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Quiescence as an Explanation of Gompertzian Tumor Growth

M. Gyllenberg[1] and G.F. Webb[2]

[1]Academy of Finland and
Helsinki University of Technology
Institute of Mathematics
SF-02150 Espoo, FINLAND

[2]Vanderbilt University
Department of Mathematics
Nashville, TN 37235

In this paper we propose a mathematical model for the growth of solid tumors which employs quiescence as a mechanism to explain characteristic Gompertz-type growth curves. The model distinguishes between two types of cells within the tumor, proliferating and quiescent. Empirical data strongly suggest that the larger the tumor, the more likely it is that a proliferating cell becomes quiescent and the more unlikely it is that a quiescent cell reenters the proliferating cycle. These facts are taken as the basic assumptions of the model. It is shown that these assumptions imply diminishing of the growth fraction (i.e. proportion of proliferating cells), a phenomenon found in most tumors.

Three qualitatively different cases are analyzed in detail and illustrated by examples. In the case of a tumor forming a necrotic center the model predicts that the tumor grows monotonically to its ultimate size according to a typical *S*-shaped Gompertz curve, and that the growth fraction tends to zero.

In the case of true quiescence, where the dormant cells retain their capability of becoming proliferating, we distinguish between two types of tumors: one in which only proliferating cells can die and one in which there is mortality among quiescent cells, too. In the first case the predicted tumor growth occurs in the early stages in a way that is very similar to that of tumors forming a necrotic center; the growth fraction still tends to zero, but ultimately the tumor grows without bound. In the second case the tumor grows to a finite limit depending only on the vital rates, while the growth fraction decreases to a strictly positive value.

In 1825 Benjamin Gompertz published his famous empirical law of human mortality (Gompertz, 1825). Expressed in modern terminology he found that the age distribution $L(t)$ of many communities is given by

$$L(t) = k\exp(-\exp(a - bt)), \qquad (1.1)$$

where t denotes age and k is a positive, a a real and b a negative constant. Almost exactly one hundred years later Wright (1926) proposed to use the function L given by (1.1) to describe the growth of individual organisms. In this interpretation t denotes time and $L(t)$ is the size of the individual at time t. Observe that now the constant b should be *positive* and the organism grows monotonically to its final size k.

Since the appearance of Wright's (1926) book review a vast number of authors have fitted the Gompertz curve (1.1) with remarkable success to growth data for several different animals and organisms (Laird, Tyler and Barton, 1965, Laird, 1965a). In particular the growth of solid tumors seems to follow the Gompertz growth curve very precisely, at least in the early stages (Laird 1964, 1965b, McCredie *et al.*, 1965, Norton *et al.*, 1976). On the other hand Burton (1966) pointed out that in the last stages a straight line with positive slope fits the data better than the horizontal asymptote of Gompertz' curve.

The Gompertz growth function is completely empirical and there is no obvious reason why tumors, for example, should grow according to this function. Kendal (1985) claims that Gompertzian growth is simply a consequence of tumor heterogeneity, but as Swan (1987) correctly points out there is no biological justification for the assumptions on which Kendal's model is based. It would be desirable to explain Gompertzian growth by mathematical models based on some mechanism within the tumor. As a step in this direction Summer (1966) derived a model for tumor growth starting with the assumption that tumor growth is limited by transcapillary flux of nutrients and showed that

this model predicted a growth curve quite similar to the Gompertz curve. Burton (1966) considered spherical tumors which develop necrotic centers. He assumed that the supply of oxygen is maintained at the surface of the tumor, but oxygen reaches the central core only by diffusion. When the oxygen tension value falls below a critical value in some part of the tumor this part turns necrotic and its cells become forever incapable of dividing. Burton's (1966) diffusion-limitation theory predicts Gompertzian-like growth with the exception that ultimately the tumor grows linearly.

A tumor is a population of cells. Frenzen and Murray (1986) presented a cell kinetics model for the growth of cell populations. It is similar to the well known model of maturity-time representation due to Rubinow (1968), but in contrast to the Rubinow model the muturation velocity is not assumed to be constant. Frenzen and Murray (1986) showed that if the interaction between individual cells and the entire tumor is such that an increase in the total number of cells leads to a decrease in the individual maturation rate, then, in their model, the tumor will grow in a Gompertzian way.

The model of Frenzen and Murray (1986) provides a mechanism explaining Gompertzian growth which seems to be appropriate for ascitic tumors for which it has been found that the duration of all the phases of the cell cycle increased with the size of the tumor (Frindel and Tubiana, 1967, Tannock 1969). On the other hand this is not the case for solid tumors. According to Tubiana's (1971) review article most results show that the mean duration of the cell cycle in solid tumors is relatively constant and that for a given solid tumor, variation in growth rate is mainly due to variations in the ratio between proliferating and quiescent cells. These facts have subsequently been repeatedly confirmed, for instance by Martinez and Griego (1980).

