Discrete model for cancer tumor growth and effect of chemotherapy

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Abstract

Many mathematical models have focused on growth of a single tumor with their spreading rate with some have included its metastasis. Some of the earlier models focus on exponential growth and its shift with time on to a linear model. The Gompertzian model involves a quadratic terms and that limit growth. We looked into Iwata et al paper it discusses a different model and takes into account the growth and metastasis of a tumor population but does not look into tumor shrinking or chemotherapy. Our new model focuses on the extending Iwata et al model to take into account tumor regression, we design with a discrete tumor size model which focuses on a limited number of tumors and this will help us to extend the model to consider tumor size into continuum model.

Cancer is the world’s deadly health killer and is the second leading cause of death in the United States [13]. Cancer has been found throughout history. Some evidence is also found in fossilized bone tumors and in human mummies and from ancient Egypt times. Cancer is largely a manifestation of abnormal cell growth with the potential of spreading to different parts of the body. They can form a new tumor, which is a group of the cells that undergoes unregulated growth often forming a mass or lump in certain parts of the body, it can distribute diffusely [13]. Untreated cancer usually causes serious illness and sometimes death. There are many signs of a cancer, like the formation of mass or lump growth, abnormal bleeding, weight loss, a change in bowl movement and so on. There are many different kinds of a cancer, like melanoma which kills about 8000 people in the US annually and 40000 people worldwide [14]. There are many causes associated with various cancers like tobacco use, obesity, poor diet, and consumption of alcohol and so on. Cancer productivity can also be hereditary where it can be passed from parents DNA [15]. It is very difficult to know exactly what could have caused any one person’s cancer. Cancer cells form tumors and invade other parts of the normal tissue. There are some cancers that rarely form tumors like leukemia where cancer cells involves the blood and blood forming organs and they circulate through other tissues as they grow. When cancer cells gets into the blood stream they can form new tumors after invading other normal tissue. This process of spreading is called metastasis [15].

Introduction
Cancer treatment is an ongoing research but much advancement has been made in the field in which a cancer patient can survive for a longer period of time. According to the American cancer society, in 2013 there were 1.6 million cases expected to be diagnosed whereas 580000 Americans were projected to die of cancer this is equivalent to 1600 people per day [13]. This makes the cancer the second most common cause of death in the USA. Cancer cells grow abnormally and out of control while invading other tissue in the body. Cancers of different types behave differently. Lung cancer, skin cancers are cancers where cells grow at different rates and there are different treatments. Thus people with cancer need treatment aimed at that kind of cancer.

There are many treatments available to kill cancer cells using powerful chemicals one such approach to treatment is chemotherapy [15]. We focused more on Chemotherapy because it kills the cancer cells directly before it spreads to other parts of the body. Chemotherapy treatment was first developed during World War II where the soldier was exposed to mustard gas. This gas was found to cause toxic changes in bone marrow which develops into blood cells. During that period the US army found effective agents for war. Compound called nitrogen mustard was found to work against a cancer of the lymph nodes called lymphoma [15]. This was a good breakthrough because this agent served as the model for similar agents called alkylating agents that killed rapidly growing cancer cells by damaging their DNA. Aminopterin was another such discovery it blocks a critical chemical reaction needed for DNA replication [21]. Methotrexate a cancer drug that is commonly used today is a predecessor of Aminopterin. Since then many other drug have come into the market. Choriocarcinoma is a rare tumor was first cured using methotrexate. Chemotherapy has been very successful in treating people with cancer. Today adjuvant therapy is often used to treat cancer cell, adjuvant therapy is the combination of chemotherapy and surgery [22].

Chemotherapy is a drug treatment that typically kills fast growing cells in body. There are some speculations that it also kills healthy cells in our body. Chemotherapy drugs are used to treat wide variety of cancers. There are many types of chemotherapy drugs available [22]. It is often an effective way to treat cancer but there are also many side effects that come with chemotherapy. Some side effects are. Nausea, Vomiting, Diarrhea, Hair loss, Loss of appetite, Fatigue, Fever, Mouth sores, Pain, Constipation, easy bruising. Often doctor’s use chemotherapy in addition to other methods, for example chemotherapy can be used to shrink a tumor size so other treatments like surgery and radiation could be possible. Chemotherapy kills cancer cells which many relieve the signs and symptoms of cancer.

Chemotherapy drugs are selected based on the person and cancer type. It is mostly determined based on the following method.

- Type of cancer
“Chemotherapy is given in the following different ways as seen.

- **Chemotherapy infusions.** Chemotherapy is most often given as an infusion into a vein (intravenously). The drugs can be given by inserting a tube with a needle into a vein in your arm or into a device in a vein in your chest.
- **Chemotherapy pills.** Some chemotherapy drugs can be taken in pill or capsule form.
- **Chemotherapy shots.** Chemotherapy drugs can be injected with a needle, just as you would receive a shot.
- **Chemotherapy creams.** Creams or gels containing chemotherapy drugs can be applied to the skin to treat certain types of skin cancer.
- **Chemotherapy drugs used to treat one area of the body.** Chemotherapy drugs can be given directly to one area of the body. For instance, chemotherapy drugs can be given directly in the abdomen (intraperitoneal chemotherapy), chest cavity (intrapleural chemotherapy) or central nervous system (intrathecal chemotherapy). Chemotherapy can also be given through the urethra into the bladder (intravesical chemotherapy).
- **Chemotherapy given directly to the cancer.** Chemotherapy can be given directly to the cancer or, after surgery, where the cancer once was. As an example, thin disk-shaped wafers containing chemotherapy drugs can be placed near a tumor during surgery. The wafers break down over time, releasing chemotherapy drugs. Chemotherapy may also be injected into a vein or artery that directly feeds a tumor.” [17]

