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RESEARCH ARTICLE

Computer modeling of the *in vitro* growth of living cells as a biological diffusion process

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Abstract

In the present work we look at 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 matters yet both of them are a random walk process.

In this paper we introduce a computer model simulating the free growth of biological cells in a nutrient media considering the stochastic nature of the growth. 2D computer model is employed to simulate a virtual model of cell growth. The model follows the actual cytokinetics rules of normal growth. Hence the diffusion coefficient was calculated as a function of time and loss factor.

The results show that the diffusion coefficient of normal cells is time dependent, unlike the case of other matters, as well as it depends on the loss factor. Also, it was possible to trace the diffusion of different phases of the mitotic cycle as related to the loss factor and time.

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Introduction

Many scientists have attempted to provide an appropriate computer model to describe the cell population dynamics. In a series of publications, Duchting and Vogelsaenger (1981), (1982), and (1987) have produced models of cell growth simulation. They considered a very limited number of cells that obey the rules describing the cell-cell interactions. Their work extended to cover tumor growth and considered virtual surgical and chemotherapeutic treatments. Gilbert (1982) has produced a model that considers the asynchronized nature of cellular division. This is due to the variability of mitotic time among cellular population. ElMessiery (1990) implemented Mont-Carlo technique to study the spatial considerations of cellular distribution that affect the overall asynchronous process of population growth. Duchting *et al.* (1986) studied the cellular growth process in the light of the control theory. This approach has enabled the researchers to interpret cancer as an unstable closed-loop control circuit. Cristini *et al.* (2003) studied the cellular growth, in particular malignant cells, as a nonlinear regime using boundary-integral simulations. A new formulation of the classical models is developed. Hence, the tumor evolution is described by a reduced set of 2D parameters, which is qualitatively unaffected by the number of spatial dimensions. Cecka led a team of researchers (2006), to modify a computational tumor model developed at Los Alamos National Laboratory (LANL). This model simulates doses of a specific chemotherapy drug to treat cancers. Drasdo *et al.* (2007) showed that many collective phenomena in multi-cellular systems can be explained by models in which cells are represented as simple particles which are parameterized mainly by their physical properties. Gevertz (2009) produced a theoretical Mathematical model of tumor growth. The general goal of his research was to develop a model that account for the feedback between a growing tumor and the evolving host. Shirinifard (2009) presented a 3D multi-cell simulation of a vascular tumor growth which can be extended to describe more specific vascular tumor types and host tissues. Boondirek *et al.* (2011) produced a stochastic cellular automata (CA) model of tumor growth in a cubic lattice. The dynamics of tumor growth was incorporated to describe tumor cell invasion of normal tissue.

The present work accommodates a stochastic dynamic model which agrees with most of the previously reported models for simulation of cellular growth. To come closer to reality, it considers that the most dominant factor that

regulates the cytokinetics of cellular growth is the presence of enough space for division. We present a new concept of evaluating the growth as indicated by the *biological diffusion factor* which is already used in studying the penetration of tracers in host matters.

Diffusion is the tendency of the molecules of a substance (solid, liquid, or gas) to move from a region of higher concentration to that of a lower one, due to random walk mechanism.

Fick's first and second laws relate the diffusive flux (J_x) to the concentration gradient (∇C) as well as time in accordance to the following equations:

$$J_x = -D \nabla C \qquad (1)$$

and

$$\frac{\partial C}{\partial t} = D \nabla^2 C \qquad (2)$$

Where:

