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Difference Equation for chemotherapeutic cancer treatment Model

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Abstract

We consider a difference equation for chemotherapeutic cancer treatment including both the tumor size of cancer and the accumulated drug level.

At first we investigate a condition such that the model will be able to have a stable solution. Next under this condition, we will have general analytic solutions using methods of complex analysis. Then under the condition, we can get an analytic stable solution for each patient.

We hope this theory would be useful in cancer treatment.

keywords: Difference equations, Analytic solutions, Functional equations.

1 Introduction

Chemotherapy has been important in the treatment of cancer diseases especially in cases where surgery proves ineffective. A. Novak and G. Feichtinger [1] investigated a differential equation for chemotherapeutic cancer treatment including both the tumor size of cancer and the accumulated drug level. But indeed we can get the data of the treatment at only discrete times. So it is very important to investigate the model for difference equation.

When we analyze a difference model with a computer, then we need values of all the parameters. So the results of it have not generality. Then we want to have analytic solutions which have generality for the parameters. Analytic solutions of difference equations have been investigated in [3]-[8]. But if the model is not stable, then the results is far from real phenomenon. At first, we consider the quasi stable conditions.

Under the conditions we have an analytic solution of the difference model with theories of complex analysis. Finally we can have general analytic solutions of the model using a functional equation in [3].

From their differential equation in [1], we obtain the following difference model which including both the tumor size x of cancer and the accumulated drug level y :

$$\begin{cases} \Delta x(t) = x(t+1) - x(t) = G(x(t)) - h(x(t))f(y(t)), \\ \Delta y(t) = y(t+1) - y(t) = \psi(a) - \delta y(t), \end{cases} \tag{1.1}$$

$$\begin{cases} G(x) = gx\log\frac{\theta}{x} \quad (\theta : \text{fixed interval of treatment}, g : \text{constant}), \\ h(x) = x^{\beta} \quad (h : \text{concave}, \beta : \text{constant}, 0 < \beta < 1), \\ f(y) = \frac{by}{c+y} \quad (b, c : \text{constant}), \\ \psi(a) = a \quad (a : \text{parameter}), \\ \delta : \text{natural cleaning rate}, (0 < \delta < 1). \end{cases}$$

Then we consider the following difference equation.

$$\begin{cases} x(t+1) = x(t) + gx(t)\log\frac{\theta}{x(t)} - x(t)^{\beta}\frac{y(t)}{c+y(t)} \\ y(t+1) = y(t) + a - \delta y(t) \end{cases}. \tag{1.2}$$

If the radius of tumor is smaller than 10 cm, some hospital uses the chemotherapeutic cancer treatment with a little drug to stop its growth, even though it would be impossible to put off all of them. This treatment gives little influence to body by drug. Hence in this paper we want to have a solution $x(t) \to \gamma > 0$, $y(t) \to \zeta(small)$.

If we suppose the existence of a fixed point $(x, y) = (\gamma, \zeta)$, $\gamma > 0, \zeta > 0$, then this model has a stable solution and we have

$$\begin{cases} g\gamma\log\frac{\theta}{\gamma} = \gamma^{\beta}\frac{a}{c\delta+a} \\ \delta\zeta = a \end{cases}. \tag{1.3}$$

Put $h(\gamma) = \gamma e^{\frac{1}{g}\gamma^{\beta-1}\frac{a}{c\delta+a}}$, then we have $h(\gamma) \uparrow +\infty$, $(\gamma \to +0, \gamma \to +\infty)$, and have a minimum value of $h(\gamma)$ such that

$$h\left(\left(\frac{g(c\delta+a)}{a(1-\beta)}\right)^{\frac{1}{\beta-1}}\right). \tag{1.4}$$

So that if we take θ bigger than (1.4), then there is a solution γ_0 of $h(\gamma) = \theta$, i.e., this pair (γ, θ) is satisfies the first equation of (1.3). For convenience' sake, we put $\gamma_0 = \gamma$ and $u(t) = x(t) - \gamma$, $v(t) = y(t) - \zeta$, then we have from (1.2)

$$\begin{cases} u(t+1) = u(t) + g(u(t)+\gamma)\log\frac{\theta}{u(t)+\gamma} - (u(t)+\gamma)^{\beta}\frac{v(t)+\zeta}{c+v(t)+\zeta} \\ v(t+1) = (1-\delta)v(t) \end{cases}. \tag{1.5}$$

2 Conditions of the Difference Model for the existence of asymptotically stable solutions

Here we consider analytic solutions $u(t)$ of (1.5).

