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## CLASSROOM NOTES

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*This section contains brief notes which are essentially self-contained applications of mathematics that can be used in the classroom. New applications are preferred, but exemplary applications not well known or readily available are accepted.*

*Both “modern” and “classical” applications are welcome, especially modern applications to current real world problems.*

*Notes should be submitted to M. S. Klamkin, Department of Mathematics, University of Alberta, Edmonton, Alberta, Canada T6G 2G1.*

### ACTIVATOR-INHIBITOR CONTROL OF TISSUE GROWTH\*

JOHN A. ADAM†

**Abstract.** This note develops a simple model for the competition between activator and inhibitor control mechanisms in one-dimensional tissue growth. The pedagogic usefulness of such a model is that it is easily accessible to undergraduate applied mathematicians and is suggestive of behavior known to occur in more realistic biological systems (e.g., some types of cancer). The limitations of the model are obvious and can provide a basis for discussion of the applicability of complementary levels of description in mathematical modeling.

**Key words.** activator–inhibitor mechanisms, tissue growth, diffusion

**AMS(MOS) subject classification.** 92A05

In this note we examine the effect of competing activator–inhibitor control mechanisms on tissue growth. The motivation for this problem arises from complementary levels of description for models of cancer growth [1]–[3]. This simple generalization of a one-dimensional model [4] is easily accessible to undergraduate students of applied mathematics, and has the advantage that it is suggestive of behavior known to occur in some realistic biological systems. This does not, of course, imply any more than the possibility that models suitably generalized to more realistic geometries and biology may be of value in describing observed tissue growth characteristics. We use the notation of Glass [4].

Consider a one-dimensional slab of “target tissue” embedded in “host tissue” of infinite extent. The host tissue is considered to be passive insofar as it is permeable to enzymes produced within the target tissue, and as the latter grows, the former offers no packing resistance to slow down or stop the growth of target tissue. We assume that two basic enzymes are produced at a uniform rate within the target tissue: the “inhibitor” has concentration  $C_1$  and production rate  $P_1$  and the “activator” has concentration  $C_2$  and production rate  $P_2$ . If  $\lambda_i$  and  $D_i$  represent the respective depletion (or decay) rates and diffusion coefficients of enzyme  $i$  ( $i = 1$  or  $2$ ) then under the assumption of diffusive equilibrium the  $C_i$  satisfy equations of the form

$$(1) \quad D_i \frac{d^2 C_i}{dx^2} - \lambda_i C_i = -P_i S(x),$$

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where

$$(2) \quad \begin{aligned} S(x) &= 1, & |x| \leq L/2, \\ &= 0, & |x| > L/2. \end{aligned}$$

Furthermore, we suppose that there exists a discontinuous switch-like mechanism governing the mitotic part of the cell cycle. If  $M(x)$  is a general mitotic rate and  $M_o$  is the normal rate, then we consider the following concentration-dependent switches:

- (I) If  $C_1(x_o) > \theta_o$  and  $C_2(x_o) < \phi_o$  then  $M(x_o) = 0$ , i.e., no mitosis. The quantities  $\theta_o$  and  $\phi_o$  are threshold concentrations.
- (II) If  $C_1(x_o) > \theta_o$  and  $C_2(x_o) > \phi_o$  then  $M(x_o) = M_<$ , where  $0 \leq M_< < M_o$  (decelerated mitotic rate).
- (III) If  $C_1(x_o) < \theta_o$  and  $C_2(x_o) < \phi_o$  then  $M(x_o) = M_o$ .
- (IV) If  $C_1(x_o) < \theta_o$  and  $C_2(x_o) > \phi_o$  then  $M(x_o) = M_>$  where  $M_o < M_>$  (accelerated mitotic rate).

Glass solved system (1) and (2) for a single growth inhibitor with concentration  $C$  [4], i.e., no activator/inhibitor interaction. Later, however, Shymko and Glass [5] did solve system (1) for point sources, i.e.,  $S(x) \propto f[C_i]\delta(x - x_i)$ ,  $i, j = 1, 2$ . We are interested here in uniform production rates across the target tissue, and subsequent limiting tissue sizes.

The formal solution to (1) and (2) is

$$(3) \quad C_i(x) = P_i \int_{-\infty}^{\infty} G(x - x') S(x') dx',$$

where the Green's function

$$(4) \quad G(x) = \frac{1}{2\sqrt{D_i\lambda_i}} \exp(-\alpha_i |x|),$$

where  $\alpha_i = \sqrt{\lambda_i/D_i}$ .

The conditions implicit on  $C_i(x)$  are

- (i)  $C_i(0) < \infty$ ,
- (ii)  $C'_i(0) = 0$ ,
- (iii)  $\lim_{|x| \rightarrow \infty} C_i(x) = 0$ ,
- (iv)  $C_i(x), C'_i(x)$  continuous at  $|x| = L/2$ .

