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On a Negative Relation between Bacterial Taxis and Turing Pattern Formation

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Abstract—In this paper we introduce a bacteria-leukocyte model with bacteria chemotaxsis. We assume that bacteria develop a tactic defence mechanism as a response to Leukocyte phagocytosis. We explore the effect of this tactic motion on Turing space in two parameter spaces. A fine tuning of bacterial chemotaxis shows a significant effect on developing a non-uniform steady state.

Keywords—Chemotaxis-diffusion driven instability, bacterial chemotaxis.

I. Introduction

THE cellular response to antigen invasion is termed an inflammation [1]. The antigen can be any microorganism. Examples include bacteria, viruses or even a macroorganism such as fungi [2]. The reaction against an invading antigen is a sophisticated process which can involve various scenarios either chemical or physical [4]. Typically, phagocytes (a type of white blood cells) surges to the location of infection as a response to the antigen entrance into the body [1], [3]. Leukocytes aim to halt the establishment of the antigens by phagocytosis or by secreting cytotoxic enzymes [6], [7]. The antigen, in some sense, acts as a chemoattractant to the phagocytes. This increase in the emigration rate of leukocytes towards the infected area will return back to normal (intrinsic rate) as the antigen is eradicated from the tissue. The whole infection process is vast and complicated. Recently there have been extensive efforts to develop mathematical models for these sorts of regimes [8]–[12]. Since the process of infection is essentially based on movement, reaction-diffusion-chemoataxis models are suitable candidates for this purpose. Motivated by their work in [4] which describes a lumped model for tissue inflammation dynamics, the authors extend the model to include the random motility of phagocytes and bacteria as well as phagocytes chemotaxis [5]. One of the advantages of this extension is that it serves to check the possibility of forming non-uniform steady states which is, pathologically, of a particular importance where the spatial heterogeneity of bacteria can lead to adverse effects. Specifically, it has been shown that when ρ (the scaled bacteria random motility) is higher than 1, the system can never exhibit such non-uniform spatial patterns. In this chapter, we extend the model constructed in [5] by incorporating bacterial taxis. We assume that bacteria develop this behaviour as a response to phagocytosis. Our assumption, whilst not observed in any laboratory based systems, can not be ruled out [13], [14]. We examine the effect of this hypothetical bacterial taxis on the possibility of forming a Turing pattern in some specific parameter spaces.

In Section II, we introduce our extended model with its necessary assumptions. An analysis of steady states and their stability properties is given in Section III. In Section IV the possibility of developing a non-uniform steady state, due to chemotaxis and diffusion, is discussed. In Section V, we use numerical simulations to check the effect of bacterial chemotaxis on the system's ability to exhibit a Turing regime.

A. Preliminaries

By way of introduction, we start with a stranded reaction diffusion system:

$$\frac{\partial u}{\partial t} = f(u) + D\nabla^2 u. \tag{1}$$

Here f is the reaction part whereas D is the diffusion matrix of the states vector u. Linearisation of the reaction diffusion system around a homogeneous, stable equilibrium state yields

$$\frac{\partial x}{\partial t} = (A - \omega^2 D)x,$$

where A is the linearisation of the reaction part and ω is a wave number derived by taking Fourier transform $\hat{u}(x,t) = \int u(t,x)e^{i\omega x}dx$ in space. If A is stable, then system 1 exhibits diffusion driven instability (DDI) or Turing pattern [15], if the matrix $A - \omega^2 D$ has at least one eigenvalue with a positive real part for some wave number ω. In other words, there will be no-DDI when all eigenvalues of $A - \omega^2 D$ lie in the left half of the complex plane $\mathbb{C}_-$ for all ω. It is worth adding here that the same analysis can be carried out if chemotaxis is involved. The only difference is that the matrix D does not have to be diagonal. Chemotaxis-diffusion driven instability (CDDI) will happen if at least one eigenvalue of $A - \omega^2 D$ has at least one eigenvalue with a positive real part.

