

Mathematical Model for Stiffness and Energy of Extracellular Matrix in the Growth of Cancer

Ganesh Prasad Pokhariyal

Department of Mathematics, Graphic Era Hill University, Dehradun, India.

Email: gppokhariyal@gmail.com

Nilesh Patel

Department of Medical Physiology, University of Nairobi, Kenya.

Email: npatel@uonbi.ac.ke

Sudhakar Kumar Chaubey*

Section of Mathematics, Department of Information Technology, University of Technology and Applied Sciences, Shinas, Oman.

*Corresponding Email: sudhakar.chaubey@utas.edu.om

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Abstract: Stiffness of Extracellular matrix (briefly, ECM) plays an important role in providing a tumor microenvironment and the increased stiffness has been associated with the development of tumor. The notions of potential energy and kinetic energy are developed and used to explain the growth of cancer from incubation stage to the asymptotic stage by maintaining the law of conservation of energy. The product of model parameters γ , $p_0(I)$, t_c and L is shown to be constant, which reflects their complimentary nature for the growth of cancer in patients and can be used to formulate control strategies for treatment.

Keywords: Infection proportion, tumor mass, velocity of growth, potential and kinetic energy, machine learning.

1. Introduction

Extracellular matrix (ECM) has many important functions including providing structure to the tissues and regulating behaviour during growth, repair, regeneration and homeostasis. It is understood that during embryogenesis, ECM provides structural support and mechanical cues to direct tissue movement and organization¹. In addition, the ECM locally controls cell behaviour and defining the stiffness of the microenvironment as well as activating intercellular signalling through binding with cell surface

receptors. Furthermore, ECM is thought to play a key role in paracrine signalling vital to development through growth factor requestation. It is generally accepted that ECM composition undergoes dramatic remodelling during tissue formation, leading to changes in tissue mechanics and cellular behaviour. However, it is not yet completely known about how the three-dimensional organization of these ECM components varies as a function of development². Human body is made of different type of tissues and physical as well as chemical regulators that play important role in tissue development. By employing particle-tracking microrheology (PTMR), it was shown by Baker *et al.*³ that ECM stiffness and architecture can strongly influence the intracellular mechanical state of cancer cells. The geometry, rigidity and other physical properties of ECM are sensed by the cells and ultimately direct their differentiation and the complex spatial and structural arrangements they form in tissues⁴.

Major role in degrading ECM components during normal tissue remodelling and wound healing is attributed to matrix metalloproteinase (MMPS) and there seems to be an increase in the prevalence of cross-linking within tumor stroma⁵. Increase in the stiffness is caused due to cross-linking⁶, which in turn increase the invasiveness of several types of connected cells⁷. As a consequence, elevated lysyle oxidase (LOX) expression was correlated significantly with metastasis and decreased survival in cancer patients.

Transport and hydrogen ion gradients across the mitochondrial membrane is disrupted. With cells getting injured or becoming cancerous, sodium and water flows into the cells and as a consequence calcium, Zink, potassium, and magnesium are lost from the cell interior that results in membrane potential to drop^{8,9}.

It is seen that certain chemicals, viruses and bacteria modify the electrical charges of the cell surface, which is responsible for creating cancers. Therefore, the process of re-establishing a healthy membrane potential in the body's cells is seen as a key component for cell repair and cancer treatment¹⁰. Potential energy is seen as associated with the structure as well as location of matter. The aspect of potential energy which exists within chemical bonds and is released on breaking of these bonds is referred to as chemical energy and is considered responsible for providing energy to the living cells from food one eats, by virtue of breaking molecular bonds within food molecules. Co-culture induced lipolysis in β -oxidation and adipocytes reveals that adipocytes acts as an energy source for cancer cells and their rapid growth¹¹. It is believed that Ectopic Myelocytomatosis (MYC) expression in cancer seems to concurrently induce oxidative phosphorylation as well as aerobic glycolysis to provide enough energy and anabolic substrates for growth of

cells and their proliferation in the tumor micro-environment. In commonly occurring human cancers deregulated MYC expression is found¹².

