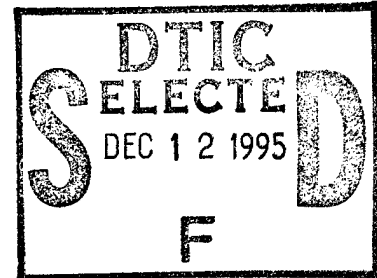


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**NOTE ON AN ALTERNATIVE MECHANISM
FOR LOGISTIC GROWTH**

D. P. Gaver
P. A. Jacobs
R. L. Carpenter
November 1995

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Naval Medical Research Institute/Toxicology Detachment
Wright-Patterson Air Force Base, Ohio

U.S. Army Biomedical Research & Development Laboratory
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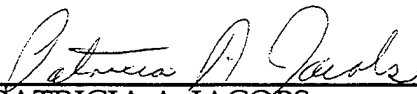
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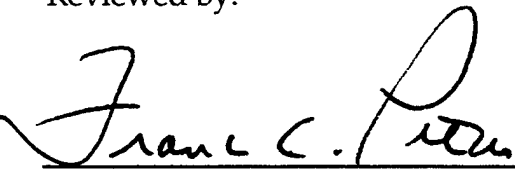
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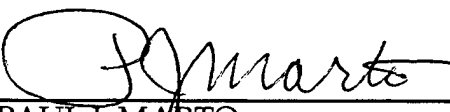

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Note on An Alternative Mechanism for Logistic Growth

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ABSTRACT

Populations of cells that make up organ tissue grow and contract. A traditional approach to modeling organ size restriction to an observed "normal" level is to postulate a physical carrying capacity: effectively a limit on the physical region that can be occupied by the organ. The purpose of this note is to provide a very simple model for a cell population that grows under the control of positive and negative growth factors. It will be seen that such a model can result in logistic growth without the necessity of postulating a physical carrying capacity.

Key Words: Logistic growth curves, growth factors

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1. Introduction

Populations of cells that make up organ tissue grow and contract in a manner that is roughly analogous to the fluctuations of other natural populations. Since organs are of bounded size their growth is not entirely uncontrolled and exponential overall, or otherwise a human or rat liver would either assume a totally outlandishly large size, or else shrink to zero. Neither such alternative is seen in nature, although organ sizes do vary among otherwise comparable members of the same species. And organs of mature hosts can change in size as a result of disease, toxic insult, or an operation such as partial hepatectomy, from which a liver can recover again to normal size and function.

A traditional approach to modeling population (= organ) size restriction to an observed "normal" level is to postulate a *carrying capacity*: effectively a limit on the physical region that can be occupied by the population. This formulation apparently goes back to Verhulst (1836); see Murray (1989) for recent discussion. In the organ situation this might correspond to a space of approximately pre-ordained dimension that, say, liver cells in liver tissue cannot exceed in the body of a mature human male. The space can be taken as given, introduced into other models as a parameter, and in particular cases estimated from data. It would be the maximum size of the liver compartment in a PB-PK model, for example.

There is another alternative to the above approach that depends upon recognition and measurement of the presence of various biological agents called *growth factors*. There are a number of such factors that both stimulate (positively) and inhibit (negatively) cell population growth. Growth factors are discussed by Alberts *et al.* (1994). Aaronson (1991) provides an overview of growth factors in cancer; see also Rubin, Bottaro, and Aaronson (1993). The purpose of this note is to provide a very simple model for a cell population that grows under the control of positive and negative growth factors. It will be seen that such a model can result in logistic growth without the necessity of postulating a *physical* carrying capacity. An *effective carrying capacity* appears as a result of presumed growth factor interaction with cells.

2. Model for a Cell Population Under Growth Factor Control

Suppose a population of cells is of size $C(t)$ at time t . Its individual cell growth or birth rate is λ_0 , and its death rate is μ_0 , so its net growth rate, $\lambda_0 - \mu_0$, governs the manner and rate of growth. Starting with $C(0)$ members, and left alone, the population would grow roughly like $C(t) \sim C(0)e^{(\lambda_0 - \mu_0)t}$, which means either to

a large size ($\lambda_0 - \mu_0 > 0$), or to zero ($\lambda_0 - \mu_0 < 0$). Clearly such unrestricted behavior is inappropriate for describing a population of cells that constitutes an entire organ, although essentially such a model has been used to describe growth of tumors within an organ; see Tan (1991) for an overview; in particular the work of Moolgavkar and co-authors, cited in Tan (1991), is relevant.

