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PDE PROBLEMS ARISING IN MATHEMATICAL BIOLOGY

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Abstract. This article reviews biological processes that can be modeled by PDEs, it describes mathematical results, and suggests open problems. The first topic deals with tumor growth. This is modeled as a free boundary problem for a coupled system of elliptic, hyperbolic and parabolic equations. Existence theorems, stability of radially symmetric stationary solutions, and symmetry-breaking bifurcation results are stated. Next, a free boundary problem for wound healing is described, again involving a coupled system of PDEs. Other topics include movement of molecules in a neuron, modeled as a system of reaction-hyperbolic equations, and competition for resources, modeled as a system of reaction-diffusion equations.

1. **Introduction.** Recent years have seen a dramatic increase in the number and variety of new mathematical models describing biological processes. Many of these models are formulated in terms of dynamical systems, i.e., ODEs and PDEs, or mixture thereof. Relevant biological questions give rise to interesting questions regarding properties of the solutions of the dynamical systems. In this review we introduce some of these models, report on recent mathematical results, and raise open and challenging questions. We shall consider models that describe tumor growth and wound healing, both being free boundary problems for systems of PDEs. We shall then consider reaction-hyperbolic equations that model, for instance, the movement of motor proteins in axon. Finally we review recent mathematical results for systems of diffusion equations pertaining to models in ecology and evolution.

2. **Tumor growth.** We denote a tumor domain in $\mathbb{R}^3$ by $\Omega(t)$, and its boundary by $\Gamma(t)$; $\Gamma(t)$ is a "free boundary," i.e, it is not prescribed in advance, and needs to be solved together with a system of PDEs that are to be satisfied in $\Omega(t)$. We assume that there are three types of cells in the tumor: proliferating cells with (mass) density $p(x,t)$, quiescent cells with density $q(x,t)$, and dead cells with density $n(x,t)$.

Following [30], we assume that quiescent cells become proliferating cells at a rate $K_P(c)$ which depends on the concentration c of nutrients and they become necrotic at death rate $K_D(c)$. We also assume that proliferating cells become quiescent at a rate $K_Q(c)$ and their death rate is $K_A(c)$. The density of proliferating cells is

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increasing at a rate $K_B(c)$. Finally, we assume that dead cells are removed from the tumor at a constant rate K_R.

We next assume that all the cells are physically identical in volume and mass and that their density is constant throughout the tumor, so that

$$p + q + n = const. = \theta. \tag{1}$$

Due to proliferation and removal of cells, there is a continuous motion of cells within the tumor. We shall represent this movement by a velocity field $\mathbf{v}$. We can then write the conservation of mass law for the densities of the proliferating cells p, the quiescent cells q, and the dead cells n within the tumor region $\Omega(t)$ in the following form:

$$\frac{\partial p}{\partial t} + div(p\mathbf{v}) = [K_B(c) - K_Q(c) - K_A(c)]p + K_P(c)q, \tag{2}$$

$$\frac{\partial q}{\partial t} + div(q\mathbf{v}) = K_Q(c)p - [K_P(c) + K_D(c)]q, \tag{3}$$

$$\frac{\partial n}{\partial t} + div(n\mathbf{v}) = K_A(c)p + K_D(c)q - K_R n. \tag{4}$$

We assume that movement of cells within $\Omega(t)$ is similar to that of a flow in a porous medium. Hence the velocity $\mathbf{v}$ is related to the pressure σ of the flow by means of Darcy's law

$$\mathbf{v} = -\nabla\sigma. \tag{5}$$

If we add equations (2)-(4) and use (1), we get

$$\theta \; div \; \mathbf{v} = K_B(c)p - K_R n, \tag{6}$$

and we may replace (4) by (6).

We assume that the nutrient concentration satisfies the diffusion equation

$$\beta\frac{\partial c}{\partial t} = \Delta c - \lambda(p+q)c \text{ in } \Omega(\mathrm{t}). \tag{7}$$

Eliminating n from (6), by (1), and taking, for simplicity, $\theta = 1$, and recalling (5), we obtain, in addition to (7), the following equations:

$$\frac{\partial p}{\partial t} - \nabla\sigma \cdot \nabla p = f(c,p,q) \text{ in } \Omega(\mathrm{t}), \mathrm{t} > 0, \tag{8}$$

$$\frac{\partial q}{\partial t} - \nabla\sigma \cdot \nabla q = g(c,p,q) \text{ in } \Omega(\mathrm{t}), \mathrm{t} > 0, \tag{9}$$

$$\Delta\sigma = -h(c,p,q) \text{ in } \Omega(\mathrm{t}), \mathrm{t} > 0, \tag{10}$$

where

$$f(c,p,q) = [K_B(c) - K_Q(c) - K_A(c)]p + K_P(c)q - h(c,p,q)p,$$
$$g(c,p,q) = K_Q(c)p - [K_P(c) + K_D(c)]q - h(c,p,q)q,$$
$$h(c,p,q) = -K_R + [K_B(c) + K_R]p + K_R q.$$

