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Mathematical Modeling of Cancer Cell Population Doubling Time and Cell-Cycle Time

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Abstract- Mathematical models, that depict the dynamics of a cancer cell population growing out of the human body (in vitro) in unconstrained microenvironment conditions, will be considered in this thesis. Cancer cells in vitro grow and divide much faster than cancer cells in the human body, therefore, the effects of various cancer treatments applied to them can be identified much faster. These cell populations, when not exposed to any cancer treatment, exhibit exponential growth that we refer to as the balanced exponential growth (BEG) state. This observation has led to several effective methods of estimating parameters that thereafter are not required to be determined experimentally.A mathematical description of the cell-cycle control is shown for one-compartment and two-compartment populations, where a compartment refers to a cell population consisting of cells that exhibit similar kinetic properties. We have incorporated into our mathematical model the required growing/aging times in each phase of the cell cycle for the biological viability. Moreover, we have derived analytical formulae for vital parameters in cancer research, such as population doubling time,the average cell-cycle age, and the average removal age from all phases, which we argue is the average cell-cycle time of the population. One option to extend this model would be to derive the cell-cycle time from a single experimental measurement.

Key Words - Cancer, Balanced Exponential Growth (BEG), Cell-cycle. Population doubling time,average cell cycle age, in vitro, in vivo.Based Anonymization, Big Data Privacy.

I. INTRODUCTION

A cell cycle is a progression of a cell through steps of growth and chromosome duplication to complete cell division. The cell cycle of a eukaryotic cell is traditionally divided in four phases - G1, S , G2 and M. Phases G1, S and G2 together are called the interphase. A gap phase G1 (G for gap) is an interval before the DNA synthesis (S -phase) that is followed by another gap phase named G2, where the cell keeps growing until mitosis takes place (M-phase). A cell cycle consists of various cyclins and cyclin-dependent kinases that have to react at certain cell-cycle control checkpoints. During its cell cycle, a cell makes two vital decisions: first, the decision of "entering into S -phase" is made in late G1-phase, called G1 checkpoint. DNA replication begins when the cell is ready to undergo the entire cell cycle. Second decision is the "entry into mitosis", mitosis will proceed through all its stages once initiated, called G2 checkpoint. The cell-cycle control system, the key proteins of the control system, initiates and controls the progression of the cell cycle and can arrest it at specific checkpoints. Cells in a cell cycle are called dividing or proliferating cell. If a cell is non-dividing or quiescent it is said to be in G0-phase. A cell in G0-phase can return to the G1-phase again under the influence of mitogenic signals

(growth factors, tumor viruses etc.), A diagram outlining cell-cycle control with key checkpoints is shown in Figure 1.1. Some non-dividing cells like neurons and skeletal muscle fibre cells are unable to re-enter the cell cycle. Others, like fibroblasts and lymphocytes are ordinarily in the G0 - phase but can be activated by external agents.

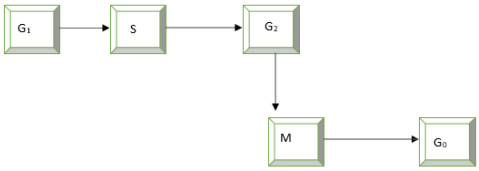


Figure 1.1: The cell-cycle control diagram. During

G1-phase cell grows then DNA is replicated and new chromatin is formed, denoted as S -phase. During G2-phase cell prepares for mitosis or M- phase, where it divides into two daughter cells. A cell passing through the cell-cycle control checkpoints in G1 and G2 phases and completing cell division is called proliferating. G0 depicts the non-proliferating cell phase.

