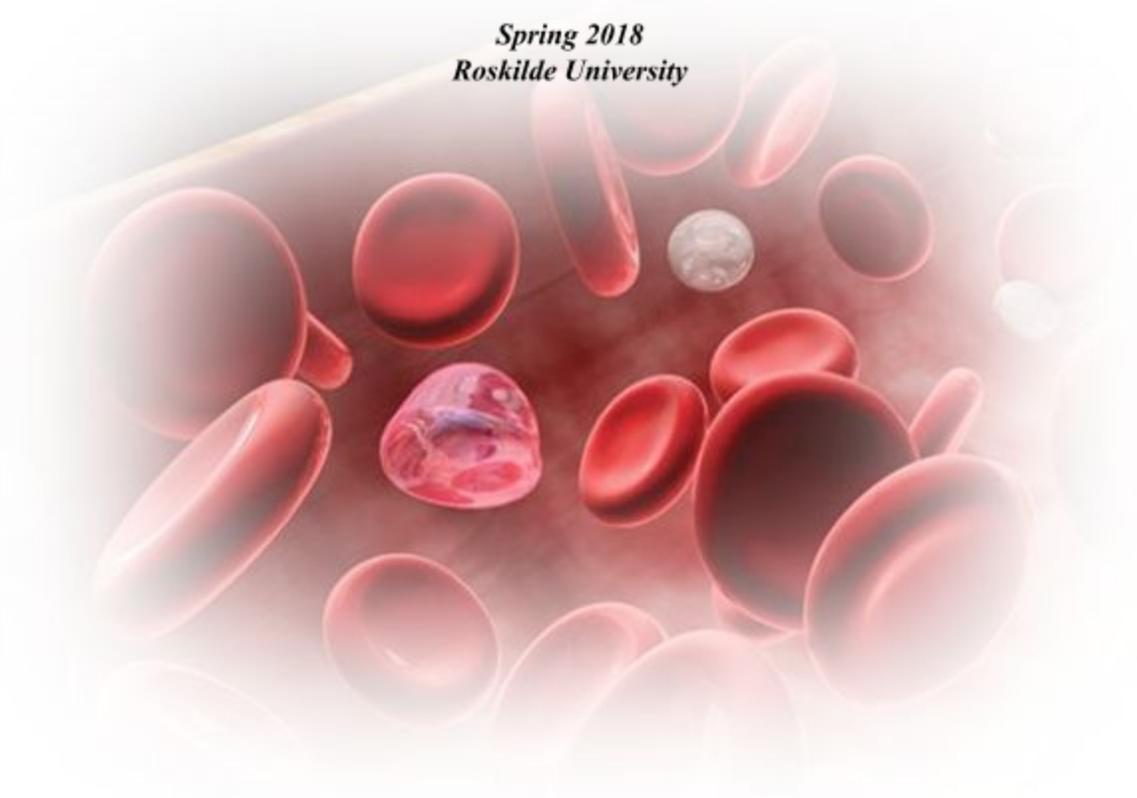




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A microscopic view of blood cells is shown in the background, featuring various red blood cells (erythrocytes) and a few white blood cells (leukocytes) in shades of red and pink, set against a light, hazy background.

How can a mathematical model aid in curing leukaemia?

Project by:

*Mathis Brette Mortensen 62653
Natalia Stati 63997
Irida Gkouzou 62656
Magnus Skjold Frederiksen 64051*

Supervisor:

Johnny T. Ottesen

Abstract

Leukemia is better known as blood cancer. The bone marrow produces white and red blood cells which have specific functions in the body. Leukemia is characterized by a high number of abnormal white blood cells which have no function in the body and cause shrinkage in the normal blood cells. Over the years, treatments have been able to maintain leukemia at a lower level, in a steady state, but none of them can totally cure it. One of the main reasons of failure to find ultimate and effective solutions is the mutations that happen in the tumour cells that lead to drug resistance. The report analyzes a simple mathematical model of a serious type of leukemia called chronic myeloid leukemia or CML. This mathematical model explains the interplay between the normal and the tumour stem cells, and the differentiated healthy and tumour cells. The simulations done upon an ideal model showed that a cure is possible, if we target tumor stem cells and maintain them in a steady state by continuing a treatment for the whole life.

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Preface

This report is submitted as a part of the second semester education of the International Bachelor Programme in Natural Science at Roskilde University in Denmark. The topic constraint is “Interplay between theory, model, experiment and simulation in science.” While brainstorming about cancer, specific types of cancer, models, mathematical models and how all these can be related to each other, the specific research question was revised several times. The final research question ends up as “How can a mathematical model aid in curing leukemia ?”.

Introduction

In a living and healthy organism everything has a specific and important role. One of the most crucial function in the body is the production of blood cells in the bone marrow. If these cells change, there is a risk the whole body will be harmed. Leukemia is commonly referred to blood cancer and characterized by a high number of abnormal white blood cells. These cells have restricted or no function in the body and are causing limitation of action in the normal blood cells.

The number of cases of patients being diagnosed with leukemia is increasing every year. Between 2011 and 2015, 13.8% of every 100,000 people were diagnosed with leukemia, while 6.7% of every 100,000 people died from it every year. On the other hand, the rate of survival reached a high number of 61.4% between 2008 and 2014. Although leukemia is known as a childhood cancer (Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, n.d.), in the majority of cases, 92%, are diagnosed in 20 years of age adults and older. Studies show that elders have less chances for successful treatment, than adults or children. Their body is not able to receive large quantities of drugs during treatment, so the rate of survival is lower. It is estimated that 24,370 leukemia deaths in USA will occur until the end of 2018 (Brooks et al., 2018).

Knowing the severity of this condition, several efforts have been done in order to find a cure. When we use the word cure, we imply the limitation of the disease in a steady state. That means that the patient is going to be in a state where the disease is present, but not lethal and it

does not affect his/her life expectancy or quality. When we mention the total cure, we refer to the complete eradication and treatment of leukemia.

To succeed and reach at least one of these points, researchers, scientists and doctors have worked every day for years, in the development of different treatments. Some examples of those are the chemotherapy, which employs the use of drugs for a specific time period. Targeted therapy has as a goal of inhibiting the protein production that helps tumour cells to grow. Radiation therapy uses radiation from x-rays, gamma rays, etc. Lastly, stem cell transplantation can be done after chemotherapy or radiation therapy, and it replaces the affected cells with healthy ones from a donor (National Cancer Institute, 2017). Due to introduction of targeted drugs, the survival rate for chronic myeloid leukemia has more than doubled from 5 years to over 10 years (Brooks et al., 2018).

To make predictions and illustrate how the disease works, scientists found different ways to prove their relevance. This is clearly illustrated, when a model implies the mathematical concepts that are intended to answer real world questions. The interaction between biology and modeling could lead to improvements in the near future.

Aim

The aim of this project is to deeply analyze and understand leukemic cell behavior in an organism with the purpose to modify or create a mathematical model for curing leukemia or more likely, restricting it in a steady state. Therefore, choosing a specific type of leukemia, chronic myeloid leukemia (CML), and including different factors that could affect it, a model could be designed in relation with specific conditions. Our hypothesis is that by transforming biology into equations, we can understand this complicated disease called cancer more scientifically, and manipulate treatment outcomes. Also, we conceive that theory varies from practice and that the model could be called utopic, so in effort to manage all of this, we will start with small steps by analysing a simple mathematical model for leukemia. As a result, we will be able to completely understand it as if we were its authors.

Problem Area

Chronic myeloid leukemia (CML) is a disease with slow progression, and this is clearly illustrated by the fact that the first symptoms start to appear 6 years after the appearance of the first malign stem cell in the organism. Studies show that in USA about 8,430 new cases will be diagnosed with CML (4,980 in men and 3,450 in women) and about 1,090 people will die of CML (620 men and 470 women) in 2018 (National Cancer Institute, 2017). Also, the average age of diagnosis for CML is around 64 years old and almost half of the incidents diagnosed in people over 65 years old. Furthermore, it is possible for CML to suddenly turn into acute myeloid leukemia (AML), a more aggressive and dangerous type of leukemia, with rapid and uncontrolled progression. From 2005 to 2014, the AML incidents increased by 3.9% per year. The rate of getting cured is very low while the rate of relapse is very high, and even though doctors achieve to decrease the rate of death caused by CML by 1% per year, they have only been able to keep AML stable (Brooks et al., 2018).

Limitations

While leukemia is a broad topic, we restrict this report to chronic myeloid leukemia (CML). This type is an uncommon, but severe, form of leukemia and mathematical models are already available for this disease. We will utilize one such model to study CML and use the factors we can find in literature to further add on to it. Another limitation that came up was the lack of our own clinical data, as the process to get it would be very long. Furthermore, the creation of a complex model that includes too many variables and factors could neglect the most important ones. Other approaches exist but go beyond the scope of this project.

Research question

Our research question is “How can a mathematical model aid in curing leukemia?” and the focus is on the analysis of a specific model. In order to be able to understand and answer it, we had to answer other questions first. We took the main question and dissected it, analyzed it and

came up with the theory behind it. The first two questions that came up, were on the basis of the main one, and they were more general in nature; “What is leukemia ?” and “What is a model ?”. As a result of research on leukemia, more questions such as “ What are the types of leukemia?”, “ How do mutations occur?”, “What is a cancer cell?”, “Do cancer cells have a specific action in the bone marrow?”, “How can leukemia be treated?” were generated. Also the broad question of “What is a model?” made us think that we need to know more about it; “How do you build a good model?”, “What assumptions are made?”, “What are the assumptions due to?”, “What factors are included?”, “Why are these factors included?”, “What factors are not included?”, “Why are these factors not included?”, “What is the focus of the model?”, “What is the goal of the model?”.

A better illustration of how we worked in order to make our sub-questions, is in a picture in *Appendix 1*.

Methodology

The report is an analysis of mathematical models to keep leukemia at a controlled level. Necessary and relevant information was found from online libraries such as Scopus, Rub, cancer.gov, PubMed and Web of Science were used as the source of scientific papers. Keywords included i.e. “cancer mutations,” “ leukemia,” “types of leukemia,” “model,” “characteristics of a good model” , see *Appendix 2*.

The theoretical background helped in understanding what leukemia is, how the cancer cells mutates and what the major problems are, in treating the disease. This includes the difference among the several types of leukemia and how they work, to decide the most suitable one for our project. By doing further research in the literature on how a mathematical model relates to leukemia, an appropriate fit was to analyze a simple model and explain the basis for it. After the complete analysis, we aim to enrich the model with additional factors, since it focus mainly on treatments of CML. For instance, inserting a second mutation in the model. A representative figure is going to be given of how leukemia and further mutations work and where the treatment should target, in order to cure them completely. The Michor’s paper (Dingli & Michor, 2006), that has been used as a template, describes the interaction of four variables and by studying supplementary literature, two other factors were added to the model. The connection between

these factors was analyzed and the conclusion is going to be based on the available information.

Theory

An Introduction to Cancer

In general, cancer is known as a severe and really hard to treat disease, being the result of different mutations in our body. One simple mutation on one cell does not result in cancer, since our body undergoes a lot of mutations during its life due to different mutagenic agents. These can be dangerous and very strong, like UV sunlight, viral infection and the use of chemical compound, or less dangerous like chewing tobacco, cigarette smoke and many more. But usually these mutations do not really affect our metabolism and our health, as cells being mutated are mostly destroyed by immune system cells or macrophages (*Whitworth et al., 1990*). Therefore, cancer is in a certain way, harder to destroy by the action of just the immune system. Indeed, cancer is not only a single mutation, but a sum of multiple mutations located on specific genes, which control the cell-cycle.

- Cancer Cell

A cancer cell is a cell that escapes the control mechanisms that normally limit their growth. During the cell-cycle, a normal cell encounters several steps regulated by dozens of proteins, called regulatory proteins, which tell the cell whether it can replicate or not. In the case of cancer cells, some will no longer respond to external growth regulators, while others fail to produce the internal regulators that ensure orderly growth (*A.Campbell, 2018*). This leads to an uncontrollable cell growth and division which result in a mass of cancer cells, called a tumor. Although not all tumors are cancerous, they are the main cause of cancer infection. Tumors are said to be non-cancerous or benign (*A.Campbell, 2018*), when they do not spread to other locations, otherwise they're malignant. The process of spreading is called metastasis. A tumor is very often benign and becomes malignant afterwards, because of additional mutations or excessive time before treatment, as shown in *figure 1*. This figure taken from the eleventh edition of "Biology, a global approach" by A.Campbell, describes the expansion of cancerous cells in the colon, with an additional explanation in terms of gene mutation, from a small benign

tumor to a big malignant tumor. Each organ infected by cancer, can follow the same pathway as these colon cells. While many cancers develop as “solid” tumors, leukemia develops a “liquid” one, since it is targeting blood cells and the bone marrow. Thus, analysing the stage of leukemia in a patient, is characterized by counting the amount of blood cells and leukemia cells (Schork,2012).

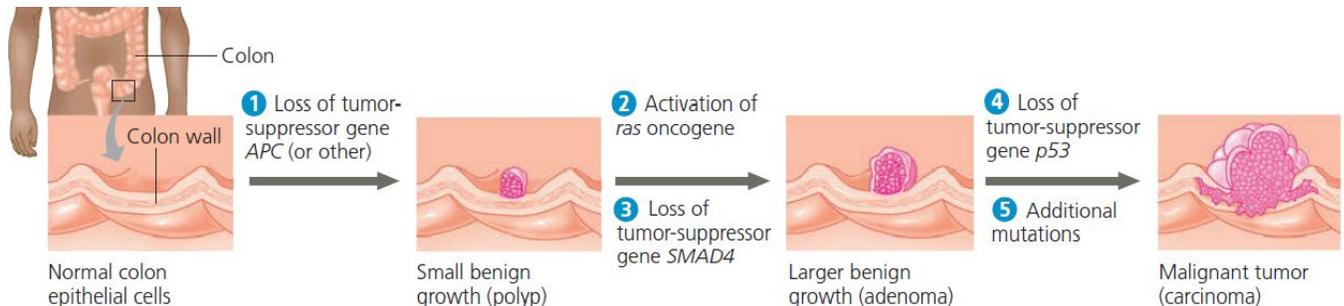


Figure 1: Tumor Turns Malignant (A.Campbell, 2018)

Picture illustrating a tumor development. Normal colon epithelial cells from the colon undergo a (1) loss of tumor suppressor gene (e.j. *APC*) and thereby become cancerous, leading to a small benign tumor (polyp). More mutations occur resulting in the (2) activation of *ras* oncogene and the (3) the loss of tumor-suppressor gene *SMAD4*. This leads to a larger benign tumor (adenoma). After the (4) loss of tumor-suppressor gene *p53* and (5) further additional mutations, the tumor gets big enough to becomes malignant (carcinoma) and undergoes metastasis.

- Mutation

Regarding the large scale of regulatory proteins, different pathways which end in the same result exist. These genetic changes occur on proto-oncogenes. They are genes coding for proteins that stimulate normal cell growth and division. Thus if they mutate, they become oncogenes and lead to cancerous cells (Fowler, Roush and Wise, 2013). They can lead to this result in 3 different ways, also shown in figure 2;

- **Translocation or transposition:** The gene moves to a new locus under new controls added by a new promoter, which gives an oncogene coding normal growth-stimulating protein in excess.
- **Gene amplification:** Giving multiple copies of the gene, and therefore again code for

normal growth-stimulating protein in excess.

