Differential Equation Models of Neoadjuvant Chemotherapeutic Treatment Strategies for Stage III Breast Cancer Patients

BU-1522-M

Edith Aguirre
University of Texas at El Paso

Tametra Smith
Howard University

Jennifer Stancil
University of North Carolina at Chapel Hill

Nicolas Davidenko
Harvard University

August 11, 1999

Abstract

In this study, we investigate different neoadjuvant chemotherapy treatment strategies for patients with Stage III breast cancer. We use two deterministic models to illustrate the effect of chemotherapy on tumor growth and a patient's health. The models consist of a system of three differential equations representing (1) the tumor growth rate, (2) the change in the patient's health (a variable between 0 and 1), and (3) the rate at which the drug combination, cyclophosphamide and adriamycin, dissipates after administration. The intrinsic growth rate of the tumor is exponential in model A, and logistic in model B. In our numerical solutions, success is determined by whether the tumor can be reduced to an operable size (1×10^9 cells) before the patient's health falls to a fatal level (0.1). By varying the frequency and dosage of chemotherapy, we evaluate the effectiveness of various treatment schedules for patients beginning treatment with different sized tumors. We observe that patients diagnosed with smaller tumors show faster success if the chemotherapy dosages are kept constant. On the other hand, patients with larger tumors survive longer when the dosage at each chemotherapy session is proportional to the tumor size and the patient's health.

1 Introduction

1.1 Epidemiology

Despite an increased awareness of breast cancer, this disease is currently the most common malignancy in women 35 to 50 years of age, claiming one out of every four lives that it affects [1]. Estimates of the portion of patients with long-term, disease-free status range only from 3% to 20% with the currently applied treatments [2]. According to a report published in 1998, one out of every nine women will develop breast cancer in her lifetime [3]. With such an imminent presence, finding effective treatment plans has become paramount.

The risk factors associated with breast cancer are related to both physiological traits and lifestyle characteristics. Physiological risk factors include late menapause (after age 50), delayed childbearing (after age 30), early onset of menstruation (before age 12), obesity, and a family history of breast cancer [1]. In addition, breast cancer risk increases with age and is higher in women over 45 whose mammograms show at least 75% dense breast tissue. Risk factors associated with lifestyle include a diet low in Vitamin A, alcohol consumption, and taking hormone replacement therapy or birth control pills for long periods of time [1],[5],[4] .

1.2 Physiology

Cancerous cells characteristically lack responsiveness to the mechanisms that control cell growth and proliferation in normal cells. As a result, cancer cells accumulate to form a solid mass (a tumor, or neoplasm) which continues to grow. Some of these cells, termed metastases, may leave the primary tumor, travel through either the circulatory or lymphatic system, leave the vascular system to enter other tissues, and establish secondary tumors. It is this type of breast tumor growth which is life-threatening to so many women [6].

Tumor growth is believed to be triggered by multiple genetic mutations, either in oncogenes (genes that stimulate cell division) or in tumor suppressor genes (genes which inhibit cell division). These mutations, in turn, may be triggered by chemical carcinogens, radiation, or (for some types of cancer) oncogenic viruses [6] .

Tumor growth rate is dependent upon a number of factors including the rate of tumor cell division, the rate of cell loss by cell death or differentiation (in general, undifferentiated tumors have higher growth rates than well-differentiated tumors), adequate blood supply, and, in some cases, stimulation by molecules called growth factors. Growth factors bind to receptors on the cell surface, inducing a series of biochemical changes in the cell that lead to cell division. In the case of breast cancer, some tumor cells (termed ER-positive) are stimulated to grow in the presence of estrogen [6].

Breast cancer is categorized into four stages, each generally determined by the size of the primary tumor and whether the tumor has metastasized (i.e., spread to other parts of the body). The mathematical models we developed for this study apply to Stage III (locally advanced) breast cancer, which is sub-divided into Stages IIIA and IIIB. In Stage IIIA, one of the following is true: a) the tumor is less than 5 centimeters in diameter and has spread to the underarm lymph nodes, which are attached to one another or to other structures or b) the tumor is greater than 5 centimeters in diameter and the tumor cells have invaded the underarm lymph nodes. In Stage IIIB, either the tumor cells have spread to tissues near the breast, such as the skin or chest wall, including the ribs and chest muscles, or the tumor cells have spread to lymph nodes inside the chest wall along the breast bone [7].

1.3 Treatment

A number of factors affect the treatment options for a female breast cancer patient including her age, menopausal status, breast size, and general health. Other physiological determinants of treatment include the location of the breast tumor, the levels of certain hormone receptors in the tumor cells (specifically, estrogen and progesterone receptors), and, most importantly, the stage of the disease. Treatment regimens for Stage III breast cancer have typically involved a combination of local (breast and underarm surgery and/or radiation therapy) and systemic treatment (hormonal therapy, chemotherapy, or both) [4]. In some cases, a tumor may be too large for immediate surgery, and a physician may choose to reduce the size of the tumor by administering neoadjuvant (preoperative) chemotherapy. This is especially true for women who wish to have breast conservation surgery

instead of a total mastectomy–breast removal [8], [9]. Our mathematical models will address treatment strategies for such cases.

Chemotherapy functions by injuring cells in a certain phase of the cell division process. Thus, chemotherapeutic drugs target rapidly dividing cells, since the probability that these cells will be in a targeted stage of development at any point in time is greater than that for other cells. Unfortunately, these drugs also affect some normally dividing cells (in addition to tumor cells), such as bone marrow cells, cells in the hair follicles, and cells lining the digestive tract. This often results in a number of short-term side effects, including hair loss, lowered resistance to infections, anemia, fatigue, loss of appetite, nausea, vomiting, diarrhea, and mouth sores. Long-term side effects are less common and can include heart disease, secondary cancers such as leukemia, ovary damage, symptoms of menapause, or infertility [10],[4]. The side effects of chemotherapy vary according to the drugs used for a given patient.

Chemotherapeutic drugs may be used alone or, more commonly, in combination. The parameter estimates of the following models are based on a standard regimen of 600 mg/m^2 of cyclophosphamide with 60 mg/m^2 of adriamycin. For example, a patient with total body surface area of 2 m^2 will receive a standard regimen of 1200 mg of cyclophosphamide with 120 mg of adriamycin. These treatments are given in cycles of alternating treatment and recovery periods, every three to four weeks for up to four to six cycles (or whenever the desired end point is reached) [9]. In our models, the desired end point is reducing a tumor to an operable size (1×10^9 cells).

