Stochastic Modelling of Tumour Immune Interactions

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Abstract— *Tumour immune interaction is modelled to evaluate the tumour cell size as a stochastic time dependent model. The life of a tumour cell is assumed to be in hypothetical phases of independently distributed time duration. The analysis uses generating functions to obtain the first few moments of the tumour cell size analyzed. The first few moments are expressed as a function of time and cell proliferation kinetics including the tumour cell escape rate from immune surveillance. Numerical results are obtained and are found to be consistent with the current theory.*

Keywords: Generating functions; Immune response system; Laplace transforms; Proliferation kinetics; Tumour size modelling.

1. Introduction

The stochastic models on carcinogenesis have received considerable interest and quite a few papers have been published [[1], [2], [3], [4]]. It is important to develop stochastic models of tumour growth that include a representation of immune response. In a recent paper [5] used Monte Carlo Simulation to evaluate the tumour cell size in the presence of immune response. The resort to simulation, it seems, was mainly due to the fact that no explicit analytic solution is possible when the proliferation rates are time or age dependent. However, if the research concern lies mainly with the determination of first few moments, the problem becomes tractable. The major contribution of this paper lies in addressing this important issue, demonstrating the possibility of obtaining explicit expressions for the first few moments of tumour cell population in the presence of an active immune system. The tumour cell life time is treated here as evolving in phases. The life time from precancerous stage to dormant or dead state is divided into three phases. In fact the method of phases has already been employed in cavity radiation problems [[6]]. The layout of the paper is as follows. Section 2 describes the formulation of the model and Section 3 derives the equations satisfied by generating functions. Section 4 derives the equations satisfied by the first two moments and their solutions. Section 5 provides numerical results under selected values of the parameters in Phases 1, 2 and 3, and explores the behaviour of tumour size over time. The last section concludes with a discussion and summary.

2. Formulation of the Model

It is well known that the immune system guards against the development of tumours and it also attempts to detect and eliminate cancerous or precancerous cells. Hence, tumour size is to be considered as a function of time and in terms of proliferation kinetics including the interaction of the immune response system with the cancerous cells. According to [7] and [8] "the tumour development can be eliminated by tumour infiltrating cytotoxic lumphocytes (TICL's) during the avascular stage." TICL's interact with tumour cells and disable them from developing into proliferating malignant cells. As a result, the tumour cells either die or escape the immune surveillance and leave the primary tumour site and attempt to form tumours elsewhere. We consider the evolution of the tumour cell population according to the process of birth, (nascent tumour cell capable of proliferation), death (immune cell) and emigration (escape of tumour cell) [[9]]. Thus the life span of any tumour cell can be divided into three phases. In the first phase, the newly born tumour cell is passive and waiting to become mature enough for proliferation. $\lambda(t)\Delta t$ is the probability for the cell to pass into Phase 2 in the time interval $(t, t+dt)$. In the second phase the tumour cell is active in proliferation and the probability of a single cell to proliferate into two cells is $\eta(t)\Delta t$ in $(t, t+dt)$. In both the first and second phases the immune system can detect and form TICLs with probability $\mu_1(t)\Delta t$ in $(t, t+dt)$. In the second phase the tumour cell has a probability $\mu_2(t)\Delta t$ to pass into Phase 3, there to die or be dormant. In the third phase the tumour cell is incapable

of proliferation. The first two phases have independent time spans and that of the third phase is indefinite. The tumour cells generated in different phases are also independent and evolve with respect to time. We assume that each tumour cell necessarily goes through the three phases. At the outset we observe that it is sufficient to deal with the tumour cell population generated by one cell each in each of the three phases. This is justified by the independence of the birth and death process of each of the cells. We also assume that the tumour cell which escapes surveillance starts the cycle as an independent cell in phase 1 or phase 2 at a secondary site. It is assumed that cancer has already set in and the immune therapy is triggered by number of immue response cells namely TICL's.