J_x: The Mass Flux per unit area perpendicular to x

D: Diffusion Coefficient

∇C: Concentration gradient

$\frac{\partial C}{\partial t}$: Change of concentration with time

Both laws are related to the random walk mechanism of a diffusant in a host media (Shewmon, 1963). The average penetration distance of the diffusant is dependent on the diffusion coefficient D in accordance with the following:

$$r_{av} = \frac{\sum_{i=1}^{m} r_i}{m} \qquad (3)$$

$$r_{av} = \sqrt{4Dt} \qquad (4)$$

$$D = \frac{r_{\mathrm{av}}^2}{4t} \qquad (5)$$

Where:

r_i: The radial distance of a boundary cell

r_{av}: Average radial distance

m: Number of boundary cells

D: Diffusion Coefficient

t: Simulated time

The Computer Model

The goal of the model is to simulate two-dimensional free cell growth and calculate the biological diffusion coefficient which indicates the cells growth rate. Performing this task cell-cycle model for normal cells has been developed. Moreover, rules describing the cell-cell interactions have been formulated.

Cellular growth mechanism:

The model assumes a matrix representing a tissue through which the cell grows; each matrix element can be occupied by a growing living cell. Individual elements carries a record of the following parameters: cell location within the tissue, cell type (normal cell in one of its phases), cell phase (proliferative, differentiated, resting, or necrosis), lifespan of each cell's phase and the cell nutrition level, some of the matrix elements are labeled as vacancies.

The following rules are considered in building the computer program representing the free cell growth, starting with only one cell in the center of the matrix, and applying the following rules to allow the cell to divide naturally and freely in a monolayer tissue according to the rules of cell-kinetics, described in the next section.

The rules of cell division:

It is based on the assumption that the most probable factor of cell division under normal circumstances is the availability of a nearby vacancy to divide in (El-Messiery, 1990). It is assumed that each newly born normal cell passes through a cell-cycle of the four phases (G1, S, G2, M), and when it reaches the end of its mitotic phase, it would have one of the following routes namely; dividing into two cells (a daughter and a mother) , resting or differentiating, as illustrated in Figure (1). It shows a schematic representation of cellular growth model, exhibits the three routes; Division, Resting, and Differentiating. The number of neighbouring vacancies "n" determines the possible fate of the cell.

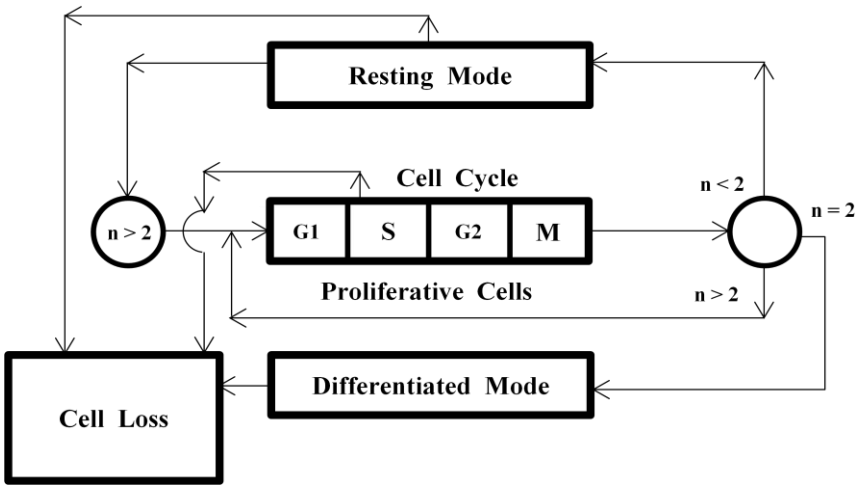

Figure 1: Schematic representation of cellular growth model, clarifying the three routes; Division, Resting, and Differentiating

If n>2 cell division occurs, the mother cell starts a new cycle while the daughter cell occupies one of the available vacancies chosen randomly.
If n=2 the cell enters into the differentiated mode. In this mode the cell is decycled, hence, keeps its viability and biological function without going through division again.
If n<2 the cell enters into the resting mode. The cell stays in this mode until the number of the neighbouring vacancies increases and becomes more than two.
The three categories of cells are subjected to cell loss and consequent necrosis leading to a creation of a vacancy.

