A Mechanistic Model for Metastatic Tumour Growth and Treatment with Radiation Therapy

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1 Introduction

Cancer is a class of diseases in which cells grow in an unregulated manner. Currently, the study of cancer rests on six hallmarks (sustaining proliferative signalling, evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis, and resisting cell death) that encapsulate a cell's progression into the neoplastic disease [1]. Generally, cancer begins at the primary tumour, which is localized and will grow to a substantial size. From the primary tumour, certain cells metastasize, thus dispersing throughout the body. Often times, new metastatic tumours will arise from existing ones. This poses a particularly difficult problem for treatment intervention because metastases are often the cause for cancer's lethality. Despite increasing knowledge about cancer growth, many complications remain unresolved. One such challenge that researchers face regarding cancer growth is the evolution of micrometastases—metastatic tumours whose small size render them difficult to detect—which limits treatment options. In recent years, mathematical biologists have taken an interest on the subject and designed mathematical models to study cancer evolution. Here, we investigated a deterministic mechanistic PDE model for cancer growth using the McKendrick-von Foerster equation, along with its initial and boundary conditions. We are interested in using the model to understand the evolution of micrometastases in tandem with simulations of radiation therapy *in silico* at 3 and 5 years. The goal is to better gauge how tumours are targeted in treatment.

2 The McKendrick-von Foerster Equation

2.1 Motivation and Derivation

In order to understand colonies of a particular size, studying the colony size distribution of tumours is vital. Let $\rho(x,t)$ represent the colony size distribution of metastatic tumours with x number of cells at time t, and let $g(x)$ represent the rate at which the tumour grows. Consider an arbitrary interval $V = [a,b]$ with $b > a \geq 1$. The total number of tumour colonies of size x contained in V is given by $\int_a^b \rho(x,t)dx$, and the rate of change of the cell number is given by $\frac{\partial}{\partial t}\int_a^b \rho(x,t)dx$. At the same time, the rate of tumour growth is also given by the difference between the "in-flux" and the "out-flux" of colony size distribution. This net flux is given by $-\rho(b,t)g(b) + \rho(a,t)g(a)$. The above relationship is summarized here:

$$\frac{\partial}{\partial t}\int_a^b \rho(x,t)dx = -\rho(b,t)g(b) + \rho(a,t)g(a) \tag{1}$$

By Gauss's theorem, the net flux of tumour size can be written as $-\int_a^b \frac{\partial}{\partial x}\rho(x,t)g(x)dx$. This yields the following relationship:

$$-\int_a^b \frac{\partial}{\partial x}\rho(x,t)g(x)dx = \int_a^b \frac{\partial}{\partial t}\rho(x,t)dx \tag{2}$$

Notice that the LHS of (1) equals the RHS of (2). Rearranging (2) gives (3):

$$\int_a^b \frac{\partial}{\partial x}\rho(x,t)g(x)dx + \int_a^b \frac{\partial}{\partial t}\rho(x,t)dx = \int_a^b [\frac{\partial}{\partial x}\rho(x,t)g(x) + \frac{\partial}{\partial t}\rho(x,t)]dx = 0 \tag{3}$$

Recall the following theorem:

Theorem 1. *Assume that function f is continuous on $[a,b]$. If $\int_V f(x)dx = 0$ for all $V \in [a,b]$ where V is a non-zero interval, then $f \equiv 0$.*

Proof. We prove Theorem 1 by showing that the contrapositive is true. Assume there exists an $x_0 \in [a,b]$ such that $f(x_0) \neq 0$. Without loss of generality, assume $f(x_0) > 0$. Since f is continuous, there exists an interval $V_\epsilon = [x_0 - \epsilon, x_0 + \epsilon] \subseteq [a,b]$ such that $x_0 \in V_\epsilon$, and $f(x) > 0$ for all $x \in V_\epsilon$. As a result, $\int_{V_\epsilon} f(x)dx > 0$. The same can be shown for $f(x_0) < 0$. Hence, $\int_V f(x)dx \neq 0$. □

Per Thm. 1, (3) becomes (4), the McKendrick-von Foerster equation:

$$\frac{\partial}{\partial x}[\rho(x,t)g(x)] + \frac{\partial}{\partial t}\rho(x,t) = 0 \tag{4}$$