From the first equation of (1.5) we have

$$u(t+2) = u(t+1) + g(u(t+1)+\gamma)\log\frac{\theta}{u(t+1)+\gamma} - (u(t+1)+\gamma)^{\beta}\frac{v(t+1)+\zeta}{c+v(t+1)+\zeta},$$

and using second equation of (1.5) we have

$$\begin{aligned} &1 - \frac{c}{c+(1-\delta)v(t)+\zeta} \\ &\quad = (u(t+1)+\gamma)^{-\beta}\{-u(t+2)+u(t+1)+g(u(t+1)+\gamma)\log\frac{\theta}{u(t+1)+\gamma}\}. \end{aligned}$$

From this equation and the first equation of (1.5), we have

$$\begin{aligned} v(t) &= -(c+\zeta) + \frac{c}{1+(u(t)+\gamma)^{-\beta}U} \\ &= \frac{1}{1-\delta}\left\{-(c-\zeta) + \frac{c}{1+(u(t+1)+\gamma)^{-\beta}U_1}\right\} \\ &= \Phi(u(t)), \end{aligned} \tag{2.1}$$

where $U = u(t+1) - u(t) - g(u(t)+\gamma)\log\frac{\theta}{u(t)+\gamma}$, $U_1 = u(t+2) - u(t+1) - g(u(t+1)+\gamma)\log\frac{\theta}{u(t+1)+\gamma}$. Hence we obtain the following second order difference equation for only $u(t)$

$$\begin{aligned} u(t+2) &= u(t+1) + g(u(t+1)+\gamma)\log\frac{\theta}{u(t+1)+\gamma} \\ &\quad + \frac{c\{(u(t)+\gamma)^{\beta}+U\}(u(t+1)+\gamma)^{\beta}}{\delta(c+\zeta)\{(u(t)+\gamma)^{\beta}+U\}+c(1-\delta)(u(t)+\gamma)^{\beta}} - (u(t+1)+\gamma)^{\beta}. \end{aligned} \tag{2.2}$$

Then we will investigate analytic solutions $u(t)$ of (2.2) such that $u(t) \to 0$.

From (2.2), we obtain the characteristic equation

$$D(\lambda) = \lambda^2 - \left\{ 1 - g + \gamma^{2(\beta-1)} \left(\gamma^{1-\beta} \left(\frac{a}{c\delta + a} - \beta(1-\delta) \right) \frac{\beta^2 c\delta}{c\delta + a} \right) \right\} \lambda$$
$$+ (1-\delta) \left\{ 1 - g + \frac{a\gamma^{\beta-1}}{c\delta + a} (1-\beta) \right\} = 0. \quad (2.3)$$

Let λ_1, λ_2 be roots of the characteristic equation, then $\lambda_1 + \lambda_2 = d_1$, $\lambda_1 \cdot \lambda_2 = d_2$, where

$$d_1 = 1 - g + \gamma^{2(\beta-1)} \left(\gamma^{1-\beta} \left(\frac{a}{c\delta + a} - \beta(1-\delta) \right) \frac{\beta^2 c\delta}{c\delta + a} \right),$$
$$d_2 = (1-\delta) \left\{ 1 - g + \frac{a\gamma^{\beta-1}}{c\delta + a} (1-\beta) \right\}.$$

If $0 < d_1 < 2$, $d_2 > 0$, and $d_1^2 - 4d_2 \geqq 0$, we can have a characteristic value λ such that $0 < \lambda < 1$. Then we will prove the existence of a stable solution of (2.2).

For example, put $a = 0.04$, $\beta = 0.4$, $\delta = 0.9$, $c = 700, \theta = 1$, $\gamma = 0.4, g = 1$, then we have $\lambda_1 + \lambda_2 = 0.01663442$, $\lambda_1 \lambda_2 = 0.0000066$. So we can have $0 < \min(\lambda_1, \lambda_2) < 1$.

In this paper, we assume that $0 < d_1 < 2$, $d_2 > 0$, and $d_1^2 - 4d_2 \geqq 0$.

Put a formal solution to (2.2) $u(t) = \sum_{n=1}^{\infty} \alpha_n \lambda^{nt}$, then we have

$$\begin{cases} \alpha_1 \cdot D(\lambda) = 0 \\ \alpha_k \cdot D(\lambda^k) = C_k(\alpha_1, \cdots, \alpha_{k-1}) \quad (k \geqq 2) \end{cases},$$

where $C_k(\alpha_1, \cdots, \alpha_{k-1})$ are written by $\alpha_1, \cdots, \alpha_{k-1}$. Since $D(\lambda) = 0$ and $D(\lambda^k) \neq 0\,(k \geqq 2)$, we have α_1 is arbitrary and α_k are determined by $\alpha_1, \cdots, \alpha_{k-1}$. Here we suppose that $\alpha_1 \neq 0$.

