J. Math. Anal. Appl. 412 (2014) 776–791

Contents lists available at ScienceDirect

Journal of Mathematical Analysis and Applications

www.elsevier.com/locate/jmaa

On the dynamics of radially symmetric granulomas

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ARTICLE INFO

Article history:
Received 24 July 2013
Available online 12 November 2013
Submitted by J. Shi

Keywords:
Granuloma
Semi-linear parabolic system
Initial boundary value problem
Free boundary value problem

ABSTRACT

A granuloma is a collection of macrophages that contains bacteria or other foreign substances that the body's immune response is unable to eliminate. In this paper we present a simple mathematical model of radially symmetric granuloma dynamics. The model consists of a coupled system of two semi-linear parabolic equations for the macrophage density, and the bacterial density. The boundary of the granuloma is free. This simple framework makes it possible to conduct a mathematical analysis of the system dynamics. In particular, we show that the model system has a unique solution, and that, depending on the biological parameters; the bacterial load either disappears over time or persists. We use numerical methods to establish the existence of stationary solutions and examine how a stationary solution changes with the reproductive rate of the bacteria. These simulations show that the structure of the granuloma breaks down as the reproductive rate of the bacteria increases.

1. Introduction

A granuloma is a collection of macrophages that contains bacteria or other foreign substances. Granulomas occur in a wide variety of diseases including, for example, rheumatoid arthritis, schistosomiasis and Crohn's disease. A typical example is the granuloma of tuberculosis which prevents residual bacteria from re-infecting the body.

In order to create a detailed, disease-specific granuloma model, one needs to consider, in addition to macrophages and bacteria, pathogen-specific cytokines, the activation state of various immune cells, and the dynamics of both extracellular and intracellular bacteria. This was done in the case of tuberculosis by D. Gammack et al. [1] using a PDE model, by J.L. Segoria-Juarez et al. [4] using an agent-based approach, and by S. Marino et al. [3] using a hybrid multi-compartment model. In the present paper we introduce a simple model of a generic granuloma. The model explicitly describes the interactions between bacteria and macrophages. Implicit in the model is the assumption that the cytokines and T cells are present in abundance, i.e. we assume that all of the macrophages have been activated by IFN-γ secreted by the T cells. Similarly, the model does not consider intracellular bacteria, although several types of granulomas, including those of tuberculosis, are caused by intracellular pathogens. We assume that the granuloma occurs in a region $\Omega(t)$ which varies in time. Inside $\Omega(t)$ the macrophage cell density, M, and the bacteria cell density, B, satisfy a system of PDEs. We also assume that the cellular density of macrophage and bacteria is fixed, thus our model does not account for necrotic cells and debris that may be present in several types of granulomas. Under the assumption that the cellular density is fixed, the free boundary of $\Omega(t)$ moves with a velocity that is determined by the proliferation of the bacteria, the immigration of macrophages, and the death of both cell types.

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0022-247X/$ – see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.jmaa.2013.11.017

The aim of this paper is to initiate rigorous mathematical analysis of the dynamics of granulomas as free boundary problems. Accordingly, in the present paper, we consider a very simple model of a generic radially symmetric granuloma, deferring the study of more inclusive models to future work. We prove the existence and uniqueness, and exhibit steady state solutions numerically.

2. Theory

The variable x varies in a bounded domain $\Omega(t)$ in $\mathbb{R}^3$ with boundary $\Gamma(t)$. We introduce the variables $M(x,t)$ and $B(x,t)$ to represent the density of macrophages and bacteria respectively. Due to cellular proliferation and death there is a velocity field $\vec{v}(x,t)$ which is assumed to be common to both macrophages and bacteria. By conservation of mass, for $x \in \Omega(t)$ and $t > 0$ we have

$$\frac{\partial M}{\partial t} - \Delta M + \nabla \cdot (M\vec{v}) = -\mu_1 MB - \alpha M, \tag{1}$$

$$\frac{\partial B}{\partial t} - (1+\delta)\Delta B + \nabla \cdot (B\vec{v}) = -\mu_2 MB + \lambda B, \tag{2}$$

where μ_1 is the rate at which macrophages are killed by bacteria, μ_2 is the rate at which bacteria are killed by macrophages, λ is the bacterial growth rate, and α is the rate at which macrophages undergo apoptosis. Intracellular bacteria do not disperse on their own but are dispersed through the dispersal of the cells that contain them, while extracellular bacteria, being smaller than macrophages, have a larger diffusion coefficient than macrophages. Hence, we consider the case where $\delta \geqslant 0$; our results can be extended, with minor changes, to the case where $\delta < 0$. In addition, we assume that the cells are evenly distributed in $\Omega(t)$ so that, after normalization,

$$M + B = 1 \quad \text{for } x \in \Omega(t),\ t > 0. \tag{3}$$

Adding Eqs. (1) and (2) and using (3), we derive the following equation for $\vec{v}$:

$$\nabla \cdot \vec{v} = -\delta\Delta M + \lambda - (\lambda + \mu + \alpha)M + \mu M^2, \tag{4}$$

where $\mu = \mu_1 + \mu_2$. In addition, replacing B with $1 - M$ in (1) yields the following equation for M:

$$\frac{\partial M}{\partial t} - \Delta M + \nabla \cdot (M\vec{v}) = -\mu_1 M(1-M) - \alpha M. \tag{5}$$

In this paper we consider only the case of radially symmetric granulomas. In this case $\vec{v}$ is determined by (4) together with $\vec{v}(0) = 0$. In the non-radially symmetric case one would need to impose a constitutive condition on the tissue where the granuloma develops. Such a condition could be the porous medium assumption characterized by Darcy's Law: $\vec{v} = \nabla p$, where p is the internal pressure, and p satisfies an appropriate boundary condition on the boundary $\Gamma(t)$. This more general granuloma model could be considered in future work.

It is easily seen that if M satisfies (5) with $\vec{v}$ defined by (4), then the pair (B, M) satisfies the system (1)–(2). In the sequel we shall primarily use the version (4)–(5) of the system (1)–(3).

We impose the boundary conditions

$$\frac{\partial M}{\partial \nu} = \beta(1-M) \quad \text{on } \Gamma(t), \tag{6}$$

$$V_{\Gamma(t)} = \vec{v} \cdot \nu \quad \text{on } \Gamma(t), \tag{7}$$

where ν is the outward normal direction, $V_{\Gamma(t)}$ is the velocity of the free boundary, $\Gamma(t)$, in the direction ν, and $\beta > 0$. Finally, we prescribe initial conditions:

$$\Omega(t)|_{t=0} = \Omega_0, \qquad M(x,0) = M_0, \quad 0 \leqslant M_0 \leqslant 1. \tag{8}$$

Note that (6) implies (by (3)) that

$$\frac{\partial B}{\partial \nu} + \beta B = 0 \quad \text{on } \Gamma(t). \tag{9}$$

In addition, (8) implies that

$$0 \leqslant B(x,0) \leqslant 1. \tag{10}$$

By the maximum principle for (1) and (2) we then have that

$$M(x,t) \geqslant 0 \quad \text{and} \quad B(x,t) \geqslant 0.$$

Thus by, (3), the solution of (4)–(5) satisfies

$$0 \leqslant M(x,t) \leqslant 1. \tag{11}$$

2.1. The radially symmetric case

We rewrite the system in the radially symmetric case. Using the notation $r = |x|$,

$$\vec{v} = v(r,t)\frac{x}{r}, \qquad M = M(r,t), \qquad \Omega(t) = \{r < R(t)\}, \quad \text{and} \quad \Gamma(t) = \{r = R(t)\},$$

(4)–(8) take the following form:

$$\frac{\partial M}{\partial t} - \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial M}{\partial r}\right) + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 vM\right) = -\mu_1 M(1-M) - \alpha M, \tag{12}$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 v\right) = -\frac{\delta}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial M}{\partial r}\right) + \lambda - (\lambda+\mu+\alpha)M + \mu M^2, \tag{13}$$

$$v(0,t) = 0, \qquad \frac{\partial M}{\partial r}(0,t) = 0, \quad \text{and} \quad \frac{\partial M}{\partial r}\big(R(t),t\big) = \beta(1-M), \tag{14}$$

$$R(0) = R_0, \qquad M(r,0) = M_0(r), \tag{15}$$

and

$$\frac{dR(t)}{dt} = v\big(R(t),t\big). \tag{16}$$

It follows that

$$v(r,t) = -\delta\frac{\partial M}{\partial r} + \int_0^r \frac{s^2}{r^2}\left(\lambda - (\lambda+\mu+\alpha)M + \mu M^2\right)ds. \tag{17}$$

