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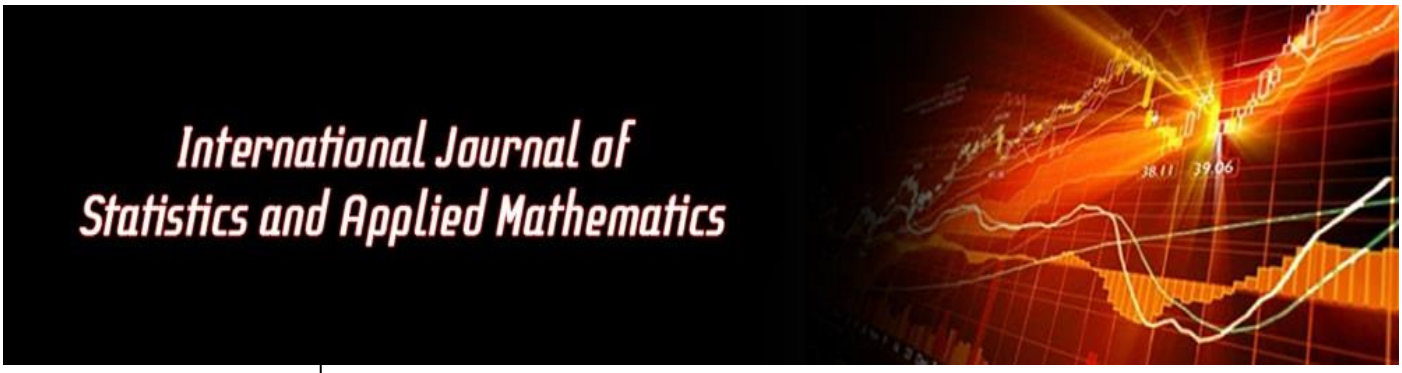

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Importance of extracellular matrix stiffness and energy in the growth of cancer in humans

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Abstract
Extracellular matrix (ECM) is considered essential for wound healing processes, but excessive matrix deposition can result in organ dysfunction, as has been observed with fibrotic disease. ECM stiffness has been shown to play critical role in encouraging a tumor microenvironment and increased stiffness being a main feature associated with tumor development. The growth of cancer through mechanical/chemical/ electrical and biological properties in discussed. A mathematical model is developed in which use of energy is made to link the mass of the stiff tissues with the aggression velocity for the growth of cancer in humans. Implicit solution of the modeled differential equation is derived. It is shown analytically that product of model parameters: initial infection growth proportion $p_0(I)$, time for highest cancer growth rate t_c, the growth parameter γ and level off value L turns out to be constant. The control and possible treatment strategies are also obtained analytically through the time of highest growth rate, maximum estimated cancer growth proportion and level off value.

Keywords: Tissue density, kinetic and potential energy, cancer growth

Introduction
Different types of tissues constitute human body. Physical and chemical regulators play important role in tissue development. Extracellular matrix is a three dimensional network of extracellular macromolecules, such as collagen, enzymes and glycoproteins that provide structural and biochemical support of surrounding cells. It directs cell adhesion and migration, as well as regulating cellular growth, metabolism and differentiation signals. Stiffness of ECM has a role in orienting cell division, maintaining boundaries of tissues, guiding cell migration and deriving differentiation. Further ECM stiffness is important for maintaining tissue homeostasis and disease progression may happen as a result when matrix mechanics get unbalanced (Handorf *et al*. 2015) [15].

In vivo, cell resides in a highly organized environment which is quite complex, containing different kind of collections of sugars, other cells as well as soluble and insoluble proteins. The exact composition and spatial orientation of the microenvironment of a cell dictates local mechanical environment that a cell is exposed to. The mechanical environment consists of internal forces generated by the cells themselves and the external forces that are applied to cells by the surrounding micro environmental (Handorf *et al*., 2015) [15]. The internal forces are mainly produced by cytoskeletal contractively within cells (Mege *et al*., 2006) [25]. On the other hand, the external forces exist in a variety of forms that include tensile and compressive forces, gravity and shear stress. Cells receive these external forces through interaction with ECM whose local stiffness affects the cell behavior. Human tissues that are composed of a variety of different ECM molecules, feature a wide range of elastic moduli and each tissue/organ has specific stiffness for fulfilling physiological needs. For example, bone in much stiffer than other tissues as its basic function is to provide structure and protect our internal organs (Handorf *et al*., 2015) [15].

