Euroasia Journal of Mathematics, Engineering, Natural & Medical Sciences
International Indexed and Refereed
ISSN 2667-6702

Study on Mathematical Model of Tumour Growth with Varying Nutrient Concentrations

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Geliş Tarihi / Received: 11.09.2023
Kabul Tarihi / Accepted: 12.11.2023

Araştırma Makalesi/ Research Article
DOI: 10.5281/zenodo.10373865

ABSTRACT

In the present paper, the growth of the tumour is mathematically studied with change in nutrients at various time intervals. The reference of necrotic core layer is considered in the analysis which varies according to metabolic changes. Various concentrations of nutrients are proposed in the model for estimating the size of the tumour and its growth rate using set of simple diffusion equations in the functional form. Initially the tumour is assumed to be sphere and later considered to be in spherical shape with feeding of nutrients. Analysis is carried out by considering the variation in the artery wall (impermeable wall) with respect to the change in tumour size. Analytical solution is obtained for set of diffusion equations with varying nutrients at various time intervals. It is noticed that there exists stability in spherical shaped tumour when compared to instability of sphere shaped tumour. Numerical results predict that the spherical tumour grows with varying size. Results are compared with others findings.

Keywords: Tumour, spherical, nutrient, Elasticity.

INTRODUCTION

The tumour is considered to be abnormal growth (swelling) of the tissue on apart of the body. This may be benign or malignant. Clinically it is assumed to be the leakage of clear protein from small blood vessels which contain the fluid. This occur between the cells. Neoplasm is a mass of new cells which proliferate without control and which serve no useful function. This lack of central is particularly marked in malignant tumours. Cancer cells are the archaists of the body**,** serve no useful function and cause disharmony and death in their surroundings. Reports say cancer of the living and breast seem to be a real increase among the human beings. A normal cell is concerned more with function than with growth while the cancer cell is concerned more with acquisition of increase reproductively than with function and the formation of the secondary growths. Since the normal function of the cellular growth is a chemical process governed by enzymes under the control of the chromosomes in the nucleus with their associated genes, cancer cell derives its energy for growth mainly from anaerobic glycolysis. The normal cell breaths but cancer cells do not breathe but ferment. By virtue of competitive struggle or nitrogen trap cells describes the fact that the esophagus passage will be blocked and causing ulceration of the mucous membrane with fatal haemorrhage in turn cancer cells make loss of weight, wasting, emaciation and finally death. As a result, cancer cells stand priority for amino acids to constitute nitrogen trap with rapid growth of neoplasms which characterize small wonders of wasting and cachexia to influence the stage of malignancy. Sometimes a benign tumour develop into a malignant one. The malignant tumour

infiltrate into the surrounding tissue which sends claws in to crab (cancer). On the other hand the benign tumour grows by expansion as a toy balloon does when blown up and is separated from the surrounding tissue. Therefore from every tissue of the body, we notice all malignant tumours appear as two groups, Carcinoma or epithelial tumours commonly occur at skin, mouth, lung, stomach, breast and uterus and Sarcoma or Connective tissue tumour occur mainly in bone, subcutaneous tissue, cartilage and muscle.

Therefore benign tumour increases in size but can hardly spread whereas the malignant tumour spreads locally and to distant parts along the lymphatic vessels particularly well seen in cancer of breath. Here the main function (proliferation) of the tumour cells carried by blood stream and arrested in the capillaries and start secondary growths or metastasis. When the cancer cells in blood removed from a vein in many cases of cancer situated, these observations are of particular interest in relation to the question of metastasis with a reference to carcinoma cells under cytoskeletal perturbation, it is necessary to study the viscoelastic properties or the magnitude of the effect of cytoskeletal perturbing agent on the viscoelastic properties which reflect the differences in the structure and function. Changes in the viscoelastic properties of cancer cells might well affect tumour cell invasion and metastasis as well as interactions between tumour cells and their micromechanical environments. However mechanical properties of cells are concerned, it was limited to blood cells because of the significance of these properties in the circulation. Since the dominance of the cytoskeleton structures in the cell deformation and locomotion, the relevance of the cell rheological properties of cytoskeleton structures has always been a topic of interest because tumour cells experience shear induced deformation, these tumour cells migrate through the blood vasculature. The study concerns the deformation movement through the microvasculature and be arrested to from metastasis with the blood shear environment. Oncologists, pathologists and many researchers have studies the cell biological behaviour of tumour cells and rheological effects of those cytoskeleton targeting agents in the clinical aspects of malignancy. Insight into these study view point, it is required to analyse the viscoelastic behaviours of tumour cells in elucidating the possible cell rheological mechanism involved in tumour cell growth, invasion and metastasis as well as the targeting agents. The aim of the present paper is to explore the details of the elastic properties and growth of tumour cells respond to the effector and the induced one (complexes).