Now introduce a quantity $\alpha(t)$ of a *positive growth factor* into the vicinity of the cell population. The amount present, $\alpha(t)$, changes cell birth rate to $\lambda_0 + \lambda_1 \alpha(t)$, where we take $\lambda_1 > 0$. Also introduce a quantity $\beta(t)$ of *negative growth factor*; it changes cell death rate to $\mu_0 + \mu_1 \beta(t)$, $\mu_1 > 0$. Then changing levels of $\alpha(t)$ and $\beta(t)$ can certainly alter the properties of the cell population, from net growth to net decline, depending upon values of $\alpha(t)$ and $\beta(t)$.

Assume that the productions of both $\alpha(t)$ and $\beta(t)$ are regulated by cell activity in such a way that

$$\frac{d\alpha}{dt} = \rho_\alpha C(t) - \delta_\alpha \alpha(t) \quad (2.1)$$

and

$$\frac{d\beta}{dt} = \rho_\beta C(t) - \delta_\beta \beta(t). \quad (2.2)$$

That is, both are stimulated to increase by the number of cells present, and to diminish in proportion to their own concentration, possibly being removed from the cell site (organ) by blood flow or metabolism or other biological processes. Of course the above equations are prime candidates for replacement by others that more accurately depict the true interactions.

In the presence of α and β -factors the cells in the organ grow and decline according to

$$\frac{dC(t)}{dt} = [\lambda_0 + \lambda_1 \alpha(t)]C(t) - [\mu_0 + \mu_1 \beta(t)]C(t). \quad (2.3)$$

So (2.1), (2.2), (2.3) form a system of three non-linear differential equations. No explicit solution seems immediately available, *unless* we make the quasi-static or quasi-steady-state assumption (QSSA); see Strogatz (1994) for its invocation so as to solve a non-linear dynamics problem along with some historical references, and Segel and Slemrod (1989) for a careful discussion of this approximation. Namely assume that $\alpha(t)$ and $\beta(t)$ are able to adapt very quickly to any current value of $C(t)$ to always reach a “temporary steady state”:

$$\frac{d\alpha}{dt} \cong 0 = \rho_\alpha C(t) - \delta_\alpha \alpha(t) \quad (2.4)$$

$$\frac{d\beta}{dt} \cong 0 = \rho_\beta C(t) - \delta_\beta \beta(t). \quad (2.5)$$

Adopt the approximation as true, so solve (2.4) and (2.5) for $\alpha(t)$ and $\beta(t)$:

$$\alpha(t) = (\rho_\alpha / \delta_\alpha) C(t) \quad (2.6)$$

and

$$\beta(t) = (\rho_\beta / \delta_\beta) C(t). \quad (2.7)$$

Let us call $(\rho_\alpha / \delta_\alpha)$ and $(\rho_\beta / \delta_\beta)$ the *prevalences* of the α and β factors respectively. Insert these into (2.3) and for convenience, put $\lambda'_1 = \lambda_1(\rho_\alpha / \delta_\alpha)$, $\mu'_1 = \mu_1(\rho_\beta / \delta_\beta)$, to obtain

$$\begin{aligned} \frac{dC(t)}{dt} &= [\lambda_0 + \lambda'_1 C(t)] C(t) - [\mu_0 + \mu'_1 C(t)] C(t) \\ &= (\lambda_0 - \mu_0) C(t) - (\mu'_1 - \lambda'_1) C^2(t) \\ &= (\lambda_0 - \mu_0) C(t) \left[1 - \frac{\mu'_1 - \lambda'_1}{\lambda_0 - \mu_0} C(t) \right]. \end{aligned} \quad (2.8)$$