3. Generating Functions of the Tumour Cell Population.

Let $X(t), Y(t)$ and $Z(t)$ represent the number of tumour cells in Phases 1, 2 and 3 respectively. The population generated by the tumour cell is of the branching type when there is no escape possible for that cell from immune surveillance. However, when such escape is possible, the population generated by the escaped cells is also independent. Thus, we define two generating functions:

$$\begin{aligned} g_i(z_1,z_2,z_3,t) =& E\Big[z_1^{X(t)}z_2^{Y(t)}z_3^{Z(t)}/X(0)=2-i, \\ & Y(0)=1-i,\upsilon=0\Big] \end{aligned} \tag{1}$$

where, $i = 1, 2$

$$\begin{aligned} G(z_1,z_2,z_3,t) =& E\Big[z_1^{X(t)}z_2^{Y(t)}z_3^{Z(t)}/ \\ & X(0)=Y(0)=Z(0)=0,\upsilon\neq 0\Big] \end{aligned} \tag{2}$$

where υ represents the escape rate from immune surveillance and E is the expectation operator.

3.1 Relation between $G(z_1, z_2, z_3, t)$ and $g_i(z_1, z_2, z_3, t)$.

$G(z_1, z_2, z_3, t)$ is the generating function of the population generated by the escaped tumour cell. We assume the time of the first tumour cell that escapes is exponentially distributed with parameter υ and that the population thus generated is independent of other cells.

$$\begin{aligned} G(z_1,z_2,z_3,t) =& e^{-\upsilon t}+\upsilon\int_0^t e^{-\upsilon u}G(z_1,z_2,z_3,t-u) \\ & \big[g_1(z_1,z_2,z_3,t-u)+ \\ & g_2(z_1,z_2,z_3,t-u)\big]du \end{aligned} \tag{3}$$

The first term represents the probability that the cell does not escape in $(0, t)$. The second term represents the probability of a tumour cell escaping immune response in $(u, u + du)$ with probability $e^{-\upsilon u}\upsilon du$. Assuming the cell is in phase 1 or 2 it generates a population during $t - u$.

The integral Equation (3) can be solved and we obtain,

$$G(z_1,z_2,z_3,t)=exp\left[-\upsilon\int_0^t\Big\{1-\sum_{i=1}^{2}g_i(z_1,z_2,z_3,u)du\Big\}\right] \tag{4}$$

3.2 Derivation of equations governing $g_i(z_1, z_2, z_3, t)$.

We now go into deriving equations for g_1, g_2 and g_3

We obtain the differential equation satisfied by g_1 by analysing in the time interval $(0, \Delta t)$ for Phase 1 [[10]]. At $t = 0$, we have a newly born tumour cell and it can:

1) Move into proliferation Phase 2 in $(0, \Delta t)$ with probability $\lambda\Delta t$;
2) Be detected by immune response and move to Phase 3 with probability $(\mu_1 + \mu_2)\Delta t$;
3) Remain as it is in the same state with probability $[1 - (\lambda + \mu_1 + \mu_2)]\Delta t$.

Combining these events we can write, with $\Delta t \to 0$

$$\begin{aligned} \partial g_1(z_1,z_2,z_3,t)/\partial t =& -(\lambda+\mu_1+\mu_2)g_1+ \\ & \lambda g_2+(\mu_1+\mu_2)g_3 \end{aligned} \tag{5}$$

In the case of Phase 2, at $t = 0$ we assume that there is a tumour cell which can actually proliferate. The following events can then happen in Phase 2 in the time $(0, \Delta t)$. It can:

1) Move straight into Phase 3 with probability $\mu_2\Delta t$
2) Move into proliferation and can spilt into 2 tumour cells with probability $\eta\Delta t$
3) Be detected by immune response and move into Phase 3 with probability $\mu_1\Delta t$
4) Remain as it is in the same state with probability $[1 - (\mu_1 + \mu_2 + \eta)]\Delta t$

Combining these events we can write, with $\Delta t \to 0$

$$\frac{\partial g_2}{\partial t}=-(\mu_1+\mu_2+\eta)g_2+2\eta g_1+(\mu_1+\mu_2)g_3 \tag{6}$$

