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Nonlinear dynamics of cancer recurrence

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In their article *Dynamics of cancer recurrence*, J. Foo and K. Leder (F-L, 2012), were concerned with the timing of cancer recurrence. The cancer cell population consists of two types of cells: Sensitive (S) to the drug administered and drug Resistant (R) cells. The replication of S cells produces mutant R cells with some probability. F-L derive uniform in time approximations for the paths of the escape from extinction processes and its components, in the limit as the initial population size tends to infinity and the mutation rate tends to zero. In addition, they derive the time at which (i) the resistant cells dominate the sensitive ones – *crossover time* - and (ii) the total population T of cancer cells T = S + R grows after the initial decline due to the drug – *turnabout time* . Their model is stochastic and they obtain their results from simulation. The large literature on the subject has focused upon calculations of the eventual probability of developing resistance and the resistant population size. By contrast, F-L focus upon the variable timing of tumor resistance.

This note concerns the same problem but uses a nonlinear variant/modification of their model. There are two parts to my note. The first is a deterministic rather than stochastic version of the model , and the qualitative solution is presented in terms of dynamics and convergence to steady states. The advantages of this alternative model are that the analytic solutions and the complete dynamic path are explicit. No approximations are made, because I focus upon qualitative solutions. The cases where reversal of the tumor size – turnabout time - occurs are explicit.

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The second part is a stochastic counterpart to the nonlinear dynamic model. Here one obtains quantitative results. Probabilistic statements can then be made about the nature of convergence. Both the tumor size and resistance cells are normally distributed with explicit expressions for expectations and variances.

I draw upon the F-L model as well as the literature on antibiotic resistance, Handel, Margolis and Levin (2008), Frank (2007) and Stewart and Levin (1977).

1. The nonlinear model

There are two types of cancer cells: sensitive and resistant. Each has its own dynamics. Equation (1) describes the dynamics of the S cells. The variant of the logistic law of population growth has two vital coefficients. The S cells tend to grow at rate aS(t) in the absence of the drug. The effect of the drug on the sensitive cells is bS(t).

(1) dS(t)/dt = S(t)(a – bS(t))

The dynamics of the resistant R cells is equation (2). Due to the immune response, the R cells decline at rate rR(t). However, as in F-L, the S cells produce mutants that are drug resistant at rate mS(t).

(2) dR(t)/dt = -rR(t) + mS(t).

The tumor size T(t) is the subject of concern.

(3) T(t) = S(t) + R(t).

2. Equilibrium solution

There are two equilibria where dS/dt = 0 and dR/dt = 0. The first is (4a) and the second is (4b).

(4a) S* = 0, R* = 0

(4b) S* = a/b, R* = (m/r)(a/b).

The resulting total tumor size T*= S* + R* is equation (4c).

(4c) T* = (a/b)(1 + m/r)

Conditions (4b) and (4c) are clear. The steady state tumor size T* is positively related to (i) the ratio (a/b) of the intrinsic growth of S cells relative to the efficacy of the drug and (ii) the ratio (m/r) of the mutation rate relative to the efficacy of the immune system. The patient will be totally cured if the equilibrium is (4a), which will not happen in this dynamic model. The tumor size will stabilize at T* in (4c). If the maximum *viable* tumor size is T-max, then the patient will only survive if T* < T.max. Thus the prognosis should be based upon V = (T.max – T*). There is hope only if V > 0. If based upon estimates of (a/b), (m/r) the value of T* exceeds T.max, alternative treatments should be considered.

3. Nonlinear Dynamics

F-L are concerned with the timing of the two types of cancer cells. (a) When will the R cells dominate the S cells? (b) When will the tumor recur after a period of decline due to the treatment? Figure 1 describes the dynamics, the qualitative solution to my alternative or variant of their model, in the form of trajectories from initial conditions.

The vectors describe the motion of S(t) and R(t) based upon equations (1), (2) and (4b). The line labeled dS/dt = 0 is the set of (S,R) where the sensitive cells are constant. The vertical vectors describe the motion of S(t) to S*. The line labeled dR/dt = 0 is the the set of (S,R) where the resistant cells are constant. The horizontal vectors describe the motion of R(t) to R*.

The total tumor size T = S + R is described the lines with a slope of -1. The equilibrium tumor size is T*. Hopefully T* is less than T.max, the maximum viable tumor size (not drawn).

The trajectory of the tumor is given by equation (5) which is just equation (1) plus (2), using (3). The solution for S(t) is equation (6), where S(t) converges to its equilibrium value in (4b). Hence T(t) converges to the value in (4c).

(5) $dT/dt = -rT(t) + S(t)(a - b\,S(t) + m + r)$

(6) $S(t) = aS(0)/[bS(0) + (a - bS(0))\exp(-a(t - t(0))],$ $\lim S(t) = a/b.$

In general, substitute (6) into (5) and one can derive the timing of T(t) to T*. When if ever will there be a reversal? One needs to know (a, b, r, m) and initial conditions P(1) – P(4) or [T(0), S(0)] or [S(0), R(0).