III. METHODOLOGY

Our mathematical model is initially designed to depict the growth of cancer cell population in the BEG state, i.e., population that has not been exposed to any cancer treatment. We assume that all cells in the population are proliferating and can be viewed as subdivided among phases G1, S , G2, and M. Due to presented experimental data, we combine subpopulations in G2 and M phases and refer to it as G2M-phase. Cells move from one phase to the next with a certain transition probability rate (r). Age (τ) is considered to be the time spent by a given cell in its current phase. Thus, each cell is at age zero when entering into a new phase of cell growth. No cells are in the non-proliferating state or G0-phase. Although cells from cell lines exhibit immortality properties, we have incorporated a probability of apoptosis in each phase (μ). Figure 1.2 presents a schematically illustrated cancer cell population in BEG.

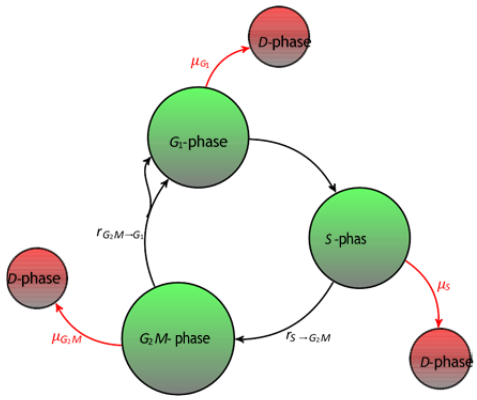


Figure 1.2: Diagram of the cell-cycle control of in vitro (outside the body) tumour cells showing the proportions in each phase.

In our model, cell cycle is subdivided into three phases: G1, S , and G2M (with combined phases G2 and M because we apply our model to flow cytometry [FC] profiles, and FC measurements cannot distinguish between G2 and M phases because DNA contents in both phases are twice that of S -phase). E a c h cell has age zero when entering into a new phase of cell growth.

Let us assume that there is a continuous function n(t, τ) that represents the number density of the cancer cell population and is a vector quantity, with

$$n(t,\tau) = [nG_1(t,\tau) \quad nS(t,\tau) \quad nG_2M(t,\tau)]^T . \quad (1)$$

Here vector components np(t, τ) with p ∈ {G1, S, G2M} are continuous functions, where
np : [0, ∞) ×[0, T) → [0, ∞), that shows the number density of cells with age τ at time t in a cell cycle phase p. Age τ states the duration of a cell in particular phase p. Let us assume that the probability rate at which cells leave phase p is given by term bp(t, τ). Assumptions that the transition probability depends on time t and age τ and is a non-negative piecewise continuous function, are comprehensible in biological terms. Here, transition rate bp(t, τ) with: p ∈ {G1, S, G2M} is defined as follows:

bG1 (t, τ) = rG1→S (t, τ) + μG1 (t, τ), bS (t, τ) = rS →G2 M (t, τ) + μS (t, τ),
bG2 M (t, τ) = rG2 M→G1 (t, τ) + μG2 M (t, τ),
where rG1→S (t, τ), rS →G2 M (t, τ), and rG2 M→G1 (t, τ) are the transition probability rates (probability

per time unit per cell) between two consecutive phases and μp(t, τ) depicts the death rate from the phase
p.
We also assume that cancer cells taken from cancer cell lines have a potential undergoing apoptosis at any phase of the cell cycle. The conservation law states that the variation of the population number density in p phasein time is caused by a transition to the next phase or death; thus, the following linear partial differential equation can be derived:
$\partial n\ (t, \tau) + \partial n\ (t, \tau) = -b\ (t, \tau) n\ (t, \tau)$
$\partial t \quad p$
$\partial \tau \quad p$
$p \qquad p$

Conservation between the various phases and the death phase, which is not explicitly modelled, follows from the continuity of the derivatives on the domain.
Additional conditions for equation (3) are provided: the initial number density distribution and renewal condition (also called Lotka equation) for each phase. The initial age distribution is defined as:
$np(t = 0, \tau) = n0(\tau)$ (4)
with the initial distribution $n0(\tau)$ in (L1 ∩ L∞)[0, T).
All cells at age zero have transferred from the previous phase and are expressed as follows:

np
$(t, \tau = 0) = \int T\ a$
$p-1$
$(t, \tau) np-1$
$(t, \tau) d\tau$
where transition rate ap(t, τ) with p ∈ {G1, S, G2M} is defined as:
aG1 (t, τ) = rG1→S (t, τ), (6)
aS (t, τ) = rS →G2 M (t, τ), aG2 M (t, τ) = 2rG2 M→G1 (t, τ).