Melanoma is the most dangerous form of skin cancer. Melanoma treatment has been the subject of ongoing research for long time. It is found that chemotherapy works better on small tumor as compared to large tumor [23]. Melanoma tumors originate in the pigment that produces melanocytes in the basal layer of the epidermis. Melanomas are black or brown colored pigment which develops during intense exposure to the UV radiation normally from sunburn [23]. Melanoma kills about 10,000 people annually in US. Melanoma is treated easily during early stages but it becomes very hard to treat once it spreads to other parts of the body. The American Cancer society estimates that 135,000 new cases of melanoma in the US are diagnosed in a year [17].
According to American Cancer society 42,670 males and 31,200 women will have invasive melanoma in 2015 [15]. In our Mathematical models to describe the dynamics of a tumor population that describes the growth rate with chemotherapy and metastasis for tumors of different sizes. Our model is based on discrete tumor growth size. We plan to apply it to a melanoma system found in the zebra fish model and to correlate it with clinical data.

Zebra fish have several advantages to be used for cancer study. Zebra fish develops cancer which is quite similar to that of humans [8]. Rapid growths of tumors allow us to monitor the large scale transgenic and see the growth of tumor cells as it develops. There are also many advantages of using Zebra fish such as their skin is translucent so it lets us observe the growth of tumors and we can easily monitor the treatment. Another advantage of zebra fish is that a mating pair produces 200-300 embryos a week, which enables us to test anti-cancer drugs in thousands of fish at a given time. Zebra fish have a tendency to develop cancer that is histological and genetically similar to that of humans [9]. Vivo visualization is the main advantage of using Zebra fish to see cancer growth and progression at single cell resolution [2].
The above image shows the anatomy of a Zebra fish it can help us locate the spread of tumor cells. There are many positive and negative effects of using zebra fish for cancer research. Some of the positive effects are that in zebra fish a single adult mating pair produces 200 or more embryos per week which allows the screening of relevant adult phenotypes using space efficient embryos [8]. These fish have the same organs as relevant to the human body and have a complex immune system with T and B cells, macrophages and monocytes. Mosaic transgenic which is a process of introducing an exogenous gene into organism so that the organism will exhibit new property and transmit it to its offspring, can also be created at the rate of 500-1000 animals per day which is very large and this stable transgenic can be found in 50% of injected animals with the transpose based systems [8]. Forward genetic and reverse genetics are highly stable and scalable. See through or transparent strains help us to monitor in vivo imaging of tumor growth, migration and metastasis. Vascular endothelium, red and white blood cells, platelets and stroma, which are cells with transgenic lines are available. There are also numerous successes of chemical screening in zebra fish, which has led to clinical trials in patients with melanoma. Also the microinjection of human genes under tissue prompter has led to tumors that are similar to that of human disease. Lastly tumors in zebra fish strongly resemble human tumors at the gene expression and genomic levels. In addition to the positive effects there are also many negative effects such as the zebra fish are short lived as compared to humans [9]. Their organs are also simpler than their mammalian counterparts; the kidneys resemble the mesonephric rather than the metanephric stage. Also some of the mammalian organs are not conserved. The genome size is approximately one-half the size of the human genome, making comparisons outside gene regions difficult. The genome underwent a genome duplication event; so many genes have a
redundant copy, which complicates loss-of-function studies of tumor-suppressor genes. Zebra fish grow at 28.5°C, rather than at 37°C, and are poikilothermic, limiting studies in which mammalian homeostatic temperature may be important to on congeneric phenotypes [9].

BRAF gene which is the gene found in the human body that is responsible to make proteins send signals inside the cell and is responsible for cell growth. It was discovered that this growth is found to be faulty in some human cancers which has led to the discovery of drugs directly targeting them; they are called BRAF inhibitors. Vemurafenib and dabrafenib are two drugs known to treat late stage melanoma. Vemurafenib treatment reduces the cancer cell in half and the survival time increases by 6 months or over [6]. This drug is approved by FDA for the treatment of BRAF mutation. In a clinical trial conducted by the New England journal of medicine it was found that the patient taking Vemurafenib have the overall survival of 84% after 6 months [6]. These drugs have the ability to interfere with the cancer cell to grow, divide, repair and communicate with other cells. These drugs are called targeted therapy drugs. They use small molecules that get into the cell and disrupt the function of the cancer cells, causing them to die. Some targeted therapy target receptors that are on the outside of the cell. Vemurafenib which is the form of target therapy target the mutated BRAF proteins (kinase) within the cancer cell [3].

BRAF gene plays an important role in normal and cancer cells. A BRAF protein which is produce from this gene is a part of a chain of molecules that relay a signal and tells cells how to grow and divide. Mutation is the change in BRAF gene that can alters the way in which BRAF protein works. Instead of waiting for its turn to signal a cell to divide or grow, the BRAF protein is out of control and this may drive the uncontrolled growth of cancer cells. Vemurafenib targets these changed BRAF proteins and may slow down the growth of cancer [5].
The above graph shows the result from the clinical study from the Vemurafenib drug showed a drastic improvement in the survival rate [11].

Although these drugs are great there are other challenges that remain in virtually every patient treated with these drugs.

Many patients develop resistances to selective RAF kinase inhibitors; these resistances to RAF inhibitors are not understood completely. Melanoma immunotherapy has made significant progress to block the dense T-cell found in Melanoma tumors. CTL4 and PD1 are the T-cell checkpoints which prevent the immune system from attacking the tumor. Ipilimumab is a treatment for Melanoma that cannot be removed by surgery but spread to the other parts of the body, blocks CTLA4 [20]. This drug is approved by FDA and the response has been very positive. Nivolumab which is the generic name for a drug called Opdivo is an inhibitor for PD1.
This drug is also approved by FDA and the response rate has been very high. In some case it was found to be 79% survival rate after 2 years [10, 20].

