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Application of Integro-Differential Equation in Periodic Chemotherapy

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Abstract - In this paper, the presentation will be on existing model called integro-differential equation of tumor growth that accounts for cell cycle arrest and cell death induced by periodic chemotherapy. Necessary and sufficient conditions for the global stability of the cancer –free equilibrium are derived, and conditions under which the system evolves to periodic solutions are determined.

Keywords- Chemotherapy, logistic growth, delay differential, periodic solution, stability analysis.

I. INTRODUCTION

In this paper, analyze the following equation which models the response of a population of tumor cells to periodic treatment with chemotherapy:

$\frac{dN}{dt}$=N(1-N-$\int_{t-a_r}^{t} \alpha(u) e^{-\rho(u)(t-u)} N(u)du$)- α(t)N. (1)

Define the functional f: $\mathbb{R}\times\mathbb{C}[-a_r,0]\rightarrow \mathbb{R}$ as

f(t,N(.))=$\int_{-a_r}^{0} \alpha(t+u) e^{-u\rho(t+u)} N(u)du$.

Define , $N_t(.) \in \mathbb{C}[-a_r,0]$ as

$N_t(x)$= N(t+x).$\int_{t-a_r}^{t} \alpha(u) e^{-\rho(u)(t-u)} N(u)du$=f(t,$N_t(.)$).Equation ,is rewritten as

$\frac{dN}{dt}$=N(1-N-f(t,$N_t(.)$))-α(t)N. (2)

This equation is called a non-local delay differential equation.

- N(t) represents the number of tumor cells at time t.
- Cells are grow logistically in the absence of treatment and chemotherapy with period τ .
- α(t) represents the rate of cell arrest with period τ.
- The integral term represents the number of cells in the arrested state at time t.
- The proliferating cells die at a rate ρ(t).

The stability of the trivial solution N(t)=0 of equation 2, corresponding to a cancer free equilibrium. Using above techniques, prove existence of a periodic solution, when the cancer free equilibrium is unstable. Finally, conclude with a brief discussion.

II. PRELIMINARIES

A. Integro - Differential Equation

In mathematics, an integro- differential equation is an equation that involves both integrals and derivatives of a function [5].

B. Delay Differential Equation

In mathematics, delay differential equations (DDEs) are a type of differential equation in which the derivative of the unknown function at a certain time is given in terms of the values of the function at previous times.A general form of the time-delay differential equation for $x(t) \in \mathbb{R}^n$ is $\frac{d}{dt}x(t)=f(t,x(t),x_t)$, where $x_t=\{x(\tau):\tau\leq t\}$.

a) Examples

- Continuous delay

$\frac{d}{dt}x(t)=f(t, x(t),\int_{-\infty}^{0} x(t+\tau)d\mu(\tau))$

- Discrete delay

$\frac{d}{dt}x(t)=f(t,x(t),x(t-\tau_1),\ldots,x(t-\tau_m))$ for $\tau_1,\ldots,\tau_m\geq 0$.

- Linear with discrete delay

$\frac{d}{dt}x(t)=A_0x(t)+A_1x(t-\tau_1)+\ldots+A_mx(t-\tau_m)$, where $A_0,\ldots,A_m\in\mathbb{R}^n\times^n$.

C. General First Order Linear Equation

The general first order, linear integro-differential equation is of the form,$\frac{d}{dx}u(x)+\int_{x_0}^{x} f(t,u(t))dt= g(x,u(x))$, $(x_0)=u_0$ $x_0\geq 0$.

III. ANALYTICAL RESULTS

Let $\bar{\alpha}=1/\tau \int_0^\tau \alpha(t)dt$.

Numerical simulations of,

$\frac{dN}{dt}$= N(1-N-f(t, $N_t(.)$)-α(t)N.

Now, when $\bar{\alpha}>1$, $\lim_{t\to\infty} N(t)=0$.

To prove the global stability of the trivial solution N=0 for $\bar{\alpha}\geq 1$.

When $\bar{\alpha}< 1$, the system evolves to a periodic solution.

Assume, $N(t)\geq 0$ for $t< 0$ and $0<N_0=N(t=0)\leq 1$, where 1 is the carrying capacity of equation 2,in the absence of treatment.

From equation 2,N(t) =N_0 exp($\int_0^t\{1-N(s)-$f(s,$N_s(.)$)$-\alpha(s)\}ds$)

A. Stability Of The Cancer Free Equilibrium

Lemma 1-Let $\bar{\alpha}\leq 1$. Then N=0 is a globally stable fixed point of$\frac{dN}{dt}$=N(1-N-f(t,$N_t(.)$))-α(t)N.

Proof: For any $\zeta\in[0,\tau]$,and for any integer $n\geq 1$.

$\int_\zeta^{\zeta+\tau} dN/N=\int_0^\tau(1-\alpha(t))t-\int_\zeta^{\zeta+\tau}$(f(t,$N_t(.)$)+N)dt

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$\Rightarrow N(\zeta+\tau)=N(\zeta)e^{\tau(1-\bar{\alpha})}e^{-\int_{\zeta}^{\zeta+\tau}(f(t,N_t(.))+N)dt}$.

