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Biological Diffusion Coefficient for 3D Tumor Growth in Homogeneous Media

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Abstract: The bio-mechanism of the spread of tumor cells in a biological tissue is highly complicated and a potent source of controversy. The study of this mechanism is considered partially as a diffusion process for both normal and tumor cells. A 3D computer model is introduced to simulate the stochastic growth of living cells in a homogeneous nutrient medium. The model follows the cytokinetic rules of living cell division. Cell-cell interactions have been formulated and developed for both types. The term BDC (biological diffusion coefficient) is introduced as a new measure to assess the tumor progression in a normal tissue. The BDC of normal and tumor cells is calculated as a function of time and loss factor. The results show that the existence of normal cells acts as a stochastic resistance to the malignant growth. Moreover, the biological diffusion coefficient of tumor cell increases with time explaining the apparent acceleration and penetration of tumor cells through a normal tissue.

Key words: Stochastic modelling, tumor growth, biological diffusion coefficient.

1. Introduction

Cancer is a complex process, in which genetic mutations occurring at a sub-cellular level manifest themselves as functional and morphological changes at the cellular and tissue scale. The importance of interactions between tumor cells and their microenvironment is currently of great interest in experimental as well as in computational modeling. Many scientists have attempted to provide appropriate computer models to describe the cell population dynamics and tumor growth pattern.

In a series of publications, Düchting et al. have produced several models for cellular growth simulation and cell-cell interactions [1-5]. Kansal et al. introduced a three-dimensional cellular automaton model of the brain tumor which predicted that the tumor growth dynamics follows a Gompertz function [6, 7].

Anderson et al. introduced a multi-scale mathematical model for cancer invasion, which considers cellular and micro-environmental factors simultaneously and interactively [8, 9]. In addition, they have also used three different modelling approaches at two different spatial scales; they also examined the impact of nutrient availability as a driving force for tumor invasion [10]. Specifically, they investigated how cell metabolism influences the tumor growth. They concluded that the tumor population is driven by extreme changes in nutrient supply during tumor progress.

Drasdo et al. examined a model in which cells are represented as simple particles which are parameterized mainly by their physical properties [11]. A new mathematical model of tumor spheroid growth that incorporates both continuum and cell-level descriptions were proposed [12].

Monte Carlo methods were also used to study tumor proliferation. These techniques were implemented by one of us to study the spatial considerations of cellular distribution that affects the overall asynchronous process of population growth [13]. Tuckwell et al. have developed a Monte Carlo model to simulate tumor cell propagation in the head and the neck squamous cell carcinoma [14]. The model aims to eventually provide a tool for radiation

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oncology that helps in planning patient treatment schedules. A cellular automaton model for the growth of an avascular tumor on a two-dimensional square lattice was presented [15]. The pattern formation and the growth of the cell population were investigated by using a Monte Carlo simulation.

A generic 3D multi-cell simulation of a vascular tumor growth which described the interaction with the tumor and the host tissues was presented by Shirinifard [16]. Although their work omitted many biological details, but nonetheless, it provided a very useful starting point to more realistic modelling.

The present work accommodates a stochastic dynamic three dimensional lattice model describing the growth of biological cells in a homogenous nutrient media. The model is based on the assumption that the most dominant factor that regulates the cytokinetics of cellular growth is the presence of enough space for division. We considered the problem of biological cellular growth as a diffusion process. Despite of the differences between the diffusion mechanism of living cells and other phases of dead matter, yet both are a random walk process. Accordingly, a new concept for evaluating the growth is indicated by the biological diffusion coefficient "BDC (biological diffusion coefficient)". Hence the tumor biological diffusion coefficient is calculated as a function of time for different loss factors. A computer simulation model for living cells is developed that considers the stochastic nature of cellular division for both normal and tumor cells.

2. Cellular Growth Mechanism

The present model introduces a 3D matrix (200 × 200 × 200) that simulates a piece of a living tissue (Fig. 1). The string of each element of the matrix contains data stating the cell type (normal, malignant or vacancy), cell phase (proliferative, differentiated, resting, or necrosis), and the lifespan of each phase.