Our model focuses on the interaction between therapy and tumor growth. There has been a long history of tumor modeling. Many models have worked on a single tumor, average tumor or a sum of 4 or 5 largest tumors and its growth rate which was earlier assumed to be exponential. It was then assumed to be a linear growth in time. Molecular beam epitaxial (MBE) which is a class of studies done on 15 lines of cells growing into 16 different types of tumors where all cell colonies were found to inhibit the same cells growth. MBE dynamics are sometimes described as a linear growth rate where a surface diffusion of cells occurs at the growing edge. MBE dynamics was experimentally studied in colonies of the tumor growth [12]. These studies challenge the concept of exponential growth and the Gompertzian growth. It is a linear growth regime where the tumor growth is conceived as the competition for space between the tumor and the host. These models account for unbounded growth terms and add other logistical terms. Another Gompertzian model which cuts off the growth due to crowding and immunity leads to a bounded sigmoid growth shape with time [12]. A different class of differential equation models each term represents the rate of a specific interaction. These models focus more on how a tumor competes with healthy cells. It also shows that tumors nucleate better on surfaces than in bulk regions. Iwata et al proposed new point of view in which tumor size is continuous. It leads to a time dependent histogram of a primary tumor vs. tumor size [1].
The above figure shows the changes in the size distribution of tumors with progression of metastasis of a hepatocellular carcinoma. In graph a, the three different times indicated by different dash lines shows the cumulative number of tumors as a function of the colony size after the first diagnosis of primary tumor. The thick curves are theoretical cumulative distributions. The thin lines are the colony size distributions for the corresponding thick curves. The shape of tumor was assumed as spheroidal ellipsoid to calculate the volume of the tumor. A tumor of 1 mm^3 was assumed to contain 10^6 cells. In graph b, the theoretical Gompertz growth is compared with the observed growth data of the primary tumor [1].

This model allowed one to track the growth of a primary tumor along with the generation of metastases. This model defines the mathematical terms and uses the numerical and asymptotic approaches that are most successful into analysis. Although this model takes into account tumor growth and metastasis generation it fails to admit the tumor shrinkage which can cause by chemotherapy [1]. This is the main topic of interest of cancer research and we would focus more into the chemotherapy term. We took Iwata et al paper into account and developed the idea of tumor shrinkage into our account. In order to study these effects we divided our study into two parts one is a discrete model where we begin by describing the tumor with discrete numbers of cells and reveal important interactions to be later used for continuous model [1].

Iwata et al model uses the idea of single cell development of metastasis and forms them into colonies which are then subject into the Gompertzian growth rate given as

\[ g(x) = a x \log \frac{b}{x}, \]

\[ \frac{dx_p}{dt} = g(x_p), \quad x_p(0) = 1. \]

Here "a" is the growth rate constant; b is the tumor size at the saturated level, g(x) is the Gompertzian growth rate and x represents number of cells in primary tumor at time t. The above equations are solved to give us the resulting equation which gives a relationship between numbers of cells in primary tumor as a function of time [1].

\[ x_p(t) = b \frac{1 - e^{-at}}{-a}. \]

\[ \beta (x) = mx^\alpha \] is the colonization rate adopted which is similar to the power law function. This equation tells us that the rate of metastasis from a tumor with size x is proportional to the number of tumor cells in contact with the blood vessels [1].
Iwata et al then used the Gompertzian growth rate along with Laplace transformation method to obtain the equation for colony size distribution of metastatic tumors with cell number \( x \) at time \( t \).

\[
\rho(x, t) = \frac{a}{mb^x \log b} \sum_{k=1}^{\infty} e^{a \lambda_k t} \left( 1 - \frac{\log x}{\log b} \right)^{(\lambda_k - 1)} \frac{1}{c(\lambda_k)}
\]

for \( 1 \leq x < x_p(t) \), \( (5) \)

The above equation was compared to the clinical data and there were some prediction made on the behavior of metastasis. Iwata et al model was the starting point for our research it gave us the basis to understand the growth rate but it fails to address the tumor shrinkage. Also the behavior of the colony size distribution of tumor changes after treatment such as chemotherapy, radiotherapy, which was not taken into account by the above model. We develop our model which takes all this effects into consideration [1].
Mathematical Model and the Program

Each year billions of dollars are being spent on cancer research. For instance, 5.4 billion dollars were spent in year 2014 just from the government in the U.S.A.\(^{(4)}\) Progress has been made in the development of new drugs and treatments for various types of cancer. However, despite huge spending and great amount of human resources there is still more work needs to be done specifically creating models of cancer tumor growth. Wide ranges of different models have been used to explain cancer tumor growth. The traditional models have been only about tumor growth and metastasis processes in a cancer tumor. Most models are based on Gompertzian growth rate of a tumor. This model describes tumor growth by an exponential growth rate followed by slower growth rate. Here we will build on Iwata et al’s Dynamical model. Iwata et al’s model focuses on metastasis process in which affected cells are spread to different parts of the body. Then these cells develop into secondary and tertiary small tumors. Their growth and numbers multiply in numbers by this process. The model assumes that colonization begins from a single cell and each colony has the possibility to evolve into metastasis. This process depends on the colony size and tumor vascularity\(^{(2)}\).

\[
\frac{dN_j}{dt} = k_1(N_{j-1} - N_j) + k_0(N_{j+1} - N_j)
\]