The radially symmetric problem can also be converted to a fixed boundary problem by setting

$$y_i = \frac{x_i}{R(t)}, \qquad \hat{M}(y,t) = M(x,t), \quad \text{and} \quad \hat{\vec{v}}(y,t) = \vec{v}(x,t),$$

so that

$$\frac{\partial M}{\partial t} = \frac{\partial \hat{M}}{\partial t} - \sum_{i=1}^{3}\frac{y_i\dot{R}(t)}{R(t)}\frac{\partial \hat{M}}{\partial y_i}, \qquad \frac{\partial M}{\partial x_i} = \frac{1}{R(t)}\frac{\partial \hat{M}}{\partial y_i}.$$

Thus, after dropping the "ˆ", the system (4)–(8) takes the form:

$$\frac{\partial M}{\partial t} - \frac{1}{R^2}\Delta M - \frac{\dot{R}}{R}\vec{y}\cdot\nabla M + \frac{1}{R}\nabla\cdot(\vec{v}M) = -\mu_1 M(1-M) - \alpha M, \tag{18}$$

$$\frac{1}{R}\nabla\cdot\vec{v} = -\frac{\delta}{R^2}\Delta M + \lambda - (\lambda+\mu+\alpha)M + \mu M^2, \tag{19}$$

with the boundary conditions

$$v(0,t) = 0, \quad \text{and} \quad \frac{1}{R}\frac{\partial M}{\partial \nu}(y,t) = \beta(1-M) \quad \text{for } |y| = 1, \tag{20}$$

initial conditions

$$R(0) = R_0 \quad \text{and} \quad M(y,0) = M_0(y), \tag{21}$$

and the free boundary dynamical equation

$$\frac{dR(t)}{dt} = v(y,t) \quad \text{for } |y| = 1. \tag{22}$$

When expressed in spherical coordinates (ρ,t), $\rho = |y|$, $M = M(\rho,t)$, (18)–(22) become

$$\frac{\partial M}{\partial t} - \frac{1}{\rho^2R^2}\frac{\partial}{\partial \rho}\left(\rho^2\frac{\partial M}{\partial \rho}\right) - \frac{\rho\dot{R}}{R}\frac{\partial M}{\partial \rho} + \frac{1}{\rho^2 R}\frac{\partial}{\partial \rho}\left(\rho^2 vM\right) = -\mu_1 M(1-M) - \alpha M, \tag{23}$$

$$\frac{1}{\rho^2 R}\frac{\partial}{\partial \rho}\left(\rho^2 v\right) = -\frac{\delta}{\rho^2R^2}\frac{\partial}{\partial \rho}\left(\rho^2\frac{\partial M}{\partial \rho}\right) + \lambda - (\lambda+\mu+\alpha)M + \mu M^2, \tag{24}$$

$$v(0,t) = 0, \qquad \frac{\partial M}{\partial \rho}(0,t) = 0, \quad \text{and} \quad \frac{1}{R}\frac{\partial M}{\partial \rho}(1,t) = \beta(1-M), \tag{25}$$

$$R(0) = R_0, \qquad M(\rho,0) = M_0(\rho), \tag{26}$$

and

$$\frac{dR(t)}{dt} = v(1, t). \tag{27}$$

From (24) it follows that

$$v(\rho, t) = -\frac{\delta}{R}\frac{\partial M}{\partial \rho} + R(t)\int_0^1 \frac{s^2}{\rho^2}\big(\lambda - (\lambda + \mu + \alpha)M + \mu M^2\big)\,ds. \tag{28}$$

From (16), (17) and (14) we see that

$$\frac{dR(t)}{dt} = v\big(R(t), t\big) = -\delta\beta(1 - M) + \int_0^R \frac{s^2}{R^2}\big(\lambda - (\lambda + \mu + \alpha)M + \mu M^2\big)\,ds.$$

Hence

$$-\delta\beta - cR < \frac{dR}{dt} < CR,$$

where c and C are positive constants, so that

$$R(t) \leqslant R_0 e^{Ct}.$$

Hence, for some positive constant c_0 and any $T > 0$,

$$\begin{aligned} &R(t) \leqslant R_0 e^{CT}, \\ &-c_0 e^{CT} \leqslant \frac{dR}{dt} \leqslant CR_0 e^{CT} \quad \text{for } 0 < t \leqslant T, \end{aligned} \tag{29}$$

provided $R(t)$ remains positive for $0 < t < T$. $R(t)$, however, may possibly converge to zero in finite time.

Definitions. By a smooth solution of (12)–(16), for $0 \leqslant t \leqslant T$, we understand a solution with M, $\frac{\partial M}{\partial r}$, $\frac{\partial^2 M}{\partial r^2}$, $\frac{\partial M}{\partial t}$ in $C^{\alpha, \frac{\alpha}{2}}_{\{0 \leqslant r \leqslant R(t),\, 0 \leqslant t \leqslant T\}}$, and $\dot{R}$ in $C^{\frac{\alpha}{2}}_{[0,T]}$. Equivalently, the solution of (18)–(22) is said to be smooth if $\frac{\partial M}{\partial y_i}$, $\frac{\partial^2 M}{\partial y_i y_j}$, $\frac{\partial M}{\partial t}$ are in $C^{\alpha, \frac{\alpha}{2}}_{\{|y| \leqslant 1,\, 0 \leqslant t \leqslant T\}}$, and $\dot{R}$ is in $C^{\frac{\alpha}{2}}_{[0,T]}$. In the sequel, all solutions are taken to be smooth solutions. A smooth solution is said to be "global" if it exists for $0 \leqslant t < T_\infty$, where either $T_\infty = \infty$ or $T_\infty < \infty$ and either $\limsup_{t \to T_\infty} |M_r|(r, t) \to \infty$ or $\liminf_{t \to T_\infty} R(t) = 0$.

3. Results

3.1. A priori estimates

Lemma 1.

(i) *If*

$$-k_1 \leqslant \frac{\partial M_0}{\partial r}$$

for $0 \leqslant r \leqslant 1$, *where* $k_1 \geqslant 0$, *then any smooth solution of* (12)–(16) *for* $0 \leqslant t \leqslant T$ *satisfies the inequality*

$$-k_1 e^{\gamma t} \leqslant \frac{\partial M}{\partial r}(r, t)$$

for $0 \leqslant r \leqslant 1$, $0 \leqslant t \leqslant T$, *where* γ *is a positive constant independent of* k_1 *and* T.

(ii) *If* $\delta = 0$ *and*

$$\frac{\partial M_0}{\partial r} \leqslant k_2$$

for $0 \leqslant r \leqslant 1$, *where* $k_2 \geqslant 0$, *then any smooth solution of* (12)–(16) *for* $0 \leqslant t \leqslant T$ *satisfies the inequality* $\frac{\partial M}{\partial r} \leqslant k_2 e^{\gamma t}$ *where* γ *is a positive constant independent of* k_2 *and* T.

