MATHEMATICAL MODELING FOR HOMOGENEOUS TUMOR WITH DELAY IN TIME

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Abstract Due to the properties of tumor cell, the tumor establishes itself in the organ and grows there, so there is a competition between the tumor cells and host cell (normal cells) for nutrients. Evidences show that high dietary phosphorus increases the rate of protein synthesis and thus the cell number. So, other than oxygen, sulfur, the important element that both tumor cells and normal cells need is phosphorus. Hence, the proliferation and growth rate of both tumor cells and healthy cells depends on the content of phosphorus available to them. So, the mathematical model with time delay is prepared in which the growth rate of tumor cells and normal cells are function of phosphorus with their restrictions. And by applying suitable implications on the model and studying the simulations we will come to know its effects on tumor growth.

Keywords: Tumor, Mathematical Modeling, Phosphorus, Extra Cellular Phosphorus, Homogeneous Tumor, Micro Vessels, Angiogenesis, Delay Differential Equations

چکیده خواص سلول سرطانی به‌گونه‌ای است که یک سلول به تکثیر سلول‌های مشابه در محیط اولیه می‌پردازد و در نتیجه در مصرف مواد غذائی با سلول‌های اصلی به رقابت می‌پردازند. شواهد نشان می‌دهد که فسفرهای رژیمی باعث ازدیاد نرخ تولید پروتئین و در نتیجه افزایش شمار سلول‌ها می‌گردند. بنابراین سلول‌های طبیعی و سرطانی علاوه بر اکسیژن، گوگرد و عنصرهای مهم دیگر، به فسفر نیز نیازمندند و در نتیجه رشد و تکثیر هر دو نوع سلول بستگی به میزان فسفر موجود مربوط می‌گردد. در اینجا مدل ریاضی با تاخیر زمانی که در آن نرخ رشد سلول‌های طبیعی و سرطانی تابعی از فسفر و محدودیت‌هایش می باشد، تعریف شده است. با توجه به مدل‌های تحریکی مناسب اثرات فسفر در رشد سلول‌های سرطانی مطالعه شده است.

1. INTRODUCTION

Every year about 6 million people throughout the world are diagnosed as having tumor being equally divided between developed and developing countries. About 4 million people die of cancer (malignant tumor) which account for about 10 % of all the deaths in the world every year.

Tumor dynamics has explained lot about tumors which help to cure or even reduce its ill effects. This is because the behavior of tumor can be examined with another suitable tool of mathematical modeling. In recent years mathematical modeling has become a field of great interest in tumor dynamics. Even though no great success has been achieved but its effective support has been noticed by geneticists and biologists working in this field.

Uncontrolled growth and division of certain body tissues forms a tumor. A tumor is formed when uncontrolled growth of tissue, occurs due to mutation in DNA of a cell or in tumor suppressor genes. This tumor suppressor gene checks the cell

cycle and regulates apoptosis if the mutant cell is unable to get repaired. A tumor is made up of billions of copies, of the original cancerous cell. Tumor is of two types; benign tumor and malignant tumor. Tumor cells can lose the molecules on their surface which keep normal cells in the right place. So they can become detached from their neighbors and have the ability to enter any part or any organ and grow there. This transfers benign tumor to malignant tumor.

Tumor commonly originates in tissues where cells are regularly replaced by mitosis. These tissues include skin, lining of digestive tract, reproductive organs, lungs and liver. It shows uncontrolled mitotic divisions of cells causes' unorganized growth. The rate of tumor cell division is much higher than the normal cells e.g. gut lining cells divide after 36 hours, skin cells after few days, RBC's after few weeks.

The tumor cells and normal cells have the same physical properties but show different characters. The divided tumor cell may not be the same as the mother cell. Tumor cells lose the normal feedback controls that prevent excessive growth, so these cells grow much more than the normal cells. They have lesser survival capability than the normal cells. Tumor cells do not show contact inhibition (check or stop). Unlike the normal cells the tumor cells on successive reproduction will not lose most of their genetic material. So, the cells become more and more primitive and tend to reproduce more quickly and even more haphazardly. Due to all these properties the tumor cells would establish in an organ and would grow there. So there is a competition for survival between the tumor cells and the host cell (normal cells). They compete with each other for nutrients. Since tumor is formed by mutant cell, so the mutations can be different and depending on them, the tumor may be formed by different kinds of tumor cells. Because of this, there is also a competition between each cell type, therefore, the nutrients and the cell type having more stable nucleoli wins the survival race.