In view of our assumption that cells in Phase 3 have zero proliferation rates the generating function g_3 is independent of z_1 and z_2 and can be evaluated explicitly as:

$$g_3(z_1,z_2,z_3,t)=1+(z_3-1)e^{-(\mu_1+\mu_2)t} \tag{7}$$

It is rather difficult to solve for g_1 and g_2 explicitly. However, the moments of $X(t), Y(t)$ and $Z(t)$ can be evaluated

4. Moments of the tumour cell population.

We introduce the first two moments of the tumour cell population by $N_k^i(t)$, $M_k^{i,j}(t)$, $N^i(t)$, $M^{i,j}(t)$ where $N_k^i(t)$ and $N^i(t)$ are the first moments of the cell population

considering cell escape rates $\upsilon = 0$ and $\upsilon \neq 0$ respectively, and $M_k^{i,j}(t)$ and $M^{i,j}(t)$ are the corresponding second moments. It is known

$$N_k^i(t) = \left.\frac{\partial g_k}{\partial z_i}\right|_{z_1=z_2=z_3=1} \tag{8}$$

$$N^i(t) = \left.\frac{\partial G}{\partial z_i}\right|_{z_1=z_2=z_3=1} \tag{9}$$

$$M_k^{i,j}(t) = \left.\frac{\partial^2 g_k}{\partial z_i \partial z_j}\right|_{z_1=z_2=z_3=1} \tag{10}$$

$$M^{i,j}(t) = \left.\frac{\partial^2 G}{\partial z_i \partial z_j}\right|_{z_1=z_2=z_3=1} \tag{11}$$

We first connect $N^i(t)$ and $N_k^i(t)$ From Equation (2) differentiating both sides

$$N^i(t) = \upsilon \int_0^t \sum N_k^i(u)du \Big|_{k=1,2} \tag{12}$$

Also by differentiating twice Equation (2) we get

$$M^{i,j}(t) = \upsilon \int_0^t \sum_{k=1}^{2} M_k^{i,j}(u)du + N^i(t)N^j(t) \tag{13}$$

We now differentiate Equation (3) and Equation (4) to obtain

$$\frac{\partial N_1^i(t)}{\partial t} = -(\lambda + \mu_1 + \mu_2)N_1^i + \lambda N_2^i|_{i=1,2} \tag{14}$$

$$\frac{\partial N_1^3(t)}{\partial (t)} = -(\lambda + \mu_1 + \mu 2)N_1^3 + \lambda N_2^3 + (\mu_1 + \mu_2)e^{-(\mu_1+\mu_2)t} \tag{15}$$

$$\frac{\partial N_2^i(t)}{\partial (t)} = -(\mu_1 + \mu_2 + \eta)N_2^i + 2\eta N_2^i|_{i=1,2} \tag{16}$$

$$\frac{\partial N_2^3(t)}{\partial (t)} = -(\mu_1 + \mu_2 + \eta)N_2^3 + 2\eta N_1^3 + (\mu_1 + \mu_2)e^{-(\mu_1+\mu_2)t} \tag{17}$$

$$\tag{18}$$

With initial conditions

$$N_1^1(0) = N_2^2(0) = N_3^3(0) = 1 \tag{19}$$

$$N_1^2(0) = N_1^3(0) = N_2^1(0) = N_2^3(0) = 0. \tag{20}$$

Solving the system of Equations (14–17) using Laplace transforms, we get

$$N_1^1(t) = \frac{\alpha + a}{\alpha - \beta}e^{\alpha t} + \frac{\beta + a}{\beta - \alpha}e^{\beta t} \tag{21}$$

$$N_1^2(t) = \frac{\lambda}{(\alpha - \beta)}[e^{\alpha t} - e^{\beta t}] \tag{22}$$

$$N_1^3(t) = \frac{(a-c)\mu_1 + c\lambda}{(\alpha + c)(\beta + c)}e^{-ct} + \frac{(a+\alpha)\mu_1 + c\lambda}{(\alpha + c)(\alpha - \beta)}e^{\alpha t} + \frac{(a+\beta)\mu_1 + c\lambda}{(\beta + c)(\beta - \alpha)}e^{\beta t} \tag{23}$$