Proof. Consider case (i). Substituting Eq. (13) into (12) we get

$$\frac{\partial M}{\partial t}-\frac{1+\delta M}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial M}{\partial r}\right)+v\frac{\partial M}{\partial r}+c(M)M=0, \tag{30}$$

where

$$c(M)=(\lambda+\alpha+\mu_1)-(\lambda+\alpha+2\mu_1+\mu_2)M+\mu M^2. \tag{31}$$

Differentiating (30) in r and setting $N=\frac{\partial M}{\partial r}$ we get the equation

$$\frac{\partial N}{\partial t}-(1+\delta M)\left(\frac{\partial^2 N}{\partial r^2}+\frac{2}{r}\frac{\partial N}{\partial r}-\frac{2}{r^2}N\right)-\delta N\left(\frac{2}{r}N+\frac{\partial N}{\partial r}\right)+\frac{\partial v}{\partial r}N+v\frac{\partial N}{\partial r}+\frac{\partial}{\partial r}\big(c(M)M\big)=0.$$

From (17) we have the estimate

$$\frac{\partial v}{\partial r}=-\delta\frac{\partial N}{\partial r}+O(1).$$

Substituting this into the previous equation we get

$$\frac{\partial N}{\partial t}-(1+\delta M)\left(\frac{\partial^2 N}{\partial r^2}+\frac{2}{r}\frac{\partial N}{\partial r}\right)-\delta N\frac{\partial N}{\partial r}+v\frac{\partial N}{\partial r}+(1+\delta M)\frac{2}{r^2}N+fN=\frac{2\delta}{r}N^2,$$

where

$$f=-\frac{\partial}{\partial M}\big(c(M)M\big)-O(1). \tag{32}$$

We introduce the function $w(r,t)=e^{-\gamma t}N(r,t)$, where γ is large enough so that $f+\gamma>0$. Then w satisfies:

$$\frac{\partial w}{\partial t}-(1+\delta M)\left(\frac{\partial^2 w}{\partial r^2}+\frac{2}{r}\frac{\partial w}{\partial r}\right)-\delta N\frac{\partial w}{\partial r}+v\frac{\partial w}{\partial r}+(1+\delta M)\frac{2}{r^2}w+(f+\gamma)w=\frac{2\delta}{r}e^{-\gamma t}w^2,$$

and, by the maximum principle, w cannot take a negative minimum in the domain $\{0<r<R(t),\ 0<t<T\}$. Since also $w=e^{-\gamma t}(1-M)$ on $r=R(t)$, w cannot take a negative minimum on $r=R(t)$. Hence w can take a nonpositive minimum only at $t=0$ and assertion (i) of the lemma follows.

The proof of (ii) is similar. □

Applying Lemma 1 to the case $k_1=0$ we get:

Theorem 1. *If $\frac{\partial M_0}{\partial r}\geqslant 0$ for $0\leqslant r\leqslant R_0$ then*

$$\frac{\partial M}{\partial r}\geqslant 0$$

for $0\leqslant r\leqslant R(t)$, $0\leqslant t\leqslant T$.

3.2. Existence and uniqueness

We shall first prove local existence and uniqueness using Schauder estimates and $W^{2,p}$ estimates. We assume:

$$0\leqslant M_0\leqslant 1,\quad M_0\in C_r^{2+\alpha}[0,R_0],\quad \text{and}\quad \frac{\partial M_0}{\partial r}=\beta(1-M_0)\quad \text{at } r=R_0. \tag{33}$$

We introduce sets

$$X_T:=\left\{R(t):\ R(0)=R_0,\ \big\|\dot R(t)\big\|_{C^\alpha(0,T)}\leqslant L_1\right\},$$
$$Y_T:=\left\{M(r,t):\ 0\leqslant M(r,t)\leqslant 1;\ M(r,0)=M_0(r);\ \|M\|=|M|_{C_{r,t}^{\alpha,\frac{\alpha}{2}}}+|M_r|_{C_{r,t}^{\alpha,\frac{\alpha}{2}}}\leqslant L_2\right\},$$

where T is sufficiently small and L_1, L_2 are constants to be determined later.

For a fixed R in X_T we define a mapping $S: M\to\hat M$ as follows: $\hat M$ is the solution of

$$\frac{\partial \hat M}{\partial t}-\frac{1+\delta M}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial \hat M}{\partial r}\right)+v\frac{\partial \hat M}{\partial r}+c(M)\hat M=0 \tag{34}$$

for $0 < r < R(t)$, $0 < t \leqslant T$, with

$$v(0,t) = 0, \qquad \hat{M}(r,0) = M_0(r), \qquad \frac{\partial \hat{M}}{\partial r}(0,t) = 0, \qquad \frac{\partial \hat{M}}{\partial r}\big(R(t),t\big) = \beta(1 - \hat{M}), \tag{35}$$

where $v(M)$ is defined as in (17).

Since $\dot{R} \in C^{\frac{\alpha}{2}}$, we can apply the Schauder estimates to obtain the estimate

$$|\hat{M}|_{C^{2+\alpha,1+\frac{\alpha}{2}}} \leqslant L, \tag{36}$$

where $L = L(L_1, L_2)$ depends on L_1 and L_2. Hence, by interpolation [2] (Prop. 4.2, p. 48), for any function $u = u(x,t)$,

$$\|u\|_{C^{\alpha,\frac{\alpha}{2}}_{x,t}} \leqslant \|u\|^{\frac{\alpha}{1+\beta}}_{C^{1+\beta,\frac{\beta}{2}}_{x,t}} \|u\|^{\frac{1+\beta-\alpha}{1+\beta}}_{L^\infty} \quad \forall \beta > 0.$$

Applying this inequality to $u = \hat{M} - M_0$ and to $\frac{\partial u}{\partial r}$, we get

$$|\hat{M}|_{C^{\alpha,\frac{\alpha}{2}}} + |\hat{M}_r|_{C^{\alpha,\frac{\alpha}{2}}} \leqslant 2|M_0|_{C^{2+\alpha}} + c_0 T^\gamma L$$

for some positive constants c_0 and γ. Hence if $L_2 = 2|M_0|_{C^{2+\alpha}} + 1$ and T is sufficiently small then $\hat{M} = S(M) \in Y_T$.

Similarly we can show that S is a contraction. The proof is obtained by estimating the difference $\hat{M}_1 - \hat{M}_2$ from Eq. (34) for M_1 and M_2, using the estimates:

$$\big|v(M_1) - v(M_2)\big|_{C^{\alpha,\frac{\alpha}{2}}} \leqslant c_1\|M_1 - M_2\|,$$
$$\big|c(M_1) - c(M_2)\big|_{C^{\alpha,\frac{\alpha}{2}}} \leqslant c_2\|M_1 - M_2\|.$$

Since S is a contraction on Y_T for T sufficiently small, given $R(T) \in X_T$ there exists a unique solution $M(r,t)$ of (12)–(15). We proceed to solve for $\hat{R}$:

$$\frac{d\hat{R}}{dt} = v\big(M\big(R(t),t\big),t\big), \qquad \hat{R}(0) = R_0$$

and define a mapping V by $VR = \hat{R}$. We claim that V is a contraction on X_T and thus has a unique fixed point.

It will be convenient to consider the equivalent fixed boundary system (23)–(27).

Given R_1 and R_2 let M_1, v_1 and M_2, v_2 solve the corresponding system (23)–(26). To estimate $M_1 - M_2$ we move all the terms with $R_1 - R_2$, $\dot{R}_1 - \dot{R}_2$ to the right-hand side and apply the Schauder estimates to get

$$|M_1 - M_2|_{C^{2+\alpha,1+\frac{\alpha}{2}}} \leqslant C|\dot{R}_1 - \dot{R}_2|_{C^{\frac{\alpha}{2}}}.$$

By interpolation, as before,

$$|M_{1,r} - M_{2,r}|_{C^{\alpha,\frac{\alpha}{2}}} \leqslant c_1 T^\gamma |M_1 - M_2|_{C^{2+\alpha,1+\frac{\alpha}{2}}} \leqslant c_0 C T^\gamma |\dot{R}_1 - \dot{R}_2|_{C^{\frac{\alpha}{2}}}. \tag{37}$$

Let $t_1 < t < t_2$ and set $R(s) = R_1(s) - R_2(s)$, $R_* = \max_{t_1 \leqslant t \leqslant t_2}|R(s)|$, then

$$\begin{aligned}
\frac{d}{dt}\big(\hat{R}(t_1) - \hat{R}(t_2)\big) = {} & \big[v_2\big(R_2(t_2),t_2\big) - v_2\big(R_2(t_2) - R_*, t_2\big)\big] \\
& - \big[v_1\big(R_1(t_2),t_2\big) - v_1\big(R_2(t_2) - R_*, t_2\big)\big] \\
& - \big[v_2\big(R_2(t_1),t_1\big) - v_2\big(R_2(t_1) - R_*, t_1\big)\big] \\
& + \big[v_1\big(R_2(t_1),t_1\big) - v_1\big(R_2(t_1) - R_*, t_1\big)\big] \\
& + \big[(v_1 - v_2)\big(R_2(t_2) - R_*, t_2\big) - (v_2 - v_1)\big(R(t_2) - R_*, t_1\big)\big].
\end{aligned} \tag{38}$$

Recalling (17) and using (37), we can estimate each of the five terms in brackets by $c_2 T^\gamma |R(t)|_{C^{\frac{\alpha}{2}}}$ and conclude that

$$\frac{d}{dt}\big|\hat{R}(t_1) - \hat{R}(t_2)\big|_{C_t^{\frac{\alpha}{2}}} \leqslant 5c_2 T^\gamma \big|R(t)\big|_{C_t^{\frac{\alpha}{2}}}.$$

It follows that the mapping $V : R \to \hat{R}$ is a contraction if T is sufficiently small. The fact that V maps X_T into itself follows from the above estimate with $R_1(t) \equiv R_0$ provided L_1 is sufficiently large.