Point mutation within either a control element or the gene: Results in either normal growth-stimulating protein in excess with a control element, or a hyperactive or degradation resistant protein with the gene. (A.Campbell, 2018[1])

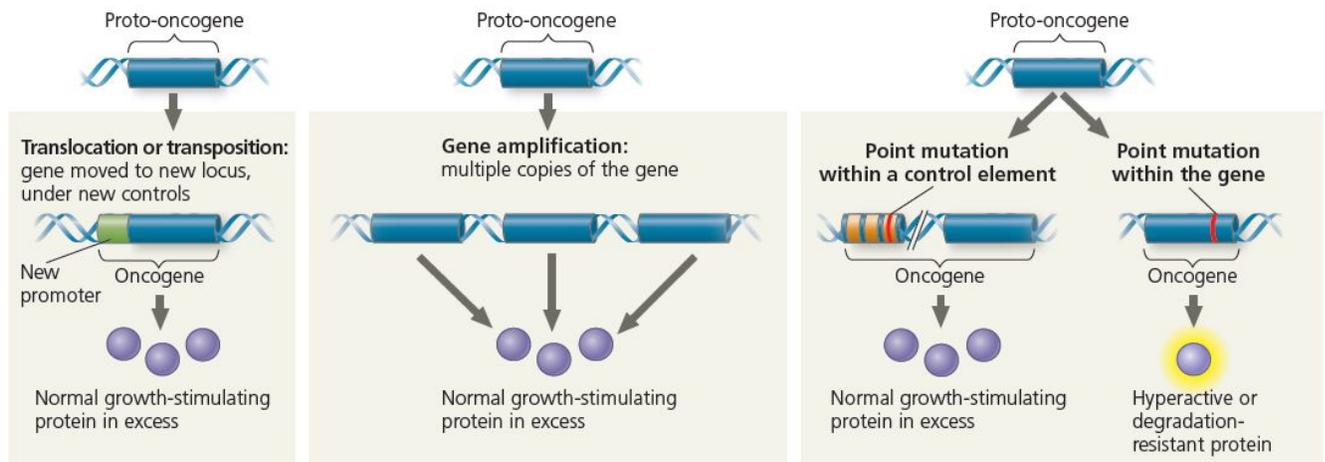


Figure 2: Genetic changes that can turn proto-oncogenes into oncogenes (A.Campbell, 2018) (1) The mutation make the proto-oncogene to moved to new locus with a new promoter which, added together, switch it into a oncogene coding normal growth-stimulating protein in excess. (2) The mutation amplifies the number of proto-oncogene which all of them code for one protein. (3) The mutation occurs directly in the control element of the proto-oncogene or the proto-oncogene itself. The first scenario leads to the same as the two previous pathway. The second one however leads to an hyperactive or degradation resistant protein.

Another possibility would be a genetic change upon a gene called p53. This gene is a tumor-suppressor gene, which promotes the synthesis of cell cycle-inhibiting proteins. Tumor-suppressor genes, in contrast with genes whose products promote cell division, inhibit the division when the cell needs to. Such a gene is vital for a cell and its growth and division. The p53 gene is important for activating multiple other genes, such as p21, which halts the cell cycle allowing the cell to repair its DNA. Thus, if p53 mutates, the cell cycle is not inhibited and the damaged DNA is replicated which leads to an increase of mutated-cell division (A.Campbell, 2018).

In addition to a lot of different possibilities of getting cancer, there is a lot of different types of cancer, including different types of leukemia.

What is Leukemia?

Leukemia is defined generally as the cancer of blood and is an entire group of multiple sub-categories of cancers, that affect the blood cells. It is possible for both adults and children to be diagnosed with these cancers which cause the production of many abnormal white and sometimes red blood cells in the bone marrow. In a healthy organism, at least three types of cells are detected in the blood: the red blood cells which transport the oxygen in the body, the white blood cells that protect and defend the body against diseases or infections and the platelets that have the function of clotting the blood (*Figure 3*). In case of leukemia the bone marrow produces a lot of abnormal white blood cells, called leukemia cells or blasts, and in excess, they cause a rapid and abundant increase of their number in the blood stream. This results in an increase in cell density and consequently the decrease of the number of healthy blood cells, as the multiplication of unhealthy cells is faster than the healthy ones.

The role of the bone marrow is to produce two types of stem cells, myeloid and lymphoid. These cells are going to mature and become actual productive platelets, or red and white blood cells. Myeloid stem cells differentiate into myoblasts, red blood cells and platelets, while lymphoid stem cells grow into lymphoblasts that, in turn, form three categories of white blood cells; B lymphocytes that make antibodies, T lymphocytes that are a support in helping B lymphocytes in their function and natural killer cells, that destroy tumour cells or other infections. The type of leukemia is named after the mutation of the stem cells into either in myeloid or lymphoid stem cells (*Figure 4*).

The symptoms of this disease are anemia, malnutrition, bleeding, bruising problems, tiredness, fever, and an increased risk of infections (American Cancer Society,.2018).

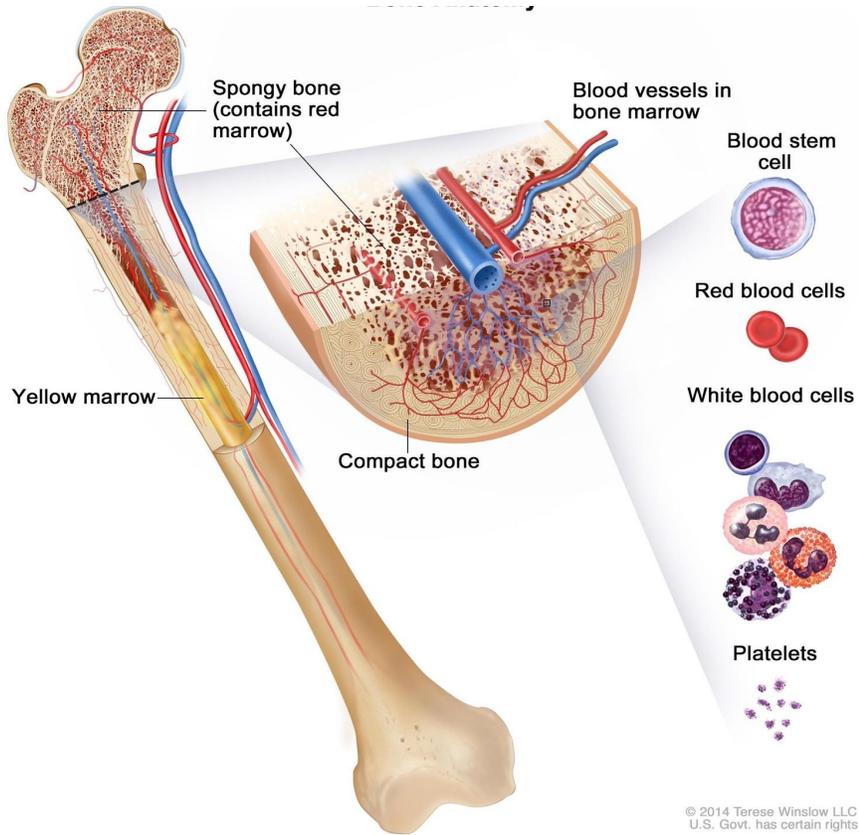
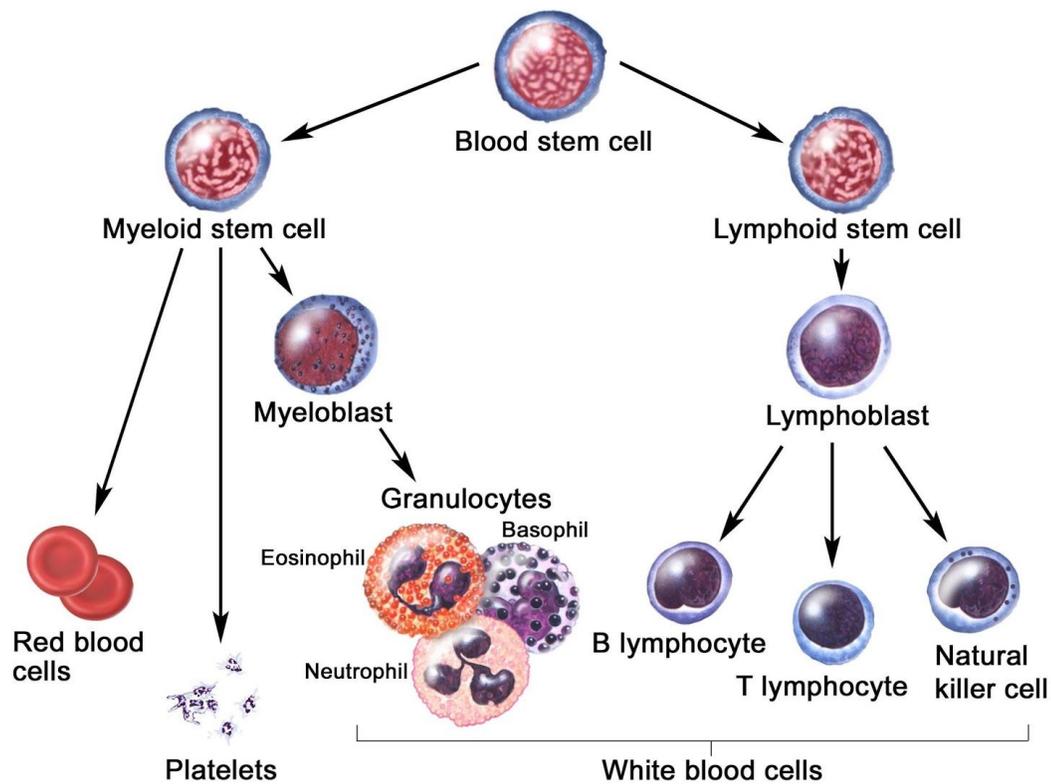


Figure 3: Bone anatomy. Glimpses of a Bone through to the blood vessels in the bone marrow. Blood vessels contain blood stem cell, red blood cells, white blood cells and platelets (National Cancer Institute, 2017).



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Figure 4: Development of blood stem cells into three kinds of mature cells. Blood stem cells first differentiate into two categories of stem cells : Myeloid stem cells and Lymphoid stem cells. Whereas Myeloids differentiates into red blood cells, platelets and granulocytes, lymphoid cells differentiates into B-cells, T-cells, and cytotoxic T-cells. Granulocytes, B-cells, T-cells and cytotoxic T-cells are regrouped as white blood cells (National Cancer Institute, 2017).

Types of Leukemia

There are four main types of leukemia and they are grouped in two ways. One way, is by how quickly the disease develops and gets worse and the other one is by the type of blood cell that is affected.

In the first case, the different types of leukemia are classified as acute or chronic. In acute leukemia the number of blasts increases rapidly before they mature and any immune function has developed. As a consequence, the normal functions are incapable to be done properly and the disease gets worse quickly. While in chronic leukemia blast cells also are present, only

some of the white cells are able to execute their basic functions. The rest of them are not fully mature, so they are not capable to fight infections, like the normal lymphocytes. Also, the number of blasts increases less rapidly than in acute leukemia, thus chronic leukemia gets worse gradually (Lisa Fayed, 2017) (Marjorie Hecht, 2016).

In the second case, it is known that leukemia lymphocytic or myeloid/ myelogenous takes its name, depending on which stem cell the cancer starts in. Myeloid leukemias start in early forms of myeloid cells, white and red blood cells, or platelet-making cells, while lymphocytic leukemia starts in the cells that become lymphocytes (Parks & Parks, 2010).

Combining these two different cases, time and type of cell, four basic types of leukemia arise:

- **Acute lymphocytic leukemia (ALL)**
- **Acute myeloid leukemia (AML)**
- **Chronic lymphocytic leukemia (CLL)**
- **Chronic myeloid leukemia (CML)**

Acute lymphocytic leukemia (ALL)

ALL is the most common cancer in children, responsible for around 25% of childhood cancers. Approximately 7,000 people at any age develop this kind of cancer each year with around 1,500 deaths, and two-thirds of those who die are adults.

This disease has quick progressed and it is characterized by a large number of immature white blood cells in the blood and bone marrow. While in the past it used to be a rapidly deadly disease, now people largely survive with chemotherapy (Lisa Fayed | Reviewed by Doru Paul, 2017).

It is both an aggressive and survivable type of cancer, and this motivates some scientists for more research. It is also considered as the simplest example in order to understand how chemotherapy works, by attacking the most rapidly dividing cells.

In an era where we have developed chemotherapy medications, having an aggressive cancer may, in a way, be considered "better" at least to treat the disease. In contrast, tumors that grow slowly, are less likely to be curable with chemotherapy. While this cancer unfortunately occurs in children, children often do much better than adults with the disease (Parks & Parks, 2010).

Acute myeloid leukemia (AML)

AML is the most common type of acute leukemia. It arises when the bone marrow starts to make blasts, which are cells that have not completely matured, and later develop into white blood cells. However, these cells do not fully develop either and they are not able to deal with an infection. Also in some cases of AML, the bone marrow may produce abnormal red blood cells and platelets. The number of these abnormal cells increases really fast, and the abnormal cells begin to crowd out the normal white blood cells, red blood cells and platelets that the body needs. Later, the cancer spreads to the blood from the bone marrow and then it has a lot of chances to spread anywhere else in the body including the organs. It is more common in men than in women and occurs in both adults and children with an occurrence of 32% from age 1 to 19 years old (American cancer society, 2017)(Parks & Parks, 2010).

One of the main things that differentiates AML from the other forms of leukemia, is that it has eight different subtypes, which are based on the cell that the leukemia developed from (American cancer society, 2017). In simpler words, the subtype of AML is determined by the stage of development that the cell stops at. (see appendix)

Chronic lymphocytic leukemia (CLL)

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults in the Western countries and is detected on adults over the age of 55 years old. Sometimes it occurs in younger adults, but never in children.

It starts from cells that are going to be specific white blood cells (*lymphocytes*) in the bone marrow. These cancer cells are gathering slowly over time and are more mature than those seen in acute leukemia. Because of this they are capable to do some functions as a normal lymphocyte. As a result, there are no symptoms, in most of cases, for at least a few years. Thus the patient would not notice the dawn of the disease in order to treat it in the early stages. Consequently, in time, the cells can spread to other parts of the body, including the lymph nodes, liver, and spleen. CLL is different than other types of leukemia because the genetic mutation not only causes an uncontrolled growth of lymphocytes in the marrow, but it also

results in cells that do not follow the normal pattern of natural cell death. This leads to an increased number of CLL lymphocytes in the bloodstream (Karen Raymaakers, 2018).

Chronic myeloid leukemia (CML)

Chronic myeloid leukemia (CML) or *chronic myelogenous/granulocytic leukemia* is a clonal disorder that develops slowly, in certain blood-forming cells of the bone marrow. In CML, the blood stem cells become a type of white blood cell called granulocytes. In the case of leukemia, this type of cell becomes abnormal and does not turn into healthy white blood cells. Also, these leukemia cells being generated are gathered in the bone marrow and the blood respectively, so there is a restricted space for the healthy cells (white, red and platelets). Consequently, the organism is more vulnerable to infections, anemia, bleeding and in the most extreme cases, thrombosis. It mostly occurs in adults but a very small number of children also develops chronic myeloid leukemia. In addition, although CML is a slowly growing leukemia, it can change into an aggressive fast-growing acute leukemia, which is hard to treat (National Cancer Institute, 2017).

From several researches, it becomes known that most people with CML have a specific gene mutation called *Philadelphia chromosome (Ph1)*. Every cell contains genetic material (DNA), which is grouped as chromosomes, that defines how the cell looks and acts in the body. But a small chromosomal translocation can cause CML. So, when a piece from the long arm of chromosome 22 and 9 cut off and exchange places, the Abelson (ABL) from chromosome 9 oncogene transfer to an area of chromosome 22 termed the breakpoint cluster region (*BCR*). This, in turn, results in the the formation of a specific gene called BCR-ABL on chromosome 22 where the piece of chromosome 9 attaches (*Figure 5*). This new modified chromosome is called *Philadelphia chromosome*. This leads to the production of a protein called *Tyrosine kinase*, that causes the disordered myelopoiesis found in CML, meaning the false production of bone marrow and blood cells. Following that, the protein acst in the bone marrow turning many stem cells into leukemia stem cells. These leukemia stem cells, differentiate into blasts /leukemia cells which divide, and go into the blood. In time, the cells can also be transferred to other parts of the body, including the spleen. Moreover, studies show that this chromosome is not hereditary, so the parents cannot pass it to their children (National Cancer Institute, 2017).

Furthermore, it is worth noting that only 10% of leukemias are CML. However, this does not make it less severe or detrimental.

