Mathematical analysis of Solutions of Drug Models

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Abstract: In this paper the behavior of solutions of permanent drug resistance model is discussed.The equilibrium points of two drugs resistance are computed. The local stability near equilibrium pionts is discussed. The boundedness, existance of periodic orbits, global stability of permanent drug resistance are studied. the probability generating function for two drugs resistance model in all possible cases is discussed. The obtained results improve and generalize some known results in the literature.
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1 . Introduction

The emergence of drug resistance has created a new challenge for experimental and theoretical studies. A great important in therapy have been in tumors of hemopoietic and lymphoreticular systems in a number of childhood and in germ cells tumors ([1]). However there has been relative little success in the case of clinical detectable dimension solid tumors. One of the reasons which can lead to the failure of chemotherapy is the possible resistance of the tumor cells to the effect of the drug. In [2], the authors used a scheme proposed for self-renewing system in which cells be either (i) system cells, (ii) early differentiated cells, or (iii) end cells, and the human tumor cells model more randomly between these three compartments with transitions in one way (i)→(ii)→(iii) (see [3] and [4]). Following [5], we assume that each tumor arises from a single cell. This may say that the first tumor cell is a stem cell and all the other cells derive from this single stem cell. More precisely, it is assumed that the divisions occur at a rate b and the rate of transmission to nonstem cells is denoted by d. So the system growth can be seen as birth process with parameter b and death one with parameter d. By a resistant cell we mean a cell which will survive administration of the drug at a therapeutic dose with propability one. Sometimes in studying the control of the emergence of drug resistence pathogen, it is important to understand the nonlinear transmission dynamics of both the drug-sensitive and the drug-resistant pathogen. We will consider the case for which both resistant and sensitive stem cells divide and grow at the same rate. We also assume that the coversion to resistance occurs spontaneously during the intermitotic period. Moreover unlike some of the previous models , we consider the availability of possible interdivisional mechanism [6].

In this paper we consider the case where a single drug is available. Define α as the rate of development of spontaneous resistance for stem cells to a given drug, which may also be referred as the mutation rate to drug resistance. Let $S(t)$ be the deterministic size of the stem cell compartment at time t. Consider two drugs T_1 and T_2, say; then four resistant exist: (i) stem cells sensitive to both drugs, S; (ii) stem cells resistant to the first but not the second drug, R_1; (iii) stem cells resistant to the second but sensitive to the first R_2; (iv) cells resistant to both drugs, R_{12}. Analogously to the single drug situation, define transition rates α_1 and α_2 for sensitive cells to become resistant to T_1 and T_2 respectively. Let α_1 and α_2 be the rates at with cells resistant to T_1 and T_2, become resistant to other agent. We will assume that cells may not develop resistance to both agents simultaneously. We will also assume that all resistant cells grow at the same rate as the sensitive cells. Define

$P_{ijk}(t) = P\{R_1(t) = i, R_2(t) = j, R_{12}(t) = k\}$,

and

$$\phi(t, s_1, s_2, s_3) = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} P_{ijk}(t) s_1^i s_2^j s_3^k \quad (1.1)$$

Then using the Kolmogorov backward equations, we have

$$\frac{dP_{ijk}(t)}{dt} = (\alpha_1 + \alpha_1)S(t)P_{ijk}(t) - (b + d + a_1)iP_{ijk}(t)$$
$$-(b + d + a_2)jP_{ijk}(t) - (b + d)kP_{ijk}(t)$$
$$+\alpha_1 S(t)P_{i-1jk}(t) + \alpha_2 S(t)P_{ij-1k}(t)$$

$+b(i-1)P_{i-1jk}(t)+b(j-1)P_{ij-1k}(t)+b(k-1)P_{ijk-1}(t)$

$+d(i+1)P_{i+1jk}(t)+d(j+1)P_{ij+1k}(t)+d(k+1)P_{ijk+1}(t) \qquad (1.2)$

$+a_1(i+1)P_{i-1jk-1}(t)+a_2(j+1)P_{ij+1k-1}(t).$

As before, set $P_{ijk}(t)=0$ for $i<0, j<0$ or $k<0$. Multiplying both sides by $s_1^i s_2^j s_3^k$ and summing $\sum_{i=0}^{\infty}\sum_{j=0}^{\infty}\sum_{k=0}^{\infty}$ yields

$$\frac{\partial\phi}{\partial t}+[(1-s_1)(bs_1-d)+a_1(s_1-s_3)]\frac{\partial\phi}{\partial s_1}+[(1-s_2)(bs_2-d)+a_2(s_2-s_3)]\frac{\partial\phi}{\partial s_2}+(1-s_3)(bs_3-d)\frac{\partial\phi}{\partial s_3} \qquad (1.3)$$

$$=S(t)[\alpha_1(s_1-1)+\alpha_2(s_2-1)].$$

Again we will use Cauchy's method of characteristics to solve this equation. Let $x_1=t$, $x_2=s_1$, $x_3=s_3$ and $x_4=s_3$ and we have the differential system of two drugs in the form