II. Model equations

Encouraged by the model introduced in [4], [5] we propose a reaction-diffusion-chemotaxis model which has the same reaction part but we incorporate bacteria chemotaxis. Assuming that $b(t,x)$ and $c(t,x)$ stand for the bacteria and the phagocyte densities at time t and position x respectively then the model considered has the structure

$$\begin{aligned}\frac{\partial b}{\partial t} &= \frac{k_g b}{1+\frac{b}{K_i}} - \frac{k_d bc}{K_b + b} + \mu_b \nabla_x^2 b + \chi_1 \frac{\partial}{\partial x}(b\frac{\partial c}{\partial x})\\ \frac{\partial c}{\partial t} &= h_0(\frac{A}{V})c_b[1 + \frac{h_1}{h_0}b] - gc + \mu_c \nabla_x^2 c - \chi_2 \frac{\partial}{\partial x}(c\frac{\partial b}{\partial x}).\end{aligned}$$

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The main assumption here is that bacteria are assumed to move chemotactically away from the leukocytes as a developing defence mechanism and we denote its tactic coefficient by χ_1. The chemotactic movement of the leukocytes (denoted by χ_2) is assumed to be towards the bacterial high gradients (i.e. the bacteria is a chemoattractant). As in [5], phagocytes and bacteria have the random motilities μ_b, μ_c respectively. The parameters K_i, K_b are the bacterial density growth and phagocytosis inhibition constants, respectively. The parameter k_g stands for the bacteria growth rate whereas k_d is the phagocytes killing rate. The parameters h_0, h_1 are the normal and the enhanced emigration rates of the Leukocytes. The fraction $\frac{A}{V}$ is the ratio of the surface area of the venule to the volume of the tissue. The phagocyte death rate is represented by g and its density in the venules is given by c_b. All the movements are assumed to be in 1-dimension ($-\infty < x < \infty$). The boundary conditions are $\frac{\partial b}{\partial x} = \frac{\partial c}{\partial x} = 0 \quad \text{as} \quad x \to \pm\infty$ Letting $c_0 = \frac{h_0(\frac{A}{V})c_b}{g}$ and using the scaling

$$v = \frac{b}{K_i}, \quad u = \frac{c}{c_0}, \quad \tau = \left(\frac{k_d c_0}{K_i}\right) t, \; \zeta = \left(\frac{g}{\mu_c \alpha}\right)^{\frac{1}{2}} x,$$
$$\gamma = \frac{k_g K_i}{k_d c_0}, \; k = \frac{K_b}{K_i}, \quad \sigma = \frac{h_1 K_i}{h_0}, \quad \alpha = \frac{g K_i}{k_d c_0},$$
$$\rho = \frac{\mu_b}{\mu_c}, \quad \delta_1 = \frac{\chi_1 c_0}{\mu_c}, \; \delta_2 = \frac{\chi_2 K_i}{\mu_c},$$

we get

$$\left.\begin{aligned} \frac{\partial v}{\partial t} &= \frac{\gamma v}{1+v} - \frac{uv}{k+v} + \rho \nabla_x^2 v + \delta_1 \frac{\partial}{\partial x}\left(v \frac{\partial u}{\partial x}\right) \\ \frac{\partial u}{\partial t} &= \alpha(1 + \sigma v - u) + \nabla_x^2 u - \delta_2 \frac{\partial}{\partial x}\left(u \frac{\partial v}{\partial x}\right) \end{aligned}\right\} \tag{2}$$

where, for convenience, we denote τ by t and ζ by x.
Here δ_1, δ_2 are the scaled bacterial and leukocytes chemotactic coefficients whereas ρ is the ratio of the bacterial diffusivity to phagocytes diffusivity. The parameter σ is the ratio of leukocyte emigration rates (enhanced/normal) whilst γ is the ratio of the bacterial maximum growth rate to maximum killing due to phagocyte. The parameter k refers to the ratio of the inhibition effect on bacteria growth due to the increase in its density to inhibition effect on its ability to kill bacteria. The ratio of phagocyte killing and death rate is given by the parameter α. For a detailed derivation of (2), see [4], [5].

