Modeling Tumor Growth in the Bladder

With Differential Equation

By

Kourosh Tavatli

Chapter 1

Tumor Growth in the Bladder

1.1 Introduction

Each year in the United States, bladder cancer is diagnosed in 38,000 men and 15,000 women. This is the most common type of cancer in men and the eighth most common in women. (According to a report from the National Cancer Institute).

Before beginning to model diagrams of this disease, I would like to discuss the possible causes, symptoms, diagnosis, treatments and rehabilitation. In addition, I will provide information to help patients cope with bladder cancer.

Scientists throughout the world are learning more about bladder cancer and its causes. They are exploring new ways to prevent, detect, diagnose and treat this disease.

1.2 The Bladder

The bladder is a hollow organ in the lower abdomen. It stores urine, the liquid waste produced by the kidneys. Urine passes from each kidney into the bladder through a tube called a urethra.

The inner lining of the bladder is surrounded by an outer layer of muscle. When the bladder is full, the muscles in the bladder wall tighten to allow for urination. Urine leaves the bladder through another tube, called the ureter.

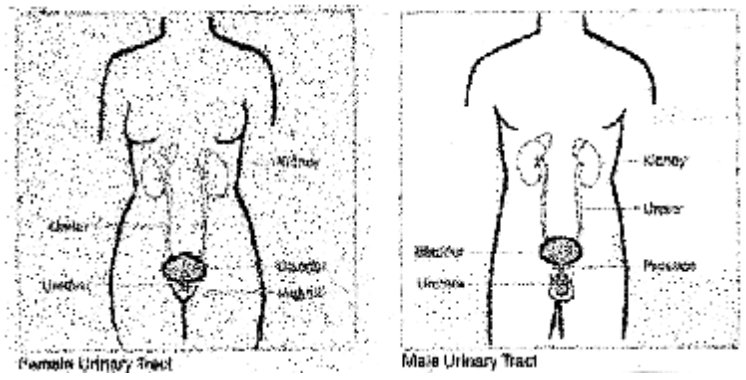


Figure 1

1.3 Defining parts of the problem

To define the parts of the problem we have to better understand cancer.

Cancer is a group of many related diseases and which begin in cells, the body's basic unit of life. As seen in basic biology, cells make up the organs of the body. When functioning correctly, cells grow and divide to form new cells as the body needs them. Normally the new cells will take the place of the old cells when they die.

Sometimes this process breaks down. The new cells form when the body does not need them, and the old cells do not die when they should. These extra cells can form a mass of tissue called a growth, or tumor.

Tumors can be divided into two categories, benign and malignant.

1.3.1 Benign Tumors

Cells from benign tumors do not spread to other parts of the body. This type of tumor is not considered cancerous, and can be removed by a doctor. In most cases once benign tumors are removed they do not reappear.

1.3.2 Malignant Tumors

Cells from malignant tumors are considered cancer. This type of cell can invade and damage nearby tissues and organs. Cancer cells can break away from a malignant tumor and enter the bloodstream, or the lymphatic system. This is how cancer cells spread from the original (primary) tumor to form new tumors in other organs. The spread of cancer is called metastasis.

The wall of the bladder is lined with cells called transitional cells and squamous cells. Studies performed by The National Cancer Institute found that more than 90 percent of bladder cancers originate in the transitional cells. This type of bladder cancer

is called transitional cell carcinoma. Squamous cell carcinoma accounts for eight percent of bladder cancer patients. When cancer is found only in the lining of the bladder, it is called superficial bladder cancer. Physicians often call this carcinoma in situ. This type of bladder cancer will often come back after treatment. If this happens, the disease most often recurs as another superficial cancer in the bladder.

In this type of cancer the superficial tumor may grow through the lining and into the muscular wall of the bladder.

This is known as invasive cancer. Invasive cancer may extend though the bladder wall. It may grow into a nearby organ such as the uterus or vagina (in women) or the prostate gland (in men). It also may invade the wall of the abdomen. When bladder cancer spreads outside the bladder, cancer cell often found in nearby lymph nodes. If cancer has reached these nodes, cancer cells may have spread to other lymph nodes or other organs, such as the lungs, liver, or bones.

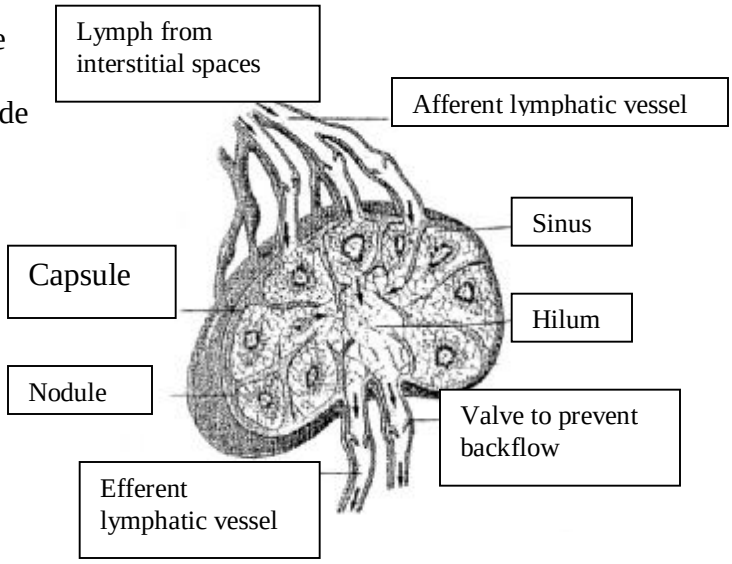


Figure 2: Lymph Node (Applegate, 2000)

If bladder cancer spreads to the lungs, the cancer cells in the lungs are actually bladder cancer cells. The disease is metastatic bladder cancer, not lung cancer. The new tumor is called “distant” disease.

1.4 Who is at risk?

Studies have found the following risk factors for bladder cancer:

1. Age- people under the age of 40 rarely get this disease
2. Tobacco- the use of tobacco is a major risk factor. Cigarette smokers are two to three times more likely to get bladder cancer.
3. Occupation- People who work in the rubber, chemical and leather industries are more at risk. Hairdressers, machinists, metal workers, printer, painters and truck drivers are also more susceptible.
4. Race- Whites get bladder cancer twice as often as people of African or Hispanic ancestry. The lowest rate of occurrence is among Asians.
5. Personal History of Bladder Cancer- People that have already had bladder cancer have an increased chance of getting the disease again.

1.4.1 Symptoms:

The following are common symptoms

1. Blood in the urine (making the urine slightly rusty to deep red.)
2. Pain during urination
3. Frequent urination or feeling the need to urinate without results.

Note: These symptoms can also signify infections, benign tumors, bladder stones or other problems.

1.4.2 Diagnosis:

According to lab test results, one of the following procedures can be performed:

1. Physical Exam- the patient's abdomen and pelvis must be tested for tumors. The physical exam may include a rectal or vaginal exam.

2. Urine test- The laboratory checks the urine for blood, cancer cells and other signs and disease.
3. Intravenous Pyelogram- The doctor injects dye into a blood vessel. The dye collects in the urine, illuminating the bladder under x-rays.
4. Cystoscopy- The doctor uses a thin, lighted tube (cystoscope) to look directly into the bladder. The cystoscope will be inserted into the bladder through the urethra to examine the lining of the bladder. The doctor can remove samples of tissue with the cystoscope, which can then be examined by a pathologist under a microscope. This removal of tissue is called a biopsy.

1.5 Staging:

The best treatment greatly depends on the stage of the disease. Staging is a careful attempt to find out whether the cancer has invaded the bladder wall, if the disease has spread, and if so, to what part of the body. According to the prognosis, more tests may be necessary: Imaging tests such as CT Scan, magnetic resonance imaging (MRI), sonogram, intravenous pyelogram, bone scan and chest x- ray. Figure 3 demonstrates the ability of the x-ray to show the progression of bladder cancer. In diagram A, the patient's bladder extends to the lateral walls. The arrows demonstrate gross marginal misses, the tumor is grossly visible. Diagram B illustrates an abnormal patient.