We impose the following boundary conditions:

$$c = \overline{c} \text{ on } \Gamma(\mathrm{t}), \mathrm{t} > 0, \tag{11}$$

$$\sigma = \gamma\kappa \text{ on } \Gamma(\mathrm{t}), \mathrm{t} > 0, \tag{12}$$

where $\overline{c}$ is a constant, γ is a surface tension coefficient representing the cell-to-cell adhesion, and κ is the mean curvature ($\kappa = \frac{1}{R}$ if $\Omega(\mathrm{t})$ is a ball of radius R). We

assume that the normal velocity V_n of the free boundary is the same as the normal velocity $\mathbf{v}\cdot\mathbf{n}$ of the cells in the outward normal direction $\mathbf{n}$, i.e.,

$$\frac{\partial\sigma}{\partial n} = -V_n \text{ on } \Gamma(\mathrm{t}), \mathrm{t} > 0. \tag{13}$$

We finally prescribe initial conditions:

$$\begin{gathered}\Omega(t)|_{t=0} = \Omega_0, \text{ the boundary } \Gamma_0 \text{ of } \Omega_0 \text{ is in } \mathrm{C}^{2+\alpha},\\ c|_{t=0} = c_0(x), p|_{t=0} = p_0(x), q|_{t=0} = q_0 \text{ in } \Omega_0,\\ p_0 \geq 0,\ q_0 \geq 0,\ p_0 + q_0 \leq 1, c_0 \geq 0;\\ c_0,\ p_0, q_0 \text{ are in } \mathrm{C}^{2+\alpha}(\overline{\Omega}_0), \mathrm{c}_0 = \overline{\mathrm{c}} \text{ on } \Gamma_0.\end{gathered} \tag{14}$$

The functions $K_i(c)$ in (2)-(4) satisfy natural monotonicity conditions; for example, $K_B(c)$ and $K_P(c)$ should be monotone increasing in c. However, such assumptions will not be needed below; we only assume that

$$\text{the functions } \mathrm{K_i(c)} \text{ are in } \mathrm{C}^{\alpha}. \tag{15}$$

Theorem 2.1. [4]. *The system (1)-(15) has a unique solution with $\Gamma(t)$ in $C^{2+\alpha,1+\alpha/2}_{x,t}$ for all $0 < t < T$, where T is some small positive number.*

The solution can be extended step-by-step provided one can establish a priori $C^{2+\alpha,1+\alpha/2}_{x,t}$ bound on $\Gamma(t)$. This is the case when $\Gamma(t)$ is a sphere $r = R(t)$:

Theorem 2.2. *If the initial data are radially symmetric then there exists a unique globally radially symmetric solution with free boundary $r = R(t)$.*

The questions that arise are:

(i) Are there radially symmetric stationary solutions, with $R(t) \equiv R$?

(ii) Are such solutions asymptotically stable? By this we mean that for any initial data "close" to a radially symmetric stationary solution there exists a unique global solution which converges to the radially symmetric stationary solution.

These questions are, in general, open except in the special case where $q \equiv n \equiv 0$, $p \equiv 1$, i.e., when all the cells are proliferating. In this case

$$\Delta\sigma = -\mu(c - \tilde{c}),\ \mu > 0,\ 0 < \tilde{c} < \overline{c} \tag{16}$$

where $\mu(c - \tilde{c})$ is the proliferating rate, and the following result holds:

Theorem 2.3. [25]. *There exists a unique radially symmetric stationary solution (c, σ) with free boundary $r = R$, given by*

$$c(r) = \overline{c}\ \frac{R}{\sin hR}\ \frac{\sin hr}{r}, \sigma(r) = C - \mu c(r) + \frac{\mu}{6}r^2 \tag{17}$$

where

$$C = \frac{\gamma}{R} + \mu - \frac{\mu\overline{c}}{6}R^2$$

and R is the solution of the transcendental equation

$$\tan hR = R/\left(1 + \frac{\tilde{c}}{3\overline{c}}\ R^2\right). \tag{18}$$

It is known that the radially symmetric solution, with fixed R but variable $M = \mu/\gamma$, develops "fingers", i.e., that there exist symmetry-breaking bifurcation branches of solutions:

Theorem 2.4. [10][26]. *Let*

$$M_\ell(R) = \frac{(\ell-1)\ell(\ell+2)}{2}\ \frac{1}{R^5 P_0(R)\{P_1(R) - P_\ell(R)\}},$$

where

$$P_n(r) = \frac{I_{n+\frac{3}{2}}(r)}{rI_{n+\frac{1}{2}}(r)},$$

$I_m(R)$ *is the modified Bessel function given by*

$$I_m(r) = \sum_{k=0}^{\infty} \frac{(r/2)^{m+2k}}{k!\Gamma(m+k+1)}.$$

For any $\ell \geq 2$, *there exists a stationary solution with free boundary*

$$r = R + \varepsilon Y_{\ell,0}(\theta) + O(\varepsilon^2)$$
$$M = M_\ell + \varepsilon M_{\ell,1} + O(\varepsilon^2),\ M = \mu/\gamma$$

for any small $|\varepsilon|$ *where* $Y_{\ell,0}(\theta)$ *is the spherical harmonic of mode* $(\ell, 0)$.

Clearly, the radially symmetric stationary solution is unstable when $M = M_2$. But it may already lose stability for smaller values of M:

Theorem 2.5. [14][15][19]. *There exists a positive number* $\overline{R}$ *such that the stationary spherical solution (17)-(18) is asymptotically stable for all* $M < M_2$ *if* $R > \overline{R}$, *but only for all* $M < M_2^*$, *with some* $M_2^* < M_2$, *if* $R < \overline{R}$.

Thus smaller stationary solutions are less stable as the tumor becomes "more aggressive," i.e., as M increases. Both $\overline{R}$ and M_2^* are determined as solutions of certain transcendental equations.

The existence of a radially symmetric stationary solution for the general problem (1)-(15) is unknown, except in the case where $q \equiv 0$ or $n \equiv 0$ [7][8]; but no explicit formula is known, although linear asymptotical stability was established in [3].

Most of the above results have been extended to the case where instead of Darcy's law assumption we assume that the tumor tissue is fluid-like and use the Stokes equation instead of Darcy's law. In this case the relation between the velocity $\mathbf{v}$ and the pressure σ is given by

$$-\nu\nabla^2\mathbf{v} + \nabla\sigma = \mathbf{f}, \tag{19}$$

$$\text{div } \mathbf{v} = \text{g} \tag{20}$$

where $\mathbf{f} = -\frac{\nu}{3}\nabla g$, and the boundary condition (12) is replaced by

$$T(\mathbf{v}, \sigma)\mathbf{n} = -\gamma\kappa\mathbf{n} \tag{21}$$

where

$$T(\mathbf{v}, \sigma) = \nu(\nabla\mathbf{v} + \nabla\mathbf{v}^T) - (\sigma + \frac{2\nu}{3}\text{div } \mathbf{v})I, \tag{22}$$

ν is the viscosity coefficient, I is the unit matrix, and g is the proliferation rate, given by the right-hand side of (6). Existence and uniqueness of a solution with prescribed initial data was proved in [11]. In the case of one population of cells ($p \equiv 1$, $q \equiv n \equiv 0$) the existence of a unique stationary solution with radially symmetric free boundary was proved in [11] and its asymptotic stability was determined in [17]. As in the case of porous medium, here too there exists a sequence of symmetry-breaking bifurcation branches of solutions [18]. For other models of tumor growth, see review article [29].

3. **Multiscale model in tumor growth.** Cancer develops when cells proliferate at higher rate than normal cells, or die at lower rate than normal cells. It is therefore important to look closely at the cell cycle and include it in the study of tumor growth.

The cell cycle is divided into four phases: S (for synthesis), M (for mitosis), and gap phases G_1 and G_2. During the S phase the DNA is replicated, that is, each chromosome is duplicated. During the mitosis phase, M, the nuclear membrane breaks down, sister chromatids are separated, new nuclear membranes are formed, and the cell divides into two daughter cells. S and M are separated by the two gap phases, G_1 and G_2. The cell cycle is controlled at two check points, R_1, located near the end of G_1, and R_2 located in G_2.

At the check point R_1 the cell decides on one of three options: (i) to commit suicide (apoptosis) if it senses that it has been damaged beyond repair during the growth phase G_1; (ii) to go into a quiescent phase G_0 and stay there for a while, if the microenvironment is hypoxic or overpopulated with other cells; or (iii) to proceed to the S phase. At R_2 the cell decides either to go into apoptosis if irreparable damage has occurred during the DNA replication, or to continue toward the M phase. A cell remains in G_0 for a period of time, at the end of which it proceeds to the S phase.