1.4 Clinical Trials

The efficacy of certain chemotherapeutic regimens appears to be related, at least in part, to the relative proliferative rates of the tumor cells. An investigation by Gardin et al. [11] used the tritiated thymidine labeling index (TLI, a technique that estimates the fraction of tumor cells in the cell division phase and, thus, the cell proliferative rate) to study the relationship between tumor cell kinetics and the effectiveness of neoadjuvant chemotherapy (in this study, a regimen of adriamycin, 5-fluorouracil, and cyclophosphamide was used) on tumor regression in a group of 36 patients. The analysis revealed

that 83% of those with high TLI had a decrease in tumor cell proliferative rate, compared to 39% of those with low TLI, suggesting that patients whose tumors grow more rapidly demonstrate a greater response to chemotherapy than those whose tumors grow less rapidly. But the effectiveness of a specific chemotherapy also depends on the specific drugs used as well as the dose intensity, frequency, and duration of treatments.

In addition to choosing the most effective drug combination, dosage and timing of chemotherapy continue to challenge researchers seeking the optimal treatment regimen. A review of randomized studies of conventional dosage of adriamycin for metastatic breast cancer (alone and in combination with cyclophosphamide and 5-fluorouracil) showed higher response rates from the high dose versus the low dose therapy (25% for low and 58% for high dosage in the adriamycin group, and 39% for low and 70% for high dosage in the adriamycin-cyclophosphamide-5-fluorouracil group)[3]. According to Cameron and Leanard, however, "all the available data suggest that, in contrast to laboratory data, dose increments of the order of 2-fold, as in most of these studies, have only marginal effects upon survival"[3],[9].

A treatment variation involving increased dosages beyond conventional limits – high dose chemotherapy, followed by a bone-marrow transplant – continues to receive a great deal of attention. Data from the Autologous Blood and Marrow Transplant Registry show, for patients with Stage III breast cancer, a 3-year progression-free survival of 60% (95% confidence interval: 53% - 67%) and an overall survival of 70% (95% confidence interval: 63% - 77%). One should note that long-term, disease-free survivors accepting either conventional dosage or high-dose chemotherapy tend to be younger, healthier individuals who have a smaller tumor burden than the overall patient population [2]. Hence, clinicians are often faced with the delicate balance between the beneficial effects of chemotherapy and its toxicity to the patient when determining an appropriate dosage.

Some studies of optimal chemotherapeutic timing, such as those conducted by Bonadonna et al. [12], have addressed the order of drug delivery, suggesting that alternating administration of drugs in multi-agent regimens is not a superior approach to delivery of a set of cycles of one drug followed by that of another [3].

1.5 Previous Mathematical Models

A number of mathematical models have been proposed to simulate the behavior of tumor growth and the effects of chemotherapy on breast cancer, in order to evaluate a variety of chemotherapeutic protocols. For example, a study by Shochat et al. considered three different modes of tumor cell growth (exponential, Gompertz, and power laws) to find the effects of three neoadjuvant chemotherapeutic protocols on tumor regression. The results suggested that high dose chemotherapy cannot eliminate metastatic breast cancer, but this treatment method may lead to a complete response if administered early in the progression of the disease. In addition, the computer simulations achieved higher success rates for very high doses compared to conventional dosages [14]. Some models account for the fact that chemotherapy targets a specific phase of the cell development cycle. Aroesty et al. [15] propose one such "compartment" model [15]. In our models, we will not only measure the effects of chemotherapy on the tumor growth, but also take into consideration the patient's health over time. In this approach, the patient's health is affected by both the chemotherapy and the invading tumor.

2 Methodology

2.1 Modeling Tumor Growth and Patient Health

Our approach is to model the effects of different chemotherapeutic treatment strategies on a growing tumor and a patient's health. The general model consists of two equations, one to represent the rate of tumor growth and the other to represent the change in the patient's health. The tumor has an intrinsic growth rate (which may depend on the patient's health), and an external decay rate due to chemotherapy treatment. The patient's health has an intrinsic recovery rate (affected by the size of the tumor) and an external decay rate due to chemotherapy treatment. We have our general model:

Tumor Growth Rate	=	Intrinsic Growth Rate	−	Tumor Reduction Rate due to Chemotherapy
Health Recovery Rate	=	Intrinsic Recovery Rate	−	Health Decay Rate due to Chemotherapy

2.2 The 2-Equation Explicit Time Model

We first attempted to model a periodic chemotherapy treatment schedule by using a sinusoidal treatment function. In this model, we have two differential equations representing the growth rate of the tumor and the recovery of the patient. The tumor size, g, is given in units of 10^{10} cells, where $g = 1$ is equivalent to a tumor with 3-cm diameter. The health, or vitality, of the patient, h, is an abstract variable that ranges from 0 to 1. Any value of h lower than 0.1 is interpreted as the death of the patient. A value of $h = 1$ represents a completely healthy patient. The interpretation of h as a biological measurement is not completely defined, but the concept of health is based on quantitative measures that are checked before administering each chemotherapy treatment, including white blood cell count, hemoglobin/hematocrit, platelet count, renal function tests, liver function tests, and tests for organ specific drug effects [16]. The variable h is a normalized function of these measures. The two variables, g and h, affect each other over time according to the following system:

$$\frac{dg}{dt} = \left[\gamma(1 - e^{-Ah}) - d_1 g \cos^{2k}\left(\frac{\pi}{T}t\right)\right] g, \tag{1}$$

$$\frac{dh}{dt} = \left[r\left(1 - \frac{h}{\frac{1}{1+(\delta g)^2}}\right) - d_2 g(\cos^{2k}\left(\frac{\pi}{T}t\right)\right] h, \tag{2}$$

In equation (1), the primary tumor, g, follows an exponential growth pattern where the intrinsic growth rate is dependent on the health of the patient. The parameter γ represents the maximal intrinsic growth rate, and the factor $(1 - e^{-Ah})$ represents the effect of the patient's health on the tumor's ability to grow. When a patient's health is very low or nearing death, the tumor growth slows down due to lack of nutrients in the body [9]. Thus, when h is very small the intrinsic growth rate of the tumor becomes small as well. The second term $d_1 g \cos^{2k}\left(\frac{\pi}{T}t\right)$ represents the effect of chemotherapy on the tumor growth. The periodic administration of chemotherapy is represented by an even powered cosine function, which allows for small periods of dosage time with large periods of rest. Here, T is the number of days between chemotherapy sessions, and $d_1 g$ denotes the amplitude (or dosage level) which is proportional to the size of the tumor.

Equation (2) represents the change in the patient's health, h, over time. The normal recovery rate of a patient, i.e. the rate at which h grows from an initial value toward to 1, in the absence of chemotherapy or a tumor, is given by a logistic equation. Here, the health carrying capacity is limited by the size of the tumor. As the tumor grows large, the carrying capacity, $\frac{1}{1+(\delta g)^2}$, decreases. The administration of chemotherapy is included just as in equation (1), but a different constant of proportionality is used to evaluate the effect of a chemotherapy dosage on the patient's health.