Cells are presumed to be in the G1-phase immediately after division. Here, subscript p −1 in equation
(5) is taken to signify the following:
G1 − 1 = G2M; S − 1 = G1; G2M − 1 = S.
We note that for the G1 - phase, the renewal condition (5) is as follows:
$n \qquad (t, \tau = 0) = \int T\ 2r$
$(t, \tau) n$
$(t, \tau) d\tau$
$G1$
0 $G2M \rightarrow G1$
$G2M$

where 2 refers to each cell that has completed mitosis producing two daughter cells.
It is assumed that rp→p+1, μp ∈ C−1([0, ∞) ×[0, T)) for all p ∈ {G1, S, G2M}, and, in addition, they are bounded and strictly positive. We also assume that derivatives of rp→p+1(t, τ) and μp(t, τ) for all p ∈ {G1, S, G2M} are bounded and piecewise continuous in t and τ. Finally, we assume that there exists a positive lower bound. Note that for biological realism, we also assume μp(t, τ) is non- negative. The simplicity of the model is due to the linearity that is present when dealing with a cancer cell population that grows in vitro exponentially without any environmental constraints. We provide the analytical solution of the problem (3) - (5) and show the condition for the existence of such solution. We impose change in variables: now arguments t and τ depend on parameter z. Thus, the number density function can be rewritten as follows:

$np(z) = np(t(z), \tau(z)$ (8)

Hence, the derivative of n¯ (z) with respect to new variable z can be expressed as follows:

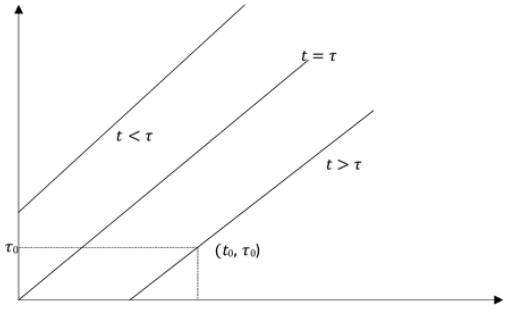
$dn \qquad d$
$= \qquad n$
$(t(z), \tau(z) = \partial np\ dt + \partial np\ d\tau$
$dz \qquad dz \quad p$
$\partial t\ dz \quad \partial \tau\ dz$

Where z varies along the characteristic cell lines:
$dt = 1, d\tau = 1$ (9)
$dz \qquad dz$
▪=z+1 (10)

Equation 3.3.3 can be written as.
$dnp\ (z) + b\ (t(z), \blacksquare(z) n\ (z) = 0 \qquad dz \qquad p \qquad p$

We choose point(t0,, ▪0) along the characteristic line (9). This point can be any point in the first quadrant as shown in figure 2.1 Thus the following expressions are derived.

$t = t0 + z.$ ▪ = ▪0 + z



$np(t, \tau = 0)$

For simplicity, we define the number density function np at point (t0, τ0) as np(t0, τ0) = n0. Therefore, equation (11) can be solved by integrating along the characteristic lines as follows:

np
$(z) = n0$
$e- \int z\ bp(t(\xi),\tau(\xi)d\xi$
$e- \int z\ bp(bp(t0+\xi,\tau0+\xi)d\xi=n0e$
$- \tau0+z\ b\ (s+t\ -\tau\ ,s)ds$ 0