We have thus completed the proof of local existence and uniqueness.

To prove global existence and uniqueness it suffices to establish, for any $T > 0$, the estimate,

$$|\dot{R}|_{C_t^{\frac{\alpha}{2}}} \leqslant L_0 \tag{39}$$

for any solution which exists for $0 \leqslant t \leqslant T$ with $R(T) > 0$, where $L_0 = L_0(T)$ is a bounded function of T.

By Lemma 1 if $\delta = 0$ then M_r is bounded by a constant $\bar{L}$ and then so is v. Hence we can use the $W^{2,p}$ estimate to conclude that M, $\frac{\partial M}{\partial t}$, $\frac{\partial M}{\partial \rho}$, $\frac{\partial^2 M}{\partial \rho^2}$ are bounded in L^p uniformly in t by another constant $\bar{L}$. It follows that

$$\left|\frac{\partial M}{\partial \rho}\right|_{C^{\alpha,\frac{\alpha}{2}}} \leqslant \bar{L}. \tag{40}$$

Proceeding similarly to (38) we deduce that

$$\left|\dot{R}(t_2) - \dot{R}(t_1)\right| \leqslant c|t_2 - t_1|^{\frac{\alpha}{2}}.$$

In summary:

Theorem 2. *Under the assumption (33) there exists a unique global solution (i.e. for $0 \leqslant t < T_\infty$) of (12)–(16) with $\dot{R}(t)$ in $C^{\frac{\alpha}{2}}$. Furthermore, if $\delta = 0$ and $T_\infty < \infty$ then $\liminf_{t\to T_\infty} R(t) = 0$.*

In the case $\delta > 0$, we are unable to rule out the possibility that $R(t)$ remains uniformly bounded by a positive constant as $t \to T_\infty$, while $M_r(r_j, t_j) \to \infty$ for sequences $0 < r_j < R(t_j)$, $t_j \to \infty$.

4. Properties of the solution

We are interested in determining the asymptotic behavior of the granuloma as $t \to T_\infty$. In particular, we would like to determine conditions on the parameters for which either the bacteria and the macrophages coexist, or one of the two goes extinct as $t \to T_\infty$.

In this section we give two examples. Theorem 3 gives conditions under which $B(r,t) \to 0$ as $t \to \infty$, and Theorem 4 gives conditions under which the bacterial load increases over time and $\limsup_{t\to\infty} R(t) = \infty$. In the next section, we demonstrate numerically that there exist stationary solutions where both M and B are nonzero; it remains an open problem to prove this result rigorously.

Theorem 3. *If $\lambda + \alpha < \mu_2$ and*

$$\big(1 - M_0(r)\big) \leqslant \epsilon \quad \text{where } \epsilon \leqslant \frac{\mu_2 - (\lambda + \alpha)}{\mu}, \tag{41}$$

then

$$\big(1 - M(r,t)\big) < \epsilon e^{-\gamma t} \quad \text{on } 0 < r < R(t),\ 0 < t < T_\infty \tag{42}$$

for any $\gamma < c(1 - \epsilon)$, where $c = \mu_2 - (\lambda + \alpha) - \mu\epsilon \geqslant 0$.

Proof. Suppose the assertion is not true. Let $B(r,t) = (1 - M(r,t))$. Then B satisfies

$$\frac{\partial B}{\partial t} - (1 + \delta M)\Delta B + v(M)\frac{\partial B}{\partial r} + (B - 1)B(\mu_2 - \lambda - \alpha - \mu B) = 0 \tag{43}$$

with the boundary condition

$$\frac{\partial B}{\partial r} + \beta B = 0 \quad \text{on } r = R(t). \tag{44}$$

Let t_0 denote the first time such that (42) is violated, and let $w = \epsilon e^{-\gamma t}$. Note that

$$B(r,t) < w \quad \text{for } 0 \leqslant r \leqslant R(t),\ 0 < t < t_0, \tag{45}$$

$$B(r_0,t_0) = w(t_0) \quad \text{for some } 0 \leqslant r_0 \leqslant R(t_0), \tag{46}$$

and w satisfies

$$\begin{aligned}
&\frac{\partial w}{\partial t}-(1+\delta M)\Delta w+v(M)\frac{\partial w}{\partial r}+(w-1)w(\mu_2-\lambda-\alpha-\mu w)\\
&\quad=-\gamma w+w(1-w)\big(\mu_2-\lambda-\alpha-\mu\epsilon e^{-\gamma t}\big)\\
&\quad\geqslant-\gamma w+w(1-w)(\mu_2-\lambda-\alpha-\mu\epsilon)\\
&\quad=w\big(c(1-w)-\gamma\big)\\
&\quad=w\big(c\big(1-\epsilon e^{-\gamma t}\big)-\gamma\big)\\
&\quad\geqslant w\big(c(1-\epsilon)-\gamma\big)>0,
\end{aligned}$$

and

$$\frac{\partial w}{\partial r}+\beta w=\beta w>0\quad\text{on } r=R(t).$$

Hence, by the comparison principle for parabolic equations $B(r,t)<w(t)$ for all $0\leqslant r\leqslant R(t)$, $0<t\leqslant t_0$, which is a contradiction to (46). □

Remark 1. Suppose that $\frac{\partial M_0}{\partial r}\geqslant 0$ so that $\frac{\partial M}{\partial r}\geqslant 0$ (by Theorem 1). Set $\gamma=\mu_2-(\lambda+\alpha)$. If $\gamma>0$ (as in Theorem 3) and ϵ is sufficiently small then from (17) and (14) we get

$$\dot R=v\big(R(t),t\big)\leqslant\left(-\frac{\alpha}{3}+O(\epsilon)\right)R(t).$$

Hence

$$\dot R<0.$$

Furthermore in (32)

$$f=\sigma+O(\epsilon),$$

where $\sigma=\frac{\alpha}{3}-\gamma$, can be positive or negative. If $\frac{\partial M_0}{\partial r}\leqslant\eta$ where

$$(1+\delta)\frac{2}{r^2}+\sigma-\frac{2\delta}{r}\eta>0\quad\text{for } 0<r<R_0,$$

then, by the maximum principle, $\frac{\partial M}{\partial r}\leqslant\eta$ for all $t<T_\infty$. In this case $M_r(r,t)$ remains uniformly bounded, $T_\infty=\infty$, and $R(t)\downarrow 0$ as $t\uparrow\infty$.

Theorem 3 shows that $M_0(r)\equiv 1$, $B_0(r)\equiv 0$, is an asymptotically stable solution. In the next theorem we show, under different assumptions on the parameters, that there exist granulomas where the bacterial load remains uniformly positive.

Theorem 4. *If $\frac{\partial M_0}{\partial r}\geqslant 0$, $\lambda>\mu_2$ and $\beta=0$ then*

$$\int_0^{R(T)} r^2B(r,T)\,dr\geqslant\int_0^{R_0} r^2B(r,0)\,dr+\int_0^T\int_0^{R(t)} r^2(\lambda-\mu_2)B(r,t)\,dr\,dt. \tag{47}$$

for $0\leqslant T<T_\infty$.

Note that if $B(r,0)\not\equiv 0$ then by (47),

$$\int_0^{R(t)} r^2B(r,t)\,dr\geqslant c_0e^{(\lambda-\mu_2)t},$$

for $c_0=\int_0^{R(0)}r^2B(r,0)\,dr$. Hence, by (47),

$$R^3(T)\geqslant c_1e^{(\lambda-\mu_2)T}$$

for $c_1=\frac{3c_0}{\lambda-\mu_2}$.

