A Turing mechanism in order to explain the patchy nature of Crohn’s disease

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Abstract
Crohn’s disease is an inflammatory bowel disease (IBD) that is not well understood. In particular, unlike other IBDs, the inflamed parts of the intestine compromise deep layers of the tissue and are not continuous but separated and distributed through the whole gastrointestinal tract, displaying a patchy inflammatory pattern. In the present paper, we introduce a toy-model which might explain the appearance of such patterns. We consider a reaction-diffusion system involving bacteria and phagocyte and prove that, under certain conditions, this system might reproduce an activator-inhibitor dynamic leading to the occurrence of Turing-type instabilities. In other words, we prove the existence of stable stationary solutions that are spatially periodic and do not vanish in time. We also propose a set of parameters for which the system exhibits such phenomena and compare it with realistic parameters found in the literature. This is the first time, as far as we know, that a Turing pattern is investigated in inflammatory models.

Keywords
Inflammatory diseases · Turing pattern · Reaction-diffusion system · Activator-inhibitor

Mathematics Subject Classification
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1 Introduction

Ulcerative colitis and Crohn’s disease represent the two main types of inflammatory bowel disease (IBD). Both are relapsing diseases and may present similar symptoms including long-term inflammation in the digestive system, however they are very different: Ulcerative colitis affects only the large intestine and the rectum whereas Crohn’s disease can affect the entire gastrointestinal tract from the mouth to the anus (see Feuerstein and A. S. C. 2017 for example). Typical presentations of Crohn’s disease include the discontinuous involvement of various portions of the gastrointestinal tract and the development of complications including strictures, abscesses, or fistulas that compromise deep layers of the tissue, while ulcerative colitis remains superficial but present no healthy areas between inflamed spots.

There is consensus now that IBD results from an unsuitable response of a deficient mucosal immune system to the indigenous flora and other luminal antigens due to alterations of the functions of the epithelial barrier. Our goal is to propose a simplified mathematical model simulating the immune response triggering inflammation. In the particular case of Crohn’s disease, we seek to understand the patchy inflammatory patterns that differentiate patients suffering from this illness from those who have been diagnosed with ulcerative colitis. For recent articles on IBD discussing the differences of patterns between Crohn’s disease and Ulcerative colitis, see for instance (Feuerstein and A. S. C. 2017; Longo et al. 2020; Puylaert et al. 2016).

IBD can be seen as an example of the acute inflammatory response of body tissues caused by harmful stimuli such as the presence of pathogenic germs or damaged cells. This protective response is also associated with the origin of other well-known diseases such as rheumatoid arthritis, the inflammatory phase in diabetic wounds or tissue inflammation, and has been extensively studied. Today it is still of central interest for researchers and, although several models have been proposed in order to understand the causes that lead to acute inflammation, the mathematical approach to this topic remains a relatively new field of research. A more complete review on the subject is provided in Vodovotz (2006); Vodovotz et al. (2004).

Among the mathematical works on inflammation we can refer to many models based on ordinary differential equations (Day et al. 2006; Dunster et al. 2014; Herald 2009; Kumar et al. 2004; Lauffenburger and Kennedy 1981; Mayer et al. 1995; Reynolds et al. 2006; Roy et al. 2009; Wendelsdorf et al. 2010). Most of the authors take into account pro-inflammatory and anti-inflammatory mediators but also pathogens and other more or less realistic physiological variables. Depending on the parameters and the initial data, these models manage to reproduce a variety of scenarios that can be observed experimentally and clinically; for example the case in which the host can eliminate the infection and also other situations in which the immune system cannot keep the disease under control or where the existence of oscillatory solutions determines a chronic cycle of inflammation. Most of the conclusions in the referenced papers are the result of stability studies of the equilibrium states and numerical analysis of the simulations by phase portraits methods. In addition, in Day et al. (2006); Kumar et al. (2004); Roy et al. (2009); Wendelsdorf et al. (2010) a sensitivity analysis of the variables to the parameters of the models is performed in order to adjust the numerical results to experimental data and achieve greater biological fidelity.
Several authors have also considered spatial heterogeneity in order to model the inflammatory response, we can mention (EL Khatib and Génieys 2007; Khatib and N., Génieys, S., Kazmierczak, B. 2011; Ibragimov et al. 2006) in the particular case of atherogenesis, Lauffenburger and Kennedy (1983); Penner et al. (2012) in the tissue inflammation context and Chalmers et al. (2015); Sullivan and Yotov (2006) for the acute inflammatory response. The main variables of the models introduced in the mentioned works vary according to the dynamics that the authors wish to describe: the density of phagocytic cells, pro-inflammatory cytokines, anti-inflammatory mediators and bacteria are some standard quantities that are often taken into account. As in the ordinary differential equations approach, the stability of the systems is systematically studied, in Chalmers et al. (2015); Cónsul et al. (2014); EL Khatib and Génieys (2007); Lauffenburger and Kennedy (1981) a vast analysis of all possible scenarios is performed depending on the values of the model parameters, the authors provide biological interpretation of such behavior as well as numerical simulations; furthermore, in Khatib and N., Génieys, S., Kazmierczak, B. (2011) the existence of travelling waves solutions is proved to be at the origin of a chronic inflammatory response.