In view of the biological terminology, the cell is a smallest unit of an organism that is able to function independently within the living organisms. Each cell is bounded by a cell membrane of lipids and proteins which controls the passage of substances into and out of the cell. Complex organisms such as man are built up of millions of cells that are specially adopted to carry out particular functions. To begin with, cancer is not a single disease, it is a name of a group of disease in which, body cells multiply and spread abnormally uncontrollably. This can happen virtually in any part of the body. Except in the blood cancer such leukaemia, the unchecked spread of cells develops into malignant tumour which generally keeps growing and invade neighbouring tissues with potentially fatal consequences. Smoking is associated with cancer, contamination of environment by chemicals (industrial substances) leads to tumour of cancer called Carcinogens. Spread of cancer cells enter the blood stream across the body cavities such as pleural and peritoneal spaces. This sets up the secondary tumours at sites distant from the original tumour which exhibits the mechanical behaviour and metastasis. Bone metastasis is very common in breast cancer but very rare in ovarian cancer.

In view of the mechanical and dynamical behaviour of the diseases cell due to morphology of membranes, physical and chemical models describes the cancerous cells for tumour growth needs the study of repair of the damaged DNA. Mathematical model in this paper concerns the causative factor such as proliferation, volume due to internal pressure bending strain energy, average time. As the membranes have pores of uniform diameter, characterization of cell is estimated by its going out and coming in via membrane pores.

