

A Qualitative Analysis of Some Models of Tissue Growth

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Received 10 March 1992; revised 28 May 1992

ABSTRACT

Using maximum principles for parabolic and elliptic operators, we examine, in a general way, some models of tissue growth. These typically consist of a model mechanism for the diffusion of a mitotic inhibitor (growth inhibitory factor, GIF) throughout the tissue. Central to the modeling is the inclusion of a source function that models the production of GIF throughout the tissue. We examine the effect this term has on the resulting distribution of GIF in the tissue and comment on the appropriateness of different source functions, in particular a uniform production rate or a nonuniform production rate of inhibitor. Given that it is more appropriate to infer from the patterns of mitosis that are observed experimentally in various tissues the GIF concentration profile rather than the source function profile, it may be more appropriate to use these types of models to determine the qualitative form of the source term rather than proposing this function *a priori*.

1. INTRODUCTION

The control of mitosis in tissues can be modeled as a schematic mechanism in which self-regulating growth is achieved as a result of negative feedback from the growing tissue [10]. In this approach mitosis is assumed to be controlled by a discontinuous switchlike mechanism, such that if the concentration of the growth inhibitory factor (GIF) C is less than some threshold level θ , say, in any region within the tissue, mitosis occurs in this region, whereas if the concentration is greater than θ , mitosis is completely inhibited. The main assumption regarding this type of negative feedback mechanism is that the GIF is produced throughout the tissue by the individual cells modeled by a source function $S(r)$, diffuses with a (constant) diffusion coefficient D , and is depleted everywhere at a prescribed rate $f(C)$. The differential equation that describes the above system (cf. Shynko and Glass [10], Adam [1]–[3]) is therefore given by

$$\frac{\partial C}{\partial t} = D \nabla^2 C - f(C) + S(r), \quad (1.1)$$

MATHEMATICAL BIOSCIENCES 114:1–11 (1992)

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655 Avenue of the Americas, New York, NY 10010

0025-5564/92 \$5.00

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A more detailed description of the background biology and the derivation of Equation (1.1) can be found in [1], [2], and [10]. Shynko and Glass [10] and Adam [1]–[3] use the function $f(C) = -\gamma C$, where γ is a loss constant, but we shall consider more general forms. Various forms of the source function $S(r)$ have been used. In the original model of Shynko and Glass [10], the GIF is assumed to be produced at a constant rate throughout the tissue, resulting in a *uniform* source function, whereas the models of Adam considered a *nonuniform* source function in an attempt to model more accurately the heterogeneity of cells within tumors. The influence of different geometric regimes on the growth pattern and stability of tissue growth was studied in previous work with reference to the following three ideal geometries (cf. [10], [2]):

- (a) A thin cylindrical tube of radius $h/2$ and length $2R$. The radius is assumed to be small enough to allow the assumption that concentration is a function of the axial distance r from the center of the tube only, that is, $C \equiv C(r)$.
- (b) A thin cylindrical disk of height h and radius R . Once again h is assumed to be small with respect to R so that $C \equiv C(r)$ depends only on the radial distance from the center of the disk.
- (c) A sphere of radius R . $C \equiv C(r)$ is assumed to depend only on the radial distance from the center of the sphere.

Comparisons were then made regarding the differences between each of the models for different ideal geometries under consideration.

It is our intention to show that the main qualitative results of the models can be obtained without having to resort to the analytical solution, which can, of course, be obtained only for very particular functions f and sources S , and often for very particular geometries and under strong symmetry assumptions, for example, that $C = C(r)$. Therefore in the following section we begin a qualitative analysis of Equation (1.1) using maximum principles. Maximum principles are powerful tools in the study of differential equations and enable one to obtain information regarding the solutions of the equations without any explicit knowledge of the solutions themselves. We include a brief statement of the theory used in the subsequent analysis in Appendix 1, and for a more comprehensive treatment of the subject interested readers are referred to the excellent book by Protter and Weinberger [9].