III. The System Without Diffusion and Chemotaxis

The system always has the steady state $(v, u) = (0, 1)$. This is termed as the elimination steady state which corresponds to the case where bacteria is absent (or eradicated) from the infected tissue. The system can have two other possible coexistence steady states, $(v_\pm > 0, u = 1 + \sigma v_\pm)$. These are termed compromise steady states and for these steady states bacteria exists at certain levels. In terms of the system parameters, the bacteria steady state density $v_\pm$ is given as

$$v_\pm = \frac{1}{2\sigma}\left[(\gamma - 1 - \sigma) \pm \sqrt{(1 + \sigma - \gamma)^2 + 4\sigma(\gamma k - 1)}\right].$$

The compromise steady state does not always exist. The existence of a physically acceptable (real and positive) compromise steady state(s) is linked to the relation between the quantities k and $(1+\sigma)^{-1}$. To see this we follow the following argument. At equilibrium we always have

$$\gamma(v) := \frac{(1+v)(1+\sigma v)}{k+v}.$$

This relation, $\gamma(v)$, has the following properties

- $\gamma'(v) = \dfrac{\sigma v^2 + 2\sigma k v + k(1+\sigma) - 1}{(k+v)^2}$,
- $\gamma(0) = \dfrac{1}{k}$,
- $\gamma'(0) = \dfrac{k(1+\sigma) - 1}{k^2}$.

If $k(1+\sigma) - 1 > 0$ then $\gamma'(v) > 0$ for all v, and hence $\gamma(v)$ increases without bound.
If $k(1+\sigma) - 1 < 0$ then $\gamma(v)$ initially decreases till some $v := \tilde{v} > 0$ where $\gamma'(\tilde{v}) = 0$ and then starts increasing again. It turns out that

$$\tilde{v} = -k + \sqrt{k^2 - \frac{k(1+\sigma) - 1}{\sigma}}.$$

This can be summarised as follows.

- If $k > (1+\sigma)^{-1}$: The system has no compromise states when $\gamma < 1/k$ and has only the upper state (v_+) for $\gamma > 1/k$.
- If $k < (1+\sigma)^{-1}$: The system has no compromise steady states when $\gamma < \tilde{\gamma}$ whereas it has two when $\tilde{\gamma} < \gamma < 1/k$. The system has only one compromise steady state if $\gamma > 1/k$. Here $\tilde{\gamma} = \gamma(\tilde{v})$.

Fig. 1 depicts the existence of the bacterial model equilibria.

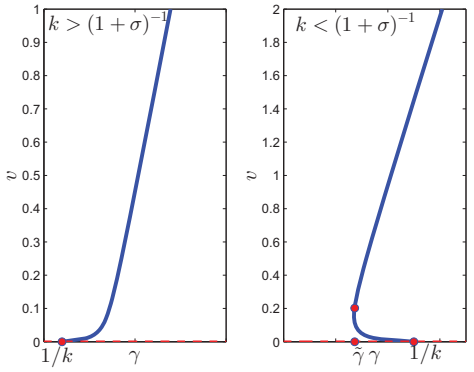

Fig. 1. The equilibria of the bacterial model in terms of the parameter γ. The elimination steady state (red dashed) always exists. The blue curve indicates the compromise steady state. If $k > \frac{1}{1+\sigma}$ there exists only one compromise steady state, the upper one, whereas if $k < \frac{1}{1+\sigma}$ there exits two compromise steady states, the upper and the lower.

Generally, the Jacobian is given by

$$A = \begin{pmatrix} \frac{\gamma}{(1+v)^2} - \frac{ku}{(k+v)^2} & -\frac{v}{k+v} \\ \alpha\sigma & -\alpha \end{pmatrix}. \tag{3}$$

Evaluating the Jacobian on the elimination steady state yields

$$A = \begin{pmatrix} \gamma - \frac{1}{k} & 0 \\ \alpha\sigma & -\alpha \end{pmatrix}.$$

