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**Qualitative Analysis of an Integro-Differential Equation Model of
Periodic Chemotherapy**

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Qualitative Analysis of an Integro-Differential Equation Model of Periodic Chemotherapy

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Abstract

An existing model of tumor growth that accounts for cell cycle arrest and cell death induced by chemotherapy is extended to simulate the response to treatment of a tumor growing in vivo. The tumor is assumed to undergo logistic growth in the absence of therapy, and treatment is administered periodically rather than continuously. 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, nonautonomous logistic growth, periodic orbit, stability analysis

1. Introduction

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

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

In equation (1), $N(t)$ represents the number of proliferating tumor cells at time t . Equation (1) derives from a mathematical model describing the response of tumor cells growing in vitro to a chemotherapeutic drug which causes proliferating cells first to become growth-arrested in response to drug-induced DNA damage, and then to die at rates which are proportional to the amount of DNA damage sustained [1]. To simulate the response to treatment of a tumor growing in vivo, the original model has been modified as follows. Cells are assumed to grow logistically in the absence of treatment and chemotherapy is administered periodically, with period τ . $\alpha(t)$ represents the rate of cell arrest in response to therapy application, and is a bounded, non-negative periodic function with period τ . $f(t, N) = \int_{t-\tau}^t \alpha(u) e^{-\rho(u)(t-u)} N(u) du$ represents the number of cells in the arrested

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state at time t . These cells are assumed to compete for space with the proliferating cells and die at a rate $\rho(t)$. We further suppose that cells remain in the arrested compartment for at most a time period, a_r ($a_r < \tau$).

Equation (1) belongs to a general class of integro-differential equations, that arise naturally in population dynamics when the past history of the species influences its current growth rate. Models of periodic chemotherapy based on the logistic equation have been studied previously [2–4]; criterion for the elimination of the tumor have been derived, and questions relating to the emergence of drug resistance, and the effect of treatment period on tumor reduction studied. A common feature of these models is the assumption that chemotherapy instantaneously stimulates cell death. We relax this assumption by supposing that the response of tumor cells to treatment is not instantaneous, but rather acts over a finite period of time.

In the sections that follow, we derive conditions for the global stability of the solution of equation (1) that corresponds to a cancer-free equilibrium. Using techniques from functional analysis, we prove the existence of a periodic solution when the cancer-free equilibrium is unstable. We conclude with a brief discussion on the relevance of our work.

2. Analytical Results

Let $\bar{\alpha} = (1/\tau) \int_0^\tau \alpha(t) dt$. Numerical simulations of equation (1) show qualitatively different behavior as $\bar{\alpha}$ is varied. When $\bar{\alpha} > 1$, $\lim_{t \rightarrow \infty} N(t) = 0$ (Figure 1, solid curve) and in § 2.1 we 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 (Figure 1, dashed curve), whose existence is proven in § 2.2. We remark that we restrict attention to biologically relevant initial conditions, that is, we 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 (1) in the absence of treatment. The positivity of solutions follows from the fact that $N = 0$ is a steady state of equation (1).

2.1. Stability of the Cancer-free Equilibrium

In this section, we prove that treatment will successfully eradicate the tumor iff $\bar{\alpha} \geq 1$.

Theorem 1. $N = 0$ is a global attractor for equation (1) iff $\bar{\alpha} \geq 1$.

PROOF. The proof follows from Lemmas 2 and 3. □

Lemma 2. Let $\bar{\alpha} \geq 1$. Then, $N = 0$ is a globally stable fixed point of equation (1).