Proof of Theorem 4. Note that B satisfies

$$\frac{\partial B(r,t)}{\partial t} - (1+\delta)\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial B}{\partial r}\right) + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 Bv\right) = -\mu_2 MB + \lambda B, \tag{48}$$

$$\frac{\partial B(r,t)}{\partial t} - (1+\delta)\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial B}{\partial r}\right) + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 Bv\right) = \mu_2 B^2 + (\lambda-\mu_2)B \tag{49}$$

with the boundary conditions

$$\frac{\partial B}{\partial r}(r,0) = 0, \qquad \frac{\partial B}{\partial r} + \beta B = 0 \quad \text{on } r = R(t). \tag{50}$$

If $\beta = 0$ we have that

$$\begin{aligned}
\int_0^{R(T)} r^2 B(r,T)\,dr - \int_0^{R_0} r^2 B(r,0)\,dr &= \int_0^T R^2(t) B\big(R(t),t\big) v\big(R(t),t\big)\,dt \\
&\quad + \int_0^T R^2(t)\left((1+\delta)\frac{\partial B}{\partial r}\big(R(t),t\big) - B\big(R(t),t\big)v\big(R(t),t\big)\right)dt \\
&\quad + \int_0^T \int_0^{R(t)} r^2 B(r,t)\big(\lambda - \mu_2 M(r,t)\big)\,dr\,dt \\
&= \int_0^T \int_0^{R(t)} r^2\big[\mu_2 B^2(r,t) + (\lambda-\mu_2)B(r,t)\big]\,dr\,dt. \qquad \square
\end{aligned}$$

Remark 2. If $\delta = 0$ and $\lambda + \alpha < \mu_2$, Theorem 3 shows that the bacterial density decreases exponentially in time for $0 < t < T_\infty$ and, by Remark 1, $T_\infty = \infty$ if ϵ is sufficiently small. On the other hand, if $\delta = \beta = 0$ and $\lambda > \mu_2$, Theorem 4 shows that the bacterial load does not decrease and the granuloma grows. These results suggest that for $\beta = \delta = 0$ and $\mu_2 < \lambda < \mu_2 + \alpha$ there should be stationary granulomas where macrophages and bacteria coexist. In the next section we exhibit stationary solutions numerically and also discuss how granulomas satisfying the conditions of Theorems 3 and 4 evolve over time.

Theorem 5. *If $\frac{\partial M_0}{\partial r} \geqslant 0$, $\lambda > \mu_2$, $\delta = 0$,*

$$R(0) > \frac{3\beta}{\lambda - \mu_2}, \tag{51}$$

and

$$\int_0^{R_0} r^2(\lambda + \mu + \alpha)B(r,0)\,dr > \frac{R_0^3}{3}(\mu + \alpha) \tag{52}$$

then

$$\int_0^{R(T)} r^2 B(r,T)\,dr \geqslant \int_0^{R_0} r^2 B(r,0)\,dr + \int_0^T \int_0^{R(T)} r^2 \mu_2 B^2(r,t)\,dr\,dt \tag{53}$$

and $R(T) > \frac{3\beta}{\lambda-\mu_2}$, for $0 \leqslant T < T_\infty$.

Proof. Setting $\delta = 0$ and integrating (49) over (r,t) we find that

$$\int_0^{R(T)} r^2 B(r,T)\,dr - \int_0^{R_0} r^2 B(r,0)\,dr = \int_0^T R^2(t) B\big(R(t),t\big) v\big(R(t),t\big)\,dt$$

$$
\begin{aligned}
&+\int_0^T R^2(t)\Big((1+\delta)\frac{\partial B}{\partial r}\big(R(t),t\big)-B\big(R(t),t\big)v\big(R(t),t\big)\Big)\,dt\\
&+\int_0^T\int_0^{R(t)} r^2B(r,t)\big(\lambda-\mu_2M(r,t)\big)\,dr\,dt\\
={}&-\beta\int_0^T R^2(t)B\big(R(t),t\big)\,dt\\
&+\int_0^T\int_0^{R(t)} r^2\big[\mu_2B^2(r,t)+(\lambda-\mu_2)B(r,t)\big]\,dr\,dt\\
\geqslant{}&\int_0^T -R^2(t)\beta B\big(R(t),t\big)\,dt+\int_0^T(\lambda-\mu_2)B\big(R(t),t\big)\frac{R^3(t)}{3}\,dt\\
&+\int_0^T\int_0^{R(t)} r^2\mu_2B^2(r,t)\,dr\,dt\\
={}&\int_0^T\left[\frac{(\lambda-\mu_2)}{3}R(t)-\beta\right]R^2(t)B\big(R(t),t\big)\,dt\\
&+\int_0^T\int_0^{R(t)} r^2\mu_2B^2(r,t)\,dr\,dt. \qquad (54)
\end{aligned}
$$

Note that

$$\int_0^t\left[\frac{(\lambda-\mu_2)}{3}R(s)-\beta\right]R^2(s)B\big(R(s),s\big)\,ds>0 \qquad (55)$$

implies

$$\int_0^{R(t)} r^2B(r,t)\,dr>\int_0^{R_0} r^2B(r,0)\,dr+\int_0^T\int_0^{R(t)} r^2\mu_2B^2(r,t)\,dr\,dt. \qquad (56)$$

Hence it suffices to show that (55) holds for all $t>0$.

Since

$$R(0)>\frac{3\beta}{\lambda-\mu_2}, \qquad (57)$$

if (55) does not hold for all $t<T_\infty$ there exists a smallest $T^*>0$ such that (55) holds for all $t<T^*$, but

$$\int_0^{T^*}\left[\frac{(\lambda-\mu_2)}{3}R(t)-\beta\right]R^2(t)B\big(R(t),t\big)\,dt=0. \qquad (58)$$

We claim that $R(t)>\frac{3\beta}{\lambda-\mu_2}$ for $t\in[0,T^*]$. Since $\delta=0$,

$$R'(t)=v\big(R(t),t\big)\geqslant\frac{1}{R^2(t)}\int_0^{R(t)} r^2\big((\lambda+\mu+\alpha)B(r,t)-(\mu+\alpha)\big)\,dr, \qquad (59)$$

and by assumption (52), $R'(0)>0$. Hence, there exists an $\epsilon>0$ so that

$$R(t) > R_0 > \frac{3\beta}{\lambda - \mu_2} \tag{60}$$

for $t \in [0, \epsilon)$. We claim that $R(t) > R_0$ for all $t < T^*$. Indeed, otherwise there exists a smallest t_1 such that (59) holds for all $t < t_1$ and $R(t_1) = R_0$. Then $R'(t_1) \leqslant 0$ and, by (59),

$$\int_0^{R(t_1)} r^2(\lambda + \mu + \alpha) B(r, t_1)\, dr < \frac{R^3(t_1)}{3}(\mu + \alpha).$$

But since (55) and inequality (56) hold for all $0 < t < T^*$,

$$\frac{R_0^3}{3}(\mu + \alpha) < \int_0^{R_0} r^2(\lambda + \mu + \alpha) B(r, 0)\, dr < \int_0^{R(t_1)} r^2(\lambda + \mu + \alpha) B(r, t_1)\, dr,$$

where the first inequality is the assumption (52). It follows that

$$R(t_1) > R_0, \tag{61}$$

which is a contradiction. Hence, $R(t) > R_0 > \frac{3\beta}{\lambda - \mu_2}$ for $t \in [0, T^*)$. It follows that

$$\int_0^{T^*} \left[\frac{(\lambda - \mu_2)}{3} R\left(T^*\right) - \beta \right] R^2\left(T^*\right) B\left(R\left(T^*\right), T^*\right) dt > 0,$$

a contradiction to (58). We have thus completed the proof of (55) and (56) and, at the same time, established the estimate $R(t) > \frac{3\beta}{\lambda - \mu_2}$. $\square$

4.1. Numerical simulations

In one dimension, the moving boundary problem can be solved by mapping the moving domain $[0, R(t)]$ into the fixed domain $[0, 1]$ by $\rho = \frac{r}{R(t)}$; see (23) and (24).

