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PERSISTENCE AND EXTINCTION IN A MATHEMATICAL MODEL OF CELL POPULATIONS AFFECTED BY RADIATION

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Dedicated to the memory of Professor Miklós Farkas

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Abstract

A mathematical model consisting of a system of two ordinary differential equations is formulated to represent the interrelationship between healthy and radiated cells at a given cite. Three different modes of radiation are considered: constant, decaying, and periodic radiation. For the constant case, precise criteria for persistence and extinction are obtained. In the decaying case, it is shown that the radiated cells always become extinct. Finally in the periodic case, criteria are obtained for a perturbed positive periodic solution.

1. Introduction

Radiation destroys cells by causing one or more chromosomes to break. When this happens, the cells cannot reproduce and eventually die off [6], [10], [12]. Sometimes this is good, such as when one is trying to kill cancer cells, and sometimes it is bad, such as in the nuclear disasters of Three Mile Island, Pennsylvania and Chernobyl, Ukraine. Hence the question of persistence or extinction of a community of cells exposed to radiation is of paramount interest. Therefore the main purpose

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of this paper is to model the effects of radiation on cell populations. We choose as our modelling medium a system of ordinary differential equations as was done in [11].

It is sometimes possible for the broken chromosomes to recombine. This may lead to the original configuration of the chromosomes, it may lead to mutation, or the recombination may be in such a way as to be completely ineffective [9], [12]. Here we view the first of these possibilities as a probability of "broken" cells becoming "whole" again.

The radiation protocol may be one of several modes [13]. In this paper we consider three modes of protocol, constant dosage, such as in the case of long term radiation after a nuclear accident, or low dose radiation leakage near atomic reactors; decaying radiation, such as radioactive material implanted to fight lung cancer; and periodic dosages. Due to limitation of space, in this paper we only consider small periodic perturbations.

The organization of this paper is as follows. In the next section we introduce the general model and derive some properties. We also remind the reader of persistence and extinction definitions. Sections 3, 4 and 5 contain both analytical and numerical analysis of the constant, decaying, and periodic cases, respectively. The last section contains a brief discussion.

2. The model

In a given cell population (for example a bodily organ) let $u(t)$ be the concentration of healthy cells, and $v(t)$ be the concentration of radiated cells, i.e. cells with one or more broken chromosomes. Our model then takes the form

$$\begin{aligned} \dot{u} &= ru\Big(1 - \frac{u}{K}\Big) - D(t)u + pv, \qquad && u(0) \geq 0, \\ \dot{v} &= D(t)u - pv - \delta v, && v(0) \geq 0, \end{aligned} \tag{2.1}$$

where $D(t)$ is continuous for all $t > 0$, and $(\dot{} = \frac{d}{dt})$. We assume that the growth of the healthy cells is logistic as in [1], [10]. Healthy cells that become radiated with broken chromosomes are represented by $D(t)u$, where $D(t)$ is the rate of radiation protocol. Finally p is the probability rate that radiated cells recombine into healthy cells. δ is the washout rate of radiated cells. K is the carrying capacity of the healthy cell population.

In this paper we consider three modes for $D(t)$:

(i) $D(t) = \Delta$, constant;

(ii) $D(t) = D_0 e^{-\alpha t}$, decay;

(iii) $D(t) = \Delta + \varepsilon D_1(t)$, $D_1(t + w) = D_1(t)$, perturbed periodic.

We now show some preliminary results for system (2.1).

LEMMA 2.1. *Let $u(t)$, $v(t)$ be solutions of system* (2.1)*, $D(t)$ be continuous and $\varepsilon \geq 0$. Then $u(t)$, $v(t)$ exist uniquely and $u(t) \geq 0$, $v(t) \geq 0$.*

PROOF. If $u(0) = v(0) = 0$, then $u(t) \equiv v(t) \equiv 0$.

If $u(t) > 0$, then $\dot{v}|_{v=0} \geq 0$ and hence solutions cannot exit the nonnegative orthant through the v axis. If $v(t) > 0$, then $\dot{u}|_{u=0} = pv > 0$, and so solutions cannot exit through the u-axis.