A different approach is presented in Penner et al. (2012), the model introduced in this paper aims to explain mathematically the patterns observed in the skin due to acute inflammation in the absence of specific pathogenic stimuli. By analyzing the stability of homogeneous and non-homogeneous states, sufficient conditions leading to the existence of such pattern solutions are obtained; several numerical examples are given as well. Similarly, in Lauffenburger and Kennedy (1983) the authors claim that the instability of the uniform steady distribution of phagocytic cells might trigger non-uniform cell density distributions which is potentially dangerous since tissue damage may occur in regions of high cell concentration. In this sense some sufficient conditions are given in order to prevent the existence of such kind of unstable states, these conditions primarily involve the phagocyte random motility coefficient and a chemotaxis coefficient included in the model.

As suggested by in vitro studies, phagocytic cells (big eaters) may move following a chemotactic impulse generated by the presence of pathogens germs, for this reason most of the authors cited above include the effect of chemotaxis by means of the classical term first introduced by Patlak in 1953 and Keller and Segel in 1970 Keller and Segel (1970); Patlak (1953). Nevertheless, there is no consensus on this assumption, as noted in Lauffenburger and Kennedy (1983), in vivo observations more often show that the phagocytes seem to move within an infected lesion randomly. This is the case in the models introduced in Cónsul et al. (2014); EL Khatib and Génieys (2007); Khatib and N., Génieys, S., Kazmierczak, B. (2011).

In this paper we propose a mechanism leading to patterns which does not rely on chemotactism. We think the inflammatory response could be modeled by an activator-inhibitor system. Such systems are known to produce the Turing mechanism, that is, periodic stationary solutions. This could possibly explain the patchy nature of Crohn’s disease.
2 The model

We propose here a reaction-diffusion system modelling the dysfunctional immune response that triggers IBD. As mentioned in the introduction, this kind of system has attracted much interest as a prototypical model for pattern formation. In this case we refer in particular to inflammatory patterns.

Roughly speaking, the first line of defense of the mucosal immune system is the epithelial barrier which is a polarized single layer covered by mucus in which commensal microbes are embedded. Lowered epithelial resistance and increased permeability of the inflamed and non-inflamed mucosa is systematically observed in patients with Crohn’s disease and ulcerative colitis, hence the epithelial barrier becomes leaky and luminal antigens gain access to the underlying mucosal tissue. In a healthy gut, the immune response by means of intestinal phagocytes eliminates the external agents limiting the inflammatory response in the gut. Unfortunately, in a disease-state, the well-controlled balance of the intestinal immune system is disturbed at all levels. This dysfunctional mechanism contributes to acute and chronic inflammatory processes. Indeed, an excessive amount of immune cells migrating to the damaged zone can engage the permeability of the epithelial barrier and thus might allow further infiltration of microbiota which aggravate inflammation. This complex network triggers the initiation of an inflammatory cascade that causes ulcerative colitis and Crohn’s diseases, see Fig.1.

For the sake of simplicity in this model we will consider just two components varying in time and space: 1. The density of non-resident bacteria leaking into the intestinal tissue through the epithelial barrier noted as $\beta$, also refereed as microbiota, pathogens or antigens and 2. The density of immune cells $\gamma$ which we will often refer to as phagocytic cells. Also, by simplicity we model a portion of the digestive tube as an interval $\Omega \subset \mathbb{R}$ of the real axis, which will be very large. The model reads:

$$
\begin{aligned}
\partial_t \beta - d_b \Delta \beta &= r_b \left( 1 - \frac{\beta}{h_i} \right) \beta - \frac{a \beta \gamma}{s_b + \beta} + f_e \left( 1 - \frac{\beta}{h_i} \right) \gamma, \\
\partial_t \gamma - d_c \Delta \gamma &= f_b \beta - r_c \gamma.
\end{aligned}
$$

We will consider Neumann boundary conditions and initial data $\beta(0, x) = \beta_0(x)$ and $\gamma(0, x) = \gamma_0(x)$ for all $x \in \Omega$.

During the immune response there is a first stage where the non-resident phagocytes, i.e. immune cells, migrate from the vasculature into the intestinal mucosa and a second stage where they move to the damaged zone and fight the bacteria. This first stage results from a transport movement through the blood vessels and it is almost instantaneous compared to the second one, so we omit it in this simplified model.

