Stability of the Zero Solution of Nonlinear Tumor Growth Cancer Model under the Influence of White Noise

Kalyan Das, M.N.Srinivas, Nurul Huda Gazi, Sandra Pinelas

Abstract: The article deals with a system of nonlinear differential equations of tumor growth cancer model under the influence of white noise. This system can be used as mathematical tools for analyzing of various real problems of tumor growth associated with cancer. Necessary and sufficient conditions for the asymptotic mean square stability of the zero solution of this system are derived in this article. The article introduces a new approach to studying such problems through construction of a suitable deterministic system with the use of Lyapunov function. Recently we observed that cell-mediated immunity plays a vital role in immune responses against cancer. Cancer cell development and survival is a multifactor process involving genetic mutation of normal cells with physiological changes within both cancer cells and the body's defence mechanisms. In this paper we considered the special impact of tumor-immune interaction along with the two immune components– resting (helper) T-cells which stimulate CTLs and converting them into hunting (active) CTL cells which attack/destroy/ingest the tumor cells. Critically we have examined the existence of the system with local and global stability analysis at different equilibrium points. We have also developed a theoretical framework for understanding the complexity of the tumor growth cell under the influence of white noise. Using various sensitive hypothetical parameter values with different initial densities the numerical simulations shown the dynamical behaviour of the tumor cells along with the resting and hunting cells showing interesting patterns in the evolution of the tumor and immune cell populations.

Keywords: Stability, Mathematical Models, Mathematical Methods

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I. INTRODUCTION

We can come across stochastic behaviour while examining many important problems of a global character in various fields of research, for example, in the theory of cancer modelling. Detailed understandings of extreme events of cancer cell proliferation which is beyond our normal expectations and is a very important topic in greatest killer disease in all over the world. Common methods of studying cancer modelling, such as the statistical approach, the empirical-physical approach or the numerical modelling approach, have some limitations, and the study of them has been largely empirical. The dynamics of cancer and tumor growth requires special attention in the modeling analysis. Cancer is such a fatal disease which is known as malignant neoplasm characterized by the abnormal growth of cells. In cancer disease, cells are dividing randomly and growing in an uncontrolled manner forming malignant tumors and invade also the neighbouring parts of the cell of the human body. Recently, mathematical modeling of tumor has been developed by the researchers using different tools. Mathematical analysis has a wide range of contribution in the field of micro molecular level of cell biology. The cancer disease may spread to distant parts of the human body through the lymphatic system or bloodstream. Obviously, all tumors are not cancerous. The tumors which do not grow in an uncontrolled manner and do not invade neighboring tissues and also do not spread throughout the body are mostly non - cancerous. There exist few stages in the growth of a tumor cell before it reaches the lethal size. The factors which trigger the changes due to gene mutations are still unknown in cancer field but have impact on both ecological with genetic effects. One of the outcomes of this series of changes is an increase in the propagation rate and a decrease in the death rate of the cells which give rise to a cluster of tumor cells rising faster than the host cells [10-12]. Also a fast growing cluster of tumor cells cannot grow beyond a certain size as there is a balance between cells inside the clusters

consuming nutrients and nutrient diffusion into the cluster. Therefore, one of the most important steps in malignant tumor growth is angiogenesis which is the main process by which tumors develop their own blood supply. For this reason novel drugs which developed specifically to target tumor blood vessels. Once, the tumors have acquired their own blood supply, the tumor cells can escape the primary tumor via the circulatory system (metastasis) and set up secondary tumors somewhere else in the body [1-3].

The immune component in mathematical modelling analysis of tumor growth reflects the clinical observation phenomena of uncontrolled growth of tumor cells and also the oscillatory behaviour of the tumor size [1-12]. Similar tumor behaviour is also predicted in ordinary differential equation model [13] with interleukine-2 (IL-2). Recently advances in cancer immunology have been facilitated by the joint work of immunologists and mathematicians [1],[14-15]. Very interesting knowledge about interactions between the immune system and tumors gives a nice result for using mathematical models. Most existing mathematical models in cancer immunology are based on sets of nonlinear ordinary differential equations [2]. Our approach has some limitations of the problems involving spatial interactions or emerging properties [16-17]. Besides these, the analysis of ordinary differential equations model is associated with a high level of aggregation of the system entities. An alternative to ordinary differential equations modeling which overcomes these limitations is a system of stochastic modeling. It is a set of methodologies and applications which reflects the behavior of a real system [2],[18-19]. Also, stochastic modeling having benefits compared with the real-world experimentation in immunology including time and costing due to the resource-intensiveness of the biological environment. But in simulation environment, it is also possible to generate different scenarios for conducting experiments. Cancer is one of the main causes of mortality in the recent world. In last few decades, mathematical modeling analysis of tumor in differential equations using different mathematical tools and computational techniques. Tumor cells have different mechanisms for escaping from host immunity to defeat cancer immunotherapy. Typical immunity-escaping strategies employed by tumor cells including the down regulation of target antigens and antigen-presenting machinery associated with the recruitment of specialized subset of $CD4^+$ T cells and $CD4^+CD25^+$ regulatory T cells (TRegs) into the tumors [20–22]. In fact, the activation of TRegs is one of the major tumor immune escape mechanisms [23–27]. In this paper we summarized the role of $CD4^+$ T cells in shaping and augmenting antitumor immunity. In human body the immune system recognized by the cancer cells which strengthen its response so that it can destroy them. The immune response of the cancer specific antigens is our interest due to the development of the new vaccines and antibody therapies. Cell mediated immunity associated with the production of cytotoxic T-lymphocytes cells (CTLs), activated macrophages and release of various cytokines for response to an antigen. A cytotoxic T-cell (CTL) is a T-lymphocyte (a type of white blood cell) which kills the cancer cells which are already infected or cells that are already damaged due to some other reasons. Recently, the culture of stimulation of $CD4^+$ T helper cells in cancer immunotherapy is considered. T helper cells are a subgroup of lymphocytes which is a type of white blood cell and it play a major role particularly in the adaptive immune system. Sometimes, it helps for the activity of immune cells through release of T-cell cytokines. They also help the other white blood cells in immunologic processes including maturation of B-cells into plasma cells and memory B-cells with the activation of cytotoxic T-cells (CTLs) and macrophages.

In last few decades many researcher analysed different mathematical models which describes the interaction among the various compartments of tumor-micro environment [16-19]. But they have not concentrated their study for the immune response of tumor growth. Recently, cancer research has already developed on different control strategies and drug therapies which are focused on experimental aspects and immunology [2-5], [20], [26-30]. There are lot of ordinary differential equation models of tumor growth and tumor immune system interactions [1], [6-7], [15], [21-25], [31-34]. Some of them followed the historical approach [22] while others focused on multi-scale modelling and tumor evolution. They also studied the competition between tumor cells and immune cells of the continuous and discrete dynamical system [1], [21], [25], [35]. They also identified the evolution of the number of cells which belongs to different interacting populations of tumor cells and immune cells in different scales namely molecular, cellular and macroscopic etc. The method of the classical mathematical kinetic theory for active particles to study the immune competition is a special attention of cancer disease have been analysed by et.al [36]. They mainly focused on modelling aspects of the early stage of cancer disease and competition with the immune system.