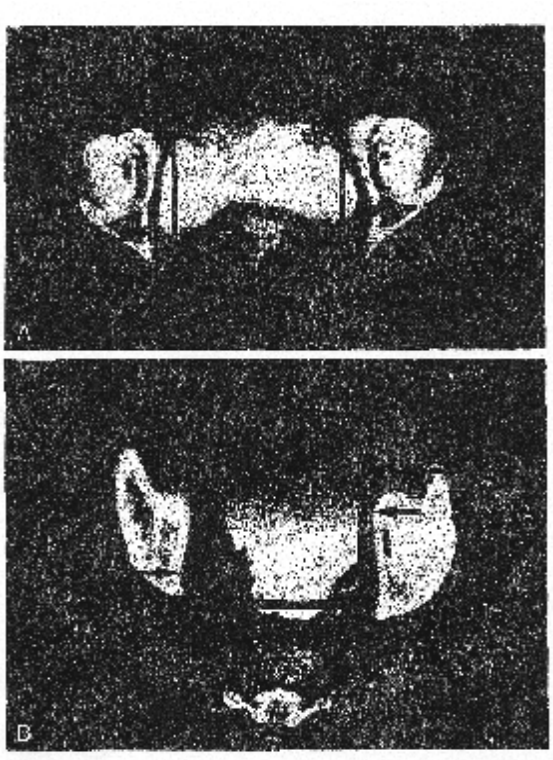


Figure 3

1.5.1 Stages of the Disease:

Stage 0	The cancer cells are found only on the surface of the inner lining of the bladder.
Stage I	The cancer cells are found deep in the inner lining of the bladder. They have not spread to the muscle of the bladder.
Stage II	The cancer cells have spread to the muscle of the bladder.
Stage III	The cancer cells have spread through the muscular wall of the bladder to the layer of tissue surrounding the bladder. The cancer cell may have spread to the prostrate (in men) or to the uterus or vagina (in women).
Stage IV	The cancer extends to the wall of the abdomen or to the pelvis. The cancer cells may have spread to lymph nodes and other more distant parts of the body such as the lungs.

1.5.2 Grading: The grade of the bladder cancer is determined by:

1. The variations in size, shape and staining qualities of the cells and nuclei.
2. The number, type and location of mitotic figures.
3. The presence or absence of abnormal cells or giant cells.
4. Increased cellularity, nuclear crowding and disturbance of cellular polarity.
5. Failure of differentiation from the base to the surface.
6. Polymorphism in the size of cells and in the shape and chromatin pattern in the nuclei.

1.6 Treatment:

The grade tells how closely the cancer cells resemble normal cells. It suggests how fast the cancer is likely to grow. Low-grade cancers usually grow and spread more slowly than high-grade cancers.

1.6.1 Method of Treatment:

The treatment that is appropriate for each patient depends on the type of bladder cancer, the stage of the disease and the grade of the tumor. There are many treatment options available and some patients will undergo a combination of these therapies:

1. Surgery
2. Radiation Therapy
3. Chemotherapy
4. Biological Therapy

1.6.2 Surgery:

The type of surgery depends largely on the stage and grade of the tumor.

1.6.3 Transurethral Resection (TUR):

In early (superficial) bladder cancer the doctor inserts a cystoscope into the bladder though the urethra. A tool with a small wire loop removes the cancer by burning away remaining cancer cells with electric current (this is called fulguration). After TUR patients may also have chemotherapy or biological therapy.

1.6.4 Radial Cysectomy:

This type of surgery will be chosen when superficial cancer involves a large part of the bladder. Radical Cystectomy is the removal of the entire bladder, the nearby lymph nodes, part of the urethra and any close organ that may contain cancer cells.

1.6.5 Segmental Cystectomy:

This type of surgery may remove only part of the bladder. When a patient has lower grade cancer that had invaded the bladder wall in just one area, this type of surgery will most often be used.

1.6.6 Radiation Therapy:

This type of treatment uses a high-energy ray to kill cancer cells. Like surgery, radiation therapy is local therapy. It affects cancer cells in only the treated area. In order to treat bladder cancer, there are two types of radiation therapy:

1. External Radiation
2. Internal Radiation

1.6.7 External Radiation- a large machine outside the body aims radiation at the tumor area. The external radiation therapy is administered 5 days a week for 5 to 7 weeks as an outpatient. Irradiation with external beam involves treating the true pelvis with a four-field technique (figure 4).

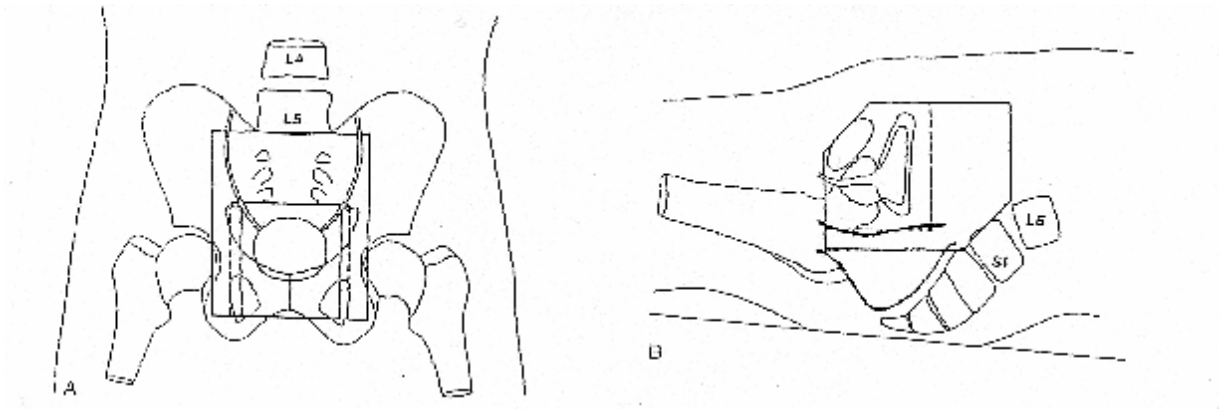


Figure 4

This technique includes the external iliac, obturator and hypoquastrio lymph nodes to a dose of 4500 cGy in 7 weeks. (Figure 4)

The technique of delivering boost dose to the bladder varies from a three-field technique to arc rotation and one interior and two lateral wedge ports (figure 5-8). Super voltage equipment should be used and all parts should be treated every day to avoid the effects of high maximum dose per fraction in surrounding normal tissues.

Figure 5

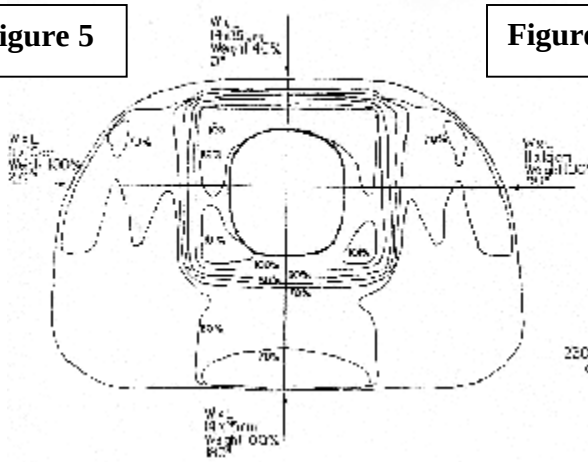


Figure 6

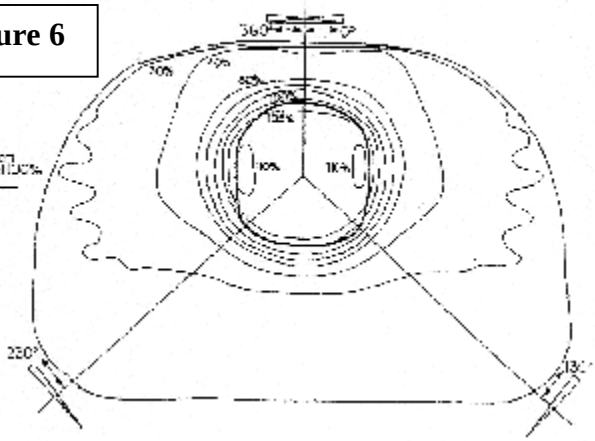


Figure 7

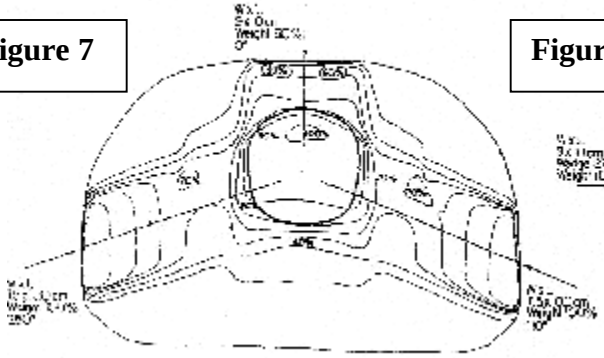
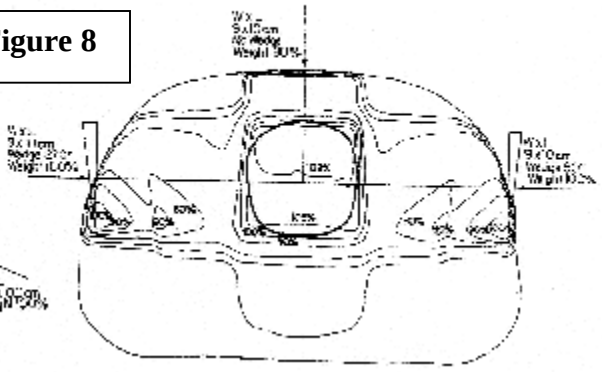


Figure 8



1.6.8 Internal Radiation- The doctor places a small container of radioactive substance into the bladder though the urethra or through an incision in the abdomen. Once this implant is removed, no radioactivity is left in the body.