We also suggest that this type of model mechanism may be more useful in obtaining the actual qualitative form of the source function given a known qualitative distribution of mitotic inhibitor (GIF) rather than vice versa. This is in view of the facts that it is easier to obtain experimentally the actual GIF concentration profile in a tissue (cf.

Greenspan [7, 8], Thomlinson and Gray [15], Vaupel et al. [16] rather than the source function profile, and that inferences can and have been drawn from experimentally observed mitotic patterns in various tissues regarding the GIF concentration profile. Finally, Section 3 contains some concluding remarks and a short discussion.

2. THE MATHEMATICAL MODELS

Consider the system

$$\frac{\partial C}{\partial t} = f(C) + D\nabla^2 C + \lambda S(\mathbf{r}) \text{ in } \Omega \times (0, \infty), \quad (2.1)$$

$$D \frac{\partial C}{\partial n} - PC = 0 \text{ in } \partial\Omega \times (0, \infty), \quad P \geq 0, \quad (2.2)$$

$$C(\mathbf{r}, 0) = C_0(\mathbf{r}) \geq 0, \quad \text{for } \mathbf{r} \in \Omega, \quad (2.3)$$

where $C = C(\mathbf{r}, t)$ is the concentration of some chemical inhibitor in a bounded region Ω of \mathcal{R}^n ($n = 1, 2, 3$), $D > 0$, $\lambda > 0$, $S \geq 0$, and P is the (constant) permeability of the tissue surface.

THEOREM 1

Let f, C_0 , and Ω satisfy the conditions of the parabolic comparison theorem, Theorem A1 in Appendix 1. Then the concentration $C(\mathbf{r}, t)$ of the inhibitor is always nonnegative, that is, $C(\mathbf{r}, t) \geq 0$.

Proof. (by parabolic maximum principle). Define $M(C) \equiv \partial C / \partial t - f(C) - D\nabla^2 C - \lambda S = 0$. Now $M[0] = -\lambda S$, and so $M(C) > -\lambda S = M[0]$. Appropriate boundary and initial inequalities also hold, so the result follows by Theorem A1. ■

In [10] it is shown that the diffusion of GIF is rapid in comparison with tissue growth, allowing time dependence to be ignored, that is, the above parabolic system can be replaced by an elliptic one. Thus we now consider the corresponding steady-state problem.

$$0 = D\nabla^2 C + f(C) + \lambda S(\mathbf{r}) \text{ in } \Omega, \quad (2.4)$$

$$D \frac{\partial C}{\partial n} - PC = 0 \text{ on } \partial\Omega, \quad P \geq 0, \quad (2.5)$$

THEOREM 2

Let f and Ω satisfy the conditions of the elliptic comparison Theorem A2 in Appendix 1. Then the solution to the above problem is unique.

Proof. Let C_1 and C_2 be two solutions to the problem. Then they are both regular supersolutions and regular subsolutions, so $C_1 \leq C_2$, $C_2 \leq C_1$ by the elliptic comparison theorem, and so $C_1 = C_2$.

For the models under consideration by Szymko and Glass [10] and Adam [1-3], we have $f(C) = -\gamma_1 C$, $\gamma_1 = \gamma + P\beta$, ($\gamma = a, b, c$), where β , α are constants depending on the geometry of the growing tissue (cf. [10], [2]), which satisfies the assumption on f . ■

For the model of Szymko and Glass [10] and those of Adam [1-3] and $C = C(r)$, we can also show that the concentration C decreases monotonically from its (central) value $C(0)$ to its value $C(R)$ at the edge of the tissue. The system we consider is (2.4) with $S = S(r)$ and

$$\frac{\partial C}{\partial r} = 0, \quad r = 0; \quad D \frac{\partial C}{\partial r} + PC = 0, \quad r = R, \quad (2.6)$$

THEOREM 3

Under the assumptions $S'(r) \leq 0$ and f differentiable, with $f' < 0$, the concentration decreases monotonically in the open interval $(0, R)$.