Many authors have already used the concept of prey-predator type interactions in population biology in the field of tumor growth studies where, in general, the immune cells play the role of predator and the tumor cells that of prey [37-40]. These types of analysis is associated with the qualitative study of ordinary differential equation model gives rise a mathematical framework exploring the interactions among the tumor cells and the different types of immune and healthy

tissue cells. This type of study of the nonlinear complex system in immunogenic tumor's growth based on parametric estimation and global bifurcation phenomenon which was carried out by N. Bellomo et.al.,[37]. Also immunotherapy of tumor-immune interaction has been studied by D. Kirschner, and J.C. Panetta [38]. They elucidated that the dynamics among the tumor cells, immune cells and IL-2 which can explain both short-term oscillations of tumor size as well as long-term tumor growth relapse. The self-remission and tumor growth stability through incorporation of stochastic perturbation have been analysed by Sarkar et.al.,[39]. Also in last few decades, retarded differential equations are used in mathematical modelling of cancer disease [41-47].The complexity of the dynamics of a vascular tumor growth by incorporating the discrete type of time-delay in the net proliferation rate of the cells studied by [48]. The effect of time delay on the two-dimensional system which represents the basic model of the immune response is analysed by [49]. They also studied the variations of the stability criteria of the equilibrium points due to incorporation of time delay and the occurrence of chaos. Recently the time delay has been incorporated in solid vascular tumor growth by [50] where the two main processes are taken into account i.e. proliferation and apoptosis. Simplified version of the Kuznetsov-Taylor model [37], where immune reactions are described by a bilinear term with constant time delay [8]. Also [9] analyzed an interaction between the proliferating cells and quiescent cells tumor growth with the impact of single delay. Also [9] showed that the existence of Hopf bifurcation as the constant time delay passes some lumping parameter critical value. Also the study on cancer self remission and tumor growth with optimal control strategies shows the changes from its unstable state to an asymptotically stable one [40].

The progress of cancer like tumor growth is multifaceted and deals with different cells in the human body. Most important components of these cells are tumor cells, immune cells and healthy tissue cells. A cancerous growth is a typical nonlinear system which is unpredictable. It grows in a multiple manner and ultimately conquers the good cells in the human body. Non-linear differential equation mathematical model [18] plays a vital role for understanding the dynamics of its exploration and identifying the tumor cells and immune cells populations with respect to time with the impact of various parameters and different initial populations [2],[19], [26]. In the last few years, a lot of researchers devoted themselves to control strategies and drug therapies specially emphasised on experimental aspects and immunology [3-5],[20-23],[27-30].

The idea of replacing the whole deterministic system with a stochastic differential equation is a very good attempt to judge the nonlinear effect on the considering system. It has a wide effect to improve the cancer growth tumor deterministic model by incorporating the influence of the fast variables in the form of random white noise. The univariate linear systems that appear in the work have been successful in describing various modes of cancer growth variability. Success of these models has inspired researchers to consider the stochastic external driving force acts as a possible source of more complex dynamics. This analysis can be treated as the beginning of describing extreme events in cancerous tumor growth by a stochastic system of differential equations in which random growth changes are expressed by a nonlinear stochastic perturbation in the form of white noise. Also we have constructed Lyapunov function, as a tool, to study stability of a stochastic system that works under the influence of white noise. We construct Lyapunov function that works under the influence of white noise.

Let (Ω, Ϝ, *F*, P) be a filtered probability space, or stochastic basis, consisting of a probability space (Ω, Ϝ, *F*) and a filtration $F = \{F_t, \forall_t \geq 0\}$ contained in *F*. On the probability space we consider the stochastic system of nonlinear differential equations of the form $dx_i(t) = f_i(x)dt + h_i(x)dw_i(t)$,

$$i = 1,2,....., m,\ t \geq 0 \qquad (1)$$

where the state function $x(t) = (x_1, x_2, ..., x_m)^T$ (the operation T denotes transposition) is a continuously differentiable m-dimensional column vector-function, $f = (f_1, ..., f_m)^T$, $h = (h_1, ..., h_m)^T$ are also continuously differentiable m-dimensional column vector functions such that $f(0) = 0, h(0) = 0, 0 = (0,0,.....,0)^T \in \Re^m$ hold. The function f represents a slow deterministic process, the product $h_i(x)dw_i(t), i = 1,2,...., m$, is the stochastic approximations to a fast phenomenon. The m-dimensional column vector-function $w = (w_1, w_2, ..., w_m)^T$ indicates a standard Wiener process. The m-dimensional Wiener process is said to be standard Wiener process if

$$w(0) = 0,\ E^{(1)}\{ds(t)\} = 0,$$

$$E^{(1)}\{dw(t)\, dw^T(t)\} = Idt \qquad (2)$$

hold for $t \geq 0, I$, is the identity matrix. Any realization of the Wiener process $w(t)$ is continuous but not differentiable

at each point. Moreover because of $E^{(1)}\{w(t)w^T(t)\} = It$, the process $w(t)$ is a non-stationary stochastic process.

For, simplicity, we denote

$h(x)dw(t) = (h_1 dw_1, ..., h_m dw_m)^T$ in our consideration. So, the product $h(x)dw(t)$ means neither a scalar product nor a vector product, but it is

a column vector with components $h_i(x)dw_i(t),.$

$i = 1, 2, ..., m$ Using this, system (1) can be rewritten into the vector form $dx(t) = f(x)dt + h(x)dw(t), \quad t \geq 0$ (3)

are interested in stability of solutions of the system. There are several various definitions of stability that can be used. Here we recall the mean square stability and the asymptotic mean square stability of the zero solution.

Definition 1 The trivial solution of system (3) is said to be mean square stable on the interval $[0, \infty)$ if, for each $\varepsilon > 0$, there exists $\delta > 0$ such that any solution $x(t)$ corresponding to the initial data $x(0)$ exists for all $t \geq 0$ and the mathematical expectation $E^{(1)}\{\|x(t)\|^2\} < \varepsilon$ whenever $t \geq 0$ and $\|x(0)\| < \delta$. The mean stability of the zero solution of system (3) is defined in a very similar way, with only $\|x(t)\|^2$ being replaced by $\|x(t)\|$

Definition 2 The trivial solution of system (3) is said to be asymptotically mean square stable on the interval $[0, \infty)$ if it is stable and moreover, $\lim_{t\to\infty} E^{(1)}\{\|x(t)\|^2\} = 0$ (4)

Remark 1 It is easy to see that (4) is satisfied if and only if the matrix $E^{(2)}\{x(t)\}$ converges to zero matrix Θ,

$\lim_{t\to\infty} E^{(2)}\{x(t)\} = \lim_{t\to\infty} E^{(1)}\{x(t)x^T(t)\} = \Theta,$

Denote a neighbourhood of the point $0 \in \Re^m$ as O(o)

Definition 3 The function $g(t, x(t))$ is said to be positive definite on O(o) if $g(t, x(t))$ is continuous with respect to $t, t \geq 0, \|x(t)\| < \infty$ on O(o), $g(t,0) = 0$ and there exists a positive definite quadratic form $V(x)$ such that $g(t, x) \geq V(x)$ whenever $t \geq 0, \quad x \in O$(o) and $\|x(t)\| < \infty$ .Recall, if a function $g(t, x(t))$ is positive definite on O(o), then the function $-g(t, x(t))$ is negative definite on this neighbourhood.

Remark 2 The previous definition is equivalent to the following one:

The function $g(t, x(t))$ is said to be positive definite on O(o) if $g(t, x)$ is continuous with respect to $t, t \geq 0, \|x(t)\| < \infty$ on O(o), $g(t,0) = 0$ and there exists a constant $k > 0$ such that for any positive definite quadratic form $V(x)$, $g(t, x) \geq kV(x)$ whenever $t \geq 0, \quad x \in O$(o) and $\|x(t)\| < \infty$.