□

LEMMA 2.2. *System* (2.1) *is dissipative. The region of dissipativity is contained in*

$$\mathcal{A} = \Big\{(u, v) : 0 \leq u + v \leq \frac{(r+\delta)^2 K}{4r\delta}\Big\}.$$

PROOF. Let $w = u + v$. From (2.1),

$$\dot{w} = ru\Big(1 - \frac{u}{K}\Big) - \delta v = (r+\delta)u - \frac{ru^2}{K} - \delta w,$$
$$\dot{w} \leq -\delta w + \frac{(r+\delta)^2 K}{4r}\,.$$

Hence, since the solution to

$$\dot{w} = -\delta w + \frac{(r+\delta)^2 K}{4r} \quad \text{is} \quad w(t) = ce^{-\delta t} + \frac{(r+\delta)^2 K}{4r\delta}\,,$$

then by the Kamke comparison theorems

$$0 \leq w(t) \leq \max\Big\{u(0) + v(0),\ \frac{(r+\delta)^2 K}{4r\delta}\Big\}$$

showing the boundedness and the dissipativity.

□

We now remind the reader of the mathematical definitions of persistence and extinction.

DEFINITION 2.3. Let $N(t)$ be a component of a dynamical system. We say that $N(t)$ persists, if $N(0) > 0 \Longrightarrow \liminf_{t\to\infty} N(t) > 0$. We say that the system persists if all components persist.

DEFINITION 2.4. For the above system we say that $N(t)$ uniformly persists if $N(0) > 0 \Longrightarrow \liminf_{t\to\infty} N(t) \geq \eta > 0$, where η is independent of $N(0)$. A system uniformly persists if all components persist uniformly.

DEFINITION 2.5. $N(t)$ exhibits extinction if $N(0) > 0 \Rightarrow \lim_{t\to\infty} N(t) = 0$.

3. The case of constant radiation

In this section, we assume that $D(t) \equiv \Delta$, a constant. Then system (2.1) becomes

$$\begin{aligned} \dot{u} &= ru\Big(1 - \frac{u}{K}\Big) - \Delta u + pv, \qquad && u(0) \geq 0, \\ \dot{v} &= \Delta u - pv - \delta v, && v(0) \geq 0. \end{aligned} \tag{3.1}$$

First we note that there are at most two equilibria for system (3.1). $E_0(0,0)$ is always an equilibrium and $E^*(u^*, v^*)$, $u^* > 0$, $v^* > 0$ may or may not exist. Solving

$$\begin{aligned} & ru\Big(1 - \frac{u}{K}\Big) - \Delta u + pv = 0, \\ & \Delta u - pv - \delta v = 0, \quad u, v \neq 0, \end{aligned} \tag{3.2}$$

we obtain that

$$u^* = \frac{K[r(p+\delta) - \Delta\delta]}{r(p+\delta)}, \quad v^* = \frac{K\Delta[r(p+\delta) - \Delta\delta]}{r(p+\delta)^2}. \tag{3.3}$$

Clearly E^* exists if and only if

$$\Delta < \frac{r(p+\delta)}{\delta}. \tag{3.4}$$

The variational matrix about a given equilibrium $(\bar{u}, \bar{v})$ is

$$\overline{M} = \begin{bmatrix} r - \frac{2r\bar{u}}{K} - \Delta & p \\ \Delta & -p-\delta \end{bmatrix}. \quad \text{Hence} \quad M_0 = \begin{bmatrix} r - \Delta & p \\ \Delta & -p-\delta \end{bmatrix}.$$

The stability of E_0 is given by the eigenvalues of M_0, which are

$$\lambda_{\pm} = \frac{r - \Delta - p - \delta}{2} \pm \frac{[(r - \Delta - p - \delta)^2 + 4(r-\Delta)(p+\delta) + 4p\Delta]^{1/2}}{2}. \tag{3.5}$$

Note that $(r - \Delta - p - \delta)^2 + 4(r-\Delta)(p-\delta) + 4p\Delta = (r - \Delta + p + \delta)^2 + 4p\Delta > 0$, and hence λ is real. Also note that $\lambda_- < 0$. The condition for λ_+ to be positive is $(r-\Delta)(p+\delta) + p\Delta > 0$, i.e. $\Delta < \frac{r(p+\delta)}{\delta}$, i.e. (3.4) holds. From this we have the following theorem.

THEOREM 3.1. *E^* exists if and only if E_0 is unstable.*

Note that if E^* does not exist, because of dissipativity and the fact that any nontrivial periodic solution must surround an equilibrium [3], E_0 will be globally asymptotically stable.