In this paper we propose a model for the growth of solid tumors which employs quiescence as a mechanism to explain characteristic Gompertz-type growth curves. In tumors a considerable portion of the cells are resting or quiescent. Although the reason why some cells go into quiescence is not exactly known it has been shown by Tannock (1968) that in parts of the tumor far from a blood vessel the proportion of quiescent cells is considerably higher than in parts close to a blood vessel. Indirectly this implies that the probability of becoming quiescent increases as the tumor grows. Theories of diffusion of oxygen and nutrients (Burton, 1966) suggest the same thing. Many experiments actually show that the growth fraction (i.e. proportion of proliferating cells) diminishes with increasing tumor size (Tubiana, 1971).

Quiescent cells do not lose their capability to divide. Some human tumor cells can start recycling after years of quiescence. It appears that the rate at which quiescent cells enter the proliferating compartment decreases with increased tumor size: Gavosto and Pileri (1971) found that this rate increased when the tumor was reduced by treatment.

In the next section we formulate a quiescence model of tumor growth and state some results concerning the behavior of its solutions. Readers unfamiliar with mathematical models of cell population dynamics are referred to the book of Eisen (1979). In the following section we discuss the implications of these results and illustrate them with some examples. The proofs of the results are given in the Appendix.

The Model and the Main Results

The model we propose distinguishes between two types of cells within the tumor, proliferating and quiescent. Proliferating cells reproduce, and may become quiescent at a rate depending on the size of the tumor. It is assumed that the bigger the tumor, the more likely it is that a cell becomes and remains quiescent. Quiescent cells do not reproduce but may reenter the proliferating cycle. Both proliferating and quiescent cells may die but mortality is not assumed to be the same in both classes. By death we understand all kinds of cell loss such as exfoliation, immunological cytolysis and migration (metastasis). The model is given by the following system of ordinary differential equations:

$$P'(t) = [\beta - \mu_P - r_o(N(t))]P(t) + r_i(N(t))Q(t), \quad (2.1)$$

$$Q'(t) = r_o(N(t))P(t) - [r_i(N(t)) + \mu_Q]Q(t), \quad (2.2)$$

$$N(t) := P(t) + Q(t), \quad (2.3)$$

$$P(0) = P_0 > 0, \; Q(0) = Q_0 \geq 0. \quad (2.4)$$

Here $P(t)$ is the number of proliferating cells at time t, $Q(t)$ is the number of quiescent cells at time t and $N(t)$ is the total number of cells in the tumor at time t and is therefore a measure of the size of the tumor. β is the birth or division rate, μ_P is the death rate of proliferating cells, and μ_Q is the death rate of quiescent cells. $r_o(N)$ is the rate at which proliferating cells become quiescent and $r_i(N)$ is the transition rate into the proliferating class from the quiescent class when the tumor size is N.

We suppose that β is a positive constant and μ_P and μ_Q are nonnegative constants, $r_o(N)$ is a continuous nonnegative nondecreasing function of N and $r_i(N)$ is a continuous nonnegative nonincreasing function of N. In the absence of quiescence $b := \beta - \mu_P$ is the specific growth rate or Malthusian parameter of the population. Throughout the paper we shall assume that b is strictly positive.

It is the increasing tendency of cells to become and to remain quiescent as the tumor becomes larger that constitutes the growth limiting mechanism. The limits

$$l_o := \lim_{N\to\infty} r_o(N), \tag{2.5}$$

$$l_i := \lim_{N\to\infty} r_i(N), \tag{2.6}$$

of the transition rates as tumor size tends to infinity will therefore play an important role in what follows. Observe that according to our assumptions about r_o and r_i, l_o and l_i are well-defined by (2.5) and (2.6) and that $0 \le l_o \le \infty$, $0 \le l_i < \infty$.

Our interest is in the qualitative behavior of solutions as time progresses. This behavior is a typical Gompertzian growth of total tumor size $N(t)$ and a diminishing of the *growth fraction*

$$G(t) := P(t)/N(t). \tag{2.7}$$

This occurs regardless of the specific choices of transition rates $r_o(N)$ and $r_i(N)$ as long as $r_o(N)$ is nondecreasing and $r_i(N)$ nonincreasing. The results stated below are proved in the appendix and illustrated by some numerical examples in section 3.