Definition 4: We define a Lyapunov function $v(x(t))$ in the form $v(x(t)) = x^T(t)Cx(t)$ (5)

where C is a $m \times m$ positive definite symmetric matrix. We also use the diagonal matrix C_d which has the same elements on the diagonal as C .

Theorem 1: Let there exist a neighbourhood O(o), in which the function

$\delta(x) = 2x^T Cf(x) + h^T(x)C_d h(x)$ (6)

is negative definite with respect to system (3). Then the trivial solution of (3) is asymptotically mean square stable on the interval $[0, \infty)$

Proof: First we calculate the differential of Lyapunov function (5) with respect to trajectories of system (3). We have

$$\begin{aligned} dv(x) &= v(x + dx) - v(x) \\ &= (x + dx^T)C(x + dx) - x^T Cx \\ &= \left(x^T + f^T(x)dt + (h(x)dw(t))^T\right) \\ &\quad C\left(x + f(x)dt + (h(x)dw(t))\right) - x^T Cx \\ &= x^T Cx - x^T Cx + x^T Cf(x)dt \\ &\quad + x^T C(h(x)dw(t)) + f^T(x)dtCx \\ &\quad + f^T(x)dtCf(x)dt \end{aligned}$$

$$+f^T(x)dtC\left(h(x)dw(t)\right)$$
$$+\left(h(x)dw(t)\right)^T Cx$$
$$+\left(h(x)dw(t)\right)^T Cf(x)dt$$
$$+\left(h(x)dw(t)\right)^T C\left(h(x)dw(t)\right).$$

After modifying the obtained equation, applying operation mathematical expectation $E^{(1)}\{dv(t)\}$, in regard to assumptions (2), and leaving aside the member with dt^2, we get the equation

$$E^{(1)}\{(d(v(x))\} = x^T Cf(x)dt + f^T(x)Cxdt + h^T(x)C_d h(x)dt \quad (7)$$

or, in view of (6), it can be written in the more simple form $E^{(1)}\{dv(x)\} = \delta(x)dt$ (8)

Because $\delta(x)$is a negative definite deterministic function, the equalities

$E^{(1)}\{\delta(x)\} = \delta(x), \delta(x) \le -kv(x), k = const.$ are true (see **Remark 2**). By using them and equation (8), we get

$$\frac{d}{dt}E^{(1)}\{v(x)\} \le -kE^{(1)}\{v(x)\},$$

So, $E^{(1)}\{v(x)\} \le e^{-kt}$, therefore,

$\lim_{t\to\infty} E^{(2)}\{x(t)\} = \lim_{t\to\infty} E^{(1)}\{x(t)x^T(t)\} =$ Θ, which implies asymptotic mean square stability of a trivial solution of the considered system.

Remark 3 Analogous result about instability can be derived in the same way as the result of Theorem 1. Namely, if there exists a neighbourhood *O*(o), in which the function

$$\delta(x) = 2x^T Cf(x)dt + h^T(x)C_d h(x)$$

is positive definite with respect to system (3), then the trivial solution of (3) is unstable on the interval $[0,\infty)$. Further we will discuss the stability of a system in the more general form

$$dx(t) = f(t,x)dt + \sum_{k=1}^{n} h_k(t,x)dw_k(t),\ t \ge 0, \quad (9)$$

where $f, h_k, k = 1,....., n$, are m-dimensional column vector-functions continuously differentiable in both variables, such that $f(t,0) = 0, h_k(t,0) = 0$ hold.

Expressions $h_k(t,x)dw_k(t), k = 1,....., n$, are again column vectors with components $h_{ik}(t,x)dw_{ik}(t), i = 1,2,....., m, k = 1,2,....., n.$

Functions $w_k = (w_{1k},....., w_{mk})^T, k = 1,2,....n$ are also m-dimensional column vector-functions indicating standard Wiener processes, such that each of them satisfies the following relationships:

$w_k(0) = 0; E^{(1)}\{dw_k(t)\} = 0;$

$E^{(1)}\{dw_k(t)dw_k^T(t)\} = Idt,\ k = 1,2,....., n$ for $t \ge 0$. (10)

The following theorem can be proved in the same way as **Theorem 1**.

Theorem 2: Let there exist a neighbourhood *O*(o), in which the function

$$\delta(x,t) = 2x^T Cf(t,x) + \sum_{k=1}^{n} h_k^T(t,x)C_d h_h(t,x) \quad (11)$$

is negative definite with respect to system (9).Then the trivial solution of (9) is asymptotically mean square stable on the interval $[0,\infty)$.

Remark 4: A similar remark as Remark 3 can be formulated in this case. Namely, if there exists a neighbourhood *O*(o), in which the function

$$\delta(x,t) = 2x^T Cf(t,x) + \sum_{k=1}^{n} h_k^T(t,x)C_d h_h(t,x)$$

is positive definite with respect to system (9), then the trivial solution of (9) is unstable on the interval $[0,\infty)$.

In the last part of this section, let us consider one special case of a stochastic system of differential equations, namely the linear system

$$dx(t) = Ax(t)dt + Hx(t)dw(t),\ t \ge 0, \quad (12)$$

where A, H are $m \times m$ constant matrices and w is a standard Wiener process that satisfies (2).

Corollary 1: Let there exist a neighbourhood *O*(o), in which the function

$$\delta(x) = x^T A^T Cx + x^T CAx + x^T H^T C_d Hx \quad (13)$$

is negative definite with respect to system (12). Then the trivial solution of (12) is asymptotically mean square stable on the interval $[0,\infty)$.

Proof: The proof of this theorem follows immediately from Theorem 1 if

$f(x) = Ax, h(x) = Hx.$

Remark5: If there exists a neighbourhood *O*(o), in which the function

$$\delta(x) = x^T A^T Cx + x^T CAx + x^T H^T C_d Hx$$

is positive definite with respect to system (12), then the trivial solution of (12) is unstable on the interval $[0, \infty)$.

Remark 6: Stability of the trivial solution of a stochastic system of linear differential equations in the form (12) was studied in the works by Korenevskii in [60]. The following stability criterion was obtained there by different methods. The trivial solution of system (12) is asymptotically mean square stable on the interval $[0, \infty)$ if and only if there exist a positive definite matrix C satisfying the matrix equation $A^T C + CA + H^T CH = -G$, where matrix G is positive definite.

The rest of the paper is structured as follows. In section 2 we present the deterministic mathematical model of tumor growth. In section 3, we studied the stability of the deterministic system. In section 4, we built and analyzed the stochastic mathematical model. Computer simulations are incorporated in section 5. Finally, section 6 contains the general discussions and conclusions of the article and epidemiological implications of our mathematical & statistical findings.

II. MATHEMATICAL MODEL

In this section we consider a deterministic mathematical model for the growth of tumor [51] and incorporated the stochastic environmental perturbation with white noise on the system whose behaviour has been investigated in section 4. The preys are the tumor cells which are attacked and destroyed by the immune cells. The predator has two states viz., hunting and resting cells which destroys the prey. The resting predator cells can interact with antigens. These resting cells cannot kill tumor cells but they are converting into a special type of T-lymphocyte cells which is called natural killer or hunting cells and begin to multiply which release other cytokines simulating more resting cells. This conversion between hunting and resting cells results in a degradation of the resting cells undergoing natural growth and an activation of hunting cells.