Where $s = \tau0 + \xi$. Further we divide analysis of the solution into two cases: $t < \tau\ and\ t > \tau$ as depicted in figure 2.1. In this case $t < \tau$ we express solution $np(z)$ as:

$t = 0 + z, \tau = \tau0 + z$
$- \int \tau0+z\ bp(s-\tau0,s)ds$
$np(z) = np(z, \tau0 + z) = np(0, \tau0)e\tau0$

Thus the number density $np(t, \tau)$ for the case $t < \tau$can be expressed as follows:

$- \int \tau\ \ bp(s+t-\tau,s)ds$
$n(t, \tau) = np(0, \tau - t)e$ $\tau-1$, $t < \tau$ (13)

We note that the analytical solution of the problem (3) – (5) in the case of $t > \tau$, portrays the growth of the cancer cell population taken from the cancer cell line culture i.e the time it takes for the cell population to grow is longer than the age ▪ that the cells have to spend in phase p for the case $t > \tau$ and solution of n¯p (z) is as follows:

t = t0 + z, τ = z,
$\hat{n} = np(t0 + z, z) = np(t0, 0)e$
$- \int z\ bp(s+t0,s)ds$

Here, the variable change gives us cell number density function np(t, τ), for the case t > τ, as:
$- \tau\ b\ (s+t-\tau,s)ds$
$np(t, \tau) = np(t - \tau, 0)e$
$\int 0\ p$
, $t > \tau$ (14)

Thus, by using the renewal condition (5), equation (14) can be rewritten in its general form as a representation of the asymptotic solution of the problem (3) - (5) as follows:

T $- \tau\ b\ (s+t-\tau,s)ds$

$np(t, \tau) = \int 0\ ap-1(t - \tau, s)np-1(t - \tau, s)ds\ e$
$\int o\ p$
, $t > \tau$
. In more general notation, McKendrick - von Foerster equation (3) can be rewritten as:

∂ ∂
n(t, τ) + n(t, τ) = −Dout(t, τ)n(t, τ), 0 < t < ∞,
∂t ∂τ 0 < τ < T, (16)

with respective side conditions defined as follows:

n(t = 0, τ) = n0(τ), initial age distribution, (17)
$\boldsymbol{n}(t, \tau = 0) = \int \boldsymbol{T}\ \boldsymbol{D}$ $\boldsymbol{t}, \boldsymbol{\tau}\ \boldsymbol{n}\ t, \tau\ d\tau, t > 0$ renewal distribution, (18)
$\boldsymbol{in}$( ) ( )

The matrix Dout represents the loss of cells from the various phases via death and transfer to other phases, and is defined as:

$\boldsymbol{D}out(t, \tau) = [$

$rG1\rightarrow s+\mu G1$ 0 0
0 $rs\rightarrow G2M+\mu s$ 0
0 0 $rG2M\rightarrow G1+\mu G2M$
$] (t, \tau)$ (19)

The renewal matrix Din represents the gain of cells at age τ = 0 in each phase and is caused by transfer from other phases. Din is defined as:

0 0 $2rG2m\rightarrow G1$
$\boldsymbol{D}in(t, \tau)$ = [$rG1\rightarrow s$ 0 0
0 $rs\rightarrow G2M$ 0
] (t, τ) (20)

Transition rates rp→p+1 and μp for p ∈ {G1, S, G2M}, with the cell- cycle control depicted in Figure
1.2. Solution to the governing differential equation (16) along the characteristic lines, already
expressed for each component of vector function n(t, τ) in equations (13) and (14), is as follows:

$\boldsymbol{n}(t, \tau)$ = [
$exp(-\int\tau$
$\boldsymbol{D}out$
$(s + t - \tau, s)ds)n(\tau - t)$, $0 \le t \le \tau$,
$exp(-\int\tau\ \boldsymbol{D}$ $(s + t - \tau, s)\ ds)n(t - \tau, 0)$, $0 \le \tau \le t$,
$\boldsymbol{out}$