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

$$\begin{aligned} \int_{\zeta}^{\zeta+\tau} \frac{dN}{N} &= \int_0^\tau (1 - \alpha(t)) dt - \int_{\zeta}^{\zeta+\tau} (f(t, N) + N) dt \\ \Rightarrow N(\zeta + \tau) &= N(\zeta) e^{\tau(1-\bar{\alpha})} e^{-\int_{\zeta}^{\zeta+\tau} (f(t, N) + N) dt} \\ \Rightarrow N(\zeta + n\tau) &= N(\zeta) E_n(\bar{\alpha}) A(\zeta) B_n(\zeta) \end{aligned} \tag{2}$$

where $E_n(\bar{\alpha}) = e^{n\tau(1-\bar{\alpha})}$, $A(\zeta) = e^{-\int_{\zeta}^{\zeta+\tau} (f(t, N) + N) dt}$, and $B_n(\zeta) = e^{-\int_{\tau}^{n\tau} (f(t, N) + N) dt}$. We claim that $\lim_{n \rightarrow \infty} N(\zeta + n\tau) = 0$. There are two cases to consider: $\bar{\alpha} > 1$ and $\bar{\alpha} = 1$.

Now, $\bar{\alpha} > 1 \Rightarrow \lim_{n \rightarrow \infty} E_n(\bar{\alpha}) = 0$. Additionally, $\alpha(t), N(t) \geq 0 \Rightarrow A(\zeta), B_n(\zeta) \leq 1$. Therefore, from equation (2) we obtain $\lim_{n \rightarrow \infty} N(\zeta + n\tau) = 0$.

When $\bar{\alpha} = 1$, $\lim_{n \rightarrow \infty} E_n(\bar{\alpha}) = 1$. Let $\lim_{T \rightarrow \infty} \int_{\tau}^T (f(t, N) + N) dt = \kappa$, where $\kappa > 0$. Suppose now that $\kappa < \infty$. Then, it follows from equation (2) that $\lim_{n \rightarrow \infty} N(\zeta + n\tau) = \eta(\zeta)$, where $0 < \eta(\zeta) = \kappa N(\zeta) A(\zeta)$ is continuous on $[0, \tau]$ (continuity follows from the boundedness of dN/dt). Therefore, $\eta(\zeta)$ must attain its minimum (say η_{\min}) in $[0, \tau]$.

As $A(\zeta)$ and $B_n(\zeta)$ are exponentials with negative exponents, the sequences $\{N(\zeta + n\tau)\}_n$, $\zeta \in [0, \tau]$ decrease monotonically, and we deduce that $N(t) \geq \eta_{\min} \forall t$ (otherwise it would be possible to construct a sequence that converges to a limit $< \eta_{\min}$). This contradicts our original assumption that κ is finite: if $N(t)$ is bounded away from zero (and positive) then $\lim_{T \rightarrow \infty} \int_{\tau}^T (f(t, N) + N) dt$ must diverge. Hence, for each ζ in $[0, \tau]$, $\lim_{n \rightarrow \infty} N(\zeta + n\tau) = 0$.

We complete our proof by first introducing $\epsilon > 0$. Since $\lim_{n \rightarrow \infty} N(n\tau) = 0$, $\exists n_{\epsilon} > 0$ such that $N(n\tau) < \epsilon e^{-\tau} \forall n \geq n_{\epsilon}$. Define $t_{\epsilon} = n_{\epsilon}\tau$ and consider any $t \geq t_{\epsilon}$. Then $t = n\tau + \zeta$, where $\zeta = \text{rem}(t, \tau)$, and $n \geq n_{\epsilon}$. Proceeding as in the first part of this lemma, $\int_0^{\zeta} (1 - \alpha(t)) dt < \tau$ for $\zeta \in [0, \tau]$, and so we have

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

Thus, $\lim_{t \rightarrow \infty} N(t) = 0$. □

Lemma 3. *If $N = 0$ is a globally attracting fixed point of equation (1), then $\bar{\alpha} \geq 1$.*