Proof. In the open interval $(0, R)$, differentiation of (2.4) with $S = S(r)$ gives

$$D\nabla^2 \left(\frac{\partial C}{\partial r} \right) + f'(C) \left(\frac{\partial C}{\partial r} \right) = -\lambda S'(r) \geq 0 \text{ in } (0, R), \quad (2.7)$$

and (2.6) implies that $\partial C / \partial r \leq 0$ at 0 and R . It follows that $\partial C / \partial r$ is a subsolution of the problem $D\nabla^2 u + f'(C)u = 0$ in Ω , with $u = 0$ on $\partial\Omega$. This has solution $u = 0$, and so by the comparison theorem for elliptic equations, Theorem A2, $\partial C / \partial r \leq u = 0$. ■

It follows immediately that the minimum value of the concentration $C(r)$ is attained at the boundary $r = R$ and the maximum value of the concentration $C(r)$ is attained at $r = 0$. For both the uniform source term

$$S(r) = \begin{cases} 1, & 0 \leq r \leq R \\ 0, & r > R \end{cases} \quad (2.8)$$

in the model of Szymko and Glass [10] and the nonuniform source term

$$S(r) = \begin{cases} 1-r/R, & 0 \leq r \leq R \\ 0, & r > R \end{cases} \quad (2.9)$$

in the models of Adam [1-3], we note that the condition $S'(r) \leq 0$ is satisfied

In the case of a uniform source term (cf. [10]) it can also be shown that the GIF concentration profile is concave, that is, $\nabla^2 C \leq 0$ (see Appendix 2 for a proof of this). As pointed out in [4] and [14], the solutions given by Adam in [2] are, in fact, incorrect. We also note that the (only) correct boundary condition to impose at $r = 0$ in geometry (a) is $\partial C / \partial r = 0$. The boundary condition $C(0) < \infty$ applied in [1], [2], [3], and [10] leads to a nonunique solution because only one equation is obtained for the two constants of integration. However, for geometries (b) and (c), both $\partial C(0) / \partial r = 0$ and $C(0) < \infty$ give well-posed problems and yield identical solutions. In light of these remarks it is apparent that $\partial C / \partial r = 0$ is the best way of stating the boundary condition at the origin, as this is correct in each of the geometries (a), (b), (c).

Finally we note that the nonuniform source term of Adam [1-3] is slightly unrealistic from a biological point of view because $S(0) \neq 0$. Perhaps an alternative nonuniform source term to consider is

$$S(r) = \begin{cases} 1 - r^2/R^2, & 0 \leq r \leq R, \\ 0, & r > R. \end{cases} \quad (2.10)$$

This satisfies $S(0) = 0$, which is smooth at $r = 0$ and hence is more realistic from a biological viewpoint, while retaining the qualitative shape of the original nonuniform source function. This function represents a smooth transition from the uniform production rate chosen in [10] and the uniform production rate confined to the necrotic region in [7] and [8]. As can be seen from Appendix 3, the solutions to the problem [in each of the geometries (a), (b), (c)] obtained using this new source term are similar to the incorrect solutions given in [2]. For this reason a similar stability analysis to determine the limiting size of tissue growth (cf. [10] and [1-3]) is possible and is being carried out at present. This will be the subject of a future paper. Finally, it is also intuitively clear and easy to show using the maximum principle that an increase in the source function leads to a corresponding increase in the GIF concentration. Thus the concentration obtained using the uniform source function (2.8) is greater than that using the parabolic profile (2.10), which is greater than that using the linear profile (2.9). This is confirmed in Figure 1, which shows the GIF concentration profile for geometry (a) using the three different source functions mentioned above with $D = 0.5 \times 10^{-6}$ cm²/s, $P = 10^{-4}$ cm/s, $\gamma = 5 \times 10^{-5}$ s⁻¹ (cf. [10]), and the proof is given in Appendix 4. Similar profiles are obtained for geometries (b) and (c).