The required mathematical model assumes that the tumor cells are being destroyed at a rate proportional to the tumor cell densities according to the law of mass action like prey-predator interaction. It is also assumed that the resting predator cells are converted into the hunting cells either by direct contact with them or by contact with a fast diffusing substance produced by hunting cells. We consider that once a cell has been converted, it will never return to the resting stage and active cells which die out at a constant probability per unit time. The dynamical system can be described by the following set of non-linear differential equations

$$\begin{aligned} x'(t) &= 1 + a_1 x(1-x) - k_1 xy - k_2 x \\ y'(t) &= a_2 yz - a_3 y - k_3 xy \\ z'(t) &= a_4 z(1-z) - a_5 yz - a_6 z - k_4 xz \end{aligned} \quad (14)$$

where $x(t)$ represents the density of tumor cells at time 't', $y(t)$ represents density of hunting predator cells at time 't', $z(t)$ represents density of resulting cells at time 't', a_1 is the growth rate of tumour cells, k_1 is the rate of killing of tumour cells by hunting cells, k_2 is the specific loss rates of tumour cells, k_3 represents the rate of killing of hunting predator cells by tumour cells, k_4 represents rate of killing of resting cells by tumour cells, a_2 represents the conversion rate of the resulting cells to hunting predator cells, a_3 is the specific loss rates of hunting predator cells, a_4 represents the growth rate of resting cells, a_5 is the conversion rate of resting cells to hunting predator cells, a_6 is the specific loss rates of the resting cells. The initial positivity conditions are $x(0) > 0;\ y(0) > 0;\ z(0) > 0$ (15)

POSITIVE INVARIANCE AND BOUNDEDNESS: Feasibility or biologically positivity studies aim to objectively and rationally uncover the strength of the proposed model in the given environment. Biologically positive insures the population never become negative and population always survive. The following theorems ensure that the positivity and boundedness of the system (14).

Theorem 3: All solution $(x(t), y(t), z(t))$ of the system (14) with the initial conditions (15) are positive for all $t \geq 0$

Proof: From (14) it is observed that

$$\frac{dx}{x} = \left[x^{-1} + a_1(1-x) - k_1 y - k_2 \right] dt = \phi_1(x, y, z)dt \ \text{(say)}$$

$$\frac{dy}{y} = \left[a_2 z - a_3 - k_3 x \right] dt = \phi_2(x, y, z)dt \ \text{(say)}$$

$$\frac{dz}{z} = \left[a_4(1-z) - a_5 y - a_6 - k_4 x \right] dt = \phi_3(x, y, z)dt \ \text{(say)}$$

where

$\phi_1(x,y,z) = x^{-1} + a_1(1-x) - k_1 y - k_2$;

$\phi_2(z) = a_2 z - a_3 - k_3 x$;

$\phi_3(x,y) = a_4(1-z) - a_5 y - a_6 - k_4 x$

and its solutions in the region $[0,t]$ are given by

$x(t) = x(0)\exp\left(\int \phi_1(x,y,z)dt\right) > 0$;

$y(t) = y(0)\exp\left(\int \phi_2(x,y,z)dt\right) > 0$;

$z(t) = z(0)\exp\left(\int \phi_3(x,y)dt\right) > 0$ for all t

Hence, all solutions starting from interior of the first octant (In R_+^3) remain positive in it for future time.

Theorem 4: All the non-negative solutions of the model system (14) that initiate in $\Re_+^3$ are uniformly bounded.

Proof: Let $x(t), y(t), z(t)$ be any solution of the system (14). Since, $x'(t) \le a_1 x(1-x)$, we have $\lim_{t\to\infty} \sup x(t) \le 1$.

Let $L = x + y + z$. Differentiate with respect to t

we get $L(t) = x'(t) + y'(t) + z'(t)$ (16)

From (14) and (16), we get

$$L'(t) + \theta L = x\left(1 + a_1 x(1-x) - k_1 xy - k_2 x\right) + (a_2 yz - a_3 y - k_3 xy)y + z(a_4 z(1-z) - a_5 yz - a_6 z - k_4 xz) + \theta(x+y+z)$$

$$L'(t) + \theta L \le x\left(1 + a_1 x(1-x) + \theta\right) + y(a_3 - \theta) + z(a_4(1-z) - a_6 + \theta) \le x\left(1 + a_1(1-x) + \theta\right) \le x\left(1 + a_1\theta\right)$$

$L'(t) + \theta L \le \mu$ since $1 + a_1 + \theta = \mu(say))$

Applying Lemma on differential inequalities Birkhoff [61] we obtain

$$0 \le L(x,y,z) \le (\mu/\theta)\left(1 - e^{-\theta t}\right) + \left(L(x(0), y(0), z(0))/e^{\theta t}\right)$$

and for $t \to \infty$ we have $0 \le L(x,y,z) \le (\mu/\theta)$. Thus all solutions of system (14) enter into the region $\Gamma = \left\{ \begin{matrix} (x,y,z) \in R_+^3 : 0 \le x \le 1, \\ 0 \le L \le (\mu/\theta) + \varepsilon, \forall \varepsilon > 0 \end{matrix} \right\}$. This completes the proof.

III. STABILITY AND DYNAMICS OF THE TUMOR GROWTH SYSTEM

For the system (14) we have the equilibrium points as (i) $E_0(0,0,0)$ which always exists.

(ii) $E_1(\bar{x},0,0)$.

where $\bar{x} = \frac{1}{2}\left[\left(1 - \frac{k_2}{a_1}\right) \pm \sqrt{\left(1 - \frac{k_2}{a_1}\right)^2 + \frac{4}{a_1}}\right]$. For $\bar{x}$ to be feasible we have $a_1 > k_2$

(iii) $E_2\left(x^\phi, 0, z^\phi\right)$ where x^ϕ and z^ϕ are: $x^\phi = \frac{1}{2}\left[\left(1 - \frac{k_2}{a_1}\right) \pm \sqrt{\left(1 - \frac{k_2}{a_1}\right)^2 + \frac{4}{a_1}}\right]$ and $z^\phi = 1 - \frac{a_6}{a_4} - \frac{k_4}{a_4}x^\phi$. For feasible existence of the equilibrium we have the parametric restriction as $a_4 > a_6 + k_4 x^\phi$.

(iv) $E_3\left(x^*, y^*, z^*\right)$ where $z^* = \frac{1}{a_2}\left[a_3 + k_3 x^*\right]$, $y^* = \frac{1 + a_1 x^*(1-x^*) - k_2 x^*}{k_1 x^*}$ with the restriction $a_1 > k_2$.