The experimental procedure

The model approach was simulated using the MATLAB v.8 programming to simulate the normal cellular free growth in homogenously nutrient media and their interaction. A 2D array is constructed 500 x 500 and assigned to present a tissue of 0.25 mm^2 area, so that each element in the array represents a possible location for a cell or a vacancy as shown in figure (2).

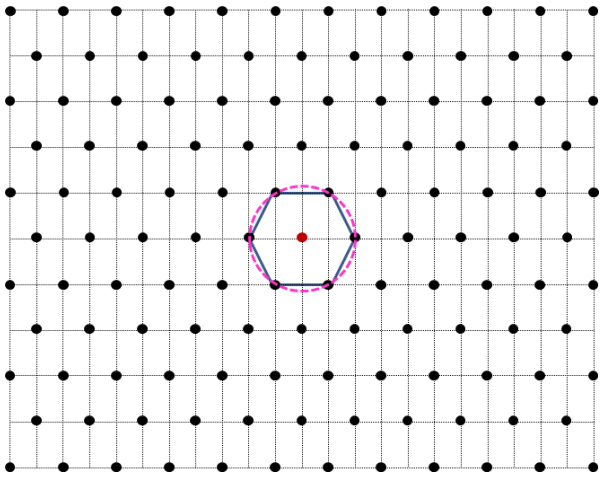

Figure 2: Schematic representation of the 2D array representing the tissue

The individual cell is assumed to be surrounded by six locations distributed in hexagonal shape as shown in figure (3a). This closely packed distribution is probable even if the shape of the individual cells is irregular as shown in figure (3b).

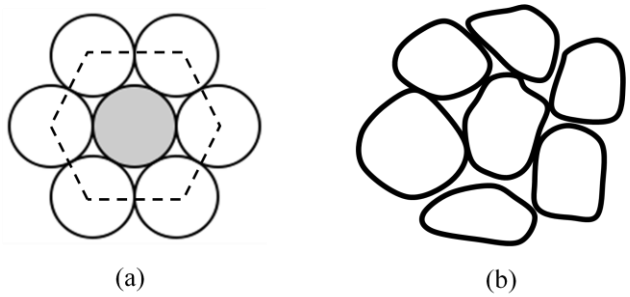

Figure 3: (a) Schematic representation of ideal closely packed cell distribution,
(b) Virtual six cellular neighbors in 2D

The cyclic time of an individual cell is distributed according to normal distribution so that after division the cell claims a mitotic time at random in accordance with the normal distribution with the assigned standard deviation. The total cell cycle time mean (T_c) is considered as 24 hours (one day); corresponding to 24 iterations, with standard deviation (σ), hence, the cyclic time ranges from 22 to 26 time steps.
Accordingly a matrix of 500 x 500 is assumed. Initially, a single cell located at the centre and the rest sites are vacant. Loss factor (0 – 2%) per iteration is assumed with homogeneous nutrition for all cells. The program runs for a virtual time corresponding to 100 days.

Results

Figure (4) shows the growth pattern of cells as they increase with time, the color code represents the cells in different phases. Since this model follows the stochastic nature of growth, the results exhibits an almost spherical growth pattern which tends to be a complete circle as the number of cells statistically increases.

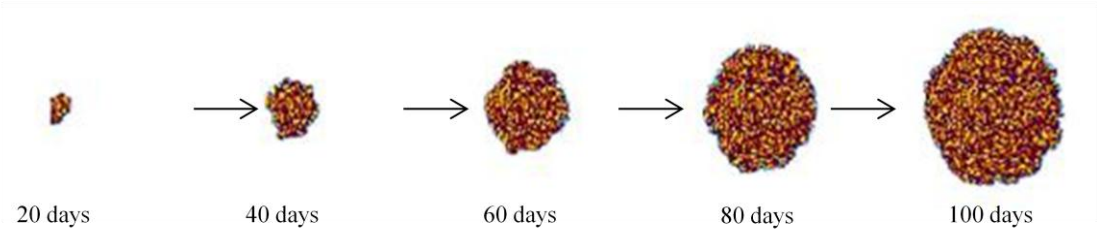

Figure 4: The free cellular growth pattern followed over 100 days

These results give confidence in the model used; also the homogeneous distribution of phases indicates that all of the four phases of growth obey the stochastic division regulations.