Both tumor cells and normal cells need nutrients like oxygen, sulfur and etc, but other than that, an important element is phosphorus. Phosphorus is present everywhere in living cells and is a part of molecular systems that involve the genetic code (DNA, RNA) and energy storage and transmission (ATP) (Vansoest [1]). We know protein synthesis is very important for the cell division and many investigations prove that supporting the conditions which favors the protein synthesis increases the cell number to great extend. Also evidences show that high dietary phosphorus increases the rate of protein synthesis (Nystroem, et al [2]). So, we can say that phosphorus plays an important role in cell division.

Techniques have developed to manage cancers that ranges from chemotherapy which inhibits uncontrolled growth to surgery, aimed at physical removal. Though, these techniques are helpful, they have many side effects and drawbacks. Chemotherapy can cause mutations in non-tumor cells, like gut epithelia, which replicate at high rates and thus become cancerous. Surgery itself can lead to complications and mortality. Modeling and simulation of tumor growth in competition with the immune system, is certainly one of the challenging frontiers of applied mathematics, which could have a great impact on both quality of life, and the development of mathematical sciences.

Here also we have prepared a mathematical model of growth rate of both healthy and tumor cells. Since, the proliferation and growth rate of both tumor cells and healthy cells depends on the content of phosphorus available to them. This model will show the growth rate of tumor cells and normal cells as a function of phosphorus with their restrictions. In this mathematical model the suitable implications will show its effect on the tumor growth, and also for improving patient's health we will consider those implications which reduce the tumor growth and favor the patient's health.

2. HOMOGENEOUS TUMOR

As we have already discussed, many types of mutant cell may form the tumor. But here we are discussing tumor having only one kind of mutant cell. Such tumors are known as homogeneous tumors. If we assume that the tumor is growing on host organ so the growth of both tumor and the host organ will be studied on basis of their masses.

Let x be the mass of healthy cells at time t and y be the mass of tumor cell at time t (assuming the both masses in kg). Since the tumor is supplied

with oxygen with blood vessels, so we assume that z is the mass of tumor micro vessels (in kg). V is the constant mass of total phosphorus available to the organ. For a cell the phosphorus is divided into two forms, one which is present inside the cell for carrying out various processes (intracellular phosphorus) and other which is needed for the cell to further proliferation (extracellular phosphorus). If a is the mass of phosphorus in 1 kg of healthy cell and b is the mass of phosphorus in 1 kg of tumor cell. Then the extracellular phosphorus available for the proliferation is given by

$$V_e = V - (ax + by + az)$$

2.1. Equation for the Growth Rate of Healthy Cells The proliferation rate of cell depends on the extracellular phosphorus then if sufficient amount of extracellular phosphorus is available to them, then let them proliferate with their maximum per capita rate p, but when the extracellular phosphorus is less than some threshold value i.e. a then the proliferation rate is given by

$$p\frac{V_e}{aS_h g}$$

Where g is the fraction (about two-third) of the total fluid within the organ, If λ_x is the death rate of healthy cell and τ_x is the time delay which the healthy cell need to divide, then $x(t-\tau_x)$ is the mass of healthy cell at time $(t-\tau_x)$. Thus the growth rate for healthy cell is given by

$$\frac{dx}{dt} = x(t-\tau_x)p\min(1,\frac{V_e}{aS_h g}) - x\lambda_x - (x(t-\tau_x)p - x\lambda_x)\frac{x+y+z}{S_h} \quad (1)$$

In this equation the first term $x(t-\tau_x).p\min(1,\frac{V_e}{aS_h g})$ is the proliferation rate depending on the amount of extracellular phosphorus available to them, the second term $x\lambda_x$ is the death rate and the third term $(x(t-\tau_x).p - x\lambda_x)\frac{x+y+z}{S_h}$ is an interesting one, it is the term when the mass of host with tumor and tumor micro vessels $(x+y+z)$ exceeds the value S_h then the growth rate dx/dy becomes negative. This is the time when the host starts 'feeling the tumor'.