Analytical solution of McKendrick-von Foerster equation (16) assumes that the solution on the boundary τ = 0 has been given. However, in our problem, we are given the renewal boundary condition (18). Substituting the formal solution from (21) into the boundary condition (18) gives us a Volterra integral equation of the second kind for n(t, 0):
$\boldsymbol{n}(t, 0) = \boldsymbol{\mathcal{F}}(t) + \int t\ K(t, s)\boldsymbol{n}(s, 0)ds$(t) (22)
where
$\mathcal{F}(t) = \ T\ D\ (t, \tau)exp(-\ \tau\ D\ (s + t - \tau,$
$s)ds)n0\ (\tau - t)d\tau$ (23)

$\int t$
in
$\int\tau-1$
out
and kernel of integro-equation is defined as follows:
$k(t, s) = \boldsymbol{D}$
in
$(t, t - s)$exp(−
$t-s$
$\int 0$ $\boldsymbol{D}$
out
$(\xi + s, \xi)d\xi)$ (24)

By the assumptions made in our problem, we know that Dout (t, τ) and Din (t, τ) are piecewise continuous: therefore, K(t, s) is piecewise continuous. Furthermore, because the components of n0(τ) are in (L1 ∩ L∞)[0, T) and the components of Din(t, τ) are bounded, we find that F(t) exists. We observe, by the piecewise continuity of Dout and Din, that F(t) is continuous.

Because kernel K(t, s) is piecewise continuous, we use method of continuation to first establish existence and uniqueness in some interval [0, T1], and then show that this solution can be continued to successive intervals [T1, T2], [T2, T3],and so on. Eventually the whole interval [0, T) is covered. We rewrite kernel K(t, s) as p(t, s)k(t, s), where k(t, s) is continuous and p(t, s) represents the piecewise continuous part (effectively p(t, s) is the same as equation
(24)); thus, we may apply the existence and uniqueness theorem from Linz (1985):

When the kernel is unbounded (or has some irregular behaviour) it is often convenient to rewrite linear second kind Volterra equation $f(t) = g(t) + \int t\ k(t, s)f(s)ds$, as follows:

t
$f(t) = g(t) + \int\ p(t, s)k(t, s)f(s)ds$,
0
where p(t, s) represents the part with the non-smooth behaviour. which tells us there is a unique continuous solution to equation (22) on [0, T) for any T > 0.
Theorem 1. There exists a unique non-negative solution n(t,τ) (along characteristic lines) to problem (16) such that each component of n(t, τ) belongs to (L1 ∩ L∞)([0, ∞) × [0, T)) for any T > 0, and each component of n(t, ·) belongs to (L1 ∩ L∞)[0, ∞) for all t ≥ 0. The solution is given by equation (21), where n(t, 0) is continuous for all t ≥ 0.

IV.CONCLUSION

In this paper, investigation of the age-structured models has led to the derivation of biologically significant parameters describing the dynamics of an

exponentially growing cancer cell population. We shall show the relationship between the average cell-cycle time (also called the average cell-removal time) and the population doubling time, where the cell-cycle time of the population is greater or equal to the population doubling time. This result is of great interest to biologists, as they generally assume that the cell-cycle time is always equal to the population doubling time.

We have proven the existence of the balanced exponential growth state for the age- structured model with piecewise continuous transition rates. For the case of piecewise constant tran- sition rates, we have derived analytical formulae for the population distribution among the cell-cycle phases, the average cell age and the expected (average) removal time for the population in BEG. We note that the average age of the cells removed from all phases is the average cell-cycle time. We shall show that a delay differential equation system can be obtained from the age-structured model with piecewise constant transition rates. We shall present the reduction of the age-structure model to the ordinary differential equation model and thereafter apply it in the analysis of the cancer cell population response to various cancer treatments. A study of a case of piecewise linear transition rates, would provide a further generalisation of the model.

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