Equation 1: Growth Metastasis

Above is a simple model for tumor growth and metastasis where \(N_j\) is a population of \(j\) size tumor. According to Iwata et al, latest technology cannot reliably detect cancer cell colonies smaller than a few millimeters in size.\(^{(1)}\) The dynamic model provided by Iwata et al and colleagues can be used to estimate number of colonies below detectability limit and to predict future behavior of metastasis.\(^{(1)}\) Knowing how it spreads through metastasis we can analyze to counteract the tumor from spreading by means of immunotherapy. Medical experts measures tumor sizes and track them to see how sizes change over long period of time. It will also be useful to investigate what effects therapy will have on this model. So we will further develop on Iwata et al’s model to solve the equation by adding chemotherapy term. There are two types of models that can be considered continuum or discrete. Here we will explore and study the discrete model in terms of tumor size for sizes from 0 to \(10^8\) cells\(^{(3)}\) and will require a model with continuous tumor sizes. Then next phase will include the continuum model. Killing the affected cells with chemotherapy helps counteract growth. Therefore, examining the effect of different
variables through chemotherapy will advance our understanding of cancer. Following is the mathematical model for discrete tumor size case.

Equation 2: \[
\frac{dN_j}{dt} = k_1(N_{j-1} - N_j) - f(N_j - N_{j+1}) + k_0(N_{j+1} - N_j) \quad (j > 1)
\]

Growth chemotherapy metastasis

The above equation models the tumor size distribution over time. The model reflects the effects of metastasis and immunotherapy on tumor growth. The imbalance of cell birth and cell death can result in tumor growth. \(^{(3)}\) Earlier models assumed only exponential tumor growth and not any immunity to growth. So there is a need to explore the other side of the story. We assume that process where cells break off from a parent tumor and seed new tumors somewhere else is a first order process. In the above equation, term \(N_j\) is a population of \(j\) size tumor. \(\frac{dN_j}{dt}\) indicates rate change population of \(j\) size tumor at time \(t\). \(k_1\) describes the effective rate constant of tumor growth which includes the term \(k_1 = k_{10}j^\alpha\) where \(k_{10}\) is the pre factor of the rate of growth. \(k_1(N_{j-1} - N_j)\) describes the change of population of tumor size from \(j\) to \(j-1\). Similarly, \(f(N_j - N_{j+1})\) indicates tumor death rate which scales back the size of the tumor from \(j+1\) to \(j\), where \(f\) is effective death rate containing \(f = f_0 j^\beta\). This is the term that is omitted in traditional models. The last term on right hand side of equation 2 is a metastasis term which includes any affected cell break off to form new tumors in the body. Matlab code is written incorporating the above equation to explain tumor distribution and longtime effect of therapy.

<table>
<thead>
<tr>
<th>Notation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(j)</td>
<td>Number of cells in tumor</td>
</tr>
<tr>
<td>(t)</td>
<td>Time</td>
</tr>
<tr>
<td>(N_j)</td>
<td>Probability of selecting tumor of size (j) randomly for tumor distribution</td>
</tr>
<tr>
<td>(k_1)</td>
<td>Cell growth rate constant</td>
</tr>
<tr>
<td>(f)</td>
<td>Cell death rate constant</td>
</tr>
<tr>
<td>(k_0)</td>
<td>Cell metastasis constant</td>
</tr>
<tr>
<td>(k_0')</td>
<td>Metastasis implantation rate</td>
</tr>
<tr>
<td>(\alpha)</td>
<td>Factor for growth dependence on tumor size</td>
</tr>
<tr>
<td>(\beta)</td>
<td>Factor for death dependence on tumor size</td>
</tr>
<tr>
<td>(\gamma)</td>
<td>Factor for metastasis dependence on tumor size</td>
</tr>
</tbody>
</table>
Summary of Method

A second order accurate Runge-Kutta type time discretization was used to solve the system of ODE needed to find the tumor size distribution. The code used was originally written in the Matlab programming language by Professor Horacio Rotstein and Professor David Rumschitzki. The ODE and boundary conditions are described below. Equation 1 defines a total of \( j_{\text{max}} - 2 \) ODE where \( j_{\text{max}} \) is the maximum tumor size allowed in the simulation. Equations 2 and 3 define the boundary conditions for the system at \( j = 1 \) and \( j = j_{\text{max}} \).

\[
\frac{dN_j}{dt} = k_1 [(j - 1) \alpha N_{j-1} - j \alpha N_j] + f [(j + 1) \beta N_{j+1} - j \beta N_j] + k_0 [(j + 1) \gamma N_{j+1} - j \gamma N_j] \tag{1}
\]

\[
\frac{dN_1}{dt} = -k_1 N_1 + f [2 \beta N_2 - N_1] + k_0 2 \gamma N_2 + k_0 \sum_{j=2}^{j_{\text{max}}} j \gamma N_j \tag{2}
\]

\[
\frac{dN_{j_{\text{max}}}}{dt} = k_1 (j_{\text{max}} - 1) \alpha N_{j_{\text{max}} - 1} - f j_{\text{max}} \beta N_{j_{\text{max}}} - k_0 j_{\text{max}} \gamma N_{j_{\text{max}}} \tag{3}
\]

An important limitation to this set of equations is the necessity to include a boundary condition at \( j_{\text{max}} \). Ideally, the system is unbounded at the upper end. Due to the limitations of computing power however, \( j_{\text{max}} \) must be finite. To that end, the boundary condition describe in Equation 3 was chosen so that mass will be conserved in the system. That is, no tumors disappear due to it. However, this means \( N_{j_{\text{max}}} \) has the potential to grow in an unbounded fashion. The error introduced by this boundary condition will be discussed further in the following text.