Another main assumption is to consider that immune cells and bacteria move randomly through the damaged tissue and the epithelial barrier. As mentioned in the introduction, it is generally accepted that diffusion provides an adequate description of molecular spreading but, in the case of phagocytic cells, chemotaxis is claimed to be crucial establishing the direction of movement in the sense of the pathogen gradient. However, there are in vivo experiments that corroborate our hypothesis (Lauffenburger and Kennedy 1983) and several authors have made similar assumptions (Cónsul et al.)
(a) Bacteria (red line) break through the epithelium (dotted zone); phagocytes (blue dashed line) are recruited in order to neutralize them.

(b) Phagocytes spread rapidly through blood vessels. A high spot of bacteria remains with a lateral inhibition by phagocytes.

(c) Other spots appear.

Fig. 1 Initiation of the inflammatory process
Nevertheless, by neglecting chemotaxis in our model we do not claim that it is an unimportant phenomenon, instead, this assumption must be seen as a simplification and an idealization of the physiological mechanism we seek to describe.

The coefficients $d_b > 0$ and $d_c > 0$ are the diffusion rates of bacteria and phagocytes, respectively. The parameter $r_b > 0$ is associated with the reproduction rate of bacteria.

In healthy conditions the density of bacteria within the lumen remains almost constant and they are not able to penetrate the epithelial barrier. We associate this quantity to the parameter $b_i > 0$. We remark that this parameter $b_i$ is in some sense a carrying capacity; in fact, in the total absence of the epithelial barrier, the maximum amount of bacteria in the colon would not be greater than $\beta = b_i$. This is the reason why we add the logistic term $1 - \frac{\beta}{b_i}$ in the first equation, Verhulst (1845); Perthame (2015).

The parameter $f_b > 0$ is associated with the immune response rate of the organism sending cells to fight bacteria in the damaged zones. In others words, phagocytes appear as soon as the presence of pathogens is detected.

The term $-a \beta \gamma s_b + \beta$ with $a > 0$ and $s_b > 0$ corresponds to the effect of the immune system on the pathogen agents. In particular $\frac{a \beta}{s_b + \beta}$ is the phagocytosis rate or intake rate. It suggests that the attack rate of immune cells on bacteria varies with the density of the pathogen. This functional response term takes into account the rate $p_c$ at which phagocytes encounter a bacterium per unit of bacteria density, which is $p_c := \frac{a}{s_b}$ and the average time $\tau$ that it takes a phagocyte to neutralize a bacterium (or handling time) which can be computed as $\tau := \frac{1}{a}$. Experiments presented in Leijh et al. (1980); Stossel (1973) reflect this dynamic. In the mathematical literature this type of term is often referred as a Holling Type II functional response, see Holling (1965); Perthame (2015).

We consider $f_e > 0$ as a measure of the negative effect of the phagocyte’s concentration for the epithelial resistance, and therefore it has a positive impact on the bacteria density, i.e. the larger the epithelial gap, the more bacteria there are, the more immune cells there are drifting to the damaged zone and the more porous is the epithelium and so on.

Finally, a self-regulation function of anti-inflammatory cells limits their life-time, so immune cells have an intrinsic death rate which is noted in the model as $r_c > 0$.

### 3 On turing patterns

Since one of our main interest is to explain patchy inflammatory bowel patterns often observed in patients suffering from Crohn’s disease, we seek to demonstrate that the model we propose may present Turing-type instabilities under certain conditions. This denomination is due to Alan Turing who was the first to describe spatial patterns caused by the effects of diffusion in his article on morphogenesis theory published in 1952, Turing (1952).

Roughly speaking, a Turing system consist of an activator that must diffuse at a much slower rate than an inhibitor to produce a pattern. We recall that diffusion
causes areas of high concentration to spread out to areas of low concentration. In such kinds of systems the activator component must increase the production of itself while the inhibitor restrains the production of both. Turing’s analysis shows that in certain regimes those systems are unstable to small perturbations, leading to the growth of large scale patterns.

In the model we previously introduced, the bacteria are the activator and the immune cells the inhibitor. Indeed, the bacteria reproduce at a certain rate $r_b$ and immune cells neutralize bacteria by phagocytosis (Holling-type term) and self-regulate their own life-time $r_c$. In practice, we should look for steady state solutions of eq.(1) which are linearly unstable, i.e. such that there are perturbations for which the linearized system has exponentially growing solutions in time. To be sure that a Turing-type phenomena is occurring it is important to exclude the cases where the corresponding growth modes are unbounded, that is solutions with infinitely high frequencies and also the cases in which solutions blow up or go to extinction (Perthame 2015).

In section 4.2 we study the conditions leading to the observation of Turing phenomena in our model.

4 Results

4.1 Non-negativity property and boundedness

We begin by establishing some elementary properties in the model to guarantee eq.(1) accuracy as a population dynamics model. In other words, it is important that whenever the initial data have a reasonable biological meaning, the solution of the differential equation inherits that property. We start by a non-negativity property:

**Proposition 41** Provided that the initial condition $(\beta_0(x), \gamma_0(x))$ is non-negative the solutions of eq.(1) remain non-negative for every $t > 0$.