Kulkarni et al.¹³ have applied the pancreatic ductal adenocarcinoma (PDAC) model to investigate dynamic alterations in nanomechanical attributes arising from the cell-ECM interactions to study the fibrosis paradigm. Several segregated studies performed on cellular and ECM components fail to recapitulate their complex collaboration. Many researchers have applied the machine learning to resolve the issues of ECM.

2. Cancer Development Model

Experiments conducted on animals, rats in particular, are unlikely to produce identical results for humans due to genetic traits, level of exercise and nutrition for growth of cancer. Infection proportion at various stages of cancer will reflect the mass of cancerous tissues, denoted by M , which is the product volume of the tissues and the density (stiffness) of the tissues. The three-dimensional structure of the tumor would provide us the measurement that can be considered as height h to describe, with the help of acceleration due to gravity g , the potential energy of the cancerous tissues denoted by Mgh .

The velocities of cells have been described by introducing the notion of the velocity gradient often with the experiments. It has been shown that during collective migration cells exert shear-stress on each other and substrate stiffness can influence the process of wound healing and tumor invasion. The work done to spread cancer has been explained with the help of various forms of energies like chemical, electrical (thermal), mechanical and electromagnetic forces. The work done can be described as a product of force and the displacement due to applied force or change in kinetic energy. The rate of change of infection can be considered as the velocity of cancer growth V , so that $(0.5MV^2)$ represents the kinetic energy.

We adopt the differential equation model¹⁴ for the development of the cancer growth, using the concept of conservation of energy. Consider $p_0(I)$ as the initial growth proportion of cancer tissues, which is assumed to be constant up to the time t_s . Through continuous change of potential energy into kinetic energy, such change in kinetic energy does the work which is considered responsible for the growth of cancer. It is in general understood that the rate of growth of an organism depends not only on heredity factors but also on structure and density of tissues of an organ, exercise and nutrition. Let at any time t the proportion of visible cancer growth be $p_t(I)$, then with the boundary condition, we have

$$(2.1) \quad \frac{dp_t(I)}{dt} = 0, \quad \text{where } 0 \leq t \leq t_s.$$

The velocity V of cancer growth is the rate of increase of proportion of cancerous tissues can be represented by $\frac{dp_t(I)}{dt}$, so that the kinetic energy = $\frac{1}{2}M(\frac{dp_t(I)}{dt})^2$. The mass M of tumor is dependent on the stiffness of tissues, so that higher the value of stiffness greater will be energy which would cause faster growth of cancer. The growth of cancer in organs of patients can continue till the availability of susceptible tissues to be converted into cancerous. The situation for the levelling off (asymptotic), where there is no appreciable visible cancer growth can be represented by the following condition:

$$(2.2) \quad \frac{dp_t(I)}{dt} = 0, \quad \text{when } t \rightarrow \infty, \quad (t > t_l).$$

where t_l is known as level off time for cancer growth. This is possible due to inadequate supply of nutrients to feed as well as non-availability of healthy cells for further growth of cancer, with likely situation where most of the kinetic energy has been converted into potential energy. This can be possibly linked with clinically the last stage of cancer growth in the patient. It is seen that cancer growth in a patient need not necessarily be 100% on the organ and as such reach the asymptotic (level off) value $L < 1$. The value of L would be different for individual patients depending upon immunity, nutrition, exercise, and applicable ongoing treatment. Thus, the proportion of healthy tissues at any arbitrary time t can be represented by $L - p_t(I)$. Hence, the growth of cancer on an organ would be proportional to the available healthy tissues to be replaced by cancerous tissues through invasion and we express it as:

$$(2.3) \quad \frac{dp_t(I)}{dt} \propto \{L - p_t(I)\}.$$

The corresponding equation, by converting the proportionality is given as:

$$(2.4) \quad \frac{dp_t(I)}{dt} = \alpha_1 \{L - p_t(I)\},$$

where α_1 is the proportionality constant which depends on immunity level in the patient to resist the cancer growth, nutrition and dynamics opposing or favouring of cancer growth at the particular time period. The non-cellular components ECM and hypoxia, critically derive tumor progression by virtue of increased ECM deposition, cross-linking as well as remodelling. The progressive stiffness of ECM has been attributed to hypoxia and remodelling which created a micro-environment context that is considered to enhance tumor cell survival, migration, growth, and lymph angiogenesis⁷. The value

of α_1 can be estimated as the average value of rate of change of infection proportion in cancer patients which is likely to have different patterns at different stages as seen in the clinical observations. Consider $N(0)$ to be the number of tissues that represent initially visible cancer in the patient. With the development of cancer, the number of cancerous tissues also increases, which is likely to be responsible for the increased potential energy. Some of this potential energy is then converted to kinetic energy which in turn reflects increase in the rate of growth of cancer in the patient. Let after time $t > t_s$ the total number of cancerous tissues be $N(t)$, then we can have the following proportionality:

$$(2.5) \quad \frac{dp_t(I)}{dt} \propto \{N(t) - N(0)\}.$$

Converting proportionality into equation, we have

$$(2.6) \quad \frac{dp_t(I)}{dt} = \alpha_2 \{N(t) - N(0)\},$$

where α_2 depends on available healthy tissues to be converted into cancerous, decreasing compactness of tissues, lack of replication of a tissue DNA, exercise, habits of patient, environment as well as other external factors supporting and opposing the growth of cancer. It is difficult to estimate the exact number of cancerous tissues in patient's body, but the proportion of cancer $p_t(I)$ is likely to be estimated with relatively more accuracy. Thus, we can mathematically express $N(t) \propto p_t(I)$, with dependency factors connecting these variables. The relation (2.5) can be expressed as:

$$(2.7) \quad \frac{dp_t(I)}{dt} \propto \{p_t(I) - p_0(I)\}.$$

Combining proportionalities (2.3) and (2.7), we get

$$(2.8) \quad \frac{dp_t(I)}{dt} \propto \{L - p_t(I)\}\{p_t(I) - p_0(I)\}.$$

By converting the proportionality into equation, we have Pokhariyal¹⁴

$$(2.9) \quad \frac{dp_t(I)}{dt} = \gamma \{L - p_t(I)\}\{p_t(I) - p_0(I)\} = f_t(I), \text{ for } t_s < t < t_L,$$

where γ is time constant and has the dimension of inversetime and depends on the factors mentioned for α_1 and α_2 . The constant γ is also referred to as growth parameter responsible for different growth patterns and level off values for different patients.

The rate of growth of cancer with respect to time t , denoted by $f_t(t) = P'_t(I)$ can be expressed as

$$(2.10) \quad f_t(I) = \begin{cases} \gamma \{L - p_t(I)\}\{p_t(I) - p_0(I)\}, & \text{for } t_s < t < t_L. \\ 0, & \text{elsewhere} \end{cases}$$

The time for mean (central) cancer growth proportion is denoted by t_a and the time for 50% (median) infection growth rate is denoted by t_M . The time for highest infection proportion t_c would be the value of t for which $f_t(I)$ is maximum. The time for highest infection proportion growth is obtained by

$$(2.11) \quad f'_t(I) = 0 \text{ and } f''_t(I) < 0,$$

provided it lies in the interval $[t_s, t_l]$. Differentiating (2.10) with respect to time and putting $f'_t(I) = 0$, we get