Cell cytokinetic rules of division of cells are applied to each element obeying a modified cell cycle [13, 17] such that cellular growth is simulated and monitored with time in accordance with the following rules:

- A central element is surrounded by 12 neighbouring sites at approximately equal distances in a closed-pack arrangement as shown in Fig. 1. Some of these sites could be vacant.
- The distance between two neighbouring cells equals to the average diameter of the cells.
- The division of a normal cell only occurs if it reaches its mitotic phase and finds at least two adjacent vacant sites in its immediate vicinity. Two vacancies are the appropriate space for division without disturbing the surrounding cells.
- The tumour cells divide regardless of the existence of nearby vacancies.
- The daughter cell pushes the adjacent cells and occupies its location.
- The cyclic time of the tumour cell is shorter than the normal one.
- The nutrient is homogeneously distributed over the tissue and the effect of the immune system is neutralized.

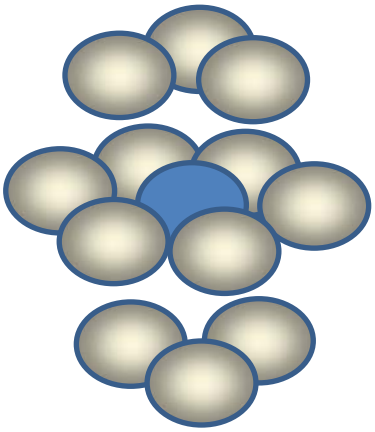

Fig. 1 A schematic representation of an ideal closely packed cell distribution showing the nearest neighbors of equal distance.

- The stochastic nature of growth as well as the spatial randomization of cells and vacancies is employed.
- The loss factor is simulated by removing a certain percentage of the cellular population from the

matrix (tissue) and eventually their locations become vacant. The spatial distribution of these lost cells is taken at random.

In this work two cases are reported: firstly, Free growth is simulated by starting with only one cell in the center of the matrix (the tissue) while the rest of the sites are vacant. Secondly, competitive growth assumes the existence of normal and tumor cells in the same tissue.

3. Biological Diffusion Coefficient

The spread of cells in a tissue is the result of a random occupation of vacancies under a stochastic biological mechanism. This process is similar to the classical diffusion process in solids. The main differences are: firstly, the number of diffusing particles in solids is kept constant, while the number of living cells varies with time. Secondly, as a percentage of cells dying with time (loss factor), the creation of vacancies varies dynamically. Thirdly, the daughter cell jumps to one of the available vacancies conditionally when the mother cell has ended its mitotic phase.

Calculating the BDC, which indicates the cells growth rate, allows comparing the results of different growth rates for normal and tumor cells. The average radius of cellular expansion of the growing cells is taken as the *rms* of the maximum radial distance R_i after a certain time t:

$$R_{average} = \sqrt{\frac{\sum_i^N R_i^2}{N}} \quad (1)$$

where, N is the number of iterations. Hence the biological diffusion coefficient BDC is calculated accordingly as

$$BDC = \sqrt{\frac{R_{average}^2}{6t}} \quad (2)$$

The program considers that the average cell cyclic time (T_c) as 24 time steps, with 10% standard deviation, σ, as illustrated in Table 1. Each cycle corresponds to one day. Hence, the number of iterations in the program is correlated to time in days so that one day corresponds to 24 iterations.

On the other hand, considering the average cyclic time for tumour cells being 12 hours (12 iterations) with a standard deviation σ = 10%, the possible different timings for the different phases are listed in Table 2.

4. Results and Discussion

An element that represents a single normal cell is assumed to occupy the center of a 3D matrix (200 × 200 × 200). This virtual cell follows the cytokinetics of division and follows through a number

Table 1 Assumed normal cells cyclic durations (iterations) with its four cyclic times.

T_c	T_{G1}	T_S	T_{G2}	T_M
22	10	7	4	1
23	10	8	4	1
24	11	8	4	1
25	12	8	4	1
26	12	9	4	1

Table 2 Assumed tumour cells cyclic durations (iterations).

T_c	T_{G1}	T_S	T_{G2}	T_M
10	5	2	2	1
11	5	3	2	1
12	6	3	2	1
13	7	3	2	1
14	7	4	2	1

of iterations that simulate the growth for an equivalent of 20 days. During its growth the cellular population was subjected to loss factors of 0% and 0.01%.

Fig. 2 shows the increase in the number of normal cells with time; as they divide in a homogenous medium with all positions that are available for division. Apparently, the growth rate follows the Gompertzian model with minimal effect of the growth factor. Fig. 3 illustrates the variation of the biological diffusion coefficient BDC of the normal cells versus time. In this case, the average radius of the spherical growth was calculated in accordance with Eqs. (1) and (2).