$$\begin{aligned}
\frac{dx_1}{dt}&=1\\
\frac{dx_2}{dt}&=(1-x_2)(bx_2-d)+a_1(x_2-x_4),\\
\frac{dx_3}{dt}&=(1-x_3)(bx_3-d)+a_2(x_3-x_4)\\
\frac{dx_4}{dt}&=(1-x_4)(bx_4-d), \qquad (1.4)\\
\frac{d\Phi}{dt}&=S(x_1)[\alpha_1(x_2-1)+\alpha_2(x_3-1)],
\end{aligned}$$

where the growth of the stem cell compartment may be viewed as a birth and death process with rates b and d respectively. Without loss of generality we set $x=x_2$, $y=x_3$ and $z=x_4$ we have the reduced system

$$\begin{aligned}
\frac{dx}{dt}&=(1-x)(bx-d)+a_1(x-z),\\
\frac{dy}{dt}&=(1-y)(by-d)+a_2(y-z), \qquad (1.5)\\
\frac{dz}{dt}&=(1-z)(bz-d).
\end{aligned}$$

The organization of the paper is as follows. In the next section, we discuss the existence of equilibria and their local and global stability . In the section that follows, we calculate the probability generating function for two drugs resistance model in all possible cases of equilibria. Then we give a conclusion for our results.

2. **The equilibria: existence and Stability**

The equilibria of system (1.5) are obtained by solving the system of isocline equations

$$\begin{aligned}
&(1-x)(bx-d)+a_1(x-z)=0,\\
&(1-y)(by-d)+a_2(y-z)=0, \qquad (2.1)\\
&(1-z)(bz-d)=0.
\end{aligned}$$

The possible equilibria are of the form $E_1=(1,1,1)$, $E_2=\left(\frac{a_1+d}{b},1,1\right)$, $E_3=\left(1,\frac{a_2+d}{b},1\right)$, $E_4=\left(\frac{a_1+d}{b},\frac{a_2+d}{b},1\right)$, $E_5=\left(\frac{d}{b},\frac{d}{b},\frac{d}{b}\right)$, $E_6=\left(\frac{d}{b},\frac{a_2+b}{b},\frac{d}{b}\right)$, $E_7=\left(\frac{a_1+b}{b},\frac{d}{b},\frac{d}{b}\right)$ and $E_8=\left(\frac{a_1+b}{b},\frac{a_2+b}{b},\frac{d}{b}\right)$. The existence and local stability of the prospective equilibria are analysed as follows. The Jacobian matrix due to the linearization of (1.5) about an arbitrary equilibrium $E=(x,y,z)\in R_+^3$ is given by

$$J_{E=(x,y,z)}=\begin{pmatrix} b(1-x)-(bx-d)+a_1 & 0 & -a_1\\ 0 & b(1-y)-(by-d)+a_2 & -a_2\\ 0 & 0 & b(1-z)-(bz-d)\end{pmatrix}.$$

(2.2)

Let J_i denotes $J_{E=(x,y,z)}$ at E_i , $i=1,2,3,4,5,6,7,8$ respectively. Assuming that the difference between the birth and death rates is $\delta=b-d \ \geq 0$,then from (2.2) we have

$$J_1=\begin{pmatrix} a_1-\delta & 0 & -a_1\\ 0 & a_2-\delta & -a_2\\ 0 & 0 & \delta\end{pmatrix},$$

$$J_2=\begin{pmatrix} -\delta-a_1 & 0 & -a_1\\ 0 & a_2-\delta & -a_2\\ 0 & 0 & \delta\end{pmatrix},$$

$$J_3=\begin{pmatrix} a_1-\delta & 0 & -a_1\\ 0 & \delta-a_2 & a_2\\ 0 & 0 & -\delta\end{pmatrix},$$

$$J_4=\begin{pmatrix} \delta-a_1 & 0 & -a_1\\ 0 & \delta-a_2 & a_2\\ 0 & 0 & -\delta\end{pmatrix},$$

$$J_5=\begin{pmatrix} \delta+a_1 & 0 & a_1\\ 0 & \delta+a_2 & -a_2\\ 0 & 0 & \delta\end{pmatrix},$$

$$J_6=\begin{pmatrix} \delta+a_1 & 0 & -a_1\\ 0 & -\delta-a_2 & -a_2\\ 0 & 0 & \delta\end{pmatrix},$$

$$J_7=\begin{pmatrix} -\delta-a_1 & 0 & -a_1\\ 0 & \delta+a_2 & -a_2\\ 0 & 0 & \delta\end{pmatrix},$$

$$J_8=\begin{pmatrix} -\delta-a_1 & 0 & -a_1\\ 0 & \delta-a_2 & a_2\\ 0 & 0 & \delta\end{pmatrix}.$$

Form the above matrices, we have:

(1) The eigenvalues at $E_1=(1,1,1)$ are
$\lambda_1=-\delta,\ \lambda_2=a_1-\delta$ and $\lambda_3=a_2-\delta.$