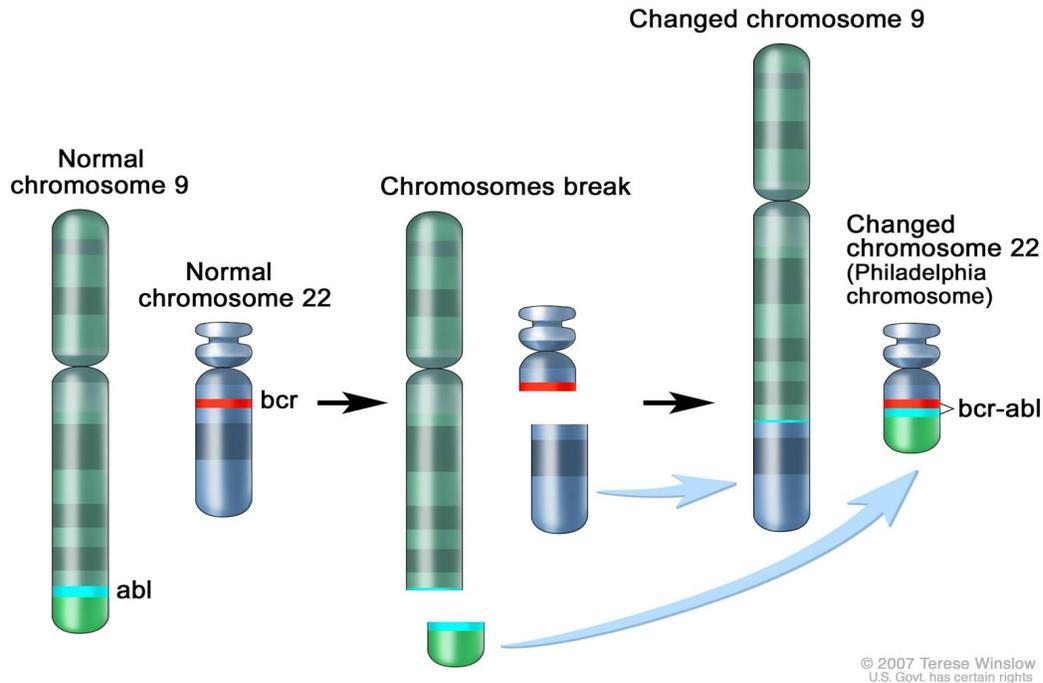


Figure 5: Creation of the Philadelphia chromosome by a Crossing-Over. The normal chromosome 9 has the gene *abl* and chromosome 22 has the gene *bcr*. When these two chromosomes break and cross-over, the gene *abl* in Chr 9 is replaced by a fragment of the Chr 22 determined by its breaking cluster region or BCL. At the end, the two chromosomes have interchanged their genes and the Chr 22 is now termed Philadelphia chromosome containing a new modified gene called *bcr-abl* (National Cancer Institute, 2017)

Basics of mathematical modeling

The following chapter is based on the knowledge found in (Marion, 2008) and (Pfenninger, 2013).

What is a Mathematical Model?

In the real world there are problems where a solution has yet to be discovered. It might be that there is a lack of information on the subject, or it could be the complexity of the problem.

A mathematical model is a, often, simplified perception of reality. In a mathematical model, only the most important aspects of the problem are included. This can help gain insight in the problem and understand core mechanisms of it. A mathematical model can thus solve or gain insight into some of the problems that are otherwise too complicated to understand.

There are several reasons why mathematical models can be beneficial for finding a solution. Mathematics is a very precise language and it is not possible to break the rules. It is only possible to manipulate the rules to make them apply for your special case. Modelling a system can be quite restrictive. It is generally not possible to account for everything when making a model, thereby forcing you to identify and only use the most important aspects. The exercise of identifying these aspects will give an overview and clarity of the problem. In general, a model can be used to represent, analyze, gain insight or make predictions of an outcome for a system. It could be that you are interested in modelling the concentration of a solution in a liquid. The system would consist of the input of a solution, S_{input} , and a variable being the concentration, C_{liquid} , in the liquid. If we then assume that the change in concentration is instantaneous when there is an input of solution, the system can be described as

$$C_{liquid}(S) = \text{Some function of } S_{input} = f[S_{input}]$$

If there is a set of data with the input and corresponding concentration, those values can then be processed to find how the function $f[S_{input}]$ would look. It could be that when the data is plotted, it gives a linear relation and the model would look as following

$$C_{liquid}(S) = p \cdot S_{input}$$

Where p is a model parameter, calculated by doing regression on the data, finding the average change in concentration, C_{liquid} , per input, S_{input} . The bar above signifies that it is the mean of

$$\sum \frac{C_{liquid}}{S_{input}}$$

$$p = \overline{\left(\frac{C_{liquid}}{S_{input}} \right)}$$

This model is a static model, meaning that for every S there is a unique C . A characteristic for a static model is that the change is immediate. Thus, a static model will only inform you on the magnitude of a change, not giving information on how it changed. Another type is a dynamic model. This type of model generally describes the rate of which C would change when there is a certain input of S .

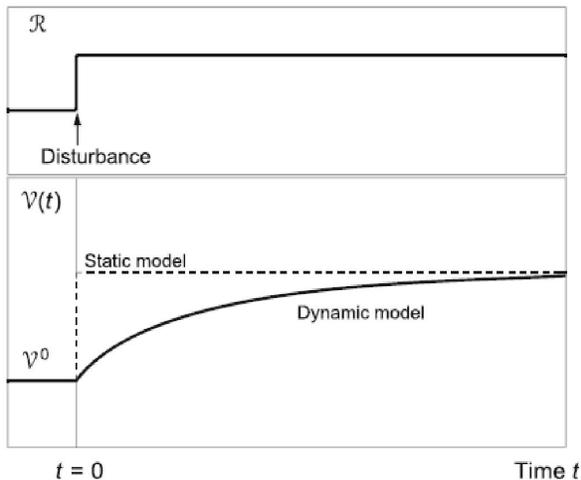


Figure 6 – The \mathcal{R} is a static model and the $v(t)$ is a dynamic model, Pfenninger, 2013[4]

Figure 6 visualizes the difference between a static and dynamic model, with \mathcal{R} representing a static model and $v(t)$ representing a dynamic model, where the dynamic model changes gradually over time and the static model does not.

In the different model types, there is also a difference on the kind of result that the model gives. A model can either be deterministic, which means that a certain input will always give the same output. This could be the example of the concentration in a liquid, where the same amount of solution added to the liquid, will give the same concentration. Instead, a model can be stochastic where the same input doesn't always give the same output. This type of model is more statistical, predicting a distribution of possible outcomes.

How Do You Create a Model?

To create a model over a system, the system must be well-defined, and the focus of the model has to be clear. There must be some boundaries for what to include in the model and then find the equations for it.

1. The first step is to have a well-defined research question. This will make it easier to set the boundaries for the model since the scope and focus of the model will be clear. If it is not clear what is being modeled, it is near impossible to know what limitations to set.
2. The second step is to define the boundaries. It is here that you define what exactly is to be modeled within the research question.

3. The third step is to define the factors that are included in the model. The factors are the most important aspects of the real-world problem that should be included. The model should only include the minimum number of factors while still adequately describing the system. Excess factors or factors that aren't relevant should not be included. They will convolute the model by making it more confusing.
4. The fourth step is to make assumptions on how the different factors function. It could be the decrease of a population might only be observed, but the exact intricacies of the decrease is unknown. To model this decrease, assumptions would be made on how the decrease happened and they would fit with the factors.
5. The fifth step is to find the equations. A mathematical model is a series of equations that interact in some way. Since mathematical modelling started a plethora of equations have been made. To find the equations for the model, researching existing models and altering them to fit the system is a way to do it. Making your own equations based on the factors and assumptions is also an option. When the equations are made or found, the model is done. It might be that the model has led to new boundaries or overcome some of the boundaries set. The steps should therefore be revisited to optimize the model.
6. The sixth step is to test the model. A model can be accurate in only a certain range of values. The test can be done by fitting the model to some data and find what ranges the model is accurate.

General methods used by biologists to count blood cells

Before creating a model, it is mandatory to have a precise overview of the biosystem and be aware of how the outcoming data from the model would be able to be used in the labs. In biology, unlike mathematics, advanced technicians and doctors use several methods like, differential or complete blood counting (CBC) to measure the amount of white blood cells in the body. Usually, differential counting is a procedure included in CBC. The white blood cells can be determined manually in the laboratory or more fast through an automatic analyzer (Blumenreich, 1990). The absolute count (CBC) is applied more often after chemotherapy or bone marrow transplantation to evaluate the overall number of cells.

The leukocytes differential counting is a complicated method and requires the blood samples to be analyzed in the laboratory because, doctors have to count one hundred cells and classify them manually. However, this method is not always valid. It has some statistical and distributional errors related to the cell identification and interpretation. Comparing to the manual method, the automated method is able to count thousands of cells with less possible errors (Buttarelli & Plebani, 2008). For instance, a medical doctor can use the differential count to numbers a specific type of white blood cells to find their death or renewal rate and CBC method in order to have a general view of the normal range for the number of cells.

How equations arise from Biology

Mathematical model is still a new area in the research of biology facts. Correspondingly, there are question marks that remain unsolved between these two fields. As biology takes in consideration all the factors that could affect the subject, modeling is more difficult to create a complex set. There are three important perspectives. Firstly, the biological assumptions used in mathematics should present a precise amount of cells. Instead of suggestions about the growth of cells, it is better to analyze the model and test it through simulations. Secondly, a model with a limited number of parameters describes better the interplay between them. The most important of them should be used in order to have a simple and valid mathematical model. Thirdly, a complex set is more complicated in terms of stability because of the competition for the limited space between hematopoietic stem cells (HSC) and leukemic stem cells (LSC) in the bone marrow. As leukemia is a progressive disease, LSC have a higher rate of division than the HSC. (MacLean, A. L., Celso, C. L., & Stumpf, 2016).

The proliferation rate of HSC can be estimated using tests as bromodeoxyuridine (BrdU), Histone H2B green fluorescent protein (H2B- GFP), and Carboxyfluorescein succinimidyl ester (CFSE) (MacLean, A. L., Celso, C. L., & Stumpf, 2016). BrdU can be introduced in DNA in the S-phase of the stem cell cycle. The proliferating cells assimilate the BrdU and are identified with anti-BrdU when applying techniques as flow cytometry, immunofluorescence, immunohistochemistry. Flow cytometry is a cell analysis technique that can measure the size and the number of the cells by cell suspension. Immunofluorescence is another technique which uses the antibody to create fluorescent dyes in order to count HSC (Levkoff et al., 2008). The last one, immunohistochemistry analyses the components of a cell as proteins or

macromolecules by using the fluorescent microscope(O’Hurley et al., 2014).

The Histone H2B green fluorescent protein (H2B- GFP) test determine HSC in two colors, red and green, due to the GFP antibody that is jointed with H2B (Challen & Goodell, 2008). Carboxyfluorescein succinimidyl ester (CFSE) is used to count the lymphocyte division. The stem cells are labeled with CFSE and when HSC divides CFSE become half for each of the progenitors. As a result, the fluorescence is less and can be counted via flow cytometry(Quah & Parish, 2010).The estimation can be reliable if the system does not have any perturbations as infections, etc. (MacLean, A. L., Celso, C. L., & Stumpf, 2016).

The model

Instead of having a problem that we want to gain insight into, we are going to take an existing model and analyses it as though we were going to make it ourselves. The model, (*figure 7*), in question was made to gain insight into the relevance of the stem cells in CML. It has been taken from the article *“Successful Therapy Must Eradicate Cancer Stem Cells”*, by David Dingli and Franziska Michor .

Hematopoietic stem cells (normal stem cells) have the potential for unlimited cell reproduction. That same mechanic also exists in leukemic stem cells. Leukemia regroup mutated hematopoietic stem cells (tumor stem cells) that are no longer producing fully functionally cells (differentiated tumor cells). If tumor stem cells are the cells that are producing the differentiated tumor cells, then a therapy that is only targeting the produced cells would fail. A solution must target the origin of a problem in order to be a permanent solution.

To explain how the model is set up, we will follow the first three steps of creating a model. Specifics and the rest of steps will be explained later in the report.

- 1) The first step is to have a well-defined research question, to define what is to be modeled. The model is supposed to investigate the target and how to eradicate all the tumor cells to totally cure a patient. To define what is to be modeled a system is made.

The system is therefore the bone marrow where the stem cells reside.

- 2) Define what the boundaries are. How large is the system going to be and how many mechanics are going to be included? It is the importance of eradicating tumor stem cells, so only mechanics directly related should be included. The stem cells themselves are the cause, so they should be included. It is the differentiated tumor cells that are the cause of death, so they should be included. It is also only the differentiated tumor cells that the doctors can measure to gain insight in the cell count for the tumor stem cells since the stem cells are in the bone marrow.
- 3) Determine what factors that is to be included. The system is now consisting of some normal stem cells and some tumor stem cells. Stem cells can renew themselves, so a self-renewal rate should be included. Both normal and tumor stem cells are producing differentiated cells. The production rate of the differentiated cells should therefore be included. All cells are going to die at some point, so a death rate for each type of cells should be included.

In the bone marrow there are some inhibitors that cause the normal stem cells not to proliferate indefinitely. Tumor stem cells has a risk to not be inhibited is the same way as normal stem cells, so an inhibitory factor should be included for the stem cells.

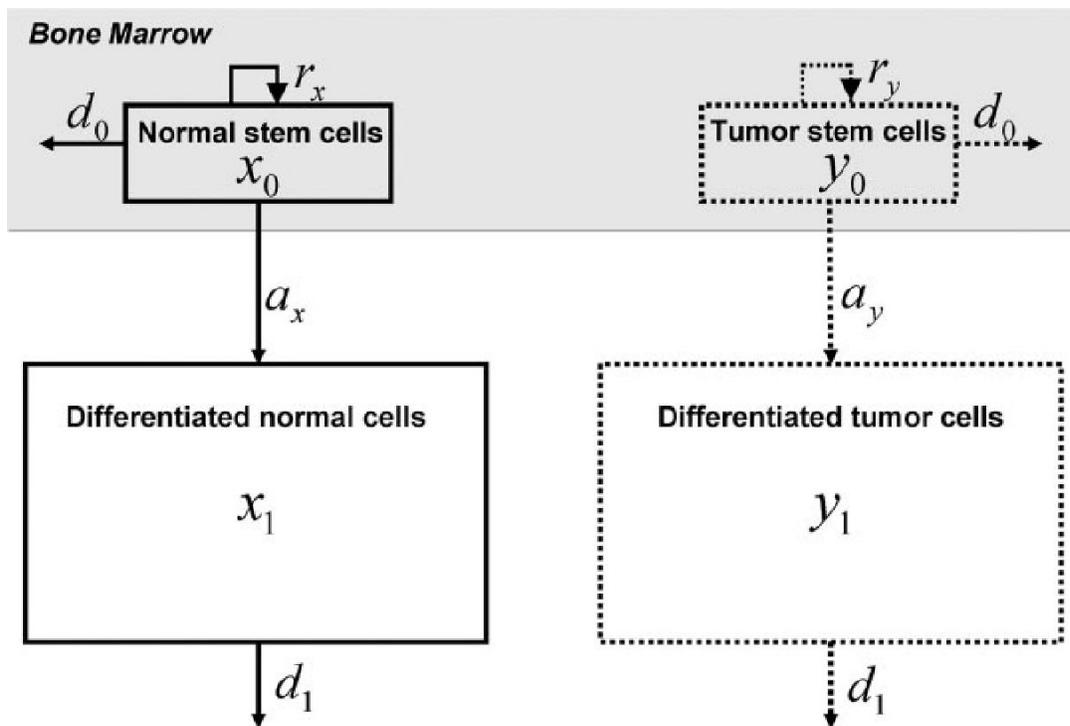


Figure 7 - A model describing the biological system that is being analyzed by using the factors included [5]. Here all the x_0 , x_1 and y_0, y_1 follow mathematical rules stated by the understanding of the biosystem. d_0 is the death rate for all stem cells

while d_1 is for all mature cells. r_x and r_y are the self-renewal rate of cells, how fast they create clones of them. Finally, a_x and a_y are the differentiation rate, so how fast stem cells turns into mature cells.

The factors are all the different aspects included in the model. Here we list all the factors in the model and explain why each factor has relevance to what the model wants to achieve. $x_0, x_1, y_0, y_1, r_x, d_0, d_1, a_x, a_y$ and c_x (Dingli and Michor, 2006). r_y and c_y will be factors we'll state ourselves. We will also change the others, but after adding the treatment. Moreover, we know that from one assumption $c_y = c_x/2$

the sign representing the factor	A description of what the factor is.	at t_0
x_0	The amount of normal hematopoietic stem cells	$2 \cdot 10^4$ cells
x_1	The amount of differentiated normal cells	$2.11 \cdot 10^{11}$ cells
y_0	The amount of tumor hematopoietic stem cells	1 cells
y_1	The amount of tumor differentiated cells	0 cells
r_x	The self-renewal rate of normal stem cells per day	0.005 cell/day
r_y	The self-renewal rate of tumor stem cells per day	r_y cell/day
d_0	The death rate of both normal stem cells and tumor stem cells per day	0.002 cell/day
d_1	The death rate of both normal differentiated cells and tumor differentiated stem cells per day.	1 cell/day
a_x	The rate of which normal differentiated stem cells are produced per day	$1.065 \cdot 10^7$ cell/day
a_y	The rate of which tumor differentiated cells are produced per day	$1.065 \cdot 10^7$ cell/day

c_x	A dimensionless parameter that introduces a crowding effect for healthy stem cells per cell in the bone marrow	$0.75 \cdot 10^{-4}$
c_y	A dimensionless parameter that introduces a crowding effect for tumor stem cells per cell in the bone marrow	c_y

Table 1 - A table listing the different factors that is included in the model. A small description of the function of the factor and if the factor has a set value, that value is displayed. Only biological values for healthy components are shown. Values taken from (Dingli & Michor, 2006).