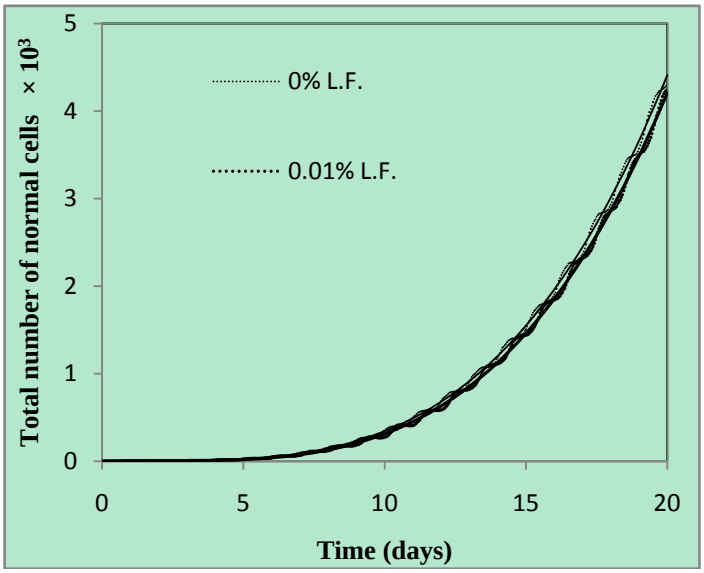

Fig. 2 Total number *N* vs. time for the 3D normal free growth for two loss factors. The solid lines represent the best fit of the data.

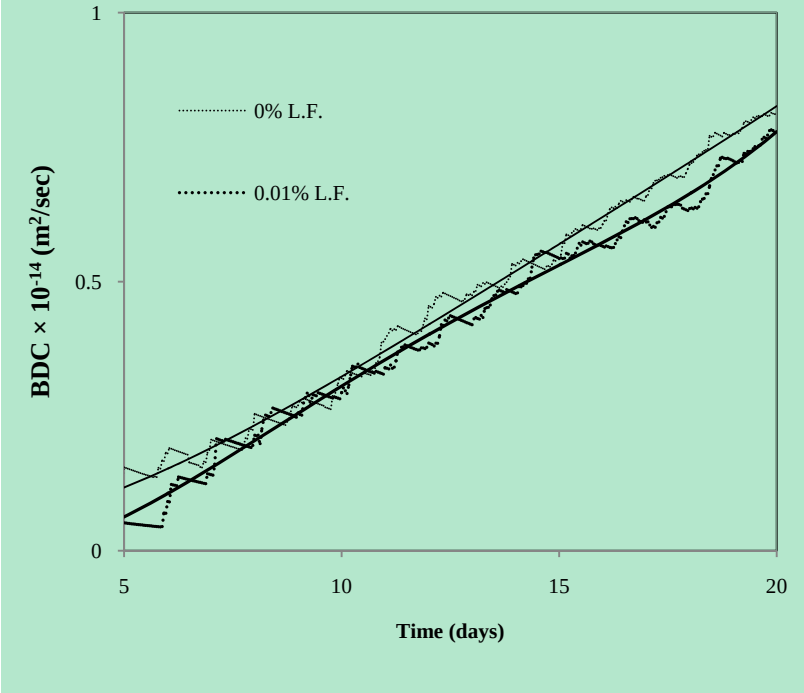

Fig. 3 The BDC vs. time for the 3D normal free growth for two loss factors. The solid lines represent the best fit.

On the other hand, the free growth of a virtual single tumor cell is simulated in a 3D matrix (200 × 200 × 200) as a function of time (for the equivalent of 20 days). Fig. 4 shows the increase in the total number of cells versus time. The average radius of growth is illustrated in Fig. 5. The pattern of growth is consistent with the theoretical expectations.

Despite the fact that the mitotic time of the tumor cells is only half of that of the normal cells, the results show that within the same period of time the number of tumor cells is 100 folds greater than that of the normal cells. The increase of the BDC of tumor cells with time is depicted in Fig. 6. It is noteworthy that unlike the conventional diffusion coefficient, the BDC increases drastically. This is attributed to the progressive increase in the number of diffusing elements and the dynamics of vacancy creation and occupation.