Similarly, we establish a boundedness property associated with the carrying capacity of the population environment:

**Proposition 42** If $\beta_0(x) < b_i$ then for all $t > 0$ one has $\beta(t, x) < b_i$ and $\|\gamma\|_{L^2(\Omega)} \leq \max\{\kappa b_i, \|\gamma_0\|_{L^2(\Omega)}\}$.

4.2 Stability analysis

Let us study now the steady states of the model and their stability properties. The equation (1), for positive values of the parameters, has exactly two non-negative homogeneous steady states. One of them is the trivial solution $(\beta, \gamma) = (0, 0)$ associated with the absence of bacteria and immune cells. The other one, that we denote $(\beta, \gamma) = (\bar{\beta}, \bar{\gamma})$, satisfies:

$$0 = (r_b + f_e \kappa) \left(1 - \frac{\bar{\beta}}{b_i}\right) - \frac{a \kappa \bar{\beta}}{s_b + \bar{\beta}},$$

(2)
where \( \kappa := \frac{f_b}{f_c} \) and \( \bar{\gamma} = \kappa \bar{\beta} \). We refer the reader to the proof of the Proposition 43 for a more detailed demonstration of the existence of this positive steady state.

We remark that \((0, 0)\) is unstable. Indeed, the linearized matrix around this steady state has negative determinant and thus an eigenvalue with positive real part. For the non-trivial equilibrium point \((\bar{\beta}, \bar{\gamma})\) the stability analysis is less straightforward. The following proposition establishes the conditions leading to the linear stability of this steady state.

**Proposition 43** Consider the O.D.E system associated with eq.(1) with positive real parameters \( a, r_b, r_c, f_b, f_e, b_i \) and \( s_b \),

\[
\begin{align*}
\frac{\partial \beta}{\partial t} &= r_b \left( 1 - \frac{\beta}{b_i} \right) \beta - \frac{a \beta \gamma}{s_b + \beta} + f_e \left( 1 - \frac{\beta}{b_i} \right) \gamma, \\
\frac{\partial \gamma}{\partial t} &= f_b \beta - r_c \gamma.
\end{align*}
\]

This system has a unique positive steady state solution \((\beta(t), \gamma(t)) = (\bar{\beta}, \bar{\gamma})\) which is linearly stable if and only if

\[
\frac{a \kappa \bar{\beta}^2}{(s_b + \bar{\beta})^2} - r_b \frac{\bar{\beta}}{b_i} - f_e \kappa < r_c.
\]  

We conjecture that the model might show some unexpected behavior around this steady state which could be at the origin of patchy inflammatory patterns. Hence, let us focus on conditions leading the formation of Turing patterns for the reaction diffusion system (1), that is perturbations around the steady state \((\bar{\beta}, \bar{\gamma})\) such that the linearized system has exponential growth in time and for which the corresponding growth modes are bounded. The following proposition establishes the necessary conditions for the occurrence of such phenomenon.

**Proposition 44** Consider eq.(1) and its unique positive homogeneous steady state solution \((\bar{\beta}, \bar{\gamma})\); assume that there exist real non-negative values of the parameters \( a, r_b, r_c, s_b, f_e, f_b, b_i \) such that the following condition holds:

\[
0 < \frac{a \kappa \bar{\beta}^2}{(s_b + \bar{\beta})^2} - r_b \frac{\bar{\beta}}{b_i} - f_e \kappa < r_c
\]  

Then for \( \frac{db}{dc} \) small enough the reaction diffusion system (1) shows Turing instabilities around this steady state.

**5 Parameters of the model**

In this section we want to estimate the values of the parameters of the model and to prove the non emptiness of the parameter set defined by (5). As long as it is possible we will rely on values obtained from real observations or in vitro experiments. However,
in some cases the exact values are unknown due to the difficulty of measuring them \textit{in vivo} or even \textit{in vitro}.

Let us start with an estimation of the reproduction rate of the bacteria, represented in our model as $r_b$. The bacterium’s generation time, which is the time it gets to the population to double the number of individuals, might vary from 12 minutes to several hours depending on temperature, nutrients, culture medium, among others factors. For E. Coli, for instance, it is around 20 minutes in standard conditions, Korem et al. (2015). We can then consider that the evolution of bacteria population is given by $\partial_t b = r_b b$ and so $r_b = \frac{\ln(2)}{20}$ measured in bacteria per minute. That gives us an approximate value $r_b = 3.47 \times 10^{-2} \text{ u/min}$ which is in the estimated range of values given in Lauffenburger and Kennedy (1983) for this parameter.