The number of hematopoietic stem cells x_0 and y_0 .

A stem cell has three main properties. They are capable of self-renewal and dividing into another type of cell. Stem cells are unspecialized. Stem cells can give rise to specialized cells. Being unspecialized means stem cells does not have any tissue-specific structures. Stem cells aren't capable performing specific task, such as retracting a muscle to give a limp functionality. The stem cells, instead, differentiate, giving rise to specialized cells that can perform the task the stem cells aren't able to do. If the stem cell is mutated and is cancerous, the cells differentiated are also mutated. This can cause the differentiated cells not to be fully developed, causing the body not to operate fully since it doesn't have the cells it needs.

Stem cells can self-renew and proliferate for a long period of time, meaning the cell can divide into one or two identical daughter cells. Mutated stem cells most likely have the same property.

A mutation could cause the stem cell to self-renew at twice the rate of a healthy stem cell yet be able to self-renew for the same period of time.

By having both the healthy and tumor stem cells as factors, the model should be able to indicate the effect a treatment targeting the tumor stem cell would have on the system. The stem cells are the dominating factor in the model, giving rise to all the other factors. The model represents the biological system surrounding the stem cells. Change in the cell number of the stem cells, both healthy and tumor, will influence some of the surrounding factors. (Dingli & Michor, 2006)(Bethesda, MD: National Institutes of Health, U.S. Department of Health and Human Services, 2016, chapter 5)

The number of differentiated cells, x_1 and y_1 .

The differentiated cells are a simplification of all the cells that are differentiated from the stem cells. By including the differentiated cells, the model will be able to give insight into the effect that change in the stem cell count has on the number of differentiated cells. The stem cells reside in the bone marrow making it difficult to measure the cell count. It is substantially easier to measure the differentiated cell count, which can be done by various blood samples. The model gives a ratio between the number of either healthy or tumor stem cells and the number of healthy or tumor differentiated cells and measure the allele burden from which the cell counts. By having these as factors it will give insight for doctors what chance they can expect from a treatment targeting the tumor stem cells by measuring the tumor differentiated cell number. (Bethesda, MD: National Institutes of Health, U.S. Department of Health and Human Services, 2016, basics)

Self-renewal rate of stem cells per day, r_x and r_y .

Both the healthy stem cells and the tumor stem cells are capable of self-renewal. They can divide and renew for long periods. The self-renewal process is important since it is one of the mechanics that allow the tumor stem cells to outcompete the healthy stem cells. If the self-renewal rate of the tumor cells is greater than that of the healthy stem cells, the tumor stem cells will outgrow the healthy cells and they will become majority of cells. The inclusion of self-renewal as a factor will make the model capable to predict whether targeting the self-renewal rate directly will have a meaningful impact of the dominance of the tumor stem cells. (Bethesda, MD: National Institutes of Health, U.S. Department of Health and Human Services, 2016, chapter 5)

The death rate of stem cells per day, d_0

The death rate of stem cells is the expected period in which the stem cells can differentiate and renew. The cell cycle of a stem cell is quite a lot longer than that of a differentiated cell. A longer cell cycle allows the cell to divide an indefinite amount of times. By including death rate as a factor in the model, it will be able to make predictions on how large an effect targeting the death rate will have on the accumulation of differentiated tumor cells. If the death rate is split into

accounting separately for healthy and tumor stem cells, it will be possible to make predictions on the effect a treatment that affects both the healthy stem cells death rate and the tumor stem cells death rate. It should be possible from the model to make assumptions on how much the increase in the tumor cell death rate should be compared to the death rate of the healthy cells. (Bethesda, MD: National Institutes of Health, U.S. Department of Health and Human Services, 2016, chapter 5)(Dingli & Michor, 2006)

The death rate of differentiated cells per day, d_1 .

The death rate, d_1 , is the number of the differentiated cells that die per day. If the death rate is not included as a factor, the amount of differentiated cells would only be able to grow.

It is not feasible to measure the cell count of the stem cells directly because, that would require a sample directly from the bone marrow. Instead, blood cells will be measured to indicate the number of the stem cells. In this model it has been simplified to differentiated cell, all the cells that stem cells can divide in to. This simplification is still relevant (Dingli & Michor, 2006).

The rate of which differentiated cells are produced per day, a_x and a_y .

The rate of produced differentiated cells is included as a mean of quantifying and representing how the differentiated cells is produced. This factor could have been hidden and been written as the number of differentiated cells as a function of the number of stem cells. By having the production rates as factors, the model will be able to see the direct impact a change in the rates will cause in the number of differentiated cells. It could be that it would be more effective to lower the production rate of differentiated tumor cells to treat the cancer symptoms.(Dingli & Michor, 2006)

- Assumptions

Throughout our analysis of the model, we noticed assumptions made by the author to simplify their calculation and results. Again, these assumptions are possible to make with the knowledge that such a hypothesis gives a close enough result as expected from a simple model.

These are the following assumptions.

First of all, “we assume that normal and tumor stem cells as well as normal and tumor differentiated cells have the same respective death rates” (Dingli & Michor, 2006, page 2) which means that $d_{x0} = d_{y0}$ and $d_{x1} = d_{y1}$. This assumption is made for the basic form of the mathematical model. Indeed, in the real biosystem, d_{x0} is not equal to d_{y0} nor $d_{x1} = d_{y1}$ because cancer cells do not go through programmed death like apoptosis, or usual death by time, they tend to have a different lifespan (Sun and Peng, 2009). If $d_{x0} > d_{y0}$, then all the tumor stem cells will have an inhibited proliferation factor. This is clearly explained through the following simulations. If the death rate of tumor cells is 0 then the amount of tumor stem cells and mature tumor cells will increase significantly without inhibition from 1 to $7 * 10^8$, as it is shown in *figure 8*.

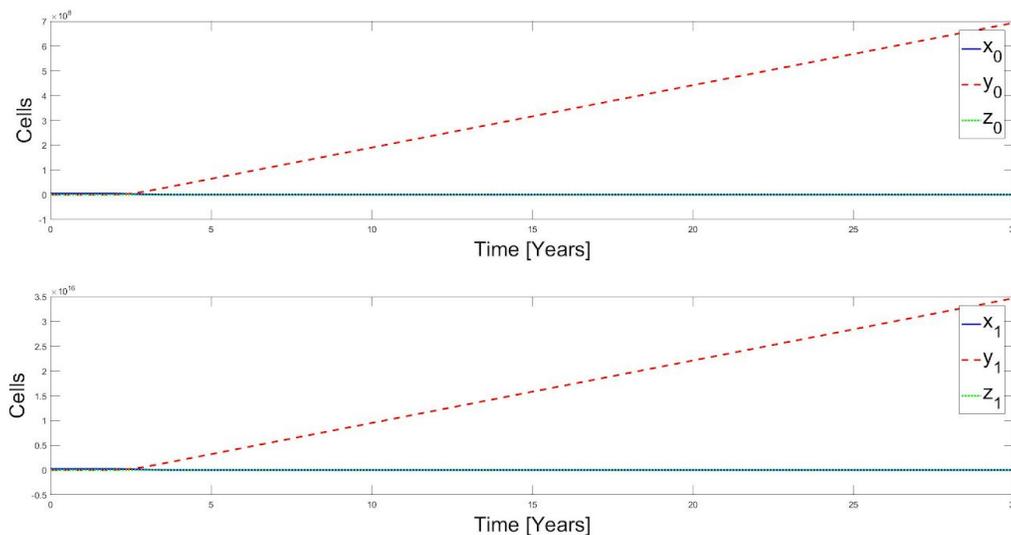


Figure 8 - simulation of CML in a body system when, $d_{y0} = 0$

However, if we equalize the death rate of the healthy stem cells and the tumor stem cells, using the model, it is obvious that there is bigger competition between them. After 5 years, since the tumor cells are more competitive, requiring more and more space, they will eventually take over the healthy ones, even though they both have the same death rate. Figure 9 below demonstrates the biosystem under this conditions.

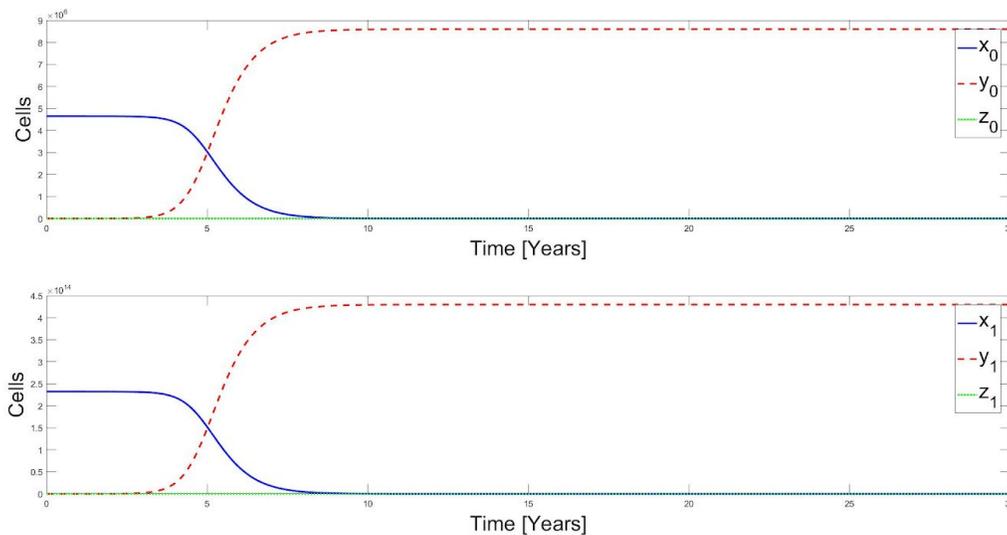


Figure 9 - simulation of CML in a body system with the same death rate for both tumor and healthy stem cells/cells.

They die when they do not have any possibility to sustain themselves, or they are too mutated to divide. Stem cells can live for months, years and sometimes for an entire lifetime (*Stem Cell Basics II.* | stemcells.nih.gov, no date), while normal cells have a shorter life. As explained below, these factors could be assigned with individual values but because the differences between d_{x0} and d_{y0} are not important in the case of a basic model, they do not consider it.

Secondly, “Normal stem cells are assumed to divide every 200 days and to die every 500 days” (Dingli & Michor, 2006, page 2) which means that $r_x = 0.005$ cells/day and $d_0 = 0.002$ cells/day. Why these values? They’re average. Since the lifespan and the rate of division of the stem cells vary within a large range, because these are stochastic values, taking the average will represent the reality to a fair extent.

“For the purpose of the analysis, normal and tumor stem cells differentiate at the same rate” (Dingli & Michor, 2006, page 3) or $a_x = a_y$. They almost do. Mutated stem cells do indeed interact with the differentiation of stem cells into cells. However, they differentiate into the heterogeneous lineages that comprise the tumor. Therefore, the mutation only highly affects the offspring, not the rate. Again, this has been set to make the result as easy and true as possible.

“Therapy change only one parameter at a time (so only the death rate or growth rate or mature rate...” (Dingli & Michor, 2006, page 2) Obviously the therapy affects more than only one parameter, which could be death rate, self-renewal rate of normal cells or tumor cells and such. However, to be able to find out which parameter should be targeted during the

therapy, changing one parameter at a time, is the most efficient way to understand it for the sake of clarity. For instance, a possible change is the self-renewal rate of the tumor stem cell, r_y . Throughout the figures 10, 11, 12 and 13, the increase of r_y leads to faster overtake of the tumor stem cells than when there is no modification, so $x_0 < y_0$. This has as a result, the early death of the healthy cells.

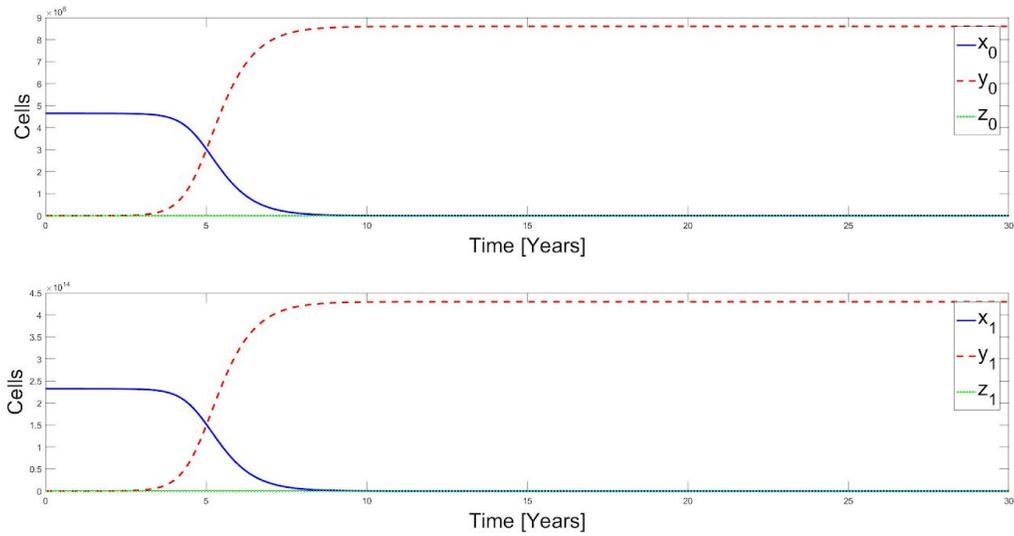


Figure 10 - simulation of CML in a body system with no treatment nor modifications.

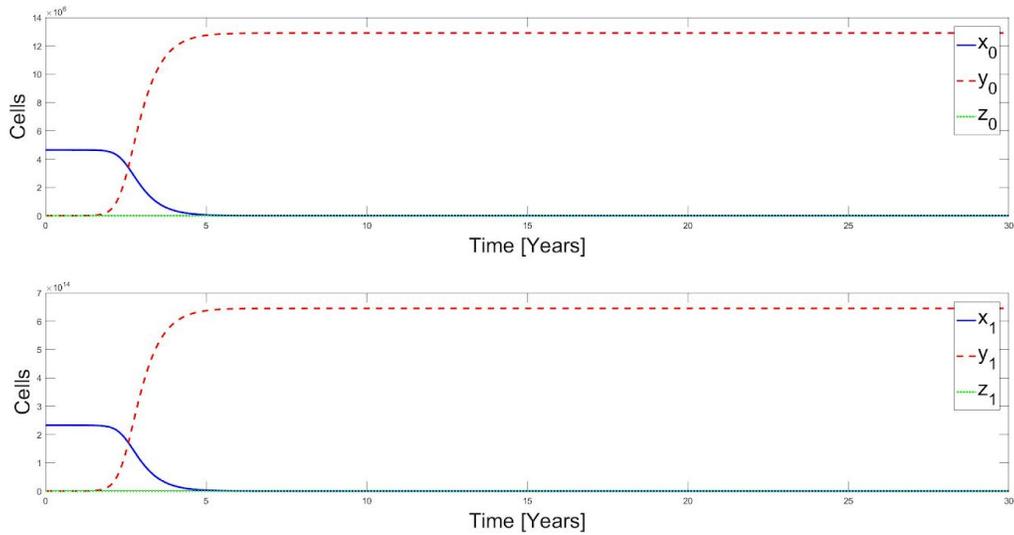


Figure 11 - Simulation of CML in a body system with a tumor stem cells self-renewal rate multiply by 1.5

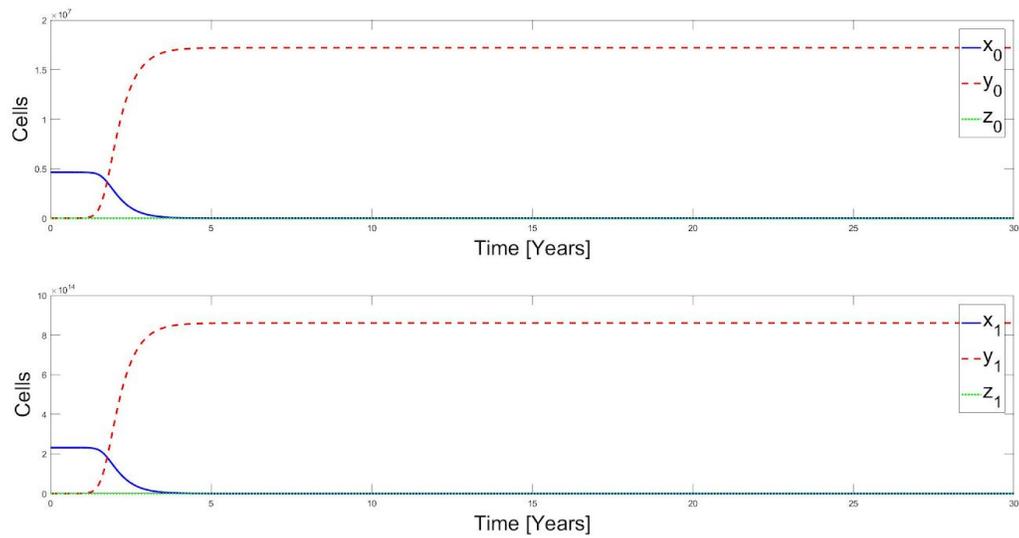


Figure 12 - Simulation of CML in a body system with a tumor stem cells self-renewal rate multiply by 2.