(2) The eigenvalues at $E_2=\left(\frac{a_1+d}{b},1,1\right)$ are
$\lambda_1=-\delta,\ \lambda_2=-\delta+a_1$ and $\lambda_3=\delta-a_2.$ (2.1)

(3) The eigenvalues at $E_3=\left(1,\frac{a_2+d}{b},1\right)$ are
$\lambda_1=-\delta, \lambda_2=\delta-a_1$ and $\lambda_3=\delta-a_2.$

(4) The eigenvalues at $E_4 = \left(\frac{a_1+d}{b}, \frac{a_2+d}{b}, 1\right)$ are
$\lambda_1 = -\delta,\ \lambda_2 = \delta - a_1$ and $\lambda_3 = \delta - a_2$.
(5) The eigenvalues at $E_5 = \left(\frac{d}{b}, \frac{d}{b}, \frac{d}{b}\right)$ are
$\lambda_1 = \delta,\ \lambda_2 = \delta + a_1$ and $\lambda_3 = \delta + a_2$.
(6) The eigenvalues at $E_6 = \left(\frac{d}{b}, \frac{a_2+b}{b}, \frac{d}{b}\right)$ are
$\lambda_1 = \delta, \lambda_2 = \delta + a_1$ and $\lambda_3 = -\delta - a_2$.
(7) The eigenvalues at $E_7 = \left(\frac{a_1+b}{b}, \frac{d}{b}, \frac{d}{b}\right)$ are
$\lambda_1 = \delta,\ \lambda_2 = \delta + a_2$ and $\lambda_3 = -\delta - a_1$.
(8) The eigenvalues at $E_8 = \left(\frac{a_1+b}{b}, \frac{a_2+b}{b}, \frac{d}{b}\right)$ are
$\lambda_1 = \delta,\ \lambda_2 = -\delta - a_1$ and $\lambda_3 = -\delta - a_2$.
From the above discussion we have the following conclusion.

Proposition 2.1 Whenever $\delta \to 0$, then $E_5 \to E_1$ and so the system (1.5) have seven equilibria. Moreover if $\delta \to 0$ and $a_1 = a_2$, then $E_4 = E_8$ and the system has only six equilibria. Whenever $\delta > 0$ the system (1.5) have eight equilibria, where

for δ=max(a_1,a_2) , E_1 is locally asymptotically

stable while for $\delta \in (a_1, a_2)$ E_3 is locally asymptotically stable. For $\delta \in (a_1, a_2)$, E_2 is locally asymptotically stable. For $\delta < a_i$, $i = 1,2$ E_4 is locally asymptotically stable. The equilibria E_i, $i = 5,6,7,8$ are unstable. Now we discuss the boundedness of solutions of (1.5).

Theorem 2.1 All solution of (1.5) which initiate in R^3 are uniformly bounded.
Proof. Define a function
$w = x + y + x$ (2.3) (2.3)
The time derivative of (2.3) along the solutions of (1.5) is
$\frac{dw}{dt} = (b+d)w - b(x^2+y^2+z^2) + a_1(x-2) + a_2(y-2) - 3d$

$\leq (b+d)w + a_1x + a_2y - (a_1+a_2)z.$
For each $D > 0$, the following inequality holds
$\frac{dw}{dt} + \big(D - (b+d)\big)w \leq (a_1+D)x + (a_2+D)y - (a_1+a_2-D)z$
(2.4) (2.4)
Now if we take $\max(b+d) < D < \min(a_1+a_2)$, the Eq. (2.4) reduced to
$$\frac{dw}{dt} + \tilde{D}w \leq (a_1+D),$$
where $\tilde{D} = D - (b+d)$. Then we can find a constant $L > 0$, say such that $\frac{dw}{dt} + \tilde{D}w$. Applying the theorem of differential inequality (see[7] and [8]) we obtain
$0 < w(x,y,z) \leq$
$\frac{L}{\tilde{D}}\left(1 - e^{-\tilde{D}t}\right) + w(x(0),y(0),z(0))e^{-\tilde{D}t},$

and for $t \to \infty$, we have
$$0 < w < \frac{L}{\tilde{D}}.$$
Hence all solutions of (1.5) that initiate in $\{R_+^3 - 0\}$ are confined in the region.

Now we use the idea of [12] and write the system (1.5) in the form
$\frac{dz}{dt} = (1-u)(bu-d) = p(x_i, z),$ (2.5)
$\frac{dx_i}{dt} = (1-x_i)(bx_i - d) + a_1(x_i - z) = p(x_i, z)$
$i = 1,2$. and have the following result regarding the nonexistence of periodic orbits.