To check the local stability of the system (14), it is necessary to check the nature of eigenvalues of characteristic equation of the variational matrix J

where $J = \begin{vmatrix} -\frac{1}{x} - a_1 x & -k_1 x & 0 \\ -k_3 y & 0 & a_2 y \\ k_4 z & -a_5 z & -a_4 z \end{vmatrix}$

It is found that the characteristic equation of the system (14) cannot be defined about the steady state $E_0(0,0,0)$. Also, it is observed that the system (14) is semi negative definite at steady states $E_1(\bar{x},0,0)$ and $E_2(x^{\phi},0,z^{\phi})$. About $E_3(x^*,y^*,z^*)$, the characteristic equation of (14) is in the form of $\lambda^3 + A\lambda^2 + B\lambda + C = 0$

where $A = \frac{1}{x^*} + a_1 x^* + a_4 z^*$;

$B = a_1 \frac{z^*}{x^*} + a_1 a_4 x^* z^* + a_2 a_5 y^* z^* - k_1 k_3 x^* y^*$;

$C = a_2 a_5 \frac{y^* z^*}{x^*} + a_1 a_2 a_5 x^* y^* z^* - a_4 k_1 k_3 x^* y^* z^* - a_2 k_1 k_4 x^* y^* z^*$;

By Routh-Hurwitz criteria, it can be stated that the model (14) is locally stable around the interior equilibrium point E_3, if the following set of conditions involving the parameters are satisfied. $A>0; C>0; AB-C>0$. Clearly we observe that A is positive. For C to be positive, we should have

$a_2 a_5 \left(1 + a_1 (x^*)^2\right) > k_1 (x^*)^2 \left(a_4 k_3 + a_2 k_4\right)$ and for $AB-C$ to be positive, we should have $a_2 k_4 x^* z^* > \left(1 + a_1 (x^*)^2\right) k_3$. Thus the above conditions are necessary and sufficient for the stability of the interior equilibrium point.

Theorem 5: If the parametric conditions $a_2 a_5 \left(1 + a_1 (x^*)^2\right) > k_1 (x^*)^2 \left(a_4 k_3 + a_2 k_4\right)$ and $a_2 k_4 x^* z^* > \left(1 + a_1 (x^*)^2\right) k_3$ holds, then the equilibrium point $E_3(x^*, y^*, z^*)$ is locally asymptotically stable in $\Re_3^+$.

The numerical solution of the set of equation is shown in figures 1 and 2. The figure shows that the system is stable around E_3. The numerical simulation also depicts that the system is unstable under certain parameter values such as $a_1 = 0.6;\ k_1 = 0.9;\ k_2 = 0.5;\ a_2 = 0.99;\ a_3 = 0.1;$ $k_3 = 0.05;\ a_4 = 0.6;\ a_5 = 0.06;\ a_6 = 0.07;$ $k_4 = 0.02;$ .This phenomenon is shown in Figure 2. The simulation results show that the solution of the system of equation is periodic as depicted in figure 2. It has very important implication of the model system. It implies that the stage of the tumor is alarming. This phenomenon is known as the self-regression of tumor.

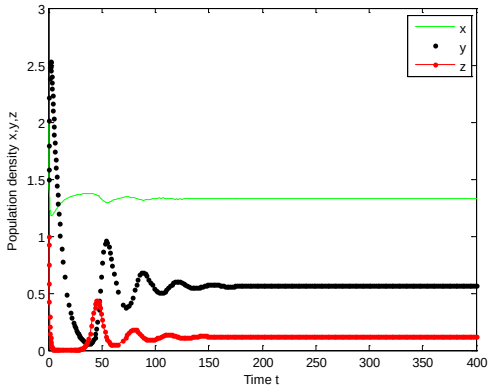

Figure 1

Figure 1: The time series evolution of the three populations of the system (14) showing the stable oscillation of the population towards $E_3(1.3213,\ 0.5656,\ 0.1186)$.

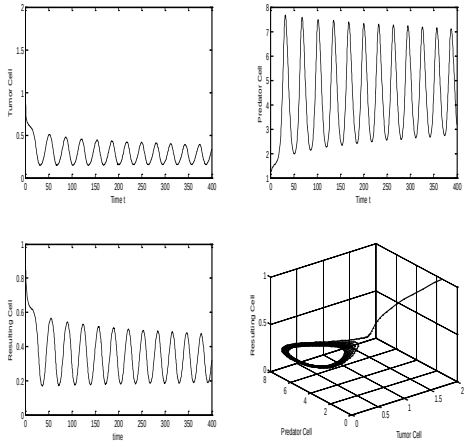

Figure 2

Figure 2: Periodic time series evolution of the three populations of the system (14) showing the unstable oscillation of the population towards $E_3(1.3213,\ 0.5656,\ 0.1186)$ for parameter values $a_1 = 0.6;\ k_1 = 0.9;\ k_2 = 0.5;\ a_2 = 0.99;\ a_3 = 0.1;$ $k_3 = 0.854;\ a_4 = 0.6;\ a_5 = 0.06;\ a_6 = 0.118;$ $k_4 = 0.02$.

Theorem 6: The equilibrium point $E_3(x^*, y^*, z^*)$ is also globally asymptotically stable in $\Re_3^+$.

Proof: To verify the global stability at the interior equilibrium point E_3, we construct the following Lyapunov function as given by

$$V(x,y,z,E)=\left[(x-x^*)-x^*\ln\frac{x}{x^*}\right]$$
$$+l_1\left[(y-y^*)-y^*\ln\frac{y}{y^*}\right]+l_2\left[(z-z^*)-z^*\ln\frac{z}{z^*}\right]$$
$$\frac{dV}{dt}=\left(\frac{x-x^*}{x}\right)\frac{dx}{dt}+l_1\left(\frac{y-y^*}{y}\right)\frac{dy}{dt}+l_2\left(\frac{z-z^*}{z}\right)\frac{dz}{dt};$$

$$\frac{dV}{dt}=-\left(a_1+\frac{1}{xx^*}\right)\left(x-x^*\right)^2$$
$$-\left(k_1+l_1k_3\right)\left(x-x^*\right)\left(y-y^*\right)$$
$$-\left(l_2a_5-l_1a_2\right)\left(y-y^*\right)\left(z-z^*\right)$$
$$-l_2k_4\left(x-x^*\right)\left(z-z^*\right)-l_2a_4\left(z-z^*\right)^2;$$

by choosing, $l_1=\frac{k_1}{k_3};\ l_2=\frac{k_1a_2}{k_3a_5}$,

$$\frac{dV}{dt}\le-\left(a_1+\frac{1}{xx^*}\right)\left(x-x^*\right)^2$$
$$-2k_1\left[\frac{\left(x-x^*\right)^2}{2}+\frac{\left(y-y^*\right)^2}{2}\right]$$
$$-\frac{a_2k_1k_4}{a_5k_3}\left[\frac{\left(x-x^*\right)^2}{2}+\frac{\left(z-z^*\right)^2}{2}\right]$$
$$-\frac{a_2k_1}{a_5k_3}\left(z-z^*\right)^2;$$

Therefore, we have, $V'(t)<0$, which proves that the given system is globally asymptotically stable about the equilibrium point E_3. This phenomenon is very important as it tells that at several initial states of the tumor cells the immune cells have sufficient strength to keep the tumor cells under control. Numerically, it is shown in the following Figure no 3**.**

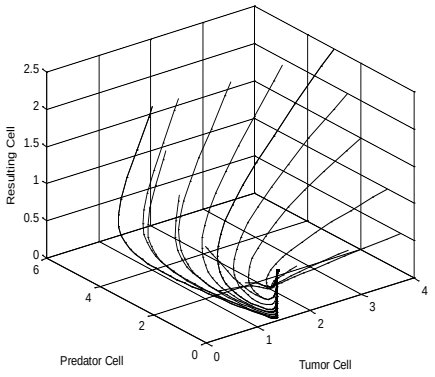

Figure 3

Figure 3: Global phase portrait of three populations of the system (14) showing the stable oscillation of the population towards

$E_3(1.3213,\ 0.5656,\ 0.1186)$ for many initial conditions.

