1992

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Original Publication Citation
Adam, J. A. (1992). Solution uniqueness and stability criteria for a model of growth factor production. *Applied Mathematics Letters*, 5(2), 89-92. doi:10.1016/0893-9659(92)90119-t

Appl. Math. Lett. Vol. 5, No. 2, pp. 89–92, 1992
Printed in Great Britain.

0893-9659/92 $5.00 + 0.00

SOLUTION UNIQUENESS AND STABILITY CRITERIA FOR A MODEL OF GROWTH FACTOR PRODUCTION

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(Received November 1991)

Abstract—Uniqueness and stability criteria are established for the steady states of a nonlinear model of growth factor production. A specific expression for the nonlinearity is chosen, containing three parameters which can be adjusted to fit a specific biological context, but much of the analysis applies to a general class of source terms that exhibit the same qualitative behavior.

Recent experimental and theoretical studies [1–4] have been concerned with the multifunctional nature and concentration-dependent behavior of so-called transforming or tumor growth factors (TGF's). In this note, we examine some of the implications of a particular analytic representation of TGF production in terms of solution uniqueness and stability for a nonlinear equation governing the existence of low and high concentration steady states of TGF in a spatially homogeneous system. In so doing, we are able to exploit some of the theory that has been applied in the study of chemically reacting systems [5]. We also show that the uniqueness analysis carries over to the case of a localized TGF source in a spatially *non*-homogeneous system, thus complementing some earlier work [3]. The concentration $c(t)$ of TGF satisfies the following equation, where γ is a depletion or decay rate and λ is a production rate (in appropriate units):

$$\frac{\partial c}{\partial t} + \gamma c = \lambda f(c), \tag{1}$$

$$\text{where } f(c) = (c_0 - c)e^{-\delta/(c+c_1)}, \qquad 0 \le c \le c_0 \tag{2}$$

is a specific functional form consistent with earlier analyses [3,4]. (Much of what follows, however, is independent of this particular form). c_0 and c_1 are positive constants, which are utilized in the following changes of variables

$$y = 1 + \frac{c}{c_1}, \quad \beta = \frac{c_0}{c_1}, \quad \delta = \epsilon c_1$$

to yield

$$\gamma^{-1}\dot{y} + y - 1 = \alpha G(y), \tag{3}$$

where $\alpha = \lambda/\gamma$ and

$$G(y) = (1 + \beta - y)e^{-\epsilon/y}. \tag{4}$$

Equations (3) and (4) are essentially the same as those studies by Aris [5] in a different context. We state, without proof the properties of $G(y)$ as given in [5] (see Figure 1 below), where $1 \le y \le 1 + \beta$.

$$G'(y_m) = 0 \text{ where } y_m = \frac{1}{2}\epsilon\left\{-1 + \left[\frac{1 + 4(1 + \beta)}{\epsilon}\right]^{1/2}\right\}.$$

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If $\beta\epsilon < 1$, $y_m < 1$ and $G'(y) < 0$ for $1 \le y \le 1 + \beta$. The point of inflection y_i is

$$y_i = \frac{\epsilon(1+\beta)}{\{\epsilon + 2(1+\beta)\}}.$$

This will lie outside the interval $(1, 1 + \beta)$ if $\beta(\epsilon - 2) < 2$. Define the tangent line height intercept $H(y)$ as

$$H(y) = G(y) - (y - 1)G'(y) \tag{5}$$

$$= \{y^2(\beta + \epsilon) - \epsilon(2 + \beta)y + \epsilon(1 + \beta)\}y^{-2}d^{-\epsilon/y} \tag{6}$$

The minimum value of H is

$$H_{\min} = \left(\frac{4(1+\beta) - \beta\epsilon}{\epsilon}\right)\exp\left(-\left[2 + \frac{\epsilon}{1+\beta}\right]\right).$$

$H_{\min} > 0$ if $\beta(\epsilon - 4) < 4$.

The above three inequalities in the $\epsilon - \beta$ plane are easily visualized. As in earlier analysis for a localized source of TGF [3], a necessary condition for the existence of a unique steady state of the related system

$$y - 1 = \alpha G(y) \tag{7}$$

is that $\alpha G'(y) < 1$. When this condition is violated at least two steady states exist (see Figure 1): three steady states exist for $\alpha\epsilon(\alpha_1, \alpha_2)$. At the points of tangency ($\alpha = \alpha_1$ and $\alpha = \alpha_2$)

$$\alpha G'(y) = 1 \qquad \text{and} \qquad H(y) = 0.$$

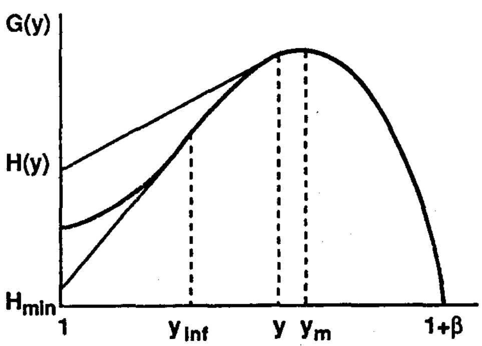

Figure 1a. Schematic representation of $G(y)$, illustrating significant points referred to in the text.