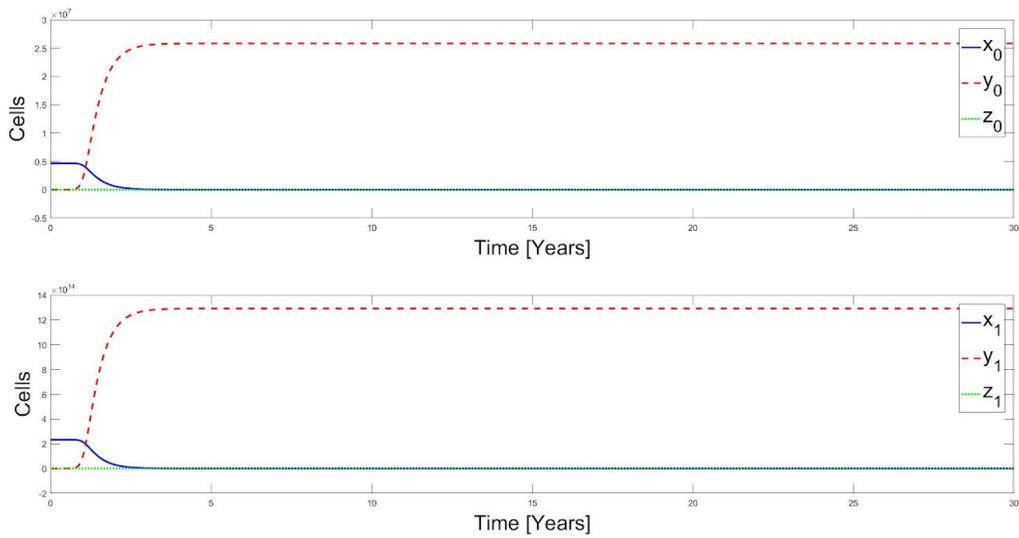


Figure 13 - Simulation of CML in a body system with a tumor stem cells self-renewal rate multiply by 3.

“Therapy decreases parameter linearly” For clarification, this assumption follows the same point of the previous one.

All these assumptions are legitimate. They’re not distorting the world that is being simulated.

However, the first assumption stating that $d_{x0} = d_{y0}$ and $d_{x1} = d_{y1}$ could be avoided. Indeed, finding these information could be difficult but not impossible if they could have the access to these data. New assumptions can be make while adding new factors.

- *Analysis of the model*

The equations making up the model are

$$\dot{x}_0 = (r_x \phi - d_0)x_0 \quad (1)$$

$$\dot{y}_0 = (r_y \psi - d_0)y_0 \quad (2)$$

$$\dot{x}_1 = a_x x_0 - d_1 x_1 \quad (3)$$

$$\dot{y}_1 = a_y y_0 - d_1 y_1 \quad (4)$$

They are found by examining the biological system. \dot{x}_0 is the change in x_0 , this will be explained later in the chapter. \dot{x}_0 is found by dissecting what it represents. There is a production of cells that is the total cell count for the normal stem cells, how many times they reproduce and how they are affected by their environment, $\text{prod}(x_0) = r_x * \phi * x_0$. There are some cells that die, which is the death rate times the total number of stem cells, $d_x * x_0$. The change in stem cells, x_0 , is the number of cells that produced minused with the number of cells that die, $\dot{x}_0 = \text{production} - \text{cell death} = r_x * \phi * x_0 - d_0 * x_0$

\dot{x}_0 , \dot{y}_0 , \dot{x}_1 and \dot{y}_1 all denotes time derivatives for their given function, for example $\dot{x}_0 = \frac{dx_0}{dt}$. A time derivative (\dot{x}_0) is the rate at which its integrated function changes (x_0). It is not necessary to know the integrated function, it is only required to know the number of cells present at the start of using the model. If the start value is known, the rate of change will be able to tell how the value grows or decrease. It is assumed there is one tumor stem cell at t_0 so $y_0 = 1$ and no tumor mature cell at time t_0 so $y_1 = 0$. This is because the model assumes to start when leukemia starts. As we have discussed above, the stem cells divide into multiple types of cells, including a clone of the cell that is dividing. Under this self-renewal, there can occur a mutation, but that is not considered in the model. It only focuses on when the first mutation has occurred and how it develops. But not having a mechanic that converts normal stem cells to tumor stem cells, the model must start at $y_0 = 1$.

If it is assumed that the model starts at the same time as the cancer, y_0 will be one cell. For the normal stem cells, self-renewal rate and death rate, the start value is based upon prior research. It is assumed that the samples are taken at hemostasis. The crowding factor can then be calculated, by making $\dot{x}_0 = 0$ and solving for x_0 .

$$0 = \frac{r_x x_0}{1 + c_x x_0} - d_0 x_0$$

$$d_0 x_0 = \frac{r_x x_0}{1 + c_x x_0}$$

$$d_0 = \frac{r_x}{1 + c_x x_0}$$

$$d_0 (1 + c_x x_0) = r_x$$

$$1 + c_x x_0 = \frac{r_x}{d_0}$$

$$c_x x_0 = \frac{r_x}{d_0} - 1$$

$$x_0 = \frac{1}{c_x} \left(\frac{r_x}{d_0} - 1 \right)$$

since it would mean that the cell number for x_0 isn't changing.

The bone marrow has limited space for stem cells to reside since it is a closed environment. The stem cells are not free to grow as much as possible. At a certain point, an equilibrium is achieved. This is called homeostasis, where the optimal number of stem cells for optimal functionally occur. To introduce homeostasis in the model, the function ϕ is made.

$$\phi = \frac{1}{1 + c_x(x_0 + y_0)} \quad (5)$$

The c_x is the biological restraint for how many stem cells there can be in an area of the bone marrow. It is called the crowding effect. $x_0 + y_0$ are the total amount of normal and tumor stem cells and it is assumed that the crowding effect affect x_0 and y_0 equally.

The limited space also affects the tumor stem cells and they will reach homeostasis. The degree of which they are affected is not necessarily the same. The function ψ is introduced for the equilibrium to occur for the tumor stem cells.

$$\psi = \frac{1}{1+c_y(x_0+y_0)} \quad (6)$$

c_y is the crowding restraint for the tumor stem cells.

It is the crowding factors, c_x and c_y , that dictates when hemostasis is reached. If the tumor stem cells crowding factor is smaller than the crowding factor for the healthy stem cells, the cancer will grow, $c_x > c_y$.

By diving with the total stem cell count, the functions ϕ and ψ introduce competition between x_0 and y_0 . The system starts in hemostasis and then a mutation occur that alters $r_x \rightarrow r_y$ or $c_x \rightarrow c_y$ for the mutated cell type. If $r_y > r_x$ or $c_x > c_y$, then \dot{y}_0 is positive and y_0 grows. As y_0 grows, \dot{x}_0 turns negative and x_0 decrease, since ϕ decrease with the increasing y_0 .

$$\begin{aligned} \dot{x}_0 &= (r_x \phi - d_0)x_0 \Leftrightarrow \\ \dot{x}_0 &= \left(\frac{r_x}{1+c_x(x_0+y_0)} - d_0 \right)x_0 \Leftrightarrow \\ \dot{x}_0 &= \frac{r_x x_0}{1+c_x(x_0+y_0)} - d_0 x_0 \end{aligned}$$

So y_0 grows only if $r_y * \phi > d_0 \Leftrightarrow \frac{r_y}{d_0-1} > c_y * z_0$ where z_0 is the total cell count at , which have to be exactly the hematopoietic steady state value of x_0 . At the same time $x_0 + y_0$ will grow and

$\frac{r_x x_0}{1+c_x(x_0+y_0)}$ will decrease because the denominator increases. This occurs because if, as stated, $r_x < r_y$ or $c_x > c_y$, then $\frac{r_y y}{1+c_y(x_0+y_0)} > d_0 y_0$ causing \dot{y}_0 to be positive and y_0 increase.

Treatment would then cause the reverse making \dot{x}_0 and \dot{y}_0 , until either hemostasis for x_0 has been reached or a steady state. It is this interaction that is the competition between x_0 and y_0 .

In \dot{x}_1 and \dot{y}_1 , $a_x x_0 > d_1 x_1$ and $a_y y_0 > d_1 y_1$ for the respective differentiated cells to be produced. \dot{x}_1 consists of the amount of normal stem cells times the rate of which normal stem cells produce normal differentiated cells, $a_x x_0$. This has to be larger than the number of differentiated cells that die in the same time span $d_1 x_1$, for the population of normal differentiated cells to grow, $\dot{x}_1 > 0$. For the normal differentiated cells population to decrease, $\dot{x}_1 < 0$ and thus

$d_1x_1 > a_x x_0$. Homeostasis is when there is no change in the population, so homeostasis before any mutation is achieved when $d_1x_1 = a_x x_0$. When the mutation happens x_0 is reduced by one and x_1 will decrease after $t=0$. It is the same for the tumor differentiated cells y_1 . The linking between y_1 and x_1 is that initially $y_0=1$ and $y_1=0$, so $a_y \cdot y_0 - d_1 \cdot y_1 > 0$ at $t=0$, thus y_1 will increase while x_1 decrease.

The model is a deterministic, dynamic model. It is deterministic because the same input will always give the same output. It is dynamic since the change is not instantaneously. The model's equations give information on how the change happens (Dingli & Michor, 2006).

Discussion

The factors not included in the model

When making a mathematical model, it is not possible to consider all the factors in the model. The model is a simple representation of the real world, not an exact representation, since that would require that every factor present in the real world is included in the model. Instead it is only the minimum number of factors that gives a satisfactory representation of the system modeled who gets included. This model investigates the importance of the cancerous stem cells in chronic leukemia. The model is simplistic in its nature, only focusing on the factors directly in contact with the stem cells and discarding everything else. To make this model more complicated and more accurate of the real world, there are several different factors that could have been included.

- *The immune response.*

When the body detects malfunctioning cells, it has an immune response. The immune response consists partially of neutrophils, T-cells and B-cells.

Neutrophils are white blood cells that can move to infections, stick to bacteria, virus or fungal and swallow or destroy it with a chemical process. B-cells have antibodies as receptors all over their membrane. When it encounter a virus, a bacteria or a damaged cell, it will gather the

information from it and, after a short proliferation process, start producing antibodies which will help killing damaged cells. There are two types of T-cells. Helper T-cells that stimulate the B-cells to produce the antibodies and killer T-cells that kill the body's own cells. '

Leukemia can weaken the immune response. Leukemia alters the stem cells which are the cells producing the neutrophils, B-cells and T-cells. The mutation can alter the cells that the stem cells produce, causing them to be unable to mature or alter their effectiveness. The cells must mature to be functional (*Cancerresearchuk, the immune system and cancer, 2017*).

It would be complicated to find data on how each of these cells affect the cancer. They could be simplified into the immune response, including all the body's responses. The simplification would still interact with many different aspects of the leukemia. The interactions that would be required to model is above the scope of the model that is analyzed. To improve upon the model and shift the focus from the importance of stem cells and towards a close representation of real life, the immune response would be critical. If an expansion of the model were to be made, it would be one of the factors that shall be included.

- *Stem cell migration.*

Stem cells are able to migrate in and out of the bone marrow. The cells not in the bone marrow are not dividing. Cancerous stem cells are likely to also be able to migrate in and out of the bone marrow. If such a cell migrates, a treatment that doesn't affect the entire body would not terminate those cells. The patient could risk going in to remission when the cancerous stem cells migrate in to the bone marrow again.

To include the risk of remission by migrating stem cells could prove difficult. There is not a lot of knowledge on how and why the stem cells migrate. Finding useful data in an area that is not understood could be impossible. Technological advances and greater research of the area has to be done to model the risk of remission by migration, not just the risk of remission.

The model in this paper focuses on the stem cells in the bone marrow and the importance of their destruction to be totally cured from CML. The tumor stem cells that migrate still must migrate back in to the bone marrow to be harmful. The inclusion however would still be of meaning. The model's focus would not change, only the scope would. It would give insight into how long the patient needs to be healthy to stop treatment and checkups. (Bethesda, MD: National Institutes of Health, U.S. Department of Health and Human Services, 2016, chapter 5)

- *More than one type of mutation*

When a cell divides, there is a risk a mutation occurs. A mutation isn't necessarily dangerous or harmful. The same cell can risk getting another mutation and develop into a cancerous cell. The same cancerous cell can get a second mutation, forming a new type of cancer and become the dominant cell. The previous cancer cell then remains in lower numbers. If the dominant cancer is treated there is a risk the treatment does not affect the other mutations. The first submissive cancer cell would then become the dominant cell and the patient would have a new type of cancer. (A.Campbell, 2018)

By including multiple strands of mutations, a model would be able to predict the risk of a new cancer appearing. The relevance of such model would be investigating the risks and dangers of multiple types of cancers. The model that is worked with in this paper is focused on the relevance of the tumor stem cell and what it's survival means for the health of a patient. Having multiple types of cancer, that is suppressed by a dominant type does not give an indication of the relevance of the stem cell. It gives insight into the risk associated with treatment and what symptoms that should be tested for.

After building the entire model, we will add a new factor, a new mutation. Regarding to the theory, we've explained that CML after treatment can somehow turn into AML. Here we will add a new variable: z_0 which will represent the amount of AML tumor stem cells. That is, z_1 , a_z , r_z will also be created through collected data. This new factor will follow the same equations as x_0 and y_0 but since AML is an aggressive cancer, when CML will stop competing for space thanks to the treatment, AML can take over and grow faster as it is clear at *figure 20*. That is, $r_y < r_x < r_z$ and $c_y > c_x > c_z$ after the treatment has been added and AML can spread. Moreover, in this case, the entire model equations structure is a bit changed. Regarding the competitions functions, the denominator $(y_0 + x_0)$ is for both functions changed into $(y_0 + x_0 + z_0)$ because now AML cells are competing as well. Thus AML has its own competition function :

$$\phi(z) = \frac{1}{1+c_z(x_0+y_0+z_0)}$$

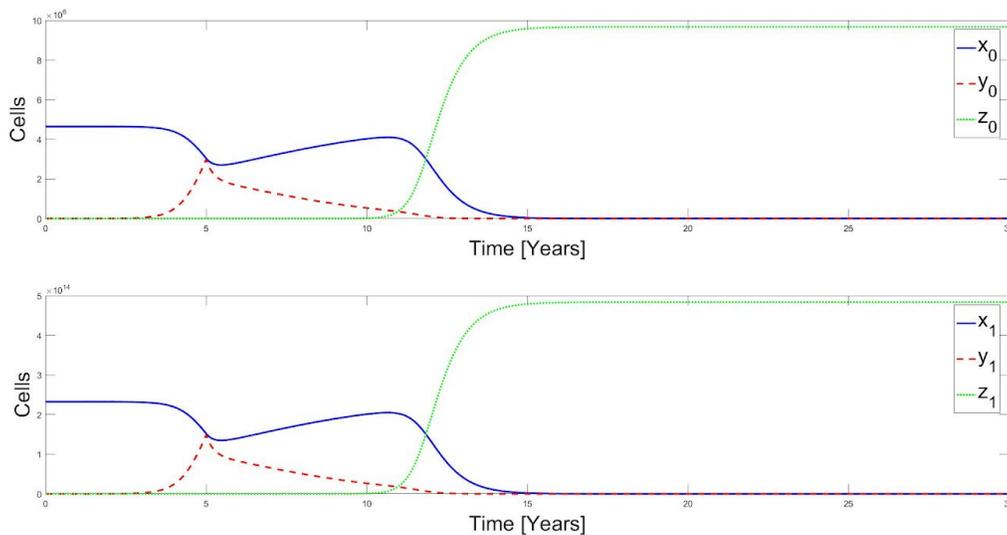


Figure 14: A figure representing what would happen if a second mutation occur. Here the mutation that occurs as an effect of the first mutation being treated.