PROOF. Suppose $\bar{\alpha} < 1$ and choose $\delta > 0$ such that $\bar{\alpha} < 1 - \delta < 1$. Let $\alpha_m = \max_{t \in [0, \tau]} \alpha(t)$. Then, $f(t, N) \leq \alpha_m \int_{t-a_r}^t N(u) du$. Since $\lim_{t \rightarrow \infty} N(t) = 0$, 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,

$$\begin{aligned} \frac{1}{N} \frac{dN}{dt} &= 1 - N - f(t, N) - \alpha(t) \\ &\geq \left(1 - \frac{\delta}{1 + \alpha_m a_r} - \frac{\delta}{1 + \alpha_m a_r} \alpha_m a_r - \alpha(t) \right), \forall t \geq t_{\epsilon} + a_r \\ \Rightarrow N(t + \tau) / N(t) &\geq \exp \{ \tau (1 - \delta - \bar{\alpha}) \} > 1 \end{aligned}$$

by suitable choice of δ . We can therefore construct a sequence $\{N(t_{\epsilon} + n\tau)\}_n$ that is strictly increasing, which contradicts the assumption that $\lim_{t \rightarrow \infty} N(t) = 0$. □

2.2. Existence of Periodic Solutions

Here, we prove that if a tumor is under-treated ($\bar{\alpha} < 1$), then equation (1) admits an oscillatory solution whose period matches that of $\alpha(t)$ and determine a condition for the local stability of this oscillatory solution in the extreme case when therapy is administered continuously.

Theorem 4. *If $\bar{\alpha} < 1$, then \exists a nontrivial τ -periodic solution of equation (1).*

In order to prove this theorem, several preliminary results are required. As before, let $\delta > 0$ such that $\bar{\alpha} < 1 - \delta < 1$, and define $\mu = \delta / (1 + \alpha_m a_r e^{\alpha_m a_r (1 + a_r)})$ where $\alpha_m = \max(\alpha(t))$. Further, $N(t) \leq 1 \forall t \geq 0$, since, if t_1 is the first time such that $N(t_1) = 1$, then $dN(t_1)/dt \leq N(1 - N) = 0$. Therefore,

$$\frac{1}{N} \frac{dN}{dt} = 1 - N - f(t, N) - \alpha(t) \geq -f(t, N) - \alpha(t) \geq -\alpha_m a_r - \alpha_m \quad (3)$$

$$\Rightarrow N(t_0 - t) \leq N(t_0) e^{\alpha_m (1 + a_r) t} \leq N(t_0) e^{\alpha_m (1 + a_r) a_r}, \forall 0 \leq t \leq a_r. \quad (4)$$

Further, if $A = \max\{1, \alpha_m a_r + \alpha_m\}$, as $N(t) \leq 1$, from equation (3) it follows that:

$$-\alpha_m a_r - \alpha_m \leq \frac{dN}{dt} \leq 1 \Rightarrow |N(t_1) - N(t_2)| \leq A|t_1 - t_2|, \forall t_1, t_2 > 0 \quad (5)$$

Lemma 5. *Let $N(t)$ be a solution of equation (1) and suppose $\exists t_0$ such that $N(t_0) = \mu$. Then $\exists \theta > 0$ such that $N(t) \geq \theta \forall t \geq t_0$.*

PROOF. Let $N(t_0) = \mu$. We first show that if $N(t) < \mu$ for $t_0 < t \leq T$, where T is the maximum possible time for which this is true, then $T \leq t_0 + \tau$. We proceed by contradiction. If $T > t_0 + \tau$, then equation (4) supplies:

$$\begin{aligned} \frac{1}{N} \frac{dN}{dt} &\geq 1 - \mu - \mu \alpha_m a_r e^{\alpha_m (1 + a_r) a_r} - \alpha(t), \forall t_0 < t \leq t_0 + \tau \leq T \\ \Rightarrow N(t_0 + \tau) &\geq N(t_0) e^{\tau(1 - \delta - \bar{\alpha})} > \mu \end{aligned}$$

since $\bar{\alpha} < 1 - \delta$ and $\mu + \mu \alpha_m a_r e^{\alpha_m (1 + a_r) a_r} = \delta$. This contradicts the definition of T . Finally, by combining the result above with from equation (3), we deduce that $\min_{t \in [t_0, t_0 + \tau]} N(t) = \mu e^{-(\bar{\alpha} + \alpha_m a_r) \tau} (= \theta, \text{ say})$. \square

We remark that the above results imply that a solution $N(t)$ of equation (1), with $N(t = 0) = N_0 \geq \mu$, satisfies $N(t) > \theta \forall t \geq 0$.