Moreover, we studied the case when the biological tissue has initially normal cells occupying almost all

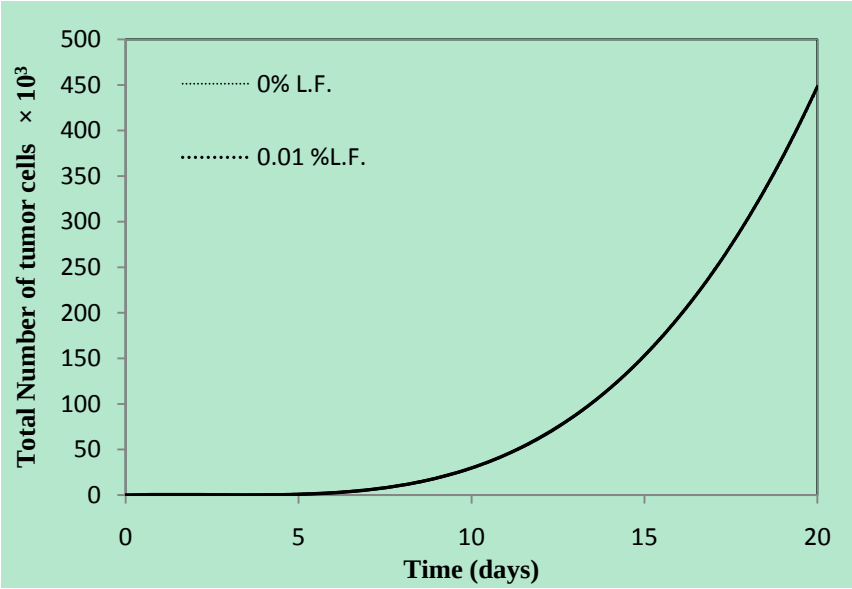

Fig. 4 Total number *N* vs. time for the 3D tumor free growth.

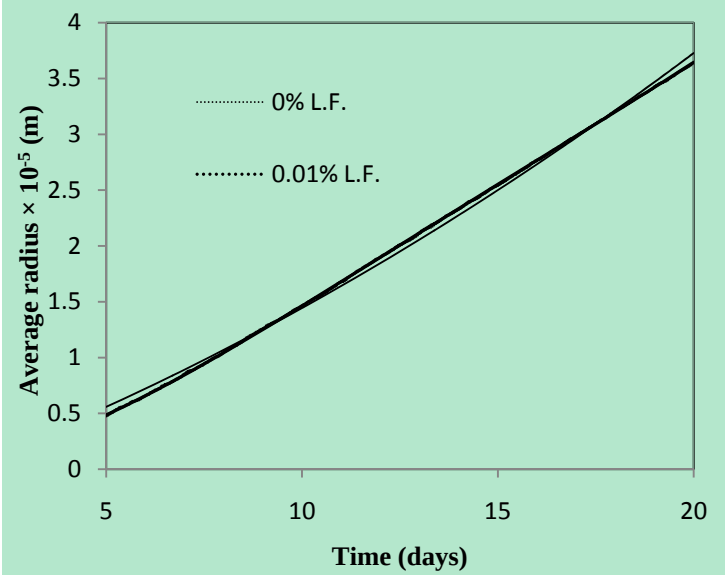

Fig. 5 R_{avg} vs. time for the 3D tumor free growth.

the sites of the 3D matrix with a fraction of randomly distributed vacancies. One single malignant cell is assumed to exist at the center. Each type of cells follows its own kinetics of division. As the time progesses the computer simulation determines the spread of the malignant cells and their pentration in the normal tissue.

The average radius of growth of the tumor cells is plotted versus time for two values of loss factors, namely 0% and 0.01%, as shown in Fig. 7. The plot shows that the average radius of the tumor growth exhibits a linear increase with time. The variation in the loss factor has a negligible effect on the pattern of growth. This is attributed to the fact that the dividing tumor cells constantly push their neighbors regardless of the existence of vacancy.