The averaged values of density of different body matters gathered from multiple sources on web are shown in the following table:

Densities of Different Body Matters

Type	Average Density Value (g/ml)	Range (g/ml)
Blood	1.0428	1.009 to 1.061
Bone	1.7500	1.50 to 1.90
Fat	0.9094	0.9 to 0.9196
Muscle	1.0599	1.0597 to 1.06

Reference: Densities of different body matter; Scroll Seek, 2010.

The ECM is considered essential for wound healing process, but excessive matrix deposition, as mostly observed with fibrotic diseases, can lead to organ dysfunction. ECM stiffness modulates the amplitude of force received and a stiff matrix provides enough power for cell spreading, proliferation and migration. If the matrix is compliant then the cells will instead deform the matrix and round up that would result in different signaling and phenotypic outcomes (Grinnell, 2000) [14].

ECM Stiffness plays critical role in supporting a tumor micro-environment and increased stiffness is considered one of the guaranteed feature associated with tumor development. In fact, breast cancer tissue can be upto 10 fold stiffer than normal breast tissue (1.5k Pa and 150Pa respectively) Kaas *et al*., 2007; Butcher *et al*., 2009 [17, 3].

Increasing substrate stiffness increased collective cell migration speed, persistence and directionality as well as the coordination of cell movement. It was further shown that the propagation was faster and further reaching on stiff substracts (Ng MR, *et al*., 2012) [27]. Cells have been shown to exert shear stress on each other during collective migration (Trepat *et al*., 2009) [39] and cadherin-mediated cell-cell forces (Maruthamuthu *et al*., 2011) [23]. Further, these forces are able to direct all protrusions (Weber *et al*., 2012) [42]. Collagen is the main structural protein in the extracellular space in the various connected tissues in mammals, making upto 25% to 35% of the whole-body protein content (Di Lullo *et al*., 2002) [10]. Geometrically it is understood that a single collagen molecule consists of three left handed helices that are twisted together into a right handed triple helix, often referred to as super helix, which is a cooperative quaternary structure stabilized by many hydrogen bonds.

One thousand mutations have been identified in 12 out of more than 20 types of collagen. These mutations can lead to various diseases at the tissue level (Mahajan *et al*., 2010) [22]. Tough bundles of collagen called collagen fibers are a major component of the ECM that supports tissues and gives cells structure from the outside, but collagen is also found inside certain cells. Collagen has great tensile strength and is the main component of fascia, cartilage, ligaments, tendons, bone and skin (Fratzl, 2008; Buehler, 2006) [13, 2]. It strengthens blood vessels and plays a role in tissue development. The collagen microfibrils interdigitate and cross-link, thus preventing separation from each other in an intact form (Shoulders and Raines 2009) [36]. Increased collagen content and tumor stiffness may also be a product of reduced remodeling. Matrix metalloproteinase (MMPS) are well established as having major role in degrading ECM components during normal tissue remodeling and wound healing. In addition, there is an increase in the prevalence of cross-linking within tumor stroma (Ng, MR and Brugge, 2009) [26]. Increased cross-linking results in increased stiffness (Levental *et al*., 2009) and has been shown to increase the invasiveness of many types of connect cells (Kirschmann *et al*., 2002) [18]; Erler and Weaver, 2009) [11]. As a result, elevated lysyle oxidase (LOX) expression was found to be significantly correlated with metastasis and decreased survival in cancer patients. It was observed that certain level of cross linking is favorable for mechanical properties of collagen fibrils, but excessive cross-linking results in extremely brittle collagen fibrils, a fairly common symptom in aging persons (Buehler 2006) [2]. It was further observed that nature has evolved a length for the Touch Collagen (TC) manomer which is considered to maximize the robustness of the assembled collagen fibril through energy dissipation (Buehler, 2006) [2]. Simulation results indicate that TC manomers either longer or shorter than~300nm (which is considered as the length of a type I collagen triple helix) is likely to form collagen fibrils with less favorable mechanical properties.