We now show that [for the case of a uniform source function and for geometry (a)] as the tissue size increases (i.e., as R increases), the concentration at any point increases.

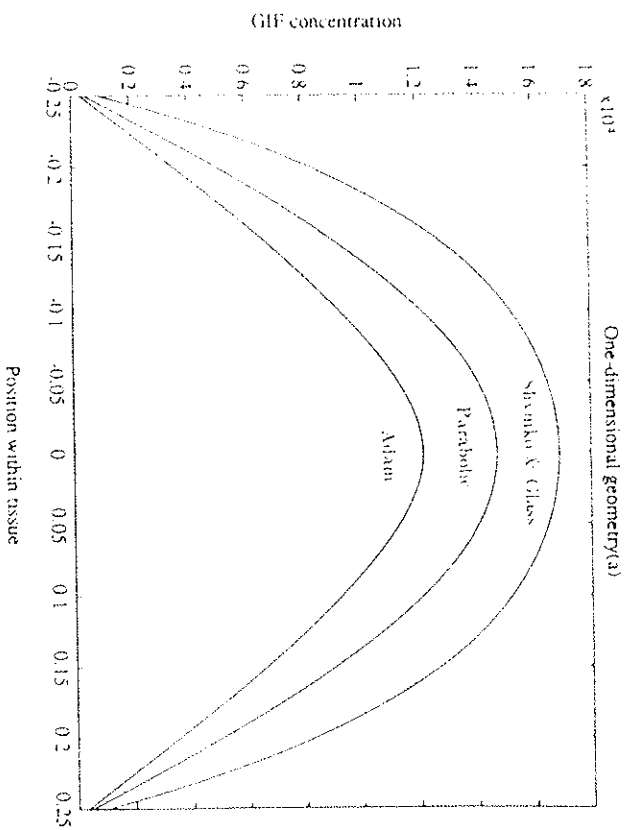


FIG. 1. Plot of GIF concentration throughout one-dimensional tissue [geometry (a)] using all three source terms.

THEOREM 4

Let f satisfy the conditions of Theorem A2. Consider the case of geometry (a). Let $R_1 < R_2$, and suppose C_1 and C_2 satisfy

$$N[C_1] = D \nabla^2 C_1 + f(C_1) + \Delta S(r) = 0,$$

$$\frac{\partial C_1}{\partial r} = 0, \quad r = 0; \quad D \frac{\partial C_1}{\partial r} + P C_1 = 0, \quad r = R_1,$$

for (1.2), where $S(r)$ is the uniform source function as described earlier. Let C_1 and C_2 be functions of r only. Then $C_2 \geq C_1$.

Proof. We show that C_2 is a supersolution of the problem for C_1 . Firstly, $N[C_2] \leq N[C_1]$. We also have $\partial C_2(0) / \partial r \geq \partial C_1(0) / \partial r$ (trivially), and, finally, for the uniform source function, both C_1 and C_2 satisfy $\nabla^2 C_1 \leq 0$ and $\nabla^2 C_2 \leq 0$. For geometry (a) and C_1 (cf. (1.2)) a function of r only, this implies that $\partial C_1 / \partial r$ is a decreasing function of

r . Thus,

$$\begin{aligned} D \frac{\partial C_1(R_1)}{\partial r} - PC_1(R_1) &\geq D \frac{\partial C_1(R_2)}{\partial r} + PC_2(R_2) \\ &= 0 = D \frac{\partial C_1(R_1)}{\partial r} + PC_1(R_1) \end{aligned}$$

since both C_1 and $\partial C_1/\partial r$ are decreasing functions of r . Hence C_2 is a supersolution of the problem for C_1 so $C_2 \geq C_1$, and as the tissue size increases the concentration at any (fixed) point also increases.