IV. STOCHASTIC DIFFERENTIAL EQUATION MODEL

In this section, we extend the deterministic differential equations model (14) to a system of stochastic differential equations, where relevant parameters are modeled as suitable stochastic processes, or stochastic processes are added to the driving system equations. This approach assumes that the dynamics are partly driven by noise. There are a number of ways in which environmental noise may be incorporated in system (14). However, real biological systems will always be exposed to influences that are not completely understood or not feasible to model explicitly and therefore there is an increasing need to extend the deterministic models to models that embraces more complex variations in the dynamics. A way of modeling these elements is by including stochastic influences or noise. All biological dynamical systems evolve under stochastic forces, if we define stochasticity as the parts of the dynamics that we either cannot predict or understand or that we choose not to include in the explicit modeling. To be realistic, models of biological systems should include random influences, since they are concerned with subsystems of the real world that cannot be sufficiently isolated from effects external to the model. Generally, the environmental noise is distinguished from demographic or internal noise, for the variation over time is due to different causes. External noise may arise either from random fluctuations of the parameters around some known mean values or from stochastic fluctuations of the population densities around some constant values. In this section, we compute the

population intensities of fluctuations, i.e., variances around the positive equilibrium E_3 due to noise, according to the method introduced by Nisbet and Gunney [52]. If the amplitudes of the different cells are large from their average levels the populations are in unstable situation. Here we have the average values of the populations as the equilibrium state of the populations. Different sources of errors will require different modeling of the noise, and these factors should be considered carefully as the modeling of the deterministic part, in order to make the model predictions and parameter values possible to interpret. It is therefore essential to understand and investigate the influence of noise in the dynamics. In many cases the noise simply blurs the underlying dynamics without qualitatively affecting it, as is the case with measurement noise or in many linear systems. However, in nonlinear dynamical systems with system noise, the noise will often drastically change the corresponding deterministic dynamics. In general, stochastic effects influence the dynamics and may enhance, diminish or even completely change the dynamic behavior of the system.

In 2006, Carletti [53] studied a delay differential equations model with bacteriophage infection and discussed the robustness of the positive equilibrium with respect to stochastic perturbations of the environment using two different approaches. He investigated the analytical estimates of the population intensities with fluctuations by Fourier transform methods. Extensive numerical simulation suggested that a noisy environment for the bacteria population has much more destabilizing effect on the concentrations at the equilibrium point than a noisy environment for the phage. In this model, we introduce the fluctuating term $\xi_i(t)$ in the deterministic growth of the tumour cells, hunting predator cells and resulting cells at time t. The growth rate a_i ($i=1,2,3$) adjusted by the fluctuation, is rewritten as $a_i+\xi_i(t)$. We can address the final stochastic differential dynamical equation as given by

$$x'(t)=1+a_1x(1-x)-k_1xy-k_2x+\alpha_1\xi_1(t)$$

$$y'(t)=a_2yz-a_3y-k_3xy+\alpha_2\xi_2(t) \qquad (17)$$

$$z'(t)=a_4z(1-z)-a_5yz-a_6z-k_4xz+\alpha_3\xi_3(t)$$

where $x(t)$, $y(t)$ and $z(t)$ be the density of tumour cells, density of hunting predator cells and density of resulting cells respectively at time 't'. α_1, α_2 and α_3 are real constants and $\xi(t)=[\xi_1(t),\xi_2(t),\xi_3(t)]$ is a three dimensional Gaussian white noise process satisfying

$$E[\xi_i(t)]=0; i=1,2,3;$$
$$E[\xi_i(t)\xi_j(t')]=\delta_{ij}\delta(t-t'); i=j=1,2,3 \quad (18)$$

where δ_{ij} is the Kronecker symbol; δ is the Dirac-delta function. Using the below perturbations $x(t)=u_1(t)+S^*$; $y(t)=u_2(t)+P^*$; $z(t)=u_3(t)+T^*$, the linear part of the system (17) is

$$u_1'(t)=-a_1u_1(t)S^*-k_1u_2(t)S^*+\alpha_1\xi_1(t)$$

$$u_2'(t)=a_2u_3(t)P^*-k_3u_1(t)P^*+\alpha_2\xi_2(t) \qquad (19)$$

$$u_3'(t)=-a_4u_3(t)T^*-a_5u_2(t)T^*-k_4u_1(t)T^*+\alpha_3\xi_3(t)$$

Taking the Fourier transform on both sides of (19) we get,

$$M(\omega)\tilde{u}(\omega)=\tilde{\xi}(\omega) \qquad (20)$$

where $M(\omega)=\begin{pmatrix}A_{11}(\omega) & A_{12}(\omega) & A_{13}(\omega)\\ A_{21}(\omega) & A_{22}(\omega) & A_{23}(\omega)\\ A_{31}(\omega) & A_{32}(\omega) & A_{33}(\omega)\end{pmatrix}$;

$$\tilde{u}(\omega)=\begin{bmatrix}\tilde{u}_1(\omega)\\ \tilde{u}_2(\omega)\\ \tilde{u}_3(\omega)\end{bmatrix};\quad \tilde{\xi}(\omega)=\begin{bmatrix}\alpha_1\tilde{\xi}_1(\omega)\\ \alpha_2\tilde{\xi}_2(\omega)\\ \alpha_3\tilde{\xi}_3(\omega)\end{bmatrix};$$

$$A_{11}(\omega)=i\omega+a_1S^*;\ A_{12}(\omega)=k_1S^*;\ A_{13}(\omega)=0;$$
$$A_{21}(\omega)=k_3P^*;\ A_{22}(\omega)=i\omega;\ A_{23}(\omega)=-a_2P^*;$$
$$A_{31}(\omega)=k_4T^*;\ A_{32}(\omega)=a_5T^*;\ A_{33}(\omega)=i\omega+a_4T^*$$

Equation (20) can also be written as $\tilde{u}(\omega)=[M(\omega)]^{-1}\tilde{\xi}(\omega)$. Let $[M(\omega)]^{-1}=K(\omega)$, therefore, $\tilde{u}(\omega)=K(\omega)\tilde{\xi}(\omega)$; where

$$K(\omega)=\frac{X_{ij}^2+Y_{ij}^2}{|M(\omega)|}, i, j=1,2,3, \text{where}$$
$$|M(\omega)|=R(\omega)+iI(\omega)$$

Real part of $|M(\omega)|$ =

$$R(\omega)=-\omega^2(a_1S^*+a_4T^*)+(a_1a_2a_5-a_4k_1k_3-a_2k_1k_4)S^*P^*T^*$$

Imaginary part of $\left|M(\omega)\right|$ =

$$I(\omega) = -\omega^3 + \omega\left(a_1a_4S^*T^* + a_2a_5P^*T^* - k_1k_3S^*P^*\right)$$

The intensities of fluctuations in the variable u_i; $i = 1,2,3$ are given by

$$\sigma_{u_i}{}^2 = \frac{1}{2\pi}\sum_{j=1}^{3}\int_{-\infty}^{\infty}\alpha_j\left|K_{ij}(\omega)\right|^2 d\omega;\ i = 1,2,3 \tag{21}$$