Corollary 6. *Consider $0 < \eta < \mu$. If $N(t = 0) = N_0 \geq \eta$, then $\exists T_\eta(\tau, \eta)$ such that $N(t) \geq \theta \forall t \geq T_\eta$.*

PROOF. We first show that if $0 < N_0 < \mu$, then $\exists 0 < T < \infty$ such that $N(t) < \mu$ for $t < T$ and $N(T) = \mu$. Proceeding as in Lemma 5, $N(\tau) > N_0 e^{\tau(1 - \delta - \bar{\alpha})}$. Similarly, $\forall n \in \mathbb{Z}^+$, $N(n\tau) > N_0 e^{n\tau(1 - \delta - \bar{\alpha})}$. Define $g(x) = \lceil (1/(\tau(1 - \delta - \bar{\alpha}))) \ln(\mu/x) \rceil$, $x \in (0, 1]$, and let $m_0 = g(N_0)$. Then, $N_0 e^{m_0 \tau(1 - \delta - \bar{\alpha})} > \mu$ since, by definition, $1 - \delta - \bar{\alpha} > 0$. Thus, $T \leq m_0 \tau$.

If $N_0 \geq \mu$, we are done by Lemma 5. If $\eta \leq N_0 < \mu$, the corresponding solution $N(t)$ crosses μ by time $g(N_0)\tau$. Observing that $g(x)$ is an decreasing function of x , we may take $T_\eta = g(\eta)\tau$. Once again, the application of Lemma 5 completes the proof. \square

PROOF OF THEOREM 4. The proof follows from Horn's Fixed Point Theorem [5]:

Let $X_0 \subset X_1 \subset X_2$ be non-empty convex sets in a Banach space X with X_0 and X_2 compact and X_1 open relative to X_2 . Let W be a continuous mapping $X \rightarrow X$ such that, for some $m \in \mathbb{Z}^+$, $W^j(X_1) \subset X_2$ for $1 \leq j \leq m - 1$, and $W^j(X_1) \subset X_0$ for $m \leq j \leq 2m - 1$,

where $W^j = \underbrace{W \circ \dots \circ W}_{j\text{-times}}$. Then W has a fixed point in X_0 .

Let $X = \mathcal{C}[-a_r, 0]$ be equipped with the supremum norm $\|\cdot\|_\infty$. Define:
 $X_2 = \{f \in X : f(0) \geq \eta, 0 \leq f(x) \leq 1, |f(x) - f(y)| \leq A|x - y| \forall x, y \in [-a_r, 0]\}$,
 $X_0 = \{f \in X : \theta \leq f(x) \leq 1, |f(x) - f(y)| \leq A|x - y| \forall x, y \in [-a_r, 0]\}$, and
 $X_1 = \{f \in X_2 : f(0) > \eta\}$, where $A = \max\{1, \alpha_m a_r + \alpha_m\}$ as in equation (5), $\theta = \mu e^{-(\bar{\alpha} + \alpha_m a_r)\tau}$ as in the proof of Lemma 5 and $0 < \eta < \theta$. We remark that X_2 is pointwise bounded by definition, and is uniformly equicontinuous since any $f \in X_2$ satisfies a Lipschitz condition. Further, let $\{f_n\}_n$ be a sequence in X_2 converging to some limit function f in X . Then, $f(x) = \lim_{n \rightarrow \infty} f_n(x) \in [0, 1]$, $f(0) = \lim_{n \rightarrow \infty} f_n(0) \geq \eta$, and $|f(x) - f(y)| = \lim_{n \rightarrow \infty} |f_n(x) - f_n(y)| \leq A|x - y|$. Thus, $f \in X_2$, and X_2 is closed. By the Arzelà-Ascoli Theorem [6], it follows that X_2 is compact in X . Likewise, X_0 is compact in X . A similar argument shows that X_2 , X_1 and X_0 are convex subsets of X .