$$\begin{aligned}
&\frac{\partial M}{\partial t} + \left(\frac{v - \rho \dot{R}(t)}{R(t)} - \frac{2}{\rho R(t)^2} \right) \frac{\partial M}{\partial \rho} - \frac{1}{R^2} \frac{\partial^2 M}{\partial \rho^2} = -\frac{2v}{\rho R} M - \frac{1}{R} \frac{\partial v}{\partial \rho} M + E(M), \\
&\frac{\partial}{\partial \rho}\left(\rho^2 v\right) = -\frac{\delta}{R} \frac{\partial}{\partial \rho} \left(\rho^2 \frac{\partial M}{\partial \rho} \right) + \rho^2 R F(M),
\end{aligned} \tag{62}$$

where $E(M) = -\mu_1 M(1 - M) - \alpha M$ and $F(M) = \lambda - (\lambda + \mu + \alpha) M + \mu M^2$. Let us denote the numerical solution at the n-th time step by

$$\left(M_j^n, V_j^n, R_j^n\right)$$

at $x_j = (j - 1)h$, $1 \leqslant j \leqslant J$ with $(J - 1)h = 1$. We first compute V^{n+1} by the trapezoidal rule:

$$\rho_{j+1}^2 V_{j+1}^{n+1} - \rho_j^2 V_j^{n+1} = M^c + \frac{R^n}{2} \Delta\rho \left[\rho_{j+1}^2 F_{j+1}^n + \rho_j^2 F_j^n\right],$$

where

$$M^c = -\frac{\delta}{R} \left[\rho_{j+1}^2 \frac{M_{j+2}^n - M_j^n}{2\Delta\rho} - \rho_j^2 \frac{M_{j+1}^n - M_{j-1}^n}{2\Delta\rho} \right] \quad \text{for } j \leqslant J$$

and

$$M^c = -\frac{\delta}{R} \left[\rho_{j+1}^2 R^n \beta\left(1 - M_j^n\right) - \rho_j^2 \frac{M_{j+1}^n - M_{j-1}^n}{2\Delta\rho} \right] \quad \text{for } j = J$$

is the central scheme approximation for the first term on the right-hand side. The Euler method is used to update the radius:

$$R^{n+1} = R^n + \Delta t V^{n+1}(1, t).$$

We write the advection–diffusion–reaction equation in the following form:

$$\frac{\partial M}{\partial t} + A_1 \frac{\partial M}{\partial \rho} + A_2 \frac{\partial^2 M}{\partial \rho^2} = r(M, v, R)M,$$

where

$$A_1 = \frac{v - \rho \dot{R}(t)}{R(t)} - \frac{2}{\rho R(t)^2}, \qquad A_2 = -\frac{1}{R^2},$$

and

$$r(M, v, R) = -\left(\frac{2v}{\rho R} + \frac{1}{R}\frac{\partial v}{\partial \rho} + \mu_1(1 - M) + \alpha\right).$$

We use the scheme

$$\frac{M_j^{n+1} - M_j^n}{\Delta t} + (A_1)_j^{n+1} \frac{M_{j+1}^{n+1} - M_{j-1}^{n+1}}{2\Delta \rho} + (A_2)_j^{n+1} \frac{M_{j+1}^{n+1} - 2M_j^{n+1} + M_{j-1}^{n+1}}{(\Delta \rho)^2} = r\big(M_j^n, V_j^{n+1}, R^{n+1}\big)M_j^{n+1}, \tag{63}$$

where the derivative term, $\frac{\partial v}{\partial \rho}$, in $r(M, v, R)$ is approximated by the forward difference, i.e.

$$\frac{\partial v}{\partial \rho} \approx \frac{V_{j+1}^{n+1} - V_j^{n+1}}{\Delta \rho}.$$

This discretized equation (63) can be written in the form

$$b_j M_{j-1}^{n+1} + d_j M_j^{n+1} + a_j M_{j+1}^{n+1} = S_j, \quad j = 2, \dots, J - 1,$$

where

$$a_j = \left(\frac{(A_1)_j^{n+1}}{\Delta \rho} + 2\frac{(A_2)_j^{n+1}}{(\Delta \rho)^2}\right)\Delta t,$$

$$b_j = \left(-\frac{(A_1)_j^{n+1}}{\Delta \rho} + 2\frac{(A_2)_j^{n+1}}{(\Delta \rho)^2}\right)\Delta t,$$

$$d_j = 2 - 2\left(2\frac{(A_2)_j^{n+1}}{(\Delta \rho)^2} + r\big(M_j^n, V_j^{n+1}, R^{n+1}\big)\right)\Delta t,$$

$$S_j = 2M_j^n.$$

For $j = 1$, we have the boundary condition

$$M_0^{n+1} = M_2^{n+1},$$

which implies that

$$a_1 = \left(4\frac{(A_2)_1^{n+1}}{(\Delta \rho)^2}\right)\Delta t,$$

$$d_1 = 2 - 2\left(2\frac{(A_2)_1^{n+1}}{(\Delta \rho)^2} + r\big(M^n\big)\right)\Delta t,$$

$$S_1 = 2M_1^n.$$

For $j = J$, we have the boundary condition

$$\frac{1}{R^{n+1}} \frac{M_{J+1}^{n+1} - M_{J-1}^{n+1}}{2\Delta \rho} = \beta\big(1 - M_j^{n+1}\big).$$

Thus,

$$b_J = \left(4\frac{(A_2)_j^{n+1}}{(\Delta \rho)^2}\right)\Delta t,$$

$$d_J = 2 - 2\left(2\big(1 + \Delta \rho \beta R^{n+1}\big)\frac{(A_2)_j^{n+1}}{(\Delta \rho)^2} + r\big(M^n\big) + (A_1)_J^{n+1}\beta R^{n+1}\right)\Delta t,$$

$$S_J = 2M_j^n - 2\Delta t\left((A_2)_J^{n+1}\frac{2}{\Delta \rho}\beta R^{n+1} + (A_1)_J^{n+1}\beta R^{n+1}\right).$$

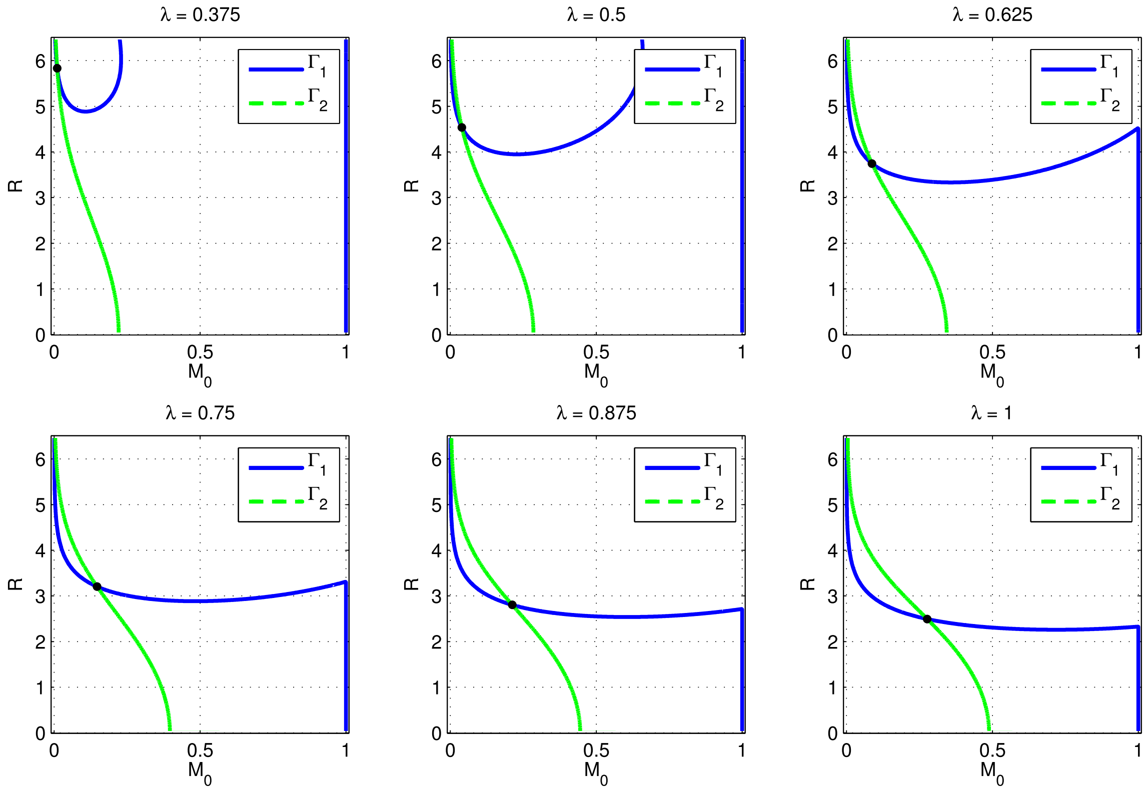

Fig. 1. The intersection points for Γ_1 and Γ_2 for $\lambda = 0.375 : 0.125 : 1$, $\mu_1 = 0.4$, $\mu_2 = 0.6$, $\delta = 0.05$, $\alpha = 0.5$, $\beta = 0.8$. As λ increases, the radius, R, decreases and the concentration of macrophages at the core of the granuloma, M_0, increases.