Thus (21) becomes

$$\sigma_{u_1}{}^2 = \frac{1}{2\pi}\left\{\int_{-\infty}^{\infty}\frac{1}{R^2(\omega)+I^2(\omega)}\begin{bmatrix}\alpha_1\left(X_1{}^2+Y_1^2\right)\\ +\alpha_2\left(X_2{}^2+Y_2^2\right)\\ +\alpha_3\left(X_3{}^2+Y_3^2\right)\end{bmatrix}d\omega\right\}$$

$$\sigma_{u_2}{}^2 = \frac{1}{2\pi}\left\{\int_{-\infty}^{\infty}\frac{1}{R^2(\omega)+I^2(\omega)}\begin{bmatrix}\alpha_1\left(X_4{}^2+Y_4^2\right)\\ +\alpha_2\left(X_5{}^2+Y_5^2\right)\\ +\alpha_3\left(X_6{}^2+Y_6^2\right)\end{bmatrix}d\omega\right\}$$

$$\sigma_{u_3}{}^2 = \frac{1}{2\pi}\left\{\int_{-\infty}^{\infty}\frac{1}{R^2(\omega)+I^2(\omega)}\begin{bmatrix}\alpha_1\left(X_7{}^2+Y_7^2\right)\\ +\alpha_2\left(X_8{}^2+Y_8^2\right)\\ +\alpha_3\left(X_9{}^2+Y_9^2\right)\end{bmatrix}d\omega\right\}$$

where $X_1 = -\omega^2 + a_2a_5P^*T^*$; $Y_1 = \omega a_4T^*$;
$X_2 = -a_4k_1S^*T^*$; $Y_2 = -\omega k_1S^*$;
$X_3 = -a_2k_1S^*P^*$; $Y_3 = 0$; $X_4 = -(a_2k_4 + a_4k_3)P^*T^*$;
$Y_4 = -\omega k_3P^*$; $X_5 = -\omega^2 + a_1a_4S^*T^*$;
$Y_5 = \omega\left(a_1S^* + a_4T^*\right)$; $X_6 = a_1a_2S^*P^*$; $Y_6 = \omega a_2P^*$;
$X_7 = a_5k_3P^*T^*$; $Y_7 = -\omega k_4T^*$;
$X_8 = (k_1k_4 - a_1a_5)S^*T^*$; $Y_8 = -\omega a_5T^*$;
$X_9 = -\omega^2 - k_1k_3S^*P^*$; $Y_9 = \omega a_1S^*$.

If we are interested to find the dynamics of the system (17) with either $\alpha_1 = 0$ or, $\alpha_2 = 0$ or, $\alpha_3 = 0$, then the population variances are the following . If $\alpha_1 = \alpha_2 = 0$ or $\alpha_2 = \alpha_3 = 0$ or $\alpha_1 = \alpha_3 = 0$, then

$$\sigma_{u_1}{}^2 = \frac{\alpha_3}{2\pi}\int_{-\infty}^{\infty}\frac{X_3{}^2}{R^2(\omega)+I^2(\omega)}d\omega;$$

$$\sigma_{u_2}{}^2 = \frac{\alpha_3}{2\pi}\int_{-\infty}^{\infty}\frac{\left(X_6{}^2+Y_6^2\right)}{R^2(\omega)+I^2(\omega)}d\omega;$$

$$\sigma_{u_3}{}^2 = \frac{\alpha_3}{2\pi}\int_{-\infty}^{\infty}\frac{\left(X_9{}^2+Y_9^2\right)}{R^2(\omega)+I^2(\omega)}d\omega$$

$$\sigma_{u_1}{}^2 = \frac{\alpha_1}{2\pi}\int_{-\infty}^{\infty}\frac{\left(X_1{}^2+Y_1^2\right)}{R^2(\omega)+I^2(\omega)}d\omega\ ;$$

$$\sigma_{u_2}{}^2 = \frac{\alpha_1}{2\pi}\int_{-\infty}^{\infty}\frac{\left(X_4{}^2+Y_4^2\right)}{R^2(\omega)+I^2(\omega)}d\omega;$$

$$\sigma_{u_3}{}^2 = \frac{\alpha_1}{2\pi}\int_{-\infty}^{\infty}\frac{\left(X_7{}^2+Y_7^2\right)}{R^2(\omega)+I^2(\omega)}d\omega$$

$$\sigma_{u_1}{}^2 = \frac{\alpha_2}{2\pi}\int_{-\infty}^{\infty}\frac{\left(X_2{}^2+Y_2^2\right)}{R^2(\omega)+I^2(\omega)}d\omega;$$

$$\sigma_{u_2}{}^2 = \frac{\alpha_2}{2\pi}\int_{-\infty}^{\infty}\frac{\left(X_5{}^2+Y_5^2\right)}{R^2(\omega)+I^2(\omega)}d\omega;$$

$$\sigma_{u_3}{}^2 = \frac{\alpha_2}{2\pi}\int_{-\infty}^{\infty}\frac{\left(X_5{}^2+Y_5^2\right)}{R^2(\omega)+I^2(\omega)}d\omega$$

The above analysis is illustrated numerically in Figures 4-6**.** The figures show that the system undergoes a stable state under the influence of the random noise of the environment. The time series of the volumes of the tumor cell, predator cell and the resulting are close to their equilibrium values. So under such influence of the environment the system remains stable. On the other hand in Figures 7-9, the fluctuations of the populations from the equilibrium states are higher. The reason of such increment is the influence of the environment, that is, the activation of the tumor cells are more that the strength of the predator cells. As a result the system is vulnerable to cancer. The treatment in that case is extremely urgent.

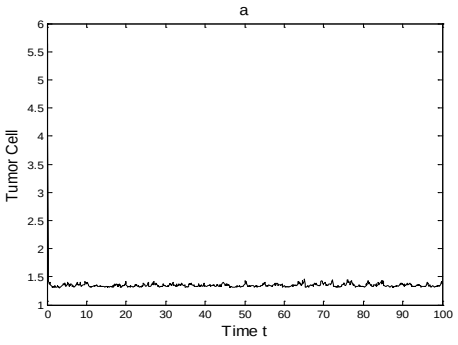

Figure 4

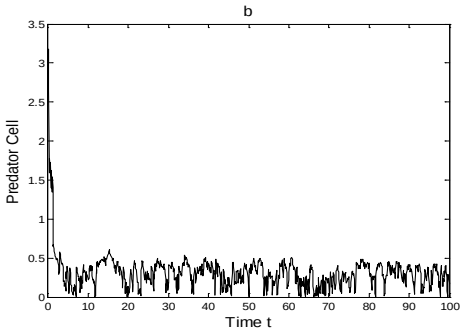

Figure 5

Figure 4: The time series evolution of the Tumor Cell of the stochastic system showing the stable oscillation of the population around 1.3213. Figure 5: The time series evolution of the Predator Cell of the stochastic system showing the stable oscillation of the population around 0.5656.

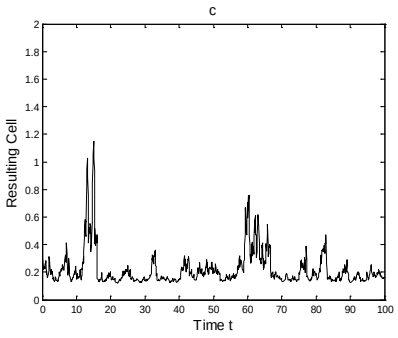

Figure 6

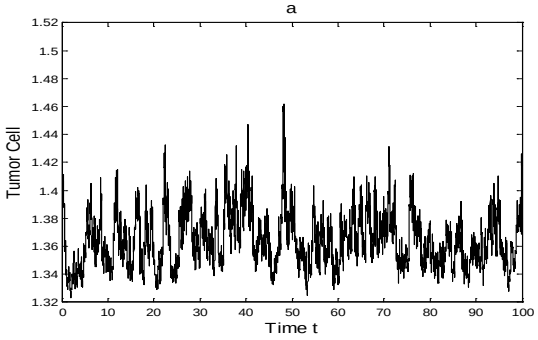

Figure 7

Figure 6: The time series evolution of the Resulting Cell of the stochastic system showing the stable oscillation of the population around 0.1186. Figure 7: The time series evolution of the Tumor Cell of the stochastic system showing the chaotic behaviour of the population.