We describe a multiscale model in a simple case where the only cells are proliferating cancer cells with possible mutations in a set of genes $\gamma = (\gamma_1, \gamma_2, \dots, \gamma_\ell)$.

Following [12] we introduce the following notation:

$$
\begin{aligned}
&p_1(x,t,s_1) = \text{density of cells in phase } \mathrm{G}_1, 0 \le \mathrm{s}_1 \le \mathrm{A}_1;\\
&p_2(x,t,s_2) = \text{density of cells in phase } \mathrm{S}, 0 \le \mathrm{s}_2 \le \mathrm{A}_2;\\
&p_3(x,t,s_3) = \text{density of cells in phases } \mathrm{G}_2 \text{ and } \mathrm{M}, 0 \le \mathrm{s}_3 \le \mathrm{A}_3;\\
&p_0(x,t,s_0) = \text{density of cells in phase } \mathrm{G}_0, 0 \le \mathrm{s}_0 \le \mathrm{A}_0;\\
&p_4(x,t) = \text{density of dead cells,}
\end{aligned}
$$

where x varies in the tumor region $\Omega(t)$, with boundary $\Gamma(t)$.

We denote by $w(x,t)$ the oxygen concentration and by $Q(x,t)$ the combined density of live cells in phases G_1, S, G_2, M and G_0. Then, by conservation of mass,

$$\frac{\partial p_i}{\partial t} + \frac{\partial p_i}{\partial s_i} + div(p_i \mathbf{v}) = \lambda_i(w) p_i \text{ for } 0 < s_i < A_i (i = 1, 2, 3), \tag{23}$$

$$\frac{\partial p_0}{\partial t} + \frac{\partial p_0}{\partial s_0} + div(p_0 \mathbf{v}) = -\lambda_0 p_0 \text{ for } 0 < s_0 < A_0, \tag{24}$$

$$\frac{\partial p_4}{\partial t} + div(p_4 \mathbf{v}) = \mu_1 p_1(x,t,A_1) + \mu_2 p_2(x,t,A_2) - \lambda_r p_4 \tag{25}$$

where $\lambda_i(w)$ are growth rates, and $\mu_i = \mu_i(\gamma)$.

Since the density of cells does not change during the time of replication,

$$p_1(x,t,0) = p_3(x,t,A_3). \tag{26}$$

In the following equation (27) the first term on the right-hand side represents the cell's decision at check point R_1 whether to go to apoptosis (μ_1), to quiescent phase, or to proceed to S; the decision depends on the environment (w, Q) and on the state of the genes in γ. The last term in (27) represents cells that moved from G_0 to S,

$$p_2(x,t,0) = (1 - \mu_1 - K(w(x,t), Q(x,t); \gamma)) p_1(x,t,A_1) + p_0(x,t,A_0). \tag{27}$$

The decision at R_2, whether to go to apoptosis, is expressed by the equation

$$p_3(x,t,0) = (1-\mu_2)p_2(x,t,A_2), \tag{28}$$

and the quiescence phase begins with

$$p_0(x,t,0) = K(w(x,t),Q(x,t);\gamma)p_1(x,t,A_1). \tag{29}$$

In order to determine the velocity $\mathbf{v}$ we introduce the quantities

$$Q_i(x,t) = \int_0^{A_i} p_i(x,t,s_i)ds_i \ (0 \le i \le 3),\ Q_4(x,t) = p_4(x,t),$$
$$\vec{Q}(x,t) = \{Q_i\}_{i=0}^4,$$

and note that

$$Q(x,t) = \Sigma_{i=0}^3 Q_i(x,t).$$

We integrate equations (23)-(24) over their respective s_i-intervals and combine the result with (25). Using (26)-(29) we find that all the boundary terms cancel out, so that

$$\sum_{i=0}^4 \left[\frac{\partial Q_i}{\partial t} + div(Q_i\mathbf{v})\right] = \sum_{i=1}^3 \lambda_i(w)Q_i - \lambda_0 Q_0 - \lambda_4 Q_4. \tag{30}$$

If we now assume, as in (1), that

$$\sum_{i=0}^4 Q_i(x,t) \equiv const. = \theta, \tag{31}$$

and take $\theta = 1$, then (30) yields

$$div\ \mathbf{v} = H(\vec{Q},w) \tag{32}$$

where

$$H(\vec{Q},w) = \sum_{i=1}^3 \lambda_i(w)Q_i - \lambda_0 Q_0 - \lambda_4 Q_4. \tag{33}$$

Finally, the oxygen concentration satisfies a diffusion equation

$$w_t - D_w \cdot \nabla^2 w + \overline{\lambda} Q w = 0 \tag{34}$$

where $\overline{\lambda}$ is a positive constant.