For implantation, the tumor should be well localized, with muscle invasion not beyond Stage I and with the total area not more than 5 cm in diameter. The technique requires surgically opening the bladder and resection of the tumor to its base. The base, with a 2cm margin establishes the target volume requiring implantation.

Radiation and tantalum have been used frequently. Recently, Iridium (Ir) has become popular. Iridium has certain advantages over both tantalum and radium because its energy is only 0.3 MeV, as compared to 1.4 MeV and 1.1 MeV for tantalum and radium respectively.

Total tumor dose (TD) given by this technique is 6000 cGy to 6500 cGy within 6 or 7 days.

Note: The material in this introduction was adapted from references 1.1 and 1.12.

1.7 How Mathematics Can Help

Under the right conditions, because the malignant tumor grows deadly, the scientist and mathematicians have tried to better understand how tumors grow. By understanding the problem, perhaps they will find the way to detect and treat cancer earlier.

According to mathematics, the modeling for tumor growth can be divided into two different categories: probabilistic and deterministic.

1.7.1 Probabilistic:

In order to complete the modeling of tumor growth from a cellular level, we begin with a review of the primary problem by stochastic processes, as well as how to describe a set of measurements to evaluate the behavior of individual cells. By reviewing the probabilities, we then gain greater insight into this disease.

1.7.2 Deterministic:

This model explains the behavior of large populations of cells and their growth by changing the state in the transition from an active reproducing cell to a cell that is not reproducing.

In this paper I explain, using deterministic models and involving the first differential equations, some basic aspects of tumor growth to fit any mathematical model.

1.8 Models of Tumor Growth (Malthusian Law)

Instead of dealing with individual cells, this model represents the population of the tumor or the tumor's volume. We will consider the growth of a population as a function of time.

Note:

Population actually increases discontinuously by whole number amounts if there is no treatment, like radiation or drug therapy. However, if the population is very large, such individual increases are essentially negligible compared to the entire population itself. In other words, the population increase is approximately continuous and in fact differentiable function of time.

Now, given the population of the tumor, we let x be the number of individual cells at time t.

If we assume that the rate of change of the population is proportional to the number of individuals in it at any time, we have the differential equation;

$$\frac{dx}{dt} = g\,x \qquad (1)$$

Where γ is a constant of proportionality. The population x is positive and is increasing.

Therefore, $\frac{dx}{dt} > 0$ and from equation (1) we must have $\gamma > 0$.

Suppose at time, t_0 the population of tumors is x_0 then in addition to the differential equation (1) we have the initial condition:

$$x\left(t_0\right) = x_0 \qquad (2)$$

The differential equation (1) is separable. Separating variables, integrating and simplifying, we have:

$$x = c\,e^{y\,t}$$

Applying the initial condition (2), $x = x_o$ at $t = t_o$ to this we have:

$$x_0 = c\, e^{-g\, t_0} \tag{3}$$

From equation (3), solving for c we obtain:

$$x = x_0\, e^{g\,(t - t_0)} \tag{4}$$

This law of population tumor growth is called Malthusian Law.

Equation (4) is the equation for exponential growth. Here γ is related to the tumor's doubling time. This equation (4) is a good model for a tumor of the earliest stages of growth.

This model is not good for the steady state that is observed in more developed solid tumors supported by diffusion.

Figure 9: Spindle shaped muscle cells contract (tighten) in the bladder wall to allow urination.

1.9 Logistic Law & the Bernoulli Equation

The tumor's cell population growth is represented more realistically in many cases by assuming that the number x (t) of individual cells in the population at time t is described by a differential equation (Bernoulli equation) of the form.

$$\frac{d\,x}{d\,t} = y\,t - b\,x^2 \tag{5}$$

Where γ>0 andβ>0 are constants.

The additional term $-bx^2$ is the result of some cause that tends to limit the ultimate growth of the population. For example, such a cause could be the radiation therapy, chemotherapy, or biological therapy when the population becomes sufficiently large, as the tumor grows.

Concerning the choice of $-b\ \ x^2$ for the term representing the effect of the cause, one can argue as follows:

Suppose the cause affects the entire cell population in the tumor with x members, then the effect on any one individual cell is proportional to x. Thus the effect on all x individuals in the population would be proportional to $x \cdot x = x^2$.

Assuming that the tumor cell population is described by a differential equation of the form (5) with constant $\gamma>0$ and $\beta>0$, and initial condition of the form (2).

In such cases, it turns out that the constant β is very small compared to the constant γ ($\gamma>>\beta$).

Thus, for a sufficiently small number x of cells, the term γx predominates, and so the tumor cell population grows very rapidly for a time.

However, as the tumor grows by diffusion and x becomes sufficiently large, the term $-bx^2$ (by radiation, chemo, or biological therapy) is of comparatively greater influence, and the result of this is a decrease in the rapid growth rate.

Note: The differential equation (5) is a separable equation.

Also, the law of population growth so described is called the logistic law of cancer tumor growth.

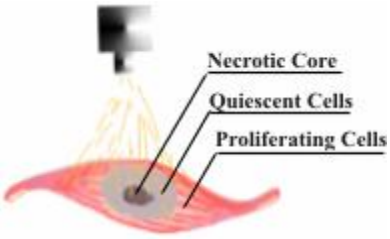


Figure 10: The structure of a radiation therapy involving $-bx^2$ on a solid tumor supported by diffusion of nutrients.

$$\frac{dx}{dt} = gx - bx^2$$

where γ and β are positive constant and γ>>β

$$\frac{dx}{gx - bx^2} = dt$$

$$\frac{dx}{x(g - bx)} = dt$$

and hence:
$$\frac{dx}{x\left[1 - \frac{b}{g}x\right]} = dt$$

using partial fraction, this becomes:
$$\left[\frac{1}{x} - \frac{-b}{g - bx}\right] dx = dt$$

by integrating and solving for x, we obtain:
$$x = \frac{gce^{xt}}{1 + bce^{xt}} \qquad (6)$$

Now solving for c and applying the initial condition equation (2), we obtain:

$$x = \frac{\frac{gx_0}{(g - bx_0)}e^{g(t - t_0)}}{1 + \frac{bx_0}{(g - bx_0)}e^{g(t - t_0)}} \qquad (7)$$

Let $y_0 = \dfrac{x_0}{g - b\,x_0}$ then we have:

$$x = \frac{g\,y_0\,e^{g(t-t_0)}}{1 + b\,y_0\,e^{g(t-t_0)}} \qquad (8)$$

Now to see how large the cancer cell population will ultimately be.

We can assume that the differential equation (5) applies for time $t \to \infty$ then we can

evaluate lim x as $t \to \infty$ by using solution (8) of (5).

$$\lim_{t \to \infty} x = \lim_{t \to \infty} \frac{g\,y_0\,e^{g(t-t_0)}}{1 + b\,y_0\,e^{g(t-t_0)}} = \frac{g}{b}$$

Note: The content of this section was inspired by certain material in reference 1.7.

Balance Law: Growth model by first order partial differential equation

Suppose we consider the tumor as a population of cancer cells during a time period when no individual cancer cells leave the population by termination through radiation therapy, chemotherapy, or biological therapy.

Let u (x,t) denote the numbers of cancer cells with age x present at time t. We offer a partial justification for assuming that u (x,t) satisfies the balance law.

$$u_x + u_t = 0 \qquad x > 0 \qquad t > 0 \qquad (1)$$

Justification:

Suppose the number of cells grows discretely so that if there are n cells present at the n^{th} time interval, then there will be a·n cells present at the end of the (n+1) interval.