Since $\alpha > 0$, the elimination steady state is stable if

$$\gamma < \frac{1}{k}.$$

For the compromise steady state 3 can be written as

$$A = \begin{pmatrix} \frac{v(1+\sigma v)(1-k)}{(1+v)(k+v)^2} & -\frac{v}{k+v} \\ \alpha\sigma & -\alpha \end{pmatrix}.$$

So the compromise steady state is stable when

$$\det(A) = \frac{\alpha v}{1+v}\gamma'(v) > 0 \quad \text{and,}$$
$$\text{trace}(A) = (\frac{v(1+\sigma v)(1-k)}{(1+v)(k+v)^2} - \alpha) < 0.$$

At all possible lower compromise steady states, $\gamma' < 0$ and therefore $\det(A)$ is always negative. Consequently, the lower compromise steady state v_- is always unstable and hence it can never show a Turing pattern.

IV. Possibility of Developing a Non-Uniform Steady State

Throughout this section we will set $v_+ = v$. The system (2) will develop a non-uniform steady state if the matrix

$$X := A - \omega^2 D = \begin{pmatrix} \frac{v(1+\sigma v)(1-k)}{(1+v)(k+v)^2} - \rho\omega^2 & -\frac{v}{k+v} - \delta_1 v\omega^2 \\ \alpha\sigma + \delta_2 u\omega^2 & -\alpha - \omega^2 \end{pmatrix},$$

has an eigenvalue with a positive real part for some ω. In the case of elimination steady state, this matrix reduces to

$$X = \begin{pmatrix} \gamma - 1/k - \rho\omega^2 & 0 \\ \delta_2 & -\alpha - \omega^2 \end{pmatrix}.$$

Assuming the stability of the elimination steady state $(0, 1)$ ($\gamma < 1/k$), it is easy to see that all the eigenvalues are real and negative for all possible wave numbers. Hence the elimination steady state will never yield a non-uniform steady state. For the compromise steady state we first write X as

$$X = \begin{pmatrix} a_{11} - \rho\omega^2 & a_{12} - \delta_1 v\omega^2 \\ \alpha\sigma + \delta_2 u\omega^2 & -\alpha - \omega^2 \end{pmatrix},$$

where

$$a_{11} = \frac{v(1+\sigma v)(1-k)}{(1+v)(k+v)^2} \quad \text{and} \quad a_{12} = -\frac{v}{k+v}.$$

The corresponding characteristic equation of X is

$$\lambda^2 - (\text{trace}(A) - (1+\rho)\omega^2)\lambda + (\rho + \delta_1\delta_2 uv)\omega^4 - (a_{11} - \rho\alpha - \delta_1\alpha\sigma v + \delta_2 a_{12} u)\omega^2 + \det(A) = 0. \quad (4)$$

Since we always have

$$\text{trace}(A) - (1+\rho)\omega^2 < 0,$$

equation 4 can have roots with positive real parts only if

$$(\rho + \delta_1\delta_2 uv)\omega^4 - (\text{trace}(A) + (1-\rho)\alpha - \delta_1\alpha\sigma v + \delta_2 a_{12} u)\omega^2 + \det(A) < 0.$$

Completing the squares we eventually get the necessary conditions

$$\text{trace}(A) + (1-\rho)\alpha - \delta_1\alpha\sigma v + \delta_2 a_{12} u > 0, \quad (5)$$

$$(\text{trace}(A) + (1-\rho)\alpha - \delta_1\alpha\sigma v + \delta_2 a_{12} u)^2 - 4(\rho + \delta_1\delta_2 uv) > 0. \quad (6)$$

It is evidently clear that from condition 5 the value δ_1 can not be too large in order to maintain the inequality in the same direction and large bacterial taxis will violate this necessary condition, hence CDDI will not be possible. Following [5], a necessary conditions for this is

$$\rho < 1 + \frac{\text{trace}(A)}{\alpha} + \frac{\delta_2 a_{12} u}{\alpha} + \frac{\delta_1\alpha\sigma v}{\alpha} = \rho_c, \quad (7)$$

where ρ_c is the critical bacterial random motility necessary for CDDI. Here, the bacterial taxis shifts the upper bound of ρ obtained in [5] to the left and this, in turn, narrows the region of ρ admissible values necessary for CDDI. Fig. 2 shows how the set of critical values of ρ_c changes as the bacterial taxis changes. The rest of the parameters are fixed.