The second order Runge-Kutta time stepping method used in the code is described by Equation 4.

\[
N_j^{n+1} = N_j^n + \frac{\Delta t}{2} \left( \frac{dN_j^n}{dt} + \frac{dN_j^*}{dt} \right) \tag{4}
\]

Here, \( \frac{dN_j^n}{dt} \) is \( \frac{dN_j}{dt} \) from Equation 1 calculated from the solution for the distribution at time \( t = n \Delta t \), \( N^n \), and \( \frac{dN_j^*}{dt} \) is calculated using the distribution obtained from Equation 5. The formula for \( \frac{dN_j^*}{dt} \) is given explicitly in Equation 6. It is convenient to note that the bracketed term in Equation 6 is simply the second derivative of \( N_j \) calculated using \( N^n \). The compact formula for \( \frac{dN_j^*}{dt} \) is shown in Equation 7.

\[
N_j^{n*} = N_j^n + \Delta t \frac{dN_j^n}{dt} \tag{5}
\]
\[
\frac{dN^*_j}{dt} = \frac{dN^*_j}{dt} + \Delta t \left[ k_1 (j - 1)^\alpha \frac{dN^*_{j-1}}{dt} - (k_1 j^\alpha + f j^\beta + k_0 j^\gamma) \frac{dN^*_j}{dt} + (f (j + 1)^\beta + k_0 (j + 1)^\gamma) \right] \frac{dN^*_j+1}{dt} \quad (6)
\]

\[
\frac{dN^n_j}{dt} = \frac{dN^n_j}{dt} + \Delta t \frac{d^2 N^n_j}{dt^2} \quad (7)
\]

Incorporating Equation 7 into Equation 4 gives Equation 8. It is clear from comparing Equation 7 to the Taylor series expansion of \( N_f(t+\Delta t) \) around \( t \) that the error accrued during a time step, \( \epsilon \), is \( O(\Delta t^3) \) as stated in Equation 9. The overall error for \( n \) time steps is the \( O(\Delta t^2) \) as shown in Equation 10.

\[
N^n_j + 1 = N^n_j + \Delta t \frac{dN^n_j}{dt} + \frac{\Delta t^2}{2} \frac{d^2 N^n_j}{dt^2} \quad (8)
\]

\[
\epsilon = N_f(t + \Delta t) - N^n_j + 1 = O(\Delta t^3) \quad (9)
\]

\[
n \cdot \epsilon = t_{\text{max}} O(\Delta t^2) \quad (10)
\]

**Analysis Using Model Solutions:**

Since the Runge-Kutta method is an explicit discretization method, the size of the time step used must be limited to ensure the solution of the simulation does not become unstable. A useful method of determining appropriate time steps assumes a form of the exact solution to the system of equations. The time steps that achieve a stable solution can then be obtained.

One potential form for the solution of the system of equations is given by Equation 11. \( N_j \) and \( t \) are specified as above and \( \eta_j \) is some function of the size coordinate \( j \). This form is related to the expected form of the equations when diffusion is the dominant process occurring, given in Equation 12. Here, \( \eta \) is a function of the size coordinate. This solution will be useful when \( k_1 \) and \( f \) are equal. Since Equation 12 shrinks faster with increasing time than Equation 11, it is reasonable to assume that if Equation 11 is bounded for \( t > 0 \), then Equation 12 is also bounded.

\[
N_j = e^{-\eta_j/t} \quad (11)
\]

\[
f(t) = \frac{c}{\sqrt{t}} e^{-\frac{\eta}{t}} \quad (12)
\]

Equation 13 is an equation showing the ratio of magnitudes of the solution over a time step. The condition necessary to show the solution is bounded, described by Equation 14, is that the magnitude ratio is less than or equal to 1 as \( t \) approaches infinity. It is obvious from Equation 13 that this condition is satisfied as time is in the denominator of the two rightmost terms.
$$\frac{N_{j}^{n+1}}{N_{j}^{n}} = 1 + \frac{\eta_{j} \Delta t}{t^2} + \frac{(\eta_{j}^2 - 2\eta_{j} t) \Delta t^2}{2 t^4}$$

(13)

$$\lim_{t \to \infty} \left| \frac{N_{j}^{n+1}}{N_{j}^{n}} \right| \leq 1$$

(14)

Another model exact solution to the system is a traveling wave, Equation 15. This solution is applicable when the convective term in the equation dominates diffusion as when \( k_l - f \) is very positive or very negative. A similar analysis as above results in the magnitude ratio is shown in Equation 16. The fact that the right hand side of Equation 16 is complex means that it is appropriate to convert it to amplitude-phase form as shown in Equation 17. The amplitude and phase for the simulation solution are stated in Equations 18 and 19 respectively.

$$N_{j} = e^{-i \eta_{j} t}$$

(15)

$$\frac{N_{j}^{n+1}}{N_{j}^{n}} = 1 - i \eta_{j} \Delta t - \frac{\eta_{j}^2 \Delta t^2}{2}$$

(16)

$$\frac{N_{j}^{n+1}}{N_{j}^{n}} = A e^{i \theta}$$

(17)

$$\left| \frac{N_{j}^{n+1}}{N_{j}^{n}} \right| = A = 1 + \frac{\eta_{j}^4 \Delta t^4}{4}$$

(18)

$$\theta = \tan^{-1}\left(\frac{2 \eta_{j} \Delta t}{\eta_{j}^2 \Delta t^2 - 1}\right) = -\eta_{j} \Delta t + \frac{5 \eta_{j}^3 \Delta t^3}{6} + O(\eta_{j}^4 \Delta t^4)$$

(19)

Equation 18 shows that the solution method is unconditionally unstable as the magnitude ratio is always larger than 1. Although it is unstable, the amplitude of the solution increases very slowly. As long as the time step and frequency constant, \( \eta_{j} \), are reasonable small, the amplitude will not be unduly large. This is supported by the fact that the total error in amplitude for all time steps is third order, as depicted in Equation 20. The total error in phase, Equation 21, is second order. Assuming a positive \( \eta_{j} \), Equation 19 shows that the phase of the simulation solution always lags behind that of the exact solution.