Ex. Suppose there are M cells present at time t=0, having just become cancerous. At time t=1, there are a·M+M cells present, a·M of age zero, M of age one. At time t = 2,

$$a\left[\left(a+1\right)M\right]+aM+M=\left(a+1\right)^{2}M$$

Cells present with:

a (a + 1) M are at age zero

a M are at age one

M are at age two

At time t = 3, we have

$$a\left[\left(a+1\right)^{2}\right]+\left(a+1\right)^{2}M=\left(a+1\right)^{3}M$$

cells present.

$a\left(a+1\right)^{2}M$ at age zero

$a\left(a+1\right)M$ at age one

aM at age two

M at age three

By induction prove:

$u\left(x,t\right)=a\left(a+1\right)^{t-1-x}\cdot M$ for

$0\le x\le t-1;$

$u\left(t,t\right)=1\cdot M$

Therefore:

$$u_x = a\left(a+1\right)^{t-1-x}\ln\left(a+1\right)\left(-1\right).M,$$

$$\left(a>0, so,\ a+1>1 \Rightarrow \ln\left(a+1\right)>0\right)$$

$$u_T = a\left(a+1\right)^{t-1-x}\ln\left(a+1\right)\left(+1\right).M,$$

Then applying the argument that cancer cells increase with time, by induction, we find that u (x ,t) satisfies (equation (1)).

Now if we assume that at time t=0 the cancer cells structure in the population is given by:

$$u\left(x,0\right) = f\left(x\right) \qquad x>0 \qquad (2)$$

and the individual number of cancer cell zero (newborn) individuals is given at time t by:

$$u\left(0,t\right) = g\left(t\right) \qquad t>0 \qquad (3)$$

Then we can find that the population density in this cancer cell-structured population satisfies the initial-boundary-value problem by equations 1, 2 and 3.