Szent-Gyorgyi (1968) [38] proposed that the cells of the body possess electrical mechanism and use electricity to regulate and control the transduction of chemical energy and other life processes (that are essential for living organisms). Presman (1970) [33] was of the view that normal cells possess the ability to communicate information inside themselves and between other cells. In the case of cancer, cells are no longer regulated by the normal control mechanisms. Cone (1975) [5] found that in cancerous tissue the electrical potential of cell membranes is maintained at a lower level than that of healthy cells and electrical connections are disrupted.

The normal energy production process that utilizes electron transport and hydrogen ion gradients across the mitochondrial membrane is disrupted when cells becomes cancerous (Stipanuk, 2000) [37]. It was reported that overall membrane changes, mitochondrial dysfunction, loss of normal cellular electrical connections and enzyme changes are some of the main factors that contribute to the permanent reliance of cancer cells on glycolysis for energy production. When cells are injured or are cancerous, then sodium and water flows in to the cells and as a result potassium, magnesium, calcium and zinc are lost from the cell interior, which causes cell membrane potential to fall (Cone 1985, Cope 1978) [6, 7].

It has been reported that certain chemicals, viruses and bacteria create cancers by modifying the electrical charges of the cell surface. This causes alterations in cell membrane and organelle membrane electrical potential, the functions of these membranes, intercellular mineral content, energy production and genetic expression. Therefore, a key component of cell repair and cancer treatment would be to re-establish a healthy membrane potential in the body's cell (Nieper *et al*, 1999) [29].

Potential energy is not only associated with location of matter, but will also be associated with the structure of matter. The type of potential energy that exists within chemical bonds and is released when those bonds are broken is known as chemical energy. This chemical energy is responsible for providing living cells with energy from food one eats. The release of energy occur when the molecular bonds within food molecules are broken. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. Co-culture induced lipolysis in adipocytes and β-oxidation in cancer cells, suggested that adipocytes act as an energy source for cancer cells (Nieman *et al*, 2011) [28].

Ectopic *Myelocytomatosis* (MYC) expression in cancer is likely to concurrently induce aerobic glycolysis and/or oxidative phosphorylation to provide sufficient energy and anabolic substrates for cell growth and proliferation in the context of the tumor micro-environment. Deregulated MYC expression is found in many commonly occurring human cancers, (Dang *et al*., 2009) [8].

Mathematical Model

Various models including exponential, linear, power law, Gompertz, logistic and generalized logistic were reviewed by

Benzekry *et al*., 2014 [1]. A mathematical model for cancer based on energy conservation was derived, to show that regardless of the different masses and development times, all terms share a common growth pattern, (West *et al*., 2001) [43]. Gompertz and exponential linear models were used for breast cancer data. Similarly Gompertz and power law models were used for lung cancer data. It was suggested that principles of tumor growth might result from general growth laws, often through differential equations. Gompertz model makes use of the operations of exponential and logarithm on the function consecutively, which are mathematically inverse operations and therefore, need not be used in this manner.

Through experiments, the velocity gradient has been introduced to describe velocities of cells. Cells have been shown to exert shear- stress on each other during collective migration and substrate stiffness can influence the properties of collective migration during wound healing and tumor invasion. It does not seem feasible to accurately measure the velocity gradients for human, due to individual variations. Further, the incidence and spread of cancer is likely to be influenced also by genetic traits, nutrition and level of exercise for humans, which is unlikely to produce identical results as for experimental rats.

Mechanical and electromagnetic forces as well as electrical (thermal) and chemical energies have been used to explain the work done to spread cancer. The work done is described as the product of applied force and the corresponding displacement caused by the force. Alternatively, the change in (kinetic) energy also defines the work done. A proposition is made that the cancer growth cannot be considered explicit, as it can spread to all neighboring organs simultaneously. Therefore, the following model for cancer growth is suggested, which has implicit solution. On differentiation, this solution gives back the differential equation representing the growth rate and is therefore mathematically consistent. Further, the aspects of kinetic and potential energy are incorporated to explain the growth pattern of cancer.

Clinically infection proportion at various stages of cancer in patients is likely to be measured with relatively ease. Therefore, the rate of change of change of infection can be considered to represent the velocity of cancer growth.

Let M be the mass of the cancerous tissues, which is the product of volume of the tissues and the density (stiffness) of the tissues. The potential energy is represented by Mgh, where g is the acceleration due to gravity and h can be taken as width, which in 3D structure of the tumor can be taken the traditional height for describing the potential energy of the tissues.