Theorem 2.2 The system (2.5) does not have nontrivial periodic orbits.
Proof. Consider the system (2.5) for $x_i > 0$ and $z > 0$. Taking a Dulac function
$$D(x_i, z) = e^{\frac{2b}{a_1}x_i t}.$$
Then
$div[D(x,y)F(x,y)]$

$$= div \begin{matrix} D(x,y)[(1-x)(bx-d) + a_1(x_i - z)] \\ D(x,y)[(1-z)(bz-d)] \end{matrix}$$
$$= \frac{\partial(D_p)}{\partial x} + \frac{\partial(D_q)}{\partial x}$$
$$= -be^{\frac{2b}{a_1}x}[x^2 - Ax - B].$$
where $A = 1 + \frac{2(b-d)}{a_1} > 0$ and $B = 2 + \frac{3d+2a_1}{b} > 0$. Therefore for the value of x in the interval $\left(\frac{A}{2} - \frac{1}{2}\sqrt{A^2+4AB}, \frac{A}{2} + \frac{1}{2}\sqrt{A^2+4AB}\right)$ we have
$$\frac{\partial(D_p)}{\partial x} + \frac{\partial(D_q)}{\partial x} < 0,$$
Thus by Bendixon-Dulac Theorem ([8]) the conclusion follows.

Now we have seen the local stability of all the equilibria of the 3-dimensional system (1.5), but it is interesting to know about the global stability of these equilibria. Our approach depends on the Lozinski measure ([8]).
Applying this measure on the variational matrix J_1 we obtain
$\mu_1(A) = \max\{a_1 - \delta, a_2 - \delta, a_1 + a_2 - \delta\}.$
Since $a_1 > 0$, $a_2 > 0$ and $\delta > 0$, then clearly $\mu_1(A) = a_1 + a_2 - \delta$ and if $a_1 + a_2 < \delta$, then $E_1 = (1,1,1)$ is globally asymptotically stable. This with the discussion in Proposition 2.1 shows that if $\delta > a_1 + a_2$, then $E_1 = (1,1,1)$ is locally and globally asymptotically stable.

Thus we can summurize the situation about the eight equilibria when δ, the difference between the rate of birth and death rate is positive, as follows

(1)
n the case of $\delta > A$ where $A = \max\{a_1, a_2\}$, $E_1 = (1,1,1)$ is locally asymptotically stable. Moreover if δ going to be larger such that $\delta > a_1 + a_2$, then by Lozinski measure, $E_1 = (1,1,1)$ is globally asymptotically stable.

(2)
f $a_1 > \delta > a_2$, then $E_2 = \left(\frac{a_1+d}{b}, 1, 1\right)$ is locally asymptotically stable.

(3)
f $a_2 > \delta > a_1$, then $E_3 = \left(1, \frac{a_2+d}{b}, 1\right)$ is locally asymptotically stable, while if $\delta > a_1 + a_2$, then $E_3 = \left(1, \frac{a_2+d}{b}, 1\right)$ is globally asymptotically stable.

(4)
f $\delta < a_i, i = 1,2$, then $E_4 = \left(\frac{a_1+d}{b}, \frac{a_2+d}{b}, 1\right)$ is locally asymptotically stable.

(5)
he remaining equilibrium points E_5, E_6, E_7 and E_8 are unstable.

3. Probability generating function at equilibria

In this section we calculate the probability generating function $\phi(t,x,y,z)$ for the two drugs resistance model in all possible cases. Following Coldman et al [5] we consider the probability generating function in the form

$$\phi(t,x,y,z) - \exp\{I_1(t) + \alpha_1 I_2(a_1,x) + \alpha_2 I_2(a_2,y)\}, \quad (3.1)$$

where

$$I_1(t) = -\delta(\alpha_1+\alpha_2)(z-1)\int_0^t \frac{S(t-u)}{I_3(u)}du, \quad (3.2)$$

$$I_2(a,s) = \int_0^t \frac{S(t-u)e^{(\delta-a)u}[I_3(u)]^{-2}}{\left([\delta^2(s-z)]^{-1} - b\int_0^u e^{(\delta-a)v}[I_3(v)]^{-2}dv\right)}du, \quad \mathbf{(3.3)}$$

(3.3)

$$I_3(u) = b(z \quad 1)e^{\delta u} \quad (bz \quad d), \quad (3.4)$$

(3.4)

$\delta = b - d$, $a = (\ a_1$ or $a_2\ )$, $s = (x$ or $y)$ and $S(t) = Ae^{\delta t}$ with $A = S(0)$. The probability that there are no resistant cell present at time t , $\{\phi(t,0,0,1)\}$ is an upper bound to the probability that the tumor will eliminated by the drug under consideration. Therefore the value $\phi(t,0,0,1)$ is of considerable interest during the following discussion.

Now, we consider the following cases:

Case 1. If $d \neq 0$, $b = 0$, $a_1 = 0$ and $a_2 = 0$, then $\delta = -d$ and the system (1.5) becomes

$$\frac{dx}{dt} = -d(1-x)$$
$$\frac{dy}{dt} = -d(1-y)$$
(3.5)
$$\frac{dz}{dt} = -d(1-z).$$

Let us consider the initial conditions $x(0) = \beta_1, y(0) = \beta_2,\ z(0) = \beta_3$.

Then the solutions of (3.5) are

$x(t) = 1 + (\beta_1 - 1)e^{dt}$,
$y(t) = 1 + (\beta_2 - 1)e^{dt}$ and
$z(t) = 1 + (\beta_3 - 1)e^{dt}$.