2.2. Equation for the Growth Rate of Tumor Cells Here also we are assuming that tumor grows to its max mass S_t (kg). Let tumor cells proliferate with their maximum per capita rate q but when the extracellular phosphorus is less than some threshold value i.e. b for the tumor cells then the proliferation rate is given by

$$q\frac{V_e}{bS_h g}$$

Not only phosphorus is enough for the proliferation of tumor cells, but also the growth of tumor very much depends on a process called angiogenesis by which a tumor develops a blood supply. Small tumors can survive without a network of blood vessels to deliver oxygen and nutrients. When the amount of blood supply provided for the tumor cell is less than some threshold value, and then the proliferation rate of tumor cell slows up. Therefore, when k (z-hy)/y < 1, then the maximum proliferation rate of tumor cell becomes k (z-hy)/y, where h represents the mass of cancer cells that one unit of blood vessels can just barely maintain, and k measures sensitivity of tumor tissue due to lack of blood. Further if λ_y is the death rate of tumor cells and τ_y is the time delay that the tumor cell needs to divide, then $y(t-\tau_y)$ is the mass of the tumor cell in time $(t-\tau_y)$. Thus the growth rate of the tumor cell is given by

$$\frac{dy}{dt} = y(t-\tau_y)q\min(1,\frac{V_e}{bS_e g})\min(k\frac{(z-hy)}{y}) - y\lambda_y - (y(t-\tau_y)q - y\lambda_y)\frac{y+z}{S_t} \quad (2)$$

In this equation the first term $y(t-\tau_y).q\min(1,\alpha\frac{V_e}{aS_h g})\min(k\frac{(z-hy)}{y})$ is the proliferation rate depending on the amount of extracellular phosphorus available to them and also to blood supply, the second term $y\lambda_y$ is the death rate and the third term $(y(t-\tau_y).q-y\lambda_y)\frac{y+z}{S_t}$ is the term when the mass of tumor and tumor micro vessels ($y+z$) reaches the value S_h, at this point the proliferation rate becomes equal to death rate and the tumor does not grow further.

2.3. Equation for the Growth Rate of Tumor Micro Vessels In order to grow larger and spread (metastasize), a tumor needs its own blood supply. Blood vessels give a tumor the oxygen and nutrients it needs to maintain rapid growth. Blood vessels also offer access to other areas of the body. Without a blood supply, a tumor remains very small and localized. The growth rate of tumor micro vessels is not as complex. The tumor micro vessels first grow and take time for activation after which it starts growing. So, τ_z is the time delay which the tumor micro vessel takes from its birth to its activation. If r is the max per capita rate for proliferation tumor micro vessels then the proliferation rate is given by $y(t-\tau_z).r$. It has not been yet proved that the tumor micro vessels is phosphorus limiting, but if they depends on phosphorus then the proliferation rate is given by $y(t-\tau_z)\frac{V_e}{aS_h g}.r$. If λ_z is the death rate of tumor micro vessels then the growth rate of tumor micro vessels is given by

$$\frac{dz}{dt}=y(t-\tau_z)\min(1,\frac{V_e}{aS_h g})r-z\lambda_z) \quad (3)$$

2.4. Homogeneous Tumor with Dietary Regulation If we assume that the phosphorus depends on the diet which is ingested with food at the rate of m (g/day).into the organ. Similarly we assume that the phosphorus is removed from the organ at constant proportion, n as dead material.

Hence, the above model when modified by adding time-variable phosphorus content changes to

$$\frac{dV}{dt}=m-n(a(\lambda_x x-\lambda_z z)+(x(t-\tau_x)p-x\lambda_x)$$
$$ax\frac{x+y+z}{S_h}+b\lambda_y y+(y(t-\tau_y)q-y\lambda_y)b\frac{y+z}{S_t}) \quad (4)$$

The negative terms represents phosphorus liberated by the dying cell, which is washed out of the tumor by the blood.