Figure (5) exhibits the relationship between the total number of cells and the time expressed in days considering that each cycle takes 24 hours. It also shows the effect of cell loss (L.F.) on the cellular growth in the range of 0% to 2%. It is obvious that the increase in the loss factor results in a decrease of the total number of cells but the growth pattern is still consistent.

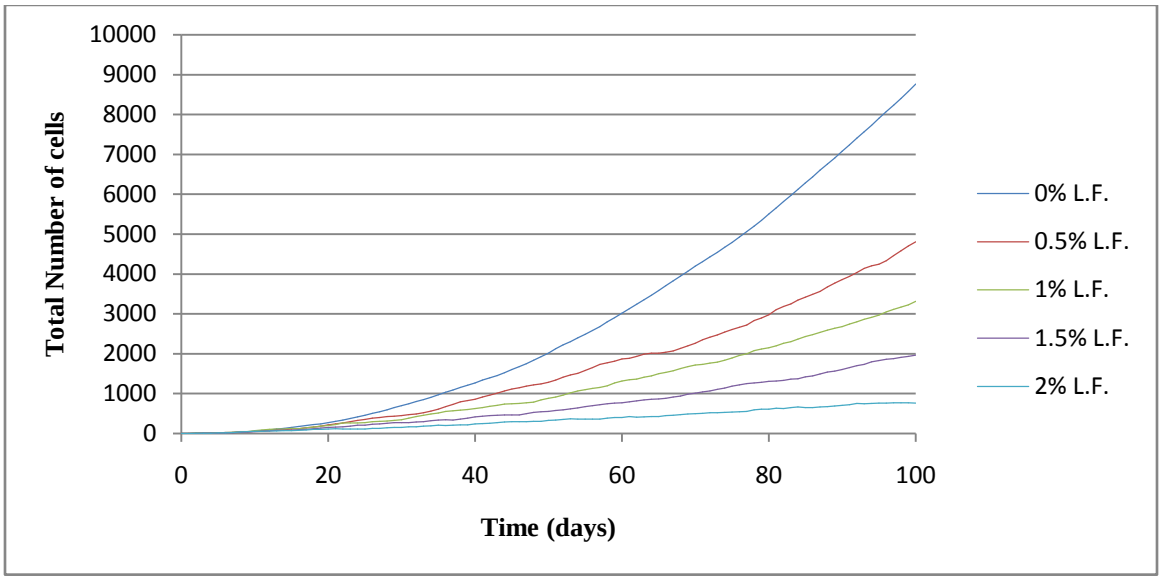

Figure 5: Total number of cells versus time

Figure (6) shows the reduction of the number of vacancies which is complementary to the increase of the number of cells.