To find the stationary state solution, i.e. M and v which satisfy

$$\frac{\partial^2 M}{\partial r^2} - M\frac{\partial v}{\partial r} = \left(v - \frac{2}{r}\right)\frac{\partial M}{\partial r} - E(M) + \frac{2}{r}vM,$$
$$\frac{\partial v}{\partial r} = \frac{1}{1+\delta M}\left[\delta E(M) + F(M) - \delta v\frac{\partial M}{\partial r} - 2\frac{(1+\delta M)v}{r}\right],$$

we first write the problem as a system of first-order equations

$$\begin{bmatrix} u_1' \\ u_2' - u_1 u_3' \\ u_3' \end{bmatrix} = \begin{bmatrix} u_2 \\ (u_3 - \frac{2}{r})u_2 + \frac{2}{r}u_3 u_1 - E(u_1) \\ \frac{1}{1+\delta u_1}[\delta E(u_1) + F(u_1) - \delta u_3 u_2 - 2\frac{(1+\delta u_1)u_3}{r}] \end{bmatrix}$$

where $u_1 = M$, $u_2 = \frac{\partial M}{\partial r}$, $u_3 = v$, and the initial conditions are

$$\begin{bmatrix} u_1(0) \\ u_2(0) \\ u_3(0) \end{bmatrix}_{\rho=0} = \begin{bmatrix} M_0 \\ 0 \\ 0 \end{bmatrix}.$$

For a given set of the parameters δ, λ, μ, α, and β, we solve the system of equations in the interval $r \in [0, R]$ with various M_0 and R and then find the intersection points of the curves Γ_1 and Γ_2, which satisfy

$$\Gamma_1 : u_2(1) - \beta\big(1 - u_1(1)\big) = 0 \quad \text{(boundary conditions for } M\text{)},$$
$$\Gamma_2 : u_3(1) = 0 \quad \text{(stationary free boundary)}.$$

Intersection points of these two curves represent stationary solutions. After finding an intersection point, $(\tilde{M}_0, \tilde{R})$, we can then find the corresponding solution $M = u_1$ and $v = u_3$. Some stationary points and the corresponding solutions are shown in Figs. 1 and 2. Numerical simulations (not shown here) indicate that the stationary solutions shown in Figs. 1 and 2 are not stable. For the parameter values satisfying the conditions of Theorem 4 there is no stationary solution since $\limsup_{t\to\infty} R(t) = \infty$. In the simulations of Figs. 1 and 2 the parameter β is nonzero, so that the conditions of Theorem 4 are not satisfied.

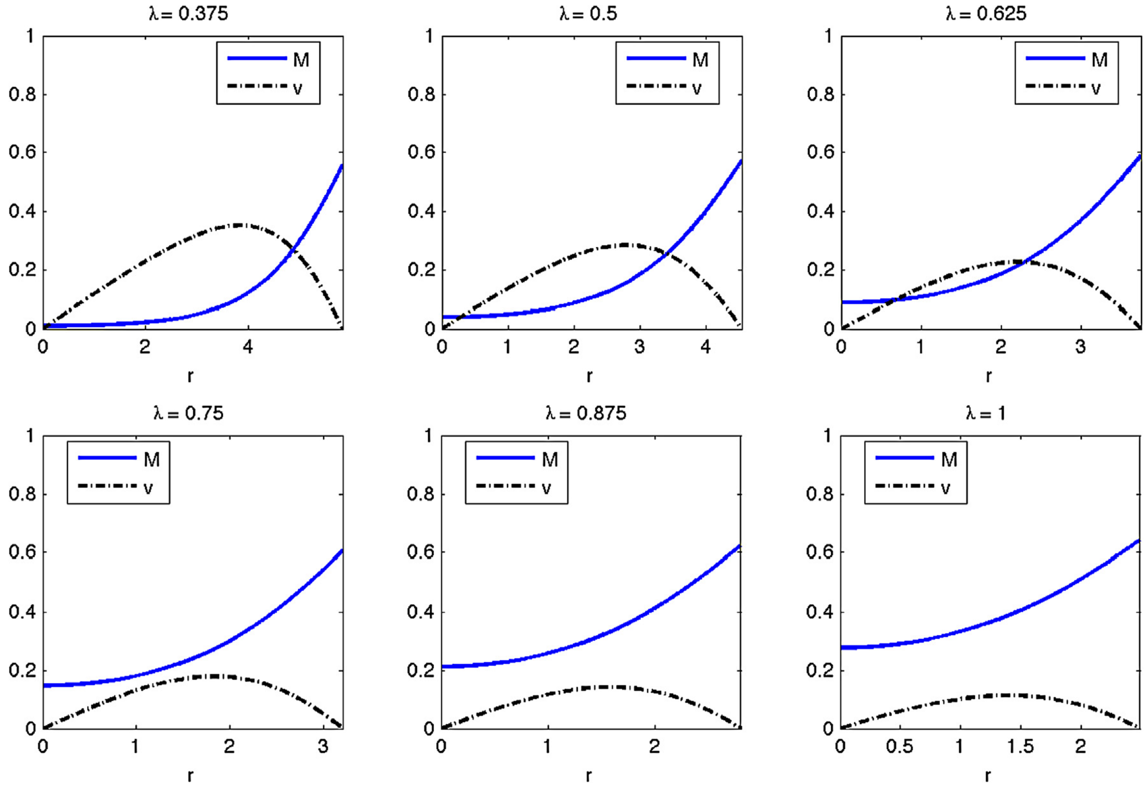

Fig. 2. The corresponding stationary solutions for $\lambda = 0.375:0.125:1$, $\mu_1 = 0.4$, $\mu_2 = 0.6$, $\delta = 0.05$, $\alpha = 0.5$, $\beta = 0.8$. As λ increases the structure of the granuloma breaks down in that macrophages infiltrate its core.

It is interesting to consider how stationary solutions change as a function of the biological parameters. Figs. 1 and 2 illustrate how the location of a stationary point (in (R, M) space) and the corresponding stationary solution change as a function of λ (the reproductive rate of the bacteria). When λ is small, bacteria are concentrated at the granuloma's core while macrophages are primarily found at its boundary. As λ increases the granuloma becomes smaller and less structured with macrophages distributed throughout. We interpret this to mean that the faster growing bacteria require a greater concentration of activated macrophages for containment. Higher macrophage concentrations, in turn, result in a smaller granuloma with a lower bacterial load.

Next we compare time dependent solutions that satisfy the conditions of Theorem 3 to those that satisfy the conditions of Theorem 4. In Fig. 3, we show the evolution of the time dependent solution of the system (62) with parameters that satisfy the conditions of Theorem 3 for $\epsilon = 0.25$: $\lambda = 0.5$, $\mu_1 = 0.4$, $\mu_2 = 1.5$, $\delta = 0.05$, $\alpha = 0.5$ and $\beta = 0.8$. The initial radius is chosen as $R(0) = 4.5374$ and the initial macrophage concentration is chosen as $M = 0.75 + 0.25\rho^2$. As time goes on, the macrophage concentration becomes one everywhere, and the radius of the granuloma shrinks.