(These conditions do not all have to be imposed: (i) and (ii) are implied by (iii) and (iv).)

The solutions are as follows:

(a)  $|x| \leq L/2$ ,

$$(5) \quad C_i(x) = \frac{P_i}{\lambda_i} \left\{ 1 - (\cosh \alpha_i x) \exp\left(-\alpha_i \frac{L}{2}\right) \right\}.$$

(b)  $|x| \geq L/2$ ,

$$(6) \quad C_i(x) = \frac{P_i}{\lambda_i} \left( \sinh \alpha_i \frac{L}{2} \right) \exp(-\alpha_i |x|).$$

We note that

$$C_i(0) = \frac{P_i}{\lambda_i} \{1 - \exp(-\alpha_i L/2)\}$$

and

$$(7) \quad C_i(|L/2|) = \frac{P_i}{2\lambda_i} \{1 - \exp(-\alpha_i L)\}.$$

Define the following dimensionless quantities:

$$(8a) \quad n_1 = \frac{P_1}{2\lambda_1\theta_o},$$

$$(8b) \quad n_2 = \frac{P_2}{2\lambda_2\theta_o}.$$

Furthermore, define the following functions:

$$(9a) \quad f_i(n_i) = \frac{1}{\alpha_i} \ln \left( \frac{n_i}{n_i - 1} \right) \quad (n_i > 1),$$

$$(9b) \quad g_i(n_i) = \frac{2}{\alpha_i} \ln \left( \frac{2n_i}{2n_i - 1} \right) \quad \left( n_i > \frac{1}{2} \right).$$

(Note that  $g_i(n_i) = 2f_i(2n_i)$ .)

We consider various different states throughout the tissue.

(i)  $M = 0$  for all  $x \in [-L/2, L/2]$ , i.e., no mitosis throughout the tissue (switch I).

Since  $C_i(x)$  is a monotone decreasing function, we require the following conditions to hold simultaneously:  $C_1(|L/2|) > \theta_o$  and  $C_2(0) < \phi_o$ . After a little algebra it follows that  $L$  must satisfy the condition

$$(10) \quad f_1(n_1) < L < g_2(n_2).$$

(ii)  $M = M_<$  for all  $x \in [-L/2, L/2]$  (switch II). We now require that  $C_1(|L/2|) > \theta_o$  and  $C_2(|L/2|) > \phi_o$ ,

$$(11) \quad L > \max_i \{f_i(n_i)\}.$$

(iii)  $M = M_o$  for all  $x \in [-L/2, L/2]$  (switch III). It is necessary that  $C_1(0) < \theta_o$  and  $C_2(0) < \phi_o$ , implying

$$(12) \quad L < \min_i \{g_i(n_i)\}.$$

(iv)  $M = M_>$  for all  $x \in [-L/2, L/2]$  (switch IV). This requires  $C_1(0) < \theta_o$  and  $C_2(|L/2|) > \phi_o$ , i.e.,

$$(13) \quad g_2(n_2) < L < f_1(n_1).$$

We are now in the position to prove several lemmas. Let  $p = \alpha_2/2\alpha_1$  and  $n_i > 1$ . Then we have Lemma 1.

LEMMA 1.  $f_1(n) > g_2(n)$  for all  $n > 1$  and  $p \geq \frac{1}{2}$ .

*Proof.* Since  $n/(n-1) > (2n/(2n-1))^2$ , it follows from the nature of  $\ln x$ ,  $x > 0$ , that  $\ln(n/(n-1)) > 2 \ln(2n/(2n-1))$ , i.e.,  $f_1(n) > 2pg_2(n)$ , establishing the result.

LEMMA 2. For any given  $p$ ,  $0 \leq p \leq \frac{1}{2}$ , there exists a unique  $n = n_c$ ,  $1 < n_c < \infty$ , such that  $f_1(n_c) = g_2(n_c)$ . Equivalently, for any given  $n > 1$ , there exists a  $p = p_c < \frac{1}{2}$  such that  $f_1(n) = g_2(n)$ .

*Proof.* We define  $h(n) = \ln(2n/(2n-1))/\ln(n/(n-1))$ ,  $n > 1$ . It is seen that  $\lim_{n \rightarrow 1^+} h(n) = 0^+$  and, using l'Hôpital's rule,  $\lim_{n \rightarrow \infty} h(n) = \frac{1}{2}$ . Either  $h \rightarrow \frac{1}{2}$  monotonically or  $h'(n) = 0$  for at least one  $n > 1$ . After some algebra it can be shown that this latter result occurs if and only if

$$\left[ \left( \frac{2n}{2n-1} \right) \left( \frac{2n-2}{2n-1} \right) \right]^n \left( \frac{2n-1}{2n-2} \right) = 1$$

or

$$(14) \quad n \ln \left[ 1 - \frac{1}{(2n-1)^2} \right] = \ln \left[ 1 - \frac{1}{(2n-1)} \right].$$

Clearly this cannot occur for  $n > 1$ , since (14) implies  $n < 1$ . Thus  $h$  is monotone increasing (see Fig. 1). Therefore, for  $p < \frac{1}{2}$  there is a unique  $n = n_c$  such that  $h(n_c) = p$ , i.e.,

$$(15) \quad f_1(n_c) = g_2(n_c).$$

Hence we have the following corollary.