In addition, the initial and boundary conditions are given by:

$$\rho(x,0) = 0 \tag{5}$$

$$g(1)\rho(1,t) = \int_1^\infty \beta(x)\rho(x,t)dx + \beta(x_p(t)) \tag{6}$$

$$\frac{dx_p}{dt} = g(x_p(t)) \tag{7}$$

$$x_p(0) = 1 \tag{8}$$

2.2 Obtaining an Analytic Solution

We solve the McKendrick-von Foerster equation using the Laplace transform, as shown previously by Iwata et al. [2]. Since the Laplace transform operator $\mathcal{L}$ is a linear operator, we can apply the Laplace transform to each term of (4) separately and add them together, as shown in (9):

$$\mathcal{L}[\frac{\partial \rho(x,t)}{\partial t}] + \mathcal{L}[\frac{\partial [g(x)\rho(x,t)]}{\partial x}] = 0 \tag{9}$$

Suppose that $\mathcal{L}[f(t)] = \tilde{f}(s)$. First, we evaluate $\mathcal{L}[\frac{\partial \rho(x,t)}{\partial t}]$. Recall the following relationship:

$$\mathcal{L}[f^{(t)}] = s^n \tilde{f}(s) - s^{t-1} f(0) - ... - f^{(t-1)}(0)$$

By performing the operation, we have $\mathcal{L}[\frac{\partial \rho(x,t)}{\partial t}] = s\tilde{\rho}(x,s) + \rho(x,0)$, where $\rho(x,0) = 0$ from the initial condition. The result is given as:

$$\mathcal{L}[\frac{\partial \rho(x,t)}{\partial t}] = s\tilde{\rho}(x,s) \tag{10}$$

Next, we evaluate $\mathcal{L}[\frac{\partial g(x)\rho(x,t)}{\partial x}]$:

$$\begin{aligned}\mathcal{L}[\frac{\partial g(x)\rho(x,t)}{\partial x}] &= \int_0^\infty \frac{\partial}{\partial x} g(x)\rho(x,t)e^{-st}dt = \frac{\partial}{\partial x} g(x) \int_0^\infty \rho(x,t)e^{-st}dt \\ &= \frac{\partial}{\partial x} g(x)\mathcal{L}[\rho(x,t)] = \frac{\partial}{\partial x} g(x)\tilde{\rho}(x,s)\end{aligned} \tag{11}$$

By the linearity of the operator $\mathcal{L}$, the Laplace transform of (4) is the sum of results in (10) and (11), which gives us the following:

$$s\tilde{\rho}(x,s) + \frac{\partial}{\partial x} g(x)\tilde{\rho}(x,s) = 0 \tag{12}$$

We continue to solve for $\tilde{\rho}(x,s)$. We first make the following substitution:

$$A(x) = g(x)\tilde{\rho}(x,s) \tag{13}$$

such that (12) becomes:

$$s\frac{A(x)}{g(x)} + \frac{dA(x)}{dx} = 0$$

We solve as follows:

$$\begin{aligned} s\frac{A(x)}{g(x)} + \frac{dA(x)}{dx} &= 0 \\ \frac{dA(x)}{dx} &= -s\frac{A(x)}{g(x)} \\ \frac{dA(x)}{A(x)} &= -s\frac{dx}{g(x)} \\ \ln|A(x)| &= -s\int \frac{dx}{g(x)} + C(s) \end{aligned} \tag{14}$$

Substituting (13) into (14), we arrive at the following:

$$\begin{aligned} \ln|g(x)\tilde{\rho}(x,s)| &= -s\int_1^x \frac{du}{g(u)} + C(s) \\ g(x)\tilde{\rho}(x,s) &= e^{-s\int_1^x \frac{du}{g(u)} + C(s)} \end{aligned} \tag{15}$$

Let $F(s) = e^{C(s)}$. (15) becomes the following:

$$g(x)\tilde{\rho}(x,s) = F(s)e^{-s\int_1^x \frac{du}{g(u)}} \tag{16}$$

where F is an arbitrary function of s. Next, we take the Laplace transform of (6). Again, we take the Laplace transform of each term separately.