Sussan et. al [1] analyzed the cancer study with reference to Crabs. Skalak [2] described the theoretical aspects of microcirculation. M. A. J. Chaplain [3], present several mathematical models for solid tumour growth and development at various stages uses multicell spheroid model by considering the growth of tumour to a diffusion-limited size of a few millimetres in diameter. E. L. Stott et. al [4], uses the Potts model for simulation to the growth of a benign avascular tumour in normal tissue by energy minimisation method checked for variation of adhesion between different cell types. Shangbin Cui et.al [5], studied the model for growth of necrotic tumour cells which receives the nutrients from both through diffusion from the boundary as well as blood flow of the capillary vessels. A.R. Kansal et. al [6],developed a novel cellular automaton model of proliferative brain tumour growth, which is able to simulate Gompertzian tumour growth and predicted composition and growth rates are in agreement with a medical literature. K. R. Swanson et. al [7], developed a mathematical model to explain the growth and invasion of glioma cells in virtual human brain and found the effects of operation on these lesions which predicts the similar behaviour to that observed clinically. R.P. Araujo et.a [8], elucidated the phenomenon of vascular collapse by developing mathematical model for growing vascular tumour. Yuri Mansary et.al [9], investigated the genotype-phenotype link in a polyclonal cancel cell by introducing evolutionary game theory for heterogeneous cell population. Paul Macklin et.al [10], investigated the features of the tumour microenvironment is incorporated and using nonlinear simulations to explore the effects of interaction on the resulting tumour growth and morphology. Manu Milal et.al [11], conducted the experiments using a resistance heater to simulate the heat produced by tumour in the biological tissue and are estimated using genetic algorithm and Pennes bioheat equation. Kristin R. Swanson [12], developed that mathematical model to describe and quantify the growth and invasion of gliomas which shows well agree with in vivo imaging studies of gliomas and demonstrated the model's agreement with in vitro experimental data. S. M. Wise et. al[13],develop, analyze and simulate continuum model of multispecies tumour growth and tumour angiogenesis in two or three dimensions. M. Welter et.al [14], formulated theoretical model for solid tumour growth to analyse the arterio-venous vessel network. Monika Joanna Piotrowska et. al [15], developed a model to give good accuracy to experimental data on a wide range of tumour kinetics and necrosis measurement. Yanglin Kim et.al [16], developed a mathematical model for role of adhesion and patterns of cell migrations which depends on haptotactic and chemotactic parameters. Ender Konukoglu et. al [17], proposed a novel method for estimating the tumour infiltration from its visible mass as in the patients' MR images which is time independent and used a reaction–diffusion models to formulate the variable margins through determining the amount of targeted tumour cells and healthy tissue. Marco Di Francesco et.al [18], presented the tumour growth based on reaction–diffusion system with chemotaxis term and nutrient, developed mathematical formulation convergence of solutions to constant, stationary states in the one-dimensional case for small perturbation of the equilibria. Stefan Bauer [19], a novel approach was presented on Image-based modelling of tumour growth combines cancer simulation and medical imaging by adapting a healthy brain atlas to MR images of tumour patients accounting for cell proliferation and tissue deformations. Monika Joanna Piotrowska et. al [20], considered a model of immune reaction against malignant glioma which explains the interactions between tumour cells and the immune system and concluded that the effects of uncertainties of the tumour growth rate. Jianjun Yuan et.al [21], proposed a modified reaction–diffusion model for the diffusion of glioma brain cells, using a weighted parameter for the diffusion coefficient of the grey and white matters. Juan Belmonte-Beitia et. al [22], obtained a small number of effective equations explaining the dynamic solutions of Fisher–Kolmogorov type equations are parametrized by means of an ordinary differential equations and found for the growth progression of certain types of primary brain tumours. Ines Njeh et. al [23], investigated in different modalities, the fast distribution-matching and data-driven algorithm for 3D multimodal MRI glioma tumour. Filip Szczepankiewicz et. al [24],studied the relation between the diffusional variance and the tissue heterogeneity by diffusional variance, due to Microscopic anisotropy and

isotropic heterogeneity. Blandine Romain et.al [25], analyzed perfusion model to assess the parameter estimation from dynamic imaging data using compartment model.

Therefore, understanding the mechanics of individual cell is of importance to the understanding of tumour growth mechanics and many other pathological behaviour of living tissues, red blood cell resists the increase of surface area and deformed at the constant area. But the incidence of cancer is an increasing function of age, cancerous growth needs the physical relationships of mathematico-biophysical theory.Growth equation is developed in the mathematical modelling formation. For a given concentration of the nutrient, the growth of tumour cells vary in the presence of effectors but decreases in the presence of complexes.

FORMULATION

With reference to stability analysis of stretch ratios λ_1 and λ_2 of two tensions T_1 and T_2 for mechanical behavior, we have,

$$\lambda_1 = \frac{dy_1}{dx_1}, \lambda_2 = \frac{dy_2}{dx_2} \tag{1}$$

When cells are deformed, for mechanical properties of the cells we consider the material strain tensor with a reference to membrane as,

$$\bar{U}_{jk} = \frac{1}{2}\left[D_j x_j D_k x_i - \delta_{jk}\right] \tag{2}$$

Setting $D_j x_j = D_k x_i = \lambda_l$

For homogeneous isotropic media $\delta_{jk} = 1$

$$[\bar{U}_{jk}]^1 = \lambda_{l1}, [\bar{U}_{jk}]^2 = \lambda_{l2} \tag{3}$$

Strain invariants I1 and I2 are determined by equation (3)

$$I_1 = [\bar{U}_{jk}]^1 + [\bar{U}_{jk}]^2 \tag{4}$$

$$I_2 = [\bar{U}_{jk}]^1 \times [\bar{U}_{jk}]^2 \tag{5}$$

The axial extensions in terms of tensions are

$x_1$direction,

$$h_1 = \frac{T_1}{\mu [U_{jk}]^1 + \lambda\{[U_{jk}]^1 + [U_{jk}]^2\}} \tag{6}$$

x_2 direction,

$$h_2 = \frac{T_2}{\mu [U_{jk}]^2 + \lambda\{[U_{jk}]^1 + [U_{jk}]^2\}} \tag{7}$$