$$n \cdot \epsilon_{amp} = t_{max} O(\Delta t^3)$$

(20)

$$n \cdot \epsilon_{phase} = t_{max} O(\Delta t^2)$$

(21)

**Error Introduced through \( j_{max} \) Boundary Condition:**

As mentioned above, the \( j_{max} \) boundary condition introduces an error to the simulation. This is because, in order to conserve mass, the boundary condition of use allows \( N_{j_{max}} \) to grow in an unbounded fashion under certain conditions. This is most prone to occur when the convection
terms in the equation move the tumor distribution to larger sizes. Firstly, it should be noted that no error is introduced until \( t > (j_{\text{max}} - j_0)\Delta t \), where \( j_0 \) is the largest tumor size with a non-zero probability at \( t = 0 \). This is because the tumor distribution “information” travels only size step for each time step. In other words, \((j_{\text{max}} - j_0)\Delta t\) is the smallest amount of time required for the tumors present at \( t = 0 \) to grow to the size \( j_{\text{max}} \). Secondly, the condition required for \( N_{j_{\text{max}}} \) to grow is given by Equation 22. Since \( k_1 \) and \( f \) the parameters of the model that are frequently varied, it is not reasonable to try to always satisfy Equation 22. Finally, it is reasonable to state that the error introduced by the boundary condition is proportional to \( N_{j_{\text{max}}} \). Therefore, Equation 23 might describe a useful condition to gauge how simulation results are affected by the boundary condition. If \( N_{j_{\text{max}}} \) is small enough to satisfy Equation 23, it would be reasonable to assume the boundary condition error is negligible.

\[
k_1 (j_{\text{max}} - 1)^a > f j_{\text{max}}^b \tag{22}
\]

\[
\frac{N_{j_{\text{max}}}}{\sum_{j=1}^{j_{\text{max}}} N_j} \leq 0.01 \tag{23}
\]

Potential Improvements to Code:

- Continuum approximation and change of size variable to accommodate larger tumor sizes
- Higher order time discretization method or implicit time discretization to get a better quality solution
Results and Discussion

It is important to see how tumors grow and shrink with different criteria applied. This research result can be used to apply better treatment options for cancer patients. There has been tumor modeling on one particular tumor throughout history but not many models available for multi-size tumors. Iwata et al. proposed a model based on multiple sizes of tumors which doesn’t only track one initial tumor but also accounts for a population of tumors and for the growth of metastasis [1]. Some of the variables involved in the calculation here are tabulated below along with their nomenclature. Arbitrary units can be used for certain parameters [1].

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<td>Cutoff j</td>
<td>Tumor size after which chemotherapy is not effective</td>
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Table 1. (Parameters used for calculation)

Plots

Here we have plotted different sets of variables and analyzed the resulting plots. A total of 38 sets have been created each by changing one parameter from a previous runs. We will discuss a few key sets out of these 38 sets. A total of six different plots are generated by the Matlab code for each one of 38 sets. The first graph is the population distribution of different tumor sizes. The second graph combines three plots into 1 page, including average tumor size vs. time and total cell numbers at different times. The third plot verifies the initial condition values of the growth
rate and the death rate which we set equal to each other at t=0. The fourth plot shows if any metastasis rate has been utilized or not in an experiment at run. There is also a figure that shows distribution tumor number vs. tumor size at six time intervals. These time intervals can be set to analyze different curves. The next figure is important in terms of comparing the distribution curves on one plot at different times. It is helpful to show if a tumor travels to left or right. The last graph displays the time at which tumor size is maximum throughout the treatment. Initially different tumor sizes \( (j_i) \) are tried along with varying numbers of tumors one by one. The maximum tumor size \( (j_{\text{max}}) \) that a tumor can reach is also adjusted along with \( t_{\text{max}} \). There is a tumor cutoff size also added later on to reflect a limited influence of chemotherapy on tumor cells. All these variables can be changed to suit the experiment according to need. There are 7 different plots for each set of parameter values. These curves will give a clear picture of the assumed model and help to recognize any deficiencies in the model.

**Effect of \( t_{\text{max}} \)**

To start with, we investigate the tumor distribution over different \( t_{\text{max}} \). \( t_{\text{max}} \) is the maximum time that an experiment is carried on. We can continue the experiment over long periods of time to see the effects of chemotherapy and on different sizes of tumor. The values of \( k_1(j_0) = k_{10}j_0^\alpha k_1 \) and \( f(j_0) = f_0j_0^\beta f \) are kept equal (0.05) and since \( \alpha \) and \( \beta \) are set to zero, \( k_{10} \) and \( k_1 \) effective as well as \( f_0 \) and \( f \) effective are equal. There is no metastasis or cutoff size used in this trial. A few different values of \( t_{\text{max}} \) are used and results are compared below for two unique \( t_{\text{max}} \) values.