Let $p_0(I)$ denote initial growth proportion of cancer tissues, which is assumed to remain constant up to time t_s. It is considered that, in general, the rate of growth of an organism is dependent not only on heredity factors but also on nutrition, exercise, structure and density of the tissues of various organs. With the continuous change of potential energy into kinetic energy, this change in kinetic energy does the work which is considered instrumental in the growth of cancer. Let $p_t(I)$ be the proportion of cancer growth, when it becomes visible at any time t, out of the maximum possible growth, then the initial boundary condition is given by

$$\frac{dp_t(I)}{dt} = 0, \text{ when } 0 \le t \le t_s \quad \ldots (1)$$

The kinetic energy responsible for cancer growth is expressed as $\frac{1}{2}MV^2$, where the velocity V is the rate of increase of cancerous (tissue) proportion with time and is given by $\frac{dp_t(I)}{dt}$.

Thus, the kinetic energy $= \frac{1}{2}M(\frac{dp_t(I)}{dt})^2$.

Mass of the tumor depends upon the stiffness of tissues, which in turn influences the generation of energy. It can be inferred that higher the stiffness of the tissues, greater will be the energy and therefore faster will be the growth of cancer.

The cancer in the organs of patients continues to grow till the susceptible tissues are available for invasion and for being replaced to be cancerous. In this manner the level off (asymptotic) situation is reached and the corresponding boundary condition is expressed as

$$\frac{dp_t(I)}{dt} = 0, \text{ when } t \to \infty, \ (t > t_l) \quad \ldots (2)$$

where t_l is known as level off time, after which there is no appreciable visible growth of cancer on the corresponding organ(s) of the patient, as there is inadequate supply of the remaining material/nutrients to keep on feeding the cancerous tissues. In such situation most of the kinetic energy is likely to be converted to potential energy, with almost no growth in cancer that can be linked clinically with the last stage of cancer in the patient.

Observed cancer growth (in patient) need not be necessarily 100% on the organ and as such the cancer growth may not approach level off (or become asymptotic) at value 1. In such cases the asymptotic values, denoted by $L < 1$, are the maximum possible cancer growth, which are different for different patients depending upon immunity, exercise, nutrition and where applicable ongoing treatment. The proportion of healthy tissues at time t is represented by $L - p_t(I)$. Hence the growth of cancer would be proportional to the healthy tissues available to be invaded and replaced by cancerous tissues. This is expressed as:

$$\frac{dp_t(I)}{dt} \propto \{L - p_t(I)\} \quad \ldots (3)$$

Converting the proportionality into equation, we get

$$\frac{dp_t(I)}{dt} = \beta_1 \{L - p_t(I)\} \quad \ldots (4)$$

Where β_1 is a constant which depends on the level of immunity in the patient to resist the growth of cancer, exercise (to maintain adequate level of adipose tissues in the body), nutrition and the dynamics favoring or opposing the cancer growth, at the particular time. It is seen that the growing cancer becomes malignant due to its ability to breakdown tissue architecture, invade through disrupted boundaries and metastasize to distant organs, which can only be successful if the 3D microenvironment is permissive for the multistep process. ECM and hypoxia, the non-cellular components, critically derive tumor progression through increased ECM deposition, cross-linking and remodeling. The hypoxia and remodeling lead to progressive stiffening of the ECM and create a micro-environmental context that enhances tumor cell survival, migration, growth and tumor as well as lymph angiogenesis (Erler and Weaver, 2009) [11]. Clinically, the rate of change of infection proportion in cancer patients is likely to have different patterns at different stages and

therefore β_1 can be estimated as the average value over the growth period.