Proposition 2.1

Suppose $\mu_Q = 0$, $r_i(N) = 0$ for all $N \ge 0$ and $l_o > b$. Then $N(t)$ is increasing, bounded and $\lim_{t\to\infty} N(t) = N^*$, where N^* is the unique solution of

$$b(N^* - Q_0) = \int_{N_0}^{N^*} r_o(N)\,dN. \tag{2.8}$$

If $r_o(N_0) > b$, then $N(t)$ is concave, but if $r_o(N_0) \le b$, then $N(t)$ has a turning point at the unique value of N such that

$$r_o(N) = b. \tag{2.9}$$

Further, $\lim_{t\to\infty} P(t) = 0$ and, consequently, $G^* := \lim_{t\to\infty} G(t) = 0$.

The assumption $\mu_Q = 0$, $r_i = 0$ means that a cell that has once entered the quiescent class will neither die nor reenter the proliferating cycle but remain inactive forever. Thus in this case the model does not really describe quiescence but rather the situation where part of the tumor becomes necrotic. The assumption $l_o = \lim_{N\to\infty} r_o(N) > b = \beta - \mu_P$ has a natural biological interpretation. It says that for very large tumors the rate at which cells become quiescent or die is greater than the rate of recruitment of new cells. If we suppose that transition to quiescence and death take place immediately after mitosis, then the assumption means that for very large tumors on average more than one of the two cells produced at mitosis will either become quiescent or die.

The next proposition applies to the situation in which there is still no mortality in the quiescent class but quiescent cells can become proliferating again.

Proposition 2.2

Suppose $\mu_Q = 0$ and there exist positive constants $\underline{r}_i, \bar{r}_i$ such that $\underline{r}_i \le r_i(N) \le \bar{r}_i$ for all $N \ge 0$. Then $N(t)$ is increasing and $\lim_{t\to\infty} N(t) = \infty$. Let $G^* = \lim_{t\to\infty} P(t)/N(t)$. If $r_o(N)$ is bounded in N, then $\lim_{t\to\infty} P(t) = \infty$ and

$$G^* = (L + (L^2 + 4bl_i)^{1/2})/(2b), \tag{2.10}$$

where $L := b - l_i - l_o$. If $r_o(N)$ is unbounded, then

$$\limsup_{t\to\infty} P(t) \le \limsup_{N\to\infty} Nr_i(N)/r_o(N), \tag{2.11}$$

$$\liminf_{N\to\infty} Nr_i(N)/r_o(N) \le \liminf_{t\to\infty} P(t) \tag{2.12}$$

and consequently, $G^* = 0$.

Our last result is concerned with the case in which quiescent cells can also suffer from death. This time we have to assume that r_o is not only nondecreasing but actually strictly increasing. The assumption about r_i remains the same as before.

Proposition 2.3

Suppose (i) $\mu_Q > 0$, (ii) $r_o(0) < b(1 + r_i(0)/\mu_Q)$, (iii) $b(1 + l_i/\mu_Q) < l_o$, and (iv) $b < r_i(N) + r_o(N) + \mu_Q$ for all $N \ge 0$. Then there exists a unique nontrivial equilibrium (P^*, Q^*). This equilibrium is globally asymptotically stable in the sense that all solutions of (2.1)-(2.4) approach (P^*, Q^*) as $t \to \infty$. The total tumor size $N(t)$ tends to the unique solution N^* of

$$r_o(N^*) = b(1 + r_i(N^*)/\mu_Q) \tag{2.13}$$

and the growth fraction $G(t)$ tends to $G^* := \mu_Q/(b+\mu_Q)$ as $t \to \infty$.

Assumptions (ii) and (iii) mean, roughly speaking, the following: for very small tumors the tendency to become quiescent is low and the tendency of quiescent cells to become proliferating again is high, whereas the opposite holds true for very large tumors. If for instance r_o is linearly proportional to the total tumor size, then both (ii) and (iii) are automatically satisfied. Assumption (iv) is a technical assumption which is hard to interpret biologically since it involves all the vital rates.

Discussion

The basic assumption in our tumor growth model is that transition into quiescence and back into the proliferating cycle depends on the total size of the tumor in the following way: an increase in tumor size increases the tendency of proliferating cells to enter quiescence and decreases the tendency of quiescent cells to reenter proliferation. Even if tumor size is not directly a factor determining the probability of quiescence, our assumption is a logical consequence of the hypotheses supported by Burton (1966) and Tannock (1968) that nutrient supply and distance from a blood vessel are such quiescence determining factors.