Now suppose E^* exists. We use Dulac's theorem [1, Ch. VI] to show that there are no periodic solutions in this case. Consider

$$\begin{aligned}&\frac{\partial}{\partial u}\left\{\frac{1}{uv}\left[ru\Big(1-\frac{u}{K}\Big)-\Delta u+pv\right]\right\}+\frac{\partial}{\partial v}\left\{\frac{1}{uv}\left[\Delta u-(p+\delta)v\right]\right\}\\&\quad=\frac{\partial}{\partial u}\left[\frac{r}{v}-\frac{ru}{Kv}-\frac{\Delta}{v}+\frac{p}{u}\right]+\frac{\partial}{\partial v}\left[\frac{\Delta}{v}-\frac{(p+\delta)}{u}\right]\\&\quad=-\frac{r}{Kv}-\frac{p}{u^2}-\frac{\Delta}{v^2}<0\end{aligned}$$

in the first quadrant. Hence Dulac's theorem shows that there are no periodic solutions in this quadrant. Together with dissipativity we get the following result.

THEOREM 3.2. *If E^* exists, it is globally asymptotically stable with respect to $R^2_+\backslash E_0$.*

We illustrate the above situations with some numerical examples. Figure 3.1 illustrates Theorem 3.1.

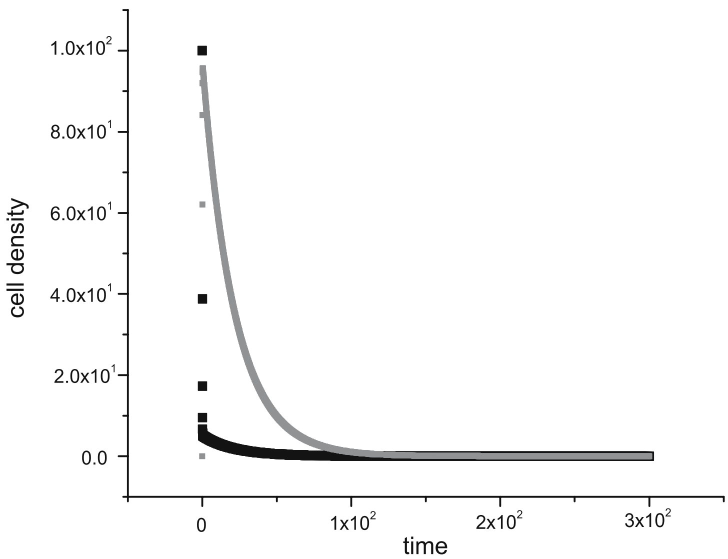

FIGURE 3.1. *Case where E^* doesn't exist and E_0 is globally stable: $\Delta = 20$, $r = 1$, $K = 100$, $p = 1$, $\delta = 0.1$, $u(0) = 100$, $v(0) = 0$, black = healthy cells, grey = radiated cells*

Figures 3.2 and 3.3 illustrate Theorem 3.2.

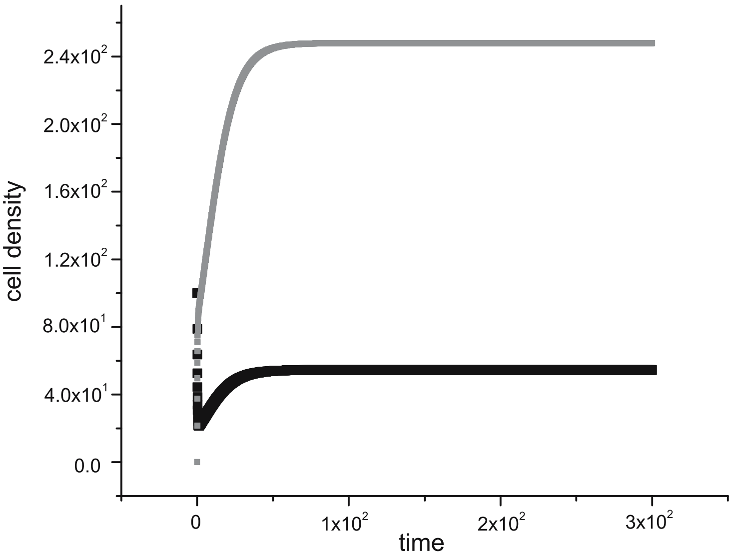

FIGURE 3.2. *Case where E^* exists and is globally stable:* $\Delta = 5$, $r = 1$, $K = 100$, $p = 1$, $\delta = 0.1$, $(u(0), v(0)) = (100, 0)$, *black = healthy cells, grey = radiated cells; healthy cells approach a low level equilibrium*