Finally, writing all the equations and representing the model for homogeneous tumor with varying total phosphorus.

$$\frac{dx}{dt}=x(t-\tau_x)p\min(1,\frac{V_e}{aS_h g})-x\lambda_x-$$
$$(x(t-\tau_x)p-x\lambda_x)\frac{x+y+z}{S_h} \quad (1)$$

$$\frac{dy}{dt}=y(t-\tau_y)q\min(1,\alpha\frac{V_e}{bS_e g})\min(k\frac{(z-hy)}{y})$$
$$-y\lambda_y\eta-(y(t-\tau_y)q-y\lambda_y)\frac{y+z}{S_t} \quad (2)$$

$$\frac{dz}{dt}=y(t-\tau_z)\min(1,\frac{V_e}{aS_h g})r-z\lambda_z) \quad (3)$$

$$\frac{dV}{dt}=m-n(a(\lambda_x x-\lambda_z z)+(x(t-\tau_x)p-x\lambda_x)$$
$$ax\frac{x+y+z}{S_h}+b\lambda_y y+(y(t-\tau_y)q-y\lambda_y)b\frac{y+z}{S_t}) \quad (4)$$

Here in Equation 2 we have introduced an extra parameter η into the model where η is the affect in death rate of tumor cells due to any outside therapy or drug dosage. When the death rate of tumor cell is unaffected then η = 1 and when therapy is instituted then η > 1.

A parameter α is artificially limiting phosphorus in such a way that making it available to healthy cells and not to cancer cells, by inhibiting membrane transport of phosphate. When there is not such therapeutic intervention, α = 1; when therapy is instituted, α < 1.

For a healthy person of 60 kg in weight, we

estimate their daily consumption of nutritious solid food of about 1 kg/day. If we assume the phosphorus content of food is about 1.2 g for each kilogram, then daily dietary phosphorus intake is about 1.2 g. For an 8-kg organ (like liver), its share of phosphorus is about 16 g/day, assuming a homogeneous distribution throughout the body. These considerations put n = 0.001 when p = 3 and a = 10, S_h = 8 at tumor free equilibrium. For a tumor growing on liver q = 5 (for liver) and b = 20. For liver tumor grows to its max mass S_t = 2.5, g = 2/3 = 0.6667, λ_x = 1.2, λ_y = 1.5, λ_z = 0.5, τ_x =5, τ_y = 4, λ_z = 8. Initially we take x (0) = 7.2, y (0) = 0.01, z (0) = 0.001.

Hence this is the mathematical model for homogeneous tumor. In this model, if we keep different values for α and η and study its positive and negative effects on the patients' health. We will study those values, which favor the patient's health and reduce the ill effects of tumor. Our aim for this paper is to cut off all the resources available for tumor growth and give no space for its survival, without having any ill effects on the patient's health.

3. NUMERICAL ILLUSTRATION

In this section, we present the numerical results to explore the effects of phosphorus on growth rate of healthy cells and tumor cells with time delay. For this purpose we use Equations 1-3 for phosphorus dependent growth rates of healthy cells, tumor cells and tumor micro vessels with their respective time delays. Computer program is developed in software MATLAB and run on Pentium IV.

In case 1, we get a graph of growth rate of tumor cell mass, healthy cell mass and tumor micro vessels. Here we kept α = 1 and η = 1 that means phosphorus is not artificially obstructed and neither any artificial therapy is applied.

In Figure 1 all the values are the same as that of case 1 but only the amount of phosphorus available to them is reduced to 120 from 150. The figure shows a gradual decrease in the tumor cell mass. But there is also a great reduction in the healthy cell mass, which shows that the patient will suffer a bad health.