$$\mathcal{L}[g(1)\rho(1,t)] = g(1)\tilde{\rho}(1,s) \tag{17}$$

$$\begin{aligned}\mathcal{L}[\int_1^\infty \beta(x)\rho(x,t)dx] &= \int_0^\infty e^{-st}\int_1^\infty \beta(x)\rho(x,t)dxdt \\ &= \int_1^\infty \beta(x)\int_0^\infty \rho(x,t)e^{-st}dtdx \\ &= \int_1^\infty \beta(x)\tilde{\rho}(x,s)dx \end{aligned} \tag{18}$$

$$\mathcal{L}[\beta(x_p(t))] = \int_0^\infty \beta(x_p(t))e^{-st}dt \tag{19}$$

Combining (17)-(19) according to the relationship in (6), we have:

$$g(1)\tilde{\rho}(1,s) = \int_1^\infty \beta(x)\tilde{\rho}(x,s)dx + \int_0^\infty \beta(x_p(t))e^{-st}dt \tag{20}$$

Choosing $x = 1$ and using the condition in (20), (16) becomes (21):

$$F(s)e^{-s\int_1^1 \frac{du}{g(u)}} = F(s)e^0 = F(s) = \int_1^\infty \beta(x)\tilde{\rho}(x,s)dx + \int_0^\infty \beta(x_p(t))e^{-st}dt \tag{21}$$

For ease of calculation, we make the following substitutions:

$$B_p(s) = \int_0^\infty \beta(x_p(t))e^{-st}dt \tag{22}$$

$$G(x,s) = \frac{1}{g(x)}e^{-s\int_1^x \frac{du}{g(u)}} \tag{23}$$

From (18) and (19), and using the substitution in (22) and (23), we have the following relationship:

$$\tilde{\rho}(x,s) = [\int_1^\infty \beta(x)\tilde{\rho}(x,s)dx + B_p(x)]G(x,s) = [\int_1^\infty \beta(x)\tilde{\rho}(x,s)dx]G(x,s) + B_p(x)G(x,s)$$

$$\tilde{\rho}(x,s) - G(x,s)\int_1^\infty \beta(x)\tilde{\rho}(x,s)dx = B_p(x)G(x,s) \tag{24}$$

By observation from (16) and (23),

$$F(s)G(x,s) = \tilde{\rho}(x,s)$$

or equivalently,

$$G(x,s) = \frac{\tilde{\rho}(x,s)}{F(s)}$$

By substituting this observation into (24), we have the following:

$$\tilde{\rho}(x,s) - \frac{\tilde{\rho}(x,s)}{F(s)} \int_1^\infty \beta(x)F(s)G(x,s)dx = B_p(x)G(x,s) \tag{25}$$

Since $F(s)$ is defined as independent of x (despite the known dependence in (21)), $F(s)$ can be factored out of the integrand in (25), which is reduced by $F(s)$ in the denominator to unity. The result, after factoring and rearrangement, is the following:

$$\tilde{\rho}(x,s) = \frac{B_p(x)G(x,s)}{1 - \int_1^\infty \beta(x)G(x,s)dx} \tag{26}$$

In this analysis, we adopt the exponential growth rate law

$$g(x) = ax \tag{27}$$

The solution for $x = x_p$, where x_p is the number of cells in the primary tumour, with initial condition of (8) is

$$x_p(t) = e^{at} \tag{28}$$

To find $\tilde{\rho}(x,s)$ per (26), we first evaluate each of its components:

$$\beta(x_p) = m(x_p(t))^\alpha = m(e^{at})^\alpha \tag{29}$$

$$\begin{aligned} B_p(s) &= \int_0^\infty \beta(x_p)e^{-st}dt = \int_0^\infty m(e^{at})^\alpha e^{-st}dt = \int_0^\infty me^{(a\alpha-s)t}dt \\ &= \frac{1}{a\alpha - s} me^{(a\alpha-s)t}\big|_0^\infty = \frac{1}{a\alpha-s}m(-1) = -\frac{1}{a\alpha-s}m \end{aligned} \tag{30}$$

$$\begin{aligned} G(x,s) &= \frac{1}{g(x)} e^{-s\int_1^x \frac{du}{g(u)}} = \frac{1}{ax} e^{-s\int_1^x \frac{du}{au}} = \frac{1}{ax} e^{-\frac{s}{a}\ln|u|\big|_1^x} \\ &= \frac{1}{ax} e^{-\frac{s}{a}\ln|x|} = \frac{1}{ax} x^{-\frac{s}{a}} = \frac{x^{-\frac{s}{a}-1}}{a} \end{aligned} \tag{31}$$