$\Rightarrow N(\zeta+n\tau)=N(\zeta)E_n(\bar{\alpha})A(\zeta)B_n(\zeta)$

Where, $E_n(\bar{\alpha})=e^{n\tau(1-\bar{\alpha})}$, $A(\zeta)=e^{-\int_{\zeta}^{\tau}(f(t,N_t(.))+N)\,dt}$ and $B_n(\zeta)=e^{-\int_{\tau}^{n\tau}(f(t,N_t^{(.)})+N)dt}$.

Claim: $\lim_{n\to\infty} N(\zeta+n\tau)$.

Case (1): $\bar{\alpha} > 1$

Now, $\bar{\alpha} > 1, \Rightarrow \lim_{n\to\infty} E_n(\bar{\alpha})=0$.

Additionally, $\alpha(t), N(t)\geq 0$.

$\Rightarrow A(\zeta), B_n(\zeta)\leq 1$.

Therefore from above equation,

we have, $\lim_{n\to\infty} N(\zeta+n\tau)=0$.

Case (2): $\bar{\alpha}=1$.

When $\bar{\alpha}=1$, $\lim_{n\to\infty} E_n(\bar{\alpha})=1$.

Let $\lim_{T\to\infty}\int_{\tau}^{T}(f(t,N_t(.))+N)dt=k$, where $k>0$.

Now, suppose that $k<\infty$. Then, $\lim_{n\to\infty} N(\zeta+n\tau)=\eta(\zeta)$, where $0<\eta(s)=k(N(\zeta)A(\zeta)$ is continuous on $[0,\tau]$.

As $A(\zeta)$ and $B_n(\zeta)$ are exponentials with negative exponents, the sequences $\{N(\zeta+n\tau)\}, \zeta\in[0,\tau]$ decrease monotonically , and deduce that $N(t)\geq\eta_{min}\forall t$.This contradicts original assumption that k is finite: if N(t) is bounded from zero then,

$\lim_{T\to\infty}\int_{\tau}^{T}(f(t,N_t(.))+N)dt$ must diverge.

Hence, for each $\zeta\in[0,\tau]$ then, $\lim_{n\to\infty} N(\zeta+n\tau)=0$.

By introducing $\epsilon > 0$, since $\lim_{n\to\infty} N(n\tau)=0$, $\exists n_{\epsilon}>0$

Such that $N(n\tau)<\epsilon e^{-\tau}$, $\forall n \geq n_{\epsilon}$.

Define, $t_{\epsilon}=n_{\epsilon}\tau$. Consider any $t\geq t_{\epsilon}$.

Then $\exists\ n\geq n_{\epsilon}$ such that $t = n\tau+\zeta$,

where $\zeta\in[0,\tau)$.

By first part of this lemma,

$\int_0^{\zeta}(1-\alpha(t))dt<\tau$ for $\zeta\in[0,\tau]$

We have,

$N(t)=N(n\tau)\exp\{\int_0^{\zeta}(1-\alpha(t))dt-\int_{n\tau}^{n\tau+\zeta}(f(t,N_t(.)+N(t)dt\}< \epsilon\forall t\geq t_{\epsilon}$.

Thus $\lim_{t\to\infty} N(t)=0$.

Lemma 2-If N=0 is a globally attracting fixed point of $\frac{dN}{dt}=N(1-N-f(t,N_t(.)))-\alpha(t)N$, then $\bar{\alpha}\geq 1$.

Proof:Suppose $\bar{\alpha}>1$ and choose $\delta>0$ such that $\bar{\alpha}<1-\delta<1$.

Let $\alpha_m=\max_{t\,\varepsilon[0,\tau]}\alpha(t)$

Then , $f(t,N_{t(.)})\leq \alpha_m\int_{t-a_r}^{t} N(u)du$.

Since $\lim_{t\to\infty} N(t)=0$, given $\epsilon>0$, $\exists t_{\epsilon}>0$, such that $N(t)<\epsilon\forall t\geq t_{\epsilon}$.

Choose $\epsilon=\delta/(1+\alpha_m a_r)$.

Then, $\frac{1}{N}\frac{dN}{dt}dt=1-N-f(t,N_t(.))-\alpha(t)$

$\geq(1-\frac{\delta}{1+\alpha_m a_r}-\frac{\delta}{1+\alpha_m a_r}\alpha_m a_r-\alpha(t)), \forall t\geq t_{\epsilon}+a_r$

$\Rightarrow\frac{N(t+\tau)}{N(t)}\geq\exp\{\tau(1-\delta-\bar{\alpha})\} > 1$, by suitable choice of δ.

Therefore, the sequence $\{N(t_{\epsilon}+n\tau)\}_n$ is strictly increasing, which contradicts the assumption that,

$\lim_{t\to\infty} N(t)=0$.

Theorem 1:

N=0 is a global attractor for equation 2,iff $\bar{\alpha}\geq 1$.

Proof:

The proof follows from lemmas 1& 2.