This model presented several problems (see Figure 1). First, the potentiated cosine curve caused such a steep spike, that the numerical integration process became unreliable, as the heights of the spikes were often measured with an error of 30% or above. Second, a cosine function makes time explicit, and the analysis of the equation becomes difficult. Third, and most importantly, the sinusoidal function does not accurately match the actual administration of chemotherapeutic drugs. According to the model, the concentration of the drug in the body smoothly increases and then decreases, while in actual practice, the drug is administered instantaneously and then decays over time. For this reason, we modified our model to a 3-equation system which more accurately represents how chemotherapy is administered and how it decays once it is in the patient's bloodstream.

2.3 The 3-Equation Implicit Time Models

In these models, we keep the same intrinsic growth rates for g and h, but we model the change in the amount of drug effect, c, with a separate differential equation. We assume that the drug effect decays at a particular rate λ. To represent the periodic administration of the drug, we reinitialize the value of c at the beginning of each period, using two different protocols. In the first protocol, the reinitialized value is always the same, and in the second protocol, the reinitialized value is proportional to the health and tumor size at the end of the previous period.

Using this new chemotherapy equation, we set up two models, Model A and Model B, where the intrinsic tumor growth rate is exponential and logistic, respectively.

2.3.1 Model A

$$\frac{dg}{dt} = [\gamma(1 - e^{-Ah}) - d_1 c]g, \tag{3}$$

$$\frac{dh}{dt} = \left[r\left(1 - \frac{h}{\frac{1}{1+(\delta g)^2}}\right) - d_2 c\right] h, \tag{4}$$

$$\frac{dc}{dt} = -\lambda c, \tag{5}$$

In equation (3), the tumor size, g, follows an exponential growth pattern where the intrinsic growth rate is dependent on the health of the patient. The parameter γ represents the maximal intrinsic growth rate and the factor $(1 - e^{-Ah})$ represents the effect of the patient's health on the tumor's ability to grow. In this system, the chemotherapy factor is introduced as an exponential decay with coefficient d_1.

In equation (4), the change in patient's health, h, over time is represented. The normal recovery rate of a patient, i.e. the rate at which h grows from an initial value toward to 1 in the absence of chemotherapy or a tumor, is given by a logistic equation. Here, the health carrying capacity is limited by the size of the tumor. As the tumor grows large, the carrying capacity, which is given by $\frac{1}{1+(\delta g)^2}$, decreases. The chemotherapy cycles are included just as in equation (3), but a different constant of proportionality, d_2, is used to determine the effect of a chemotherapy dosage on the patient's health.

In equation (5), the drug effect c undergoes exponential decay with rate λ. We note that the actual drug in the body is eliminated within a day, but the effect on both the tumor and the patient's health lasts for several days.

2.3.2 Model B

$$\frac{dg}{dt} = \left[\gamma\left(1 - \frac{g}{\frac{K}{1-h}}\right) - d_1 c\right] g, \tag{6}$$

$$\frac{dh}{dt} = \left[r\left(1 - \frac{h}{\frac{1}{1+(\delta g)^2}}\right) - d_2 c \right] h, \tag{7}$$

$$\frac{dc}{dt} = -\lambda c, \tag{8}$$

This model is based on Model A, with the difference that the tumor growth is logistic, to account for the fact that a tumor actually slows down its growth when the patient is dying. The carrying capacity term $\frac{K}{1-h}$ depends on h as follows. When h is large (or 1), the carrying capacity is very large (or ∞) allowing exponential growth of the tumor. When h is small (close to 0), the carrying capacity approaches K (the tumor size correlated with the death of the patient). Other models have also used a logistic growth rate for tumors [14]. This modification prevents the tumor from growing infinitely, whereas this is allowed in Model A. For this reason, Model A may be a more appropriate model for small tumors, while Model B can model treatment of both small and large tumors.

2.4 Parameter Values

In each of the two models we analyzed (Model A and Model B), there are 7 parameters. We note that the units of g are in 10^{10} cells, the units of c are grams, and the unit of time is one day. For model A, we have parameters γ, A, d_1, r, δ, d_2, and λ. For model B, we have parameters γ, K, d_1, r, δ, d_2, and λ.

- γ is the maximal intrinsic growth rate of the tumor. From the data in E. Shochat's simulations [14], we found the average doubling time for Stage III tumors to be approximately 200 days (although the variance is very high). Therefore, the value of $\gamma = \frac{\log 2}{200} = 0.0035$.
- A is a factor controlling the dependence of the tumor growth rate on the health of a patient. The higher the value of A is, the lower the health must be in order to slow down the tumor. We choose a value of 3.5.
- d_1 is the strength of the chemotherapy effect on the tumor growth. Data suggests that a normal chemotherapy dosage (1 gram = 910 mg of

cyclophosphamide + 90 mg of adriamycin) will result in approximately 15% reduction of the tumor [14]. By solving the system numerically with constant health value of 1, we determine that $d_1 = 0.08$.

r is the intrinsic logistic growth rate of h, the patient's health. We know that the recovery time from a normal chemotherapy dosage (1 gram) is approximately 28 days, the period between chemotherapy sessions [9]. By starting with a health value of 0.5, we find this recovery time is best matched with a value of $r = 0.1$.

δ is the factor that controls the tumor's effect on health. We remark that in breast cancer, the local tumor itself does not kill the patient. Instead, the metastases associated with tumors of a certain size affect the patient's health and eventually lead to death. Still, since we are measuring only the local tumor, we interpret the local tumor as the indicator of the extent of the disease. We determine the value of δ by letting a tumor of size 1.2×10^{11} cells (note: $g = 12$ is equivalent to a tumor with diameter of 7 cm) reduce the health to $h = 0.1$ (the point at which we consider the patient's chance of survival to be zero). This constraint leads to a value of $\delta = 0.3$.

d_2 is the strength of the chemotherapy effect on the patient's health. We estimate the value of d_2 by looking at the lethal dosage, which in healthy patients is approximately $2\text{g}/m^2$ ($c = 3.2$). By forcing this dosage to bring the value of h from 1 to 0.1, we interpolate that the effect of a normal dosage ($c = 1$) should bring the patient's health down from 1 to about 0.7. The numerical solution produces in a value of $d_2 = 0.3$.

λ is the decay rate of the chemotherapy effect from the body. We estimate that the remaining drug effect after 7 days is approximately $\frac{1}{10}$ of the original dosage, and obtain a value of $\lambda = 0.35$.

K is the lower limit of the tumor's carrying capacity. We take this value to be 1.2×10^{11} cells, or $K = 12$.

2.5 Stability Analysis

In order to analyze Model A or Model B mathematically, we consider only one dose of chemotherapy, which decays exponentially. The equilibrium points

are determined and the Jacobian matrix (J) of the system of equations is evaluated at each equilibrium point to determine the local stability of the points. If the real part of all the eigenvalues is negative, the point is stable. Otherwise, the point is unstable.