**COROLLARY 1.** *For each  $p < \frac{1}{2}$  there exists a unique  $n = n_c > 1$  such that  $h(n_c) > p$  for  $n > n_c$ , and  $h(n_c) < p$  for  $1 < n < n_c$ . That is,  $g_2(n) > f_1(n)$  for  $n > n_c$ , and  $g_2(n) < f_1(n)$  for  $1 < n < n_c$ .*

From equations (10) and (13) this signifies that if  $n$  is induced to change through the value  $n_c$ , the tissue growth may change from zero mitotic rate to  $M_>$ , or vice versa. That is, the graphs of  $f_1(n_1)$  and  $g_2(n_2)$ , plotted against the same independent variable  $n_1 = n_2 = n$ , actually intersect and cross for  $p < \frac{1}{2}$ , i.e., for  $\alpha_2 < \alpha_1$ , at  $n = n_c$  (see Fig. 2).

Figure 2 depicts the graph of  $g_2(n_2)$  superimposed on the graph of  $f_1(n_1)$ . This provides a convenient description of the regions of the  $f_1 - n_1$  and  $g_2 - n_2$  graphs wherein growth characteristics corresponding to (10) and (13) may occur. Since  $f_1(n)/f_2(n) = \alpha_2/\alpha_1 = 2p$ , we are in a position to describe condition (11) graphically, in a similar fashion. Thus, for  $p > \frac{1}{2}$ ,  $L > f_2(n_2)$  for  $M = M_<$  throughout the tissue. For  $p < \frac{1}{2}$ ,  $L > f_1(n_1)$ . Condition (12) can be similarly described.

Clearly the most interesting implication for a biological context is that this model (highly simplified though it is) indicates that a change may occur from no mitotic activity in  $[-L/2, L/2]$  to accelerated mitosis in  $[-L/2, L/2]$  (or vice versa) as  $n_1$  and  $n_2$  change appropriately through  $n_c$  for  $p < \frac{1}{2}$ . (These changes in  $n_i$  may occur as a result of internal or external factors affecting the state of the tissue—it is beyond the scope of this note to

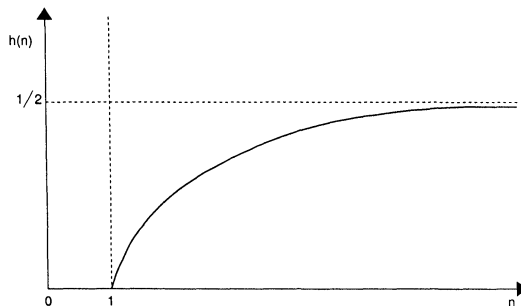


FIG. 1. The function  $h(n) = \ln(2n/(2n-1))/\ln(n/(n-1))$  for  $n > 1$ .

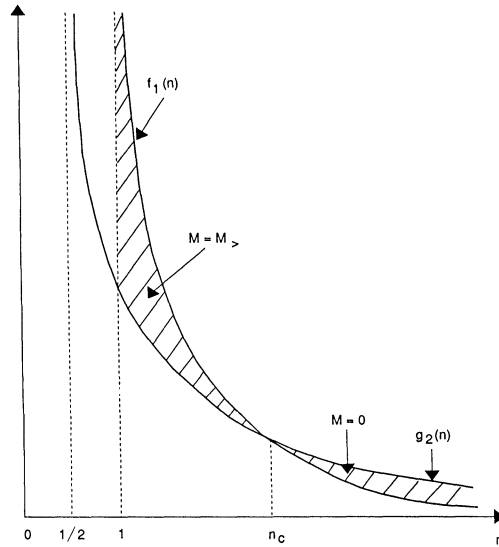


FIG. 2. Composite representation of  $f_1(n)$  and  $g_2(n)$  for  $p = \alpha_2/2\alpha_1 < \frac{1}{2}$ .

speculate further.) For given  $p < \frac{1}{2}$ , this critical value of  $n$ ,  $n_c$ , may be found from equation (15). Note that this behavior change is not the same as that discussed by Glass [4], in which there is only inhibitor present and the transition from “stable” to “unstable” tissue growth occurs at  $n = 1$  (where the expression for  $f_1$  is undefined).

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