Theorem 2:

For $0<\alpha<1, 0<\rho$ and $0\leq a_r$, N_p is a locally stable steady state of $\frac{dN}{dt}=N(1-N-f(t,N_t(.)))-\alpha(t)N$, if $\alpha<4\rho e^{2\rho a}{}_r$.

Proof:

The following system of delay differential equations, on making the substitution;

$M(t) = f(t,N_t(.))/\alpha$:

$\frac{dN}{dt}=N(1-\alpha-N-\alpha M)$

$\frac{dM}{dt}=N-\gamma N(t-a_r)-\rho M$.

The steady states of above equations are (0,0) and $(N_\rho, N_\rho(1-\gamma)/\rho)$.

The non- zero steady state, obtain the following characteristic equation;

$\lambda^2+(N_p+\rho)\lambda+(\rho+\alpha)N_p-\alpha\gamma N_p e^{-\lambda a}{}_r=0$.

When a_r, the roots of above equation are

$\lambda=-\rho$ and $\lambda=-(1-\alpha)$.

So, N_p is stable.

To show that this is not possible when $4\rho e^{2\rho a}{}_r>\alpha$.

If possible, let $\lambda=y\in\mathbb{R}$be a root of above equation. Then y satisfies,

$-y^2+(\rho+\alpha)N_p-\alpha\gamma N_p\cos(y\alpha_r)=0$

$(N_p+\rho)y+\alpha\gamma N_p\sin(y\alpha_r)=0$

From above equation, it follows that, $y^4+By^2+C=0$, where $B=N^2{}_p-2\alpha N_p+\rho^2$ and

$C=(1-\gamma)^2\alpha^2+2\alpha\rho+\rho^2$.

In particular, $4\rho e^{2\rho a}{}_r>\alpha$.

$\Rightarrow B^2-4C<0$

That is, $y\in\mathbb{R}$, a contradiction.

IV. APPLICATION

Phase Specific Models For Cancer Chemotherapy As Optimal Control Problems:

Recent models for cancer chemotherapy are cell-cycle specific and treat the cell cycle as the object of control [3],[6]. Each cell passes through a sequence of phases from birth to cell division. Since most drugs are active in a specific phase of the cell-cycle.

- The starting point is a growth phases G_1 after which the cell enters a phase 's' where DNA synthesis occurs.
- The second growth phase G_2 take place in which the cell prepares for phase M.

The drug is proportional to the number of ineffective cell divisions in G_2/M phase with a factor s, $0<s\leq 1$.Therefore, while all cells a_2N_2 leave the compartment G_2/M only a fraction (1-

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su)a_2N_2 of cells reenters phase G_1/s and undergoes cell division.Thus the controlled mathematical model becomes

$\dot{N}_1 = -a_1N_1 + 2(1\text{-}su)a_2N_2, N_1(0)=N_{10}$
$\dot{N}_2 = a_1N_1 - a_2N_2, N_2(0)=N_{20}$

With all initial conditions positive. For $s\leq\frac{1}{2}$ the total number of cancer cells cannot be reduced and thus we will generally also assume that $s>\frac{1}{2}$.

If the set $N=(N_1,N_2)$ then the general form of the system
$\dot{N}(t) = (A+suB)N(t), N(0) = N_0$
Where A and B are fixed (2×2) matrices given by
$A = \begin{pmatrix} -a_1 & 2a_2 \\ a_1 & -a_2 \end{pmatrix}$, $B = \begin{pmatrix} 0 & -2a_2 \\ 0 & 0 \end{pmatrix}$.

Clearly only states N(t) for which each coordinate is positive. If each coordinate of $N(t_0)$ is positive, then all coordinates of N(t) remain positive for all times $t\geq t_0$.
Therefore, $s\leq\frac{1}{2}$ the total number of cancer cells cannot be reduced but if $s>\frac{1}{2}$, the cancer cell can be reduced.

V. CONCLUSION

An integro - differential equation that models the response of a tumor growing in periodic exposure to a chemotherapy which causes cells first to become growth arrested and then induces cell death within a fixed time period.The global stability of the cancer free equilibrium and the existence of a periodic solution in the case when the cancer free equilibrium was unstable is studied.The periodic solution found in existence of periodic solutions is globally attracting. In terms of using phase specific models for cancer chemotherapy as optimal control problems and determining a minimum amount of drug required to eliminate the cancer.

REFERENCES

[1] Michiels,"Stability and stabilization of time-delay systems",Aneigen value based approach ISBN 78-0-89871-632-0, (2007).
[2] J.C.Panetta, "A Logistic model of periodic chemotherapy with drug resistence",Appl.Math(1997).
[3] A.Swierniak,A.Polanski and M.Kimmel,"optimal control problems arising in cell cycle specific cancer chemotherapy", cell proliferation, 29, pp.117-139,(1996).
[4] J.C.Panetta", A logistic Model of Periodic chemotherapy", Appl.Math.(1995).
[5] VangipuramLakshmikantham,M.RamaMohanaRao,"Theory of Integro-Differential Equations," CRC press,(1995).
[6] A.Swierniak,"cell cycle as an object of control",41-54,(1995).
[7] N.MacDonald, "Time Delay differential in simple models",(1976).