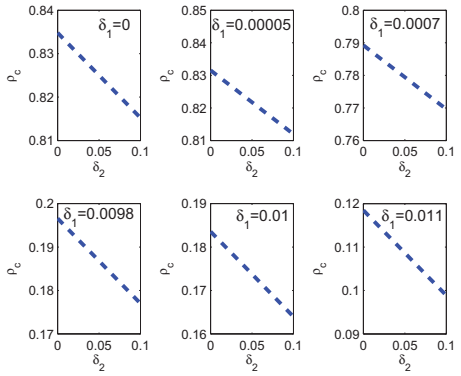

Fig. 2. Leukocytes critical random motility ρ_c necessary for CDDI as a function of Leukocytes chemotaxis, for different choices of bacterial chemotaxis. The increase in bacterial chemotaxis narrows the values of ρ_c necessary for CDDI. The parameter values used here are : $k = 0.01$, $\alpha = 320$, $\sigma = 350$ and $\gamma = 400$.

V. Numerical Results

Here we will apply the two necessary conditions (5) and (6) to study the effect of bacterial chemotaxis on the possibility of forming non-uniform steady states. Our focus will be on the spaces (ρ, δ_2) and (α, γ). In both cases we will consider the situations $\delta_1 = 0$ (no bacterial chemotaxis) and $\delta_1 \neq 0$ (bacteria move away from phagocytes).

A. Bacterial diffusion vs. leukocytes random motility

Without bacterial chemotaxis ($\delta_1 = 0$) and with the parameter values $\gamma = 400$, $\alpha = 320$, $\sigma = 350$ and $k = .01$, the system has only one compromise steady state (the upper one). Fig. 3 shows a region in the parameter space (ρ,δ), shaded green , where CDDI is possible. The boundary curve establishes a set of critical phagocytic chemotaxis values where at a certain level of bacterial random motility ρ the

phagocytic movement has to be faster than a value given by the intersection of the horizontal line containing ρ with the curve. For instance, with bacterial diffusion $\rho = .01$ the phagocytes needs to move faster than $\delta_2 \approx 2.75$ in order to halt the forming of spatial heterogeneity.

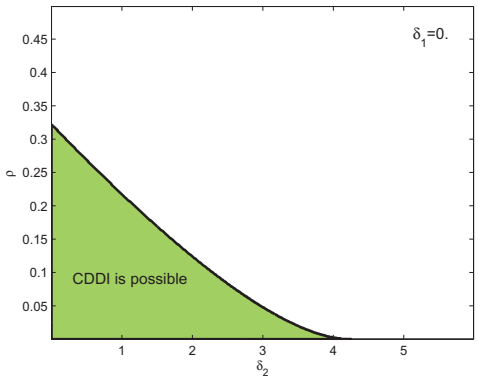

Fig. 3. The bacteria-leukocyte model with parameters $k = 0.01, \gamma = 400, \alpha = 320, \sigma = 350, \delta_2 = 3.75$ and $\delta_1 = 0$. The stability region (all the parameter space) is divided to two parts. One where CDDI is possible (shaded green) and the other where it is not.

Fig. 4, shows how the region of no Turing pattern responds to the change in bacterial taxis. Evidently, there is a negative relation between the intensity of bacterial tactic behaviour and the possibility for the system establishing a non-uniform steady state. The values of δ_1 used are 0, 0.0015, 0.005 and 0.0071.

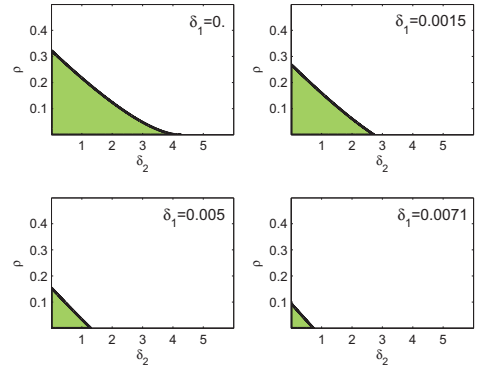

Fig. 4. The bacteria-leukocyte model with bacteria chemotaxis (δ_1) values : 0, 0.0015,0.005 and 0.0071. The rest of the parameter are taken as in Fig. 3. The possibility of forming patterns decreases as bacteria chemotaxis increases.