For Model A, the equilibrium points are: $(g = 0, h = 1, c = 0)$ which represents a healthy patient with no tumor, and $(g, h = 0, c = 0)$ which represents a dead person with a sitting tumor of size g .

$$J(0,1,0) = \begin{pmatrix} \gamma(1-e^{-}A) & 0 & 0 \\ -r & -r & 0 \\ 0 & 0 & -\lambda \end{pmatrix}, \tag{9}$$

$$J(g,0,0) = \begin{pmatrix} 0 & \gamma g A & -d_1 g \\ 0 & r & 0 \\ 0 & 0 & -\lambda \end{pmatrix}, \tag{10}$$

Both of these points are unstable because at least one eigenvalue from each Jacobian has a positive real part.

For Model B, the equilibrium points are:

$$(0,0,0), (0,1,0), (K,0,0), (\frac{K}{1-R}, \frac{1}{1+(\frac{\delta K}{1-R})^2}, 0),$$

where $R = (\frac{-1}{2}(\delta K)^2 + \frac{1}{18}(\delta K)^2\sqrt{4(\delta K)^2 + 27}\sqrt{3})^{\frac{1}{3}} - \frac{1}{3}\frac{(\delta K)^2}{(\frac{-1}{2}(\delta K)^2 + \frac{1}{18}(\delta K)^2\sqrt{4(\delta K)^2+27}\sqrt{3})^{\frac{1}{3}}} +$ 1.

The Jacobians for the first three equilibrium points are:

$$J(0,0,0) = \begin{pmatrix} \gamma & 0 & 0 \\ 0 & r & 0 \\ 0 & 0 & -\lambda \end{pmatrix}, \tag{11}$$

$$J(0,1,0) = \begin{pmatrix} \gamma & 0 & 0 \\ 0 & -r & -d_2 \\ 0 & 0 & -\lambda \end{pmatrix}, \tag{12}$$

$$J(K,0,0) = \begin{pmatrix} -\gamma & \gamma K & -d_1 K \\ 0 & r & 0 \\ 0 & 0 & -\lambda \end{pmatrix}, \tag{13}$$

All of these points are unstable because at least one eigenvalue from each Jacobian has a positive real part.

For the Jacobian of the fourth equilibrium point, see the appendix.

2.6 Simulations

We obtained numerical solutions to the system of equations using the application *Matlab* 5.2.0. To test the efficacy of different treatment protocols, we ran approximately 500 simulations, and varied four factors simultaneously in Model A and Model B: the period length between chemotherapy dosages, the initial chemotherapy dosage, the initial tumor size, and the method of choosing the reinitialized value of c. The period length varied between 20 and 40 days, with four-day intervals. The initial chemotherapy dosage varied between 0.6 grams and 2.6 grams, with 0.4-gram intervals. The initial tumor sizes were 3×10^9 cells, 1×10^{10} cells, 4×10^{10} and 1×10^{11} cells. Finally, there are two methods of choosing the reinitialized value of c. In the first, the fixed dosage scheme, the initialized value of c is kept fixed for every administration of chemotherapy. In the second, the adaptive dosage scheme, the initialized value of c at each period is proportional to the current value of $g \times h$ (i. e. proportional to the tumor size and health of the patient) and the constant of proportionality is $\frac{c_0}{g_0 \cdot h_0}$ (the initial conditions of the simulation).

We run each simulation for a certain maximum number of periods such that the total length of time is approximately one year. After each run, we determine one of five possible events:

(1) *success* - the tumor was reduced to a size of 1×10^9 cells, or $g = 0.1$;
(2) *death* - the patient's health, h, was reduced to a value of 0.1;

and in the cases where neither *success* nor *death* occurs, we identify

(3) *progress* - h was increasing over time by the end of one year;
(4) *deterioration* - h was decreasing over time; and
(5) *steady state* - h was oscillating over time, without any upward or downward trend.

When *success* occurs, we note the time at which the tumor reached $g = 0.1$ and the minimum value of h in the simulation. When *death* occurs, we note the time at which h reached 0.1 and the value of g at that time. When *progress*, *deterioration*, or *steady state* occurs, we note the minimum value of h (if it ever got below 0.2), and the g and h values at the end of one year. For a few examples of simulations, see Figures 2 and 3, where we compare the effect of a fixed dosage scheme (Figure 2) to an adaptive dosage scheme (Figure 3). For a complete list of the simulation results, see the tables in the appendix.

3 Results

We divide our observations into three sections. In Section 1, we observe how varying the initial dosage and period length proportionally affects the *success* rate. In Section 2, we vary initial dosage and period length proportionally, but compare how the *progress* cases were affected. In Section 3, we describe the most effective treatment strategies for patients beginning treatment with different sized tumors.

3.1 Section 1

First, we look at successful simulations (i.e. simulations where the tumor sinks to below 0.1 before the health does). We focus on period lengths and dosages that remain proportional. Specifically, we look at dosages of 1 gram with period 20 days, 1.4 grams with 28 days, and 1.8 grams with 36 days. Only simulations done with the fixed dosage scheme (FDS) produced *success* for these treatment schedules. As seen in Figure 4(A), an increase in dosage with equivalent increase in period length causes a decrease in the time to *success* (A). Although the minimum health the patient sustains also decreases

(Figure 4(B)), the overall effect may be desirable.

3.2 Section 2

Next, we observe the simulations in which neither *death* nor *success* occurs by the end of the first year. We focus on simulations using the adaptive dosage scheme (ADS). We use the same proportional treatment schedules as previously mentioned. Figures 5(A) and 5(B) show that, as in the above case, an increase in dosage with equivalent increase in period length has beneficial results for the patient. Specifically, these patients end the year with lower tumor sizes and higher health value, even though the cumulative drug administered is the same as in the patients with lower dosages and shorter period lengths.

3.3 Section 3

For patients diagnosed with small tumors, we find overall that the FDS is more beneficial than the ADS. Specifically, patients with initial tumor sizes of $g = 0.3$ ($\times 10^{10}$ cells) showed an 86% *success* rate under the FDS and only a 50% *success* rate under the ADS. However, it must be noted that 3% of patients in the FDS died due to chemotherapy toxicity while none of the patients in the ADS died.

In contrast, patients diagnosed with large tumors show higher survival when treated with an adaptive dosage scheme. Specifically, patients with initial tumor sizes of $g = 10$ ($\times 10^{10}$ cells) show a 100% *death* rate under the FDS. On the other hand, 47% of patients under the ADS survive after one year of treatment.

4 Limitations of the Models

The main difference between the models developed in this project and other existing chemotheraputic treatment models is our inclusion of a health variable. Health is a difficult concept to quantify because there are too many as-

pects of a woman's physiology that affect her health. Also, since chemotherapy affects the patient in so many ways, and since people's responses are so varied, it is difficult to estimate the effect of chemotherapy on our variable h. Thus, the parameters in the second differential equation (4) and (7), especially the parameter d_2, cannot be accurately estimated.