CML can be cured, if the treatment is used after a time period of 5 years. Once the tumor cells are eradicated, the space in the bone marrow becomes larger and allows to a suppressed by then, second mutation (AML) to come out. Acute myeloid leukemia will grow exponentially and it will be even more aggressive than CML. The *Figure 14* illustrates the decrease of the number of the tumor cells from the first mutation which can cause the release of a second one that can be worse.

Treatment of Leukemia

The incidents of leukemia are increasing year by year and the treatments are becoming more efficient in keeping the disease stable. Medical progress has been made and doctors have managed to extend the survival possibilities of the patient. Depending on age and the health state of each person, treatments differ from each other.

The most applied treatment is chemotherapy, since the rate of success is higher than for others. Chemotherapy mainly uses strong drugs for a certain period of time to decrease the high number of tumor cells and tumor stem cells. Depending the stage and the severity of the disease, these drugs can be applied as single drugs or in a combination. Also, a strong

advantage that makes that type of treatment the most successful, is the ability that it can be combined with other treatments (American Cancer Society, 2016).

Another type of treatment is target therapy. It inhibits the protein produced by the gene BCR-ABL, called *Tyrosine kinase*, that helps the tumour cells grow, through small-molecule drugs and monoclonal antibodies. The most common drug is called *tyrosine kinase inhibitors* (or TKIs), but there are several others. For example, imatinib (Gleevec®), dasatinib (Sprycel®), nilotinib (Tasigna®), bosutinib (Bosulif), and ponatinib (Iclusig®). The small-molecule drugs can get into the cell and inhibit the function of specific targets, while monoclonal antibodies attached on the outer surfaces of the targets that help the tumor cells to grow. All these drugs are taken every day as a pill and side effects like liver problems, blood clotting, etc. can occur in case of an overdose. This type of treatment is rare. The production of these drugs is difficult, due to their complex structure (The American Cancer Society medical and editorial content team, 2014).

Radiation therapy is another treatment against cancer. It uses x-rays and gamma ray radiation to reduce and kill the immature and mature cancer cells to an extent. The radiation damages the tumour cell DNA immediately or it passes off charged particles that destroy it over time. However, radiation has also disadvantages. In the process of killing the tumour cells, it damages and kills the healthy ones as well. This can cause side effects to the patient (National Cancer Institute, 2017).

Last but not least, is the stem cell transplantation procedure. By applying this therapy, the patient receives blood-forming cells from a donor. This therapy is recommended after other treatments such as chemotherapy or radiation when the quantity of the destroyed cells is very high. The new- received cells inserted into the organism and replace the dead ones. The procedure is expensive and can cause serious problems, especially if the blood-forming cells do not match the host (National Cancer Institute, 2017).

In order a treatment to be successful and cure leukemia, it has to target the stem cells. As it is going to be explained further down at the analysis of the model, treatments that increase the death rate or decrease the production of the mature tumour cells are turned down. When the therapy stops, the tumour cells rebound. So, this has as a conclusion that only if the drugs or any other treatment manage to affect the source, leukemia will fade away.

Simulation of a mathematical model for CML

We have simulated CML using a math model to see and test how CML cells behave over time and seek which variable should be target to get rid of any tracks of leukemia, or at least reach the steady state.

The simulation is based on the model equations. They are all differential equations, meaning they represent the change over time. The simulation uses time steps instead of being continuous and include a starting total. At each time step, the change is calculated and added to the total for the next time step. If the total at the start is zero, $x(t_0) = 0$, and the change is two, $\frac{dx}{dt_1} = 2$, then if the next time step is $t_1 - t_0 = 1$ the total would be two, $x(t_1) = 2$. However if the time step is different $Dt_1 = t_1 - t_0$ you get $x(t_1) = \frac{x(t_0) - dx}{dt_1 \cdot Dt_1} = 0 + 2 \cdot Dt_1$ The next change could then be negative, $\frac{dx}{dt_1} = -1$ and the total would become $x(t_2) = \frac{x(t_1) - dx}{dt_1 \cdot Dt_2} = 2 - 1 \cdot Dt_2 = 1$ where Dt_2 is the second timestep.

We are implementing different forms of treatment in the simulation to gain insight into how the model predicts the treatment will affect CML. A treatment is implemented by altering the effect of one of the parameters after a certain timestep. If a treatment kills the tumor stem cells in the real world, it is reflected in the simulation by increasing the death rate of the tumor stem cells.

The graphs below illustrate exactly these predictions:

Without treatment

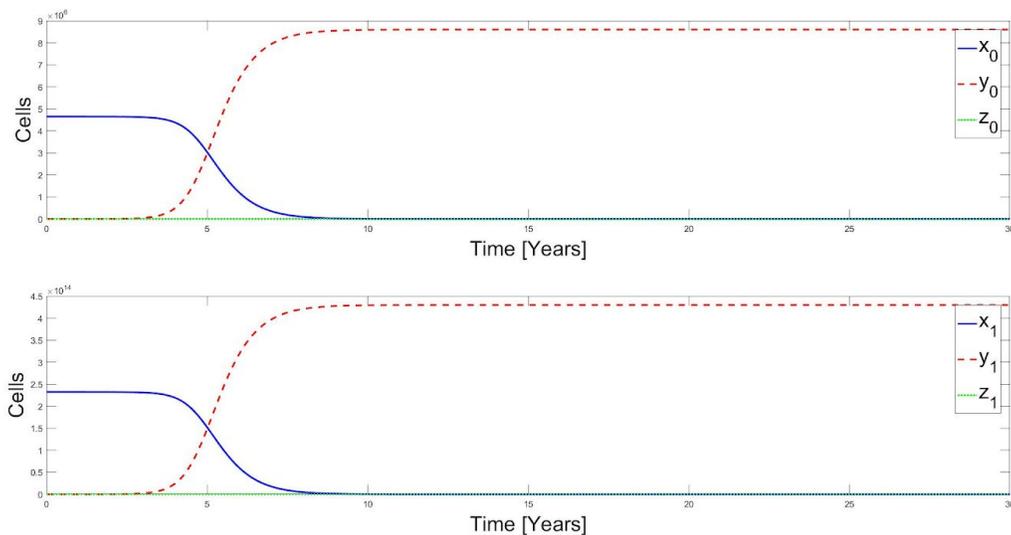


Figure 15: The progress of leukemia without applying any treatment. The figure shows that with no treatment there is no intervention with CML. As a result, both normal stem cells and normal mature cells will decrease to fatal levels. The equation used in Matlab can be seen in Appendix 5.5.4.

The parameters used in *Figure 15* are inserted according to the values from *Table 1*. With no change in the parameters or introduction of a treatment, CML will have a continuously development and will lead to the death of the patient. After 7 years the individual will have a critical health condition and after 3 years more the cancer cells will take all the space from bone marrow leading to death.

With a treatment that targets only the tumor stem cells

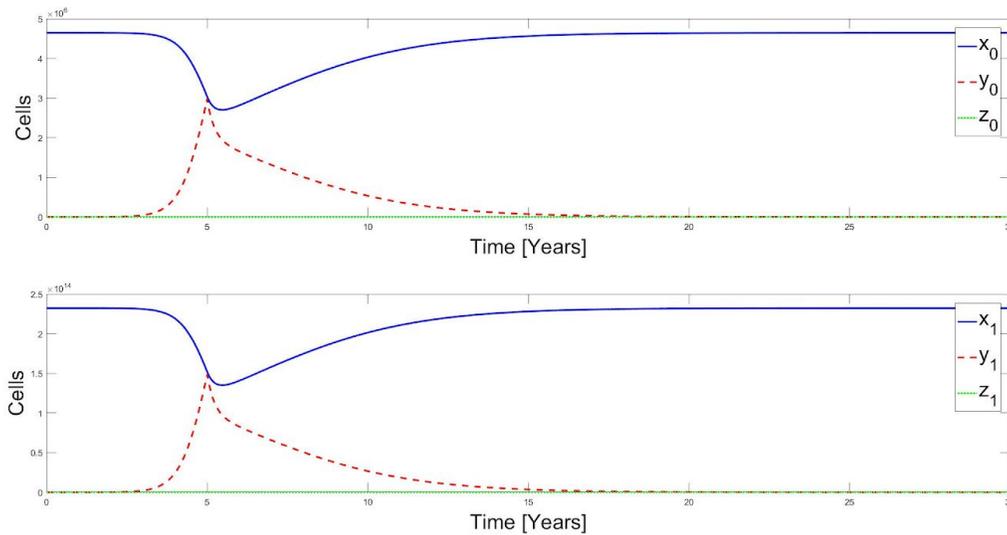


Figure 16 : The development of CML where a treatment has increased the death rate of tumor stem cells. If the increase is large enough, so $d_0 > r_y$, such increase lead to the elimination of the tumor stem cells and thus results in curing the patient. The equation used in Matlab can be seen in Appendix 5.5.2.

The hypothesis of the paper is that in order to cure CML, one must eradicate all of the tumor stem cell. In *Figure 16* the death rate of the tumor stem cells has been increased by introducing a treatment at year five. As seen by the figure, if the reduction of the differentiated tumor cells will follow the same decrease as the tumor stem cells. This indicates that if a treatment is developed to target the tumor stem cells the most efficiently, the treatment would have the same effect on the differentiated tumor cells.

With a continuous treatment that targets the tumor stem cells and keep them in a steady state

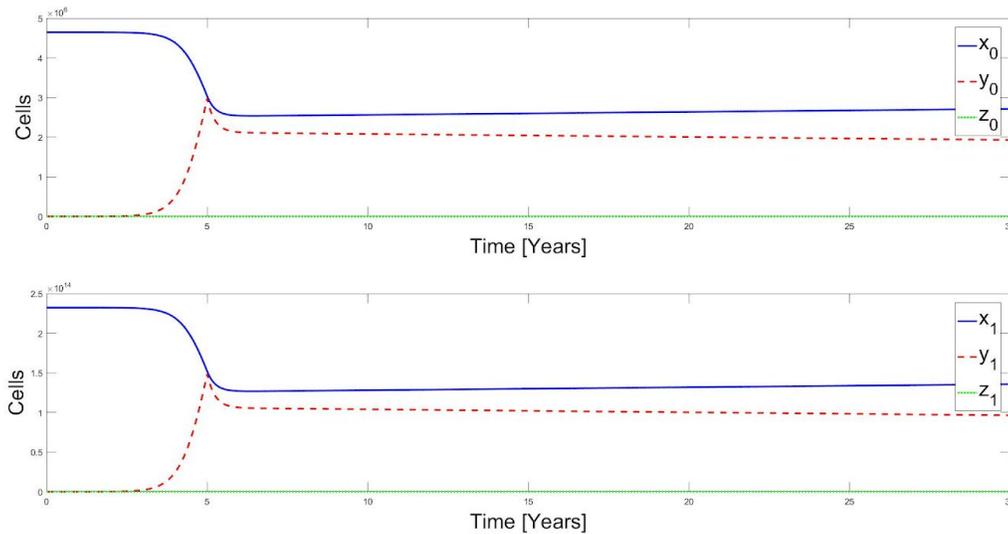


Figure 17 : By targeting the tumor stem cells it is possible to reach a steady state where the cancer has next to no change, as long as the treatment is continued. Such treatment would result in the patient being able to live and possibly only have to put up with the side effects the treatment cause. The equation used in Matlab can be seen in Appendix 5.5.1.

The initiation of a treatment for a long time period could have successful results (Figure 17). Nevertheless, an excessive and long time use of it could cause side effects.

With a treatment that targets only differential tumor cells for a certain time

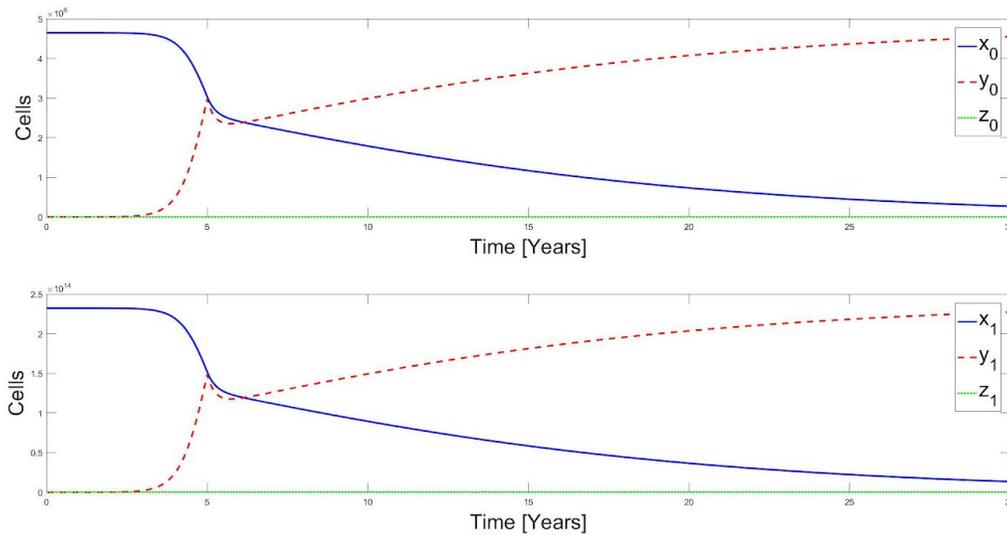


Figure 18: A treatment that doesn't affect the tumor stem cells enough can reduce the tumor stem cell count for a period, but will ultimately end in the cancer being fatal. The equation used in Matlab can be seen in Appendix 5.5.3.

As seen in *Figure 18* a treatment has to be watched. If the treatment isn't effective enough, meaning bringing the patient towards total cure or at least steady state, then the effect will not be that noticeable. The decrease a bad treatment has on the tumor stem cells only slows the growth of the tumor stem cells. *Figure 18* shows that before the treatment, the growth resembles exponential growth and after the growth is closer to a linear growth. This is not an acceptable solution, since the patient will still die.

A resistance to treatment occur.

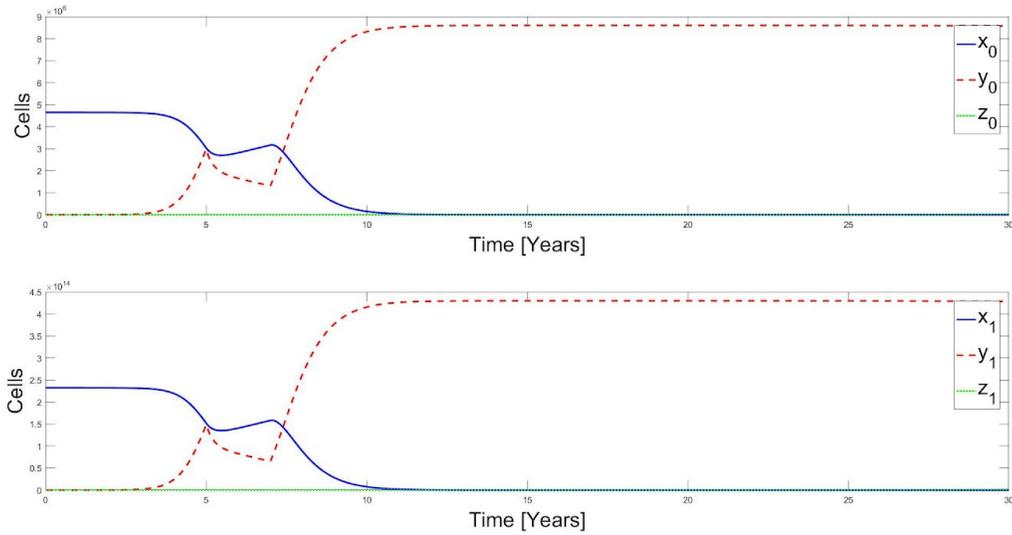


Figure 19: At year five there is initiated treatment, but at year seven, two years later, the leukemia build a resistance to the treatment and the patient goes into remission. See Appendix 5.5.5

As seen by *figure 19*, a treatment should be carefully tracked. Failure to do so, could mean that a resistance to the treatment is not discovered in time. As seen on the figure, that if the tumor stem cell number is lowered by the treatment, then the period that doctor has is extended. According to the figure a decrease in tumor stem cells has what looks to be the same effect on the differentiated tumor cells, thus increasing the time period.