Now, form (3.2), (3.3) and (3.4) we obtain

$I_3(u) = d$,
$I_1(t) = A(\beta_3 - 1)t$,
$I_2(a_2, x) = \frac{A}{d}(\beta_1 - \beta_3)(1 - e^{-dt})$,
$I_2(a_2, y) = \frac{A}{d}(\beta_2 - \beta_3)(1 - e^{-dt})$,

and

$$\phi(t,x,y,z) = \exp\left\{\begin{array}{l} A(\beta_3-1)t + (\alpha_1+\alpha_2)t + \alpha_1\frac{A}{d}(\beta_1-\beta_3)(1-e^{-dt}) \\ +\alpha_2\frac{A}{d}(\beta_2-\beta_3)(1-e^{-dt}). \end{array}\right\}$$

T (3.6)

Remark 3.1 From the above probability generating function we have

(i) If $x = y = z = 1 + (k-1)e^{dt}$, then (3.6) takes the form $\phi(t,x,x,x) = \exp\{A(k-1)(\alpha_1+\alpha_2)t\}$,

(ii) $\phi(0,x,y,z) = 1$.

Case 2. If $d = 0$, $b \neq 0$, $a_1 = 0$ and $a_2 = 0$, then $\delta = d$ and the system (1.5) becomes

$$\frac{dx}{dt} = -bx(1-x)$$
$$\frac{dy}{dt} = -by(1-y)$$
(3.7) (3.7)
$$\frac{dz}{dt} = -bz(1-z).$$

Then the solutions of (3.7) are

$x(t) = \beta_1 e^{bt}\left(1 + \beta_1(e^{bt} - 1)\right)^{-1}$,
$y(t) = \beta_2 e^{bt}\left(1 + \beta_2(e^{bt} - 1)\right)^{-1}$,
$z(t) = \beta_3 e^{bt}\left(1 + \beta_3(e^{bt} - 1)\right)^{-1}$.

Now, form (3.2), (3.3) and (3.4) we obtain

$$I_3(u) = \frac{-be^{bu}}{1+\beta_3(e^{bu}-1)}$$

$$I_1(t) = -\frac{A(\alpha_1-\alpha_2)(\beta_3-1)}{1+\beta_3(e^{bt}-1)}\left(\frac{\beta_3-1}{b}(e^{bt}-1) - \beta_3 t e^{bt}\right)$$

$$I_2(0,s) = Ae^{bt}\int_0^t \frac{e^{-au}\left(1+\beta_3(e^{bt}-1)\right)^2}{\frac{e^{2bu}}{s-z} - be^{2bu}\int_0^u e^{(b\ \ a)v}\left(1+\beta_3(e^{bv}-1)\right)^2 dv}du,$$

and

$\phi(t,x,y,z) = \exp\{I_1(t) + \alpha_1 I_2(0,x) + \alpha_2 I_2(0,y)\}$.
(3.8)

Remark 3.2 From the above probability generating function we have

(i) If $x = y = z = 1 + (k-1)e^{dt}$, then (3.8) takes the form $\phi(t,x,x,x) = \exp\{A(k-1)(\alpha_1 + \alpha_2)t\}$,

(ii) $\phi(0,x,y,z) = 1$.

(iii) $\phi(t,1,1,1) = 1$.

Case 3. If $d \neq 0$, $b \neq 0$, $\alpha_1 = 0$ and $\alpha_2 = 0$, then $\delta = b - d$ and the system (1.5) becomes

$$\frac{dx}{dt} = (1-x)(bx-d),$$
$$\frac{dy}{dt} = (1-y)(by-d), \qquad (3.9)$$
$$\frac{dz}{dt} = (1-z)(bz-d).$$

Then the solutions of (3.9) are

$$x(t) = 1 + \frac{(d-b)(\beta_1-1)}{b(\beta_1-1)+(d-b\beta_1)e^{(b-d)t}},$$
$$y(t) = 1 + \frac{(d-b)(\beta_2-1)}{b(\beta_2-1)+(d-b\beta_2)e^{(b-d)t}},$$
$$z(t) = 1 + \frac{(d-b)(\beta_3-1)}{b(\beta_3-1)+(d-b\beta_3)e^{(b-d)t}}.$$

Now, form (3.2), (3.3) and (3.4) we obtain

$$I_3(u) = \frac{(d-b)^2 e^{(b-d)u}}{b(\beta_3-1)+(d-b\beta_3)e^{(b-d)u}},$$
$$I_1(t) = \frac{(\alpha_1+\alpha_1)}{(d-b)^3}(\beta_3-1)I_3(t)\left[(d-b\beta_3)t + b(\beta_3-1)e^{(b-d)t} - 1\right],$$

$$I_2(0,s) = Ae^{(b-d)t}\int_0^t \frac{[I_3(u)]^{-2}}{[(b-d)^2(s-z)]^{-1} - b\int_0^u e^{(b-d)v}[I_3(v)]^{-2}dv}\,du,$$

and

$\phi(t,x,y,z) = \exp\{I_1(t) + \alpha_1 I_2(0,x) + \alpha_2 I_2(0,y)\}$.
(3.10)

Remark 3.3 From (3.10) we get the following

(i) $\phi(0,x,y,z) = 1$.