Our model excludes several relevant physiological features of breast cancer. We do not include the age of the patient, which is one of the factors affecting tumor doubling time. We do not consider the role of estrogen receptors, in order to exclude the effect of hormone therapy. Furthermore, we do not take into account the heterogeneity of a tumor. Another difficulty we encounter is that tumor measurements during the treatment of breast cancer are not reliable, due to the extensive scar tissue that surrounds the tumor.

Finally, in our model, we measure only the local tumor size, and from this deduce the extent of metastasis. We do not specify the exact location of the primary tumor, nor do we specify where metastases will colonize and produce secondary tumors. These locations are crucial in determining the patient's prognosis.

Despite all of these limitations and assumptions, our model may offer insight into a variety of treatment strategies. Adaptive dosage schemes were shown to be beneficial to patients with certain tumor sizes, and detrimental to others. In the future, more adaptive dosage schemes can be formulated for the model and tested for efficacy.

5 Acknowledgements

This study was supported by the following institutions and grants: National Science Foundation (NSF Grant DMS 9977919); National Security Agency (NSA Grants MDA 9049710074); Presidential Faculty Fellowship Award (NSF Grant DEB 925370) and Presidential Mentoring Award (NSF Grant HRD 9724850) to Carlos Castillo-Chavez; the Office of the Provost of Cornell University; Intel Technology for Education 2000 Equipment Grant. Special thanks to Ted Greenwood of the Sloan Foundation, and to those who supported us through this study: Dr. Carlos Hernandez-Suarez, Dr. Car-

los Castillo-Chavez, Dr. Stephen Wirkus, Harold Figueroa, Ricardo Saenz, Baojun Song, Dr. David Duggan, Maria Laux, Cesar Cardona, Abdul Aziz Yakubu, Ariel Cintron, and Saul Franco.

References

[1] Wallis, Claudia. (1991) A Puzzling Plague. *Time Magazine.* January 14, 1991:48-52

[2] Martin, M., et. al. (1998) Long-Term Disease-Free Survival in Disseminated Breast Cancer Patients Treated with Conventional and High-Dose Chemotherapy: Predictive Factors and Therapeutic Implications. *Dose and Timing: The Pillars of Successful Chemotherapy.* G. Rosti, ed. Elsevier Science B. V., 33-51

[3] Cameron, D. A., Leonard, R. C. F. (1998) The Importance of Dose and Time in the Treatment of Breast Cancer. *Dose and Timing: The Pillars of Successful Chemotherapy.* G. Rosti, ed. Elsevier Science B. V., 19-31

[4] Breast Cancer. July 20, 1999. World Wide Web Page. http://cancernet.nci.nih.gov/wyntk_pubs/breast.htm

[5] Warmuth, M. A., Sutton, L. M., Winer, E. P. (1997) A Review of Hereditary Breast Cancer: From Screening to Risk Factor Modification. *The American Journal of Medicine.* **102**:407-415

[6] Phillips, J., Murray, P., ed. (1995) *The Biology of Disease* Blackwell Science Ltd

[7] National Cancer Institute PDQ: Treatment - Patients - Breast Cancer. July 20, 1999. World Wide Web Page. http://cancernet.nci.nih.gov/clinpdq/pif/Breast_cancer_Patient.html

[8] National Cancer Institute PDQ: Treatment - Health Professionals - Breast Cancer. July 20, 1999. World Wide Web Page. http://cancernet.nci.nih.gov/clinpdq/soa/Breast_cancer_Physician.html

[9] Dr. David Duggan. July 22, 1999. Chairman of Medicine at SUNY Health Science Center at Syracuse, New York. Personal Communication

[10] Questions and Answers About Adjuvant Therapy for Breast Cancer. July 20, 1999. World Wide Web Page. http://cancernet.nci.nih.gov/clinpdq/therapy/Questions_and_Answers_About_Adjuvant_Therapy_for_Breast_Cancer.html

[11] Gardin, G., et. al. (1994) Relationship of Variations in Tumor Cell Kinetics Induced by Primary Chemotherapy to Tumor Regression and Prognosis in Locally Advanced Breast Cancer. *Breast Cancer Research and Treatment.* **32**:311-318

[12] Buzzoni, R., Bonadonna, G., Valagussa, P., Zambetti, M. (1991) Adjuvant Chemotherapy With Doxorubicin Plus Cyclophosphamide, Methotrexate, and Fluorouracil in the Treatment of Resectable Breast Cancer With More Than Three Positive Axillary Nodes. *J Clin Oncol.* **9**:2134-2140

[13] Retsky, M. W., Wardwell, R. H., Swartzendruber, D. E., Hendley, D. L. (1987) Prospective Computerized Simulation of Breast Cancer: Comparison of Computer Predictions with Nine Sets of Biological and Clinical Data. *Cancer Research.* **47**:4982-4987

[14] Shochat, E., Hart, D., Agur, Z. (1999) Using Computer Simulations for Evaluating the Efficacy of Breast Cancer Chemotherapy Protocols. *Mathematical Models and Methods in Applied Sciences.* **9**:599-615

[15] Aroesty, J., Lincoln, T., Shapiro, N., Boccia, G. (1973) Tumor Growth and Chemotherapy: Mathematical Methods, Computer Simulations, and Experimental Foundations. *Mathematical Biosciences.* **17**:243-300

[16] OncoLink: Introduction to Chemotherapy. August 6, 1999. World Wide Web Page. http://cancer.upenn.edu/specialty/med_onc/chemo/general/chemo_intro.html

Appendix

Here, we present the raw data tables and the source code for our Matlab programs.

5.1 Raw Data Tables

Each table page presents the simulations for a particular beginning tumor size, a particular model (A or B), and a particular dosage scheme (constant or varying). The first two columns are the quantities we vary in each page: the period length (from 20 to 40 days with 4-day intervals) and the initial chemotherapy dosage (from 0.6 to 2.6 grams with 0.4-gram intervals). The third column has a letter code (s=success, d=death, n=neither). Next we record whether there was progress (p), deterioration (det), or steady state (ss) in the health variable. The next column shows the duration of the simulation in days. The next shows the final tumor size, the final health value, and the minimum health sustained during the entire simulation.

5.2 Programs

The chemo_model* files are ODEFILES which describe the differential equations pertaining to our models. chemo_model.m has the equations for Model A (exponential tumor growth) and chemo_model_log.m has the equations for Model B (logistic tumor growth).

The chemo_therapy* files compute the chemo_model trajectories. These programs allow the periodic reinitialization fo the variable c. chemo_therapy.m computes the trajectories for Model A, with varying chemotherapy. chemo_therapy_log.m computes the trajectories for Model B, with varying chemotherapy. chemo_therapy_const.m computes the trajectoreis for Model A, with constant chemotherapy. chemo_therapy_log_const.m computes the trajectories for Model B, with constant chemotherapy.

