloor + n + \left\lceil -\frac{n}{m} \right\rceil$$

$$= \left\lfloor \frac{n}{m} \right\rfloor + n - \left\lceil \frac{n}{m} \right\rceil$$

$$= n$$

By taking $m = 2$

$$\left\lfloor \frac{n}{2} \right\rfloor + \left\lceil \frac{n}{2} \right\rceil = n. \tag{86}$$

But it is known that

$$\left\lceil \frac{n}{2} \right\rceil = \left\lfloor \frac{n+1}{2} \right\rfloor$$

So, (89) implies

$$\left\lfloor \frac{n}{2} \right\rfloor + \left\lfloor \frac{n+1}{2} \right\rfloor = n \tag{87}$$

Now, letting $n = r - 1$,

$$\left\lfloor \frac{r-1}{2} \right\rfloor + \left\lfloor \frac{r}{2} \right\rfloor = r - 1 \tag{88}$$

as claimed. □

Theorem B.3. *For all natural numbers $r \geq 1$*

$$2\left(\left\lfloor \frac{1}{2} \right\rfloor + \left\lfloor \frac{2}{2} \right\rfloor\right) + \cdots \left\lfloor \frac{r-2}{2} \right\rfloor + \left\lfloor \frac{r-1}{2} \right\rfloor\right) = \frac{r(r-1)}{2} - \left\lfloor \frac{r}{2} \right\rfloor$$

Proof. The proof is by induction on r. The basis is trivial, for $r = 1$ both left hand side and right hand side equals to 0. Next, let $r \geq 1$ be arbitrary and assume that the statement holds for $r - 1$ or, in other words,

$$2\left(\left\lfloor \frac{1}{2} \right\rfloor + \left\lfloor \frac{2}{2} \right\rfloor\right) + \cdots \left\lfloor \frac{r-3}{2} \right\rfloor + \left\lfloor \frac{r-2}{2} \right\rfloor\right) = \frac{(r-1)(r-2)}{2} - \left\lfloor \frac{r-1}{2} \right\rfloor$$

With this assumption,

$$2\left(\left\lfloor\frac{1}{2}\right\rfloor + \left\lfloor\frac{2}{2}\right\rfloor\right) + \cdots\cdots + \left\lfloor\frac{r-1}{2}\right\rfloor\right) = 2\left(\left\lfloor\frac{1}{2}\right\rfloor + \left\lfloor\frac{2}{2}\right\rfloor + \cdots\cdots + \left\lfloor\frac{r-2}{2}\right\rfloor\right)$$

$$+ 2\left\lfloor\frac{r-1}{2}\right\rfloor$$

$$= \frac{(r-1)(r-2)}{2} - \left\lfloor\frac{r-1}{2}\right\rfloor + 2\left\lfloor\frac{r-1}{2}\right\rfloor$$

$$= \frac{(r-1)(r-2)}{2} + \left\lfloor\frac{r-1}{2}\right\rfloor$$

$$= \frac{(r-1)(r-2)}{2} + \left((r-1) + \left\lfloor\frac{r}{2}\right\rfloor\right)$$

[by Lemma B.4]

$$= \frac{(r-1)r}{2} - \left\lfloor\frac{r}{2}\right\rfloor,$$

as claimed. □

Lemma B.4. *For all non-negative integers r,*

$$\left\lfloor\frac{r}{2}\right\rfloor + \left\lfloor\frac{r-1}{2}\right\rfloor = r - 1.$$

Proof. By proving a more general statement, namely that for all integers $m, (m \neq 0)$, and n

$$\left\lfloor\frac{n}{m}\right\rfloor + \left\lceil\frac{(m-1)n}{m}\right\rceil = n.$$

$$\left\lfloor\frac{n}{m}\right\rfloor + \left\lceil\frac{(m-1)n}{m}\right\rceil = \left\lfloor\frac{n}{m}\right\rfloor + \left\lceil\left(n - \frac{n}{m}\right)\right\rceil$$

$$= \left\lfloor\frac{n}{m}\right\rfloor + n + \left\lceil\cdot\frac{n}{m}\right\rceil$$

$$= \left\lfloor\frac{n}{m}\right\rfloor + n - \left\lceil\frac{n}{m}\right\rceil$$

$$= n$$

By taking $m = 2$

$$\left\lfloor\frac{n}{2}\right\rfloor + \left\lceil\frac{n}{2}\right\rceil = n. \tag{89}$$