B. The ratio of maximum bacterial growth rate to maximum phagocyte killing rate vs. ratio of phagocyte death rate to maximum phagocytic killing

Here we will use the parameter values $\sigma = 350$, $\rho = 0.01$, $\delta_2 = 3.75$, $k = 0.01$ and $\delta_1 = 0$. Fig. 5 shows the region where CDDI is possible :

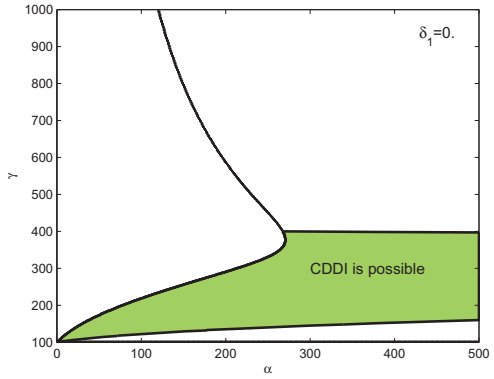

Fig. 5. The bacteria-leukocyte model without bacteria chemotaxis (i.e. $\delta_1 = 0$). The other parameter values are: $\rho = 0.01$, $\sigma = 350$, $k = 0.01$ and $\delta_2 = 3.75$. Stability region is right to the black curve. The region where CDDI is possible is shaded green.

For a sequence of increasing values of δ_1, namely, δ_1=0, .004, 0.09 and 0.2, Fig. 6 shows how the region where pattern formation is possible shrinks as a response to the increase in bacterial chemotaxis.

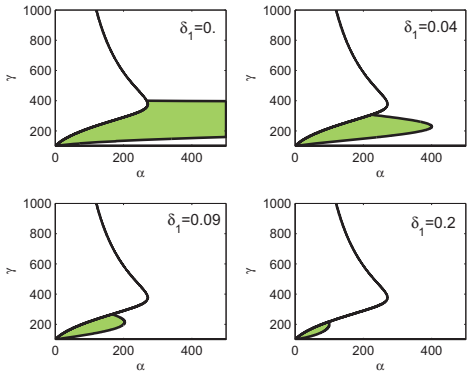

Fig. 6. The paremeter space (α, γ) for various values of bacteria chemotaxis (in an increasing order), namely, 0, 0.01, 0.09 and 0.2. The other parameters are taken as in Fig. 5. The possibility of developing non-uniform steady state decreases as the bacteria taxis increases

VI. Conclusion

Reaction-diffusion-chemotaxis models are useful for modelling many spatio-temporal interactions involving motion. These mechanistic models link biological processes to mathematical quantities. Parameters in the models can be easily tuned and so the models provide a cause and effect framework to explore the biological process even when the empirical evidence does not exist or is not known. In this paper we extend the model introduced in [5]. Specifically we assume that bacteria develops a defence mechanism in response to an increased concentration of leukocytes. This might be ascribed to the bacterial memory recognising the chemical cues produced by phagocytes. The main question we aimed to address is: Does bacterial chemotaxis have an effect on the system's capability to exhibit non uniform spatial

patterns? This in turn determines whether bacterial movement can prevent biased distribution of its own population. According to [5] this can have an impact on the persistence of the infection. We showed that the extent of the values of leukocytes random motility, necessary for CDDI derived in [5], has been narrowed due to the incorporation of bacterial chemotaxis (7). In the both parameter spaces, we chose, it seems that the possibility of forming a non-uniform steady state is negatively correlated to bacterial taxis. This finding could have a significant implications on our understanding of the mechanism of infection and immuno-defence and should now be confirmed by laboratory research.

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