$$(2.12) \quad p_{t_c}(I) = \frac{L+p_0(I)}{2}$$

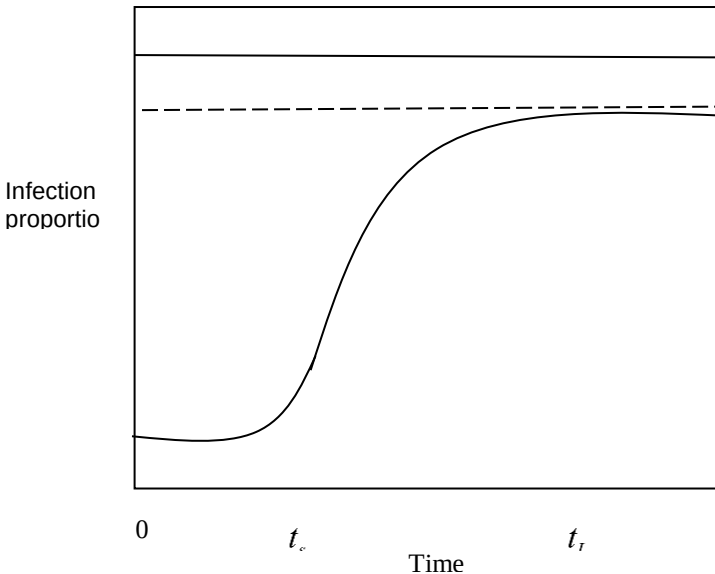
and $f''_t(I) < 0$, is also satisfied. Substituting (2.12) in (2.10), the highest cancer proportion growth at time $t = t_c$ is given by Pokhariyal¹⁴

$$(2.13) \quad \hat{m} = f_{t_c} = \gamma \left[\frac{L-p_0(I)}{2} \right]^2.$$

At the time t_c the kinetic energy will be maximum which would cause highest cancer growth rate in the patient.

The growth of cancer as observed in the clinical studies is such that it also likely to spread into the neighbouring organs simultaneously, therefore a proposition is adopted that the cancer growth cannot be considered as explicit. Thus, the model for the cancer growth rate provided by (2.10) gives the following implicit solution

$$(2.14) \quad p_t(I) = L - \{L - p_0(I)\} \exp \left[-\gamma \int_0^t \{p_t(I) - p_0(I)\} dt \right], 0 < t < \infty, p_0(I) < L \leq I$$



The implicit solution satisfies the boundary conditions and is of non-linear nature which is considered suitable to represent the natural aspect for the growth of cancer in patients. Further, differentiating (2.14) we get back (2.10). The exponent part of (2.14) represents the area function, which provides the S-shape to the disease growth curve and its significance is recognized by Van Der Plank¹⁵ and Kranz¹⁶.

Putting $t = t_c$ in (2.14) and using (2.12), Pokhariyal and Rodrigues¹⁷ obtained

$$(2.15) \quad \gamma_{t_c}\{L - p_0(I)\} = 2 \ln 2 = 1.386294361.$$

This relationship shows that the product of model parameters is a constant, which reflects the complementary nature of parameters for the growth of cancer during the life span of cancer patients. This result can be used to devise an effective control strategy to treat cancer patients.

3. Control and Preventive Strategy

3.1. Model approach

Using constructed model, we consider the following cases.

Case(i): When $P_0(I)$ is relatively small and L is relatively large

Under such condition the right-hand side of (2.13) will have a larger magnitude and the time for highest cancer growth proportion t_c will be reached after a relatively longer time from the time of visible cancer t_s as compared to the normal situation. Thus, the control action like chemotherapy or other treatment methods need to be taken up much before the highest cancer growth time t_c . In this manner the energy level and the health of cells are raised though polarization and supply of oxygen and as a consequence cancer cells become weak as well as less resistant to the adopted treatment.

Case(ii): When $P_0(I)$ is relatively large and L is relatively small

Under such condition the right-hand side of (2.13) will have a smaller magnitude and the time for highest infection growth proportion t_c will be reached after relatively shorter time. Therefore, the preventive measures in such a situation could be taken around the time of highest cancer growth or soon after it. In these cases, the likely loss of minerals such as zinc, magnesium, potassium and calcium from the cell's is not much due to water flow and sodium into calls and patients are most likely to respond to the treatment. This could possibly put patient into recovery path.

For each individual patient, there would be a typical combination of $\gamma, P_0(I), t_c$ and L values, such that the time for mean (average) growth proportion t_a , the time for highest cancer growth proportion t_c and the time

for 50% (median) growth proportion t_M would provide us with the following curves showing rate of cancer growth.