We consider three special cases of the model. In all three cases the model predicts Gompertzian-like tumor growth, although the asymptotic behavior is qualitatively different in all three cases. These different situations will be illustrated by numerical examples and plots. It should be noted that all our examples and plots are chosen to illustrate the general qualitative features of the model and they are not based on real data. The units of time and tumor size are completely arbitrary.

Proposition 1 describes the growth dynamics of a tumor forming a necrotic center. The ultimate size N^* of the tumor is finite and depends on the initial state. $N(t)$ grows montonically to N^* and has a unique turning point, which is attained at the moment when the net rate of production of new cells equals the transition rate into quiescence. Thus the growth curve $N(t)$ has the typical S-shape of the Gompertz and logistic curves. Incidentally, if the transition rate $r_o(N)$ is a logarithmic or linear function of the tumor size N, then the solutions $N(t)$ of (2.1)-(2.4) are exactly Gompertz or logistic curves, respectively, for certain choices of initial values. For example take $b = \beta - \mu_P = 1$, $r_i = 0$, $r_o(N) = 1 + \log N$, $P_0 = 1$, $Q_0 = 0$ and the solution of (2.1)-(2.4) is

$$P(t) = \exp(1 - t - \exp(-t)), \tag{3.1}$$

$$Q(t) = \exp(1 - \exp(-t))(1 - \exp(-t)), \tag{3.2}$$

$$N(t) = \exp(1 - \exp(-t)). \tag{3.3}$$

Thus $N(t)$ has the Gompertzian form (1.1). On the other hand, if $b = 2$, $r_i = 0$, $r_o(N) = N$, $P_0 = 1$, $Q_0 = 1$, then one can easily check that the solution $N(t)$ of (2.1)-(2.4) satisfies the logistic equation

$$N' = 2N - \frac{1}{2}N^2. \tag{3.4}$$

The two examples above are mentioned merely as curiosities and we do not attach any special significance to them. Feller (1939) showed that there is nothing unique about the logistic law of growth and his arguments apply to the Gompertz growth law as well. In the situation of Proposition 1, different choices of transition rates and initial states lead to very similar S-shaped curves of $N(t)$ which, however, are neither exactly Gompertzian nor logistic. We illustrate this by showing the tumor growth curve for a quadratic transition rate in Figure 1. In Figure 2 the corresponding growth fraction is plotted against time.

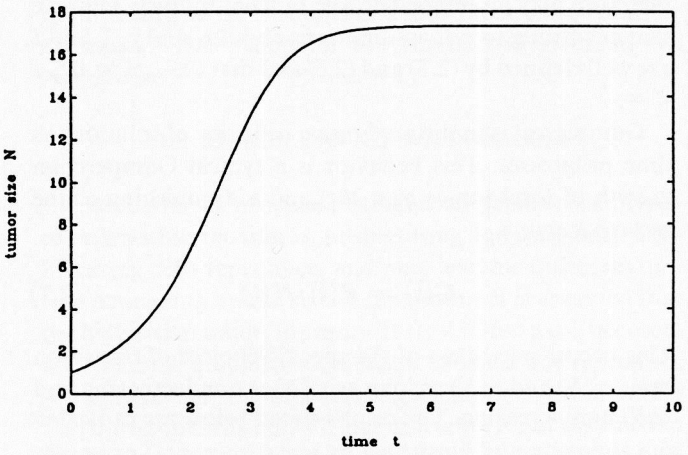

FIGURE 1. Tumor size as function of time. $b = 1$, $\mu_Q = 0$, $r_o(N) = 0.01N^2$, $r_i = 0$, $P_0 = 1$, $Q_0 = 0$.

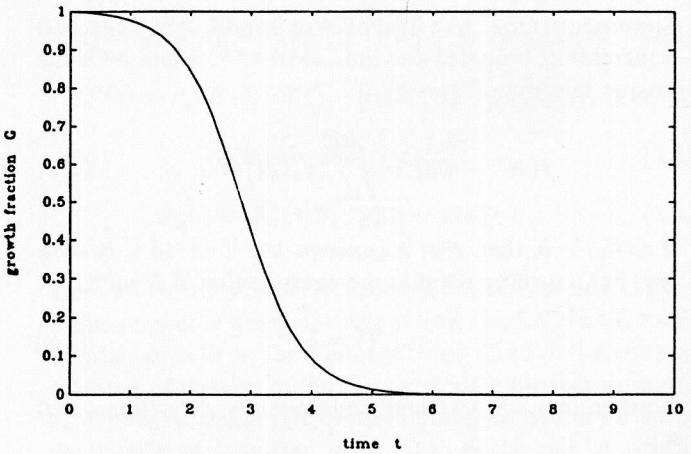

FIGURE 2. Growth fraction as a function of time. $b = 1$, $\mu_Q = 0$, $r_o(N) = 0.01N^2$, $r_i = 0$, $P_0 = 1$, $Q_0 = 0$.