Then we can determine a formal solution

$$u(t) = \sum_{n=1}^{\infty} \alpha_n \lambda^{nt}. \quad (2.4)$$

3 Existence of an analytic stable solution

Time t is of course a real variable. But in this section we consider t to be a complex variable, and we will prove existence of an analytic stable solution of (2.2) with theories of complex analysis. But here we will omit the details. The proof will be appear in another journal [7].

Put $u(t) = s, u(t+1) = w, u(t+2) = z$, and

$$H(s,w,z) = -z + w + g(w+\gamma)\log\frac{\theta}{w+\gamma} - (w+\gamma)^\beta + \frac{c\{(s+\gamma)^\gamma + w - s - g(s+\gamma)\log\frac{\theta}{s+\gamma}\}(w+\gamma)^\beta}{\delta(c+\zeta)\{(s+\gamma)^\gamma + w - s - g(s+\gamma)\log\frac{\theta}{s+\gamma}\} + c(1-\delta)(s+\gamma)^\beta}. \tag{3.1}$$

Then the equation of (2.2) can be written such as

$$H(u(t), u(t+1), u(t+2)) = 0. \tag{3.2}$$

Then $H(s,w,z)$ is holomorphic in a neighborhood of (0,0,0) and we have $H(0,0,0) = 0$ easily. Furthermore we have

$$\frac{\partial H}{\partial s}(0,0,0) = -\lambda_1 \cdot \lambda_2 < 0.$$

Hence using the theorem on implicit function for the equation $H(s,w,z) = 0$, we have a holomorphic function ϕ such that

$$s = \phi(w,z) \quad \text{for} \quad |w|,\ |z| \leqq \rho \tag{3.3}$$

for some $\rho > 0$.

Our aim is to show the existence of $u(t)$ such that $u(t) = \phi(u(t+1), u(t+2))$. Formal solution is given by (2.4). It suffices to prove the convergence of the (2.4).

Let N be a positive integer. Put the partial sum of (2.4) as $P_N(t) = \sum_{n=1}^{N} \alpha_n \lambda^{nt}$. If the stable solution $u(t)$ of (2.2) would exist, then writing $p(t) = u(t) - P_N(t)$ and we would obtain from $u(t) = \phi(u(t+1), u(t+2))$. Conversely if $p(t)$ would exist, then we have a exact solution $u(t)$ of (2.2) by $u(t) = p(t) + P_N(t)$.

Put

$$S(\eta) = \{t \in \mathbb{C} : |\lambda^t| \leqq \eta\}$$
$$J(A,\eta) = \{p : p(t) \text{ is holomorphic and } |p(t)| \leqq A|\lambda^t|^{N+1} \text{ for } t \in S(\eta)\}.$$

Take $A > 0$ and $0 < \eta < 1$, which will be determined later. For $p(t) \in J(A,\eta)$, put

$$T[p](t) = g_3(t, p(t+1), p(t+2)), \tag{3.4}$$

where $g_3(t, p(t+1), p(t+2)) = \phi(p(t+1) + P_N(t+1), p(t+2) + P_N(t+2)) - P_N(t)$. We can show that constant A and ρ may be chosen such that T has a fixed point $p(t) = p_N(t) \in J(A,\eta)$ by Schauder's fixed point theorem in [2].

Furthermore we can prove the uniqueness of the fixed point, and that the solution $u(t) = p_N(t) + P_N(t)$ is independent of N. But here we omit the details.

Thus we have proved that a solution $u(t)$ is defined and holormorphic in $S(\eta)$ for a $\eta > 0$, which has the expansion $u(t) = \sum_{n=1}^{\infty} \alpha_n \lambda^{nt}$.

By the way, we can not assure following condition

$$\frac{\partial H}{\partial s}(s, w, z) \neq 0, \qquad \text{for all} \quad w, z.$$

So that the solution $u(t)$ can be continued analytically by making use of the relation

$$u(t-2) = \phi(u(t-1), u(t)),$$

keeping out of branch points, up to $\mathbb{R}[t] \geqq 0$. The solution obtained may be multivalued.

