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On the stability of steady states in a granuloma model

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Abstract

We consider a free boundary problem for a system of two semilinear parabolic equations. The system represents a simple model of granuloma, a collection of immune cells and bacteria filling a 3-dimensional domain $\Omega(t)$ which varies in time. We prove the existence of stationary spherical solutions and study their linear asymptotic stability as time increases to infinity.

1. Introduction

Granuloma is a medical term for a collection of immune cells known as macrophages. Granulomas are formed when the immune system attempts to wall off bacteria or other foreign substances that is unable to eliminate. A typical example is the granulomas of tuberculosis. When a person inhales Micobacteria tuberculosis, macrophages in the lung surround the bacteria, engulf them and attempt to digest them. However, once inside macrophages the bacteria multiply so that instead of a macrophage killing the bacteria, the bacteria inside a macrophage may end up killing the host macrophage.

Recent review articles [5,9] describe the involvement of other types of immune cells, e.g., T cells and dendritic cells, in the formation of granulomas associated with Micobacteria tuberculosis. A PDE model with several different populations of macrophages, defined by the number

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of bacteria within them, was introduced in [6]; an agent-based model was considered in [8], and a more recent hybrid model was developed in [7].

Approximately one third of the human population are infected by Micobacteria tuberculosis, yet only a few millions are clinically sick. The reason for this disparity is that under small amount of bacteria inhalation the granulomas formed by the macrophages are small and either remain stable or eventually shrink to zero.

In the present paper we develop a simple mathematical model of granuloma and consider, mathematically, the linearized stability/instability of small radially symmetric steady states.

The model involves just macrophages and bacteria, and was introduced earlier, in the radially symmetric case, in [1]. We first establish the existence of radially symmetric steady state granulomas with any radius R, $0 < R \leqslant R_*$, where R_* is given explicitly by one of the model's parameters. Next we proceed to study the linear asymptotic stability when R is sufficiently small. To do this we express the linearly perturbed non-radially symmetric solution in terms of spherical harmonics $Y_{n,m}(\theta, \varphi)$ $(n \geqslant 0, |m| \leqslant n)$ and prove that the steady state is linearly unstable in mode $n = 0$ and is linearly stable for all modes $n \geqslant 2$. Perturbations of modes $n \geqslant 2$ do not change the initial volume of granuloma, while the perturbation of mode $n = 0$ either decreases or increases the volume of the granuloma. Thus, the steady granuloma is stable only under a perturbation that leaves the initial volume fixed.

In Section 2 we introduce the dynamical model, and in Sections 3 to 6 we establish the existence of steady radially symmetric solutions for granulomas with any radius $R \in (0, R_*]$.

In Sections 7–9 we consider the stability/instability of the linearized model about the radially symmetric stationary solution with initial condition expanded through spherical harmonics. Linear stability results of this type have been proved in [2] for a different PDE system modeling tumor growth.

Finally, in Section 10 we we give a biological interpretation of some of our analytical results.

2. The mathematical model

The model variables are

- $M(x,t) =$ density of macrophages,
- $B(x,t) =$ density of bacteria

where x varies in a 3-d domain $\Omega(t)$ which evolves with time t. The model equations are

$$\begin{cases} \dfrac{\partial M}{\partial t} + \nabla \cdot (M\vec{v}) - \Delta M = -\mu_1 MB - \alpha M, \\ \dfrac{\partial B}{\partial t} + \nabla \cdot (B\vec{v}) - \Delta B = -\mu_2 MB + \lambda B. \end{cases} \tag{2.1}$$

Here $\vec{v}$ is the velocity by which both macrophages and bacteria are moving within the granuloma, μ_1 is the rate by which bacteria kill macrophages, μ_2 is the rate by which macrophages kill bacteria, λ is the growth rate of bacteria, and α is the natural death rate of macrophages; we take $\mu_1 > 0$, $\mu_2 > 0$, $\lambda > 0$ and $\alpha \geqslant 0$. For simplicity we assume in the model (2.1) that all the bacteria reside within the macrophages so that they move with the same velocity and have the same dispersion coefficient 1. Actually $\lambda = \lambda(B, M)$ is a nonlinear function of the bacteria B residing in infected macrophages M. The bacterial population B grow in M and when the M die