We can proceed to complete the model by assuming that the tissue either obeys Darcy's law or Stokes law. These models were studies in [12][13] where local existence and uniqueness was proved for any initial data, and global existence was proved in the radially symmetric case. Some asymptotic estimates were derived in [20].

We pick up two genes, γ_1 which transcribes SMAD and γ_2 which transcribes APC. SMAD blocks cell cycle at R_1 when the oxygen level is low, and APC blocks cell cycle at R_1 when the microenvironment is overpopulated with cells. It is known that in colorectal cancer these two genes are mutated. In our model mutation of both genes means that $K(w,Q,\gamma) = const$; however, if only γ_1 is mutated, the cell cycle can still be blocked at R_1 under overpopulation conditions.

It was proved in [21] that cancer occurs if both genes γ_1 and γ_2 are mutated, in the sense that in the radially symmetric case the tumor radius $R(t)$ increases to ∞ as $t \to \infty$. However, if only γ_1 is mutated, the cells can control overpopulation conditions so that $R(t)$ will remain bounded for all $t > 0$.

The multiscale approach to cancer described above includes two time scales, t and s_i, and spatial scales from genes to tissue. This direction of research is just at its initial stage of development. It would be very interesting to include a broader set of genes and the constraints on the control they have within these genes network, as the cell reaches the check points R_1 and R_2.

4. **Wound healing.** Consider a cutaneous, or dermal, wound which occupies a region

$$W(t) = \{(x_1, x_2, x_3); (x_1, x_2) \in W_0(t), -h(x_1, x_2, t) \leq x_3 \leq 0)\}$$

where $W_0(t)$ is the surface of the wound, lying in $\{x_3 = 0\}$. Healing occurs as $W_0(t)$ and $h(x_1, x_2, t)$ decrease in t. Taking a fixed cylindrical domain

$$R = \{(x_1, x_2, x_3); \sqrt{x_1^2 + x_2^2} < L, -H < x_3 < 0\}$$

such that $\overline{W(0)} \subset R$, we view the tissue undergoing healing, as occupying the region

$$\Omega(t) = R \backslash W(t).$$

Let ρ denote the density of the extracellular matrix (ECM). During the healing process ρ is expected to increase until, with complete recovery, it reaches the density ρ_0 of healthy normal tissue.

Following [27] [33], we assume that the partially healed region $\Omega(t)$ is viscoelastic, in fact upper connected Maxwell fluid, and we neglect inertia; we further assume that the healing process is quasi-stationary. As healing proceeds so will the isotropic pressure P, which we take to be

$$P = P(\rho) = const.\ F\left(\frac{\rho}{\rho_0} - 1\right)$$

where F is a smooth approximation to the Heaviside function. We then obtain the following elliptic system for the velocity ($\mathbf{v} = (v_1, v_2, v_3)$) of the ECM:

$$\eta \sum_{i=1}^{3} \frac{\partial}{\partial x_i}\left(\frac{\partial v_j}{\partial x_i} + \frac{\partial v_i}{\partial x_j}\right) - \frac{\partial P}{\partial x_j} = 0 \text{ in } \Omega(t),\ (j = 1, 2, 3), \tag{35}$$

where η is a positive constant.

We denote by $\Gamma(t)$ the part of the boundary of $\Omega(t)$ which lies in $\{x_3 < 0\}$. It is natural to assume that there is no stress at the free boundary $\Gamma(t)$. Hence

$$\eta \sum_{i=1}^{3}\left(\frac{\partial v_j}{\partial x_i} + \frac{\partial v_i}{\partial x_j}\right)\nu_i - P\nu_j = 0 \text{ on } \Gamma(t),\ (j = 1, 2, 3) \tag{36}$$

where $\mathbf{n} = (\nu_1, \nu_2, \nu_3)$ is the outward normal. The boundary conditions for $\mathbf{v}$ at the fixed boundaries are

$$\begin{aligned} &v_1 = v_2 = v_3 = 0 \text{ on } \{x_3 = -H\} \text{ and on } \{x_1^2 + x_2^2 + L^2\}, \\ &\frac{\partial v_1}{\partial x_3} = \frac{\partial v_2}{\partial x_3} = 0,\ v_3 = 0 \text{ on } \{x_3 = 0, (x_1, x_2) \notin W_0(t), x_1^2 + x_2^2 < L^2\}. \end{aligned} \tag{37}$$

We assume that the free boundary moves in the normal direction with velocity $V_n = \mathbf{v} \cdot \mathbf{n}$. We can represent this relation in the form

$$\psi_t + \mathbf{v} \cdot \nabla\psi = 0 \text{ on } \Gamma(t) \tag{38}$$

where $\Gamma(t)$ is given by the zero set of ψ, i.e., by $\psi(t, \mathbf{x}) = 0$ where $\mathbf{x} = (x_1, x_2, x_3)$.