Since the living system is considered to be a dissipative system which is far from equilibrium such a system is considered to be nonlinear. Using theory of deformation to calculate the bending strain energy and the flow parameters of the incidence cancerous cell, the proliferation of cancerous cell is related with mechanical behaviour. Introducing the new parameters to the analogy of cancerous cell as E_f - effector, E_c - Complexes, K_B - Binding value, P_L - Proliferation, a – is cell diameter [0.25µm to 3.5µm], V- velocity (speed) of the cancerous cell is determined as,

$$V = 2aP_L\left[1 - \frac{K_B}{P_L}\{E_f + E_c\}\right]^{0.5} \tag{8}$$

The power 0.5 is chosen for initial setting. The living system is considered to be nonlinear, hence the dissipative system is far from the equilibrium.

The study of spherical tumour by quantifying the role of heat conduction, convection and metabolism is reported by the statistical analysis of heat transfer distributions in tumours under the cases of normothermic and hyperthermia. Temperature rise in tumours is always due to metabolism as a function of tumour weight (between 2gm to 20gm). The corresponding metabolic heat rate (between 0.00 to 5.2) and the temperature difference between (0.01850C to 0.240C) have been considered. The blood temperature almost equilibrates with tissue temperature, but no correlation was found between the thermal variation and the tumour size variation. Therefore it is necessary to establish the relation between the small increase in temperature and the corresponding increase of metabolic heat generation tumours. The temperature in the periphery of the necrotic tumour is higher than that in the central necrotic core. Taking the spherical shape of the tumour growth initially with radius 'a' and with time 't' (constant time periods), the varying radius of the tumour is given by,

$$r = R(t) \tag{9}$$

Clearly

$$R(0) = a \tag{10}$$

The equations for the tumour consisting of pressure P and the nutrient concentration σ (by anaerobic) are,

$$\nabla^2 P = S_v \tag{11}$$

Where S_v is the rate of volume loss (model does not include the motivated cell loss mechanism and shrinkage necrosis)

$$\nabla^2 \sigma = 0 \qquad \text{(outside the surface of the tumour layer)} \tag{12}$$

Taking the constant nutrient initially σ and attains maximum σ_m at r = R(t)

$\sigma = \sigma_{max}$ at $|R(t)| = |R_{max}| = |r|$

$\hat{n}\,\nabla\sigma = \mu\sqrt{\sigma - \sigma_1}$ at r = R(t)

Transforming equation (12) into spherical polar form

$$\frac{1}{r^2} \times \frac{\partial}{\partial r}\left[r^2 \times \frac{\partial \sigma}{\partial r} \right] \leq 0, \; r \geq r(t) \tag{13}$$

Boundary conditions are given by the cell proliferation and cell loss parameters for average time variation, as E_c describes the term complexes, we consider,

$V_{real} = V_{minimum}$ [for global stability]

$\Delta t \to 0, E_f \to \infty$, P_L (slow)

$\Delta t \to \infty, E_f \to 0$, P_L (fast)

ANALYSIS

Due to shear induced deformation and locomotion of tumour cells in the shear induced blood circulation, the motility of the tumour cell varies as initial radius r_0 and the varying radius r_v (r_0 = 0.004µm to r_v = 5.5µm) Growth structure and the function of tumour cell exhibits the stress and strain values while penetrating the membrane pores, the thickness and the bending parameter under deformation conditions as the cells enter the membrane, the thickness varies as the diameter of the pore.