The BDC is plotted versus time for the tumor penetration in a tissue of normal cells, as shown in

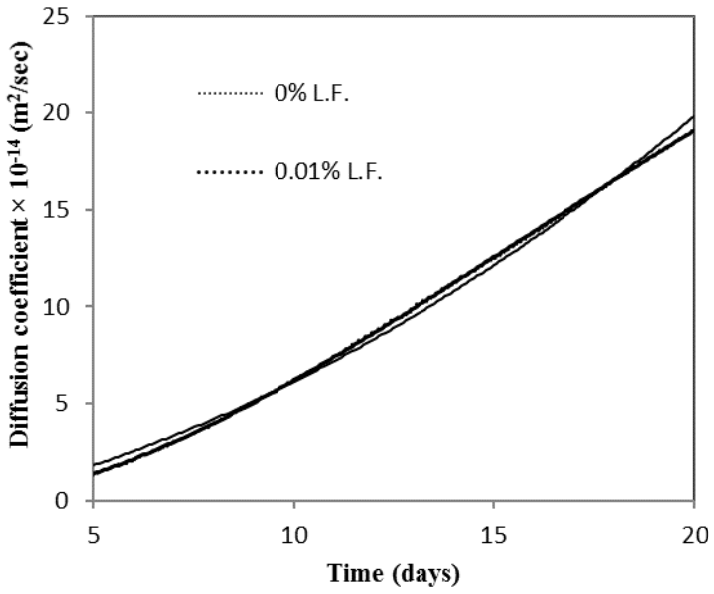

Fig. 6 BDC vs. time for the 3D tumor free growth.

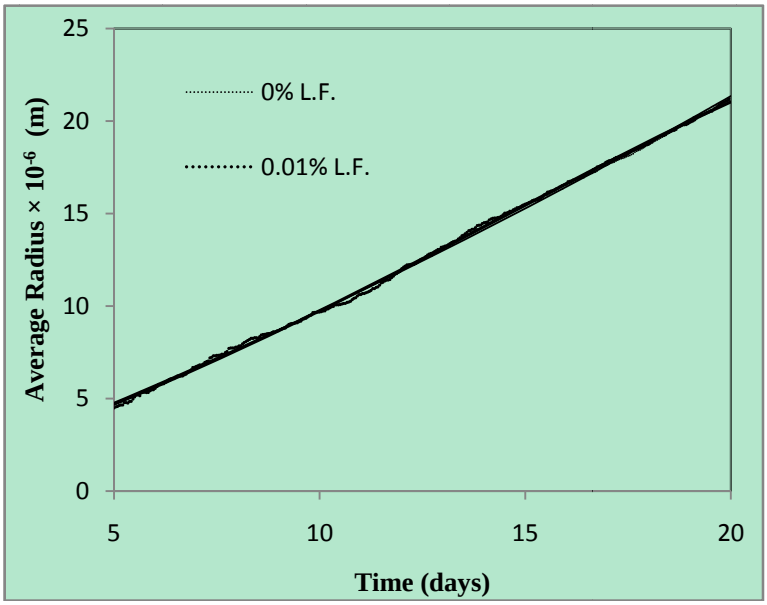

Fig. 7 R_{avg} vs. time for the 3D tumor growth in a normal tissue.

Fig. 8. The value of the BDC is followed for 20 days and the figure indicates that it is increasing almost in a linear pattern and that the effect of the loss factor is insignificant.

A comparison is drawn for the number of growing cells in three cases, namely the free progression of the normal cells, the free progression of the malignant cells, and finally the progression of tumor cells with time as they compete with the normal cells in a living tissue; our results are illustrated in Fig. 9. The progression is considered for a time that is equivalent to 20 days. The figure shows that at the end of the 20 days the number of tumor cells in a vacant tissue (free growth) becomes 450×10^3, however, it drops to 50×10^3 cells in the case of tumor progression within a normal tissue due to the existence of normal cells. These values are insenstive to the change of the loss factor. This indicates that the propagation of the tumor in a living normal tissue is impeded by the existence of normal cells.