We assume that

$$\begin{aligned} &\Gamma(0) \in C^{3+\alpha}, \overline{\Gamma(0)} \text{ intersects } x_3 = 0 \text{ orthogonally}, \\ &\sup_{0\le t\le T_0} |P(t,\cdot)|_{C^{1+\alpha}} < \infty \end{aligned} \tag{39}$$

for some $T_0 > 0$.

In the following theorem $\Gamma(t)$ is parametrized by (θ, φ, t) and we set $\lambda = (\theta, \varphi)$.

Theorem 4.1. [24] *The system (35)-(39) has a unique solution for $0 \le t < T$ for some $T < T_0$, with $\Gamma(t)$ which is in $C^{2+\alpha}$ in λ, and its t-derivative is in $C^{1+\alpha}$ in λ.*

In order to prove the theorem we first reflect v_1 and v_2 across $x_3 = 0$ and anti-reflect v_3 across x_3. In this way we obtain a free boundary which does not intersect the fixed boundary. If $\Gamma(0)$ does not intersect $x_3 = 0$ orthogonally, then we expect that singularities will occur at $\overline{\Gamma(t)} \cap \{x_3 = 0\}$, and this case has not been investigated.

We would like to find conditions which will ensure that healing takes place and that the wound shrinks. Consider for example the case of axial symmetry, so that $\varphi = \psi(t, r, x_3)$ where $r = (x_1^2 + x_2^2)^{1/2}$. We can then represent $\Gamma(t)$ in the form

$$x_3 = Z(t, r)$$

and the free boundary condition by

$$Z_t + v_1 Z_r - v_2 = 0.$$

It follows that the wound will begin to shrink if $Z_t > 0$ at $t = 0$, i.e., if

$$v_1 Z_r^0 - v_2 < 0 \tag{40}$$

where $Z^0 = Z(0, r)$.

Problem: Find conditions on $\Gamma(0)$ and $P(0, r, x_3)$ which ensure that (40) is satisfied.

Note that this open problem is a purely elliptic one, with no free boundary.

So far we assumed that P is a given function. But, of course, P is a function of ρ, and ρ evolves according to the law of mass conservation.

$$\frac{\partial \rho}{\partial t} + \operatorname{div}(\rho \mathbf{v}) = G$$

where

$$G = \frac{kw}{w + K}\ f\ \left(1 - \frac{\rho}{\rho_{\max}}\right) - \lambda\rho.$$

Here w is the concentration of oxygen, and f is the concentration of fibroblasts. Furthermore, the variables ρ, w, f and $\mathbf{v}$ are involved in a larger system of drift-diffusion equations which includes several cell types and several growth factors. The existence and uniqueness of a solution for the complete system was also proved in [24], for a small time interval.

Consider next a simpler model introduced in [33] where the dermal wound is flat, so that all the variables, including the velocity v, are functions of (x_1, x_2, t); let us further specialize to the radially symmetric case, where $v = v(r, t)$ and all other variables are functions of (r, t). The wound region is then a circle $r < R(t)$, and the healing region is defined by $R(t) < r < L$. We assume that the wound is ischemic, i.e, the capillary system is damaged so that not enough oxygen w enters through $r = L$:

$$(1 - \gamma)(w - w_0) + \gamma \frac{\partial w}{\partial r} = 0 \tag{41}$$

where $0 < \gamma < 1$; if $\gamma = 1$ the capillary system is completely cut off and we do not expect that the wound will heal, whereas if $\gamma = 0$ then the oxygen level at $r = L$ is the same as the normal oxygen level w_0 in healthy tissue, and we may expect complete healing.

We impose similar ischemic boundary conditions on f and all the other cells and signaling molecules.

Theorem 4.2. [23] *Under the above conditions the wound healing model has a unique global solution with free boundary $r = R(t)$ in $C^{1+\alpha/2}$, and $dR/dt \le 0$ for all $t > 0$. Furthermore, if γ is near 1 then there exists a finite time T_* such that $R(T_*) > 0$ and*

$$R(t) > R(T_*) \text{ if } t < T_*$$
$$R(t) = R(T_*) \text{ if } t > T_*.$$

The last result means that very ischemic wounds stop healing after time T_*. Numerical results with biological parameters for the complete system show that healing takes place if γ is near 0, but there is no mathematical proof for such a result, even when $\gamma = 0$. Indeed all is known for the case $\gamma = 0$ is that $dR/dt < 0$ for all $t > 0$; see [23] for more details.