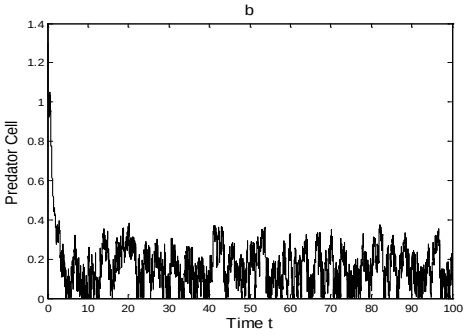

Figure 8

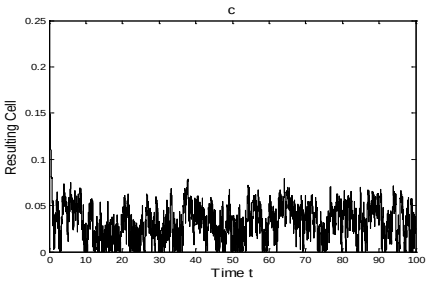

Figure 9

Figure 8: The time series evolution of the Predator Cell of the stochastic system showing the chaotic oscillation of the population. Figure 9: The time series evolution of the Resulting Cell of the stochastic system showing the chaotic situation of the population.

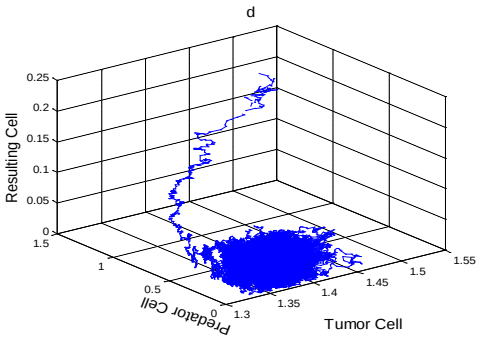

Figure 10

Figure 10: The phase-portrait of the three populations of the stochastic system showing the chaotic behaviour of the system.

V. SIMULATIONS ANALYSIS

Based on the above numerical simulations and diagrams i.e Figures 1-10 along with the model studied above the following analysis is carried out. Model with and without environmental factors and fluctuations are studied and simulated in the above sections. In the above sections the model and its graphical results allow us to know more about the influence of our noise induced fluctuations can be discussed here. We have modeled the system with a set of differential equation which is non-linear in nature. We have given both deterministic as well as stochastic effect with white noise of the system. The analytical results show some restrictions on the parameters for the control of the system. The stability property definitely shows how we can keep the tumor in our control. The numerical simulations have been carried out for both kinds of situations where tumor cell will remain in control and also the situation in which the disease becomes malignant in human body. (i) We have obtained the stability situation of the populations. It means that the tumor growth is under control. We have also obtained the criteria for which the populations exhibit periodic oscillations. This implicates that the tumor is malignant.

We have used the deterministic differential equations and we have considered a hypothetical value of the system parameters. In our theoretical work, original experimental or clinical data is very difficult to collect. We have chosen the following values: $a_1 = 0.6$; $k_1 = 0.9$; $k_2 = 0.5$; $a_2 = 0.99$; $a_3 = 0.1$; $k_3 = 0.05$; $a_4 = 0.6$; $a_5 = 0.06$; $a_6 = 0.07$; $k_4 = 0.02$ .The above values of the parameters satisfy the feasibility and existence criteria of the equilibrium states. The growth of the tumor cells is shown in the Figure 1. The simulation result shows that the system is stable around the interior equilibrium point E_3 (1.3213, 0.5656, 0.1186). Now, if the value of the rate of killing of the hunting predator cells and specific loss rate of the resting cells are increased by approximately150 times then at $k_3 = 0.854$ and $a_6 = 0.118$, the oscillations of the tumor cells become periodic. This type of oscillations indicates the system to become less immune. The tumor cells, predator cells and the resulting cells are changing periodically over a period of time. In this situation the tumor cells become malignant.

Under certain set of parameters, the numerical simulation suggests that the growth of the tumor may become alarming. This situation is shown in Figure 2. The global stability criterion is one of the important features in tumor growth. At several initial stages the system behavior has shown to be stable. We have illustrated the phenomena in Figure 3 with same parameter value.

In Figures 4-6, we have illustrated the simulation of the stochastic system. The figures show that the environmental noise has the key role in shaping the growth of the tumor cells in human body. We do not know the complex phenomena of the growth of the tumor cells. We cannot exactly model the system using any kind of mathematical formula (differential equations and others). As this is a modeling, we could find some value of the activation of the tumor cells or of resulting cells/predator cells which give different kind of growth from their average values. The amplitudes of the populations say what could happen to the system. Figures 7-10 show that the system becomes chaotic with some different value of the parameters for which the system behaves abruptly. This is because the change of the strength of the environmental noise. As the noise is increased the amplitude of the populations are increased about their mean values. As do not know how the tumor cells grow in the complex system in human body, we can trust on the modeling to obtain an approximate answer.

VI. CONCLUDING REMARKS

Our concept of studying asymptotic mean square stability of the zero solution of stochastic differential equations is more effective in comparison with previously known methods and it can also be used in various application problems. For example, by stochastic equation of the type

$dx(t) = [a_1 x(t) - a_2 x(t) \ln x(t)]dt + \sigma x(t) dw(t)$. We can describe a tumor growth, where the expected size of the tumor is contaminated with white noise [33], [54]. Such type of equations can be used also in biomedical research [55, 56], epidemic modelling [57], in describing animal motion [58], receiving signals [56, 59] and many others. However, the approach to the study of these models in the cited works is different compared to our method. They use numerical or statistical methods and estimation methods in there.

In this paper we have incorporated white noise in the form of stochastic perturbation of the immune system through the growth mechanism of the hunting cells and some other terms involved in the non-linear system. It is also assumed that hunting cells do not respond to the killing of tumor cells, as soon as they have signal from resting cells and they will be activated after some fixed time. Cancer is a stochastic process affected by random mutations and cell proliferation. The dynamics and the behavior of stability results of our system showed three main types of solutions: (i) existence of stable equilibrium (ii) appearing limit cycle (iii) chaotic attractor. In real problems, all the three cell populations coexist as a limit cycle or as periodic solution. In our case, the tumor is termed as mildly malignant so the existence of periodic solutions are relevant feature in our tumor growth cancer model analysis which implies that the tumor levels are oscillating around a fixed point in the absence of any treatment.

When the hunting cells are too tired in their response for killing the tumor cells (i.e. when they are large in numbers), all the three cell populations will grow in irregular fashion with respect to time shows chaotic attractors. This is indeed the case when the tumor is said to be malignant and a serious treatment strategy is required due to continuous

changing the density of tumor cells over time. It is well known from ecological-model analysis results that stochastic white noise gives the insight of the dynamics of irregular fluctuations leading to the instability of equilibrium points. We observed that instability in the form of chaotic attractors in cancer model is a challenging issue and interesting outcome of our study. For existence of some sensitive parameters involved in our system preserving the stability and also detect the mode of action for controlling the disease. In our model extensive numerical simulation suggested that a noisy environment for the tumor growth has much more destabilizing effect on the concentrations at different equilibrium points.

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