(ii) If $\beta_3 = \frac{d}{b}$, then $z = \frac{d}{b}$ and $\phi\left(t,x,y,\frac{d}{b}\right) = \exp\left\{\frac{A}{d-b} + (\alpha_1(1-\beta_1) + \alpha_2(1-\beta_2)\left(e^{(b-d)t} - 1\right)\right\}$

(iii) From the above relation, we get

$\phi(t,1,1,\frac{d}{b}) = 1$.

Case 4. If $d \neq 0$, $b = 0$, $\alpha_1 \neq 0$ and $\alpha_2 = 0$, then $\delta = -d$ and the system (1.5) becomes

$$\frac{dx}{dt} = -d(1-x) + \alpha_1(x-y),$$
$$\frac{dy}{dt} = -d(1-y), \qquad (3.11)$$
$$\frac{dz}{dt} = -d(1-z).$$

Then the solutions of (3.11) are

$$x(t) = 1 + (\beta_3 - 1)e^{dt} + (\beta_1 - \beta_3)e^{(d+\alpha_1)t},$$
$$y(t) = 1 + (\beta_2 - 1)e^{dt},$$
$$z(t) = 1 + (\beta_3 - 1)e^{dt}.$$

Now, form (3.2), (3.3) and (3.4) we obtain

$I_3(u) = d$,

$$I_1(t) = \frac{A}{\alpha_1}(\alpha_1 + \alpha_1)(\beta_3 - 1)(1 - e^{-\alpha_1 t}),$$
$$I_2(\alpha_1,x) = \frac{A(\beta_1-\beta_3)}{d+\alpha_1}\left(1 - e^{-(d+\alpha_1)t}\right),$$
$$I_2(0,y) = \frac{A}{d}(\beta_2 - \beta_3)(1 - e^{-dt}),$$

and

$$\phi(t,x,y,z) = \exp\left\{\begin{array}{l}\frac{A}{\alpha_1}(\alpha_1+\alpha_1)(\beta_3-1)(1-e^{-\alpha_1 t}) \\ +\frac{A(\beta_1-\beta_3)}{d+\alpha_1}\alpha_1\left(1-e^{-(d+\alpha_1)t}\right) \\ +\frac{A}{d}(\beta_2-\beta_3)\alpha_2(1-e^{-dt})\end{array}\right\}. \qquad (3.9)$$
(3.12)

Remark 3.4 It follows from (3.12) that

(i) $\phi(t,1,1,1) = 1$ for $\beta_1 = \beta_2 = \beta_3 = 1$.

(ii) $\phi(0,x,y,z) = 1$.

(iii) If $y = 0$ at $t = t_1$, then

$$\phi(t_1,x,0,z) = \exp\left\{\begin{array}{l}\frac{A}{\alpha_1}(\alpha_1+\alpha_1)(\beta_3-1)(1-e^{-\alpha_1 t_1}) \\ +\frac{A(\beta_1-\beta_3)}{d+\alpha_1}\alpha_1\left(1-e^{-(d+\alpha_1)t_1}\right) \\ +\frac{A}{d}(\beta_2-\beta_3)\alpha_2\beta_2\end{array}\right\}.$$

Now, we use the above cases to compute the probability generating functions at the equilibrium points which help in calculating the probability that resistance is generated after treatment.

(i) The probability generating function at $E_1(1,1,1)$:

Using (3.1), (3.2), (3.3) and (3.4), if the probability generating function at $E_1(1,1,1)$ is $\phi_1(t,1,1,1)$, then

$\phi_1(t,1,1,1) = \exp\{I_1(t) + \alpha_1 I_2(\alpha_1,x) + \alpha_2 I_2(\alpha_2,y)\}$,

where

$I_1(t) = 0$,

$I_2(\alpha_1,x) = I_2(\alpha_1,1) = 0$,

$I_2(\alpha_2,y) = I_2(\alpha_2,1) = 0$.

Hence from the definition of probability generating function , we get

$$\phi_1(t,1,1,1) = 1. \qquad (3.11)$$

Similarly

(ii) The probability generating function at

$E_2(\frac{a_1+d}{b},1,1)$is
$\phi_2\left(t,\frac{a_1+d}{b},1,1\right) = exp\{I_1(t)+\alpha_1 I_2(\alpha_1,x_1)+\alpha_2 I_2(\alpha_2,x_2)\}$,

such that
$I_1(t)=0, I_2(a_2,y)=I_2(a_2,1)=0,$
$I_2(a_1,x) - I_2(a_1,\frac{a_1+d}{b}) - \frac{(a_1+d-b)}{b}\int_0^t S(t-u)du.$
Then
$\phi_2\left(t,\frac{a_1+d}{b},1,1\right) = \exp\{\alpha_1 \frac{(a_1+d-b)}{b}\int_0^t S(t-u)du\}.$

Now, if we consider the case $S(t) - Ae^{(\delta-a)t}$, then
$I_2(a_1,\frac{a_1+d}{b}) = \frac{A}{b}[1-e^{(\delta-a_1)t}]$.
Hence again from the definition of probability generating function , we obtain
$\phi_2\left(t,\frac{a_1+d}{b},1,1\right) = \exp\{-\alpha_1\frac{A}{b}[e^{(\delta-a_1)t}-1]\}$.
Thus at equilibrium point $E_2(\frac{a_1+d}{b},1,1)$, if $a_1=\delta$, then the probability that single resistance will persist in is independent on δ .