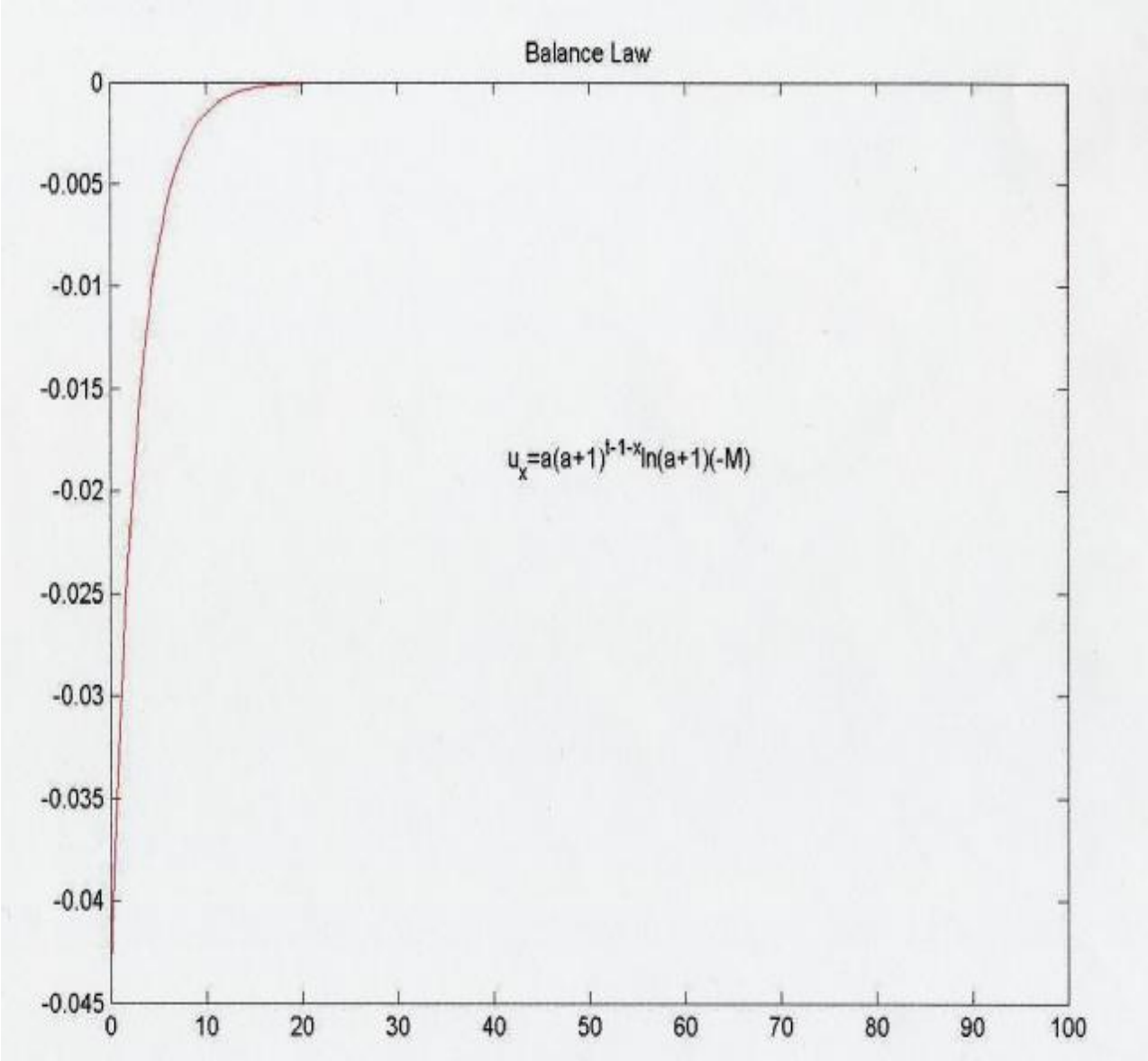


Figure 11

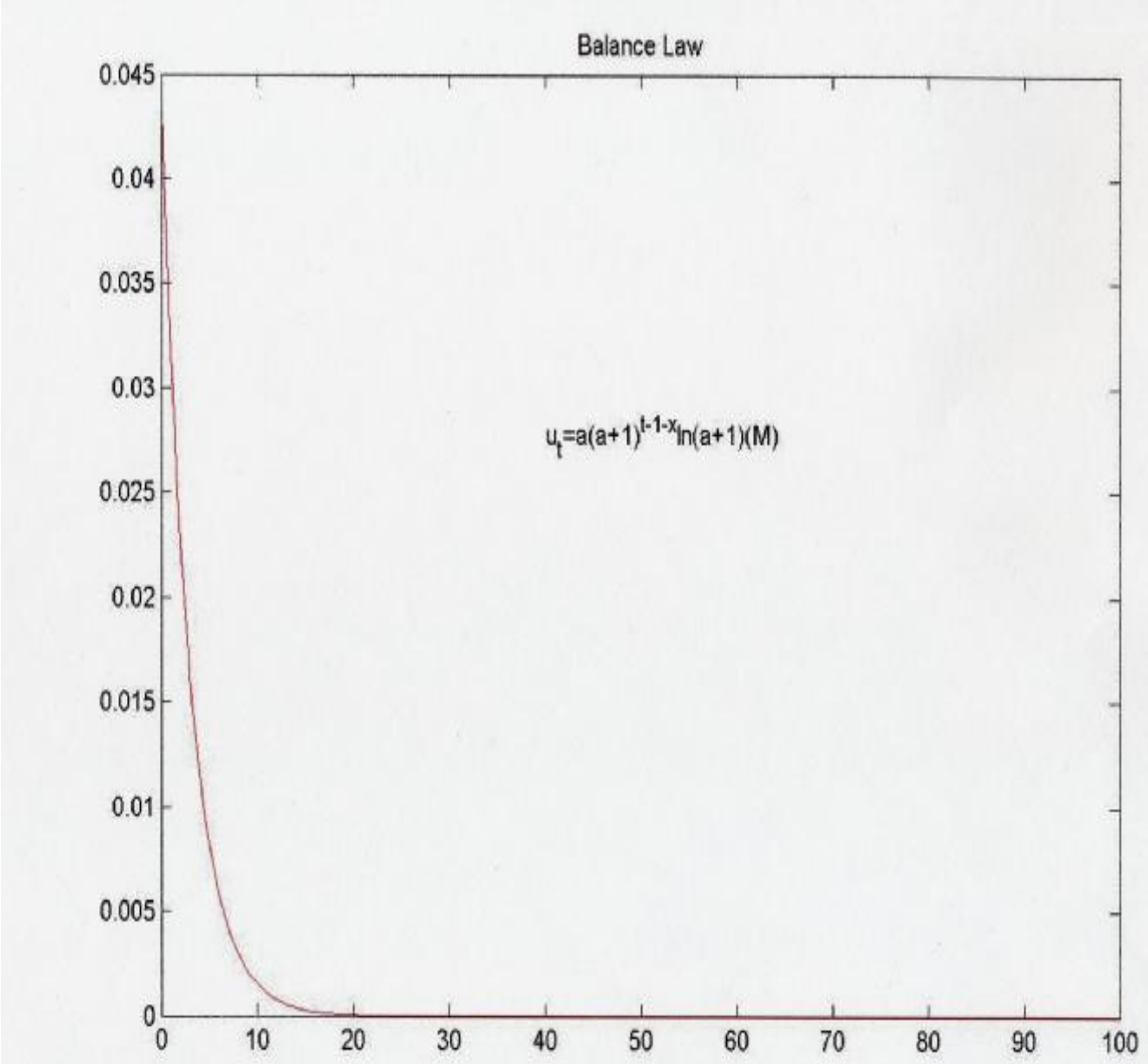


Figure 12

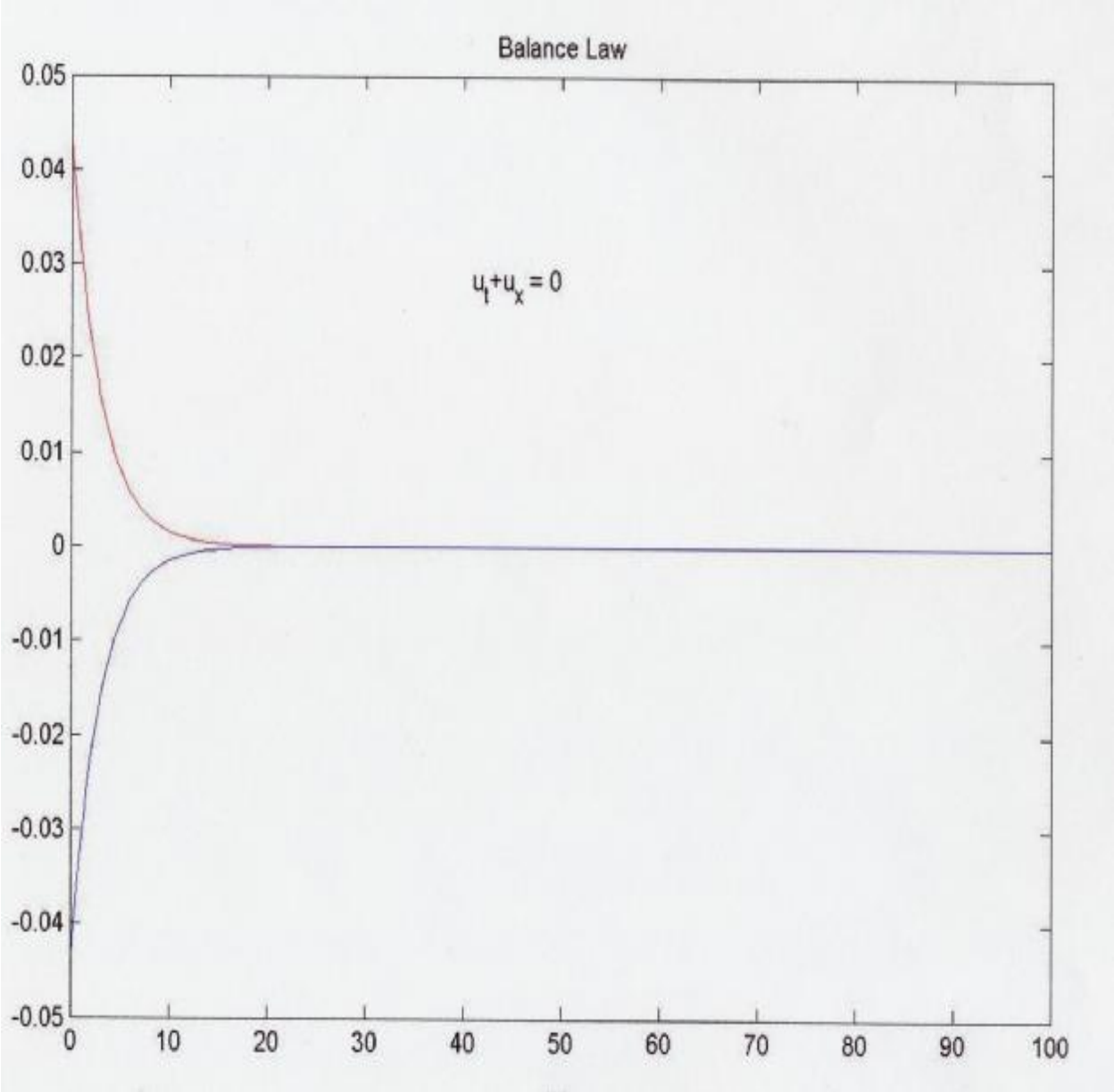


Figure 13

1.11 Introduction for Diffusion

There are various types of diffusion, but here we mean that the boundary of the tumor is moving and is unknown except in the initial stages. One of our goals is to formulate a mathematical model which will enable us to study the movement of the tumor outer cell layers, to examine the movement of the outer boundary and to study the stability of the tumor. The latter is central to determining whether the tumor is benign or growing and moving like a malignant tumor.

Through lab experiments (see reference 1.6), scientists found out that a solid malignancy growing by diffusion alone leads the tumor to a dormant state.
In the early stages when the tumor is small, every cell will receive adequate nourishment by diffusion. This circumstance will not persist for much time because, as nutrients are consumed, fewer nutrients will reach the center of the tumor. Eventually the stoppage of nutrients to the center of the cell will cause the cell to die. Then a central necrotic core will develop and the growth rate of the tumor makes it more difficult for the cell to receive nourishment. When the cells below the surface cannot receive enough support and nutrients, they will eventually die and the tumor will dispose of the dead waste by diffusion. (See Section 1.5 for a brief discussion of the various stages of tumor growth.)
Now we analyze the central core of the necrotic debris in various stages of disintegration. Because of the difficulty in determining the various rate of growth, we can assume the diffusion constants are non-dimensional. Also, the boundary of the tumor is moving and is unknown except at the beginning stage of the mathematical model, which enables us to focus attention on the movement of the tumor outer cell layers, to "track" its movement and to examine its stability.

Stability

It is extremely important to know whether the tumor is inactive or growing and changing, because we want to determine whether it is non-malignant or malignant. Most tumors involve some vascularization. This is the ability to develop capillaries which enable the tumor to spread in several directions. It is important to be able to control vascularization in cancer cells.

1.11.1 Tumor Angiogenesis Factor (TAF)

Cancer cells produce a distinct chemical factor call tumor angiogenesis factor, which stimulates the rapid formation of new capillaries. When the tumor reaches its diffusion limit size, the tumor angiogenesis factor increases and it makes the other blood vessels around the tumor grow into the cell colony (see 1.6). The malignancy becomes vascularized and "perfusion replaces diffusion" (according to 1.6) as the dominant mechanism for the supply of nutrients and the removal of wastes. (This seems to mean that particles that were just moving from an area of higher concentration to an area of lower concentration in the same general area begin to move through a region into new territory.) When tumor connects the circulatory system, all constraints imposed by diffusion are eliminated and subsequent growth is explosive. If scientists could block this chemical message for vascularization sent from the tumor to surrounding tissue, it might be possible to maintain the tumor indefinitely in its dormant or non-malignant state.

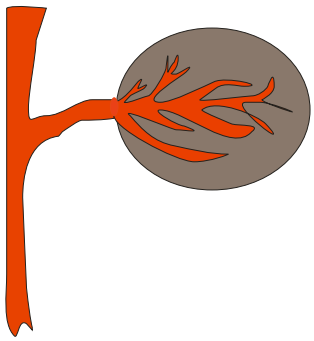


Figure 14: Vascularization (after necrotic core begins to break up)

1.11.2 Mathematical Diffusion Model

We can discuss the growth of tumor by diffusion by the following assumptions

a. Assume that the tumor has a two-layer structure:
    i. Outer shell
    ii. Inner core of necrotic debris
b. Let u denote a function of nutrient supply u (x , y, z; t). Let u_1 be the critical level of nutrient below which the cell (or cell colony) dies. Let y_1 be the thickness of the layer of living cell. Here y_1 depends only on u_1 and on the value of u at the outer surface.