Similarly, it is known that in healthy conditions phagocytes have, in average, a half-life of two days (Labro 2000), and so from $\partial_t c = -r_c c$ we get $r_c = \frac{\ln(2)}{2880}$ cells per minute which means that the death rate of phagocytes is ideally of the order of $10^{-4} \text{ u/min}$, which coincides with that considered in Waugh and Sherratt (2007) for immune cells in diabetic wounds or in Lauffenburger and Kennedy (1983) for bacterial infection causing tissue inflammation. However, there is no consensus, some authors assume this parameter to be of the order of $10^{-3} \text{ u/min}$ in the inflammatory response framework (Chow et al. 2005) or even of the order of $10^{-6} \text{ u/min}$ in the case of early atherosclerosis (Chalmers et al. 2015). For such parameters, corresponding to a healthy organism, we do not expect to observe Crohn’s disease. Indeed, the mechanism we describe below occurs with $r_c = 2 \times 10^{-2} \text{ u/min}$ (see Table 1). For $r_c = 10^{-3} \text{ u/min}$, the range of parameters for which a Turing pattern occurs is quite narrow, Fig. 3.

The diffusion coefficient of immune cells might also vary according to the type of cell and the part of the body where they act. In the consulted literature the value of this parameter varies from $10^{-12} \text{ m}^2/\text{min}$ to $10^{-10} \text{ m}^2/\text{min}$ depending on the context (Cónsul et al. 2014; Khatib and N., Génieys, S., Kazmierczak, B. 2011; Lauffenburger and Kennedy 1983; Stickle et al. 1985). In the absence of experimental data providing more precise information about the order of this parameter in the particular case of bacterial infection in the intestinal track, we consider this coefficient to remain within this range in damaged areas of the intestine.

Although there is not precise information concerning the diffusion rate of bacteria through the epithelial barrier, it is known that in aqueous solutions like the lumen, the diffusion rate might vary from $10^{-11}$ to $10^{-8} \text{ m}^2/\text{min}$ depending on the type of bacteria. However, in a non-liquid framework, which is the case of bacteria penetrating through the epithelial barrier, motility should be reduced.

We will now roughly compute a value for the parameter $a$, we suppose that there is a significant density of bacteria in a certain position $x = x_0$, and we study the time evolution of the population within this point. If $\beta$ is large enough, the term $1 - \frac{\beta}{b_1}$ is negligible, moreover the term $-\frac{a\beta y}{s_b + \beta}$ tends to approach $-a\gamma$, so we can approximately write

$$\partial_t \beta(t, x_0) = -a\gamma(t, x_0).$$

(6)
Table 1 Assigned values for the parameters of the model (1)

| Parameter | Interpretation                           | Value          | Units       |
|-----------|-----------------------------------------|----------------|-------------|
| $r_b$     | Reproduction rate of bacteria            | 0.0347         | (u/min)     |
| $r_c$     | Intrinsic death rate of phagocytes       | 0.02           | (u/min)     |
| $d_b$     | Diffusion rate of bacteria               | $10^{-13}$     | ($m^2$/min) |
| $d_c$     | Diffusion rate of phagocytes             | $10^{-10}$     | ($m^2$/min) |
| $b_i$     | Density of bacteria in the lumen         | $10^{17}$      | (u/m$^3$)   |
| $f_b$     | Immune response rate                     | 0.002          | (u/min)     |
| $a$       | Coefficient proportional to the rate of phagocytosis ($a = s_b p_c$) | 0.3129         | (u/min)     |
| $s_b$     | Proportionality coefficient between $p_c$ and $a$ | $10^{15}$      | (u/m$^3$)   |
| $f_e$     | Related to the porosity of the epithelium| 0.0856         | (u/min)     |

Let us now define $\tau$ as the average time it takes a phagocyte to neutralize a bacterium, which is around 3 minutes in the in vitro observations, which implies that

$$\beta(t + \tau, x_0) = \beta(t, x_0) - \gamma(t, x_0)$$

and consequently $\partial_t \beta(t, x_0) \approx -\gamma(t, x_0)/\tau$. Replacing this into (6) we conclude that $a$ is of the order of $1/\tau$ units per minute. An underlying assumption here is that one phagocyte is needed in order to neutralize one bacterium. If two phagocytes were needed, it would give rise to a quadratic term $\gamma^2$ for example. This assumption is based on in vitro observations, but it might become irrelevant in particular frameworks or it might depend on the type of phagocytes. We stick to it here in order to simplify the analysis.