On the other hand, the growth of cancer in patients also depends on the increased number of cancerous tissues ready or capable of invading the healthy tissues, which can be detected from the increased number of cancerous tissues in patients body as compared to the initial numbers. This in turn, is likely to be reflected in the increased potential energy, some of which is then converted into kinetic energy that is responsible for the rate of increase of cancer in the patients. Let $N(0)$ be the number of tissues that are responsible for initial cancer and $N(t)$ be the total number of cancerous tissues at any time $t > t_s$, then we have

$$\frac{dp_t(I)}{dt} \propto \{N(t) - N(0)\} \quad \ldots (5)$$

Changing proportionality into equation, we get

$$\frac{dp_t(I)}{dt} = \beta_2 \{N(t) - N(0)\} \quad \ldots (6)$$

Where β_2 is a constant which depends upon increased *Storage Protein 2* (SP_2 protein), which has no homology with any known anti-apototic protein and decreasing compactness of tissues, failure in the replication of a tissue DNA, environment factors and age as well as habits of patient. In the real situation it is difficult to estimate the exact number $N(t)$ at time t, but the proportion of cancer $p_t(I)$ is likely to be estimated more accurately in the patient's body. Thus, it can be mathematically seen that $N(t) \propto p_t(I)$, with dependency conditions linking these variables. Thus, the relation (5) can be expressed as:

$$\frac{dp_t(I)}{dt} \propto \{p_t(I) - p_0(I)\} \quad \ldots (7)$$

Combining the proportionalities (3) and (7), we get

$$\frac{dp_t(I)}{dt} \propto \{L - p_t(I)\}\{p_t(I) - p_0(I)\} \quad \ldots (8)$$

Converting the proportionately into an equation, we get

$$\frac{dp_t(I)}{dt} = \gamma \{L - p_t(I)\}\{p_t(I) - p_0(I)\} = f_t(I), \text{ for } t_s < t < t_L \quad \ldots (9)$$

where γ is a constant at a particular time, depending on factors mentioned for β_1 and β_2. However, it is noticed that γ has the dimension of inverse time and can be treated as time constant, referred to as growth parameter, which is responsible for exhibiting different cancer growth patterns, to reach the variable level of values of L, in different patients.

The explicit solution of equation (9) using methods like separation of variables does not agree with the boundary conditions. Therefore, we obtain an implicit solution of equation (9), which satisfy the boundary conditions and express it in terms of $p_t(I)$ as follows (Pokhariyal, 1986) [30]:

$$p_t(I) = L - \{L - p_0(I)\} \exp\left[-\gamma \int_0^t \{p_t(I) - p_0(I)\} dt\right], \quad 0 < t < \infty, p_0(I) < L \leq 1 \quad \ldots (10)$$

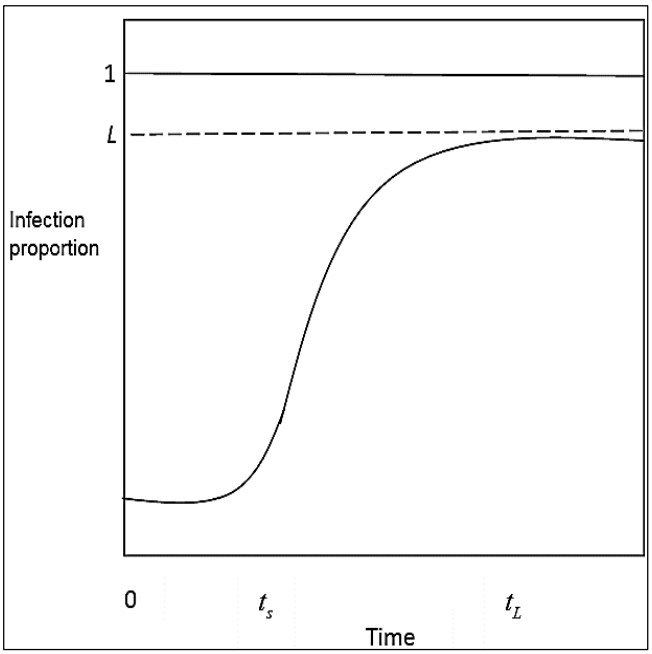

Fig 1: The infection proportion becomes asymptotic at *L (L<1) at the time t* ^{L}

This implicit solution is non-linear in nature and would be suitable to represent the natural phenomena for the growth of cancer in patient which on differentiation gives back the rate of growth of cancer proportion given by (9), see appendix. The exponent part of (10), which represents the area function, provides characteristic S-shape to the growth curve. Kranz (1974) [20] and Van Der Plank (1963) [41] and others have intuitively recognized the significance of the area under the disease progress curve.

The various measures for cancer growth in a patient with respect to time can be computed as follows.