Now we find $\tilde{\rho}(x,s)$:

$$\begin{aligned} \tilde{\rho}(x,s) &= \frac{B_p(x)G(x,s)}{1 - \int_1^\infty \beta(x)G(x,s)dx} = \frac{-\frac{m}{a\alpha-s}\frac{x^{-\frac{s}{a}-1}}{a}}{1 - \int_1^\infty mx^\alpha \frac{x^{-\frac{s}{a}-1}}{a}dx} = \frac{-\frac{m}{a\alpha-s}\frac{x^{-\frac{s}{a}-1}}{a}}{1 - \frac{m}{a}\int_1^\infty x^{\alpha-\frac{s}{a}-1}dx} = \frac{-\frac{m}{a\alpha-s}\frac{x^{-\frac{s}{a}-1}}{a}}{1 - \frac{m}{a}\left(\frac{a}{a\alpha-s}x^{\alpha-\frac{s}{a}}\right)\big|_1^\infty} \\ &= \frac{-\frac{m}{a\alpha-s}\frac{x^{-\frac{s}{a}-1}}{a}}{1 + \frac{m}{a\alpha-s}} = \frac{-\frac{m}{a\alpha-s}\frac{x^{-\frac{s}{a}-1}}{a}}{\frac{a\alpha-s+m}{a\alpha-s}} = \frac{-m(a\alpha-s)x^{-\frac{s}{a}-1}}{a(a\alpha-s)(a\alpha-s+m)} = \frac{mx^{-\frac{s}{a}-1}}{a(s-a\alpha-m)} \end{aligned} \tag{32}$$

In the derivation of (32), we assumed that $\alpha - \frac{s}{a} < 0$. Next, we take the inverse Laplace transform of (32), but first, recall that the inverse Laplace transform is a linear operator, and that the following relationships are true:

$$\mathcal{L}^{-1}\left[\frac{1}{s-a}\right] = e^{at} \tag{33}$$

$$\mathcal{L}^{-1}[e^{-cs}F(s)] = u_c(t)f(t-c) \tag{34}$$

where $F(s) = \mathcal{L}[f(t)]$, and $u_c(t)$ is a Heaviside function. Now, the inverse Laplace transform:

$$\rho(x,t) = \mathcal{L}^{-1}[\tilde{\rho}(x,s)] = \mathcal{L}^{-1}[\frac{mx^{-\frac{s}{a}-1}}{a(s-a\alpha-m)}] = \frac{mx^{-1}}{a}\mathcal{L}^{-1}[\frac{e^{-\frac{\ln x}{a}s}}{s-a\alpha-m}]$$
$$= u_{(\frac{\ln x}{a})}(t)[\frac{mx^{-1}}{a}e^{(a\alpha+m)(t-\frac{\ln x}{a})}] \tag{35}$$

where the Heaviside function signifies the following:

$$u_{(\frac{\ln x}{a})}(t) = \begin{cases} 0, t < \frac{\ln x}{a} \\ 1, t \geq \frac{\ln x}{a} \end{cases} \tag{36}$$

However, since we are interested in $\rho(x,t)$ for a fixed time t, (36) can be equivalently and more conveniently written as:

$$u_{(\frac{\ln x}{a})}(t) = \begin{cases} 0, x \geq e^{at} \\ 1, x < e^{at} \end{cases} \tag{37}$$

The biological assumption is that the number of cells in metastases is always less than the number of cells in the primary tumour. From (28) and (37), we see that $x = x_p$. From the biological assumption, we conclude that $u_{(\frac{\ln x}{a})}(t) = 1$ for all defined regions of $\rho(x,t)$. We continue from (35):

$$\rho(x,t) = \frac{mx^{-1}}{a}e^{(a\alpha+m)(t-\frac{\ln x}{a})} = \frac{mx^{-1}}{a}e^{(a\alpha+m)t}e^{-(\alpha+\frac{m}{a})\ln x}$$
$$= \frac{mx^{-1}}{a}e^{(a\alpha+m)t}x^{-(\alpha+\frac{m}{a})} = \frac{m}{a}x^{-\alpha-\frac{m}{a}-1}e^{(a\alpha+m)t} \tag{38}$$

which is the analytic solution to the McKendrick-von Foerster equation using an exponential growth rate.