$$N_2^1(t) = \frac{2\eta}{(\alpha - \beta)}[e^{\alpha t} - e^{\beta t} \tag{24}$$

$$N_2^2(t) = \frac{\alpha + b}{(\alpha - \beta)}e^{\alpha t} + \frac{\beta + b}{(\beta - \alpha)}e^{\beta t} \tag{25}$$

$$N_2^3(t) = \frac{(b-c)c + 2\eta\mu^1}{(c+\alpha)(c+\beta)}e^{-ct} + \frac{(\alpha+b)c + 2\eta\mu_1}{(\alpha + c)(\alpha - \beta)}e^{\alpha t} + \frac{(\beta+b)c + 2\eta\mu_1}{(\beta + c)(\beta - \alpha)}e^{\beta t} \tag{26}$$

Where $a = \mu_1 + \mu_2 + \eta$, $b = \lambda + \mu_1 + \mu_2$, $c = \mu_1 + \mu_2$ and $\alpha \; and \; \beta$ are the roots of the equation

$$S^2 + S(a + b) + ab - 2\eta\lambda = 0 \tag{27}$$

Size of the tumour at time t when the tumour cell escape rate υ is zero is given by,

$$T(t) = \sum_{i=1}^{3} \int_0^t [N_1^i(t') + N_2^i(t') + N_3^i(t')]dt' \tag{28}$$

Size of tumour at time t when the tumour cell escape rate υ is not zero is given by,

$$T_e(t) = \sum_{i=1}^{3} N^i(t) = \upsilon \sum \int_0^t N_1^i(u)du \tag{29}$$

$T_e(t)$ is the size of tumour when a single tumour cell escapes the primary site and develops elsewhere.

The second moments can be obtained by differentiating Equations (5–7) successfully, we get,

$$\frac{\partial M_1^{i,j}(t)}{\partial t} = -(\lambda + \mu_1 + \mu_2)M_1^{i,j} + \lambda M_2^{i,j}(\mu_1 + \mu_2)M_3^{i,j} \tag{30}$$

$$\frac{\partial M_2^{i,j}(t)}{\partial t} = -(\eta + \mu_1 + \mu_2)M_2^{i,j} + 2\eta M_1^{i,j}(\mu_1 + \mu_2)M_3^{i,j} \tag{31}$$

$$\frac{\partial M_3^{i,j}(t)}{\partial t} = -(\mu_1 + \mu_2)M_3^{i,j}(t) \tag{32}$$

Since we are interested in the size of the tumour, we refrain from giving the solutions though the above equations

can be solved by Laplace transform. However as $t \to \infty$ we can obtain the steady state expression for $N_j^i(t)$.

$$N_1^1(\infty) = \frac{\mu_1 + \mu_2 + \eta}{ab - 2\eta\lambda} \tag{33}$$

$$N_1^2(\infty) = \frac{\lambda}{ab - 2\eta\lambda} \tag{34}$$

$$N_1^3(\infty) = \frac{\lambda + \eta + \mu_1 + \mu_2}{ab - 2\eta\lambda} \tag{35}$$

$$N_2^1(\infty) = \frac{2\eta}{ab - 2\eta\lambda} \tag{36}$$

$$N_2^2(\infty) = \frac{\lambda + \mu_1 + \mu_2}{ab - 2\eta\lambda} \tag{37}$$

$$N_2^3(\infty) = \frac{\lambda + \eta + \mu_1 + \mu_2}{ab - 2\eta\lambda} \tag{38}$$

5. Exploratory Numerical Results.

We proceed to evaluate the tumour size numerically for different values of λ, η, μ_1, and μ_2. The tumour cell population or size is shown as two variables: T(t) and $T_e(t)$. T(t) is the size at the primary host site and $T_e(t)$ is the size of the population generated by the escaped cell at another secondary site.