This conforms exactly to the original logistic equation *if* the ordinary net growth rate, $\Delta = \lambda_0 - \mu_0$, is *positive*, as is the effective carrying capacity

$$K = \frac{\lambda_0 - \mu_0}{\mu'_1 - \lambda'_1}. \quad (2.9)$$

Under the above conditions and starting from $C(0) > 0$, the population attains the long-run steady-state value

$$C(\infty) = K = \frac{\lambda_0 - \mu_0}{\mu_1(\rho_\beta/\delta_\beta) - \lambda_1(\rho_\alpha/\delta_\alpha)}. \quad (2.10)$$

The above version of carrying capacity makes intuitive sense in that

- (a) it increases with net population growth rate, $\lambda_0 - \mu_0$;
- (b) it *decreases* with *increased* prevalence of negative growth factor, $(\rho_\beta/\delta_\beta)$, and with *decreased* prevalence of positive growth factor, $(\rho_\alpha/\delta_\alpha)$;
- (c) the inhibition effect of negative growth factor, $\mu'_1 = \mu_1(\rho_\beta/\delta_\beta)$, must exceed the stimulative effect of the positive growth factor, $\lambda'_1 = \lambda_1(\rho_\alpha/\delta_\alpha)$.

If any of the above conditions are violated the population development becomes radically different, but can also be interesting.

The time-dependent population size is seen to be of the familiar logistic growth form

$$C(t) = \frac{KC(0)e^{\Delta t}}{K - C(0) + C(0)e^{\Delta t}} \quad (2.11)$$

with K as in (2.10), $\Delta = \lambda_0 - \mu_0 > 0$, and $0 < C(0) < K$.

Note that the formula has biological meaning even if $C(0) > K$, and also if $K < 0$: suppose that $\Delta = \lambda_0 - \mu_0 > 0$ but $\lambda'_1 > \mu'_1$; then write $K' = -K > 0$ to get

$$\frac{dC(t)}{dt} = \Delta C(t) \left[1 + C(t)/K' \right], \quad (2.12)$$

the solution to which is

$$C(t) = \frac{K' C(0) e^{\Delta t}}{K' + C(0) - C(0) e^{\Delta t}} \quad (2.13)$$

if $t < \frac{1}{\Delta} \ln \left(1 + \frac{K'}{C(0)} \right)$; it explodes when $t = \frac{1}{\Delta} \ln \left(1 + \frac{K'}{C(0)} \right)$; this might plausibly model an especially malignant tumor growth. Finally when $\Delta = \lambda_0 - \mu_0 < 0$ and $K' = -K > 0$ we simply get (2.11) with $-\Delta$ replacing Δ , once again a logistic model, but now one that decreases as t increases.

3. Stochastic Models

The above model can be "made stochastic" in various ways. One is to re-state the growth factor and cell-growth equations as a system of three non-linear Ito-type stochastic differential equations. Analytical solutions are not likely to be available, but some asymptotics might well produce explicit results.

Another approach is to *assume* that a stochastic version of $C(t)$, namely $C(t)$, is a birth-and-death process with transition rates copied from the right-hand side of (2.8). For example, $C(t)$ evolves over state space $(0, 1, 2, \dots)$ according to

$$P\{C(t+dt) = C(t) + 1 | C(t) = i\} = (\lambda_0 - \mu_0) i dt + o(dt) \quad (3.1,a)$$

$$P\{C(t+dt) = C(t) - 1 | C(t) = i\} = (\mu_1' - \lambda_1') i^2 dt + o(dt); \quad (3.1,b)$$

these holding when $\Delta = \lambda_0 - \mu_0 > 0$, $\mu_1' - \lambda_1' > 0$; otherwise modification is needed. Although $E[C(t) | C(0) = C(0)] \neq C(t)$ because of the non-linearity in the generator, (3.1), it can be of interest to study the above stochastic version's transient properties, such as first-passage times from low states (population size) to high, or the reverse, e.g. to $C(t^\#) = 0$ when the population dies out.

The described approach essentially minimizes attention to the stochastics of the growth factors and ignores non-linearity, hence is a prime candidate for an

upgraded treatment. Nevertheless it is appealing for its simplicity and easy availability, and is offered as an interim approach.

4. Summary

It is shown that classical logistic growth can be induced in a non-traditional manner by hypothesized action of growth factors, rather than by action of a physical carrying capacity (although the latter may operate as well). Modification of the effective carrying capacity to be negative has biological interpretability. The resulting models may perhaps find a use in cell proliferation and cancer modeling.

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