For Gompertzian growth rate, obtaining an analytic solution is more difficult. After applying the method of Laplace transformation to the PDE with $g(x) = ax\ln\frac{b}{x}$, we have the following for the colony size distribution, described in Iwata et al. [2]:

$$\rho(x,t) = \frac{a}{mb^{\alpha}x\log b}\sum_{k=1}^{\infty}e^{a\lambda_k t}(1-\frac{\log x}{\log b})^{\lambda_k-1}\frac{1}{c(\lambda_k)} \tag{39}$$

where

$$c(\lambda_k) = \sum_{n=0}^{\infty}\frac{(-\alpha\log b)^n}{n!(\lambda_k+n)^2} \tag{40}$$

and λ_k satisfies the following equation:

$$\frac{a}{m}\lambda_k = \sum_{n=0}^{\infty}\frac{(\alpha\log b)^n}{(\lambda_k+1)(\lambda_k+2)...(\lambda_k+n)} \tag{41}$$

The RHS of the condition for λ_k is a confluent hypergeometric function. Because this function itself is difficult to study, the analytic solution for the PDE with Gompertzian growth rate is not useful. Therefore, a numerical method of solving the PDE is crucial.

2.3 Solution Using the Method of Characteristics

The motivation for solving the McKendrick-von Foerster equation using the method of characteristics is to obtain a numerical scheme that can be used for simulation *in silico*. In order to solve a linear PDE (the McKendrick-von Foerster equation is one such case) using the method of characteristics, we must put it in the following form:

$$F(\boldsymbol{D}u, u, x) = \boldsymbol{b}(x)\cdot\boldsymbol{D}u(x) + c(x)u(x) = 0 \tag{42}$$

where $\boldsymbol{D}u(x)$ is the gradient vector of $u(x)$. We proceed to rewriting the PDE in the above form:

$$\begin{aligned}\frac{\partial \rho(x,t)}{\partial t} + g(x)\frac{\partial \rho(x,t)}{\partial x} + \rho(x,t)\frac{dg(x)}{dx} &= 0 \\ \begin{bmatrix} g(x) \\ 1 \end{bmatrix} \cdot \boldsymbol{D}\rho(x,t) + \rho(x,t)\frac{dg(x)}{dx} &= 0 \end{aligned} \tag{43}$$

For simplicity, we will denote $\dot{x}(\cdot) = \frac{dx(\cdot)}{d\cdot}$. As a result, we have the following system of equations with parameter s:

$$\begin{cases} \dot{x}(s) = g(x(s)) \\ \dot{t}(s) = 1 \\ \dot{\rho}(x(s), t(s)) = -\rho(x(s), t(s))\dot{g}(x) \end{cases} \tag{44}$$

From $\dot{t}(s) = 1$, we have $t(s) = s$ for all s. Thus, the other two equations in the above system can be simplified to:

$$\begin{cases} \dot{x}(t) = g(x(t)) \\ \dot{\rho}(x(t)) = -\rho(x(t))\dot{g}(x) \end{cases} \tag{45}$$

Now, we solve for $x(t)$ with the given initial condition $x(s) = x_0$, and we prescribe $g(x) = ax\ln(\frac{b}{x})$, the Gompertzian growth law:

$$\frac{dx}{dt} = ax\ln(\frac{b}{x}) = ax[\ln b - \ln x]$$
$$\frac{dx}{x[\ln b - \ln x]} = adt$$

Make the substitution $u = \ln x$, thus $du = \frac{1}{x}dx$:

$$\frac{du}{\ln b - u} = adt$$
$$\int \frac{du}{\ln b - u} = \int adt$$
$$-\ln[u - \ln b] = at + C_1$$
$$u - \ln b = K_1 e^{-at}$$
$$\ln x - \ln b = K_1 e^{-at}$$
$$\ln(\frac{x}{b}) = K_1 e^{-at}$$

From initial condition, we have $K_1 = e^{as}\ln(\frac{x_0}{b})$. Thus:

$$\ln(\frac{x}{b}) = e^{as}\ln(\frac{x_0}{b})e^{-at} = \ln(\frac{x_0}{b})^{e^{-a(t-s)}}$$
$$x(t) = b(\frac{x_0}{b})^{e^{-a(t-s)}} \tag{46}$$

We can now solve for $\rho(x(t))$ according to the relationship given in (45), which written explicitly is:

$$\frac{d\rho(x(t))}{dt} = -\rho(x(t))\frac{dg(x(t))}{dx}$$
$$\frac{d\rho(x(t))}{\rho(x(t))} = -\frac{dg(x(t))}{dx/dt}$$