From equation (8) we have,

as E_f is a function of $f_1(\lambda_1)$ and E_c is function $f_2(\lambda_2)$ then,

$$\frac{V}{2aP_L} = \left[1 - \frac{K_B}{P_L}\{E_f + E_c\}\right]^{0.5}$$

$$E_f + E_c = \frac{P_L}{K_B}\left[1 + \frac{V^{\frac{1}{0.5}}}{(2aP_L)^{\frac{1}{0.5}}}\right] \quad (14)$$

$$\frac{dy_1}{dx_1} + \frac{dy_2}{dx_2} = \frac{P_L}{K_B}\left[1 + \frac{V^{\frac{1}{0.5}}}{(2aP_L)^{\frac{1}{0.5}}}\right] \quad (15)$$

Solving equation (15),we have

$$y_1 = \frac{P_L}{K_B}\left[1 + \left(\frac{V}{(2aP_L)^2}\right)x_1 + C_1\right. \quad (16)$$

$$y_2 = \frac{P_L}{K_B}\left[1 + \left(\frac{V}{(2aP_L)^2}\right)x_1 + C_2\right. \quad (17)$$

h = h(r)

Solving for K_B from equation (8),

$$K_B = \frac{0.008E}{[1-\gamma^2]}\left[1 - \left(\frac{r}{r_0}\right)^2\right]^{\frac{8}{2}}\left[c_1 + c_2\left(\frac{r}{r_0}\right)^2 + c_3\left(\frac{r}{r_0}\right)^4\right]^3 \quad (18)$$

c_1, c_2, c_2 are the constants of integration

Denoting

$$h(r) = \left[1 - \left(\frac{r}{r_0}\right)^2\right]^{\frac{1}{2}}\left[c_1 + c_2\left(\frac{r}{r_0}\right)^2 + c_3\left(\frac{r}{r_0}\right)^4\right]^3$$

Since the human arteries are not straight tubes vessel/capillaries are constituted by curvature structure or elastic or distensible. Bending strain energy function for the cells when passing through the pores of the membrane,

$$W_{Br} = (0.5) \times 2.72 \times 10^{-11}[K_1^2 + 2\gamma K_1 K_2 + K_2^2]K_B \quad (19)$$

Substituting for K_B from equation (9) in to equation (10),

$$W_{Bs} = \frac{(0.0415)E}{(1-\gamma^2)}\ [K_1^2 + 2\gamma K_1 K_2 + K_2^2] \times \left[1 - \left(\frac{r}{r_0}\right)^2\right]^{\frac{8}{2}}\left[c_1 + c_2\left(\frac{r}{r_0}\right)^2 + c_3\left(\frac{r}{r_0}\right)^4\right]^3 \quad (20)$$

Substituting $\frac{\delta_{BS}}{\delta K_1}$ and $\frac{\delta_{BS}}{\delta K_2}$ in Piola Kirchoff stress tensor, we obtain the resulting bending moments in x_1 and x_2 directions respectively as,

$$M_{B1} = \frac{1}{\lambda_{l_1}}\left[\frac{\delta_{BS}}{\delta K_1}\right]$$

$$M_{B1} = \frac{1}{\lambda_{l_1}}[2K_1 + 2\gamma K_2][h(r)] \tag{21}$$

$$M_{B2} = \frac{1}{\lambda_{l_2}}[2K_1 + 2\gamma K_2][h(r)] \tag{22}$$

Stress at the bending of the cell is

$$\tau = \frac{10.1846\, Q\, \mu}{[h(r)]^3} \tag{23}$$

Where

$$Q_{at\,\Delta t} = (12.568)\, a\, \lambda \int_{r_0}^{r} r\, [V_{real}]dr \tag{24}$$

$$Q_{at\,\Delta t} = (12.568)\, a\, \lambda \int_{r_0}^{r} r\, [2aP_L]\left[1 - \frac{K_B}{P_L}\{E_f + E_c\}\right]^{0.5} dr$$

$$Q_{at\,\Delta t} = (12.568)\, a\, \lambda \int_{r_0}^{r} r\, [2aP_L]\left[1 - \frac{\frac{0.008E}{[1-\gamma^2]}\left[1 - \left(\frac{r}{r_0}\right)^2\right]^{\frac{3}{2}}\left[c_1 + c_2\left(\frac{r}{r_0}\right)^2 + c_3\left(\frac{r}{r_0}\right)^4\right]^3}{P_L}\{E_f + E_c\}\right]^{0.5} dr$$