In Figure 2 all the values are the same as that of Figure 3 only the value of time delay for tumor micro vessels has increased from 8 days to 12 days. As the figure shows there are no changes in

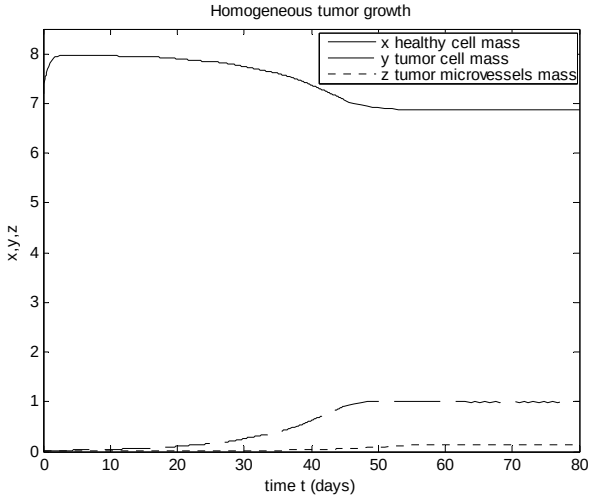

Figure 1. A solution for model with p = 3, a = 10, b = 20, V = 150, S_h = 8, q = 5, S_t = 2.5, g = 2/3 = 0.6667, λ_x = 1.2, λ_y = 1.5, λ_z = 0.5, τ_x = 5, τ_y = 4, λ_z = 8, k = 100, h = 0.5, x (0) = 7.2, y(0) = 0.01 and z(0) = 0.001. Here we assumed α = 1 and η = 1.

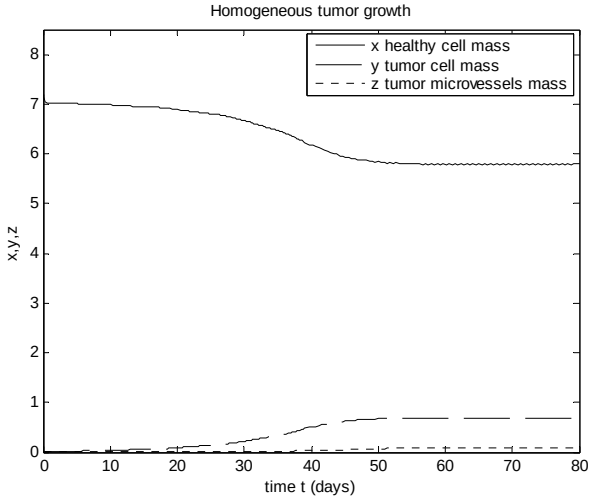

Figure 2. A solution for model with p = 3, a = 10, b = 20, V = 120, S_h = 8, q = 5, S_t = 2.5, g = 2/3 = 0.6667, λ_x = 1.2, λ_y = 1.5, λ_z = 0.5, τ_x =5, τ_y = 4, λ_z = 8, k = 100, h = 0.5, x(0) = 7.2, y(0) = 0.01 and z(0) = 0.001.

the tumor size but the days for tumor to reach its full size increases from 48 days to 65 days.

In Figure 4 the growth rate of tumor cell is reduced to 3, from 5. We see a reduction in tumor growth without having any changes in the growth of healthy cell mass. This shows good sign for the health of patient. That's something quite difficult to reduce the growth rate of tumor cells without any effect on the growth rate of healthy cells.

From Figure 5 we see that all the values are the same as that of Figure 1 except the value of α. The value of α is reduced to about 25 %. Here we see a 43 % reduction in the tumor mass. This is really good for patient's health. The clinicians and the biologist should seek possible means to make phosphorus available to the healthy cells and artificially reduce phosphorus intake by the tumor cells.

Figure 6 shows that all the values are same as that of Figure 5 but only the value of the parameter η has increased from 1 to 1.5. This figure is so far the best one for the patient's health as the healthy cell mass maintains a good graph whereas the tumor mass is restricted to about 1.20 kg. In this case parameter η is the therapies like chemotherapy and radioactivity that is being given to the patient for the killing tumor cells. This increases the tumor death rate to about 50 %.