In a series of graphs we plot T(t) and T_e (t) for an exploratory set of values of λ, η, μ_1, and μ_2 gathered from prior results in the literature. We note that they follow a piecewise Gompertz curve pattern as found by Boondreck et. al. (2006) through Montecarlo simulation. The graphs presented here in Figure 1, Figure 2, and Figure 3 show the smoothed Gompertz curve fit for these results. Next we also calculated and tabulated the number of proliferated cells P(t) over time as the parameters are varied [1]. Finally, to facilitate comparison with the simulated results in [5], using non-linear regression, we fitted Gompertz curves for the values obatined by us analytically using the exploratory set of parameter values. These graphs are shown in Figure 4, Figure 5 and Figure 6. Our analytical results from this extended model, permitting both attachment by the immune response system to incapacitate the cancer cellls and also escape from that system to another site to proliferate, confirm the growth pattern of cells and tumour size over time, derived by them through simulation. In the next and concluding section we discuss these results.

6. Summary and Discussion.

First it is interesting to note that for fixed values of the probabilites of the cell moving directly from either Phase 1 or 2 to Phase 3, i.e., for fixed μ_1 and μ_2 to become incative and for fixed values of the infection rate or probabiltiy λ, as the proliferation rate η increases the analytical results from the model show that the number of proliferated cells at the

[1]Copies of these tables can be obtained as Excel files by e-mailing the request to either one of the authors.

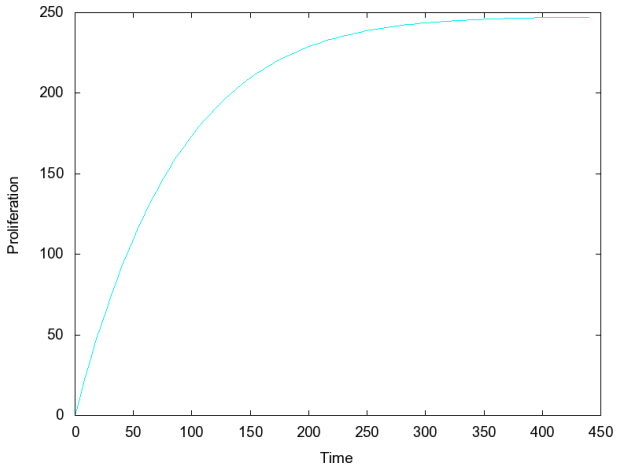

Fig. 1: Number of cells at primary site when escape rate $\upsilon = 0$, $\lambda = 0.5$, $\eta = 0.4$, $\mu_1 = 0.15$, $\mu_2 = 0.05$

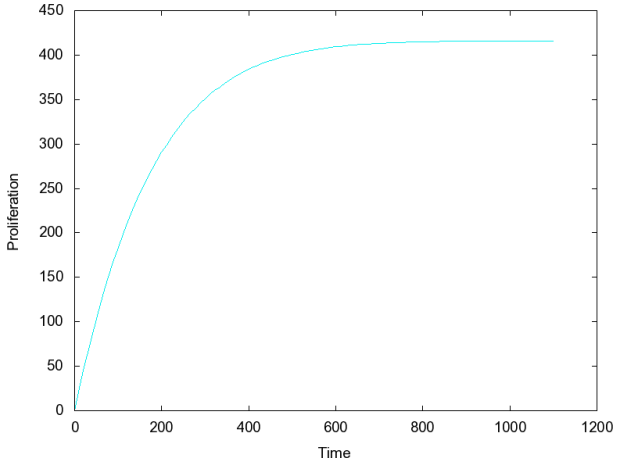

Fig. 2: Number of cells at primary site when escape rate $\upsilon = 0$, $\lambda = 0.5$, $\eta = 0.7$, $\mu_1 = 0.2$, $\mu_2 = 0.08$