Therefore:

$$y_1 = m_1 \left(\sqrt{u - u_1} \right) \qquad \text{for } u > u_1 \qquad (1)$$

$$y_1 = 0 \qquad \text{for } u < u_1$$

Suppose:

dA = area surface of tumor

and we show dV as the volume of live cells, so:

$dV = C_1 y_1 dA$ C_1 = constant

consumed nutrient by volume = $C_2 y_1 dA$

C_2 = constant

Let the loss of necrotic mass or cell volume per unit volume of debris = constant.

Surface tension force = T

Note: A surface tension force T proportional to the mean curvature K of the boundary keeps the tumor a compact and continuous mass.

Now let:

q (x, y, z; t) = particle velocity

and p (x, y, z; t) is proportional to internal pressure.

Birth of the new cells and death of the old cells creates an internal pressure. This pressure is differential and it causes the motion of cellular material. We can assume the minus gradient of pressure is defined by the following equation:

$$q = -\nabla p \qquad (2)$$

Note: The culture (tumor mass) is assumed to behave like an incompressible fliud made up of cells and cellular debris (see 1.6).

1.11.3 Using mathematical model

By combining the diffusion process with the above assumptions, we will find a set of equations which are related to the dynamics of the tumor surface with variations in the nutrient concentration function u and the internal pressure function p.

1.11.4 The Law of Conservation of Mass

Suppose unknown functional equation:

$$\Gamma\left(x,\ y,\ z;\ t\right) = 0 \qquad (3)$$

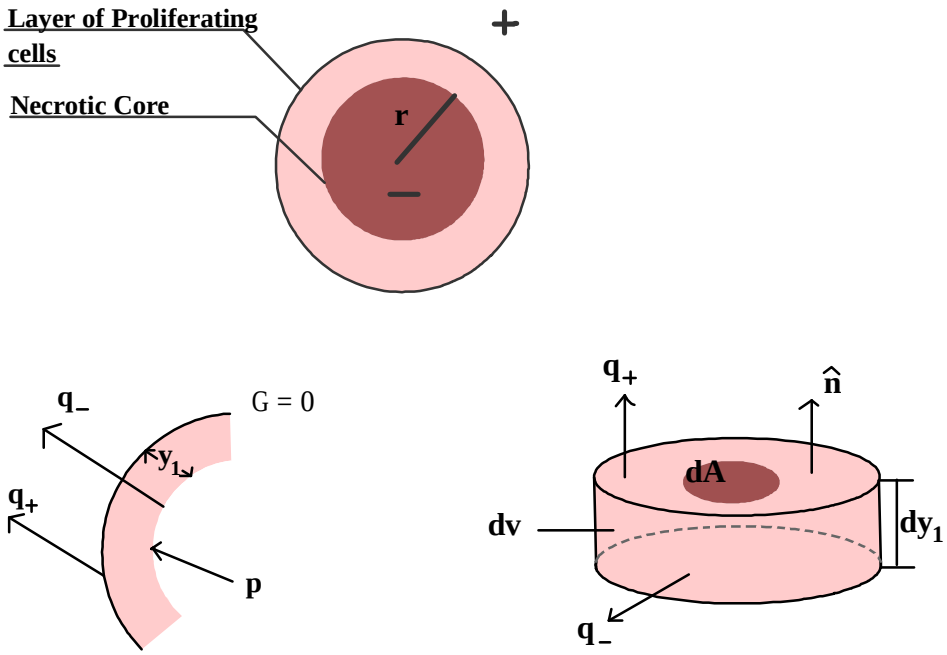


Figure 15

since y_1 is very small and the mass/volume flow out of the surface dA of the element volume, and if $\hat{n}$ denotes a unit vector then

$$\frac{volume}{time} = \left(q_+ \cdot \hat{n} - q_- \cdot \hat{n} \right) d\ A$$

with the small volume, $\beta\, y_1\, d\ A$

Therefore, we have:

$$Net\ \ flow\ \ in/out\ \ of\ \ volume\ \ /time\ = \left(\ q_+ \cdot \hat{n}\ -q_- \cdot \hat{n} \right) d\ \ A\ = \ b\ \ y_1\ d\ \ A$$

$$q_+ \cdot \hat{n}\ -\ q_- \cdot \hat{n}\ =\ b\ \ y_1$$

$$q_+ \cdot \hat{n}\ =\ q_- \cdot \ n\ +b\ \ y_1 \qquad \text{on } \Gamma = 0 \qquad (4)$$

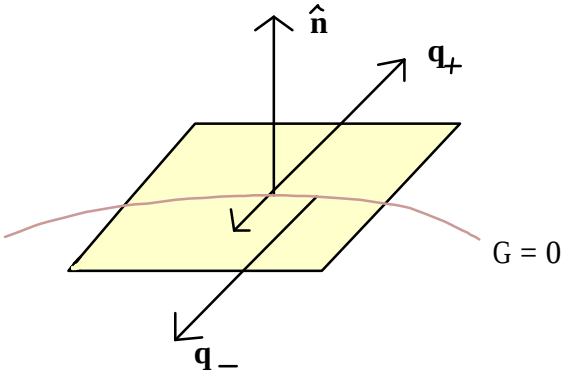


Figure 16

Figure 3 shows the particle velocity function as:

$$q_+\ =\ \lim_{(x,y,z)\to\Gamma \ \downarrow}\ q\ (\ x,\ \ y,\ \ z;\ \ t\ \ )$$

$$q_-\ =\ \lim_{(x,y,z)\to\Gamma \ \uparrow}\ q\ (\ x,\ \ y,\ \ z;\ \ t\ \ )$$

Note: I believe the above equations are worthy of study. To check whether or not they really apply, we need to find tables of actual measurements or related data against which we can test these equations. Up to this time I have been unable to do that.

Similarly the rate of nutrient diffusion into dv (diffusion constant k) through the outer surface, k $\hat{n} \cdot u$ d A, is equal to the rate at which nutrient is consumed in this small volume, a y_1 d A. Thus

$$k \ \hat{n} \cdot \nabla u = a \ y_1 \qquad \text{on } \Gamma = 0 \qquad (5)$$

In steady state of the pressure P and tangential velocity components are continuous across the outer surface of living cells.

$$p_+ = p_- = p \qquad (6)$$

$$q_+ \cdot \hat{n} = q_- \cdot \hat{n} \qquad \text{on } \Gamma = 0$$

The pressure on the surface of the tumor must equal the surface tension T and thus in turn is proportional to the mean curvature k, i.e. (according to Eq. 13.2.5 of reference 1.6)

$$P = m_2 \ k \qquad \text{on } \Gamma = 0 \qquad m_2 = \text{constant} \qquad (7)$$

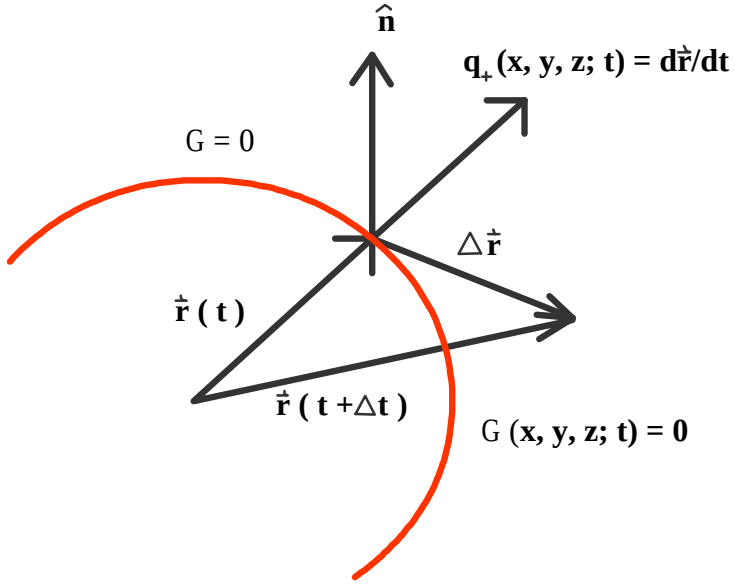


Figure 17

If a point on the outer surface is represented by the vector $\vec{r}$, then

$$\vec{q}_{+} = \lim_{\Delta t \to 0} \frac{\vec{r}\left(t + \Delta t \right) - \vec{r}\left(t \right)}{\Delta t}$$

$$\frac{d\, r}{d\, t} = q_{+} \tag{8}$$

where $\Gamma(x, y, z; 0) = 0$ is assigned given.