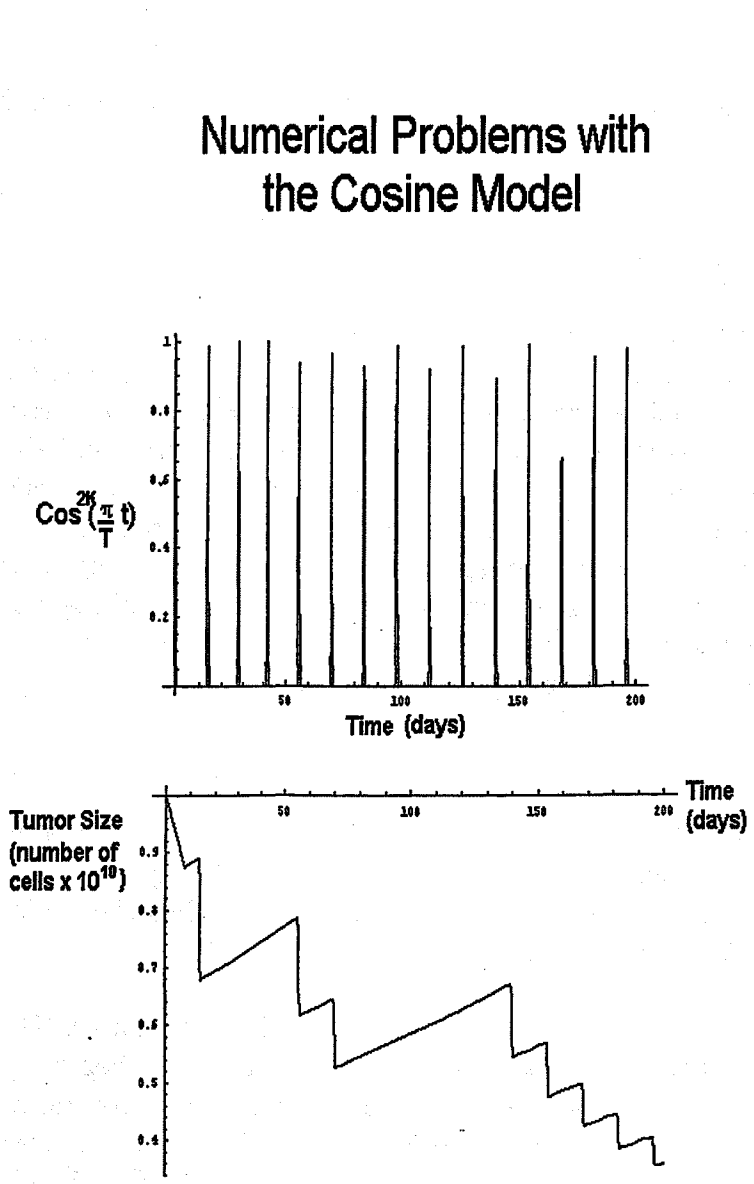

Figure 1: Using a value of $k = 500$, we can see the numerical errors in evaluating the even powered cosine function (above) and in integrating the effect of chemotherapy on the tumor dynamics (below).

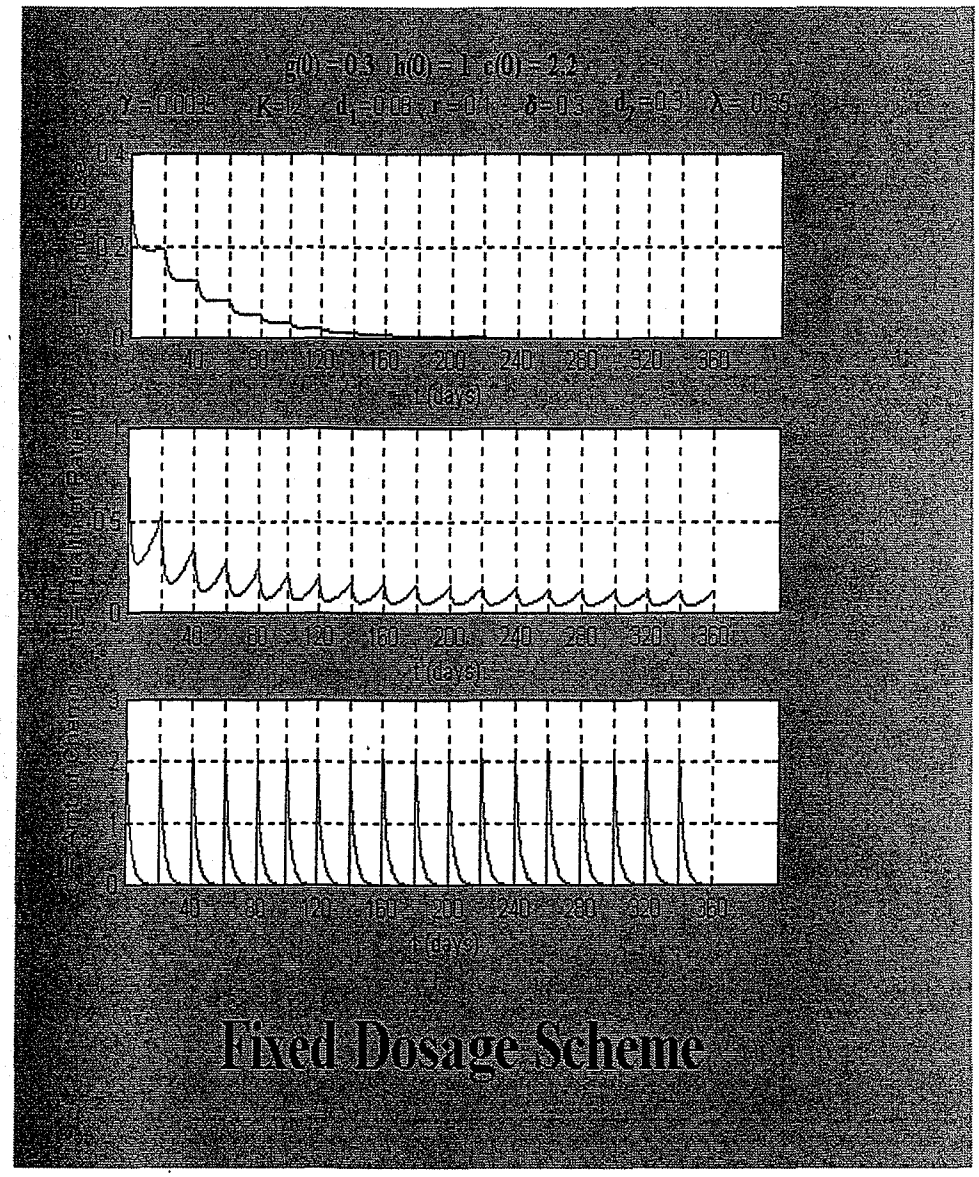

Figure 2: Using a fixed dosage scheme, this patient dies (the health variable h reaches below 0.1).