Define $W(N_i(t)) = N(t + \tau)|_{[-a_r, 0]}$, where $N(t)$ is the solution of equation (1) with initial condition $N_i \in X$. Then, $W^j(X_1) \subset X_2 \forall j$ and by Corollary 6, $W^j(X_1) \subset X_0$ for $j \geq g(\eta)$. Thus, by Horn's theorem, W has a fixed point. By uniqueness of solutions, and observing that if $N(t)$ is a solution of (1) then so is $N(t + \tau)$, the fixed point must correspond to a τ -periodic solution of equation (1), $N_{per}(t)$, say. \square

We remark that if $N_{per}(t)$ is any τ -periodic solution of equation (1), then the average total number of cells over a time period τ is $1 - \bar{\alpha}$, since \forall time $T > 0$,

$$\begin{aligned} 0 &= [\ln N_{per}]_{t=T}^{t=T+\tau} = \int_T^{T+\tau} \frac{1}{N_{per}} \frac{dN_{per}}{dt} dt = \int_T^{T+\tau} (1 - N_{per} - f(t, N_{per}) - \alpha(t)) dt \\ \Rightarrow 1 - \bar{\alpha} &= \frac{1}{\tau} \int_T^{T+\tau} (f(t, N_{per}) + N_{per}) dt. \end{aligned}$$

We finally consider the extreme case when therapy is administered continuously, that is for $\alpha(t) = \alpha$ and $\rho(t) = \rho$, α, ρ constant. Then, equation (1) admits a non-zero steady-state $N_p = \rho(1 - \alpha)/(\rho + \alpha(1 - \gamma))$, where $\gamma = e^{-\rho a_r}$. In Theorem 7, we prove a condition for the local stability of N_p .

Theorem 7. For $0 < \alpha < 1$, $0 < \rho$ and $0 < a_r$, N_p is a locally stable steady state of equation (1) if $4\rho e^{2\rho a_r} > \alpha$.

PROOF. An application of the Linear Chain Trick [7], reduces equation (1) to the following system of delay differential equations, on making the substitution $M(t) = f(t, N)/\alpha$:

$$\frac{dN}{dt} = N(1 - \alpha - N - \alpha M) \quad (6)$$

$$\frac{dM}{dt} = N - \gamma N(t - a_r) - \rho M \quad (7)$$

The steady states of equations (6) and (7) are $(0, 0)$ and $(N_p, N_p(1 - \gamma)/\rho)$. Linearizing equations (6) and (7) about the non-zero steady state, we obtain the following characteristic equation.

$$\lambda^2 + (N_p + \rho)\lambda + (\rho + \alpha)N_p - \alpha\gamma N_p e^{-\lambda a_r} = 0 \quad (8)$$

Note that $\lambda = -\rho$ is a root of equation (8). Let $\lambda = x + \iota y$, $x, y \in \mathbb{R}$. Then x, y satisfy

$$\begin{aligned} x^2 - y^2 + (N_p + \rho)x + (\rho + \alpha)N_p - \alpha\gamma N_p e^{-x a_r} \cos(y a_r) &= 0 \\ (N_p + \rho)y + 2xy + \alpha\gamma N_p e^{-x a_r} \sin(y a_r) &= 0 \end{aligned} \quad (9)$$

We show that if $4\rho e^{2\rho a_r} > \alpha$, then $x \neq 0$. Suppose $x = 0$. From equations (9) and (10) it follows that $y^4 + By^2 + C = 0$, where $B = N_p^2 - 2\alpha N_p + \rho^2$ and $C = (1 - \gamma)^2 \alpha^2 + 2\alpha\rho + \rho^2$. In particular, if $4\rho e^{2\rho a_r} > \alpha$, then $B^2 - 4C < 0$, that is $y \in \mathbb{C}$, a contradiction.