$$Q_{at\,\Delta t} = (12.568)\, a\, \lambda \int_{r_0}^{r} r\, [2aP_L]\left[P_L - \frac{\frac{0.008E}{[1-\gamma^2]}\frac{1}{r_0^3}(r_0^2 - r^2)^{\frac{3}{2}}\left[c_1 + c_2\left(\frac{r}{r_0}\right)^2 + c_3\left(\frac{r}{r_0}\right)^4\right]^3}{P_L}\{E_f + E_c\}\right]^{0.5} dr$$

$$Q_{at\,\Delta t} = \frac{[(12.568)\, 2a^2\, \lambda\, P_L]}{r_0^7} \times \int_{r_0}^{r}\left[r\, r_0^7 - \frac{0.008E}{P_L[1-\gamma^2]}(r_0^2 - r^2)^{\frac{3}{2}}[c_1 r_0^4 + c_2 r_0^2 r^2 + c_3 r^4]^3 \times \{E_f + E_c\}\right]^{0.5} dr \tag{25}$$

Pressure drop inside the cell,

$$\Delta P = \frac{V_2 - (1.5)V_1}{V_2 - (0.4)V_1} P_0(0.58)V_1 \tag{26}$$

RESULTS AND DISCUSSIONS

The elastic properties signify the role of mechanical behaviour exerted by the cell structure. Elastic parameters obtained in comparison with the structural properties of red blood cell membrane show the decisive remarks when the cancerous cell is taken as the targeted cell. Peculiar characteristics of growth change, flow rate through the blood stream, bending strain energy, wall shear stress of the membrane pore are calculated to describe the elastic properties of cancerous cell. For the diameter of the diseased cell 7.4μm, the volume is estimated 93.8μm^3 with 129.58μm^2 area. For these parameters the effector becomes the dominant by 9.53% which makes complexes to lead the bending moment. To gain the bending moment the required bending strain energy is of the order 2.23265×10^{13}dynes/cm. Therefore bending moments 0.2659×10^{9}dynes/cmalong the x_1 direction

and 0.2471 $\times 10^9$dynes/cm along x_2 direction. Wall shear stress is 402.347$\times 10^4$dynes/cm. This sets up the increase of the growth of the cancerous cell. Pressure difference at four location is determined as 26.45, 97.62, 175.41 and 220.128 dynes. The flow rate/volume of the targeted cancerous cell is calculated as 46.34, 52.56, 72.84 and 103.8728μm^3 at the selected four locations. Velocity of the cancerous cell proliferation per day shows 0.0002, 0.0009, 0.0018, and 0.0028μm needs lower binding strain energy values and lower flow rate values at the rate $\sqrt{2.23265 \times 10^{13}}$, so that the proliferation increases, effector decreases by 4.5% to make the complexes to diminish. When once binding energy decreases, the other parameters reduce accordingly, the concern of proliferation happens as successful result. It may be concluded that effector reduces as $\Delta t \to 0$, and effector $\Delta t \to \infty$, velocity and flow rate are the main parameters to decide the bending strain energy values.