Recalling that

$$\left\lceil\frac{n}{2}\right\rceil = \left\lfloor\frac{n+1}{2}\right\rfloor,$$

(89) implies

$$\left\lfloor \frac{n}{2} \right\rfloor + \left\lfloor \frac{n+1}{2} \right\rfloor = n \tag{90}$$

Now, upon letting $n = r - 1$,

$$\left\lfloor \frac{r-1}{2} \right\rfloor + \left\lfloor \frac{r}{2} \right\rfloor = r - 1 \tag{91}$$

as claimed. □

Theorem B.5. *For all natural numbers $r \geq 1$*

$$2\left(\left\lfloor \frac{1}{2} \right\rfloor + \left\lfloor \frac{2}{2} \right\rfloor \right) + \cdots + \left\lfloor \frac{r-2}{2} \right\rfloor + \left\lfloor \frac{r-1}{2} \right\rfloor \right) = \frac{r(r-1)}{2} - \left\lfloor \frac{r}{2} \right\rfloor$$

Proof. The proof is by induction on r. The basis is trivial, for $r = 1$ both left hand side and right hand side equals to 0. Next, let $r \geq 1$ be arbitrary and assume that the statement holds for $r - 1$ or, in other words,

$$2\left(\left\lfloor \frac{1}{2} \right\rfloor + \left\lfloor \frac{2}{2} \right\rfloor \right) + \cdots + \left\lfloor \frac{r-3}{2} \right\rfloor + \left\lfloor \frac{r-2}{2} \right\rfloor \right) = \frac{(r-1)(r-2)}{2} - \left\lfloor \frac{r-1}{2} \right\rfloor$$

With this assumption

$$
\begin{aligned}
2\left(\left\lfloor \frac{1}{2} \right\rfloor + \left\lfloor \frac{2}{2} \right\rfloor \right) + \cdots + \left\lfloor \frac{r-1}{2} \right\rfloor \right) &= 2\left(\left\lfloor \frac{1}{2} \right\rfloor + \left\lfloor \frac{2}{2} \right\rfloor + \cdots + \left\lfloor \frac{r-2}{2} \right\rfloor \right) \\
&\quad + 2\left\lfloor \frac{r-1}{2} \right\rfloor \\
&= \frac{(r-1)(r-2)}{2} - \left\lfloor \frac{r-1}{2} \right\rfloor + 2\left\lfloor \frac{r-1}{2} \right\rfloor \\
&= \frac{(r-1)(r-2)}{2} + \left\lfloor \frac{r-1}{2} \right\rfloor \\
&= \frac{(r-1)(r-2)}{2} + \left((r-1) + \left\lfloor \frac{r}{2} \right\rfloor \right) \\
&\qquad \text{[by Lemma B.4]} \\
&= \frac{(r-1)r}{2} - \left\lfloor \frac{r}{2} \right\rfloor,
\end{aligned}
$$

as claimed. □

APPENDIX C

THEOREMS AND PROOFS RELATING TO TISSUE

CELL LINEAGE

For $t > 0$, define the function ψ such that

$$\psi(t) = \frac{1 - e^{at}}{1 - e^{bt}} \tag{92}$$

where $a \neq b$, $b \neq 0$.

Lemma C.1. *A necessary and sufficient condition for $\psi(t)$ to be a constant, is that* $a = 0$.

Proof. First, if $a = 0$ then (92) guarantees that $\psi(t) = 0$ for all $t > 0$.

Conversely, assume $\psi(t)$ to be a constant independent of t. Thus, in particular, $\psi(1) = \psi(2)$ which amounts to

$$\frac{1 - e^a}{1 - e^b} = \frac{1 - e^{2a}}{1 - e^{2b}}.$$

However,

$$\frac{1 - e^{2a}}{1 - e^{2b}} = \frac{1 - e^a}{1 - e^b} \cdot \frac{1 + e^a}{1 + e^b}$$

and so

$$\frac{1 - e^a}{1 - e^b} = \frac{1 - e^a}{1 - e^b} \cdot \frac{1 + e^a}{1 + e^b}.$$

Since $b \neq 0$ the above is equivalent to

$$1 - e^a = (1 - e^a) \cdot \frac{1 + e^a}{1 + e^b}.$$

If $a \neq 0$ then $1 - e^a \neq 0$ and

$$1 = \frac{1 + e^a}{1 + e^b}$$

which implies $a = b$, a contradiction.

