POSITIVE FEEDBACK AND ANGIOGENESIS IN TUMOR GROWTH CONTROL

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In vivo tumor growth data from experiments performed in our laboratory suggest that basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) are angiogenic signals emerging from an up-regulated genetic message in the proliferating rim of a solid tumor in response to tumor-wide hypoxia. If these signals are generated in response to unfavorable environmental conditions, i.e. a decrease in oxygen tension, then the tumor may play an active role in manipulating its own environment. We have idealized this type of adaptive behavior in our mathematical model via a parameter which represents the carrying capacity of the host for the tumor. If that model parameter is held constant, then environmental control is limited to tumor shape and mitogenic signal processing. However, if we assume that the response of the local stroma to these signals is an increase in the host's ability to support an ever larger tumor, then our models describe a positive feedback control system. In this paper, we generalize our previous results to a model including a carrying capacity which depends on the size of the proliferating compartment in the tumor. Specific functional forms for the carrying capacity are discussed. Stability criteria of the system and steady state conditions for these candidate functions are analyzed. The dynamics needed to generate stable tumor growth, including countervailing negative feedback signals, are discussed in detail with respect to both their mathematical and biological properties.

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1. Introduction. Positive feedback control loops result in globally unstable behavior in most dynamic systems. This is as true in biology as it is in mechanical systems (Rosen, 1978). The obvious case in point is autocrine mitogenesis which, left unchecked in an infinite environment, results in exponential growth in cellular populations. Examples of such autocrine positive feedback loops exist in the immune system (e.g. up-regulation of IL-2 in IL-2 receptor positive activated T-cells), during liver regrowth
(Mead and Fausto, 1989) and in senescence (Rosen, 1978). Unless some interruption or counterbalancing negative signal is introduced into the process, the instability induced by these positive signals ultimately results in system-wide failure.

In previous studies (Michelson and Leith, 1991, 1992, 1994), we have shown that tumor dormancy—the ultimate stable state—can be described for some tumor systems as a dynamic equilibrium from which tumors may re-emerge when that equilibrium is disrupted. We found that the basis of this dynamic equilibrium is a linkage between the ability of the host to provide adequate resources to support cellular proliferation and the rate at which proliferating cells became hypoxic or quiescent. In the following discussion, we will define carrying capacity to mean the host defined level of support—in nutrients, resources, etc.—for a growing population. It is the carrying capacity, explicitly defined as a parameter in the logistic models of Verhulst, that determines the ultimate size of a population. In other logistic growth models, the carrying capacity may be implicitly defined as a function of other model parameters. However, if this carrying capacity is fixed, no matter how it is defined, the ultimate size to which the population may grow is also fixed.

Mathematical models of tumor growth have a rich history. Some of the first models to appear, however, were meant to describe normal growth in proliferating cellular populations (Von Foerster, 1959 and Truco, 1965a, b). These models predicted that to maintain a steady growing population, such as an erythropoietic stem cell system, an intrinsic loss factor removing cells from the system had to be explicitly expressed in the model. Whether due to differentiation, death or migration, this factor was needed to maintain balance.

If one assumes that a tumor is growing spherically, then the resources needed for cell proliferation, such as oxygen, must diffuse through the radial depth of the sphere to get to the core of the tumor. Under these circumstances, some cells will become quiescent. Those that continue to proliferate will reside on the surface in a shell some number of cell diameters deep. The shell is an annulus, growing with sphere radius \( r \) like an area \( r^2 \). The volume, however, grows as \( r^3 \). Therefore, the proportion of proliferating cells to total mass decreases with increasing radius.

This line of reasoning is the basis for the models developed by Gyllenberg and Webb (1989), Kendal (1985) and Wette et al. (1974a, b). All derive logistic growth in terms of Gompertz-like behavior. The primary difference between the three models is the specification of the transition rates from proliferating to nonproliferating compartments.

As a variation on a theme, Adam and Megalakis (1990) developed a tumor model containing four populations: proliferating, hypoxic, anoxic and necrotic. The epigenetic factor in this model is oxygen tension. However, their model also provides for the distribution of negative growth factors