Recall that $g(x(t)) = \frac{dx}{dt}$. Thus, the equation becomes:

$$\frac{d\rho(x(t))}{\rho(x(t))} = -\frac{dg(x(t))}{g(x(t))}$$
$$\int \frac{d\rho(x(t))}{\rho(x(t))} = -\int \frac{dg(x(t))}{g(x(t))}$$
$$\ln(\rho(x(t))) = -\ln(g(x(t))) + C_2$$
$$\rho(x(t)) = \frac{K_2}{g(x(t))} = \frac{K_2}{ax(t)\ln(\frac{b}{x(t)})}$$

From the initial condition, and suppose that $\rho(x_0, s)$ is given, we have:

$$\rho(x_0, s) = \frac{K_2}{ax(s)\ln(\frac{b}{x(s)})} = \frac{K_2}{ax_0\ln(\frac{b}{x_0})}$$
$$K_2 = \rho(x_0, s)ax_0\ln(\frac{b}{x_0})$$

Thus, the equation for $\rho(x(t))$ becomes:

$$\rho(x(t)) = \frac{\rho(x_0, s)ax_0\ln(\frac{b}{x_0})}{ax(t)\ln(\frac{b}{x(t)})}$$

Recall that $x(t) = b(\frac{x_0}{b})^{e^{-a(t-s)}}$. Making the substitution, the above equation becomes:

$$\begin{aligned}\rho(x(t)) &= \frac{\rho(x_0, s)ax_0\ln(\frac{b}{x_0})}{ab(\frac{x_0}{b})^{e^{-a(t-s)}}\ln(\frac{b}{b(\frac{x_0}{b})^{e^{-a(t-s)}}})} \\ &= \rho(x_0, s)e^{a(t-s)}(\frac{x_0}{b})^{1-e^{-a(t-s)}} \end{aligned} \tag{47}$$

3 Numerical Analysis

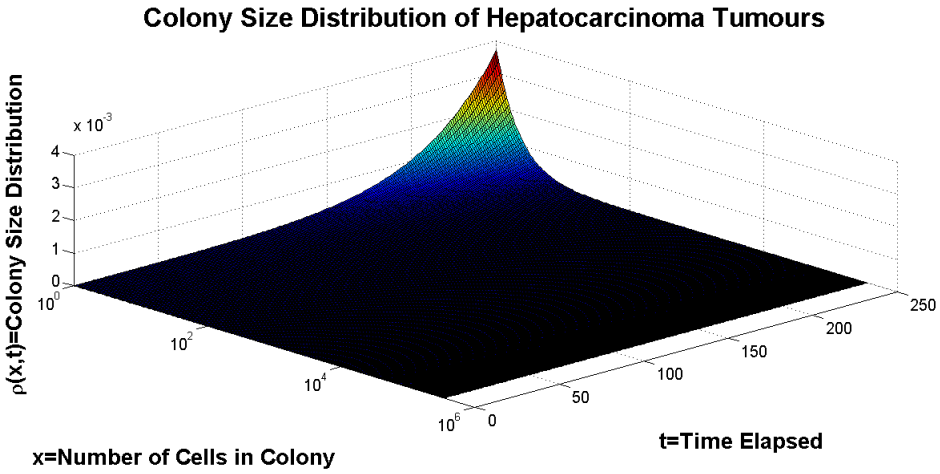
3.1 Numerical Scheme

From the parametric solution using the method of characteristics, Barbolosi et al. have formulated a numerical scheme for the model for which t is discretized from t_0 to t_i and x is discretized from x_0 to x_n [3]. Additionally, $x_n = x_p(t_n)$ where $x_p(t)$ is the solution to the Gompertzian growth equation. As such, ρ_i^n denotes the point (t_i, x_n). The numerical scheme is as follows:

$$\begin{cases} \rho_i^1 = 0, \quad 2 \le i \le N+1 \\ \rho_1^1 = \frac{1}{g(1)}\beta(x_p(0)) \\ \rho_i^n = 0, \quad i = n+2, ..., N+1 \\ \rho_i^{n+1} = \rho_{i-1}^n e^{ak} f_{i-1}, \quad i = 2, 3, ..., N+1, \quad n = 1, 2, ..., N \\ \rho_1^{n+1} = \frac{1}{g(1)}\beta(x_p(t_{n+1})) + \frac{1}{g(1)}\sum_{i=2}^{N} h_i\beta(x_i)\rho_i^{n+1}, \quad n = 1, ..., N \end{cases} \tag{48}$$

where $f_i = (\frac{x_i}{b})^{1-e^{-ak}}$ and $h_i = x_i - x_{i-1}$. Henceforth, we will use clinical values for hepatocarcinoma such that $a = 0.00286, b = 7.3 \times 10^{10}, \alpha = \frac{2}{3}, m = 5.3 \times 10^{-8}$ [3]. Figure 1 shows the surface plot of the colony size distribution for 250 days for these values.