Thus, $a = 0$, as claimed. This completes the proof of the lemma.

□

Lemma C.2. *If x and y are finite, then for all $t \in \mathbb{R}$*

$$\lim_{x \to y} \frac{e^{xt} - e^{yt}}{x - y} = te^{yt}.$$

Proof. It can be written that,

$$\frac{e^{xt} - e^{yt}}{x - y} = e^{yt} \frac{e^{(x-y)t} - 1}{x - y}$$

and so

$$
\begin{aligned}
\lim_{x \to y} \frac{e^{xt} - e^{yt}}{x - y} &= \lim_{x \to y} \left(e^{yt} \frac{e^{(x-y)t} - 1}{x - y} \right) \\
&= e^{yt} \lim_{x \to y} \frac{e^{(x-y)t} - 1}{x - y} \\
&= e^{yt} \lim_{z \to 0} \frac{e^{zt} - 1}{z} \quad [\text{where } z = x - y] \\
&= te^{yt},
\end{aligned}
$$

as claimed. $\square$

APPENDIX D

THEOREMS AND LEMMAS RELATING TO MUTANT

STEM CELL PROGRESSION

Lemma D.1. *For some α, where, $0 \leq \alpha \leq 1$*

$$1 + 2(1 - \alpha) + 3(1 - \alpha)^2 + 4(1 - \alpha)^3 + \ldots \cdots = \frac{1}{\alpha^2}$$

Proof. It is easy to see that,

$$1 + (1 - \alpha) + (1 - \alpha)^2 + (1 - \alpha)^3 + \ldots = \frac{1}{\alpha} \tag{93}$$

Now,

$$
\begin{aligned}
1 + 2(1 - \alpha) + 3(1 - \alpha)^2 + 4(1 - \alpha)^3 + \ldots \cdots = {}& 1 + (1 - \alpha) + (1 - \alpha) \\
{}+{}& (1 - \alpha)^2 + (1 - \alpha)^2) + (1 - \alpha)^2 \\
{}+{}& (1 - \alpha)^3 + (1 - \alpha)^3 + (1 - \alpha)^3 + (1 - \alpha)^3 \\
{}+{}& (1 - \alpha)^4 + (1 - \alpha)^4 + (1 - \alpha)^4 + (1 - \alpha)^4 \\
{}+{}& \ldots \ldots
\end{aligned}
$$

Now, by adding column wise R.H.S becomes,

$$
\begin{aligned}
={}& 1 + (1 - \alpha)\frac{1}{\alpha} + (1 - \alpha)\frac{1}{\alpha} + (1 - \alpha)^2\frac{1}{\alpha} + (1 - \alpha)^3\frac{1}{\alpha} + (1 - \alpha)^4\frac{1}{\alpha} + \ldots \ldots \\
={}& \frac{1}{\alpha} + \frac{1 \cdot \alpha}{\alpha} + \frac{(1 - \alpha)^2}{\alpha} + \ldots \ldots \\
={}& \frac{1}{\alpha}\left[1 + (1 - \alpha) + (1 - \alpha)^2 + \ldots \ldots\right] \\
={}& \frac{1}{\alpha^2}
\end{aligned}
$$

$\square$

VITA

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Samiur Arif received his B.S. in Computer Science from the department of Computer Science and Engineering, BRAC University, Bangladesh in 2008. Afterwards, he briefly worked at Goodrich Aerostructures Service Center, Singapore. Later that year, he joined Old Dominion University and started his PhD in Computer Science. Initially he worked under the supervision of Professor Dr. Mohammad Zubair Insert Last name, but after successfully implementing Asian Option Pricing on IBM CELL parallel architecture, he focused his research on stochastic system modeling under the supervision of Professor Dr. Stephan Olariu. His research was primarily on compartmental disease epidemic models, namely SI, SIS and SIR. He presented numerous interesting applications of epidemic models in Vehicular Network [41], Finance [44], Marketing, and Population Biology [43]. He observed stem cell growth models, a vital aspect of regenerative medicine. He successfully came up with a stochastic growth model in stem cell growth which closely mimics the predicted growth pattern in vitro. The resulting paper was awarded for excellence in the natural and computational sciences at The College of William and Mary's 11th Annual Graduate Research Symposium. He has also published his results in numerous peer-reviewed journals. Recently, Samiur has successfully defended his PhD thesis titled 'Modeling Stem Cell Population Dynamics'.

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