(iii) The probability generating function at $E_3(1,\frac{a_2+d}{b},1)$is
$\phi_3(t,1,\frac{a_2+b}{b},1)=\exp\{I_1(t)+\alpha_1 I_2(a_1,x)+\alpha_2 I_2(a_2,y)\}$,

where $I_1(t)=0$, $I_2(a_1,x)=I_2(a_1,1)=0$ and $I_2(a_2,y)=I_2(a_2,\frac{a_2+d}{b}) = \frac{A}{b}[1-e^{(\delta-a_2)t}]$. Hence as above , we get
$\phi_3(t,1,\frac{a_2+d}{b},1)=\exp\{-\alpha_2\frac{A}{b}[e^{(\delta-a_2)t}-1]\}$.
Thus at equilibrium point $E_3(1,\frac{a_2+d}{b},1)$, if $a_2=\delta$, then the probability that single resistance will persist in is independent on δ.

(iv) The probability generating function at $E_4(\frac{a_1+d}{b},\frac{a_2+d}{b},1)$:
$\phi_4(t,\frac{a_1+d}{b},\frac{a_2+d}{b},1)=\exp\{I_1(t)+\alpha_1 I_2(a_1,x)+\alpha_2 I_2(a_2,y)\}$,

where $I_1(t)=0$. Under the conditions $a_1=\delta$ and $a_2=\delta$ as in the case of E_2 and E_3 , we get
$I_2(a_1,x)=\frac{A}{b}[1-e^{(\delta-a_1)t}]$,
$I_2(a_2,y)=\frac{A}{b}[1-e^{(\delta-a_2)t}]$.
Hence
$\phi_4(t,\frac{a_1+d}{b},\frac{a_2+d}{b},1) - \exp\{\frac{a_1A}{b}[e^{(\delta-a_1)t}-1] - \frac{a_2A}{b}[e^{(\delta-a_2)t}-1]\}$.

Thus at equilibrium point $E_4(\frac{a_1+d}{b},\frac{a_2+d}{b},1)$, if $a_1=a_2=\delta$, then the probability that single resistance will persist in is independent on δ .

(v) The probability generating function at $E_5(\frac{d}{b},\frac{d}{b},\frac{d}{b})$:
$\phi_5(t,\frac{d}{b},\frac{d}{b},\frac{d}{b})=\exp\{I_1(t)+\alpha_1 I_2(a_1,x)+\alpha_2 I_2(a_2,y)\}$,

where $I_1(t)=\frac{-\delta(a_1+a_2)}{b}\int_0^t S(t-u)du$ and $I_2(a_1,\frac{d}{b})=0$. Hence,
$\phi_5(t,\frac{d}{b},\frac{d}{b},\frac{d}{b}) - \exp\{\frac{-\delta(a_1+a_2)}{b}\int_0^t S(t-u)du\}$.
As a special case if we take $S(t)=Ae^{(\delta)t}$, then $\int_0^t S(t-u)du = A\int_0^t e^{\delta(t-u)}du = A[\frac{e^{\delta t}-1}{\delta}]$. Hence
$\phi_5(t,\frac{d}{b},\frac{d}{b},\frac{d}{b}) - \exp\{\frac{-A(a_1+a_2)}{b}(e^{\delta t}-1)\}$.
Thus at equilibrium point $E_5(\frac{d}{b},\frac{d}{b},\frac{d}{b})$, if $\delta>0$, then the probability that single resistance will persist in independent on δ .

(vi) The probability generating function at $E_6(\frac{d}{b},\frac{b+a_2}{b},\frac{d}{b})$is
$\phi_6(t,\frac{d}{b},\frac{b+a_2}{b},\frac{d}{b})=\exp\{I_1(t)+\alpha_1 I_2(a_1,x)+\alpha_2 I_2(a_2,y)\}$,

Wher$I_1(t)=\frac{-\delta(a_1+a_2)}{b}\int_0^t S(t-u)du$, $I_2(a_1,\frac{d}{b})=0$ and $I_2(a_2,y)=\frac{(\delta-a_2)}{b}\int_0^t S(t-u)du$. Now, if we consider the case $S(t)=Ae^{(\delta)t}$, then $I_2(a_2,\frac{b+a_2}{b})=\frac{(\delta+a_2)}{b\delta}A[e^{(\delta)t}-1]$. It follows from the definition of probability generating function , that
$\phi_6(t,\frac{d}{b},\frac{b+a_2}{b},\frac{d}{b})=\exp\{\frac{-a_1\delta+a_2a_2}{b\delta}A(e^{\delta t}-1)\}$.
Thus at equilibrium point $E_6(\frac{d}{b},\frac{b+a_2}{b},\frac{d}{b})$,if $\delta>0$ and $-a_1\delta+a_2a_2<0$ then the probability that single resistance will persist in is independent on δ.