Case:

If the rate of volume loss/unit volume =S, where S= constant

the mass conservation is(see 1.6):

$$\nabla \cdot q = -S \tag{9}$$

and the nutrient supply's concentration u, which is assumed to be in diffusive equilibrium.

$$\nabla^2 u = 0 \tag{10}$$

outside the cell colony and

$$u = u_1$$

in the necrotic interior.

1.12 Investigation of the Model:

There are several ways which can be investigated with this model.

We can also include the effect of a nearby source of nutrient or the presence of another cell colony. By concentrating that the surrounding medium to be large and that there is a constant supply of nutrient.

$$u \rightarrow u_{\infty} \quad \text{as} \quad |r| \rightarrow \infty \tag{11}$$

Then the following equation will be convenient on the boundary conditions:

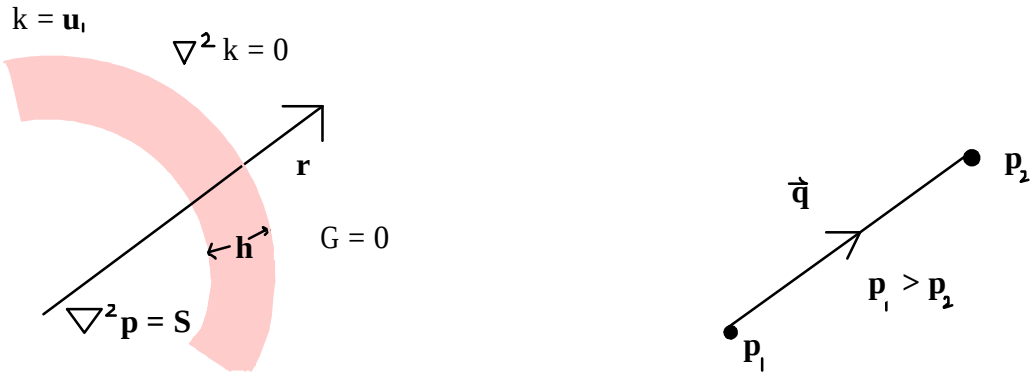


Figure 18

$$\vec{q} = -\nabla P$$

$$\nabla \cdot q = -S$$

$$\nabla \cdot (-\nabla p) = -S$$

$$\boxed{\nabla^2 p = S} \quad \text{inside } \Gamma = 0 \tag{12}$$

$$\nabla^2 u = 0 \qquad \text{outside } \Gamma = 0 \qquad (13)$$

and on the boundary of the tumor, when $\Gamma = 0$, as we saw in Eq.7 the pressure will be:

$$P = T = m_2 k$$

Now if the proliferation rate of new cells is so large that its product with small quantities, such as outer shell thickness, is of order one, ie:

$$b\ y_1 = b\ m_1 \sqrt{\left(u - u_1\right)} = l \sqrt{u - u_1} \qquad l = O(1)$$

$$a\ y_1 = a\ m_1 \sqrt{u - u_1} = m\ k \sqrt{u - u_1} \qquad m = O(1)$$

Also we have the following equation:

$$q_+ \cdot \hat{n} = -\hat{n} \cdot \nabla P + l \sqrt{u - u_1} \qquad (14)$$

and by previous equations 1, 2 and 3, we have:

$$q_+ \cdot \hat{n} = -\nabla P \cdot \hat{n} \qquad (15)$$

Also by equations 6 and 2 we will have:

$$\hat{n} \cdot \nabla u = m \sqrt{u - u_1} \qquad (16)$$

Then the boundary surface will be

$$\frac{d\ r}{d\ t} = q_+$$

and the initial configuration is given by r = a(t) at t = 0.

Note:

All the above equations that have been described will constitute a moving boundary problem which is difficult to solve numerically and analytically. For some geometric configurations we can solve the equation exactly.

A Spherical Tumor:

Suppose the shape of a tumor is a sphere with radius a(t),that is, if grows with time and remains spherical.

Because the tumor stays the same shape, the equation Γ at any time can be represented by:

$$r = R(t) \tag{17}$$

Where: R (t) = the radius of the tumor at time t.

R (0) = a

Then the equations:

$$\nabla^2 P = S \qquad \text{Inside } \Gamma = 0$$

$$\nabla^2 u = 0 \qquad \text{Outside } \Gamma = 0$$

Will expressed in spherical polar co-ordinates reduce, because of spherical symmetry, to

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial P}{\partial r}\right) = S \qquad r \le R(t) \tag{18}$$

and

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial u}{\partial r}\right) = 0 \qquad r \ge R(t) \tag{19}$$

After integrating equation 18 we will have

$$\frac{1}{r^2}\ \frac{\partial}{\partial\ r}\left(r^2\ \frac{\partial\ P}{\partial\ r}\right) = S$$

$$\frac{1}{r^2}\left(2r\ \frac{\partial\ P}{\partial\ r} + r^2\ \frac{\partial^2\ P}{\partial\ r^2}\right) = S$$

multiply both sides by r and we obtain:

$$2\ \frac{\partial\ P}{\partial\ r} + r\ \frac{\partial^2\ P}{\partial\ r^2} = r\ S$$

$$2\int\frac{\partial\ P}{\partial\ r} + \int r\frac{\partial^2\ P}{\partial\ r^2} = \int r\ S$$

$$2\ P + r\ \frac{\partial\ P}{\partial\ r} - P = \frac{S}{2}\ r^2 + B$$

$$P + r\ \frac{\partial\ P}{\partial\ r} = \frac{S}{2}\ r^2 + B \qquad (\text{i})$$

Now if:

$$f\ (\ r\ ) = c_1\ r^2 + c_2 \Rightarrow f'\ (\ r\ ) = 2\ c_1\ r$$

$$f\ (\ r\ ) + r\ f'\ (\ r\ ) = c_1\ r^2 + c_2 + r\left(\ 2\ c_1\ r\right)$$

$$f(r) + r f'(r) = 3 c_1 r^2 + c_2$$

Let:

$$P = f(r) + \frac{A}{r} \Rightarrow \frac{\partial P}{\partial r} = f'(r) - \frac{A}{r^2}$$

$$P + r \frac{\partial P}{\partial r} = 3 c_1 r^2 + c_2 \qquad \text{(ii)}$$

From equation (i) and (ii) we have:

$$3 c_1 r^2 + c_2 = \frac{S}{2} r^2 + B$$

we obtain $\boxed{c_1 = \frac{S}{6}}$ and $\boxed{c_2 = B}$

Therefore, we obtain the general solution to Equation (i) (with A and B arbitrary constants):

$$\boxed{P = \frac{S}{6} r^2 + \frac{A}{r} + B} \qquad (20)$$

Since the pressure P must be finite (actually bounded above) everywhere inside the tumor, we must choose A=0. (Otherwise for small r , if A is not zero, then P gets too large.) On the boundary r = R (t)

$$P = m_2 k = \frac{m_2}{R}$$

and so:

$$B = \frac{m_2}{R} - \frac{S}{6} R^2$$

Then the pressure is given by:

$$P = \frac{S}{6}\left(r^2 - R^2 \right) + \frac{m_2}{R} \qquad r \le R(t) \qquad (21)$$

Similarly, if we solve equation 19, then we obtain:

$$u(t) = C + \frac{D}{r(t)}$$

$$r \ge R(t) \qquad (*)$$

where C and D are constant. By condition (11) if we let

$$|r| \to \infty$$

, then

$$C = u_\infty$$

In order to determine D, we must use equation 16 or r = R (t) to get

$$\frac{\partial u}{\partial r} = m\sqrt{u - u_1} \qquad \text{on } r = R(t) \qquad (**)$$

From equations (*) and (**), we have

$$-\frac{D}{R^2} = m\sqrt{\left(C - u_1 + \frac{D}{R}\right)}$$

or

$$\frac{D^2}{R^4} = m^2\left(C - u_1 + \frac{D}{R} \right)$$

or

$$D^2 - m^2 R^3 (t) D - m^2 (C - u_1) R^4 = 0 \tag{22}$$

This equation is quadratic for D.

$$D = \frac{1}{2} m R^2 \left\{ m R \pm \sqrt{\left[m^2 R^2 + 4 (C - u_1) \right]} \right\}$$

since the concentration u must decrease as $r \to R(t)$, it is clear that we must choose

$$D = \frac{1}{2} m R^2 \left\{ m R - \sqrt{\left[m^2 R^2 + 4 (C - u_1) \right]} \right\} \tag{23}$$

thus,

$$u = C \frac{m R^2(t)}{2 r} \left\{ m R(t) - \sqrt{\left[m^2 R^2(t) + 4 (C - u_1) \right]} \right\} \tag{24}$$

Now, to know how the tumor grows with R(t), we use equation (14) to obtain:

$$R'(t) = -\frac{\partial P}{\partial r} + l \sqrt{u - u_1}$$

Therefore:

$$R'(t) = -\frac{1}{3} SR + l \sqrt{\left\{ \left(C - u_1\right) + \frac{1}{2} m R \left[m R - \left\{ m^2 R^2 + 4\left(C - u_1\right) \right\}^{\frac{1}{2}} \right] \right\}} \tag{25}$$

The equation (25) is the first order equation to determining of R (t) at any time t subject to the condition R (0) = a.