- (a) Negatively skewed, with $t_a < t_M < t_c$.
- (b) Symmetric, with $t_a = t_M = t_c$.
- (c) Positively skewed, with $t_a > t_M > t_c$.

These curves can also be used to suggest control mechanism for the growth of cancer in patients. For example, in (a) with negatively skewed curve, the preventive measures have to be taken before the time for highest cancer growth rate. Alternatively, patients should take measures that would reduce the value of level off time L and maintain it at that level as well as allow the initial growth proportion of cancer tissues $P_0(I)$ to take relatively higher value and try to control it at that level for a longer time period.

3.2. Using Clinical approach

Various measures for cancer prevention have been suggested by centres of cancer prevention and researchers.

European Union¹⁸ has suggested the ways to reduce cancer risk that include:

- i. Do not smoke and avoid use of any form of tobacco.
- ii. make home and workplace smoke free.
- iii. Maintain healthy body weight.
- iv. Be physically active in everyday life and limit the time you spend sitting.
- v. Have a healthy diet: eat plenty of whole grains, pulses, vegetables, and fruits.
- vi. Limit the consumption of calorie foods, red meat, and food high in salt.
- vii. Avoiding alcohol drinking is better for cancer prevention.
- viii. Keep away from too much sun and places with radiations.
- ix. Get vaccination for HPV, hepatitis B and C, and take part in cancer screening programmes.

Mayo Clinic¹⁹ has also provided similar lifestyle tips for cancer prevention Pucci *et al.*²⁰ suggested that nanomedicine, combined with targeted therapy, such as gene therapy, SiRNAs delivery, immunotherapy, and antioxidant molecules, offer new possibilities to treat cancer patients. The other promising alternatives to tumour resection are thermal ablation and magnetic hyperthermia. Further, radiomics and pathomics approaches are considered to assist in the management of big data set from cancer patients to improve prognosis and outcome.

4. Discussion

In our model, the mass of the tumor is defined as the product of volume and the density (represented by stiffness) of the tissues, which along with

width (representing height) and the rate of change of cancer growth (representing velocity) are then used to introduce the notions of potential energy and kinetics energy. These energies get exchanged during the growth and asymptotic (level off) stages, while maintaining law of conservation of energy. West et al.²¹ have used only potential energy for the conservation of energy and stated that one can intuit and explain observed behaviour that there would be a maximum size that tumor will attain. Tumor is stated to be feed and nourished by this maximum size due to factual pattern of the vein and through vein bifurcation a situation arises when vein is too small and due to the constraints of diffusion the nutrition supply to the cancerous cells is reduced. The use of conservation of energy requires both kinetic energy and potential energy, which is done in our model and the exchange of these energies is utilized for the growth stage (with potential to kinetic) as well as for asymptotic stage (with kinetic to potential). At the incubation stage the cancerous cells accumulate potential energy and prepare to invade healthy tissues. During this period of invasion (for spreading cancer) these cancerous cells require kinetic to replace healthy tissues by cancerous tissues, with suitable velocity of invasion. The increased number of cancerous tissues increases the potential energy and then some portion of it again gets converted to kinetic energy for further invasion of healthy tissues which continues up to time t_c . After this time t_c the growth rate starts decreasing and finally levels off at L , as there are no appreciable number of healthy tissues remaining to be replaced and as a consequence most of the kinetic energy gets converted into potential energy, maintaining the law of conservation of energy. The consequences of this mechanism can be seen by estimating the values of α_1 , α_2 and γ through clinical observations for respective patients at corresponding times. In a study Benzekry et al.²² reported that the pattern of tumor growth might result from growth laws, mostly through ordinary differential equations and various other models. Our model also utilizes the differential equations to show the entire growth pattern of cancer as well as other infections. Kivuti-Bitok *et al.*²³ developed a mathematical model for cervical cancer, using the differential equations. The boundary conditions for various stages were formulated using the actual number of patients at each stage and the numbers that changed from one stage to other stage of cancer.

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