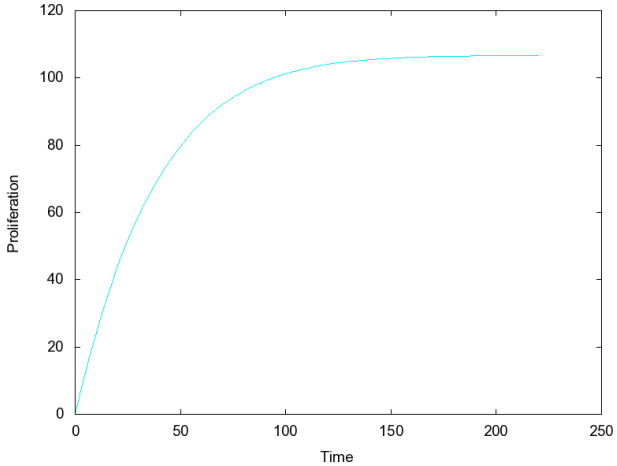

Fig. 3: Number of cells at primary site when escape rate $\upsilon = 0$, $\lambda = 0.1$, $\eta = 0.1$, $\mu_1 = 0.02$, $\mu_2 = 0.03$

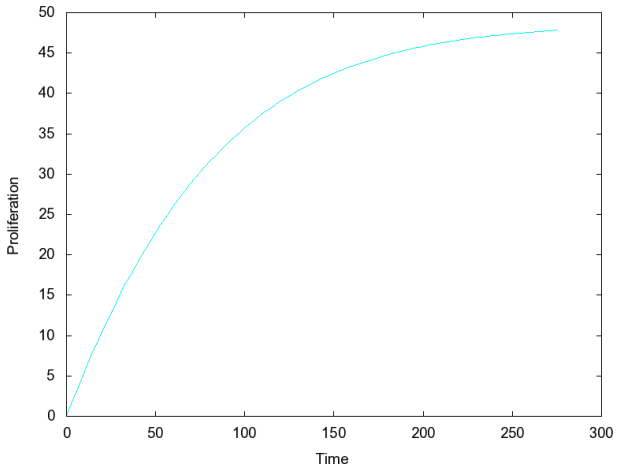

Fig. 4: Number of cells at secondary site when escape rate $\upsilon = 0, 1$, $\lambda = 0.5$, $\eta = 0.4$, $\mu_1 = 0.15$, $\mu_2 = 0.05$

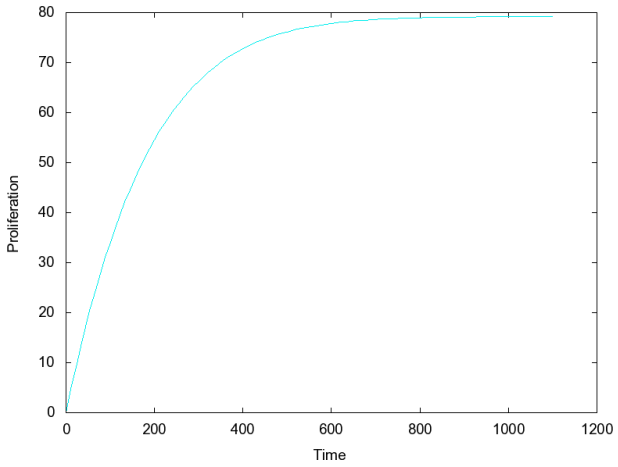

Fig. 5: Number of cells at primary site when escape rate $\upsilon = 0.1$, $\lambda = 0.5$, $\eta = 0.7$, $\mu_1 = 0.2$, $\mu_2 = 0.08$

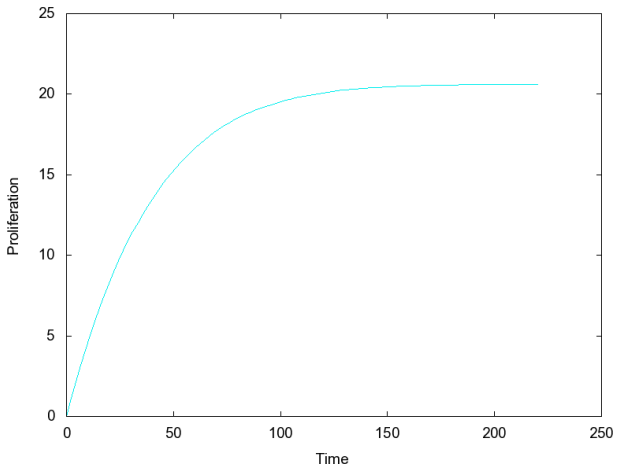

Fig. 6: Number of cells at secondary site when escape rate $\upsilon = 0.1$, $\lambda = 0.1$, $\eta = 0.1$, $\mu_1 = 0.02$, $\mu_2 = 0.03$