Figure 1: Colony Size Distribution



3.2 Colony Growth Dynamics

While the surface plot tells much about colony size distribution as a function of time and size, it provides little information regarding how detectable tumour colonies evolve over time. Rather than studying the surface plot, we look at the total number of colonies over a specific range of colony sizes. Particularly, we are interested in the following integral:

$$N_\gamma(t) = \int_\gamma^b \rho(x,t)dx \tag{49}$$

where γ is the minimum detectable size given in number of cancer cells per colony and b is the carrying capacity of the system given by clinical data. Figure 2 plots $N_1(t)$, the total number of colonies in the system, and a decomposition showing contributions from the primary tumour and metastatic tumours for hepatocarcinoma.

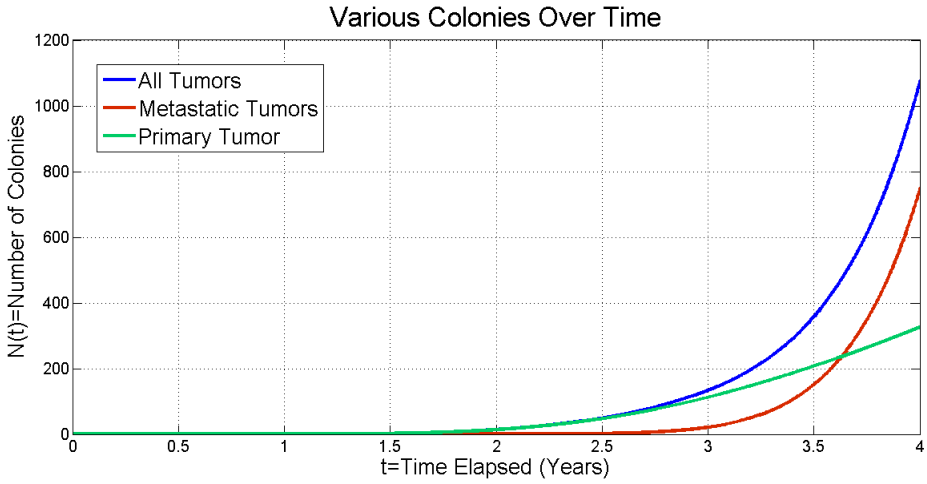
At small times, the contribution to the total number of colonies from the primary tumour is dominant while at large times, that of metastatic tumours is dominant. This observation reaffirms the notion that metastatic tumours arise from the primary tumour as well as other metastatic tumours.

3.3 Radiation Therapy Treatment

Clinical data reveals that the smallest detectable colony has 10^9 cells. Suppose our radiation therapy treatment kills 99% of all detectable colonies. Figure 3 graphically describes the total number of colonies and the number of detectable colonies over time as a result of treatment at 3 and 5 years.

Figure 3 (a) not only shows that the number of detectable colonies is small compared to the total number of colonies, but also presents the surprising result that treatment at a later stage of cancer (5 years) would kill more colonies than treatment at an earlier stage (3 years). The blue and red curves in this figure, indeed, do not converge or intersect. The reason for the unexpected effectiveness of treatment at 5 years is that by then, more colonies have grown to detectable sizes, which results in more colonies being killed. To emphasize the significance of this observation, Figure 3 (b) shows that before approximately 1.69 years, almost no colony

Figure 2: Various Colonies Over Time



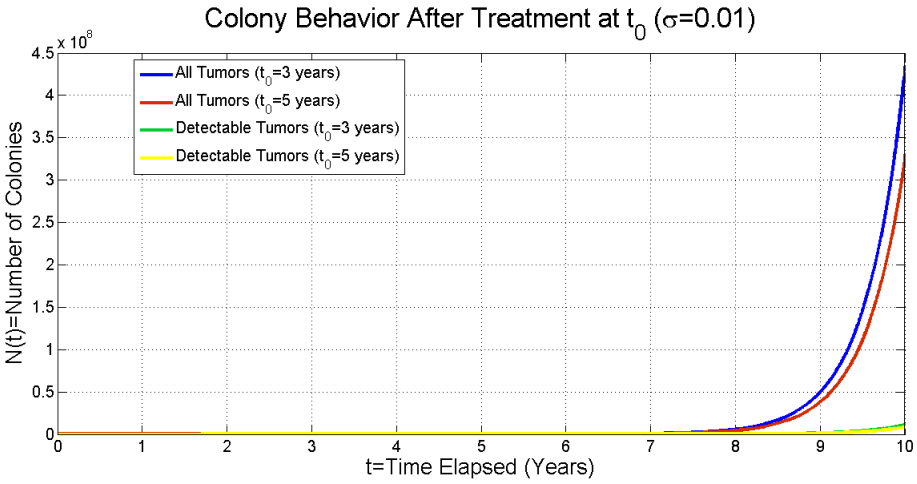
can be detected. As a result, diagnosis of cancer and its subsequent treatment cannot begin until a later time.