Truely quiescent cells retain their capability to divide. Proposition 2, which assumes that the transition rate from quiescence to proliferation is positive, applies to this situation. It is still assumed that quiescent cells do not die. If $r_o(N)$ is bounded in N, then the growth fraction $G(t)$ con-

verges to a postive value independent of the initial data. If $r_o(N)$ is unbounded in N, then $G(t)$ converges to 0 as t tends to infinity.

In the case of necrosis described by Proposition 1 the choice of $r_o(N)$ had little influence on the shape of $N(t)$. Now the situation is completely different. Since $N' = b\,P$ the relations (2.11) and (2.12) show that if $r_o(N) = a_1 + a_2 \log N$, then $N(t)$ will tend to infinity with a slope tending to infinity; if $r_o(N) = a_1 + a_2 N$, then $N(t)$ has a straight line with slope l_i / a_2 as asymptote; and if $r_o(N)$ increases faster than a linear function, then the total tumor size $N(t)$ increases very slowly (but still without limit) the slope tending to zero. This last case is illustrated in Figures 3 and 4 with the same quadratic $r_o(N)$ as before and a constant r_i which is small compared with b. This is realistic since the mean residence time in the quiescent state is typically much longer than the mean cycle time of proliferating cells. Observe how very similar the growth curves in Figure 1 and Figure 3 are.

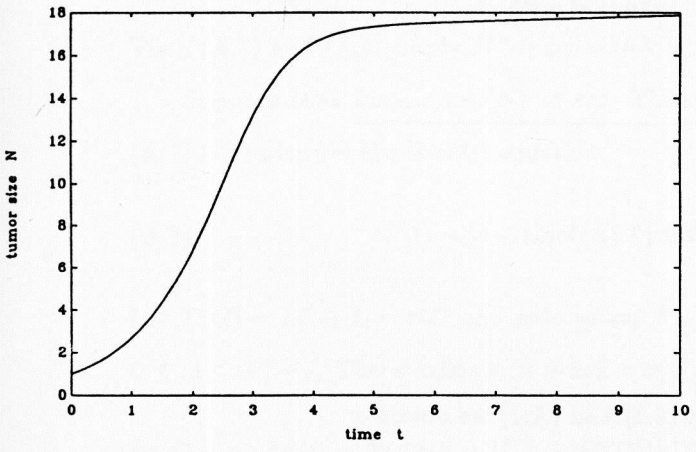

FIGURE 3. Tumor size as a function of time. $b = 1$, $\mu_Q = 0$, $r_o(N) = 0.01N^2$, $r_i = 0.01$, $P_0 = 1$, $Q_0 = 0$.

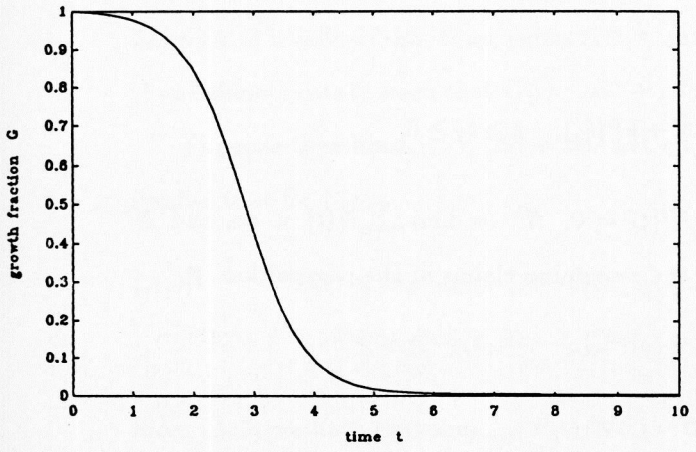

FIGURE 4. Growth fraction as a function of time. $b = 1$, $\mu_Q = 0$, $r_o(N) = 0.01N^2$, $r_i = 0.01$, $P_0 = 1$, $Q_0 = 0$.