In Fig. 4, we show the evolution of the time dependent solution of the system (62) with parameters that satisfy the conditions of Theorem 4 ($\lambda = 2.7$, $\mu_1 = 0.4$, $\mu_2 = 1$, $\delta = 0.05$, $\alpha = 0.5$ and $\beta = 0.8$). The initial radius is chosen as $R(0) = 4.5374$ and the initial macrophage concentration is chosen as $M = 0.75 + 0.25\rho^2$ which is the same as the example in Fig. 3. As time goes on, the macrophage concentration decreases to zero everywhere except for a small region near the granuloma's boundary, and, in contrast to the example shown in Fig. 3, the radius of the granuloma increases.

5. Conclusions

In this paper we initiated a study of a simple mathematical model of a generic granuloma. The model consists of a coupled system of two semi-linear parabolic equations for the macrophage density (M), and the bacterial density (B). The boundary of the granuloma is a free boundary. We proved the existence and uniqueness of a solution and proceeded to explore how granulomas evolve. Depending on the biological parameters, we showed that the bacterial load either disappears over time (Theorem 3 and Remark 1) or persists (Theorems 4 and 5). We have also shown numerically that there exist unstable stationary solutions.

Five biological parameters determine if the bacterial load and granuloma will grow or shrink: The natural death rate of the macrophages (α), the growth rate of the bacteria (λ), the flux of the macrophages from the healthy tissue into the granuloma (β), the rate at which bacteria kill macrophages (μ_1), and the rate at which macrophages kill bacteria (μ_2). Although

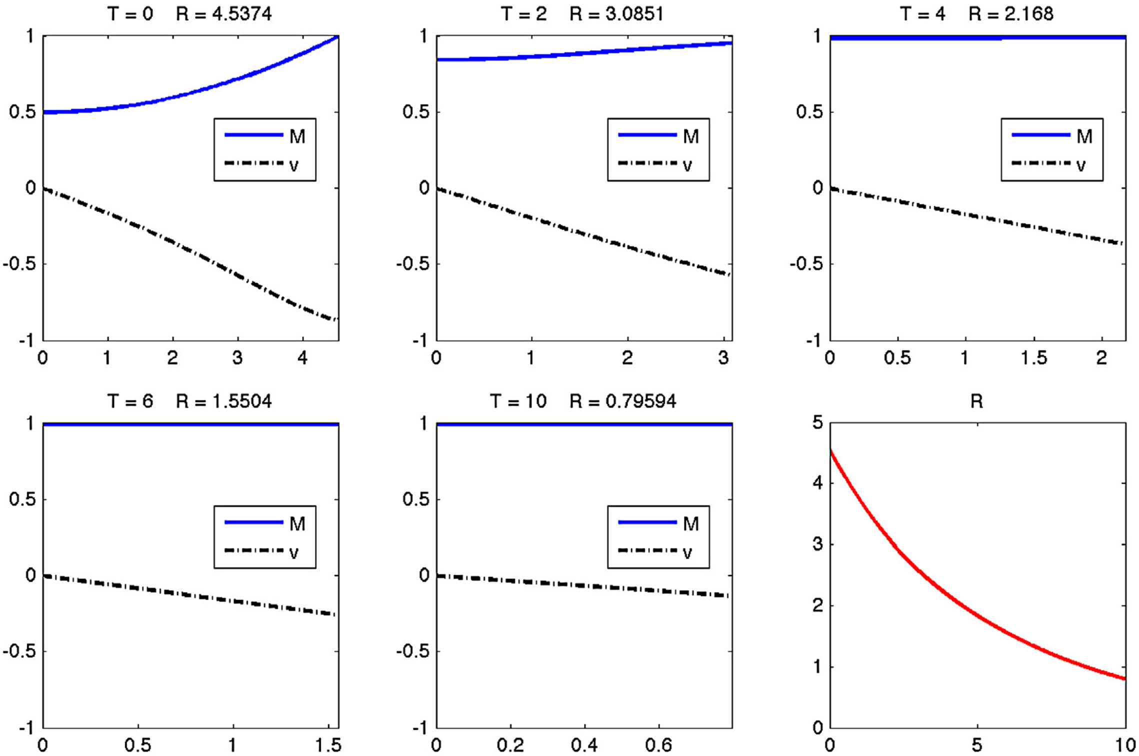

Fig. 3. The time dependent solution for $\lambda = 0.5$, $\mu_1 = 0.4$, $\mu_2 = 1.5$, $\delta = 0.05$, $\alpha = 0.5$, $\beta = 0.8$, and $R(0) = 4.5374$.

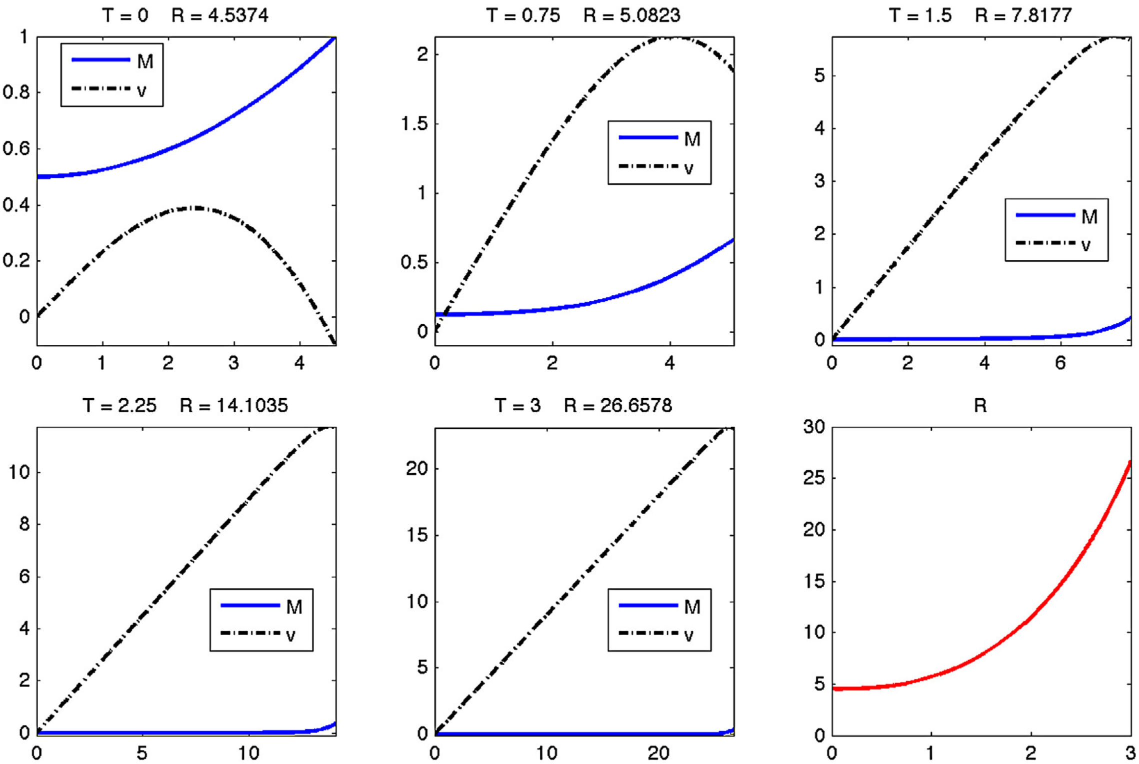

Fig. 4. The time dependent solution for $\lambda = 2.7$, $\mu_1 = 0.4$, $\mu_2 = 1$, $\delta = 0.05$, $\alpha = 0.5$, $\beta = 0.8$, and $R(0) = 4.5374$.

the model considered here is a simplification, it is able to capture certain features of real world granulomas. Indeed mathematical analysis and numerical simulations of the model indicate that, as in the granulomas of tuberculosis, macrophages are more prevalent at the granuloma's edge. The structure of stationary granulomas appears to deteriorate, however, as the bacterial growth rate increases. This observation is of special interest since unstructured granulomas are a hallmark of active tuberculosis infections. Future work should (i) better determine parameter regimes in which macrophages and bacteria coexist; (ii) rigorously establish the existence of stationary solutions as well as analyze their asymptotic stability; and (iii) include more realistic models of granulomas.

Acknowledgments

Chiu-Yen Kao is partially supported by NSF DMS-1318364. The work of Rachel Leander was partially supported by the National Science Foundation under Agreement No. 0931642.

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