(vii) The probability generating function at $E_7\left(\frac{b+a_1}{b},\frac{d}{b},\frac{d}{b}\right)$is
$\phi_7(t,\frac{b+a_1}{b},\frac{d}{b},\frac{d}{b})=\exp\{I_1(t)+\alpha_1 I_2(a_1,x)+\alpha_2 I_2(a_2,y)\}$,

where $I_1(t)=\frac{-\delta(a_1+a_2)}{b}\int_0^t S(t-u)du$,
$I_2(a_2,\frac{d}{b})=0$ and $I_2(a_1,x_1)=\frac{(\delta+a_1)}{b}\int_0^t S(t-u)du$.
Now , if we consider the special case $S(t)=Ae^{(\delta)t}$,
then, $I_2(a_1,\frac{b+a_1}{b})=\frac{(\delta+a_1)}{b\delta}A[e^{(\delta)t}-1]$. Hence
$\phi_7(t,\frac{b+a_1}{b},\frac{d}{b},\frac{d}{b})=\exp\{\frac{-a_2\delta+a_1a_1}{b\delta}A(e^{\delta t}-1)\}$.

Thus at equilibrium point $E_7(\frac{b+a_1}{b},\frac{d}{b},\frac{d}{b})$,if $\delta > 0$ and $-\alpha_2\delta + a_1\alpha_1 < 0$, then the probability that single resistance will persist in is independent on δ .

(viii) The probability generating function at $E_8(\frac{b+a_1}{b},\frac{b+a_2}{b},\frac{d}{b})$

$$\phi_8(t,\frac{b+a_1}{b},\frac{b+a_2}{b},\frac{d}{b}) = \exp\{I_1(t) + \alpha_1 I_2(a_1,x) + \alpha_2 I_2(a_2,y)\},$$

where $I_1(t) = \frac{-\delta(\alpha_1+\alpha_2)}{b}\int_0^t S(t \quad u)du,$ and $I_2(a_1,\frac{b+a_1}{b}) = \frac{(\delta+a_1)}{b}\int_0^t S(t-u)du.$ Now , if we consider the case $S(t) = Ae^{(\delta)t},$ then $I_2(a_1,\frac{b+a_1}{b}) = \frac{(\delta+a_1)}{b\delta}A[e^{(\delta)t} \quad 1]$ and $I_2(a_2,\frac{b+a_2}{b}) = \frac{(\delta+a_2)}{b}\int_0^t S(t \quad u)du.$ Now , if we consider the special case $S(t) = Ae^{(\delta)t},$ then, $I_2(a_2,\frac{b+a_2}{b}) - \frac{(\delta+a_2)}{b\delta}A[e^{(\delta)t} - 1]$. Hence from the definition of probability generating function , we get

$$\phi_8(t,\frac{b+a_1}{b},\frac{b-a_2}{b},\frac{d}{b}) = \exp\{\frac{a_1\alpha_1+a_2\alpha_2}{b\delta}A(e^{\delta t} - 1)\}.$$

Thus at equilibrium point $E_8(\frac{b+a_1}{b},\frac{b+a_2}{b},\frac{d}{b})$, if $\delta > 0$, then the probability that single resistance will persist in is independent on δ .

4. Conclusion

In this paper, we study the behavior of solutions of permanent drug resistance model. We established the existence of possible eight equilibria of the form $E_1 = (1,1,1)$, $E_2 = \left(\frac{a_1+d}{b},1,1\right)$, $E_3 = \left(1,\frac{a_2+d}{b},1\right)$, $E_4 = \left(\frac{a_1+d}{b},\frac{a_2+d}{b},1\right)$, $E_5 = \left(\frac{d}{b},\frac{d}{b},\frac{d}{b}\right)$, $E_6 = \left(\frac{d}{b},\frac{a_2+b}{b},\frac{d}{b}\right)$, $E_7 = \left(\frac{a_1+b}{b},\frac{d}{b},\frac{d}{b}\right)$ and $E_8 = \left(\frac{a_1+b}{b},\frac{a_2+b}{b},\frac{d}{b}\right)$. We introduced condtions for local stability and instability of all equilibria in Proposition 2.1. We also discussed the global stability using Lozinski measure. We deduced in Theorem 2.2 that all solutions of (1.5) which initiate in R^3 are uniformly bounded. Then we used Bendixon-Dulac Theorem to show that system (2.5) does not have nontrivial periodic orbits. The probability generating function $\phi(t,x,y,z)$ for the two drugs resistance model in all possible cases of the parameters b, d, a_1 and $a_2$is calculated. We used these probabilities to calculate the probability that resistance is generated after treatment. Our obtained results improve and partially generalize those obtained in [9]-[14].

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