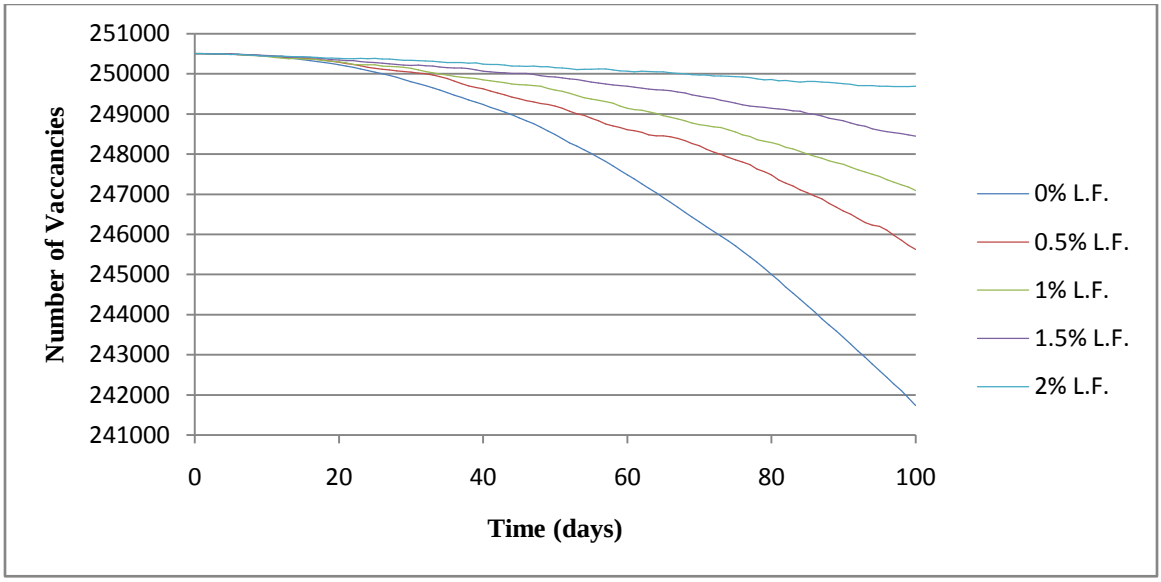

Figure 6: Number of vacancies versus Time

Figure (7) shows the relationship between the average radius of growth and time, for different phases as well as differentiating and resting cells, in this figure the radius was calculated according to equation (3) and the loss factor is kept at 1%.

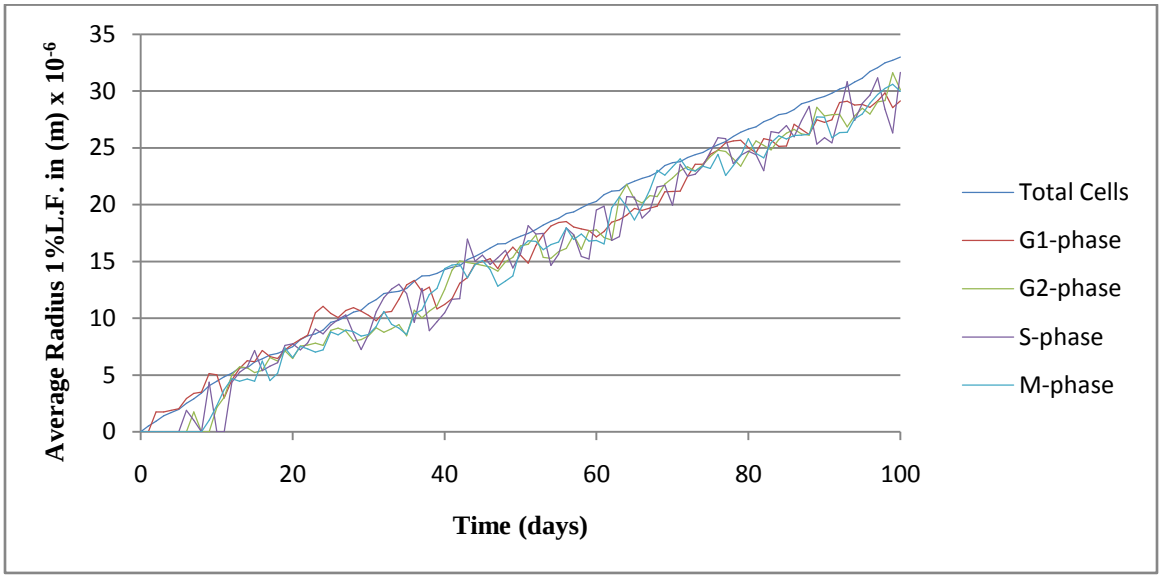

Figure 7: Average radius at 1% versus time

It should be noted that first: the average radius of individual phases is almost identical in comparison with the total average radius of growth. This indicates that the phases are spatially distributed homogeneously, second: due to the stochastic nature of cell growth there is an apparent fluctuation in the growth pattern from one cycle to the next however the general trend of the average radius is almost linearly increasing.