4 Analytic General Solutions

Analytic general solutions of some difference equations have been investigated in [5]-[6]. In this section, we will have general analytic solution of (1.5).

Let $u(\tau)$ be the solution of (2.2) in above argument. And suppose $\chi(t)$ be a solution of (2.2) such that $\chi(t+n) \to 0$ as $n \to +\infty$ uniformly on any compact set. We put

$$u(t) = \sum_{n=1}^{\infty} \alpha_n \lambda^{nt} = U(\lambda^t), \quad \alpha_1 \neq 0,$$

then U is a open map, and χ is also a open map. Since $U(0) = \chi(0) = 0$, for any $\eta_1 > 0$ there is a some constant $\eta_2 > 0$ such that

$$U(|\tau| < \eta_1) \supset \{|\chi| < \eta_2\}.$$

So that there is a large R such that, if $|t' + n| > R$ then $|\chi(t' + n)| < \eta_2$. Hence there is a $\tau = \lambda^\sigma$ such that

$$\chi(t' + n) = U(\tau) = U(\lambda^\sigma).$$

Since $\alpha_1 \neq 0$, using the theorem on implicit function we have a U^{-1} such that $\lambda^\sigma = U^{-1}(\chi(t' + n))$. Put $t = t' + n$, then $\lambda^\sigma = U^{-1}(\chi(t))$, and we write

$$\sigma = l(t) = \log_\lambda U^{-1}(\chi(t)).$$

When there is a solution $\chi(t)$ of (2.2) and we write $s(t+1) = F(s(t), w(t))$, $w(t+1) = G(s(t), w(t))$, according to [3], we can prove existence of Ψ such that

$$\Psi(F(\chi, \Psi(\chi))) = G(\chi, \Psi(\chi)).$$

Then we obtain the following first order difference equation from (2.2)

$$\chi(t+1) = \Psi(\chi(t)). \tag{4.1}$$

So that we have $\chi(t+1) = \Psi(\chi(t)) = \Psi(U(\lambda^{\sigma})) = \Psi(u(\sigma)) = u(\sigma+1)$, and $\sigma + 1 = l(t+1)$, $\quad l(t) + 1 = l(t+1)$.

Hence we obtain

$$l(t) = t + \pi(t) \quad (\pi : \ \text{arbitrarily period one}). \tag{4.2}$$

Then $\sigma = t + \pi(t)$, and $\chi(t) = U(\lambda^{\sigma}) = \sum_{n=1}^{\infty} \alpha_n (\lambda^{\sigma})^n = \sum_{n=1}^{\infty} \alpha_n (\lambda^{t+\pi(t)})^n = \sum_{n=1}^{\infty} \alpha_n (\lambda^{\pi(t)} \cdot \lambda^t)^n$. Now we put $\lambda^{\pi(t)}$ into $\pi(t)$, then $\chi(t)$ can be written as

$$\chi(t) = \sum_{n=1}^{\infty} \alpha_n \lambda^{n(\frac{\log \pi(t)}{\log \lambda} + t)} \tag{4.3}$$

Thus we have the following theorem

Theorem. *Suppose that $u(\tau)$ be the solution of (2.2) obtained in Section 3. Suppose $\chi(t)$ be an analytic solution of (2.2) such that $\chi(t+n) \to 0$ as $n \to +\infty$, uniformly on any compact set. Then there is a periodic entire function $\pi(t), (\pi(t+1) = \pi(t))$, such that*

$$\chi(t) = \sum_{n=1}^{\infty} \alpha_n \lambda^{n(\frac{\log \pi(t)}{\log \lambda} + t)},$$

where $\pi(t)$ is an arbitrarily periodic function whose period is one.

Conversely if we put

$$\chi(t) = \sum_{n=1}^{\infty} \alpha_n \lambda^{n(\frac{\log \pi(t)}{\log \lambda} + t)},$$

where π is a periodic function whose period is one, then $\chi(t)$ is a solution of (2.2).

Now we have a general solution of (2.1) such that

$$\chi(t) = \sum_{n=1}^{\infty} \alpha_n \lambda^{n(\frac{\log \pi(t)}{\log \lambda} + t)},$$

where π is an arbitrarily periodic function whose period is one. And we have general solution $v(t) = \Phi(\chi(t))$ of (1.5) by (2.1). Thus we can obtain stable analytic general solutions $(x(t), y(t))$ of (1.2) by

$$x(t) = \chi(t) + \gamma, \quad y(t) = \Phi(\chi(t)) + \frac{a}{\delta}.$$

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