In Propositions 1 and 2 we assumed no mortality in the quiescent class. This is a realistic assumption, since in some tumors the cells which die seem to be the proliferating ones (Tubiana, 1971). In other types of tumors, however, disappearing cells are for the most part quiescent (Tannock, 1968). Proposition 3 is concerned with tumors of this kind. If quiescent cells do not die then the tumor size increases and the possible limit depends on the initial state. With mortality in the quiescent class the situation is different. All solutions $N(t)$ tend to the *same* limit N^*, which depends only on the vital rates and not on the initial condition. $N(t)$ need not approach N^* monotonically. For some combinations of the vital rates $N(t)$ exhibits damped oscillations, for others $N(t)$ crosses its own asymptote at most once. The asymptotic behavior of $N(t)$ is determined by the location of the eigenvalues of the corresponding linearized system. For instance, it is easily seen that if r_i is constant and greater than or equal to μ_Q, and if $r_o(N)$ is a linear function, then damped oscillations are excluded. Whether $N(t)$ in this case aproaches N^* monotonically or not depends on the initial condition. This is illustrated in Figures 5 and 6. Notice how the monotonic growth curve in Figure 5 again resembles the characteristic S-shaped curves of Gompertzian or logistic growth.

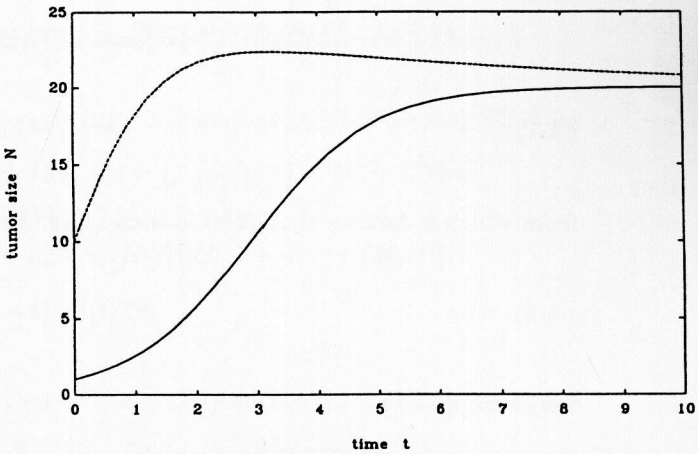

FIGURE 5. Tumor size as a function of time. $b = 1$, $\mu_Q = 0.1$, $r_o(N) = 0.1N$, $r_i = 0.1$, $P_0 = 1$, $Q_0 = 0$ (solid line) and $P_0 = 10$, $Q_0 = 0$ (dashed line).

The model we have considered in this paper is unstructured in the sense that the vital rates are assumed to be the same for all cells within the same class. However, the death rate and the transition rate into quiescence seem to depend on the phase of the cell cycle in such a way that the probability of dying or becoming quiescent is highest shortly after mitosis (Tubiana, 1971). In a previous paper (Gyllenberg and Webb, 1987) we investigated an age-size structured model, which incorporated the above mentioned behavior

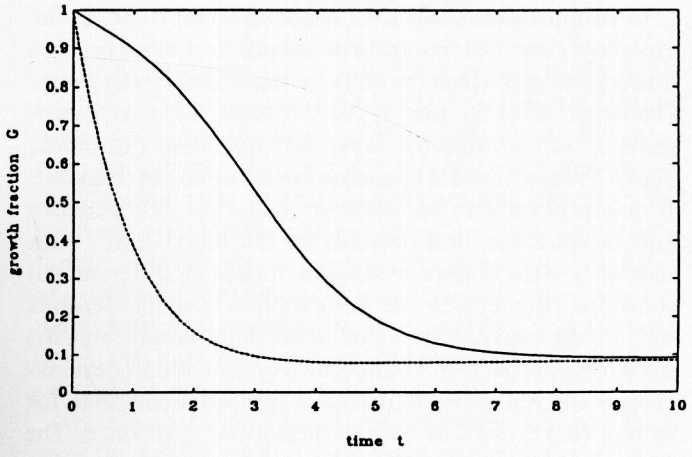

FIGURE 6. Growth fraction as a function of time. $b = 1$, $\mu_Q = 0.1$, $r_o(N) = 0.1N$, $r_i = 0.1$, $P_0 = 1$, $Q_0 = 0$ (solid line) and $P_0 = 10$, $Q_0 = 0$ (dashed line).

of individual cells. That model was, however, linear and did not take the dependence on the total population size into account. Work on nonlinear structured models with quiescence is in progress (Gyllenberg and Webb, 1989). It is our intention to apply the structured models to problems of optimal radio- and chemotherapy. Here quiescence plays an important role: It is known that quiescent cells are not as sensitive to drugs and radiation as are proliferating ones and damage to a tumor triggers a recruitment of quiescent cells into the proliferation class (Tubiana, 1982).

APPENDIX

In the analysis of the system (2.1)-(2.4) we use only elementary results and techniques from the theory of ordinary differential equations that can be found in any introductory book on the subject, e.g., Simmons, (1972).