With a treatment that targets differential tumor and normal cells

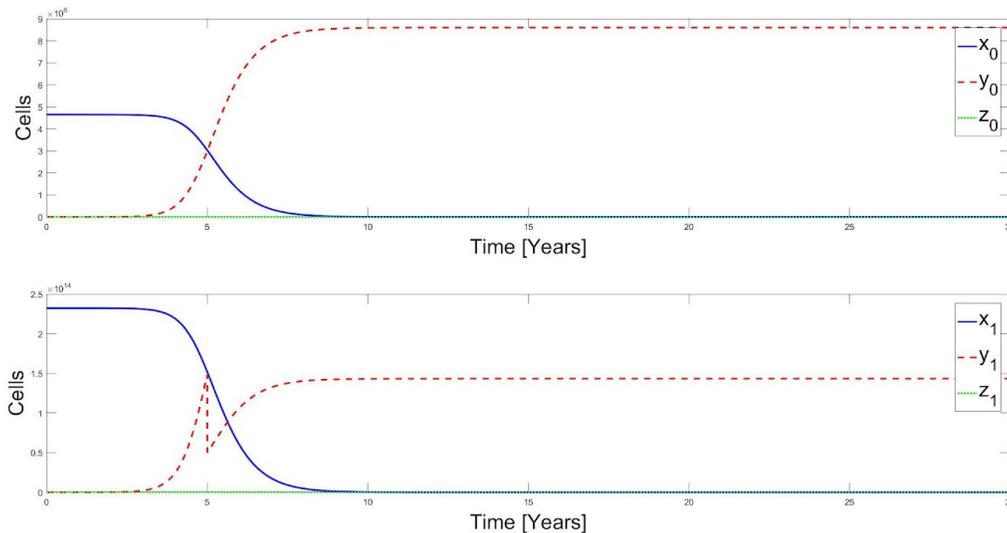


Figure 20: By increasing the death rate of mature tumor cells, the cell count could be lowered to normal amounts. Without an increase in the normal mature cells, the cancer will still be fatal since the mature tumor cells and deform cells and does not work as intended. Such treatments will not lead to a cure. The equation used in Matlab can be seen in Appendix 5.5.6.

As stated before, a doctor can only measure the concentration of defect blood cells, not the number of tumor stem cells that are present at a given time. A solution could be to decrease the amount of leukemic blood cells, in order to cure the patient. As seen from *Figure 20* such treatment would not be successful, since there is no reduction of the tumor stem cells. Without a reduction of tumor stem cells and thus an increase in normal stem cells, the production of normal blood cells will still remain low. A treatment that only affects the tumor differentiated cells is therefore not a treatment, but merely a short decrease in symptoms.

Conclusion

To sum up, as we already know, leukemia is a hard to treat disease. With the help of a mathematical model, it is possible to analyse and hypothetically test a potential cure for it. The simulations done upon the disease, can give a close answer to the reality. The mathematical model that we chose to analyse, makes clear, that in order for a treatment to be effective and considered successful, it has to have a specific target. It seems treatment targeting differential

tumor cells is largely ineffective and prologue the development of the cancer, see *Figure 18*. Also, if a treatment like blood cell transplantation is used to increase the number of healthy cells without eliminate the cancer cells and without produce normal cells will be ineffective. The number of leukemic cells will be unchangeable and the disease will not be treated. The outcome of using this type of treatment can be seen in *Figure 19*. However, an increase in the death rate of the tumor stem cells could be promising, but as it is shown in *Figure 20* hematopoietic stem cells are affected too. On the other hand, by targeting tumor stem cells and apply a treatment continuously can be effective enough to cure leukemia. This is justified in *Figure 17*, where we can see that the disease can be maintained in a steady state for a whole life.

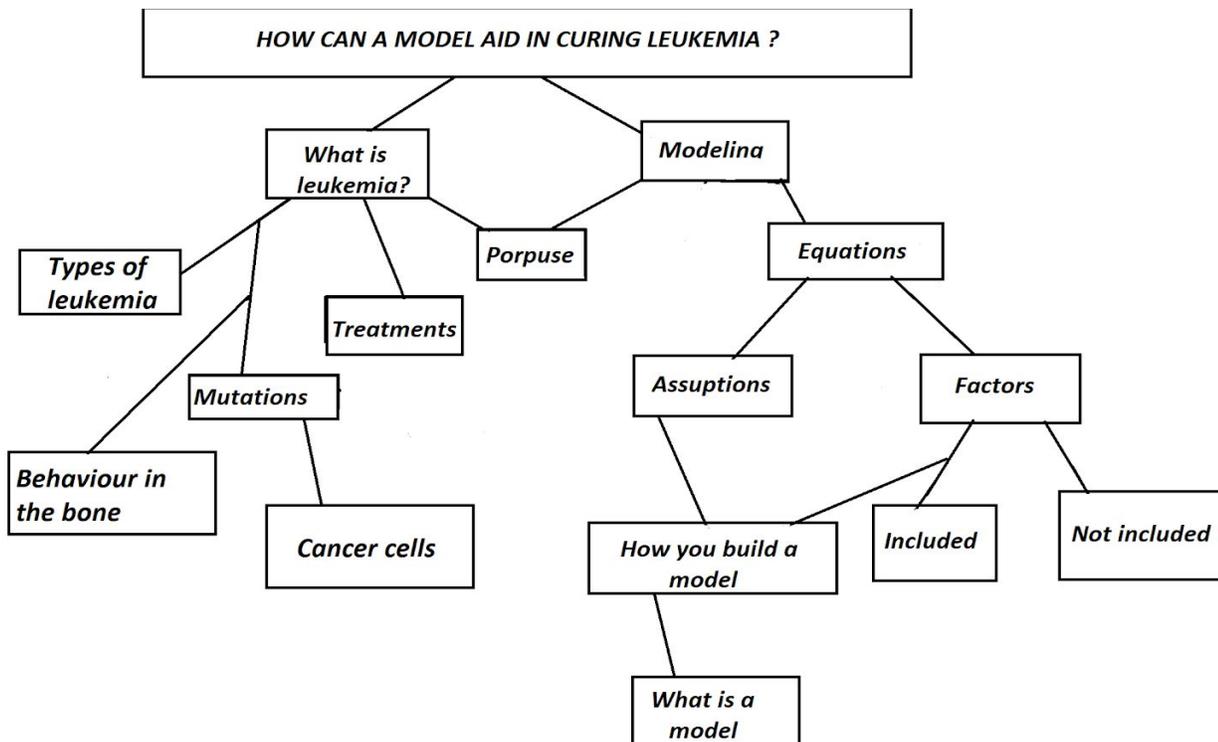
However, side effects from the treatments, can appear afterwards on the patients, especially in case of constant overdose because drugs also affect the healthy cells. Moreover, if CML is reduced at a very low level a second mutation (which could be AML) can bloom and make leukemia more aggressive. Since AML cells are strongly suppressed by CML cells, a reduction of those could lead to a even worse development.

So the answer to our question "*How can a mathematical model aid in curing leukemia?*" is that, using an ideal model in an utopian world, the proposed simulations would lead to a successful treatment.

APPENDIX

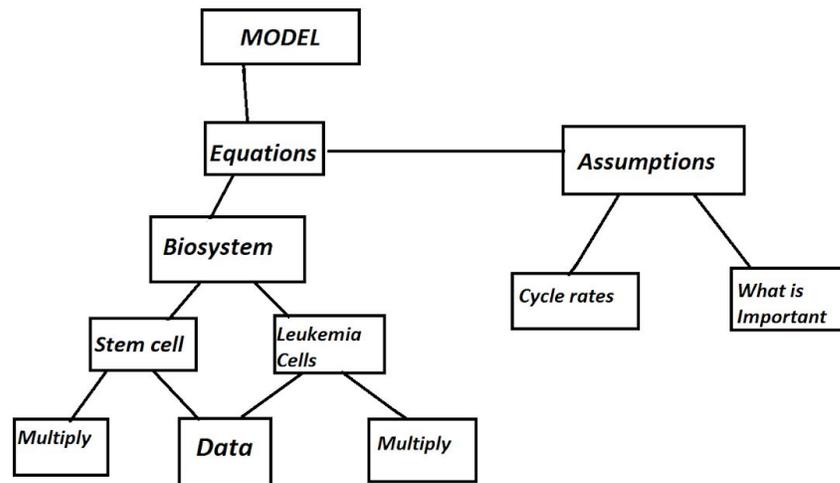
Appendix 1

Creation of our sub questions



Appendix 2

Methodology



Appendix 3

Subtypes of AML

There are two ways to classify AML subtypes – the French-American-British (FAB) system and the World Health Organization (WHO) classification system. The most common and worldwide known is the FAB. By using this system to classify AML doctors should obtain the cancer-leukemia cells that they collect during the bone marrow biopsy and analyze them.

Subsequently, a complicated process follows and the stage of development and the kind of cell they were supposed to become when they mature are determinate. The chart below explains this system.

Subtype	Subtype Name	Frequen cy	Cell Characteristics

M0	Myeloblastic	9- 12%	Leukemia cells are excessively immature and they do not have any characteristic of normal mature cell.
M1	AML with minimal maturation	16- 26%	Immature myeloid cells (or myeloblasts/ "blasts") are the main type of cell in the marrow sample.
M2	AML with maturation	20-29%	A lot of myeloblasts are exist, but they show more maturity than M1 subtype. Myeloblast is the last stage of development before the immature cell starts to form in a white or red blood cell, or platelet
M3	Promyelocytic (APL)	1-6%	Still immature leukemia cells, between the myeloblast and myelocyte stage. Quite underdeveloped, looking and acting more like a white cell.
M4	Acute Myelomonocytic Leukemia	16- 33%	Leukemic cells are a mix of granulocytic and monocytic cell types. They are still pretty immature but they look more like white blood cells than the previous stage.
M5	Acute Monocytic Leukemia	9- 26%	More than 80% of the cells are monocytes. Probably at different stages of maturity.
M6	Acute Erythroid	1-4%	Leukemic cells are still immature but they have

	Leukemia		characteristics of red blood cells.
M7	Acute Megakaryocytic Leukemia	0-2%	Leukemic cells are immature with characteristics of platelets.

The FAB Classification System (Karen Raymakers, 2017)

Appendix 4

MATLAB SIMULATIONS

% Figures ran by Driver_Cancer

time=t/365; % converts time ts in days to time in years

figure(1)

subplot(2,1,1)

```
plot(time, c(:,1),'-b', time, c(:,3),'--r', time, c(:,5),'g', time, c(:,1)+c(:,3)+c(:,5),'k','LineWidth',2)
legend('x_0','y_0','z_0','x_0+y_0+z_0','Location','NE');
xlabel('Time [Years]')
ylabel('Cells')
```

subplot(2,1,2)

```
plot(time, c(:,2),'-b', time, c(:,4),'--r', time, c(:,6),'g', time, c(:,2)+c(:,4)+c(:,6),'k','LineWidth',2)
legend('x_1','y_1','z_1','x_1+y_1+z_1','Location','NE');
xlabel('Time [Years]')
ylabel('Cells')
```

figure(2)

subplot(2,1,1)

```
plot(time, c(:,1),'-b', time, c(:,3),'--r', time, c(:,5),'g','LineWidth',2)
legend('x_0','y_0','z_0','Location','NE');
xlabel('Time [Years]')
```

```

ylabel('Cells')

subplot(2,1,2)
plot(time, c(:,2),'-b', time, c(:,4),'-r', time, c(:,6),'g','LineWidth',2)
legend('x_1','y_1','z_1','Location','NE');
xlabel('Time [Years]')
ylabel('Cells')

% This file contains the differential equations of the cancer model.

function [c_dot] = Cancer_eqs(t,c,pars)

% Define variables
x0 = c(1);
x1 = c(2);
y0 = c(3);
y1 = c(4);
z0 = c(5);
z1 = c(6);

% Define parameters rx, ax ry ay dx0 dy0 dx1 dy1 cx cy ea es rs ryq
rx = pars( 1);
ax = pars( 2);
ry = pars( 3);
ay = pars( 4);
rz = pars( 5);
az = pars( 6);
dx0 = pars( 7);
dy0 = pars( 8);
dz0 = pars( 9);
dx1 = pars(10);
dy1 = pars(11);
dz1 = pars(12);
cx = pars(13);
cy = pars(14);
cz = pars(15);
rmy = pars(16);
rmz = pars(17);

%% Algebraic relations

% % Impact of the nice on self-renewal - Hill laws

```

```

phix = 1/(1+cx*(x0+y0+z0));
phiy = 1/(1+cy*(x0+y0+z0));
phiz = 1/(1+cz*(x0+y0+z0));

%% Treatment
TreatmentYear = 5;
TreatmentResistance = (TreatmentYear+2);
%0.85 steady state
dy0t = dy0*(1+0*(t>TreatmentYear*365)); % simulate treatment by increasing death rate
for tumor stem cells
% dy0t = dy0*(1+1*(t>TreatmentYear*365)*(t<TreatmentResistance*365)); % simulate
treatment by increasing death rate and resistance to it for tumor stem cells
dy1t = dy1*(1+0*(t>TreatmentYear*365)); % simulate treatment by increasing death rate
for tumor differentiated cells

%% Differential equations

% Calculation of volume changes
c_dot = [(rx*phix-dx0)*x0 - rmy*x0; ... % dx0/dt
ax*x0 - dx1*x1; ... % dx1/dt
(ry*phiy-dy0t)*y0 + rmy*x0 - rmz*y0; ... % dy0/dt
ay*y0 - dy1t*y1; ... % dy1/dt
(rz*phiz-dz0)*z0 + rmz*y0; ... % dz0/dt
az*z0 - dz1*z1; ... % dz1/dt
];

% This file contains the differential equations of the cancer model.

function [c_dot] = Cancer_eqs(t,c,pars)

% Define variables
x0 = c(1);
x1 = c(2);
y0 = c(3);
y1 = c(4);
z0 = c(5);
z1 = c(6);

% Define parameters rx, ax ry ay dx0 dy0 dx1 dy1 cx cy ea es rs ryq
rx = pars( 1);
ax = pars( 2);
ry = pars( 3);

```

```

ay = pars( 4);
rz = pars( 5);
az = pars( 6);
dx0 = pars( 7);
dy0 = pars( 8);
dz0 = pars( 9);
dx1 = pars(10);
dy1 = pars(11);
dz1 = pars(12);
cx = pars(13);
cy = pars(14);
cz = pars(15);
rmy = pars(16);
rmz = pars(17);

%% Algebraic relations

% % Impact of the nice on self-renewal - Hill laws
phix = 1/(1+cx*(x0+y0+z0));
phiy = 1/(1+cy*(x0+y0+z0));
phiz = 1/(1+cz*(x0+y0+z0));

%% Treatment
TreatmentYear = 5;
TreatmentResistance = (TreatmentYear+2);
%0.85 steady state
dy0t = dy0*(1+0*(t>TreatmentYear*365)); % simulate treatment by increasing death rate
for tumor stem cells
% dy0t = dy0*(1+1*(t>TreatmentYear*365)*(t<TreatmentResistance*365)); % simulate
treatment by increasing death rate and resistance to it for tumor stem cells
dy1t = dy1*(1+0*(t>TreatmentYear*365)); % simulate treatment by increasing death rate
for tumor differentiated cells

%% Differential equations

% Calculation of volume changes
c_dot = [(rx*phix-dx0)*x0 - rmy*x0; ... % dx0/dt
ax*x0 - dx1*x1; ... % dx1/dt
(ry*phiy-dy0t)*y0 + rmy*x0 - rmz*y0; ... % dy0/dt
ay*y0 - dy1t*y1; ... % dy1/dt
(rz*phiz-dz0)*z0 + rmz*y0; ... % dz0/dt
az*z0 - dz1*z1; ... % dz1/dt
];