The density of bacteria in the lumen is approximately $b_i = 10^{17}$ u/m$^3$. At the positive equilibrium stage ($\bar{\beta}, \bar{\gamma}$), which is associated to an inflammatory phase, we suppose that around 30% of the total density of bacteria within the lumen might penetrate the epithelial barrier without going out of control. Therefore, we set $\bar{\beta} = 0.3 \times b_i$ units of bacteria. Even though we have no exact data concerning the density of immune cells in the damaged zone, the in vitro experiments suggest that during the inflammation stage it is around ten times less than the bacteria density, this is quite natural considering that the size of a phagocyte is much larger than the size of a bacterium. Hence, we set the hypothesis that $\kappa = \frac{1}{10}$ which means that at the equilibrium point, $\bar{\beta} = 10\bar{\gamma}$ and consequently $\bar{\gamma} = 3 \cdot 10^{-2} \times b_i$. Taking this into account from the equilibrium condition we have that $f_b = 10^{-1} r_c$ measured in units per minute.

The parameter $f_e$ is finally computed so that (2) holds at the equilibrium state.

### 6 Numerical simulations

We perform some numerical simulations in MATLAB by mean of a semi-implicit scheme to solve the system of equations (1). The results are shown in Fig. 2. We have considered the parameter values presented in the table 1 which were estimated...
in the previous section. For these values, the condition (5) associated to a Turing phenomenon occurrence established in the Proposition 44 is verified. However, there is a whole family of parameters verifying (5), as shown in Fig. 3.

For the simulations we have considered an initial datum with no phagocytes presence and a tiny spot of bacteria concentrated in the middle of the domain $\Omega$. This might be understood as a slight leak of bacteria from the lumen through the epithelium. The activator-inhibitor dynamics generated by the body’s immune response to the presence of bacteria and the contrast in the propagation rates of the two actors of the system is the reason why the patterns emerge in Fig. 2 after a certain time. This behavior is definitively associated with a Turing phenomenon.

We remark that the values we assign to the diffusion coefficients remains within the range estimated in the previous section. However, from the mathematical point of view what is really important in order to ensure the conditions leading to the Turing patterns is the smallness of the ratio $\delta = \frac{d_\beta}{d_\gamma}$. To change those values by preserving $\delta$ only represents a spatial rescaling that does not affect the pattern formation.

7 Proof of the results

Proof of the Proposition 41

Proof Assume first that $\inf_\Omega \beta_0 > 0$ and $\inf_\Omega \gamma_0 > 0$. Consider $\bar{t} > 0$ the first instant when either $\beta(t, x)$ or $\gamma(t, x)$ became non-positive, then for some $x^* \in \Omega$ one has $\beta(\bar{t}, x^*) \gamma(\bar{t}, x^*) = 0$. The Hopf lemma and the Neumann boundary conditions exclude that this minimum is reached at the boundary. Hence $x^* \in \partial \Omega$. 
Fig. 3 Region (blue) defined by the parameters \( r_c \) and \( a \) that verify condition (5) leading to Turing patterns observation

If \( \gamma(\bar{t}, x^*) = 0 \), then as \( \beta \geq 0 \) over \((0, t^*) \times \Omega\), one has

\[
\partial_t \gamma - d_c \Delta \gamma \geq -r_c \gamma \quad \text{in} \quad (0, t^*) \times \Omega.
\]

The strong parabolic maximum principle then yields \( \gamma \equiv 0 \) on this set, which contradicts the positivity of the initial condition.

Next, if \( \beta(\bar{t}, x^*) = 0 \) and \( \gamma(\bar{t}, x^*) > 0 \), the equation satisfied by \( \beta \) reads:

\[
0 \geq \partial_t \beta(\bar{t}, x^*) - d_b \Delta \beta(\bar{t}, x^*) = f_\epsilon \gamma(\bar{t}, x^*) > 0
\]

a contradiction.

We get the result for general initial data by approximation. \( \square \)

**Proof of the Proposition 42**

**Proof** The argument of this proof is similar to the one used to prove the non-negativity property. Indeed, consider \( \bar{t} \) the first instant when \( \beta \) rises the value \( b_i \), then there exists \( x^* \in \Omega \) such that \( \beta(\bar{t}, x^*) = b_i \) and one has \( \partial_t \beta(\bar{t}, x^*) \geq 0 \). Nevertheless from the equation associated with \( \beta \) one conclude that \( \partial_t \beta(\bar{t}, x^*) = -\frac{a_\beta(\bar{t}, x^*) \gamma(\bar{t}, x^*)}{s_b + \beta(\bar{t}, x^*)} < 0 \) from the positivity property. So we get a contradiction which implies that for all \( t > 0 \) one has necessarily \( \beta(t, x) < b_i \).