![Figure 1(A) \( (t_{\text{max}} = 7000) \)](image1)

![Figure 2(A) \( (t_{\text{max}} = 14000) \)](image2)
Figure 1(A) is a plot of $t_{max} = 7000$ units (set 3) and figure 2(A) is a plot of $t_{max} = 14000$ units (set 4). Both plots have initial tumor size of 100. The only difference between two plots is resulting scales. There is no other effect of $t_{max}$ on distribution. That means applying chemotherapy for long period of time may result in shrinking of certain size tumors and growth of other if no metastasis process present. As it can be seen from figures above the population distribution of size 100 tumor is 0.015 at $t_{max} = 7000$ while 0.01 at $t_{max} = 14000$. Figure 1(B) and Figure 2(B) describes total number of tumors with respect to time for different $t_{max}$. Number of tumors starts to decrease because small tumors are killed off at later time as seen in Figure 1(B) and 2(B). Tumor numbers are affected at almost same rate at for both maximum times. Figure 1(C) and figure 2(C) shows the distribution vs. tumor size at different times. The plots are almost identical for the above values except for different time values. The importance of the plots will be explained further when the difference comes up in plots for the modified values of the variables.
Effect of the number of initial tumors
Since we know the effect of \( t_{\text{max}} \) on population distribution, the next thing is to check effect of \( N_i \) (number of initial tumors) on the population. Here all the parameter values are kept to same as in the above example except the initial tumor numbers are changed. Two experiments are performed with two different initial tumor numbers. Below, plots are analyzed for 50 tumors of size 100 (set 5) as well as 100 tumors of size 100 (set 6) for \( t_{\text{max}} = 7000 \) units. At long times, we expect the population distribution peak to be higher in the graph for large tumor size compared to small tumors due to bigger volume of large tumors. Bigger tumor volume takes more time to eradicate. And it will take relatively more time to reduce these tumors. This is verified by figure 3 and figure 4. For example, the peak is at 1.75 for 100 initial tumors vs 0.85 for 50 initial tumors.

Effect of initial tumor size
Now we will check the influence of initial tumor size in this model. Again all the values are kept same as previous experiments. \( K_2 \) and \( f \) values are set 0.5 and metastasis and all the exponential parameters are neglected. The maximum tumor size that can be reached is set to 1000 units and maximum time is 7000 units. The experiment is performed for an initial tumor sizes of 200 (set 9) and 500 (set 10) individually with one of each tumor. We expect the results to be similar to each other in terms of population distribution because we did not have any restriction of chemotherapy effectiveness. Both growth and chemo terms are set to equal values. Hence, population distribution is not dependent on initial tumor size. The results are shown in figure 5 and figure 6. Although, the curve for tumor size 500 sits more toward right as expected, the distribution peaks are almost identical for both sizes. The difference, as one might notice is that total number of tumors decrease at an earlier time for initial tumor size of 200 than for initial
tumor size of 500, because the left tail of the distribution reaches zero (tumor loss) earlier for the smaller tumor size.

Figure 5 ($j = 200$)
Adding cutoff size

We began with one tumor of size $j=100$ and solved the equation 2 for the distribution plot. There was no restriction as to how effective chemotherapy is on tumor sizes. But there are some cases where literature indicates that the therapy only works for certain size of tumors. It is worth to look at this cutoff size that introduces a maximum allowable tumor size below which tumors are controllable and above which therapy does not have any effects on cancer tumors. Once one finds out the outcome, one can devise a treatment accordingly. Different parameters have been applied below where there is no metastasis and $k_1 = f = 0.5$ in figure 7 (set 8) while $k_1 = f = 0.5$ for $j < 150$ but $f = 0$ for $j \geq 150$ in figure 8 (set 28).
Figure 7 and 8 represents distribution vs. tumor size at different times and figure 8 has cutoff size of 150 while no cutoff size in figure 7. In both systems, there is initially no net growth of tumors, but rather just a diffusive spread. The spread in figure 7 is broader means there are lots of small and big tumors present. However, at later times, tumors that are larger than 150 appear in figure 8. The tumors do not get killed by therapy and this tail of the distribution grows rapidly. Hence, more tumors appear indicated by the long right tail in figure 8. These tumors grow fast and although number of tumor decreases due to the kill off of small tumors, the total number of tumor cells increases due to more volume in bigger tumors compared to model without cutoff size. This may be applicable for patients who exhibit some tumor reduction initially with therapy but suddenly start getting big tumors. This phenomenon is illustrated by the figures below.
**$K_1$ vs. $f$**

So far the influence of various parameters on the distribution has been shown. Most important is to confirm how varying $k_1$ and $f$ affects the model. Below is an example of $k_1 = f = 0.5$ vs. $k_1 = 0.9$ and $f = 0.45$ for zero value of alpha, beta and gamma. Since exponential terms are zero in this example $k_1 = k_{10}$ and $f = f_0$. For $k_1 = f$, figure 9 (set 9) shows the population distribution is symmetric about tumor size $j = 200$ but broadens about the same size at longer times. In contrast for $k_1 >> f$, as figure 10 (set 15) displays, the curve is not symmetric about the same tumor size, in fact the curve travels toward right side as it widens. Tumors keep growing symmetrically about growing tumor size with shifting to the right. This is due to rate of killing being smaller than tumor growth. Tumors are growing faster than the effect of chemotherapy. This kind of scenario is likely for a patient failing therapy treatment at long times while the cancer cell numbers keep growing.

![Figure 9 ($k_1 = f = 0.5$)](image_url)
Adding $\alpha$ and $\beta$ values separately

The implication of different variables has been observed so far, now we can check the model by putting in various values of alpha and beta separately. Once we turn on alpha and beta the effective $k_1$ and effective $f$ values will become $j$ dependent because $k_1(j_0) = k_{10}^\alpha(k_1^\beta)$ and $f(j_0) = f_0^\beta(f)$. So if alpha is higher than beta, then the effective growth surpasses effective death rate for $j > j_0$ (the opposite happens for $j < j_0$) and some tumors will become much larger and overtake chemotherapy's effect. There will be lots of small and large tumors in the system and it broadens the distribution curve at longer time. On the other hand, if beta is bigger than alpha, the immunity term dominates and instead of getting a broader curve we will get narrower curve. This indicates there won't be as many very small and very large tumors since therapy will kill most large tumors and small tumors will grow. Therefore, the curve does not broaden as much as the previous case at longer times. Figure 11 (set 34) and figure 12 (set 35) shows the distribution curves each for $\alpha > \beta$ and $\beta > \alpha$ respectively. Interestingly, the total number of tumors and number of cells starts to decrease at longer time for $\alpha > \beta$ as small tumors get killed off while number of tumors stays constant and number of cells start to increase at longer time for $\beta > \alpha$. Initially the average tumor size decreases as small tumors are lost and then increases at later time as the large tumors enlarge for $\alpha > \beta$ while the average tumor size increases continuously for $\beta > \alpha$. This is due to chemotherapy killing most of smaller tumors and
not many tumors grow back when considering $\beta > \alpha$. inversely, when alpha is bigger than beta the growth term dominates for $j > j_0$ and tumors with $j > j_0$ keep getting bigger.