The x% cancer growth is given by

$$\int_{t_s}^{t_l} \gamma \{L - p_t(I)\}\{p_t(I) - p_0(I)\} dt = \frac{x}{100} \quad \ldots (11)$$

In this manner the quartiles, deciles or percentiles can be computed to monitor and evaluate the growth of cancer in a patient's body, so that adequate treatment strategy could be devised.

In particular, 50% cancer proportion (median) growth time can be determined by solving the following equation.

$$\int_{t_s}^{t_m} f_t(I) dt = \frac{1}{2} = \int_{t_m}^{t_l} f_t(I) dt \quad \ldots (12)$$

The time for highest cancer growth rate t_c, is that value of t for which *f(t)* is maximum. Setting

$$f_t^{\bullet}(I) = 0, \text{ we get } p_{t_c}(I) = \frac{L + p_0(I)}{2} \quad \ldots (13)$$

The condition for the second derivative being negative is satisfied and t_c lies in the interval $[t_s, t_l]$. Substituting equation (13) in to equation (9), highest cancer growth rate is obtained (Pokhariyal 1986) [30].

$$\hat{m} = f_{t_c} = \gamma\left[\frac{L - p_0(I)}{2}\right]^2 \quad \ldots (14)$$

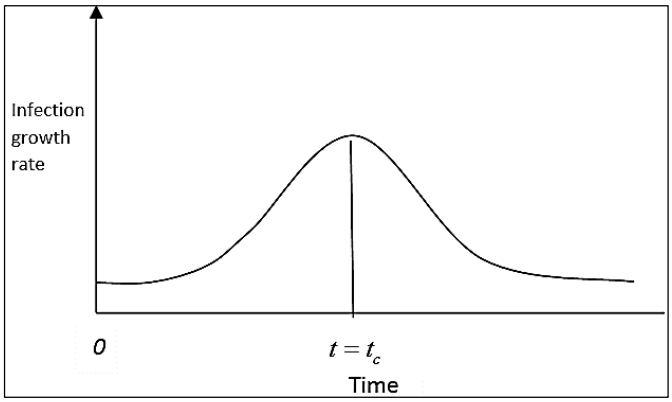

Fig 2: The highest infection growth rate $f_t(I)$ is at the time $t = t_c$

It is at this time t_c, the kinetic energy would be maximum due to highest infection growth rate, to further spread cancer with such highest rate.

Thus, the maximum cancer growth rate in a patient can be interpreted as the square of half of the difference between the maximum (level off) and the minimum (initial) cancer proportions multiplied by the growth parameter γ.

Putting $t = t_c$ in equation (10) and using equation (13), it was obtained (Pokhariyal and Rodrigues, 1993) [32].

$$\gamma t_c \{L - p_0(I)\} = 2\ln 2 = 1.386294361. \quad \ldots (15)$$

From equation (14) and equation (15), it was found that (Pokhariyal, 2002) [31].

$$t_c\sqrt{\hat{m}\gamma} = \ln 2 = 0.69314718. \quad \ldots (16a)$$

Alternatively, we have

$$\gamma \hat{m} t_c^2 = 0.480453013. \quad \ldots (16b)$$

Equation (15), (16a) and (16b) show that the product of model parameters $p_0(I), L, \gamma$ along with t_c and $\hat{m}$ (in respective powers) give us constants. These relationships reflect the balancing nature of the growth of cancer during the lifespan of cancer patients and can possibly used to formulate effective control strategy for cancer growth in humans.

Prevention and Control of Cancer (Analytical Approach)

The control action like chemotherapy or other techniques could be used around t_c. Let $\hat{p}_t(I)$ be the maximum tolerable cancer growth proportion under which the person appears to be normal, then the control strategy can be formulated in the following manner.

Case (i): When $L < \hat{p}_t(I)$, the level off value is less than the maximum estimated cancer growth proportion, then the control action like chemotherapy and other options may not be necessary and patient can prolong the status of having cancer for an appreciable (long) time period, may be due to healthy food and regular exercise. This would then be able to reestablish healthy membrane potential in the cells of the body and adequate level of adipose tissues can also be managed.

Case (ii): when $L > \hat{p}_t(I)$, then control action seems to be necessary. In such situation two possibilities are likely to be encountered.