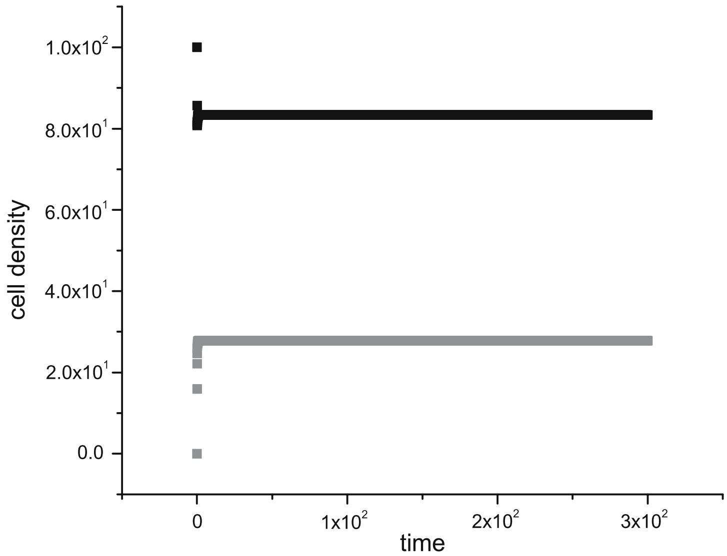

FIGURE 3.3. *Case where E^* exists and is globally stable:* $\Delta = 5$, $r = 10$, $K = 100$, $p = 10$, $\delta = 5$, $(u(0), v(0)) = (100, 0)$, *black = healthy cells, grey = radiated cells; healthy cells approach a high level equilibrium*

Note that values are chosen to illustrate the theorems and do not come from any real cell populations.

From the above we have the following result.

THEOREM 3.3. *System* (3.1) *persists (uniformly) if and only if* $\Delta < \frac{r(p+\delta)}{\delta}$. *Otherwise the cell population becomes extinct.*

4. The case of decaying radiation

In this case, system (2.1) reduces to the system

$$\begin{aligned} \dot{u} &= ru\Big(1 - \frac{u}{K}\Big) - D_0 e^{-\alpha t} + pv, \\ \dot{v} &= D_0 e^{-\alpha t} - (p+\delta)v. \end{aligned} \tag{4.1}$$

Here, we can show that the dynamics of this system is simple in that solutions will always tend to an equilibrium.

First we consider the asymptotic system by taking $\lim_{t\to\infty}$,

$$\begin{aligned} \dot{x} &= rx\Big(1 - \frac{x}{K}\Big) + py, \qquad & x(0) \geq 0, \\ \dot{y} &= -(p+\delta)y, & y(0) \geq 0. \end{aligned} \tag{4.2}$$

We now state and prove the following theorem.

THEOREM 4.1. *Let* $(u(t), v(t))$ *be a solution of system* (4.1)*. Then either* $\lim_{t\to\infty}(u(t), v(t)) = (0,0)$ *or* $\lim_{t\to\infty}(u(t), v(t)) = (K, 0)$.

Figures 4.1 and 4.2 illustrate both possibilities.

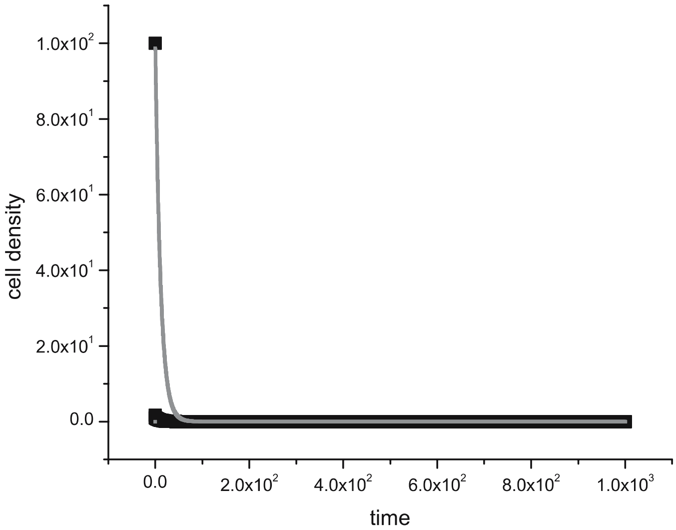

FIGURE 4.1. *Time evolution of system* (4.1) *with solutions approaching* (0,0)*:* $r = 1$, $K = 100$, $D_0 = 100$, $\delta = -1$, $p = 1$, $\alpha = 0.001$, $(u(0), v(0)) = (100, 0)$, *black* = $u(t)$, *grey* = $v(t)$