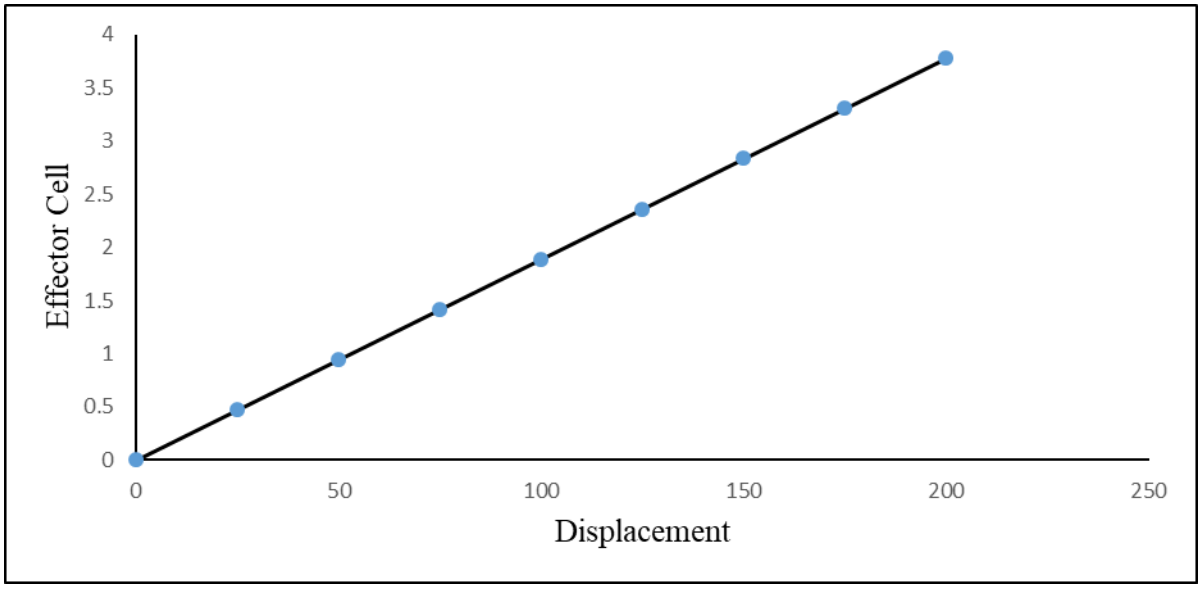

Fig.1. Variation of Effector cell with Displacement (analytical method)

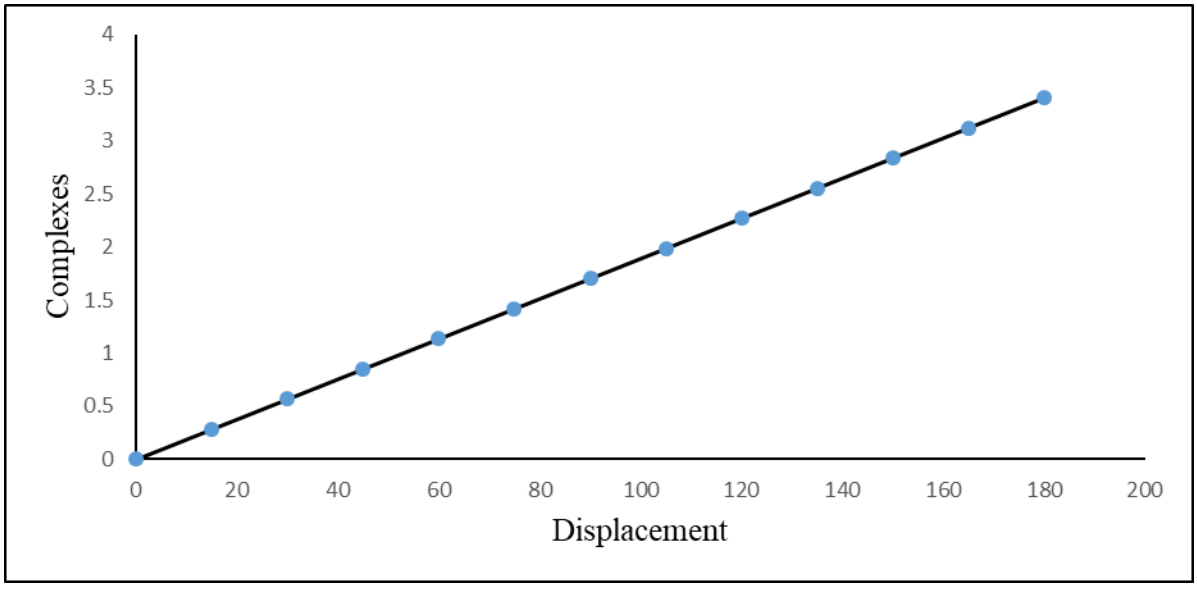

Fig.2. Variation of Complex cell with Displacement (analytical method)