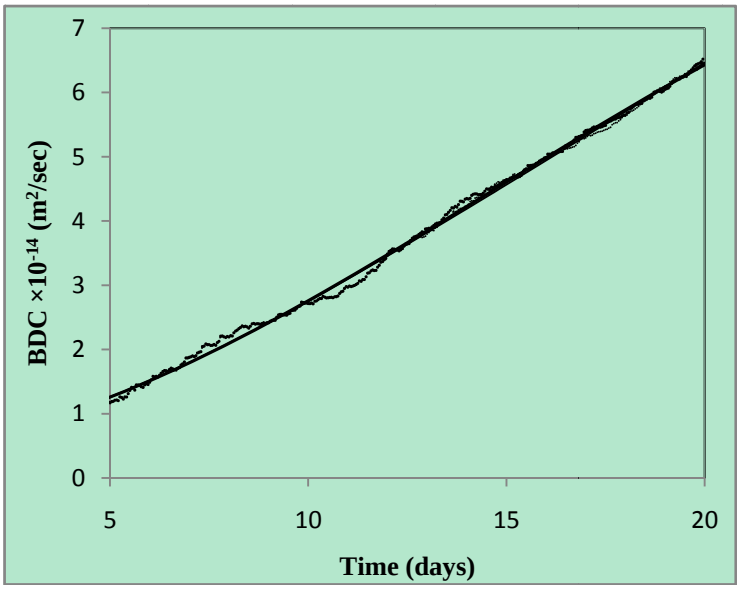

Fig. 8 BDC vs. time for the 3D tumor growth in a normal tissue.

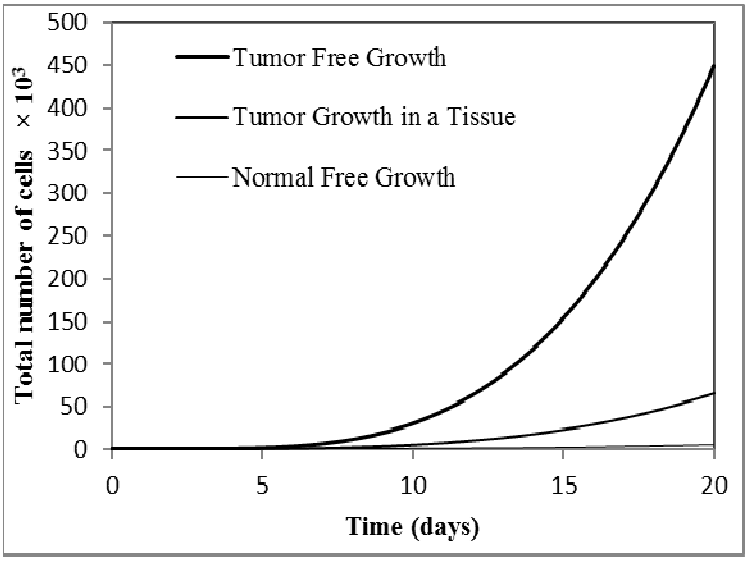

Fig. 9 Comparison between the number of cells *N* vs. time of the three cases of cellular growth in 3D lattice.

The increase in the average radius of growth versus time for the abovementioned three cases is illustrated in Fig. 10. The volume of the tumor cells that grows freely has an average radius of 39×10^{-6} m. However, due to the existence of normal cells the radius drops to 21×10^{-6} m after 20 days. A reduction of about 30% in the size of the tumor is achieved.

Moreover, the values of the BDC for those three cases are plotted versus time in Fig. 11. It is apparent that when the tumor cells are left to spread in a medium in which all the surroundings are available; the spread is three times greater than the case when the normal cells surround and resist its propagation. The value of BDC is approximately reduced from 19×10^{-14} to 6×10^{-14} m^2/s.

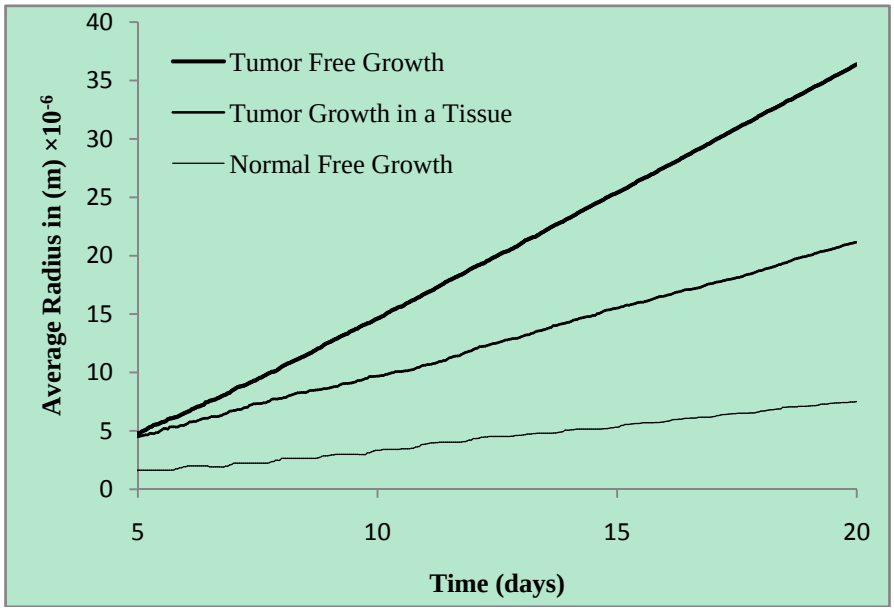

Fig. 10 Comparison between the average radius of growth vs. time of the three cases of cellular growth in 3D lattice.