Figure 7 shows the model in which we have reduced the value of phosphorus 120 from 150 and the parameter η for the outside therapy is applied. Also here the growth rate of healthy cell increases

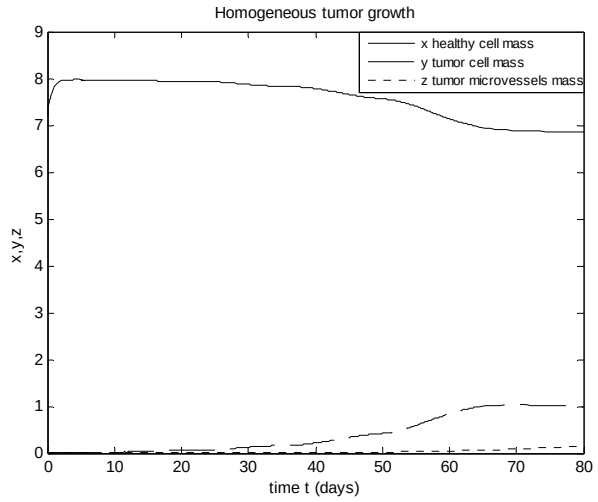

Figure 3. A solution for model with p = 3, a = 10, b = 20, S = 150, S_h = 8, q = 5, S_t = 2.5, g = 2/3 = 0.6667, λ_x = 1.2, λ_y = 1.5, λ_z = 0.5, τ_x = 5, τ_y = 4, λ_z = 12, k = 100, h = 0.5, x(0) = 7.2, y(0) = 0.01 and z(0) = 0.001.

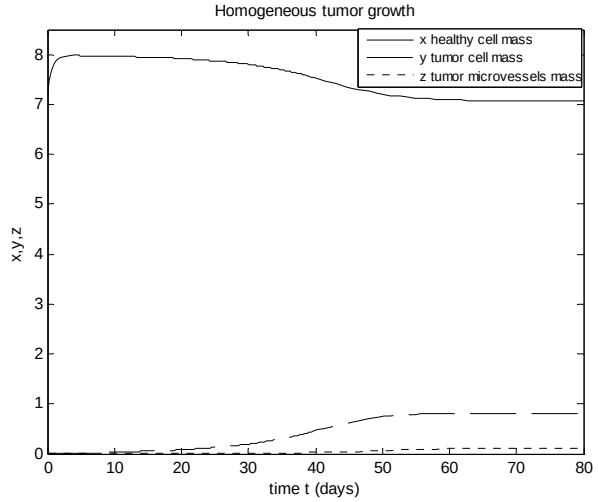

Figure 4. A solution for model with p = 3, a = 10, b = 20, S = 150, S_h = 8, q =3, S_t = 2.5, g = 2/3 = 0.6667, λ_x = 1.2, λ_y = 1.5, λ_z = 0.5, τ_x = 5, τ_y = 4, λ_z = 8, k = 100, h = 0.5, x(0) = 7.2, y(0) = 0.01 and z(0) = 0.001.

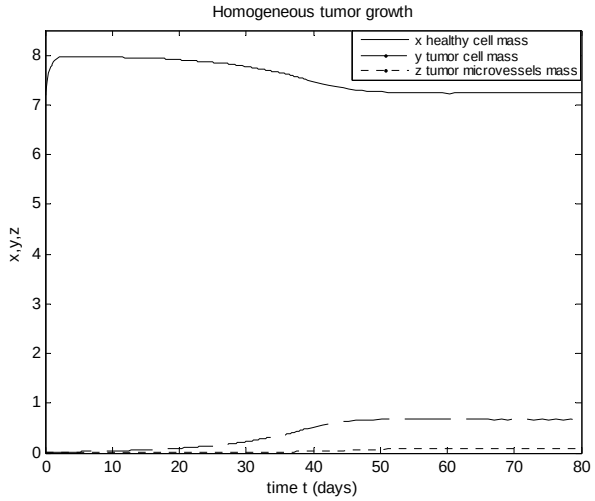

Figure 5. A solution for model with p = 3, a = 10, b = 20, S = 150, S_h = 8, q = 5, S_t = 2.5, g = 2/3 = 0.6667, λ_x = 1.2, λ_y = 1.5, λ_z = 0.5, τ_x = 5, τ_y = 4, λ_z = 8, k = 100, h = 0.5, x(0) = 7.2, y(0) = 0.01 and z(0) = 0.001. Here we assumed α = 0.75.