We further claim that for $(\alpha, \rho, a_r) = (0.5, 2, 2)$, $(N_p, N_p(1 - \gamma)/\rho)$ is a locally stable steady state of equations (6) and (7). Suppose $\exists x, y$ roots of equations (9) and (10) such that $x > 0$. From equation (10), we have $|y| \leq (\alpha\gamma N_p)/(N_p + \rho + 2x) < \alpha\gamma N_p$ since $\rho > 1$ and $x > 0$. It follows that:

$$x^2 - y^2 + (N_p + \rho)x + (\rho + \alpha)N_p > (\rho + \alpha)N_p - \alpha^2 \gamma^2 N_p^2 = 1.0037 > 0.0037 = \alpha\gamma N_p,$$

a contradiction to the fact that x is a root of equation (9). Further, as $4\rho e^{2\rho a_r} = 2.384 \times 10^4 > \alpha$, $x \neq 0$ from the preceding claim. Therefore $x < 0$, that is $(N_p, N_p(1 - \gamma)/\rho)$ is locally stable.

Observing that as the function $h : \mathbb{R}^{2+} \rightarrow \mathbb{R}$ defined as $h(b, c) = 4be^{2bc}$ is monotonic in b, c , the set $P = \{(a, b, c) \in \mathbb{R}^{3+} : 4be^{2bc} > a, a < 1\}$ is a path connected subspace of \mathbb{R}^3 . Since $(0.5, 2, 2) \in P$, and as the roots of equations (9) and (10) vary continuously with the coefficients, the theorem follows. \square

3. Discussion

We have analyzed an integro-differential equation that models the response of a tumor growing in vivo to periodic exposure to a chemotherapy which causes cells first to become growth arrested and then induces cell death within a fixed time period. Drugs that act in this manner include platinum-based compounds such as carboplatin and cisplatin that are today the gold-standard of therapy for a number of solid tumors. We derived a simple condition for the global stability of the cancer-free equilibrium and proved the existence of a periodic solution in the case when the cancer-free equilibrium was unstable. These results have practical significance in terms of determining a minimum amount of drug required to eliminate the cancer. Numerical simulations indicate that the periodic solution found in §2.2 is globally attracting. However, the proof of this result remains open problem that we are currently studying. We are also considering model extensions which would allow arrested cell recovery to a proliferating state.

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References

- [1] H.V. Jain, M. Meyer-Hermann, The molecular basis of synergism between carboplatin and ABT-737 therapy targeting ovarian carcinomas, *Cancer Res.* 71 (2011) 705-715.
- [2] J.C. Panetta, A Logistic Model of Periodic Chemotherapy, *Appl. Math. Lett.* 8 (1995) 83-86.
- [3] J.C. Panetta, J. Adam, A mathematical model of cycle-specific chemotherapy, *Math. Comput. Model.* 22 (1995) 67-82.
- [4] J.C. Panetta, A Logistic Model of Periodic Chemotherapy with Drug Resistance, *Appl. Math. Lett.* 10 (1997) 123-127.
- [5] B. Dembele, A. Friedman, A. Yakubu, Malaria model with periodic mosquito birth and death rates, *J. Biol. Dynamics.* 3 (2009) 430-445.
- [6] N. Dunford, J.T. Schwartz, *Linear operators*, vol. 1, Interscience Publishers, New York, 1958, p. 266.
- [7] N. MacDonald, Time Delay in Simple Chemostat Models, *Biotechnol. Bioeng.* 18 (1976) 805-812.

Figure Legends

When $\bar{\alpha} < 1$, equation (1) admits a periodic solution (dashed curve) while for $\bar{\alpha} > 1$, the eradication of tumor cells is predicted (solid curve). In both cases, therapy is administered on a weekly schedule starting at time $t = 19$ days.

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