The above graphs confirm that changing alpha and beta values affect the overall tumor bulk in terms of changes in tumor numbers. This situation arises when a patient has higher tumor growth compare to tumor death rate. Lots of little tumor as well as big tumors are grown in a patient’s body for high alpha. Turning on the exponential death term is equivalent to shooting up the tumor death rate with tumor size. Larger tumors are getting destroyed faster by therapy. Figure 11(A) and Figure 12(A) indicate this phenomenon. The number of tumors stays constant for alpha values turned on as compare to beta since beta can cause tumors to fully disappear.
The number of tumors start to go down after some time due to the killing of infected cells for beta value turned on. The average tumor size increases after a certain time as expected for certain alpha values, while it decreases initially before increasing at certain time for beta value as seen from the above plot.

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Table 2. Simulation Parameter for Figures

**Further improvement**

The above model tested several variables but further work needs to be done regarding different ranges of variables. First of all, metastasis and gamma values have not yet been examined. It will be interesting to see how chemotherapy is affected by metastasis. Chemotherapy could have no effect at all if lots of tumors start to spread and get bigger. One can attempt to create a scenario where values of the growth term, the death term and the metastasis can be changed alternatively or individually by keeping one of the variables constant. There are many different combinations can be tried and tested to create a real life situation for cancer patients. There are different kinds of cancer with disparities about how the tumors behave for each type. Each patient also reacts differently to the treatment and model parameters can be fit accordingly. As stated before, above model is of the discrete tumor size type. For reality tumor sizes, we will have to continue to continuous tumor cases because in real life tumor numbers vary up to $10^{10}$. Metastasis is also an important criterion that can be applied with continuous model.
References

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5) F. S. Borges, K. C. Iarosz, H. P. Ren, Model for tumor growth with treatment by continuous or pulsed Chemotherapy,
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14) National Cancer Institute, cancer.gov. 2015.
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Excel Sheet with different parameters:

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set 18 w/out cutoff
set 21
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set 23 w/out cutoff

set 24 w/out cutoff

set 24 at longer time without cutoff size
4.1: Tumor size vs Distribution at tmax for parameters in set 4
4.2: Time vs Number of cell and tumors for parameters in set 4

4.3: Tumor size vs Metastasis rate for parameters in set 4

4.4: Tumor Size vs rate for parameters in set 4
4.5: Tumor Size vs distribution for parameters in set 4

4.6: Tumor Size vs distribution at different time for parameters in set 4
5.1: Tumor size vs Distribution at tmax for parameters in set 5

5.2: Time vs Number of cell and tumors for parameters in set 5
5.3: Tumor size vs Metastasis rate for parameters in set 5

5.4: Tumor Size vs rate for parameters in set 5
5.5: Tumor Size vs distribution for parameters in set 5

5.6: Tumor Size vs distribution for parameters in set 5
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<th>$\gamma$</th>
<th>$j_i$</th>
<th>No. of tumor</th>
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6.1: Tumor size vs Distribution at $t_{\max}$ for parameters in set 6

6.2 Time vs Number of cell and tumors for parameters in set 6
6.3: Tumor size vs Metastasis rate for parameters in set 6

6.4: Tumor Size vs rate for parameters in set 6
6.5: Tumor Size vs distribution for parameters in set 6

6.6: Tumor Size vs distribution for parameters in set 6
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8.1: Tumor size vs Distribution at $t_{\text{max}}$ for parameters in set 8

8.2: Time vs Number of cell and tumors for parameters in set 8
8.3: Tumor size vs Metastasis rate for parameters in set 8

8.4: Tumor Size vs rate for parameters in set 8
8.5: Tumor size vs distribution for parameters in set 8.

8.6: Tumor size vs distribution at different times for parameter in set 8.
9.1: Tumor size vs Distribution at tmax for parameters in set 9

9.2: Time vs Number of cell and tumors for parameters in set 9
9.3: Tumor size vs Metastasis rate for parameters in set 9

9.4: Tumor Size vs Distribution for parameters in set 9
9.5: Tumor Size vs rate for parameters in set 9

9.6: Tumor Size vs Distribution for parameters in set 9
10.1: Tumor size vs Distribution at t\text{max} for parameters in set 10

10.2: Time vs Number of cell and tumors for parameters in set 10
10.3: Tumor size vs Metastasis rate for parameters in set 10

10.4: Tumor Size vs rate for parameters in set 10
10.5: Tumor Size vs distribution for parameters in set 10

10.6: Tumor Size vs distribution for different time for parameters in set 10
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15.1: Tumor size vs Distribution at $t_{\text{max}}$ for parameters in set 15

15.2: Time vs Number of cell and tumors for parameters in set 15
15.3: Tumor size vs Metastasis rate for parameters in set 15

15.4: Tumor Size vs rate for parameters in set 15
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15.6: Tumor Size vs distribution for parameters in set 15
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![Graphs](image-url)
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