Finally we note that the limiting value $\lim_{R \rightarrow \infty} C(0)$ can be found by considering the spatially independent steady-state problem, no diffusion term. In this case (i.e., $R \rightarrow \infty$), both the uniform and the nonuniform source terms tend to the same (uniform) profile, and so the model of Shymko and Glass and those of Adam are equivalent. Thus the qualitative behavior of the GIF concentration profile can be obtained using maximum principle techniques, and all the salient features of the initial analysis of Shymko and Glass [10] and Adam [1, 2] can be reproduced.

3. CONCLUSIONS

The experimental evidence that is available for this type of model certainly allows for the hypothesis of control of mitosis through a switchlike mechanism, that is, the patterns of mitosis observed experimentally in various tissues (cf. Folkman and Hochberg [6], Sutherland [12], Sutherland et al. [13], Thomlinson and Gray [15], and Vaupel et al. [16]) legitimately permits the a priori choice of the *concentration profile*, which has the qualitative features described above, and not the a priori choice of the source function. Since $S(\mathbf{r})$ is the production rate of the chemical inhibitor whose shape is chosen a priori, with a maximum at some interior point and a minimum on the boundary, the steady-state distribution of the inhibitor is bound to take on a qualitatively similar profile. In this sense, then, the qualitative profile of GIF throughout the tissue is already known before one starts, and the results obtained are essentially known beforehand and are therefore not unexpected. However, as stated by Adam [2], it is of interest nevertheless to investigate nonuniform inhibitor production rates. The real value of this model mechanism might therefore be as an "inverse problem" (cf. Adam [3]). In this way, having assumed that the qualitative profile of GIF throughout the tissue (multicell spheroid mirrors the mitotic profile in the tissue) obtained from experimental evidence (cf. [6], [12], [13], [15], and [16]), the profile of the source function could be approximated using the above system. Given that there is much experimental data available for

multicell spheroids, this model mechanism is probably of most practical use for the spherical geometry (Ω) and also for more general spheroidal geometries. Thus for a linear function f we have

$$0 = \gamma C - D \nabla^2 C - S. \tag{3.1}$$

The data for C would be analyzed in terms of the appropriate Fourier series (i.e., eigenvalues λ_n and eigenfunctions ϕ_n of the operator $-\nabla^2$ on Ω with relevant boundary conditions), giving

$$C(\mathbf{r}) = \sum_{n=0}^{\infty} a_n \phi_n(\mathbf{r}). \tag{3.2}$$

In the case of a spherical geometry, \mathbf{r} becomes the radial variable r . Then

$$S(\mathbf{r}) = \sum_{n=0}^{\infty} (\gamma + D \lambda_n) a_n \phi_n(\mathbf{r}). \tag{3.3}$$

For a more general nonlinear function f , a modification of the above scheme would be possible. Having thus obtained a more accurate profile of the source functions, the system could be solved numerically and investigated more fully in this way.

APPENDIX 1

We give a short summary of the use of the parabolic and elliptic maximum principle in the analysis of nonlinear equations.

DEFINITION

The parabolic initial boundary value problem (P) is defined by

$$N_t[C] = \frac{\partial C}{\partial t} - D \nabla^2 C - f(C) = 0 \quad \text{in } \Omega \times (0, \infty)$$

with initial conditions

$$C(\mathbf{r}, 0) = C_0(\mathbf{r}) \quad \text{for } \mathbf{r} \in \Omega$$

and boundary conditions

$$\alpha C - \beta \frac{\partial C}{\partial n} = \gamma \quad \text{in } \partial \Omega \times (0, \infty),$$

where $\Omega \subset \mathbb{R}^n$.