The boundedness of \( \gamma \) in the \( L^2 \)-norm follows directly from the boundedness of \( \beta \) and \( \gamma_0 \). In fact multiplying by \( \gamma \) in the second equality of eq.(1), integrating by parts and applying Holder inequality one gets that

\[
\frac{1}{2} \partial_t \| \gamma \|^2_{L^2(\Omega)} + d_c \| \nabla \gamma \|^2_{L^2(\Omega)} \leq f_b \| \beta \|_{L^2(\Omega)} \| \gamma \|_{L^2(\Omega)} - r_c \| \gamma \|^2_{L^2(\Omega)} \quad (8)
\]
from where we deduce

\[ \partial_t \| \gamma \|_{L^2(\Omega)} \leq f_b \| \beta \|_{L^2(\Omega)} - r_c \| \gamma \|_{L^2(\Omega)}. \]  

(9)

Keeping the notation \( \kappa := \frac{f_b}{r_c} \) introduced in the section 4.2, this last inequality implies that

\[ \| \gamma \|_{L^2(\Omega)} \leq \max \{ \kappa b_i, \| \gamma_0 \|_{L^2(\Omega)} \} \]  

(10)

which completes the proof. \( \square \)

In order to simplify the notations in the proofs of proposition 43 and 44 we will denote \( \theta := \frac{\beta}{b_i} \) and we will also keep the notation \( \kappa := \frac{f_b}{r_c} \).

**Proof of the Proposition 43**

**Proof** The existence of such a positive steady state follows from the analysis of (2). Let us define \( F(\beta) = (r_b + f_e \kappa) \left( 1 - \frac{\beta}{b_i} \right) - \frac{a \kappa \beta}{s_b + \beta} \). From the positivity of the parameters of the model we have that \( F(0) > 0 \) and \( F(b_i) < 0 \), this means that there are at least one positive value \( \beta \in (0, b_i) \) that satisfies \( F(\beta) = 0 \) or equivalently (2). Moreover, since the derivative of \( F \) is strictly negative we deduce that it has at most one root which leads to the uniqueness of \( \beta \).

Let us now study the conditions leading to the stability of this steady state. We define \( M \) as the matrix of the linearized system around this positive steady state \((\beta, \gamma)\) which writes

\[
M := \begin{pmatrix}
    r_b(1 - 2 \theta) - \frac{a s_b \kappa \beta}{(s_b + \beta)^2} - f_e \kappa \theta - \frac{a \beta}{s_b + \beta} + f_e (1 - \theta) \\
    f_b \\
    -r_c
\end{pmatrix}.
\]

We compute the determinant and the trace of this matrix

\[
tr(M) = \frac{a \kappa \beta^2}{(s_b + \beta)^2} - r_b \theta - f_e \kappa - r_c,
\]

\[
det(M) = r_c r_b \theta + f_b f_e \theta + \frac{a f_b s_b \beta}{(s_b + \beta)^2}.
\]

From the positivity of the parameters of the model it is clear that the determinant of \( M \) is positive, therefore in order to have linear stability around \((\beta, \gamma)\) it is necessary and sufficient to impose the negativity of the trace of \( M \) which is equivalent to the condition (4). \( \square \)
Proof of the Proposition 44

Proof. We linearize the system around \((\bar{\beta}, \bar{\gamma})\). For the sake of simplicity we keep the notation \(\beta(t, x), \gamma(t, x)\) for the linearized variables

\[
\begin{cases}
\partial_t \beta - d_b \Delta \beta = \left( r_b(1 - 2\theta) - \frac{a\kappa \bar{\beta}}{(s_b + \bar{\beta})^2} - f_e \kappa \theta \right) \beta + \left( - \frac{\bar{\beta}}{s_b + \bar{\beta}} + f_e (1 - \theta) \right) \gamma \\
\partial_t \gamma - d_c \Delta \gamma = f_b \beta - r_c \gamma 
\end{cases}
\]  

(11)

We are seeking in particular for solutions with exponential growth in time, so we consider that

\[
\beta(t, x) = e^{\lambda t} B(x); \quad \gamma(t, x) = e^{\lambda t} C(x)
\]  

(12)

with \(\lambda > 0\). This means that \(B(x)\) and \(C(x)\) should satisfy the following problem

\[
\begin{cases}
-d_b \Delta B(x) = \left( r_b(1 - 2\theta) - \frac{a\kappa \bar{\beta}}{(s_b + \bar{\beta})^2} - f_e \kappa \theta - \lambda \right) B(x) + \left( - \frac{\bar{\beta}}{s_b + \bar{\beta}} + f_e (1 - \theta) \right) C(x) \\
d_c \Delta C(x) = f_b B(x) + (-r_c - \lambda) C(x)
\end{cases}
\]  

(13)

or equivalently that they are eigenfunctions associated with the positive eigenvalue \(\lambda\).