Figure (8) demonstrate the effect of the loss factor on the average radius of growth apparently the increase of the loss factor decreases the radius with time.

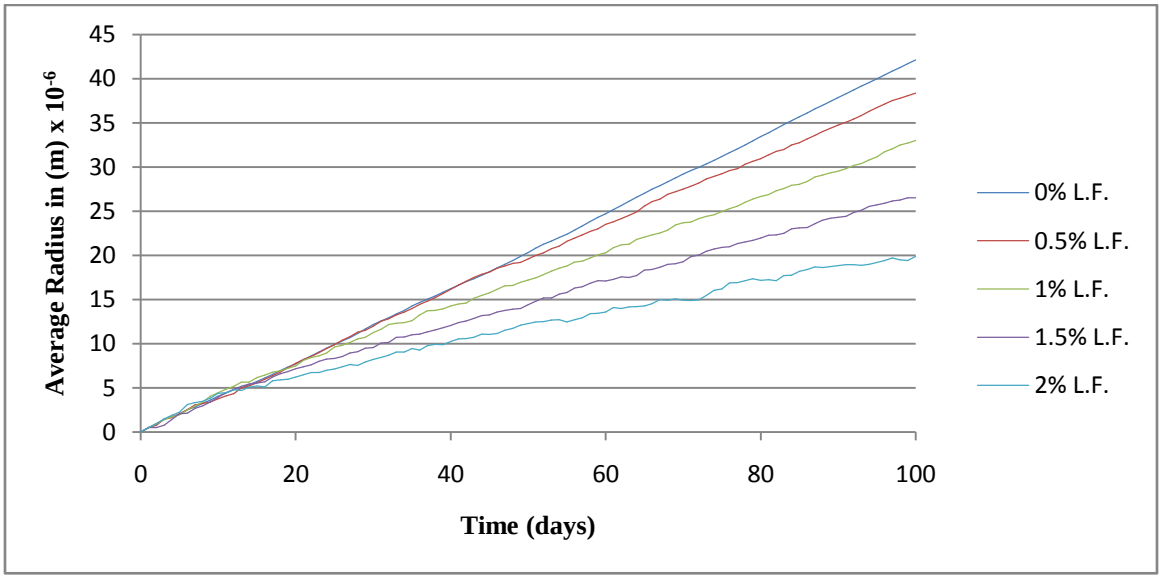

Figure 8: Average Radius at different L.F. versus Time

Figure (9) shows the relationship of the Diffusion Coefficients for different phases of growth as well as differentiating and resting cells, in this figure the Diffusion Coefficients was calculated according to equation (5) and the loss factor is kept at 1%.