We seek classical solutions $C \in X$, where X is the space of real-valued functions defined on $\Omega \times [0, \infty)$ twice continuously differentiable with respect to the spatial variables and once continuously differentiable with respect to time in the interior of the spatio-temporal domain, and sufficiently smooth at the boundary of the domain for the initial and boundary conditions to make sense.

DEFINITION

A regular supersolution of (P) is a function $\bar{C} \in X$ that satisfies

$$N_t[\bar{C}] = \frac{\partial \bar{C}}{\partial t} - D\nabla^2 \bar{C} - f(\bar{C}) \geq 0 \text{ in } \Omega \times (0, \infty),$$

$$\bar{C}(\mathbf{r}, 0) \geq C_0(\mathbf{r}) \quad \text{for } \mathbf{r} \in \Omega,$$

$$\alpha \bar{C} - \beta \frac{\partial \bar{C}}{\partial n} \geq \gamma \text{ in } \partial\Omega \times (0, \infty).$$

A regular subsolution \underline{C} is similarly defined with the opposite inequalities.

THEOREM A1 (Comparison Theorem for Parabolic Problems)

Let Ω be a bounded domain in \mathbb{R}^n that satisfies the interior sphere property. Let f be Lipschitz continuous and satisfy $|f(C)| \leq k_1 + k_2 C^2$ for all $C \in \mathbb{R}$ and for some positive constants k_1 and k_2 . Let C_0 be continuous. Let α, β , and γ be continuous functions of \mathbf{r} , and let $\alpha \geq 0, \beta \geq 0, \alpha^2 + \beta^2 > 0$. Let D be a positive constant. Let \bar{C} be a regular supersolution and \underline{C} a regular subsolution of (P). Then

$$\bar{C}(\mathbf{r}, t) \geq \underline{C}(\mathbf{r}, t) \quad \text{for } (\mathbf{r}, t) \in \Omega \times (0, \infty).$$

Note. The conditions above are more than sufficient to ensure that a classical solution of (P) exists globally in time.

Proof. See Protter and Weinberger [9, p. 172] for a proof of the maximum principle on which this theorem is based, and Smoller [11, p. 94] or Britton [5, p. 34] for a proof of the theorem.

DEFINITION

The corresponding elliptic problem (E) is defined by

$$N_t[C] - D\nabla^2 C + f(C) = 0 \text{ in } \Omega$$

with boundary conditions

$$\alpha C - \beta \frac{\partial C}{\partial n} = \gamma \text{ in } \partial\Omega,$$

where $\Omega \in \mathbb{R}^n$. We seek classic solutions $C \in X$, where X is the space of twice continuously differentiable real-valued functions sufficiently smooth at the boundary for the boundary conditions to make sense.

DEFINITION

A regular supersolution of (E) is a function $\bar{C} \in X$ that satisfies

$$N_t[\bar{C}] = D\nabla^2 \bar{C} + f(\bar{C}) \leq 0 \text{ in } \Omega,$$

$$\alpha \bar{C} + \beta \frac{\partial \bar{C}}{\partial n} \geq \gamma \text{ in } \partial\Omega.$$

A regular subsolution \underline{C} is similarly defined with the opposite inequalities.

THEOREM A2 (Comparison Theorem for Elliptic Problems)

Let Ω be a bounded domain in \mathbb{R}^n satisfying the interior sphere property. Let f be Lipschitz continuous and decreasing. Let α, β , and γ be continuous functions of \mathbf{r} , and let $\alpha \geq 0, \beta \geq 0, \alpha^2 + \beta^2 > 0$. Let D be a positive constant. Let \bar{C} be a regular supersolution and \underline{C} a regular subsolution of (E). Then

$$\bar{C}(\mathbf{r}) \geq \underline{C}(\mathbf{r}) \quad \text{for } \mathbf{r} \in \Omega.$$

Note. The conditions above are more than sufficient to ensure the existence of a classic solution of (E).

Proof. See Protter and Weinberger [9, p. 64] for a proof of the maximum principle on which this theorem is based. The proof then proceeds on exactly the same lines as for the parabolic case.