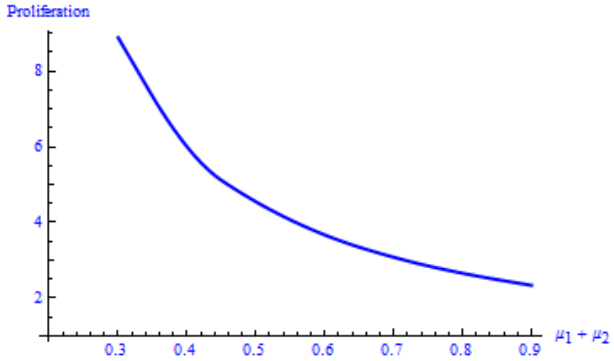

Fig. 7: Number of cells at secondary site when escape rate $\lambda = 0.2$, $\eta = 0.3$, $\mu_1 + \mu_2$ changing from 0.3 to 0.9

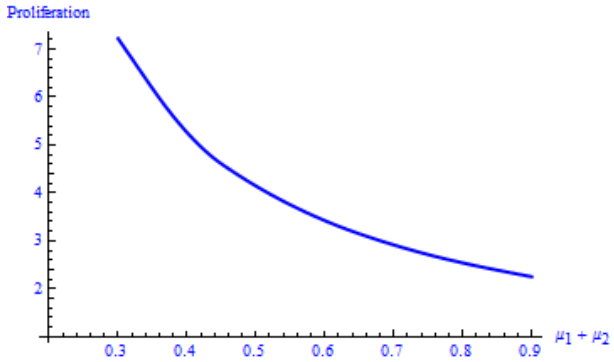

Fig. 8: Number of cells at secondary site when escape rate $\lambda = 0.05$, $\eta = 0.3$, $\mu_1 + \mu_2$ changing from 0.3 to 0.9

secondary site increases but at a decreasing rate. The rate of decrease increases as $\mu_1 + \mu_2$ increases. Furthermore, the number of these proliferated cells converges to an asymptotic limit after the expiration of a period of time. Again this convergence time is not uniform. It is reached rapidly over time for larger values of $\mu_1 + \mu_2$, and slowly for smaller values. We see a similar pattern for the total tumour size T (t) when the escape rate of an infected cell is zero and for the tumour size $T_e(t)$ when that escape rate ν is positive. One would normally expect when ν increases both T (t) and $T_e(t)$ would increase all else being held constant, and $T_e(t)$ would increase more rapidly. All these are borne out by the graphs in the respective figures when these values are obtained purely from our analytical results for expoloratory values of the rate paarmeters.

Following [5] we investigated the shape of the various curves for P(t), T (t) and $T_e(t)$ as functions of time to see if they fit the Gompertz curve shape obtained with their simulated data. The figures show that a Gompertz curve fit obtained through non-linear regression from SAS fit them remarkably well. Further analysis shows that fixed values of other rate parameters, the time required for the doubling of the number of proliferated cells increases at an increasing

rate, i.e., at greater speed as the proliferation rate η increases.

We also checked the paper [11] and collected values of μ_1 and μ_2. The graphs in Figure 7 and 8 represent the proliferation of tumour cell in the absence of TICL's and for different rates of disabling of malignant cells by TICL. It can be seen from the graphs as the rate increases the proliferation decreases. This could help in deciding the level of therapy for controlling the malignant cells. Work is in progress to prepare a table for practitioners to make use of the table.

These results have some practical implications. The major one is that any treatment that can either directly reduce, or provide more time for the body's immune response system to attack and slow down,the proliferation rate would be beneficial to the patient and slow down the spread of cancer. The same technique can be used to find the latent cell population in HIV.

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