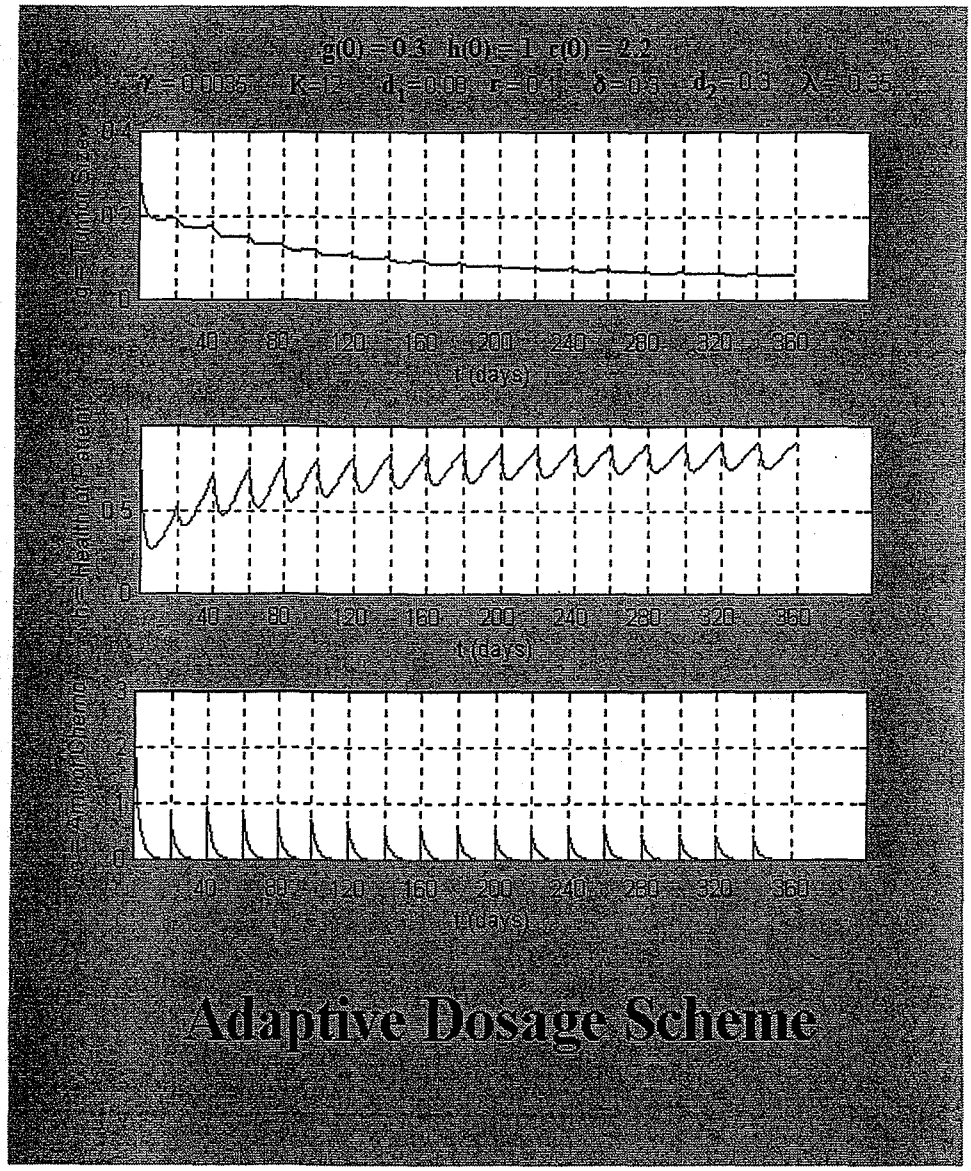

Figure 3: Using an adaptive dosage scheme, the patient survives and the tumor is reduced to an operable level (the variable g reaches below 0.1).

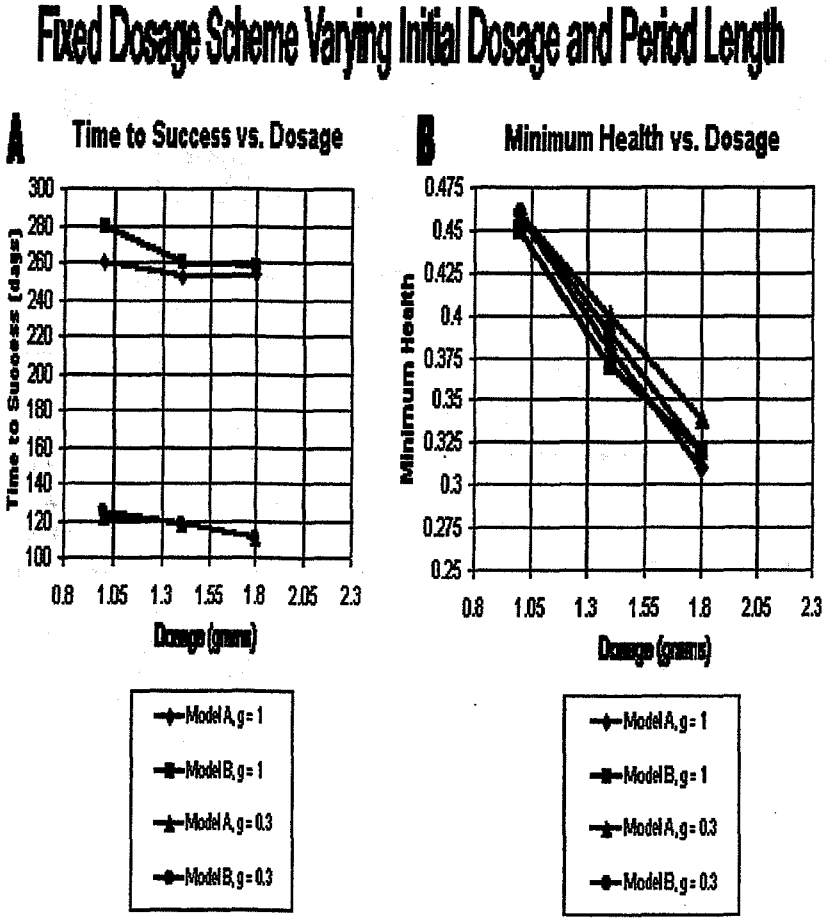

Figure 4: The effects of increasing the dosage and period length proportionally on the time to success (A) and minimum health (B), using a fixed dosage scheme.