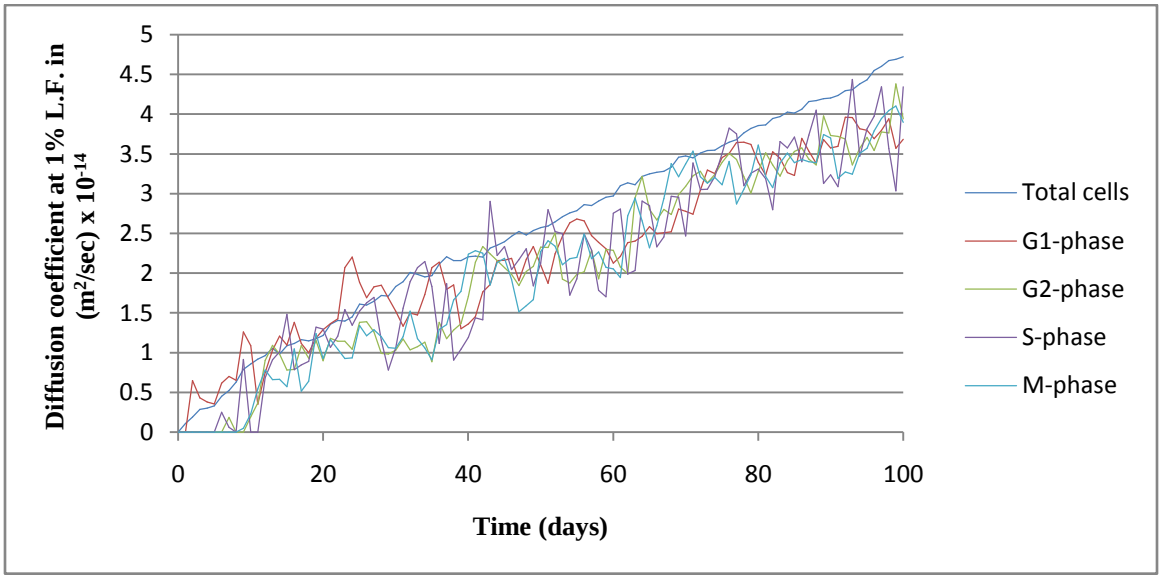

Figure 9: Diffusion Coefficient at 1% versus Time

It is noteworthy that the calculations of the diffusion coefficient require a considerable number of cells' division. Also due to the asynchronized nature of cell growth, there is apparent fluctuations of the calculated values of D which is biologically expected however there is an almost linear trend of increase of D with time.

Figure (10) demonstrates the effect of the loss factor on the Diffusion Coefficient of growth apparently the increase of the loss factor decreases the Diffusion Coefficient almost linearly.

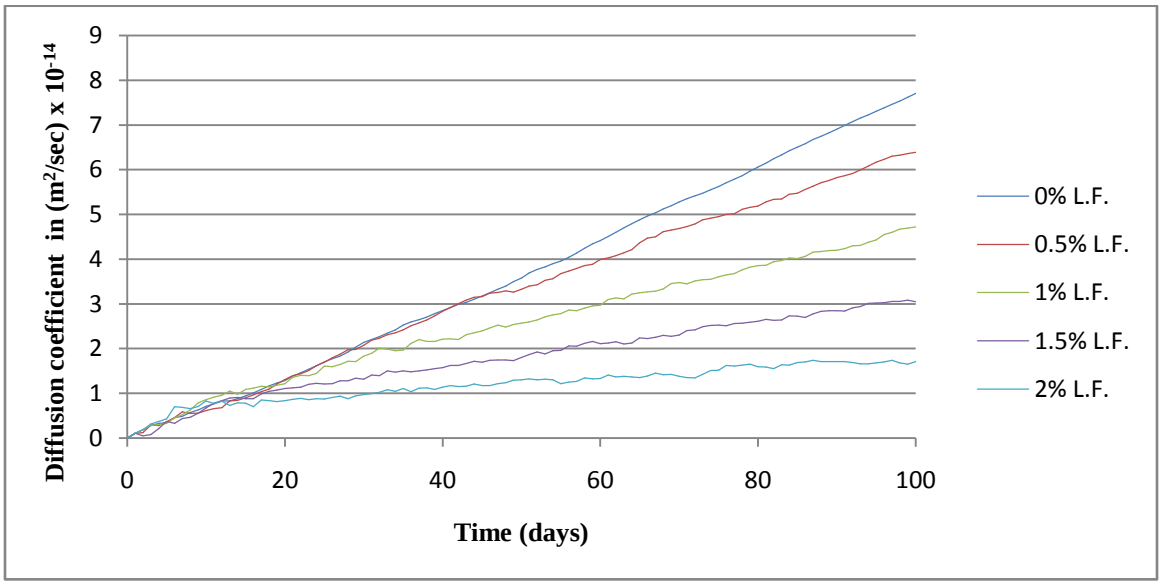

Figure 10: Diffusion Coefficient at different L.F. versus Time

Conclusion

There is no full agreement among researchers and theoreticians on the full real mechanism that regulate cellular growth, however, considerable number of models either mathematical or simulation have been produced with varying degrees of success. However in the present work we adopt a quasi-realistic computer model to study the mechanism of cellular growth in vitro. This model considers that the medium surrounding the dividing cells is homogeneous with constant nutrition supply. Also the present investigation introduces the concept of a physical constant which is the biological diffusion coefficient based on the random walk approach.