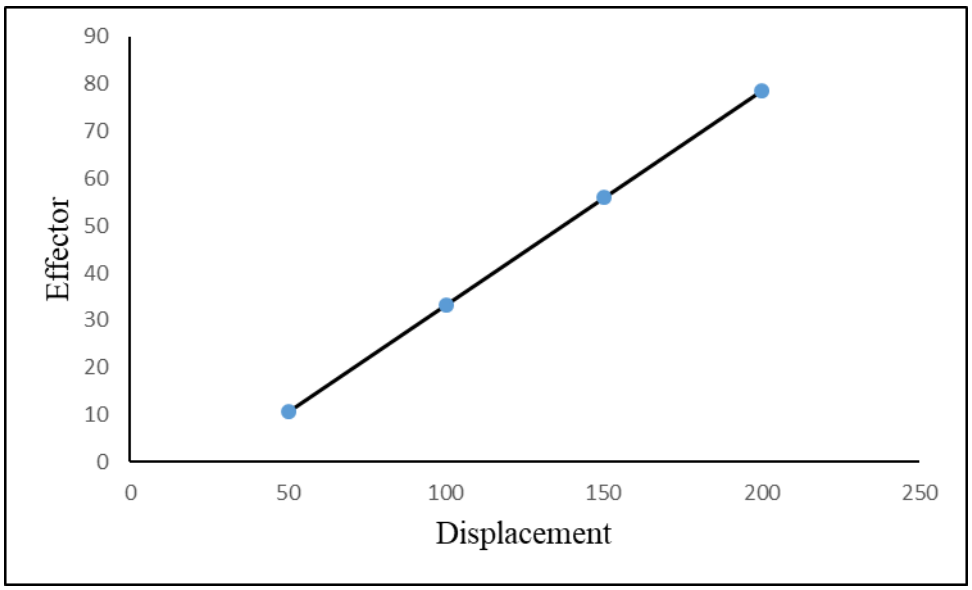

Fig.3. Variation of Effector cell with Displacement (FDM method)

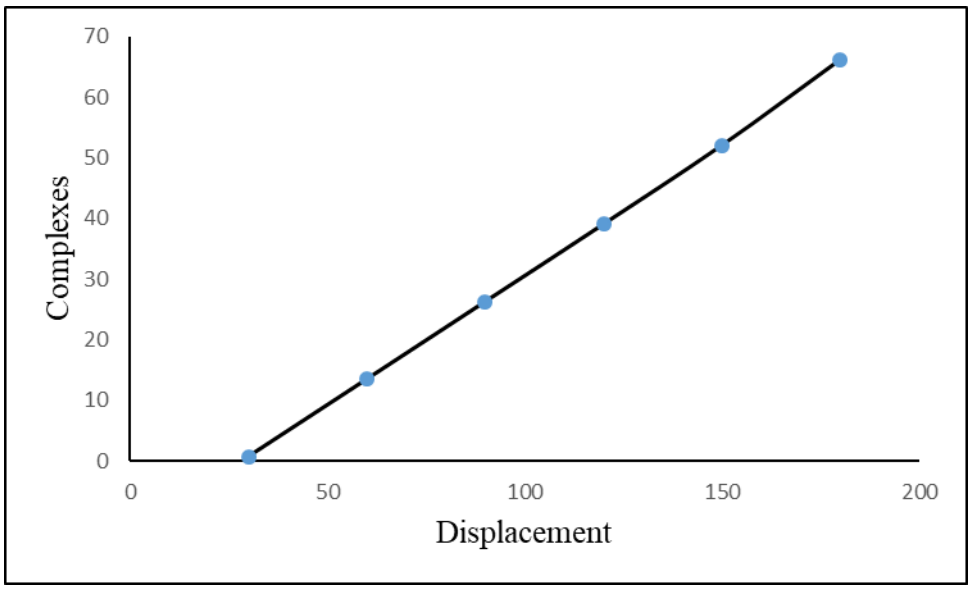

Fig.4. Variation of Complex cell with Displacement (FDM method)

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