If S(0) is close to S* = a/b, then S(t) is relatively constant at S*, that is the trajectory is close to/along the dS/dt = 0 curve in figure 1. The R cells, along the dS/dt = 0 curve, based upon (2) is equation (7), where R* is the equilibrium value given by (4b).

(7) $R(t) = R^* + [R(0) - R^*] \exp(-rt)$

When S(0) is close to S*, that is the trajectory is close to/along dS/dt = 0, the trajectory of T(t) is equation (8) where the equilibrium T = T* given by (4c). Consequently one can solve for the time t when the tumor size is equal to any arbitrary size.

(8) $T(t) = T^* + [T(0) - T^*] \exp(-rt)$.

The crucial variable for the speed of convergence in both cases, when the trajectory is along dS.dt = 0, is *r*, the effect of the immune system in equation (2).

F-L focus upon means of the distributions of the two populations as well as upon the tails. By contrast, my deterministic variant of their model can be viewed as focusing upon means and ignoring the stochastic elements which would appear in equations (1), (2).

Table 1 summarizes the discussion below concerning the trajectories in figure 1 and when there will be reversals. Consider four patients/cases P(1) – P(4). In each case assume that the tumor is below the maximum viable case T-max.

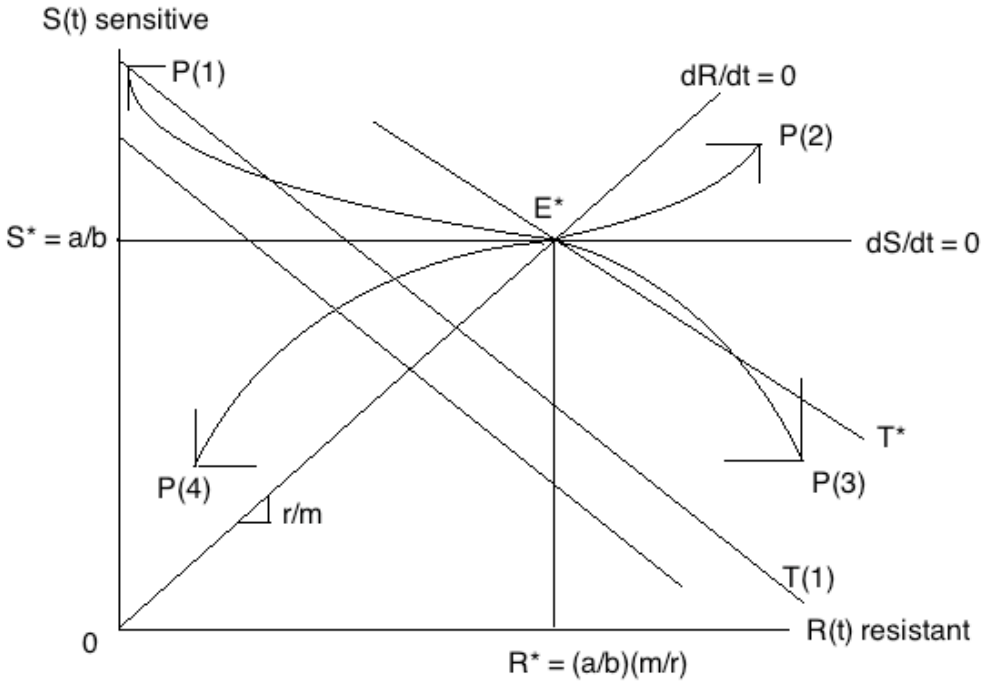

Figure 1. Dynamics of drug sensitive S and drug resistant R tumors. Total tumor size is T. Equilbria are S*,R* and T*.

Patient P(1) has a large tumor T(1), mostly of the drug sensitive type. With treatment, the sensitive cells decline, but the resistant cells rises. The total tumor first declines and then rises to the equilibrium T*. This is similar to F-L figure 1.

Patient P(2) has a large tumor T(0) > T*. Both sensitive and resistant types are high, S(0) > S* and R(0) > R*. The drug reduces the sensitive type, the resistant type declines and the tumor declines to the equilibrium value T*.

Patient P(3) has a large tumor T(0) < T*, mainly of the drug resistant type. The sensitive type rises, and the resistant type declines. Initially, the total tumor size rises above T(0) but then there is a reversal and the tumor size declines to T*.

Patient P(4) has a low value of the tumor. Both sensitive and resistant types rise and the tumor rises from T(0) to T*.

Table 1 Dynamics implied by model and figure 1.

Initial condition	S(t) sensitive	R(t) resistant	T(t) total tumor
P(1) Similar to F-L fig. 1	decrease	increase	Reversal/turnabout: T(t) first declines then rises to T*
P(2)	decrease	decrease	decrease
P(3)	increase	decrease	Reversal/turnabout: T(t) rises then declines to T*
P(4)	rises	rises	Rises to T*

Unlike F-L, for the same mutation rate, there is reversal in patients P(1) and P(3). Both start with high values of the tumor [T-max > T(0)] ≥ [T* = (a/b)(1 + m/r)]. In patient P(1) the tumor first declines and then rises. In patient P(3), the tumor first rises and then declines.