To estimate the ultimate size of a stable spherical tumor by setting $R'(t) = 0$ to get the limiting size.

$$R_{\infty} = \frac{3\ l}{S}\left(\frac{C - u_1}{3\ l\ m\ /\ S + 1}\right)^{\frac{1}{2}} \tag{26}$$

or

$$R_{\infty} = \frac{3\ l}{S}\left(\frac{S(C - u_1)}{3\ l\ m + S}\right)^{\frac{1}{2}}$$

As mentioned above, surface tension will play an important role in maintaining the compactness of the tumor. Any perturbations which allow surface tension to be overcome by pressure force could be an important feature in determining whether the tumor becomes vascularized and consequently malignant. This means that it is important to know the spherical tumor is stable with respect to small deviation from its spherical shape. The spherical model can be examined for stability but a detailed analysis is beyond the scope of this paper.

Note: All the material dealing with diffusion has been adapted from the reference 1.6.

***

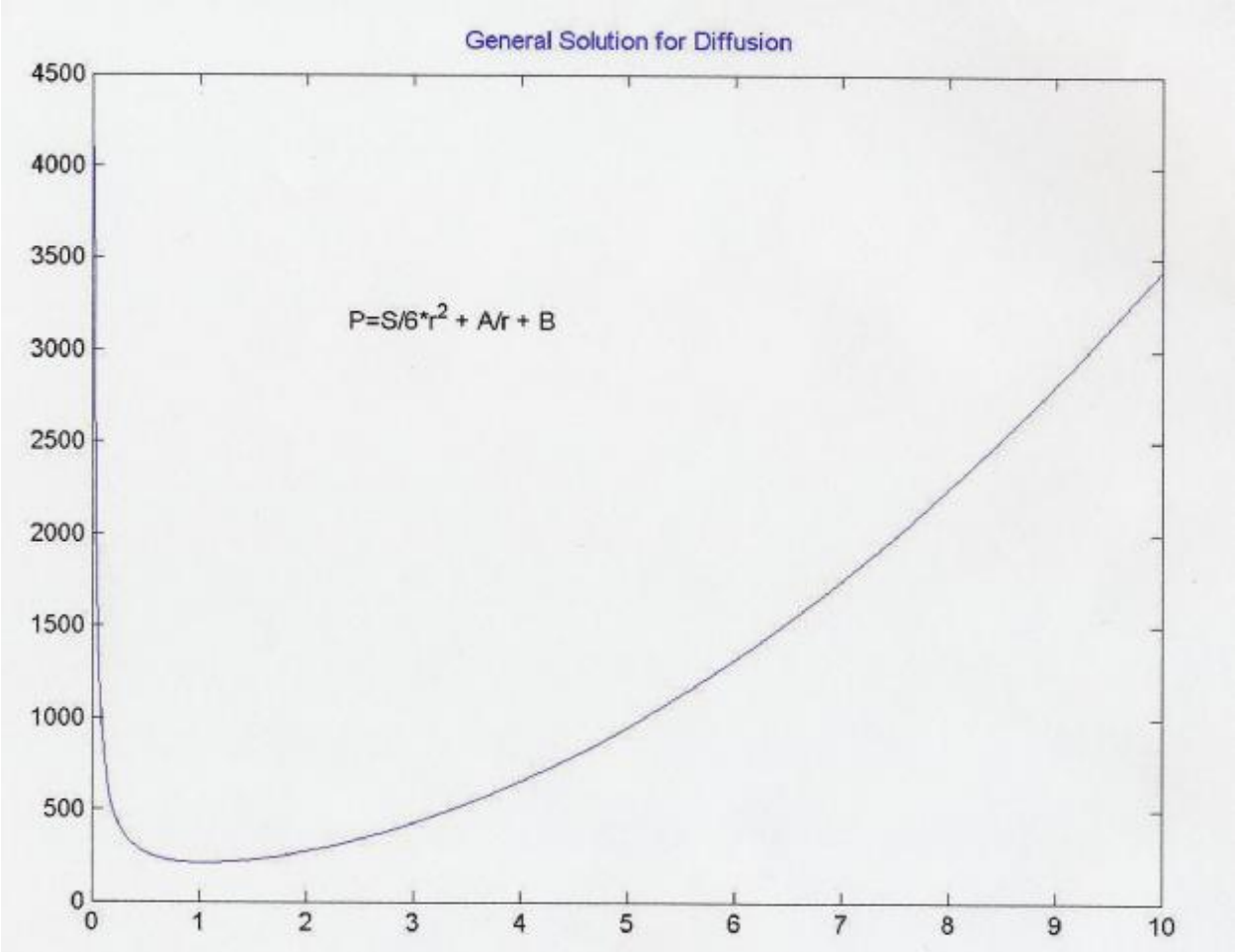


Figure 19

REFERENCES

1.1 Aziz, Hassan, Rotmann, Marvin: Bladder Carcinoma, Chapter 44

This chapter gives a history of Bladder Cancer and deeper insight into its cause and occurrence. It gives an explanation of Broder's tumor grading system. Radiation and Irradiation are included as procedures that show promising futures and should be used in combination with surgery. The article details radiation therapy techniques and their results. Retention of the bladder and sexual functions are cited as important advantages of definitive external beam therapy.

1.2 H.J.G Bloom, Treatment of Carcinoma of the bladder: a symposium 182 wire. Br. J Radiology 33:471, 1960.

1.3 P. DuChateau and D. Zachmann, Applied Partial Differential Equations, Dover, 2002.

1.4 P. Ghadirian, Cancer: Causes and Prevention, (privately printed in Persian), Toronto, 226 pages (ISBN: 416-410-3208).

1.5 DR.Goffinet, M.J. Schneider, E.J. Glatstein, et al.: Bladder cancer: results of radiation therapy in 384 patients**, Radiology** 117(1): 149 – 153, 1975.

1.6 H. P. Greenspan, Models for the growth of a solid tumor by diffusion, **Stud. Appl. Math,** 51(1972), 317 – 340.

1.7 S. Ross, Introduction to Ordinary Differential Equations, John Wiley & Sons, New York, 1989.

1.8 M. Rotman, R. Macchia, M. Silverstein, et al.: Infusion 5-Fu and concomitant radiation therapy in the treatment of bladder cancer. **Cancer,** in press**.**

1.9 C. A. Veys, Bladder tumor and occupations: A coroner's modification scheme, **Br. J. Ind. Med**. 31: 65, 1974.

1.10 http://www.mayoclinic.com, What is Bladder Cancer?

General discussion on bladder cancer, its signs and symptoms, background of its causes and what puts a person at risk. This website also addresses the diagnosis and testing of bladder cancer. The different stages of bladder cancer are explained as well as the differences between surgical, radiation, chemotherapy and biological treatments. Radiation therapy is portrayed as a secondary and highly volatile option.

1.11 http://www.cancer.gov, Bladder Cancer (PDQR): Treatment Health Professional Version, written by the National Cancer Institute, last modified 8/2002.

The information here delves more deeply into an explanation of the stages and depths of bladder cancer. The author talks about common treatments that are effective for each of the stages.

1.12 http://www.cancer.gov, What You Need to Know About Bladder Cancer, NIH Publication No. 01-1559. Posted 09/07/2001; last modified 1/22/2002.

Basic explanation of the structure of the bladder and the cancer that can form in it. Gives options for treatment geared toward what information a patient might need. Gives side effects of radiation therapy, but avoids a deeper explanation of cause. Also provides resources and a glossary.

1.13 U.S. Department of Health, Education and Welfare: Cancer patient survival report 5:215, 1976.