5. **Reaction-hyperbolic systems.** The movement of molecular motors along a microtubule, or the generation of an action potential for a membrane patch are biological processes that can be described by the stochastic differential equation

$$\frac{dx}{dt} = V(x, t, S_i)$$

where S_i are N discrete states and the transition between the states is by a Markov process. This non-autonomous jump-velocity process is modeled by a non-autonomous reaction-hyperbolic system

$$\frac{\partial p_i}{\partial t} + \frac{\partial}{\partial x}\left(v_i(x,t)p_i\right) = \frac{1}{\varepsilon}\sum_{j=1}^{n} k_{ij}p_j \tag{42}$$

where (k_{ij}) is the transition matrix and $p_i(x,t)$ is the probability density for being in state S_i at time t and position x. The parameter ε is small, reflecting the fact that the transition between the states is fast compared to the time scale of transport.

We assume that k_{ij} are constants,

$$k_{ij} \ge 0 \text{ if } i \ne j, \quad \sum_{i=1}^{n} k_{ij} = 0 \text{ for } j = 1, 2, \cdots, n, \tag{43}$$

and

$$\begin{aligned} &\text{for any } i_0 \ne i_1, \text{ there is a sequence of indices } j_1, j_2, \cdots, j_\ell \text{ such that} \\ &i_0 = j_1, i_1 = j_\ell \text{ and } k_{j_m j_{m+1}} > 0 \text{ for } 1 \le m \le \ell - 1. \end{aligned} \tag{44}$$

Under these conditions the null space of the matrix $(k_{ij})_{i,j=1}^n$ is one dimensional, and there exists a unique vector $\lambda = (\lambda_1, \cdots, \lambda_n)$ such that

$$\sum_{j=1}^{n} k_{ij}\lambda_j = 0, \quad 0 < \lambda_i < 1 \text{ for } i = 1, 2, \cdots, n, \text{ and } \sum_{j=1}^{n} \lambda_j = 1. \tag{45}$$

We shall consider the system (5.1) in

$$D_\infty \equiv \{(x,t); -\infty < x < \infty, t > 0\}$$

and prescribe initial nearly "equilibrium data",

$$p_i(x,0) = \lambda_i \left[q_0\left(\frac{x}{\sqrt{\varepsilon}}\right) + \sqrt{\varepsilon}\; q_{1i}\left(\frac{x}{\sqrt{\varepsilon}}\right)\right] \text{ for } -\infty < x < \infty,\ 1 \le i \le n. \tag{46}$$

We assume that v_j are in $C^n(D_\infty)$ with uniform bounded derivatives of all order up to n, and

$$\sum_{i=1}^{n} (v_i(x,t) - v(x,t))^2 \ge c_0 > 0, \text{ where } v(x,t) \equiv \sum_{j=1}^{n} \lambda_j v_j(x,t). \tag{47}$$

This condition is locally satisfied if and only if not all the v_j coincide.

We are interested in determining the behavior of $p_j(x,t)$ as $t \to \infty$. Following [22] we introduce the solution $g(x,t)$ of

$$g_t + v(x,t) g_x = 0 \text{ in } D_T = D_\infty \cap \{t < T\}$$
$$g(x,0) = x,\ -\infty < x < \infty$$

for any $T < \infty$, and the change of variables

$$\tau = t,\ s = \frac{1}{\sqrt{\varepsilon}}\, g(x,t),$$
$$Q_j^\varepsilon(s,\tau) = p_j(x,t).$$

Theorem 5.1. [22] *For any $0 < \alpha < 1$ there is a constant C_α such that*

$$\sup_{|s| \le \varepsilon^{-\alpha/2}, 0 \le \tau \le T} |Q_j^\varepsilon - \lambda_j Q_0| \le C_\alpha \varepsilon^{(1-\alpha)/2},\ j = 1, 2, \cdots, n,$$

where Q_0 is the bounded solution of a diffusion equation

$$\partial_\tau Q_0 = \beta_0(\tau) \partial_s^2 Q_0 + \beta_1(\tau) Q_0\ (\beta_0(\tau) > 0),$$

with initial condition

$$Q_0(s,0) = q_0(s),$$

where $\beta_0(\tau)$, $\beta_1(\tau)$ can be computed explicitly in terms of the k_{ij} and g.