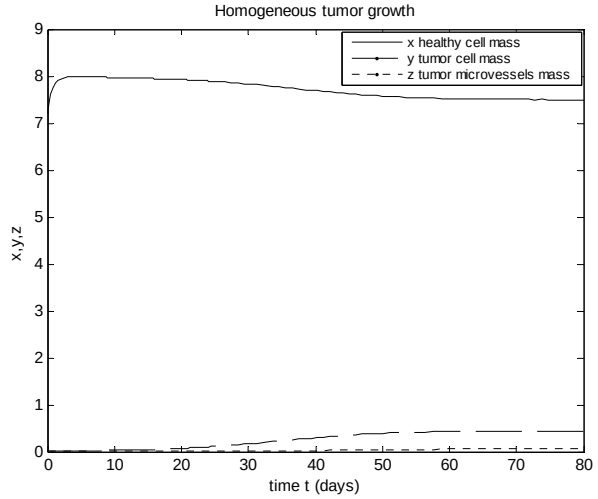

Figure 6. A solution for model with p = 3, a = 10, b = 20, S = 150, S_h = 8, q =5, S_t = 2.5, g = 2/3 = 0.6667, λ_x = 1.2, λ_y = 1.5, λ_z = 0.5, τ_x = 5, τ_y = 4, λ_z = 8, k = 100, h = 0.5, x (0) = 7.2, y(0) = 0.01 and z(0) = 0.001. Here we assumed α = 0.75 and η = 1.5.

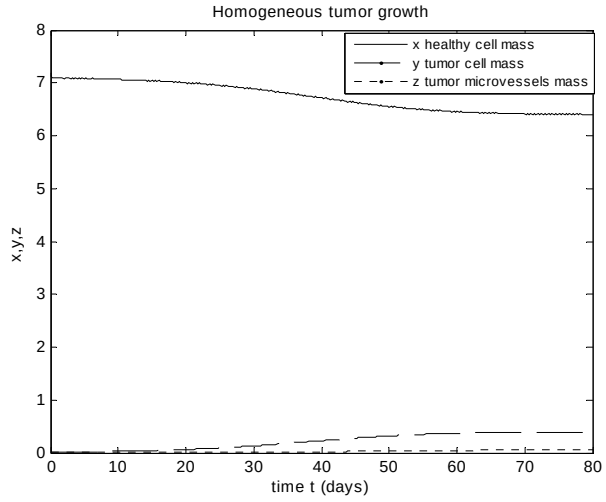

Figure 7. A solution for model with p = 5, a = 10, b = 20, S = 150, S_h = 8, q = 5, S_t = 2.5, g = 2/3 = 0.6667, λ_x = 1.2, λ_y = 1.5, λ_z = 0.5, τ_x = 5, τ_y = 4, λ_z = 8, k = 100, h = 0.5, x(0) = 7.2, y(0) = 0.01 and z(0) = 0.001. Here we assumed η = 1.5.

from 3 to 5. This solution is a boosting value for the clinicians and the biologist to keep the patient under better observation and restrict the intake of phosphorus to the patient and apply medicinal methods so that the growth rate of healthy cells increases. Also the patient is given the outside therapy, which increases the death rate of tumor cells. This method is effective since it is the most practical one.

4. CONCLUSION

The growth rate of the cells is very much affected by the extracellular phosphorus available to them. So, the growth rate of the tumor cell is decreased by the decrease in the extracellular phosphorus concentration. But the extracellular Phosphorus available to all cells less than the threshold value reduce the healthy cell growth and shows negative effect on patients health. Less doses of outside therapy like chemotherapy, radioactive therapy etc. are effective in reduction of tumor growth without affecting patient's health

The more the delay in the activation of the angiogenesis the more will be the delay of tumor to reach its capacity. The artificial restriction of the extracellular phosphorus is the parameter which is very effecting in the reduction of the tumor growth. The actual aim of this paper is that in the race of patient's health and tumor growth the patient's health should win the race

5. FUTURE WORK

This provides the clinicians and the biologists quite a boosting stuff to work on. For them if possible find the way for the artificial limiting phosphorus. We know it is impractical to restrict phosphorus intake for tumor cell and make available for the healthy cells, but if successful this is going to be great achievement in restricting the tumor growth to all most nil.

This paper gives the mathematical modeling of homogeneous tumor formed by one type of mutant cells but since most of the tumor is formed by the different types of mutated cells, so the mathematical model of tumor growth formed by different cell types can be prepared.

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