(a) When $\hat{p}_t(I) < p_{t_c}(I)$, then the control action like chemotherapy or other treatment options should be administered before time for highest cancer growth t_c. This is likely to be accomplished by increasing the polarization and oxygen supply to the cells. In this way the energy level and health of all cells are raised and at the same time the cancer cells become weak as well as less resistant to treatment.

(b) When $\hat{p}_t(I) > p_{t_c}(I)$, then all possible control actions can be done around or soon after the time for highest cancer growth t_c. Although this may seem to be a bit late, but in such situations the likely loss of potassium, magnesium, calcium and zinc from the cell's interior is not much due to sodium and water flow into the cells and patients are likely to respond to the treatments. In this manner, the cancer patients are likely to be on the path of recovery.

Prevention Measures for cancer (Clinical approach)

Researchers and cancer prevention centers have suggested various measures of cancer prevention and control. Some of these are mentioned here. Seller (2011) [35] says that as many as 70% of known causes of cancer are avoidable with healthy life style. Mayo Clinic (2012) [24] also suggest cancer prevention by not using tobacco, eating healthy diet, maintaining healthy weight and be physically active. WHO-cancer prevention offers the most cost effective long term strategy for the control of cancer. The strategy includes: *Avoid* the use of tobacco, alcohol, excessive exposure of solar (UV) radiation and environmental pollution. Seek vaccination for HPV, hepatitis B and C. Maintain proper weight, eat healthy food and do regular exercise.

US Department of Health and Human Services (2015) [40] suggest screening for cervical, colorectal and breast cancer helps prevent these diseases by finding precancerous lesions, so that they can be treated before they become cancerous, as the treatment works best at early stage. Vaccination, healthy choices and eating diet rich in fruits and vegetables are also suggested.

Fox Chase Cancer Center Temple Health (2015) [12] has three specific goals of cancer prevention and control program. Identify factors, whether they stem from host, genetic, environmental, behavioral or life style- that contribute to cancer risk. Develop and evaluate strategies to reduce risk and improve risk communication, decision making and screening. Assess interventions to reduce the burden of cancer and enhance health related outcomes following diagnosis and treatment.

Dasgupta and Basu (2015) [9] suggested use of dopamine that can kill tumors, as it cuts off blood flow to tumors causing them to shrink or die. In the animal experiments, it was

observed that dopamine acted very well on cancerous tumors, effectively countering vascular endothelial growth factor (that helps tumors grow). If human trial succeed, cancer cure will get significantly cheaper. Dopamine is a naturally occurring hormone in the human body and it is easier to absorb, having fewer side effects.

Various clinical prevention measures of cancer growth and the cancer progression data in different patients can be useful for estimating the values of the proportionality constants β_1, β_2 and γ as well as other parameters in the model differential equations representing the growth mechanism of cancer in the patients. In this manner the analytical and clinical approaches can also be compared.

Discussion

In the constructed model the stiffness representing density and the volume of tissues define the mass of the tumor, which is then used to introduce the notion of potential energy and kinetic energy. These energies keep on exchanging during growth and asymptotic stages, while maintaining law of conservation of energy.

West *et al*. (2001) [43], assuming the basic physical law of conservation of energy, by only using potential energy, stated that we can intuit and explain observed behavior that there would be a maximum size that a tumor will attain. This maximum size is due to the fractal pattern of the vein that feed and nourish the tumor. As the vein bifurcates, there comes a point that the vein is too small and the constraints of diffusion reduce nutrition supply to the cancerous cells. It was further stated that the growth rates of tumor that have metastasized do not grow as rapidly as the tumor cells from which they originated. It is understood that for the using law of conservation of energy both potential and kinetic energy need to be considered, which is undertaken in this study.

The phenomena of cancer growth can possibly be interpreted that at incubation stage the cancerous cells organize themselves and get prepared to invade by accumulate potential energy. At the time of invasion (to spread cancer) these cells require the kinetic energy, with suitable speed of invasion, to replace the healthy tissues by cancerous tissues. With increased number of replaced healthy tissues the potential energy also increases and part of it gets converted to kinetic energy to further invade the healthy tissues. This causes the increase in the infection proportion and would go on up to the time t_c with the maximum rate of increase $\hat{m}$. These consequences can be determined by estimating the values of β_1 for respective patients through clinical observations. After t_c the growth rate begins to decrease and finally tends to level off at L, with almost no more healthy tissues remaining to be invaded and replaced by cancerous, thus most of kinetic energy being converted to potential energy. In this manner there is mainly the potential energy due to increased number of cancerous tissues and the conservation of energy is thus maintained. The consequences of these aspects can be determined by estimating the values of β_2, through clinical observations for respective patients. The combined effect estimated by β_1 and β_2 can be measured through γ, for the overall growth dynamics.