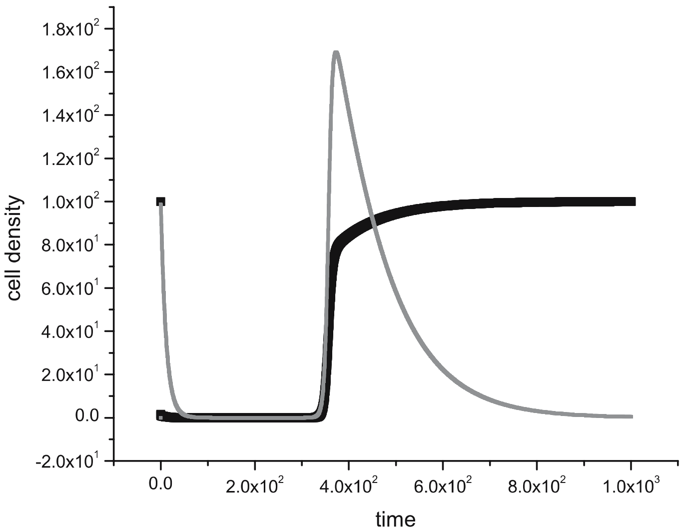

FIGURE 4.2. *Time evolution of system* (4.1) *with solutions approaching* $(K, 0)$*:* $r = 1$*,* $K = 100$*,* $D = 100$*,* $p = 1$*,* $\delta = 0.1$*,* $\alpha = .01$*,* $(u(0), v(0)) = (100, 0)$*, black* $= u(t)$*, grey* $= v(t)$

PROOF. By Theorem 1.8 of [8], the omega limit sets of system (4.1) are contained within the chain recurrent sets of system (4.2). But the only chain recurrent sets of (4.2) are $(0, 0)$ and $(K, 0)$, completing the proof.

□

5. Case of periodically perturbed radiation

Here our system becomes

$$\begin{aligned} \dot{u} &= ru\Big(1 - \frac{u}{K}\Big) - (\Delta + \varepsilon D_1(t))u + pv, \qquad && u(0) \geq 0, \\ \dot{v} &= (\Delta + \varepsilon D_1(t))u - (p + \delta)v, && v(0) \geq 0. \end{aligned} \tag{5.1}$$

We will restrict ourselves to the case where (3.4) holds, so that when $\varepsilon = 0$, (u^*, v^*) exists.

For convenience of notation, let

$$X = \begin{bmatrix} u - u^* \\ v - v^* \end{bmatrix} = \begin{bmatrix} x_1 \\ x_2 \end{bmatrix}, \quad A = \begin{bmatrix} r - \frac{2ru^*}{K} - \Delta & p \\ \Delta & -p - \delta \end{bmatrix},$$

$$F(t, X, \varepsilon) = AX - \begin{bmatrix} ru(1 - \frac{u}{K}) - (\Delta + \varepsilon D_1(t))u + pv \\ (\Delta + \varepsilon D_1(t))u - (p + \delta)v \end{bmatrix}.$$

After simplification and using $u = X_1 + u^*$, $v = X_2 + v^*$, we get

$$F(t, X, \varepsilon) = \begin{bmatrix} -\frac{r}{K} X_1^2 - \varepsilon D_1(t)(X_1 + u^*) \\ \varepsilon D_1(t)(X_1 + u^*) \end{bmatrix}.$$

Then system (5.1) can be written as

$$\dot{X} = AX + F(t, X, \varepsilon). \tag{5.2}$$

Further

$$F(t, 0, 0) = \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \quad F_X(t, X, \varepsilon) = \begin{bmatrix} -\frac{2r}{K} X_1 - \varepsilon D_1(t) & 0 \\ \varepsilon D_1(t), & 0 \end{bmatrix},$$

and so

$$F_X(t, 0, 0) = \begin{bmatrix} 0 & 0 \\ 0 & 0 \end{bmatrix}.$$

Furthermore, since we know from Section 3 that when $\varepsilon = 0$, E^* exists and is globally stable, tha linear system

$$\dot{X} = AX \tag{5.3}$$

has all eigenvalues with negative real parts and hence no periodic solution.