We consider in particular Fourier modes of the form

\[
B(x) = B e^{i \xi x}; \quad C(x) = C e^{i \xi x},
\]

and we replace it in (13) to obtain the following homogeneous linear system of equations

\[
\begin{pmatrix}
0 \\
0 
\end{pmatrix} = \begin{pmatrix}
r_b(1 - 2\theta) - \frac{a\kappa \bar{\beta}}{(s_b + \bar{\beta})^2} - f_e \kappa \theta - \lambda - d_b \xi^2 \\
\frac{\bar{\beta}}{s_b + \bar{\beta}} - r_c - d_c \xi^2
\end{pmatrix} \begin{pmatrix}
B \\
C
\end{pmatrix}
\]

Let us call \(M_{\lambda, \xi}\) the matrix associated to the previous linear system. It can be written in terms of \(\xi, \lambda\) and the coefficients of the matrix \(M\) introduced before in the proof of the Proposition 43,

\[
M_{\lambda, \xi} := \begin{pmatrix}
M_{(1,1)}(\lambda) - \lambda - d_b \xi^2 & M_{(1,2)}(\lambda) \\
M_{(2,1)} & M_{(2,2)}(\lambda) - \lambda - d_c \xi^2
\end{pmatrix}.
\]

We recall that

\[
M_{(1,1)} = r_b(1 - 2\theta) - \frac{a s_b \kappa \bar{\beta}}{(s_b + \bar{\beta})^2} - f_e \kappa \theta, \quad (14)
\]

\[
M_{(1,2)} = - \frac{\bar{\beta}}{s_b + \bar{\beta}} + f_e (1 - \theta), \quad (15)
\]

\[
M_{(2,1)} = f_b, \quad (16)
\]

\[
M_{(2,2)} = -r_c. \quad (17)
\]
In other words we look for a certain $\lambda$ with positive real part and $\xi^2$ for which $\det(M_{\lambda,\xi}) = 0$. The determinant of $M_{\lambda,\xi}$ is a quadratic polynomial function in $\lambda$.

$$\det(M_{\lambda,\xi}) = \lambda^2 + a_1 \lambda + a_2$$

with coefficients

$$a_1 = -\text{tr}(M) + (d_b + d_c)\xi^2,$$

$$a_2 = \det(M) - (M_{1,1}d_c + M_{2,2}d_b) \xi^2 + d_b d_c \xi^4.$$

Since the right-hand side inequality in (5) ensures that $\text{tr}(M) < 0$, we conclude that $a_1 > 0$. Hence, the polynomial associated to $\det(M_{\lambda,\xi})$ can have a positive root $\lambda$ if and only if $a_2 < 0$. The term $a_2$ is itself a quadratic polynomial in $\xi^2$ with positive second order coefficient. For the sake of simplicity we will define $\delta := \frac{d_b}{d_c}$, and we will study the sign of $\frac{a_2}{\delta d_b d_c}$ which has roots explicitly given by

$$\Lambda_{\pm} = \frac{M_{1,1} + \delta M_{2,2}}{2 * d_b} \left[ 1 \pm \sqrt{1 - \frac{4 \det(M) \delta}{(M_{1,1} + \delta M_{2,2})^2}} \right].$$

In the regime $\delta$ small enough the Taylor expansion gives us the following approximate values

$$\Lambda_- = -\frac{\det(M)}{d_c M_{1,1}},$$

$$\Lambda_+ = \frac{M_{1,1}}{d_c \delta}.$$

The left-hand side inequality in (5) guarantees that $\Lambda_+$ is positive and since $\delta$ can be as small as desired, $\Lambda_+ >> 1$ and the interval $(\Lambda_-, \Lambda_+)$ where $a_2$ is negative is large enough.

In other words, there exists a positive real $\lambda$ and Fourier modes for which $\det(M_{\lambda,\xi^2}) = 0$ and consequently we can find exponential growth in time solutions to the linearized system around the steady state $(\beta, \gamma)$. However, the Fourier modes for which this condition holds are bounded.

We have showed the existence of perturbations such that the linearized system has exponential growth in time. The frequency of the perturbations cannot be infinity and from Proposition 41 and 42 neither extinction nor blow-up are possible. Hence, we have finally proved the formation of Turing Patterns. Those patterns, which can be observed in the Fig. 2, correspond to a non-constant steady state. Such solutions are known to be stable with respect to periodic perturbations. But their stability with respect to more general perturbations, such as compactly supported ones, is known to be a tough question and remains unaddressed in this paper.

$\square$
8 Conclusions

This work remains a simplified approach to the question of modelling the inflammatory response in Crohn’s disease. We have made several hypotheses with the aim of globally understanding the biological mechanism behind the abnormal body reaction leading to the disease but staying relatively simple in terms of the number of variables and equations.

Though we have tried to consider parameter values true to medical and biological observations, we highlight the qualitative results over quantitative ones. In this sense, obtaining a Turing mechanism through our model might explain the patchy inflammatory patterns observed in patients suffering from Crohn’s disease and must be interpreted as another step in the aim to fully understand this illness and its causes.

It remains a question concerning the ulcerative colitis since it has several common factors that relate it to Crohn’s disease but also others that set them apart. It might be interesting to study the possibility of modelling the ulcerative colitis by mean of the same system of equations in a different parameter regime and eventually finding responses to help doctors with early diagnosis or treatments.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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