```

```

%% Differential equations

% Calculation of volume changes
c_dot = [(rx*phix-dx0-ax)*x0 - rmy*x0; ... %
dx0/dt
          ax*At*x0 - dx1*x1; ... %
dx1/dt
          (ry*phiy-(dyt+dytr)-ay)*y0 + rmy*x0 - rmz*y0; ...
% dy0/dt
          ay*A*y0 - dylt*y1; ... %
dy1/dt
          (rz*phiz-dz0-az)*z0 + rmz*y0; ... %
dz0/dt
          az*A*z0 - dz1*z1; ... %
dz1/dt
];

%% Parameters
% This function initializes the parameters for the model and
% sets initial values for the variables.

%% Simulation time span [Days]
tyears = 30;
tspan = [0:1:tyears*365];

%% ODE parameters
% ODE_TOL = 1e-6;
% DIFF_INC = 1e-2;

%% System parameters [1/day]
rx = 4*0.700;

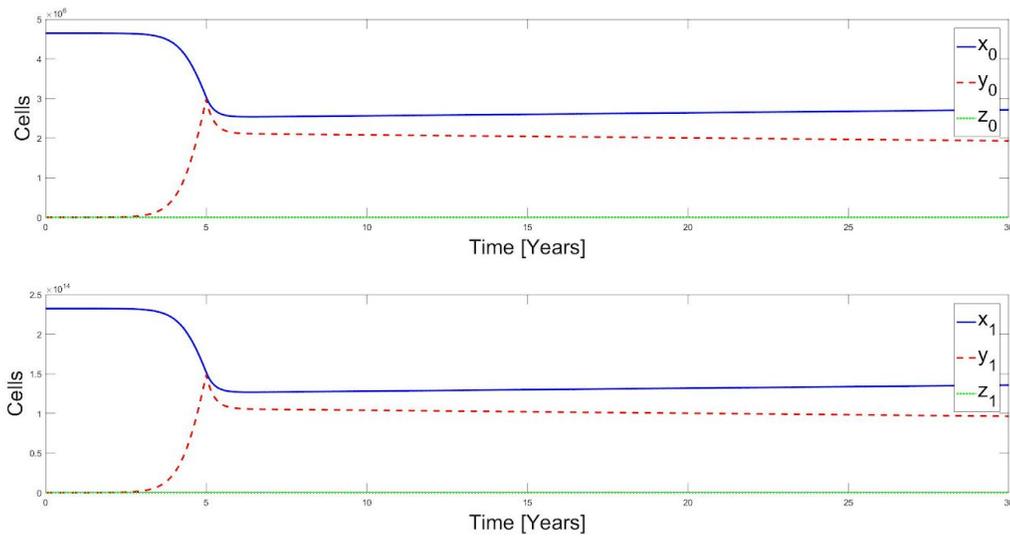
```

```
ax = 4*1.0650e-05*1e12;
ry = 4*1.0350;
ay = ax;
rz = 4*1.6000*0;
az = ax;
dx0 = 4*0.002 + 1.0650e-05;
dy0 = dx0;
dx1 = 4*0.213;
dy1 = dx1;
dz0 = dx0;
dz1 = dx1;
cx = 0.75e-4;
cy = 0.8*cx;
cz = 1.1*cx;
rmy = 4*1e-8;
rmz = 4*1e-14;
%A = 1e12;
```

```
%% Initial conditions
x0I = (rx/dx0-1)/cx;
x1I = ax/dx1*x0I;
% x0I = 4.735e5;
% x1I = 2.3671e13;
y0I = 0;
y1I = 0;
z0I = 0;
z1I = 0;
```

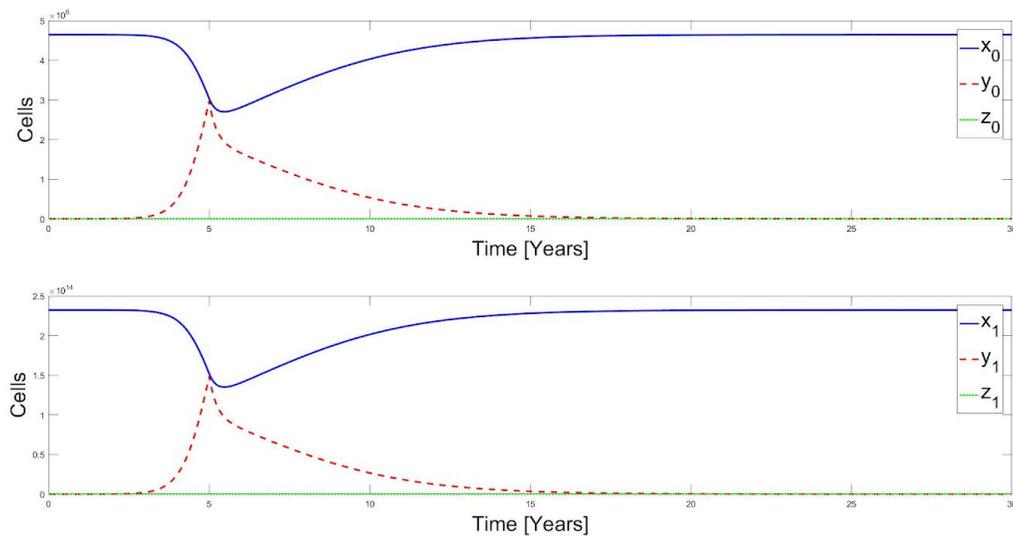
Appendix 5

5.1 Steady state targeting tumor stem cells



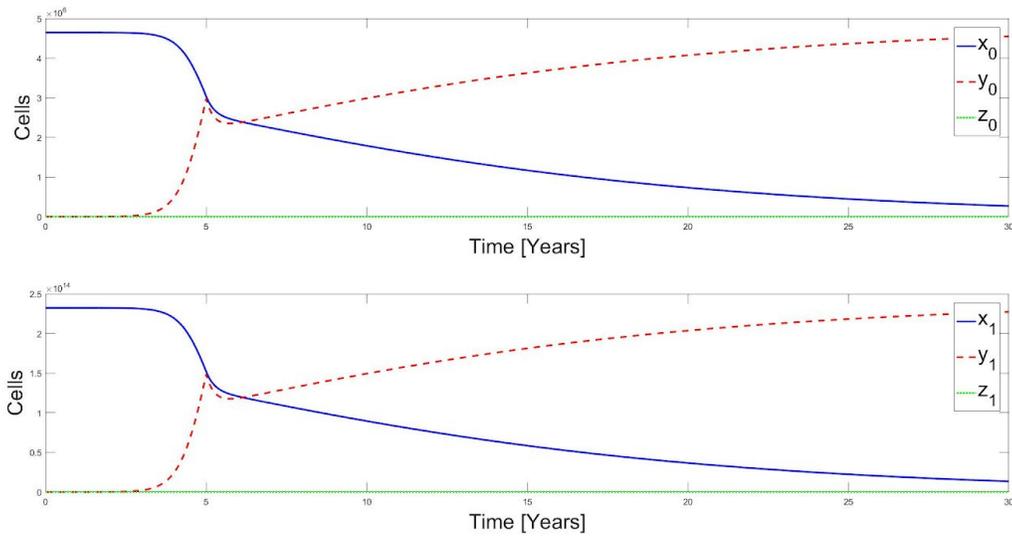
$$dyt = dy0 * (1 + 0.85 * (t > TreatmentYear * 365));$$

5.2 Treatment at 5 targeting death rate of tumor stem cells



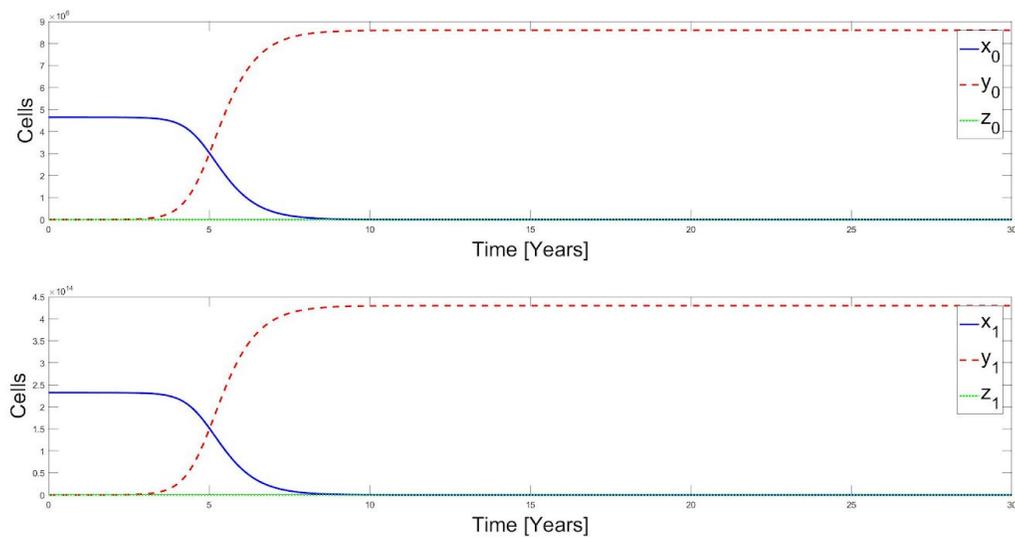
$$dyt = dy0 * (1 + 1 * (t > TreatmentYear * 365));$$

5.3 Bad treatment at 5 targeting tumor stem cells



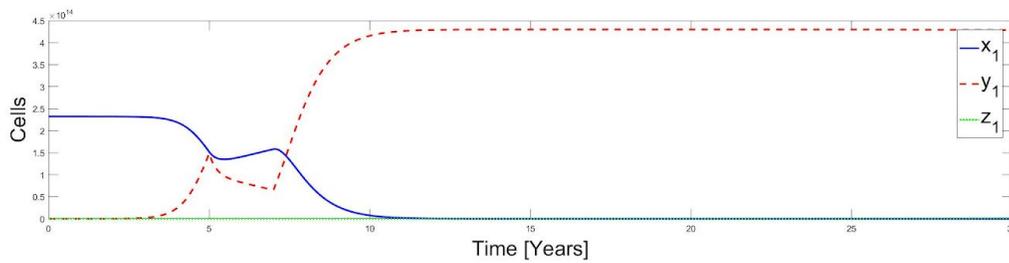
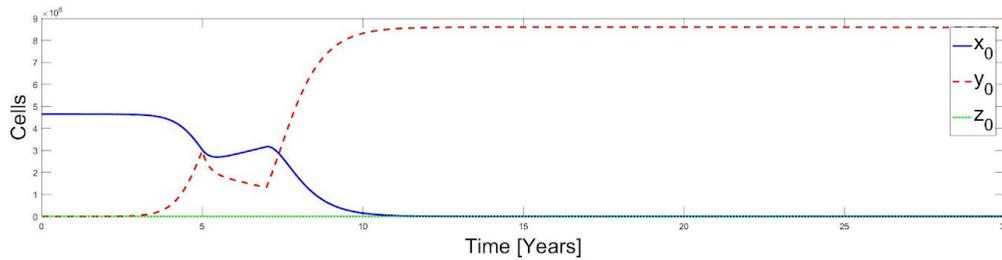
```
dyt = dy0*(1+0.78*(t>TreatmentYear*365));
```

5.4 No treatment



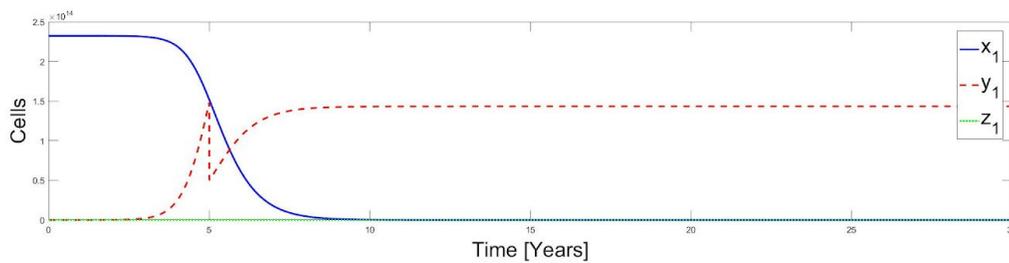
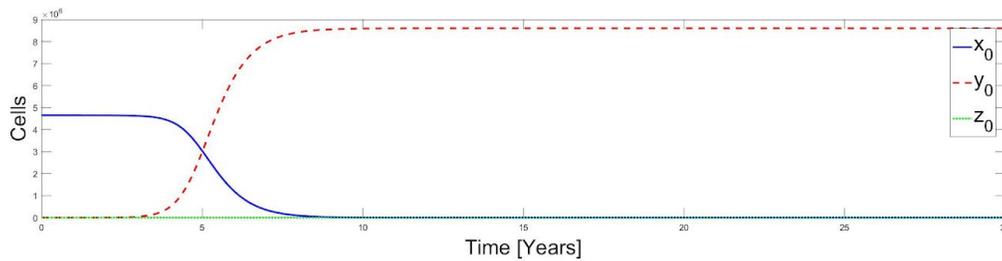
```
dyt = dy0*(1+0*(t>TreatmentYear*365));
```

5.5 Treatment - Resistance to treatment after two years



```
dy0t=dy0*(1+1*(t>TreatmentYear*365)*(t<TreatmentResistance*365))
5) % simulating a blood transplant
```

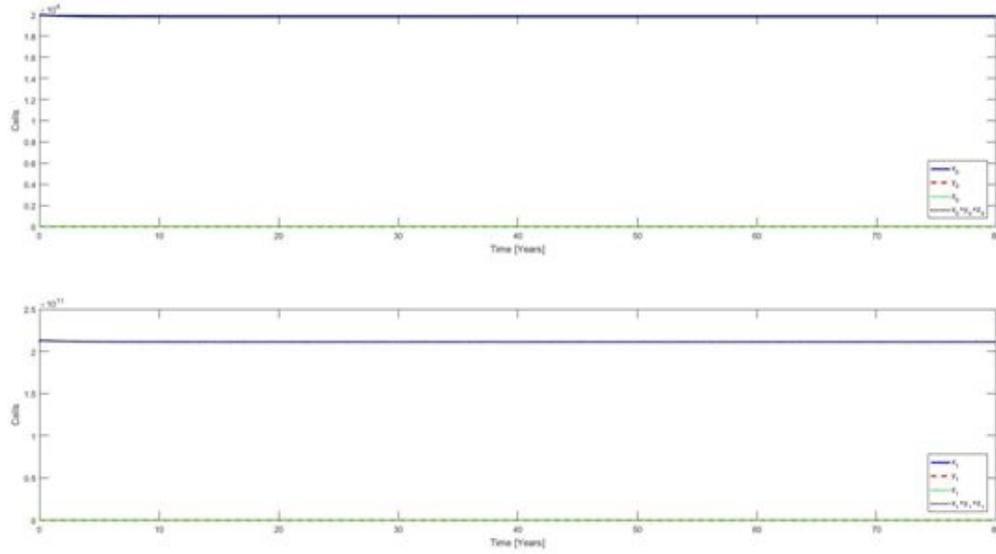
5.6 Treatment targeting death rate of mature tumor cells



```
dy1t = dy1*(1+2*(t>TreatmentYear*365)); %
```

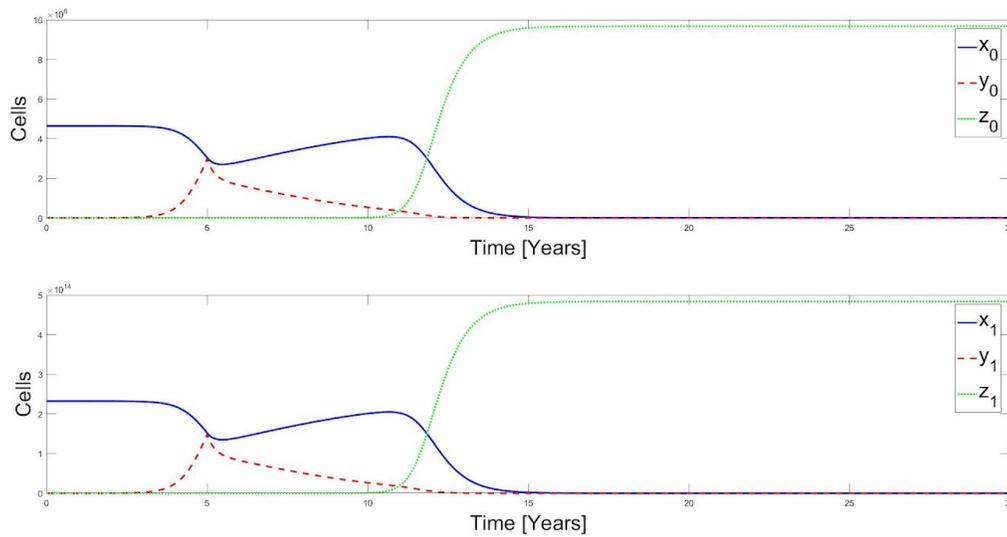
simulate treatment by increasing death rate for tumor differentiated cells

5.7 No Cancer



$r_{my} = 0;$

A second cancer.



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