From this, using Poincare's theorem [2, Ch. 14], there is a perturbed nontrivial periodic solution for system (5.2) and so for system (5.1). This is illustrated in Figure 5.2.

Of course, if Δ is sufficiently large, then solutions go to $(0, 0)$, as illustrated by Figure 5.1.

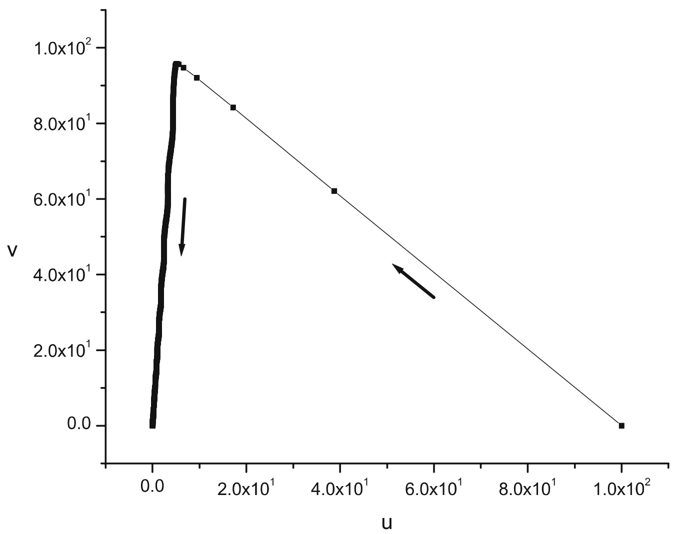

FIGURE 5.1. *Phase space in the case of periodically perturbed radiation, where solutions approach the origins:* $\Delta = 20$, $r = 1$, $K = 100$, $p = 1$, $\delta = 0.1$, $\varepsilon = 1$, $D_1(t) = \sin t$

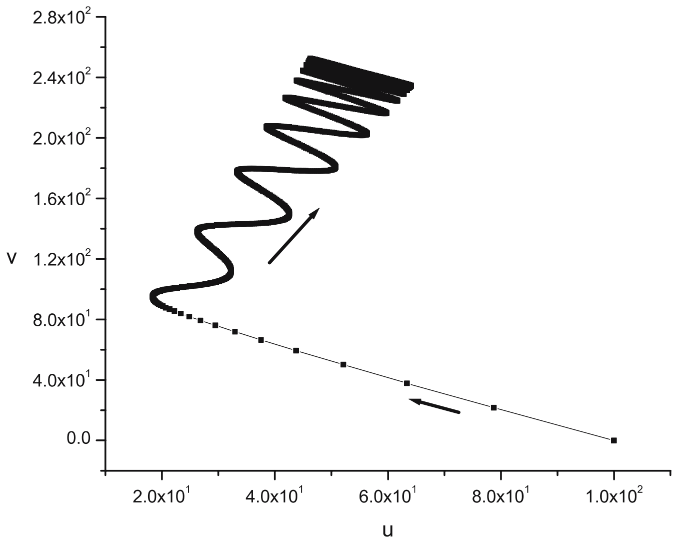

FIGURE 5.2. *Phase space in the case of periodically perturbed radiation, where solutions approach a periodic orbit:* $\Delta = 5$, $r = 1$, $K = 100$, $p = 1$, $\delta = 0.1$, $\varepsilon = 1$, $D_1(t) = \sin t$

6. Discussion

In this paper, we considered a model of a cell population subjected to radiation, incorporating recombination of radiated cells. We considered three different radiation protocols, namely constant, decaying and perturbed periodic.

In the constant case, we were able to completely analyze the model, obtaining precise criteria for the persistence or extinction of the cell population in terms of the radiation strength. In fact, we determined a threshold value of Δ $(> r)$ for persistence.

In the decay case, we showed that solutions always approach an equilibrium, either $(0, 0)$ or $(K, 0)$, so that eventually radiated cells vanish from the cell population. From the figures one can see that if the initial impulse of radiation is sufficiently high and the decay is sufficiently low, extinction of the healthy cells will occur (see Figure 4.1). However, if the decay is rapid, then the healthy cells persist (see Figure 4.2).

In the periodic case we again can show both persistence and extinction. In the persistence case solutions approach a periodic solution (see Figure 5.2).

There are three main projects arising from this paper for future research. The first is to consider general periodic radiation. The second is to consider multiple chromosome breaks. The third is to consider two competing cell populations (such as normal and cancer cells at the same site) subjected to radiation.

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