Ignacio Ramis-Cande *et al*. (2004) [16] suggested that cancer cell invasion of tissues is a process during which cell migration through ECM is facilitated by secretion of degradative enzymes. Cells can deform their cytoplasm to produce pseudopodia, anchor these pseudopodia to neighboring spatial locations in the tissue and detach earlier bonds to enable them to move and migrate in a specific direction. The cancer cells were modeled as discrete individual entities which interact with each other via potential function, while the spatio- temporal dynamic of other variables in the model are governed by partial differential equations.

Benzekry *et al*. (2014) [1] suggested that principles of tumor growth might result from general growth laws, often through ordinary differential equations, which are also used in this paper. The solution of the formulated differential equation depicts exponential growth. In a recent study Kivuti-Bitok *et al*. (2015) [19], we have used Kenyan data for the cervical cancer to develop a mathematical model. The differential equations and the corresponding boundary conditions for various stages were formulated by using the actual number of patients at each stage and the numbers that change from one stage to the other stage of the cancer.

Yorke *et al*. (1993) [44] suggested exponential growth model for cancer. It can be observed that Gompertz model describing tumor dynamics, uses the inverse operations of exp. and Ln consecutively on the function and therefore mathematically negate their combined use. Thus, the model equation analytically then reduces to a mere exponential law. However, Gompertz model suggests that tumor growth rate is greatest at the beginning stage and predicts that as tumor grows, its growth rate slows down. Tumor cells almost certainly have different growth characteristics in different patients and individual micro metastasis within a single patient may also have different growth parameters. The suggested model takes care of this aspect, as different values of model parameters would be linked with different patients.

Carmeliet and Jain (2000) [4] through *in vitro* experiments have clearly demonstrated that nutrient (in particular oxygen) diffusion limits tumor spheroid growth and paved the way for angiogenesis hypothesis, which states that in order to grow large, tumors need to obtain their own blood vessels and therefore must recruit vessels from the host vasculature through angiogenesis. This aspect is undertaken for the control strategy of the suggested model.

The constructed model fits and describes almost all natural growth patterns dealing with plant pathogen, crop development, HIV/AIDS and cancer, where growth parameters and dynamics are not completely under human control. For these growth patterns the product of model parameters $p_0(I), \gamma$, L, t_c along with $\hat{m}$ give constants, as shown analytically by equations (15), (16)a and (16)b, which almost assures that mechanism of cancer growth (and other infections) is not necessarily under individual control. These situations can be considered different from economic or GM foods growths, where model parameters and dynamics are mostly controlled and manipulated by human being and in some cases law of diminishing return also sets in. The stage and status of cancer in patients are possibly distinguished from one another by estimating the values of $\beta_1, \beta_2, \gamma, L, \hat{m}$ and t_c as well as boundary conditions from the observational data. Application of the principle of conservation of energy, West's law, angiogenesis hypothesis and other biological observations can possibly be utilized to estimate the values of parameters of cancer growth in patients.

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Appendix:

Equation (10) can be written as:

$$L - p_t(I) = \{L - p_0(I)\} e^{-\gamma \int \{p_t(I) - p_0(I)\} dt}$$

Taking log of both sides, we get

$$\log\{L - p_t(I)\} = \log\{L - p_0(I)\} - \gamma \int (p_t(I) - p_0(I)) dt$$

Differentiating, we get

$$\frac{1}{L - p_t(I)}(0 - \frac{dp_t(I)}{dt}) = \frac{1}{L - p_0(I)}(0 - 0) - \gamma \{p_t(I) - p_0(I)\}$$

.

Thus, we have

$$\frac{dp_t(I)}{dt} = \gamma \{L - p_0(I)\}\{p_t(I) - p_0(I)\}$$

.

which is same as equation (9), with β being replaced by the constant γ

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