3. Stochastic version of the model

One can consider a stochastic version of the model (1) - (3). Suppose that S(0) is close to S*, so that dS ~ 0. Then the stochastic version of the dynamics of the tumor size, equation (5) can be written as

(9) $dT(t) = - rT(t)\, dt + S^*(m + r)\, dt + \sigma\, dw(t), \qquad E(dw) = 0, E(dw^2) = dt.$

where S* is given by equation (4b). Brownian Motion is w(t). The stochastic term

$\sigma\, dw(t)$, has an expectation of zero and a variance of $\sigma^2\, dt$.

The expectation of the change in tumor size is

(10) $E(dt) = [-rE(T) + S^*(m+ r)]\, dt.$

Therefore the expectation of $T = T^*$ is equation (11). Using this, write (9) as stochastic differential equation (12).

(11) $E(T) = T^* = S^*(m + r)/r.$

(12) $dT(t) = -rT(t)\, dt + rT^*\, dt + \sigma\, dw(t)$

It is convenient to convert (12) into an Ornstein-Uhlenbeck equation. Define y(t) as (13). Then (12) can be written as Ornstein-Uhlenbeck equation (14).

(13) $y(t) = T(t) – T^*$

(14) $dy(t) = - ry(t)\, dt + \sigma\, dw(t)$

The solution of this equation is (15), where $y(0) = T(0) – T^*$.

(15) $y(t) = y(0) \exp(-rt) + \sigma \exp(-rt) \int \exp(rs)\, dw(s), \qquad t \geq s \geq 0.$

The expectation of $y(t) = E[y(t)] = y(0) \exp(-rt)$ goes to zero as t grows to infinity, (15a). This implies that lim E[T(t)] in (15b) is T^*.

(15a) $\lim E[y(t)] = 0.$

(15b) $\lim E[T(t)] = T^*.$

The variance of y(t) follows from (15) and is (16a). In the limit var y(t) is (16b). This is the variance of T(t), the tumor size.

(16a) $\text{var } y(t) = (\sigma^2/2r)\,(1 – \exp(-2rt))$

(16b) $\lim \text{var } y(t) = \text{var } T(t) = (\sigma^2/2r)$

Equations (15a) - (16b) describe the probability distribution of the tumor size. Since w(t) is Brownian Motion, the distribution of lim T is normal $N(T^*, \sigma^2/2r)$.

4. Conclusions

This note was stimulated by a seminar given by Kevin Leder, April 2012 at the Division of Applied Mathematics at Brown University. The F-L paper developed limiting stochastic approximations for the population process. They use limit approximations to characterize the distribution of the time at which the progression of the disease is observed. Moreover, they characterize the time that the resistant mutants overtake the original type in the population.

There are two main conclusions of the F-L model. (1) The time of extinction of the resistant cells depends upon $Y = (\lambda(0) + \lambda(1))$ where $\lambda(0) < 0$ is the net growth rate of the S cells and $\lambda(1) > 0$ is the net growth rate of the R cells. If $Y > 0$ then the expected extinction time is infinite. If $Y < 0$, then it is finite. (2) The turnabout time when the total tumor starts to rise after a period of decline depends positively upon the mutation rate.

The contribution of part 1 of my note is to use a deterministic variant of their model that explicitly shows the dynamics of the two types of cells and total tumor size from initial conditions to the steady state. I show under what conditions here will be reversals in the tumor growth. Unlike F-L, the S and R cells and total tumor size converge to positive constants. The key parameters for the steady states of the Sensitive, Resistant and Total tumor are: (i) the ratio (a/b) of the growth of sensitive cells/efficacy of the drug; (ii) the ratio (m/r) of the rate of mutation/immune response to the resistant cells. The steady state tumor size $T^* = [(a/b)(1 + m/r)]$. For the same mutation rate $m > 0$, the trajectories are described in terms of four patients who differ in the initial conditions. Reversal/turnabout occurs when the initial conditions are such that either $[S(0) > S^*, R(0) < R^*]$ or $[S(0) < S^*, R(0) > R^*]$.

The deterministic model provides insights into the dynamics and steady state. Part 2 of my note considers a stochastic version of the deterministic model. Let S(0) be close to the steady state value S^*. The total tumor size T(t) is described by a stochastic differential equation of the Ornstein-Uhlenbeck type. There is a drift related to the difference between the current value and the steady state value $[T(t) – T^*]$. The diffusion is σ dw,

where w(t) is Brownian Motion and $\sigma > 0$ is a constant. Then the tumor size converges to a normal distribution where E[T] = T* and the variance is $\sigma^2/2r$ where r is the decay rate of the R cells due to immunity r.

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