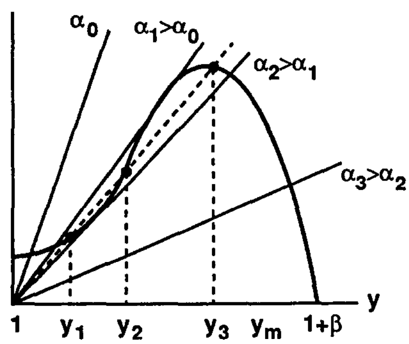

Figure 1b. Representations of $G(y)$ and $\alpha^{-1}(y - 1)$ for various values of α, and the corresponding steady states.

Eliminating β from these two equations yields, for these two values of α

$$\alpha = e^{\epsilon/y}\frac{\{\epsilon(y-1) - y^2\}}{y^2},$$

which may be used to delineate regions of non-uniqueness in the $\alpha - \epsilon$ plane for constant values of β.

SUFFICIENT CONDITION FOR UNIQUENESS.

If y_1 and y_2 are two distinct fixed points of (7), then by the Mean Value Theorem

$$G(y_1) - G(y_2) = (y_1 - y_2)G'(\xi),$$

where $1 < y_1 \le \xi \le y_2 < 1 + \beta$. If $\overline{y} = y_2 - y_1$ then using (7),

$$\overline{y}[1 - \alpha G'(\xi)] = 0,$$

from which uniqueness follows, in particular, if $G'(y) < 0$ in $(1, 1 + \beta)$. This corresponds to $\beta\epsilon < 1$ as established earlier. This can be pursued further. As $\alpha \to \alpha_2^-$, y_1, y_2 and ξ tend to the same value $\hat{y}$ by the sandwich theorem. A third steady state y_3 exists distinct from $\hat{y}$. Again it follows that if $\tilde{y} = y_3 - y_2$,

$$\begin{aligned}\tilde{y} &= \alpha\tilde{y}\left[\frac{G(y_3) - G(y_2)}{y_3 - y_2}\right]\\ &= \alpha\tilde{y}\left[\frac{G(y_1) - G(y_2)}{y_1 - y_2}\right]\\ &= \tilde{y}G'(\xi),\end{aligned}$$

so as $\alpha \to \alpha_2^-$, $\tilde{y} \to v = \alpha G'(\hat{y})v$, where $v = y_3 - \hat{y}$. Thus, $\hat{y}$ is a "bifurcation solution" satisfying the equations

$$\hat{y} - 1 = \alpha G(\hat{y}) \tag{7'}$$

and
$$v = \alpha G'(\hat{y})v, \tag{8}$$

where v is non-trivial. Manipulation of (7′) and (8) yields the result

$$\alpha H(\hat{y})v = 0.$$

Clearly, if $H(\hat{y}) > 0$ everywhere, no non-trivial v exists and, hence, there is no bifurcation solution. This corresponds to a unique solution if $\beta(\epsilon - 4) < 4$.

STABILITY OF THE STEADY STATES.

Suppose, first, that y_s is the unique steady state for the system (3). Then if $\overline{y} = y_s - y$ it follows that

$$\begin{aligned}\gamma^{-1}\dot{\overline{y}} &= -\overline{y} + \alpha\{G(y) - G(y_s)\}\\ &= -\overline{y}\{1 - \alpha G'(\eta)\},\end{aligned} \tag{9}$$

where η is bounded by y and y_s. Since y_s is unique, $\alpha G'(\eta) < 1$ and so

$$\dot{\overline{y}} = -\phi(t)\overline{y}, \qquad \phi(t) > 0.$$

If $\overline{y}(0) = \overline{y}_0$, then it follows that

$$\overline{y}(t) = \overline{y}_0 \exp\left\{-\int_0^t \phi(\tau)\,d\tau\right\}, \tag{10}$$

so $\overline{y}(t)$ does not change sign. It also follows from (9) that $u = \dot{\overline{y}}$ satisfies

$$\dot{u} = -\{1 - \alpha G'(y)\}\,u,$$

so $u(t)$ does not change sign. But $\overline{y}_0$ and u_0 have opposite signs, so the deviation from y_s tends monotonically to zero.

When three steady states arise, similar arguments [5] can be used to show that the upper steady state (y_3) is stable to perturbations that remain in $(y_2, 1 + \beta)$. Similarly, y_1 is stable for perturbations remaining in $(1, y_2)$, and y_2 is unstable with respect to any perturbation.

An alternative proof of these results uses a Lyapunov function $V(y) = 1/2(y - y_s)^2$, from which it follows that

$$\dot{V} = (y - y_s)\{1 - y + \alpha G(y)\}. \tag{11}$$

Reference to Figure 1 shows that if $y_s = y_1$, the product of the factors in (11) is negative in $(0, y_2)$. Lyapunov theorem shows that for any y_0 in this interval, y approaches y_1 asymptotically.

Similarly, for $y_s = y_3$, the domain of attraction is (y_2, ∞). If $y_s = y_2$, $\dot{V} > 0$ in (y_1, y_3): the middle steady state is unstable.

Finally, we note that the steady states $c(x)$ of a spatially non-homogeneous system

$$\frac{\partial c}{\partial t} + \gamma c - D\frac{\partial^2 c}{\partial x^2} = \lambda f(c)\delta(x), \qquad x \in \mathbf{R}, \tag{12}$$

where shown in [3] to be solutions of

$$c(0) = \hat{\beta} f(c(0)), \tag{13}$$

where $\hat{\beta} = \lambda/2\sqrt{\gamma D}$. By defining $y = 1 + c(0)/c_1$ and β, δ as above, Equation (13) becomes

$$y - 1 = \hat{\beta} G(y), \tag{14}$$

and the uniqueness criteria established above apply to this system also.

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