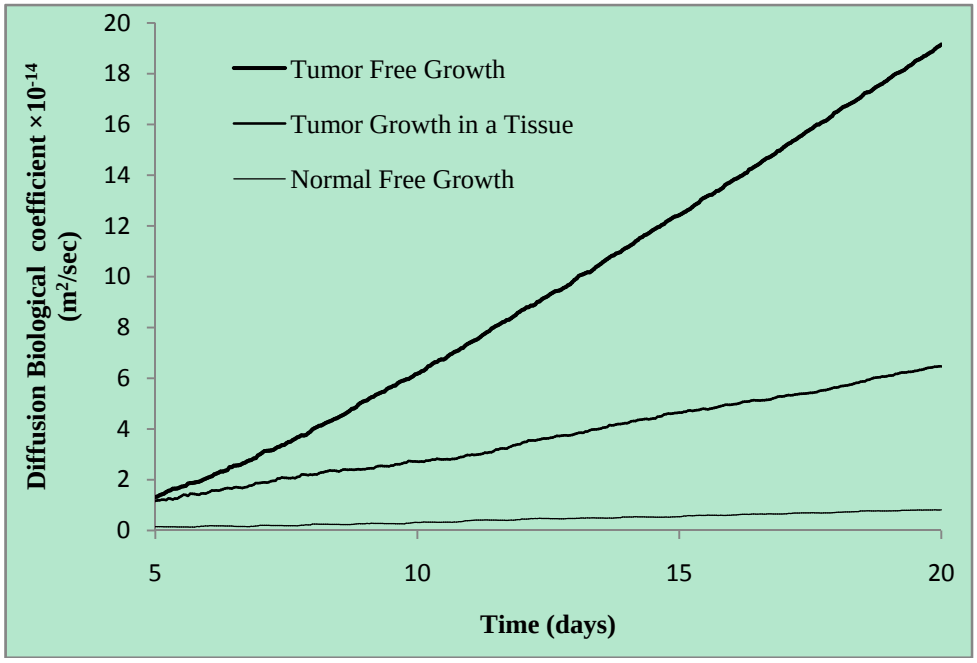

Fig. 11 Comparison between the BDC of growth vs. time of the three cases of cellular growth in 3D lattice.

5. Conclusions

This work is a continuation of the consistent efforts to put a theoretical and logical understanding of a very complicated and mysterious phenomenon of tumor growth.

A new measure of the spread of the malignant cells in living tissues is introduced, specifically the biological diffusion coefficient "BDC". Comparing the BDC to the diffusion in non-living media such as solids and liquids, the present work reaches the following conclusions:

The range of the BDC as measured (2×10^{-14}-20×10^{-14} m^2/s) is comparable with that of the solid state of some materials [18]. However, the biological diffusion mechanism differs considerably from that observed in matter. Unlike the conventional diffusion mechanism, the number of diffusing elements (cells) is time dependent. Also, the creation and occupation of vacancies complicate the differences between the two mechanisms.

The birth of a daughter cell is discrete and follows a completely different mechanism than the conventional diffusion in matter; this is illustrated in the jerkiness of the graphs.

Since the body temperature is constant, the BDC is temperature independent.

From the results obtained in this work, it is obvious that the creation of vacancies increases the probability of tumor progression. Hence surgical intervention is likely to enhance the recurrence of tumor dominance which results from the creation of a considerable number of neighboring vacancies; any minute number of malignant cells left will exploit the existence of extra vacancies for their fast division.

On the other hand, chemotherapy must specifically address the mitotic phase of the tumor cells, otherwise it will destroy the resisting normal cells and thus creating more vacancies available for tumor growth.

In all cases the calculations of the BDC would act as a good measure to assess and examine the progression and regression of tumor under the differently medical treatments.

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