A similar result was proved earlier in [16] in the case where the v_i are constants, but the space D_∞ is replaced by the half space

$$D_\infty^+ = \{(x,t);\ 0 < x < \infty,\ t > 0\}$$

and boundary conditions are imposed at $\{x = 0, t > 0\}$ on the p_i for which $v_i < 0$. This case models the transport of collagens in neurons; see [6]; see also [31].

Extension of the above results to the case where the k_{ij} are variable functions remains an open problem. We mention here one special case of a system that arise in gas kinetics:

$$\frac{\partial p_1}{\partial t} + \frac{1}{\varepsilon}\frac{\partial p_1}{\partial x} = \frac{1}{\varepsilon^2}(p_1 + p_2)^\alpha (p_2 - p_1),$$
$$\frac{\partial p_2}{\partial t} - \frac{1}{\varepsilon}\frac{\partial p_2}{\partial x} = \frac{1}{\varepsilon^2}(p_1 + p_2)^\alpha (p_1 - p_2) \tag{48}$$

where $0 \le \alpha \le 1$; by scaling, this system can be rewritten in the form (42) with $v_1 = 1$, $v_2 = -1$ and with k_{ij} multiplied by $(p_1 + p_2)^\alpha$. In this model the $p_i (i = 1, 2)$ represent the concentration of two gases. It was established (see [32] and the

references therein) that, under appropriate initial data, $p_i \to u$ as $\varepsilon \to 0$ where u satisfies the diffusion equation

$$\frac{\partial u}{\partial t} = \frac{\partial}{\partial x}\left(\frac{1}{u^\alpha}\,\frac{\partial u}{\partial x}\right).$$

Question: What is the asymptotic behavior of the above system when v_1, v_2 are arbitrary functions?

6. **Competition for resources.** In this section we briefly describe mathematical problems based on the classical models of Lotke-Volterra which represent competition between two species. If we denote by u and v the densities of the two species, and by $m(x)$ the common source they compete for, then one natural model is the following one:

$$\frac{\partial u}{\partial t} = \nabla \cdot (\mu \nabla u - \alpha u \nabla m) + (m - (u+v))u \tag{49}$$

$$\frac{\partial v}{\partial t} = \nabla \cdot (\nu \nabla v - \beta v \nabla m) + (m - (u+v))v \tag{50}$$

in a bounded domain Ω, with no-flux boundary conditions

$$\mu\,\frac{\partial u}{\partial n} - \alpha u\,\frac{\partial m}{\partial n} = \nu\,\frac{\partial v}{\partial n} - \beta v\,\frac{\partial m}{\partial n} \text{ on } \partial\Omega \tag{51}$$

Here μ and ν are the diffusion (dispersion) rates of the two species, and α and β are their respective chemotactic coefficients: each species is attracted in the direction of the gradient of the resource $m(x)$ with its own chemotactic parameter. We assume for simplicity that all the parameters are constants and $\mu > 0$, $\nu > 0$, $\alpha \geq 0$, $\beta \geq 0$.

The basic question is: Will both species survive, or will one of them become extinct as $t \to \infty$.

Consider first the case $\alpha = \beta = 0$, and assume that

$$\int_\Omega m(x)dx > 0.$$

Then, as proved in [9], for any $\gamma > 0$ there exists a unique positive solution $\theta(\cdot, \gamma)$ of the elliptic problem

$$\gamma \Delta\theta + (m - \theta)\theta = 0 \text{ in } \Omega,$$
$$\frac{\partial \theta}{\partial n} = 0 \text{ on } \partial\Omega.$$

The stationary solutions (u, v) of (49)-(51), $(\theta(\cdot, \mu), 0)$ and $(0, \theta(\cdot, \nu))$ represent the cases where only one species survives, and the interesting question is which one.

Theorem 6.1. [9] *If $\mu < \nu$ then $(\theta(\cdot, \mu), 0)$ is globally asymptotically stable among all nonnegative nontrivial initial data.*

Thus, the slower diffuser survives!

This result was extended in [1][2] to the case of general $\alpha \geq 0$, $\beta \geq 0$, and to more general systems [5], including nonlocal dispersions [28]. For some range of parameters only one species survives, while for another range of parameters coexistence was established.

It would be interesting to consider the more general case of k species u_i $(1 \leq i \leq k)$ competing for ℓ resources $m_j(x)$ $(1 \leq j \leq \ell)$, each adopting a strategy (e.g. dispersion and chemotactic parameters) with the goal of securing its own survival.

Such a model may include game theoretic considerations, such as Nash equilibrium strategies meant to represent some degree of mutual cooperation within the framework of competition. Historic biodiversity data would be useful in suggesting realistic models.

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