The results show that:
First, this diffusion coefficient is increasing with time in contrast with the constant value of diffusion coefficient in solids or liquids. This can be explained as a result of the increasing number of elements while this number is fixed in other matters.
Second, in this model we can differentiate between the diffusion coefficients of each phase of the cell cycle, hence we can predict which phase grows at higher rate. However, the four phases all complement one another and the trend of increase is almost identical.
Third, the fluctuations observed in figures (7) and (9) are due to the stochastic nature of this process which indicate that the model goes in agreement with the actual natural process of dividing cells.
Fourth, the following parameters are discarded in this model namely, the boundary effect hence the growth never reaches these boundaries. Also, the effect of nutrition, as well as, the immune system is ignored. Moreover the model considers two dimension simulation which is corresponding to a single layer growth.
Currently investigations are carried out in order to examine the growth of tumor cells in a normal tissue.

References

Boondirek, A., Teerapabolarn, K., and Triampo, W. (2011): A Stochastic Model of Tumor Growth With Immune Response: Three Dimensional Cubic Lattice. Int. J. Open Problems Compt. Math., 4(3): 29-36.
Cecka, C. *et al.* (2006): Modeling Vascular Tumor Growth, report, Harvey Muddcollege, mathematics clinic.
Cristini, V., Lowengrub, J. and Nie, Q. (2003): Nonlinear Simulation of tumor growth. J. Mathematical Biology, 46: 191–224.
Drasdo, D., Hoehme, S. and Block, M. (2007): On the Role of Physics in the Growth and Pattern Formation of Multi-Cellular Systems: What can we learn from Individual-Cell Based Models?. Journal of Statistical Physics, 128: 287-345.
Duchting, W. and Vogelsaenger, Th. (1981): 3-D Tumor Growth: Modelling and simulation**.** IEEE, pp. 586-590.
Duchting, W. and Vogelsaenger, Th. (1982): Simulation of Tumor Growth as a tool for determining the optimal moment of administering Chemotherapeutic Agents. IEEE, pp. 952-956.
Duchting, W. and Vogelsaenger, Th. (1987): An Approach of Modelling and Simulating the Spread of Heterogeneous Tumor Cells in a Three-Dimensional Tissue Segment. Comput. Math. Applic., 14: 783-792.
Duchting, W., Ginsberg, T. and Ulmer, W. (1996): Computer Simulation Applied to Radiation Therapy in Cancer Research. Applied Mathematics and Computation, 74: 191-207.
El-Messiery, M.A. (1990): Spatial and Vacancy Effects on the Stabilising Mechanisms of two-dimensional Free Growth. BioSystems, 24: 193-207.
Gevertz, J. L. (2009): Multi-scale Mathematical Modeling of Heterogeneous Tumor Growth, Ph.D., Princeton University.
Gilbert, D.A. (1982): Cell Cycle Variability: The Oscillator Model of the Cell Cycle yields transition probability alpha and beta type curves**.** BioSystems, 15: 317-330.
Shewmon, G. (1963): Diffusion in solids, McGraw-Hill, pp.47-52.
Shirinifard, A., Gens, J.S., Zaitlen, B.L., Popławski, N.J., Swat, M., Glazier, J.A. (2009): 3D Multi-Cell Simulation of Tumor Growth and Angiogenesis. Plos One, 4:1-11, Issue 10.