4 Discussion

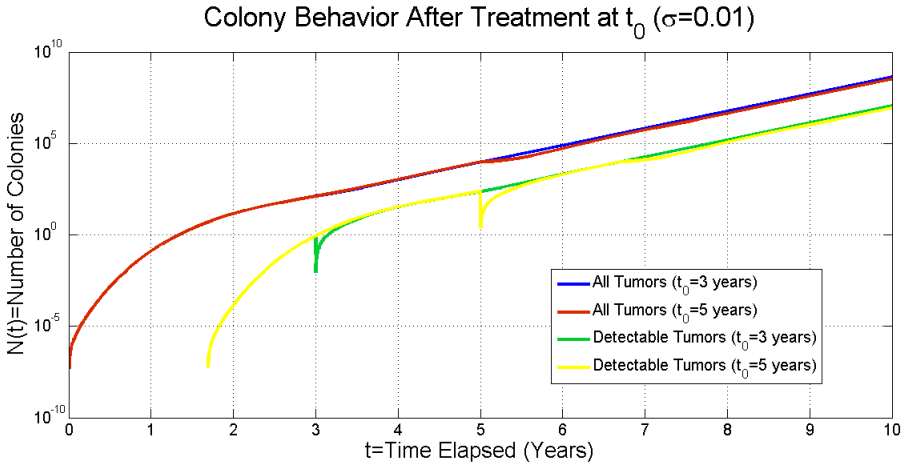
Through computer simulation of cancer growth with radiation therapy, we demonstrated that the number of tumour colonies as a result of the primary tumour dominates at small times while those as a result of metastatic tumours dominate at large times. Because metastatic tumours initially originate from the primary tumour, the ideal radiation therapy treatment option would be to target the primary tumour before it metastasizes. However, because current medical technology only allows detection of colonies whose size is at least 10^9 cells, treatment cannot begin until at least one colony has grown to this size. At the time when this occurs, the primary tumour often has already metastasized, complicating treatment. For instance, the red and blue curves in figure 3 (b) show that hepatocarcinoma begins to metastasize at 1.34 years (the red and blue curves' intersection with $N(t) = 10^0$). Ideally, treatment with radiation therapy should take place before this time. However, in the same figure, we see that even the primary tumour has not achieved detectable size according to the yellow and green curves; the earliest time for detection is not until 1.69 years, at which time metastatic activity has already commenced. One option is to improve detection capability, thus allowing for earlier treatment. Another option is to use alternative means of qualifying the presence of tumour colonies and use chemotherapy, which targets systemically, for treatment.

An interesting observation from the simulation is the advantage of radiation therapy treatment at a later time. From figure 3, we see that at large times, the number of colonies with a treatment at 3 years is greater than that with a treatment at 5 years (the blue and red curves do not converge nor intersect at large times). This is in fact not surprising because only a small number of colonies are detectable, thus treatable, at 3 years while that number is considerably larger at 5 years. With treatment defined as killing 99% of all detectable tumour colonies, greater number of colonies available for targeted treatment at 5 years compared to 3 years leads to more thorough killing. However, this does not contradict the effectiveness of treatment before metastasis. Treatment at large times only eliminates the number of tumours, but since metastasis is the cause of health complications and subsequent death for cancer patients, preventing metastasis should be the priority. Generally, radiation therapy treatment is given multiple times over a long period, which would help eliminate large number of tumours. To address the issue of metastasis, a hybrid treatment of chemotherapy and radiation therapy could be administered to prevent rapid growth of metastases for undetectable tumours, which would potentially lead to at least better treatment outcome if not a cure.

Figure 3: Colonies After Treatment



(a) Normal Viewing Window



(b) Log Viewing Window

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