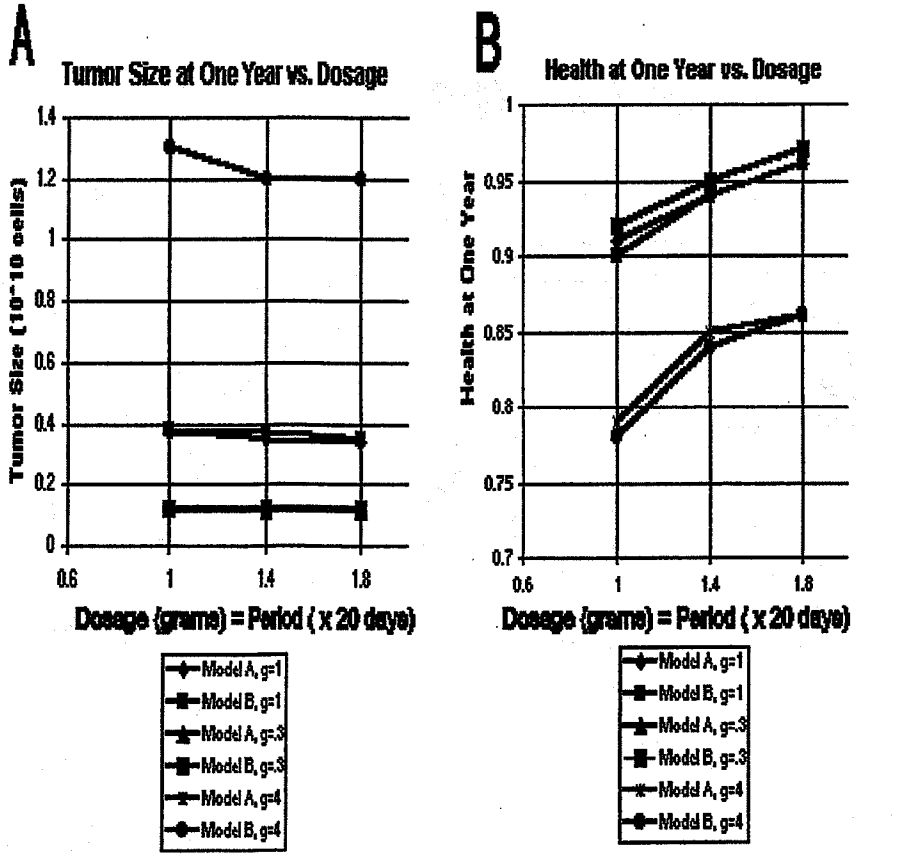

Figure 5: The effects of increasing the dosage and period length proportionally on the final tumor size (A) and final health after one year of treatment, using an adaptive dosage scheme.

```
Clear[δ, a, K, h, G, H, c, r, d1, d2]
```

$$dG = \gamma * G1 * \left(1 - \frac{G1}{\frac{K}{1-H}}\right) - d1 * c * G1;$$

$$dH = r * H * \left(1 - \frac{H}{\frac{1}{1+(\delta * g)^2}}\right) - d2 * c * H;$$

$$dc = -\lambda * c;$$

$$a = (\delta * K)^2;$$

$$h = \left(\left(\frac{-1}{2} * a + \frac{1}{18} * a * \sqrt{(4*a+27)} * \sqrt{3}\right)^{\wedge}\frac{1}{3} - \frac{1}{3} * a \Big/ \left(\frac{-1}{2} * a + \frac{1}{18} * a * \sqrt{(4*a+27)} * \sqrt{3}\right)^{\wedge}\frac{1}{3} + 1\right);$$

```
Simplify[
 MatrixForm[J = {{∂G1 dG, ∂H dG, ∂c dG}, {∂G1 dH, ∂H dH, ∂c dH}, {∂G1 dc, ∂H dc, ∂c dc}}]]
```

$$\begin{pmatrix} \frac{-c\,d1\,K+(2\,G1\,(-1+H)+K)\,\gamma}{K} & \frac{G1^2\,\gamma}{K} & -d1\,G1 \\ 0 & -c\,d2+r-2\,H\,r-2\,g^2\,H\,r\,\delta^2 & -d2\,H \\ 0 & 0 & -\lambda \end{pmatrix}$$

```
FullSimplify[J1 = J /. {G1 → K/(1-h), H → 1/(1+(δ*K/(1-h))^2), c → 0}]
```

$$\left\{\left\{-\gamma, \left(\left(\frac{3}{2}\right)^{2/3} K\gamma\left(K^2\delta^2\left(-9+\sqrt{3}\sqrt{27+4K^2\delta^2}\right)\right)^{\wedge}(2/3)\right) \Big/ \left(K^2\delta^2 - \left(K^2\delta^2\left(-9+\sqrt{3}\sqrt{27+4K^2\delta^2}\right)\right)^{\wedge}(2/3) / \left(2^{2/3}3^{1/3}\right)\right)^{\wedge}2,\right.$$
$$\left(\left(\frac{3}{2}\right)^{1/3} d1\,K\left(K^2\delta^2\left(-9+\sqrt{3}\sqrt{27+4K^2\delta^2}\right)\right)^{\wedge}(1/3)\right) \Big/ \left(-K^2\delta^2 + \left(K^2\delta^2\left(-9+\sqrt{3}\sqrt{27+4K^2\delta^2}\right)\right)^{\wedge}(2/3) / \left(2^{2/3}3^{1/3}\right)\right)\Big\},$$
$$\left\{0, \frac{1}{3}r\left(-3-6g^2\delta^2+\left(2\,2^{1/3}3^{2/3}K^2\delta^2\left(1+g^2\delta^2\right)\right) \Big/ \left(K^2\delta^2\left(-9+\sqrt{3}\sqrt{27+4K^2\delta^2}\right)\right)^{\wedge}(1/3) - 2^{2/3}3^{1/3}\left(1+g^2\delta^2\right)\left(K^2\delta^2\left(-9+\sqrt{3}\sqrt{27+4K^2\delta^2}\right)\right)^{\wedge}(1/3)\right),\right.$$
$$-d2 \Big/ \left(1+\left(\left(\frac{3}{2}\right)^{2/3} K^2\delta^2\left(K^2\delta^2\left(-9+\sqrt{3}\sqrt{27+4K^2\delta^2}\right)\right)^{\wedge}(2/3)\right) \Big/ \left(K^2\delta^2 - \left(K^2\delta^2\left(-9+\sqrt{3}\sqrt{27+4K^2\delta^2}\right)\right)^{\wedge}(2/3) / \left(2^{2/3}3^{1/3}\right)\right)^{\wedge}2\right)\Big\},$$
$$\{0, 0, -\lambda\}\}$$

```
FullSimplify[Eigenvalues[J1]]
```

$$\left\{\frac{1}{3}r\left(-3-6g^2\delta^2+\left(2\,2^{1/3}3^{2/3}K^2\delta^2\left(1+g^2\delta^2\right)\right) \Big/ \left(K^2\delta^2\left(-9+\sqrt{3}\sqrt{27+4K^2\delta^2}\right)\right)^{\wedge}(1/3) - 2^{2/3}3^{1/3}\left(1+g^2\delta^2\right)\left(K^2\delta^2\left(-9+\sqrt{3}\sqrt{27+4K^2\delta^2}\right)\right)^{\wedge}(1/3)\right), -\gamma,\right.$$
$$\left.-\lambda\right\}$$