The existence of a unique solution to (2.1)-(2.4) satisfying $P(t) > 0$ and $Q(t) \geq 0$ for all $t \geq 0$ can be established by standard methods.

Proof of Proposition 1. Addition of (2.1) and (2.2) yields

$$N'(t) = bP(t), \quad t \geq 0, \tag{A.1}$$

from which it follows that $N(t)$ is increasing. From (2.1) and (A.1) we obtain

$$N''(t) = (b - r_o(N(t)))N'(t), \tag{A.2}$$

which implies

$$N'(t) = \int_{N(t_0)}^{N(t)} [b - r_o(\hat{N})]d\hat{N} + bP(t_0), \quad t \geq t_0 \geq 0. \tag{A.3}$$

Since $\lim_{N\to\infty} r_o(N) > b$ it follows that $\lim_{t\to\infty} N'(t) = 0$, $N^* := \lim_{t\to\infty} N(t) < \infty$, and N^* satisfies (2.8). Then (A.1), (A.2), and (A.3) imply the remaining claims of the proposition. ∎

Proof of Proposition 2. From (2.1) and (A.1) we obtain for $t \geq t_0 \geq 0$

$$(A.4) \qquad P(t) = \exp\left[\int_{t_0}^{t} (b - r_o(N(s)) - r_t - (N(s)))ds\right] P(t_0)$$
$$+ \int_{t_0}^{t} \exp\left[\int_{s}^{t} (b - r_o(N(u)) - r_i(N(u)))du\right] r_i(N(s))N(s)ds$$

$$(A.5) \qquad N(t) = N(t_0) + b\int_{t_0}^{t} P(s)ds$$

Then (A.5) implies that $N(t)$ is increasing. Let $N^* := \lim_{t\to\infty} N(t) \leq \infty$. Assume $N^* < \infty$ and let $c = r_o(N^*) + \bar{r}_i - b$. From (A.4) and (A.5) we obtain

$$(A.6) \qquad P(t) > \underline{r}_i N(t_0) \int_{t_0}^{t} \exp[-c(t-s)]ds, \quad t \geq t_0 \geq 0$$
$$\geq \begin{cases} \underline{r}_i N(t_0)(t - t_0) & \text{if} \quad c \leq 0 \\ [\underline{r}_i N(t_0)/c](1 - \exp[-c(t-t_0)]) & \text{if} \quad c > 0. \end{cases}$$

Then (A.5) and (A.6) imply $N^* = \infty$, which is a contradiction.

Suppose that $\lim_{N\to\infty} r_o(N) < \infty$. Then (A.6) implies $\lim_{t\to\infty} P(t) = \infty$. From (2.1) and (A.1) $G(t)$ satisfies the Ricatti equation

$$(A.7) \qquad G'(t) = [b - r_o(N(t)) - r_i(N(t))]G(t) + r_i(N(t)) - bG(t)^2.$$

Let $F(G) = LG + \ell_i - bG^2$ and notice that $F(G^*) = 0$. Let $\epsilon > 0$ such that $F(G^* - \epsilon) < F(G)$ for $0 \leq G \leq G^* - \epsilon$. There exists $t_\epsilon > 0$ and $\delta > 0$ such that if $t > t_\epsilon$ and $G(t) < G^* - \epsilon$, then

$$(A.8) \qquad G'(t) = F(G(t)) + [\ell_o - r_o(N(t))]G(t) + [\ell_i - r_i(N(t))]G(t) + [\ell_i - r_i(N(t))]$$
$$> F(G^* - \epsilon) - \delta > 0.$$

From (A.8) it follows that there exists $t_1 > t_\epsilon$ such that $G^* - \epsilon \leq G(t)$ for $t \geq t_1$. A similar argument shows there exists t_2 such that $G(t) \leq G^* + \epsilon$ for all $t \geq t_2$. Thus, (2.10) is proved.

Suppose that $\lim_{N\to\infty} r_o(N) = \infty$. Let $\underline{c}(t) = r_o(N(t)) + \underline{r}_i - b$ and let $\underline{c}(t_0) > 0$. Then (A.4) implies that for $t \geq t_0$.

$$(A.9) \qquad P(t) \leq \exp[-\underline{c}(t_0)(t - t_0)]P(t_0) + r_i(N(t_0))N(t)\int_{t_0}^{t} \exp[-\underline{c}(t_0)(t-s)]ds$$
$$\leq \exp[-\underline{c}(t_0)(t - t_0)]P(t_0) + r_i(N(t_0))N(t)/\underline{c}(t_0).$$

From (A.9) we have that $\lim_{t\to\infty} P(t)/N(t) = 0$. Then for $\ell > 0$, $\lim_{t\to\infty} N(t+\ell)/N(t) = 1$ (since $0 < 1 - N(t)/N(t+\ell) = b\int_t^{t+\ell} P(s)ds/N(t+\ell) \leq b\ell \sup_{[t,t+\ell]} P(s)/N(s)$) and the convergence is

uniform in bounded intervals of ℓ.