APPENDIX 2

For the case of a uniform source function $S = 1$ and C symmetric, $C = C(r)$, we show that $\nabla^2 C \leq 0$ throughout the tissue. The system is given by (2.4) with $S = 1$ and boundary conditions (2.6).

Consider the function defined by $\bar{C} = f^{-1}(\dots \lambda)$ at each point of Ω . Then we have

$$D\nabla^2 \bar{C} + f(\bar{C}) + \lambda = 0,$$

$$\frac{\partial \bar{C}}{\partial r} = 0, \quad r = 0; \quad D \frac{\partial \bar{C}}{\partial r} + P\bar{C} = P\bar{C} \geq 0, \quad r = R.$$

so that \bar{C} is a supersolution of the problem for C and by the comparison theorem for elliptic problems, Theorem A2, $\bar{C} \geq C$. Then

$$D\bar{C}^2 C = -f(C) - \lambda \leq -f(\bar{C}) - \lambda = 0,$$

as required.

APPENDIX 3

Solutions to the system

$$D\bar{C}^2 C - \gamma C = -\lambda S(r), \quad (A3.1)$$

$$\frac{\partial C}{\partial r} = 0, \quad r = 0; \quad D \frac{\partial C}{\partial r} + PC = 0, \quad r = R, \quad (A3.2)$$

with nonuniform source term

$$S(r) = \begin{cases} 1 - r^2/R^2, & 0 \leq r \leq R \\ 0, & r > R \end{cases}$$

for each of the three geometries (a), (b), (c) described in Section 1, are

(a)

$$C = \frac{\lambda}{\gamma} \left[\left(1 - \frac{2}{k^2 R^2} - \frac{r^2}{R^2} \right) + \frac{\frac{2D}{P} \left(1 + \frac{P}{\gamma R} \right) \cosh kr}{1 + \eta \tanh kR} \right], \quad (A3.3)$$

(b)

$$C = \frac{\lambda}{\gamma} \left[\left(1 - \frac{4}{k^2 R^2} - \frac{r^2}{R^2} \right) + \frac{\frac{2D}{P} \left(1 + \frac{2P}{\gamma R} \right) I_0(kr)}{1 + \eta I_1(kR)/I_0(kR)} \right], \quad (A3.4)$$

(c)

$$C = \frac{\lambda}{\gamma} \left[\left(1 - \frac{6}{k^2 R^2} - \frac{r^2}{R^2} \right) + \frac{\frac{2D}{P} \left(1 + \frac{3P}{\gamma R} \right) \frac{\sinh kr}{r \sinh kR}}{1 + \eta (\coth kR - 1/kR)} \right], \quad (A3.5)$$

where $k^2 = \gamma/D$ and $\eta = Dk/P = (D\gamma)^{1/2}/P$.

APPENDIX 4

Let

$$N_1[C_1] = f(C_1) + D\bar{C}^2 C_1 + S_1 = 0, \quad (A4.1)$$

$$\frac{\partial C_1}{\partial r} = 0, \quad r = 0; \quad PC_1 + D \frac{\partial C_1}{\partial r} = 0, \quad r = R. \quad (A4.2)$$

Similarly for C_2 . Then

$$\begin{aligned} N_1[C_2] &= f(C_2) + D\bar{C}^2 C_2 + S_1 = f(C_2) + D\bar{C}^2 C_2 + S_2 + (S_1 - S_2) \\ &= N_2[C_2] + S_1 - S_2 = S_1 - S_2. \end{aligned}$$

Thus if we have $S_1 \leq S_2$, then $N_1[C_2] = (S_1 - S_2) \leq 0 = N_1[C_1]$. Boundary inequalities also hold (as equalities), and so from the comparison theorem for elliptic problems, Theorem A2, we have $C_1 \leq C_2$ in $\bar{\Omega}$.

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