To prove (2.11) let $M_1 := \limsup_{N\to\infty} Nr_i(N)/r_o(N) \le \infty$. Let $0 < \epsilon < 1$ and choose $t_1 > 0$ such that if $t \ge t_1$, then $N(t+\ell)/N(t) \le 1+\epsilon$ for $0 \le \ell \le 2$, $N(t)r_i(N(t))/\underline{c}(t) \le (1+\epsilon)M_1$, and $\exp(-\underline{c}(t)) < \epsilon$. Let $M_2 := \max(\sup_{[t_1,t_1+1]} P(t),\ (1+\epsilon)^2 M_1/(1-\epsilon))$. Let $t \ge t_1$ such that $P(t) \le M_2$ and let $1 \le \ell \le 2$. Then (A.9) implies

$$\begin{aligned} P(t+\ell) &\le \exp(-\underline{c}(t)\ell)P(t) + (N(t)r_i(N(t))/\underline{c}(t))\,(N(t+\ell)/N(t)) \\ &\le \epsilon M_2 + (1+\epsilon)^2 M_1 \\ &\le \epsilon\left[(1+\epsilon)^2/(1-\epsilon)\right] M_1 + (1+\epsilon)^2 M_1 \\ &= (1+\epsilon)^2 M_1/(1-\epsilon) \le M_2. \end{aligned}$$

Then $P(t) \le (1+\epsilon)^2 M_1/(1-\epsilon)$ on $[t_1+1, t_1+2]$, $[t_1+2, t_1+3], \cdots$, which implies (2.11).

To prove (2.12) let $\overline{c}(t) = r_o(N(t)) + \overline{r}_i - b$ and let $\overline{c}(t_0) > 0$. Then (A.4) implies that for $t \ge t_0$

$$P(t) > r_i(N(t))N(t_0)\int_{t_0}^{t} \exp[-\overline{c}(t)(t-s)]ds \tag{A.10}$$

and (A.10) implies

$$\begin{aligned} P(t_0+1) > &(N(t_0+1)r_i(N(t_0+1))/r_o(N(t_0+1))) \\ &(r_0(N(t_0+1))/\overline{c}(t_0+1)) \\ &(N(t_0)/N(t_0+1))\,(1-\exp[-\overline{c}(t_0+1)]) \end{aligned}$$

which implies (2.12). ∎

Proof of Proposition 2.3. From (2.1) and (2.2) we obtain:

$$P'(t) = [b - r_i(N(t)) - r_o(N(t))]P(t) + r_i(N(t))N(t) \tag{A.11}$$

$$N'(t) = [b+\mu_Q]P(t) - \mu_Q N(t) \tag{A.12}$$

From (A.11) and (A.12) one sees that $N' = 0$ on the straight line

$$P = (\,\mu_Q/(b+\mu_Q\,))N \tag{A.13}$$

and that $P' = 0$ on the curve

(A.14) $$P = r_i(N)N/(r_i(N) + r_o(N) - b).$$

It follows from assumptions (i)-(iii) that the curves (A.13) and (A.14) intersect exactly once, at (N^*, P^*) with N^* the unique solution of (2.13) and $P^* = G^*N^*$. Moreover, for large values of N, the curve (A.14) is below the curve (A.13). The phase portrait of (A.11), (A.12) in the (N, P)-plane thus has a clockwise flow about (N^*, P^*), and any orbit starting in $\Omega := \{(N, P) : 0 \leq P \leq N,\ N > 0\}$ is bounded. According to the Poincaré-Bendixon theorem every orbit will either tend to (N^*, P^*) or to a limit cycle. But according to the Bendixon criterion (Guckenheimer and Holmes, 1983) there are no closed orbits in Ω, since

$$\partial/\partial P\{[b - r_i(N) - r_o(N)]P + r_i(N)N\}$$
$$+ \partial/\partial N\{[b + \mu_Q]P - \mu_Q N\} = b - r_i(N) - r_o(N) - \mu_Q$$

does not change sign in Ω by virtue of assumption (iv).∎

Remark: Assumption (iv) is made in order to apply the Bendixon criterion. It is possible that one can prove the nonexistence of closed orbits without it.

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